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Old strategies and New Tools: an Amazing Cocktail for an Organic Frontier Chemistry

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Abstract

In the last three decades, the general sensitivity of public opinion toward environmental problems has certainly evolved. Indeed, a higher grade of awareness about the effect on the environment caused by industrial non-regulated production has been registered in the last century. At the same way, several chemicals were not known to be toxic and dangerous for human health. Despite the remarkable achievement carried out in this field, the mandatory goal of designing more eco-friendly procedures is not trivial and is part of the ongoing actual research. Within the aim of developing efficient organic synthetic strategies, our research group focuses on the goal of solvent elimination and maximization of energy efficiency, by means of ball milling technology. It has already been demonstrated that such method can be helpful in order to perform a process in absence of solvents, avoiding the drawback to them related. Mechanochemistry can be usefully applied to extend the scope of existing methodologies to non-soluble reactants, and to explore alternative paths not observable in solution. More specifically this thesis describes the study of mechanochemical methodologies for the synthesis of compounds of remarkable relevance. A solvent-less procedure is described for Hydroxamic acid derivatives, important synthetic target seen their important biological activity. Furthermore, object of this work has been the setting up of a methodology for the synthesis of isocyanide. Due to its extraordinary reactivity, isocyanide moiety plays a crucial role in organic synthesis and more specifically in multicomponent reactions. As a part of this study, we explored further transformation on the mechanochemical obtained isocyanide, exploiting its reactivity in a modified Bargellini reaction for the synthesis of 3-Carboxamido-Isobutyric Acids.

Catalytic methods play a crucial role in green synthesis. Their use allows to avoid stoichiometric reagents, can minimize energy waste lowering energy activation barrier, open route to reactivities otherwise not achievable. In the present work, a catalytic reaction has been

investigated with the aim of combining the catalytic approach to the mechanochemical one, starting from a solution based method. The reaction of borrowing hydrogen is characterized by a high atom economy, but common procedures implies high operational temperatures. The present work describes the investigation of the synthesis of secondary amines in presence of Ru and Os catalysts at room temperature.

Chapter I-Introduction

Ball milling as a powerful tool for green organic chemistry

Green chemistry in organic synthesis

The life quality of our developed society owes to industrial organic synthesis standards otherwise not conceivable. For instance, the discovery and development accomplished by pharmaceutical industry research along years resulted in a multitude of available drugs widespread in our daily life. Studies performed by synthetic organic chemists over the last century laid the groundwork for the modern pharmaceutical industry. However, this scientific legacy includes processes which make use of hazardous substances and produce a considerable amount of waste. Indeed, the common mind-set was characterized by a lack of awareness of actual toxicity of several reagents for the human health and for the environment.

In the last three decades, we have witnessed instead a grown attention toward the problems of chemical pollution and resource depletion. The introduction of the term “Green Chemistry” is dated to 1991 when Anastas mentioned it for the first time in a special program created by the US Environmental Protection Agency (EPA) in order to stimulate a substantial development in chemistry and chemical technology. Green chemistry was intended as an approach to chemical production that called for the reduction or wherever possible for the elimination of toxic

reagents and waste at the outset of a process, instead of cleaning up hazardous substances after the fact.

Later in 1998, the so called 12 principles of green chemistry were redacted by Anastas and Warner,[1] with the aim of establishing a set of practical guideline to be followed when designing a benign chemical process. They are listed as follows:

1. It is better to prevent waste than treat or clean it up after it is formed.

2. Synthetic methods should be designed to maximize the incorporation of all materials used into the final product (atom economy).

3. Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.

4. Chemical products should be designed to preserve efficacy of function while reducing toxicity.

5. The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.

6. Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.

7. A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.

8. Unnecessary derivatives (i.e. protecting groups) should be avoided whenever possible.

9. Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.

10. Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.

11. Analytical methodologies need to be further developed to allow for real-time, inprocess monitoring and control prior to the formation of hazardous substances.

12. Substances and the form of a substance used in a chemical process should be chosen to minimize potential for chemical accidents, including releases, explosions, and fires.

In synthesis, quoting Sheldon in his working definition: ”*Green chemistry efficiently utilizes (preferably renewable) raw materials, eliminates waste, and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products”.*[2] Ideally, would be auspicial that the higher possible number of these principle would be taken into account in realizing a synthetic process, being often not possible to deliver all of them at the same time.

Among the 12 principles, the focus of our research group relies in developing more sustainable processes avoiding the use of auxiliary substances such as solvents, as dictated from principle 5. Moreover, we aimed to optimize the energy efficiency in organic processes by using alternative energy source rather than classical thermal heating sources (see principle 6).

The importance of solvents

“No Coopora nisi Fluida” The statement of Aristotle could be translated as “No reaction occurs in the absence of solvent.” Even if this is not considerable true, solvents play a crucial role in

several reactions. Solvents allow the efficient solubilization of reagents and can serve to slow or increase the rate of reactions. Furthermore, they can act as a heat sink or heat transfer agent and they can be used to prevent hot spots and run-away reaction as well. Despite their importance for a synthetic use, solvents represent a potential risk for the environment as well as human health. Many of them are, in fact, volatile, flammable, toxic and carcinogenic.

Use of solvents is also a matter of concern because they constitute a very considerable part of the total amount of waste produced by industry. They represent a relevant issue for industry since they are highly regulated and expensive.

The last 10 years have witnessed increasing efforts devoted to avoid the use of traditional solvents, both from an academic and industrial point of view.[2,3] For instance, the use of ionic liquids or supercritical CO_2 is recommended as well as the use of water as reaction media.

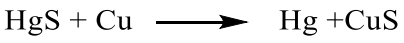
Clearly, the best way to avoid health risks due to handle such large quantities of waste generated by solvents would be not to use them at all. Unfortunately, it is not always possible to carry out a reaction in total absence of solvents by using traditional batch equipment. In this contest, mechanochemistry can help to carry out a solvent-less transformation overcoming several issues, ensuring *e.g.* a proper mixing of the reactants or the transfer of the energy in an efficient way. Besides, adopting mechanochemistry techniques can lead to an extension of scope of reactions limited by insolubility of reagents, and in some case open new unexplored reactivity routes.

Ball milling and organic chemistry

Historical perspective

The first written report of a mechanochemical reaction is ascribed to Theophrastus of Ephesus (371-286 B.C.), a student of Aristotle, in a book called, “De Lapidibus” or “On stones”.[4] He

described the formation of metallic mercury by grinding cinnabar in presence of acetic acid in a brass vessel. The mechanochemical reaction is identified as follows:



Scheme 1 *formation of metallic mercury*

Later, mechanochemistry was rather used in mining and metallurgy than for chemical transformation. In 1820 the reduction of AgCl to Ag with Zn, Cu, Sn or Fe in a pestle and mortar was reported by Michael Faraday.[5] Nevertheless, the work conducted by Carey Lea in 1892 established the emergence of mechanochemistry as a subtopic of chemistry.[6] He demonstrated how the grinding action could promote the decomposition of mercury and silver halides to their elements rather than melting or sublimation caused by heating the same reagents. The term mechanochemistry is often credited to Wilhelm Ostwald (1853-1932) who classified mechanochemistry as one of four sub-disciplines of chemistry (alongside thermochemistry, electrochemistry and photochemistry) each based on a different type of energy input. He defined the subject as "*a branch of Chemistry, which is concerned with chemical and physio-chemical changes of substances of all states of aggregation due to the influence of mechanical energy*".[7] Moreover, according to IUPAC, a mechanochemical reaction is a "*Chemical reaction that is induced by the direct absorption of mechanical energy*" with the note '*Shearing, stretching, ad grinding are typical methods for the mechano-chemical generation of reactive sites, usually macroradicals, in polymer chains that undergo mechano-chemical reactions*".[8]

During the first half of 20th century mechanochemistry was subjected to slow growth. A remarkable contribute came in 1902 from Flavitsky, who became the first to report chemical reactions in dry solid mixtures on co-grinding.[4] He developed a method for identifying 13 cations and 19 anions by rubbing small quantities of the unknown substance with an appropriate sequence of reactants, the procedure was used by student at the State University of Leningrad

to perform qualitative analysis in inorganic mixture, probably the first time mechanochemistry was taught in a laboratory.

The effect of mechanical action on polymers was investigated, seen the increased use of those, the most typical is degradation due to shortening of molecules. Later it was observed that the impact could also cause polymerization, the progress in the field were reviewed by Baramboin.[9] The mechanical initiation and sensitivity of explosives became an intensely researched subject during the Second World War, in those years it was claimed that the ignition would start thermally from the hot spots created by mechanical impact; this theory was extended to explain chemical reactions caused by sliding.[4] Even though this was the most accepted theory, already in 1933 Fink and Hoffman asserted that the fast oxidation of metal surfaces during sliding was the result of the mechanical action, arguing that the observed increase in temperature was the consequence of oxidation rather the cause of the reaction.[10]

During the second half of the 20th century mechanochemistry could benefit from the developments occurred in underlying experimental techniques, as the invention of X-ray crystallography, and from the development of more efficient mills. Besides, while previous efforts in the field were often not fully shared by individual investigators, a scientific community around mechanochemistry took shape, and the cooperation among different group became more intense.

In early time, the ball milling was mainly used as a means to achieve small particles and the development of mechanochemistry became remarkable for the possibility of obtaining metal alloys. This research area was subjected to a substantial development which grew independently form another field of mechanochemistry. For the first time in 1976 in Scientific American was reported the possibility to use ball milling to cold-weld metals with very different melting point. The process of formation of the alloy is due to the impacts that occur between the balls after the trapping of different metals between multiple ball bearings.

Following the discovery of mechanical alloying, the development of new practices for ball milling remained relatively dormant for the next two decades. This is particularly true for organic reactions, and the field of ball milling was rather a domain of inorganic chemistry and metallurgy.[11,12]

Indeed, it was claimed by Toda[13] in 1995 that '*almost all reactions are still carried out in solution, even when a special reason for the use of solvent cannot be found*'. In his pioneering work, Toda showed how a significant number of organic reactions proceed well under neat conditions; he also demonstrated how in some cases, the solid-state organic reaction occurs more efficiently and more selectively than does in the solution counterpart.[14] Since then, the methodology begun to become more sophisticated and the type of mechanochemical reactions have grown greatly. Nowadays, the field of mechanochemistry is experiencing a renaissance and is becoming a well-established technique in all area of chemistry, including organic,[15–18] organometallic,[19] and supramolecular chemistry,[20] as well as materials science.[21–23]

Milling equipment

The easiest way to transfer kinetic energy to the reaction system is represented by the mortar and pestle. It is easy to understand that method implies intrinsic drawbacks. First, the energy efficiency is obviously limited by the operator as well as the reproducibility of the grinding process. Besides, the lack of control on the transformation is further affected by the exposition to air. The advent of ball mill certainly transformed the approach to mechanochemical reactions and there has been a big engineering development for these systems. Mechanical milling is a powder processing method suitable for industrial exploitation on different scales.[24] In a typical mechanical milling experiment, an opportune powder mixture of reagents is placed in a high energy mill, together with an opportune milling tool.[25]

Periodic movement of the reactor allows the milling tools to collide with each other and with the reactant powder, subjecting the latter to mechanical load. The reduction of particle size and the blending of particles in new phase is the objective of milling. The typical mill used for these purposes has been the high energy ball mill such as tumbler ball mills, vibratory, planetary and attritor mills.[26]

Nowadays a high number of mills is present on the market.[27] For what concern the laboratory equipment two kind of miller are the most used, *i.e.* shaker mills (mixer or vibrational) and planetary mill. They can be used for reaction from milligram to gram scale. The two designs differ for the movement that causes the mixing. For instance, shaker mills move the jar containing the reaction mixture and the grinding balls back and forth several thousand times a minute.[11,28] In this case, the primary energy involved is impact force. Planetary mills, on the other side take their name from the planet-like motion imprinted to the jars, primary force involved in this type of design is shear force. The twin screw extruder (TSE) consists in two co-rotating screws that convey solid reactants through a barrel causing shearing and compression[29] (Figure 1c) This technique has been widely used in in the food, polymer and pharmaceutical industries.[30] More recently, several mechanochemical application of this design have been demonstrated.[30–33] Indeed TSE allows to overcome some of the issues related to mechanochemical synthesis, as scalability and temperature control, enabling the transfer of a mechanochemical process to an industrial scale and to continuous flow processes. As an example of organic synthesis application, it was demonstrated that this tool could be used to perform multi kilogram per hour processes for Knoevenagel, imine formation, aldol and Micheal addition condensations. In addition, is reported that the optimized procedure is not requiring any further purification. [32]

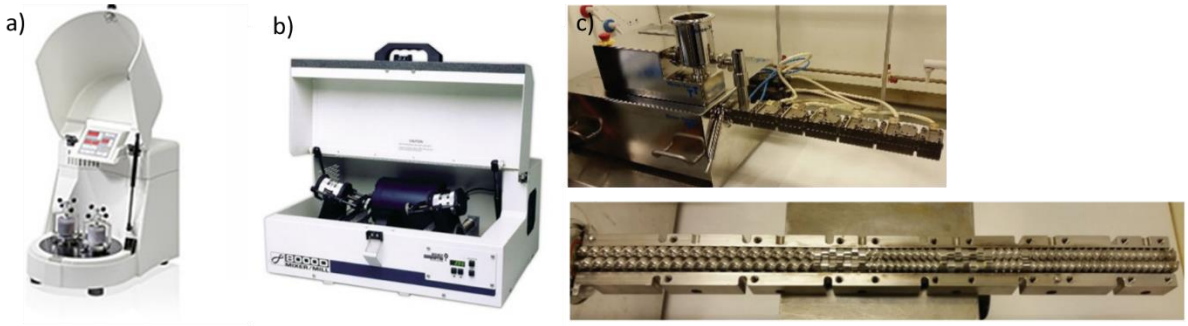


***Figure** 1 a)Planetary Micro Mill PULVERISETTE7- FRITSCH (b) 8000M Mixer/Mill® - SPEX c) Twin screw extruder and intermeshing co-rotating screws Reproduced from Ref.* [32] *with permission from The Royal Society of Chemistry*

The energetic aspects involve technical parameters as frequency of milling and trajectory. Frequency of milling is a simple way to modulate the energy input. It has also been demonstrated that different type of energy absorption can lead to different outcomes (*e.g.* impact or shear,[34] and different mills can lead to diversification in reaction performance.[35] Together with the milling regimes the outcome of a mechanochemical reaction conduced in a ball mill is affected by the material of milling media and vessel, as well as their size and number. In order to determine the most suitable material, density and Knoop index (KI), a measure of mechanical hardness, should be considered. Stainless steel (density = 7.7 g cm^{-3}, KI = 138), zirconia (density = 4.5 g cm^{-3}, KI = 1160), copper (density = 8.96 g cm^{-3}, KI = 163), alumina (density = 3.95 g cm^{-3}, KI = 138) and tungsten carbide (density = 7.7 g cm^{-3}, KI = 138) are standard materials exploited for the purpose. Moreover, one should take into consideration the occurrence of contamination of the reaction mixture due to metal leaching[36] or wearing[37] (Figure 2b). Considering thought that the release of catalytic amount of the opportune metal can be intentionally used to promote chemical reactions.[38–40]

Furthermore, a number of designed tool for the combined use of kinetic and thermal energy or photochemical have been developed.[41–43]

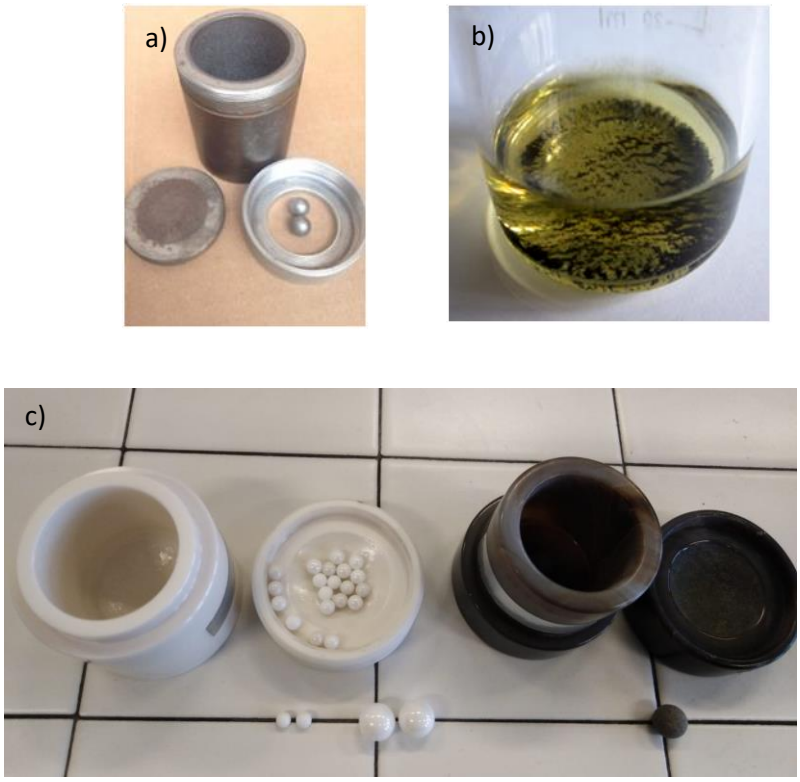


Figure 2 *milling media and jars materials a) stainless steel jar b) metal contamination c) on the left zirconia jar and balls, on the right agate jar and balls*

Whereas the presence of big amount of solvent in a mechanochemical transformation is avoided, solvent itself in catalytic quantity can be used as tool for tuning the reactivity of a particular system. The technique is called "Liquid Assisted Grinding" (LAG) and consists in the addition of small quantity (below 1 µL mg^{-1}) of liquid to the reaction mixture. Originally, the beneficial effects of LAG were discovered in the registration of a rate enhancement of co-crystallization.[44] The potential applicability of LAG was demonstrated in several studies as shown in screening for inclusion compounds,[45] cocrystals,[46] salts,[47] solvates,[48] polymorphs [49] and in organic mechanochemistry.[50,51] In many cases, the addition of liquid enhances the reaction kinetics, improves the final yields allowing to collect products not accessible by neat grinding.[52–58]

A LAG transformation is quantitatively distinguished from a slurry reaction from the value of η, given by the ratio of the added liquid (in µL) to the total weight of the solid reactants (in mg). Value of $\eta = 0$ corresponds to a neat reaction. Above the value of 1 µL mg^{-1}, we assist to a slurry reaction in which the reactant solubility on reactivity begin to be noticeable. This range

was defined empirically in a systematic investigation in which, during the co-crystallization of caffeine or theophylline with L-tartaric acid, was observed no correlation between enhancement in reactivity and solubility of the reactant in the liquid added.[59]

The milling assessment used for this project is the widespread SPEX 8000 mixer/mill. This kind of mill can contain one vial, which is fastened in the clamp and moved in a way which describes an ∞, in a motion in three orthogonal directions. The center of the vial vibrates in two-dimensional mode with the same frequency and different amplitude and its slanted axes rotates around the third direction (Figure 3). This ball mill operated at a fixed frequency of 18 Hz.

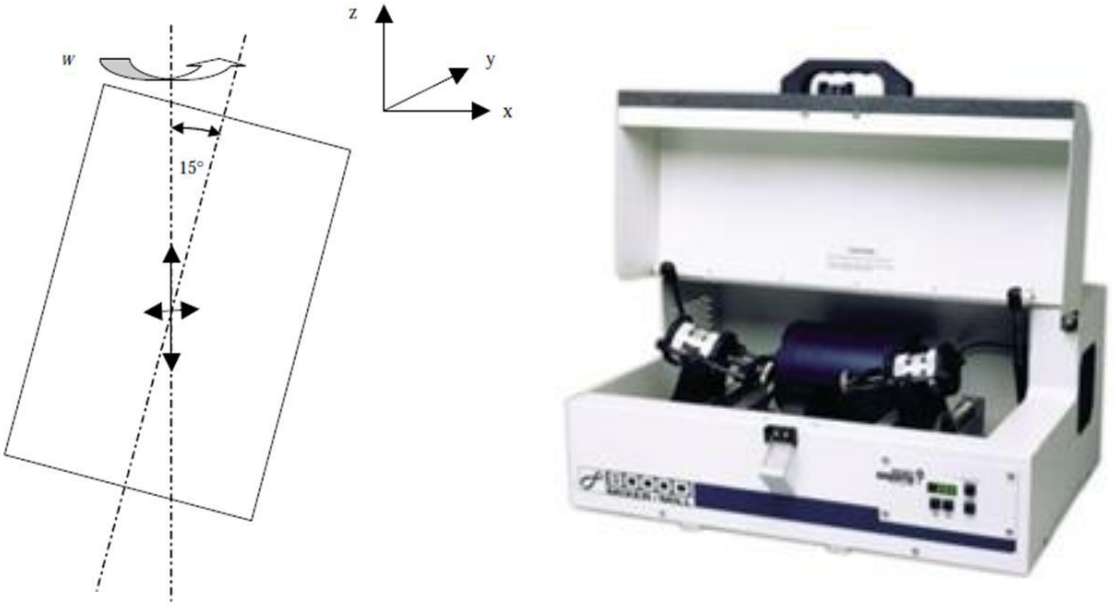


Figure 3 Picture of a SPEX 8000 mixer/mill on the left, schematic representation of the movement of the SPEX 800 on the right. This picture is reproduced according to ref [60].

Mechanistic aspects

The principle at the base of a mechanochemical process is the delivering of kinetic energy to the reactants into the reaction vessel through the balls. Depending on the type of ball mill, the energy can be delivered according to different mechanism. In general, the grinding action exercised from the balls causes several physical phenomena as (i) breaking down particles to

smaller sizes, giving greater surface area and breaking up any product coating layers to expose fresh surfaces, (ii) intimate mixing of reactants, (iii) introducing defects and eventually amorphization of the material, and (iv) frictional heating.[61]

The wide variety of reactions, which differ for conditions, type, and nature of reactants, implies an intrinsic obstacle in depict a complete vision on the mechanistic aspect of a mechanochemical process. Several models have been envisioned, especially regarding extended inorganic materials; in this contest hot spot and the magma-plasma model are the most referred, according to which is expected the occurring of local temperatures to above 1000 °C for short periods.[62,63]

Concerning molecular organic and metal organic mechanochemical reactions, a considerable decomposition would be expected if the hot spots and magma plasma sites would be the primary sites of reactivity. However, is not excluded that the heating which develops after the dissipation acts as the driving force.

The formation of a eutectic mixture is also claimed as the cause of the formation of a new covalent bond.[64] The generality of this theory would be denied by the documented absence of bulk melting and by the solid-state characteristic in some studied systems, as for example in the temperature controlled Knovenagel reaction reported by Kaupp, and organic disulphide metathesis reaction.[65,66]

Deeper inside into the understanding the mechanistic that govern a mechanochemical reaction are highly needed, indeed mechanistic studies on mechanical reaction represent a growing arising research area even because, until recently, *ex situ* technology was dominant in analysing milling processes. Powder X-Ray diffraction (PXRD) is the primary technique for this kind of analysis, where the structural analysis can be combined with the monitoring the transformation of crystalline reactants and product, as was demonstrated by Karki *et al.*[67] The ex situ monitoring by means of PXRD, mostly sensitive to crystalline materials, is often not applicable to organic transformation, in which soft organic solids can undergo to amorphization by

grinding or milling. To overcome this issue, the Fourier-transform infrared (FTIR) spectroscopy can be used to provide information on chemical composition to monitor organic chemistry transformation. Stolle group described the potential use of FTIR to study the reaction of hydroamination of alkynes with *o*-substituted anilines to form a benzannulated N-heterocyclic benzoxazine in a planetary mill.[68] The ex-situ characterization of mechanochemical obtained products can be profitably obtained by solid-state nuclear magnetic spectroscopy which can be used to analyse amorphous solids.[69–71]

Ex-situ Raman spectroscopy was used by James's group to provide a solution-like kinetic model, in which the second-order rate law is justified by the assumption that the rate-determining factor is the frequency of reactive encounters between the particles.[72]

Further insights into the understanding of reactivity features as kinetics and temperature trends and effects inside ball milling has gained a benefit from the development of *in situ* analysis.

The *in situ* monitoring was first introduced thanks to PXRD through the wall of the milling jar.[73] Further improvements were obtained by means of Raman spectroscopy technique[74] and a combined syncroton XPRD/Raman approach[75] *in situ* PXRD was exploited by Kulla *et al*. to study the effect of the ball-to-reactant mass ratio (BBR) on a mechanochemical transformation, highlighting that the BBR had no effect on the induction time but once the product is formed increasing BRR resulted in an increasing of the rate of conversion.[76]

Friščić and Halasz reported the investigation of temperature effect on the mechanochemical synthesis of a coordination polymer by means of *in situ* Synchroton Powder X-Ray diffraction. This study appears to confirm the incompatibility of the "hot-spot" or "magma-plasma models" with soft materials, showing a substantial dependence of reaction rates on change in temperature of about 45 °C.[77]

Recently, combination of synchrotron X-Ray diffraction with Raman spectroscopy and thermography to study milling reactions in real time was reported.[78] A recent study of a model organic mechanochemical transformation, as the Knoevagel condensation of vanillin and

barbituric acid, revealed sigmoidal feedback kinetics which contrast with those of the same reaction in solution, further investigation lead to the conclusion that dynamic rheological changes during the milling process affect the nature of the feedback loop.[79]

The investigation on temperature development and kinetics in ball mills are gaining a growing attention, new insight have been provided in the last year and more efforts are needed for a more complete picture.[78–81]

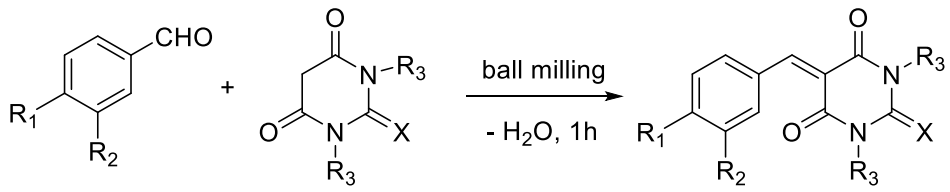
Ball milling in recent literature for synthesis of organic molecules

The last two decades have seen a remarkable increase in terms of publication in the field of mechanochemical organic synthesis.[16,18,61,82–88]

Since the pioneering work of Toda,[14] examples which demonstrate the usefulness of mechanochemistry in organic synthesis are grown exponentially. Below some example of application of mechanochemistry to organic reactions is reported.

Stoichiometric reactions

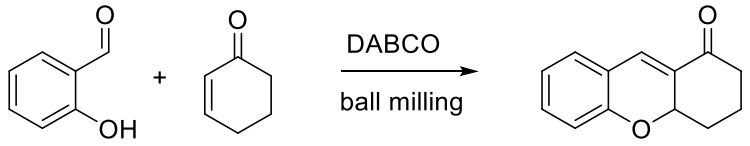
Stoichiometric reactions performed by ball-milling as various condensations have been reported. A mechanochemical version of Knoevenagel (Scheme 2) and Micheal reactions were documented by Kaupp in 2003.[65] The authors highlight the convenience in the method in terms of purity of the products obtained without further purification, rendering the process actually sustainable. The mechanochemical Knoevenagel condensation in comparison to the one accelerated by microwave demonstrated to give superior results.



R_1 = NMe_2, OH; R_2 = H, Me, Et; X = O, S

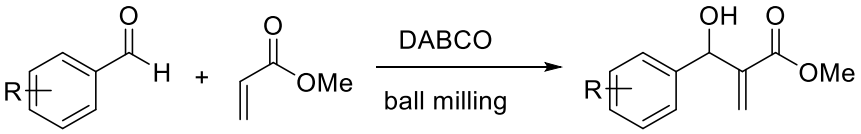
Scheme 2 *Scheme Knoevenagel mechanochemical condensation*[65]

In 2008, Bräse reported a systematic investigation of the milling parameters on the process of formation of xanthone by oxa-micheal reaction in presence of dabco (50 mol%).[89]



Scheme 3 *Domino axa- Micheal - aldol reaction by ball milling*[89]

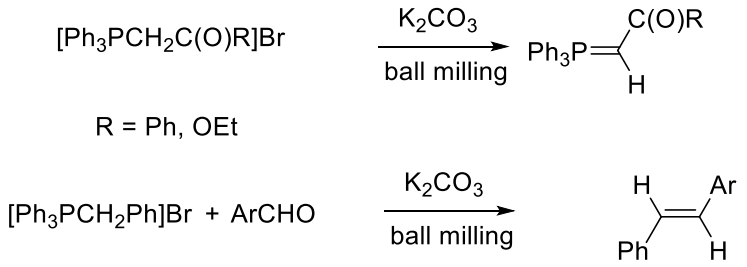
The use of DABCO revealed to be crucial also in the case of Morita-Baylis-Hilman reaction reported by Mack and coworker under ball milling conditions,[90] for which they registered an enhancement in reaction rate with respect to solution protocols.



Scheme 4 *Morita-Baylis-Hilman reaction*[90]

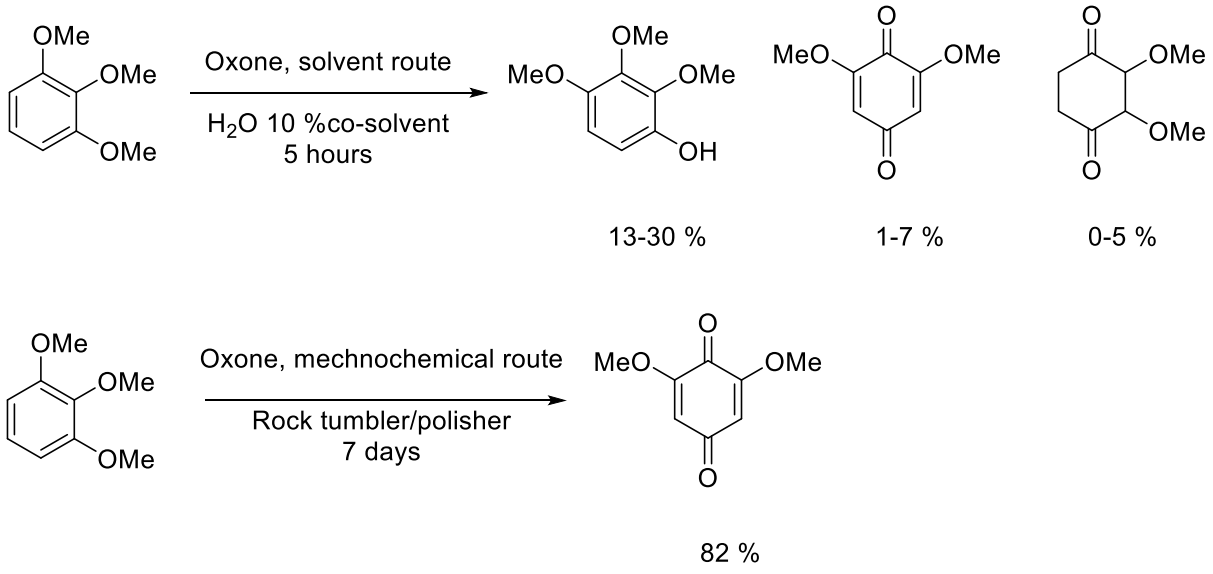
Another important C-C bond formation is the Wittig olefination. Balema and Percharsky reported the synthesis by ball milling of phosphonium salts[91] and phosphorus ylides[69] in the presence of the weak base K_2CO_3. It is interesting to note that in solution commonly stronger base are required for this purpose. Indeed, common scales of basicity and acidity are normally solvent-specific and in solvent-free conditions reactivity can differ remarkably from what expected. Posphorus ylide prepared from triphenylphosphine in presence of K_2CO_3 was utilized

for “one-pot” solvent free Wittig olefination of organic halides with aldehyde and ketones (Scheme 5).



Scheme 5 *Wittig reaction under mechanochemical conditions*[69]

The mechanochemical oxidation of lignin-like methoxylated aromatic substrate using Oxone as oxidant offers a good example of selectivity enhancement obtained by ball milling. Indeed, the same reaction performed in aqueous solution les to the formation of 2,3,4-trimethoxyphenol as major product with several other side products observed. In contrast, the reaction conducted in 7 days making use of a rock tumbler/polisher provided as unique product the quinone (Scheme 6).[92]



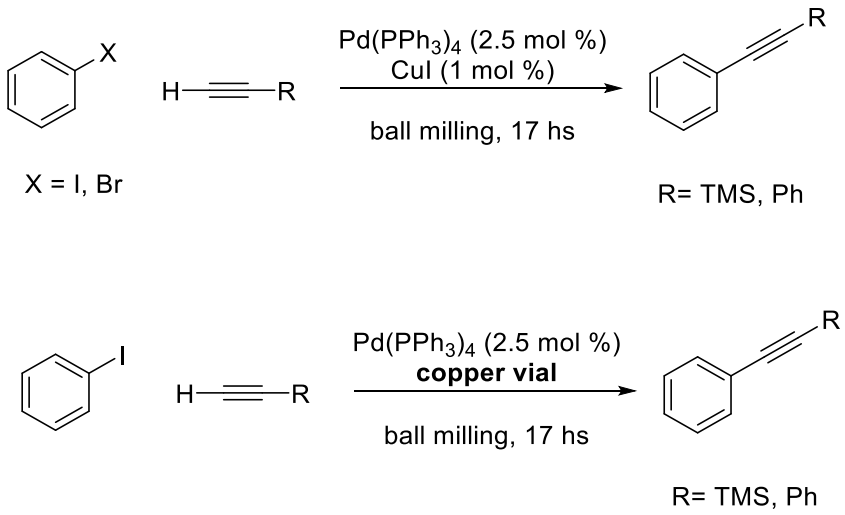
Scheme 6 *Different selectivity in mechanochemical versus conventional solution oxidation using methoxylated aromatics compound with Oxone*[92]

Metal-catalyzed organic reactions in ball mills

Metal-catalyzed reaction covers a crucial role in organic synthesis. During these years of growth in the field of mechanochemistry, numerous examples have been reported of the applicability of ball milling to metal catalyzed processes, or even to their implementation. The field have been recently reviewed by Friščić and Hernandez and still promises interesting perspective.[16]

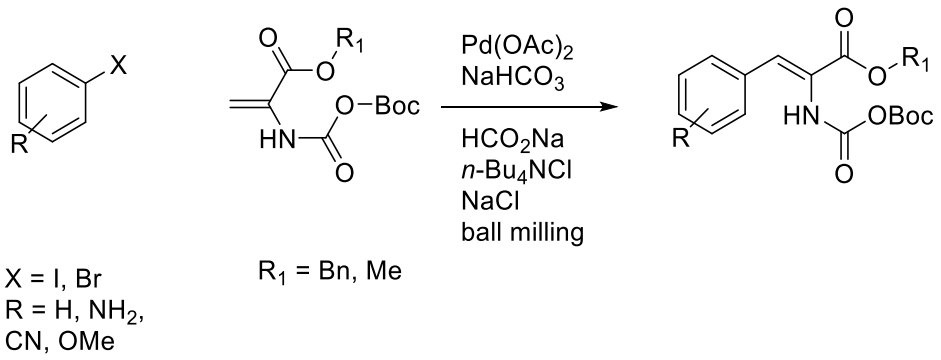
Coupling reactions such as the Suzuki, Heck, Sonogashira are of remarkable importance for the synthesis of a wide diversity of organic molecules within several field of application. Therefore, it is not surprising that they have been investigated under numerous alternative methods such as ionic liquids, microwave reactors, or water.[93–95] A conspicuous number of mechanochemically cross-coupling variants have been usefully performed. The work reported by Mack and coworker documents good performance of ball milling approach in the Sonogashira coupling in solvent free condition with a SPEX 8000 M vibratory mixer/mill.[96] Two aspect of this works are worth of being noticed. As a first instance, catalysts as palladium tetrakisphenylphosphine and many other palladium (0) catalysts used in coupling reaction are air- and moisture-sensitive and these reactions carried out in solutions often require dry solvents and inert atmosphere, while the ball milling assessment enabled to conduct these reactions in an aerobic environment.

Another interesting aspect is the enhancement in terms of yield when a copper vial is used, which show how the material of the vial and/or the ball can be used as a source of catalyst themselves (Scheme 7).



Scheme 7 *Sonogashira reaction under solvent-free ball milling condition using CuI and a copper vial as catalyst*[96]

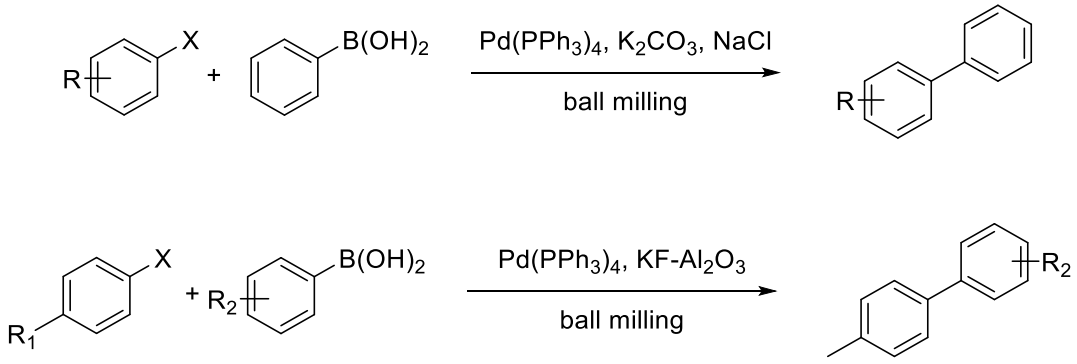
In conducting the Heck reaction under ball milling conditions (Scheme 8), Frejd *et al*. found out higher yield with the optimized conditions than alternative methods, reporting also a good diastereoselectivity toward the *Z* isomer. Energetic investigations were performed and revealed a concurrence of pressure, heat, grinding and stirring as essential for a satisfying outcome of the reaction, as the analysis of results under the action of single component gave results not comparable.



Scheme 8 *Ball milling Heck reaction*[97]

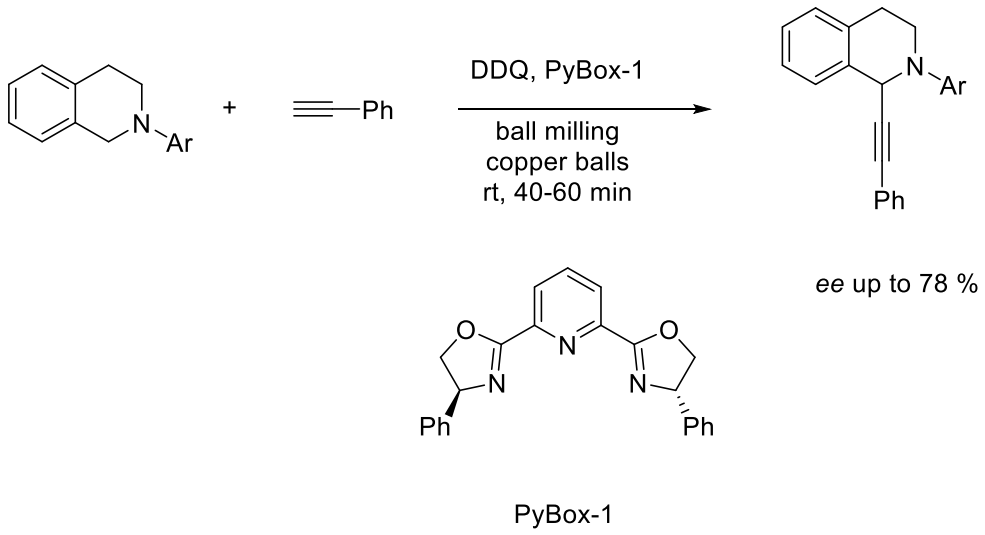
The mechanochemical version of Suzuki reaction has been firstly described by Peters et *al*.[97] in presence of potassium carbonate and sodium chloride. Subsequently, Ondrushka and coworkers applied the replacement of potassium carbonate and sodium chloride with potassium fluoride supported on basic alumina (Scheme 9). With respect to the solution counterpart, they found out the order of reactivity: aryl bromides < aril iodide was inverted. For the same

transformation, the authors reported the study of a curtate life cycle assessment. Under the applied reaction conditions ball milling has proven to be a more effective tool for energy entry than microwave irradiation. [98–100]



Scheme 9 *Suzuki mechanochemical reaction in presence of potassium carbonate and sodium chloride and KF-Al_2O_3*[98,101]

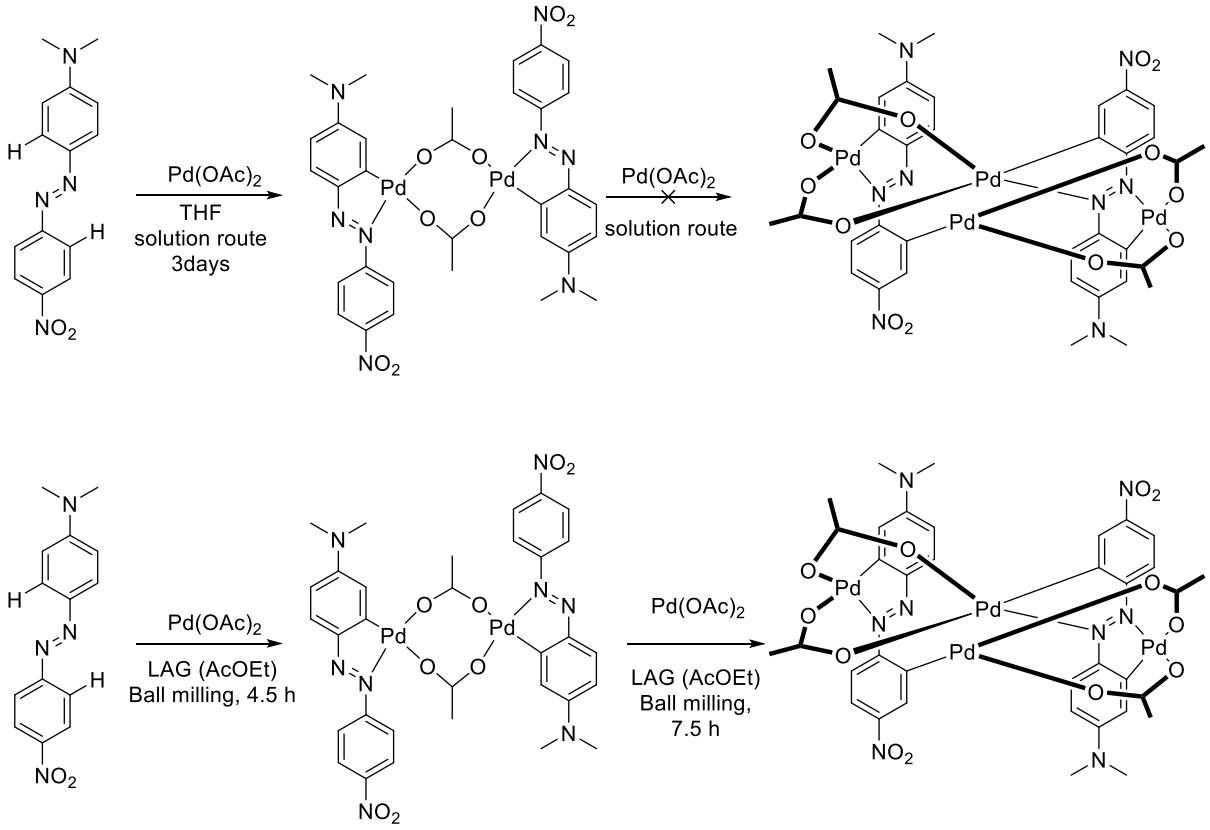
An example of asymmetric metal-catalyzed reaction by ball milling has been reported by Su and co-worker, in the enantioselective cross-dehydrogenative coupling between terminal alkynes and sp^3 C-H bonds under high speed ball milling conditions. The compounds 1-alkynyl tetrahydroisoquinoline derivatives were prepared using a pyridine-based chiral ligand (PyBox) in presence of DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone). Enantiomeric excess up to 79 % were obtained (Scheme 10).[102]



Scheme 10 *Asymmetric alkynylation of prochiral sp3 C-H bond via CDC*[102]

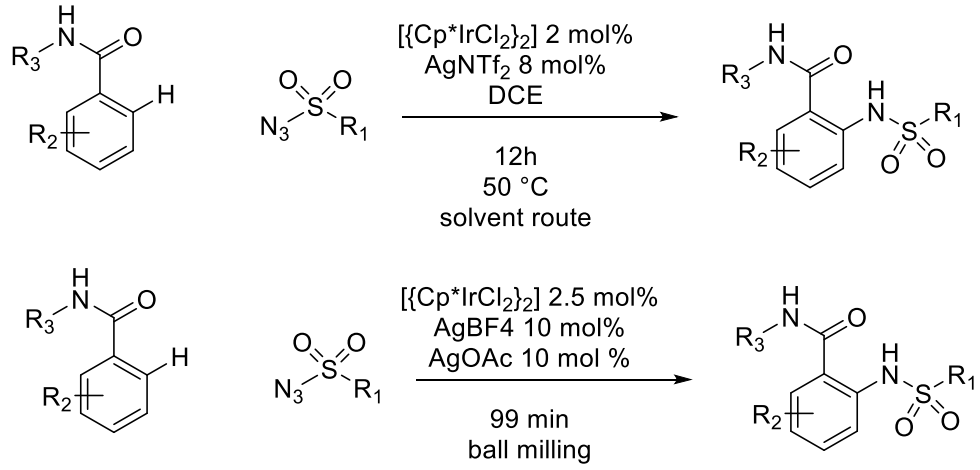
Selective functionalization of C-H bonds is a very popular transformation in organic synthesis since it allows the formation of C-C bonds with no need of pre-functionalize the starting materials. Recent progress achieved in this field are summarized in a review published by Hernandez in 2017.[103]

The first in introducing a mechanochemical C-H activation were Ćurić and co-workers.[104] This reaction provides an example of how ball-milling can be helpful to dramatically decrease time of reactions. The formation of palladacycle from asymmetrically substituted azobenzene and $Pd(OAc)_2$ by traditional solution method requires 3 days and provides the product in low yield, The ball milling approach by LAG with acetic acid lead to the formation of the desired product in 4.5 hours with a good yield Moreover, when the mixture is further grinded, the dicyclopalladated compound can be detected, whereas the same compound is not obtained in solution (Scheme 11).



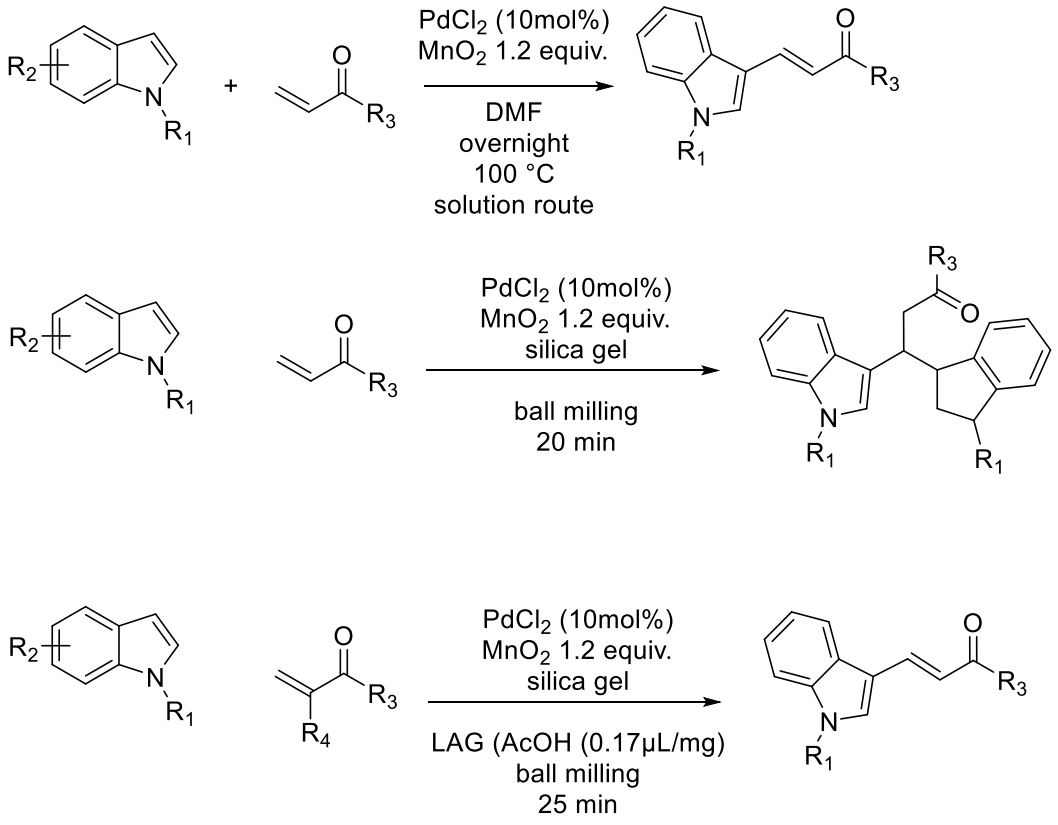
Scheme 11 *Synthesis of Palladacycle*[104,105]

Remarkably diminished reaction rates were also registered in the case of C-H activation reported by Bolm and co-workers in 2016 for the amidation of benzamides with sulphonyl azides by means of [{Cp*$IrCl_2$}$_2$] in presence of $AgBF_4$ and AgOAc. The solvent-based protocol required 12 hours[106] while the solvent-less procedure provides the product in high yield in 99 minutes (Scheme 12). [107]



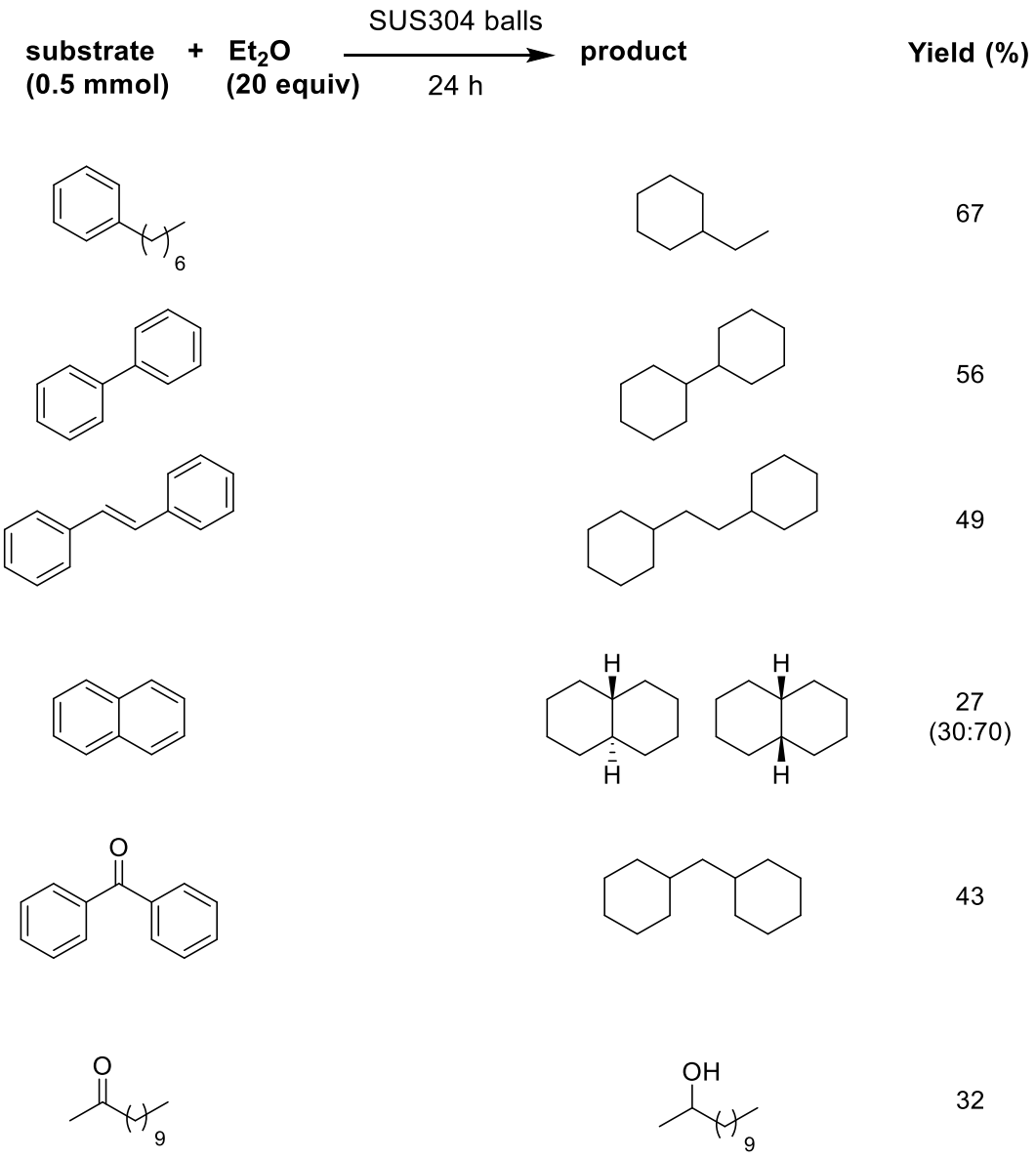
Scheme 12 *C-H amidation of Benzamides*[105]

Altering selectivity with regards to the one observed in solution is one of the focus that many ball-millers have stressed lately, an example of this behavior is demonstrated by Su and coworker for the synthesis of 3-vinilindoles and beta, beta-diindolyl propionates by Pd(II) catalyzed oxidative coupling between indoles and acrylates in presence of MnO_2 as oxidant. The authors reported the selective mechanochemical formation of beta-diindolyl propionates in absence of liquid additive and using $PdCl_2$ as source of Palladium, which is contrast to what observed in solution, where the products observed are 3-vinilindoles. Changing the source of Palladium and with acetic acid as liquid additive, the reaction lead to the selective formation of the 3-vinilindole product (Scheme 13). Further investigations performed by ESI-MS ascribed as the reason of this different selectivity the formation of a dimeric palladium intermediate under ball milling conditions.[108]



Scheme 13 *Palladium oxidative coupling of indoles and ylates*[108]

Sawama and Sajiki developed a method for the generation of gaseous hydrogen using a planetary ball mill [Fritsch Pulverisette Premium Line 7 (PLP-7)] with a stainless-steel vessel and balls. The formation of hydrogen is mediated by the metals as an element of stainless steel.[39] The same group demonstrated the reaction of hydrogen transfer utilizing alkanes and Et_2O as hydrogen source under ball milling conditions using SUS304 balls and a SUS304 vessel. They demonstrated the reduction of different functionalities on organic compound. In particular the method proved to be applicable to the hydrogenation of aromatic nuclei to produce the materially useful cycloalkane derivatives (Scheme 14). The authors claim the importance of Cr as the metal factor for the generation of hydrogen and the Ni as the catalyst for the hydrogenation reaction, even if the precise role of the single metals is still under investigations.[40]



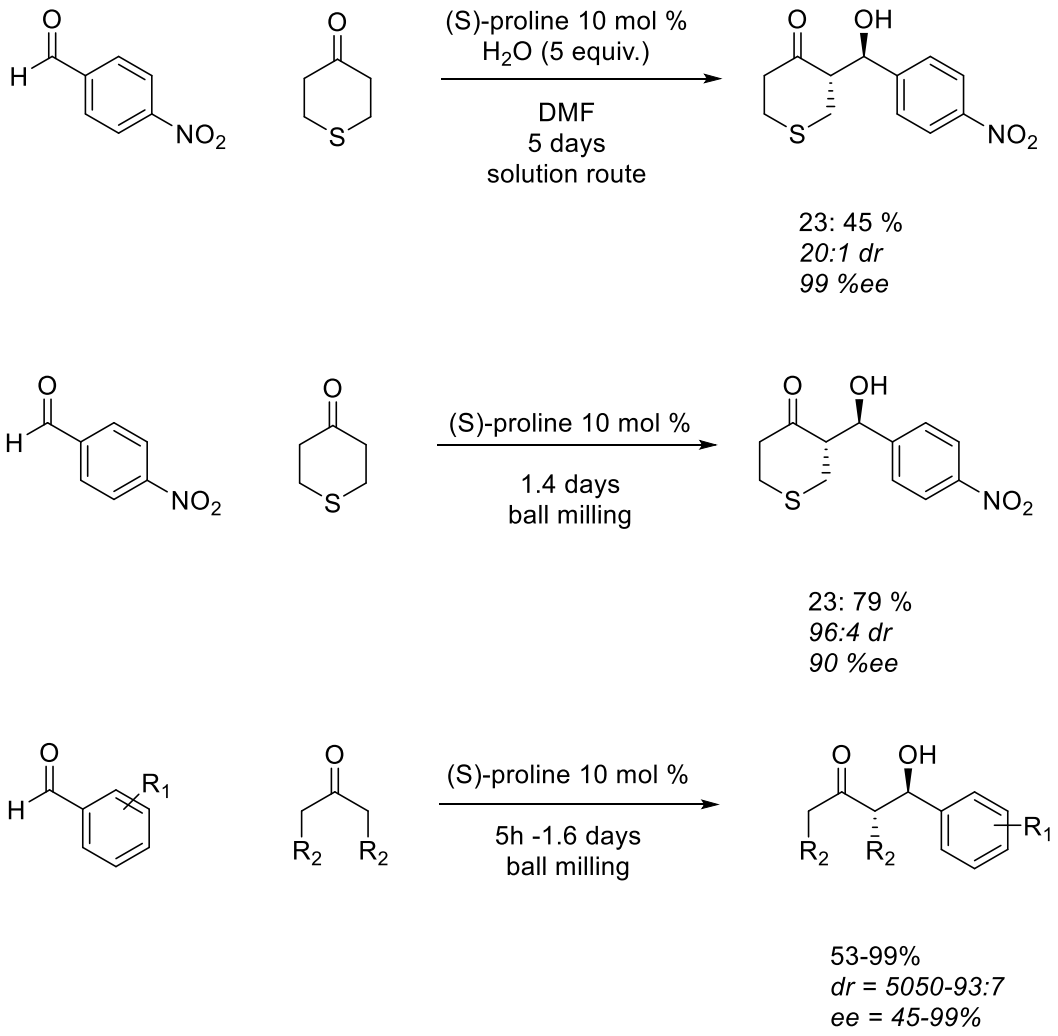
Scheme 14 *reduction of arene moiety by stainless steel-mediated hydrogen generation from alkanes and diethyl ether*[40]

Organocatalytic asymmetric reactions in ball mills

Applicability of ball milling to organocatalytic reactions was documented in several examples. Particularly important and investigated is the proline-catalyzed aldol reaction which proceed via enamine intermediate generated in situ from one of the carbonyl components and the catalyst. Frequently, reaction conditions for this transformation include the presence of high polar solvents as DMSO, DMF, whose removal after reaction is often not trivial. Bolm and coworkers reported for the first time a proline-catalyzed solvent-free aldol-reaction using

10 mol% of catalyst and almost equimolar amount of starting materials achieving the anti-aldol product with excellent yield and diastereo- and enantioselectivity. Compared to the solution counterpart, the ball-milling version showed to provide advantages as a substantial enhancement race (Scheme 15).[109–111]

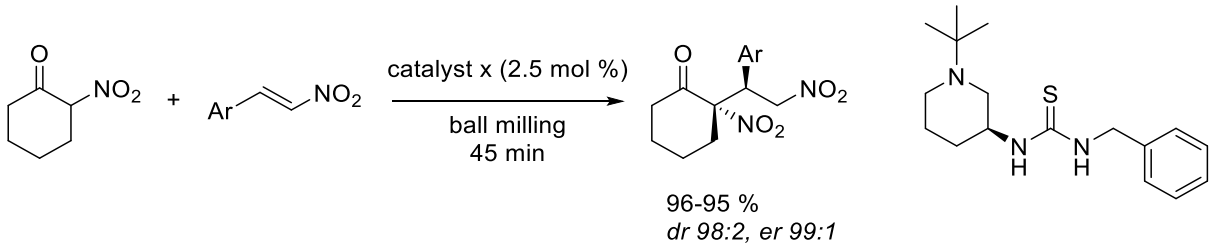
These promising studies were then followed by further investigation on secondary amines in organocatalysis[112–114]



Scheme 15 *proline catalysed enantioselective aldol reaction*[105]

The organocatalytic approach was successfully exploited in a Micheal addition in ball milling condition using the substituted thiourea based organocatalysts. The α-nitrocyclohexanone and nitroalkene derivatives underwent to Micheal addition in 30 minutes in presence of 2.5 mol%

of catalyst (Scheme 16). The reaction is characterized by an excellent stereoselectivity (98:2 diastereomeric ratio, 99:1 enantiomeric ratio). Further improvement offered by the methodology are the efficiency of the purification method together with the possibility to conduct the reaction in gram scale [115]



Scheme 16 *Mechanochemical organocatalytic asymmetric Micheal addition*

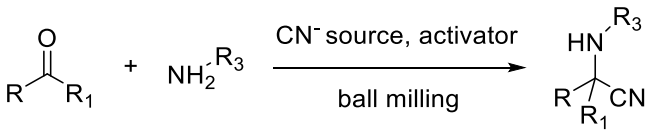
Multicomponent reactions

In a multicomponent reactions (MCRs) three or more reagents react in one vessel to give a product which contain almost all portions of substrates, This aspect extremely minimizes formation of by-product, rendering MCRs an eco-friendly synthetic approach. The combination of such methodology with mechanochemical synthesis has gained the attention of chemists interested in projecting greener synthetic routes. A review by Menendez highlights the advantages that derives by this concerted *modus operandi.* [116]

Mechanochemical versions of a wide variety of multicomponent reactions have been reported in the last years, such as the Mannich reaction, Paal-Knorr synthesis, Biginelli reaction, Hantzsch reaction, and synthesis of substituted piran, tiophene, isoquinoline derivatives.[88]

The Strecker reaction is a milestone in the field of multicomponent reactions, being the first documented in this field.[117] The transformation led to the synthesis of α-aminoacids that can be derived from the corresponding α-aminonitriles formed in the reaction between an aldehyde or a ketone, potassium cyanide and ammonium chloride. In 2016, Bolm and co-workers established a mechanochemical method for the synthesis of α-amino nitriles by using

benzaldehyde, benzylamine, KCN and the milling auxiliary SiO_2 for the obtainment of alpha-amino nitrile with yield in a range from 70 to 90 %.[118] The use of alternative solid additives as lignin was also investigated and more recently the employment of potassium exacyanoferrate as mechanochemical activated source of cianyde source has been demonstrated, depicting a scenario with prebiotic implications (Scheme 17).[119,120]

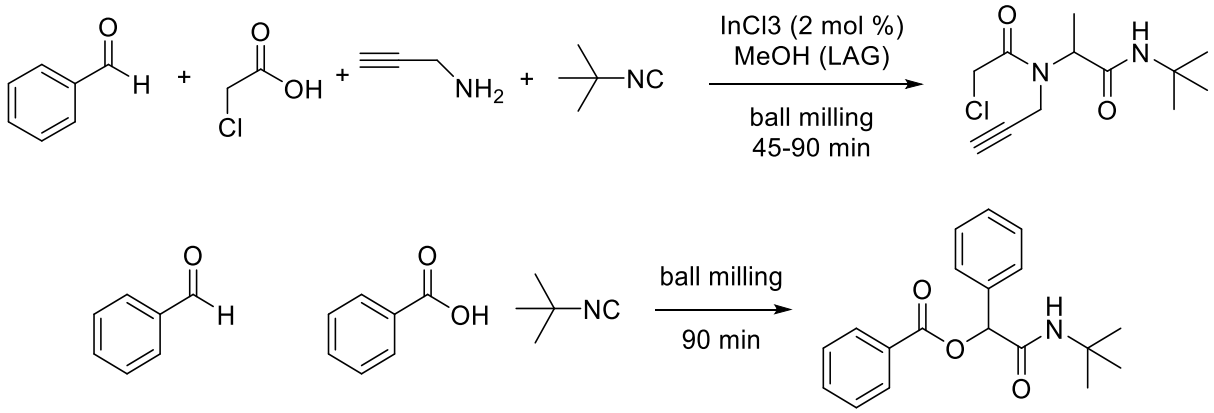


11 **12**

Scheme 17 Mechanochemical Strecker reaction[118–120]

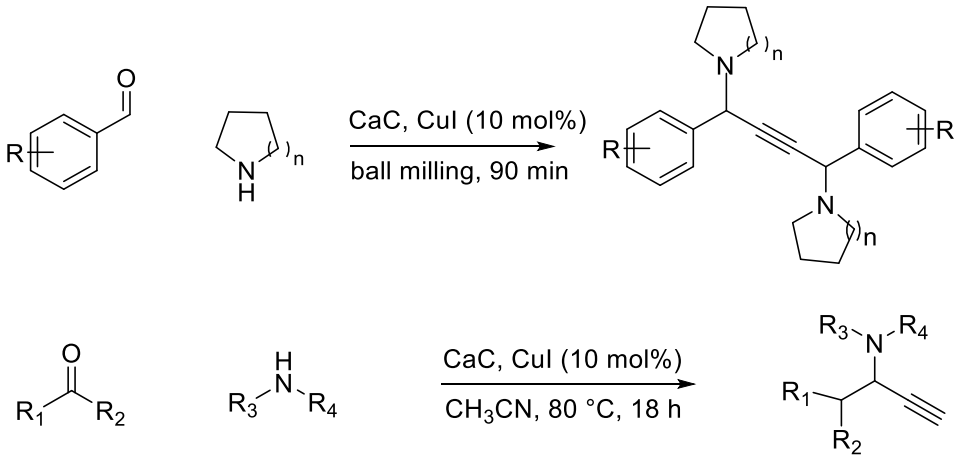
A dominant role in multicomponent reactions is played by the isocyanide moiety which is involved in several transformation for the generation of a wide variety of heteroatom-containing compounds with enhanced structural diversity. The most documented isocyanide multicomponent reactions are certainly the Ugi[121] and Passerini[122] reactions, which are widely investigated.[123]

A mechanochemical version of the Ugi 4-component reaction has been reported by Juaristi by liquid assisted grinding using MeOH. The reaction is carried out with equimolar amounts of benzaldehyde, chloroacetic acid, *tert*-butyl isocyanide, propargylamine and 2 mol% of $InCl_3$ as catalyst, providing the Ugi product in 74 % of yield (Scheme 18).[124] The high-speed ball milling condition were also evaluated for the Passerini synthesis under which tert-butyl isocyanide, benzaldehyde and benzoic acid in equimolar proportion provided 73% in yield of the Passerini product in 90 minutes. In this case the addition of catalytic amount of liquid additive resulted not beneficial for the outcome of the reaction (Scheme 18).



Scheme 18 *Mechanochemical Ugi and Passerini reaction*

A recent work reported by Hernandez and Bolm again shows the ability of mechanochemistry to alter the known chemical selectivity in solution. They described a mechanochemical version of the established Cu catalyzed A3 coupling involving aldehyde/alkyne and amine[125] using CaC_2 as acetylene surrogates as reported in solution by Zhang,[126] which is known to provide synthetically valuable propargylamines. The solvent-less conditions allowed instead to uncover the selective formation of 1,4-diamino-2-butynes.



Scheme 19 *Mechanochemical copper-catalysed A3 coupling*[127] *and solution based copper-catalysed A3 coupling*[126]

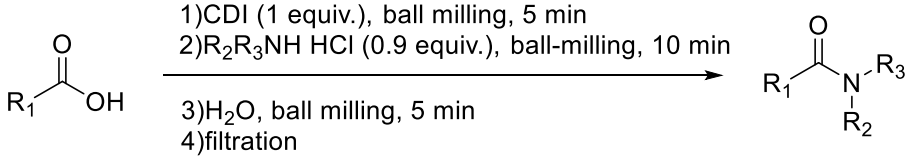
Mechanochemistry for synthesis of active pharmaceutical ingredients (APIs)

The application of ball mill in medicinal chemistry is a well-established research area and several examples of synthesis of active pharmaceutical ingredients (APIs) by use of

mechanochemistry have been reported, for instance polymorphs, cocrystals, salts and salt cocrystals.[128]

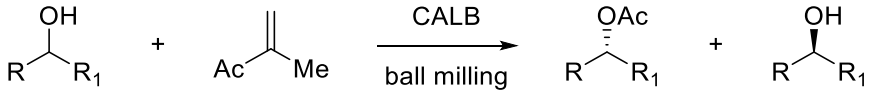
Regarding the organic synthesis of pharmaceutical compounds in solvent-less conditions, a strong contribution was given to Lamaty and co-workers, who developed a synthetic procedure for the coupling of peptides using $NaHCO_3$ and benzyl protected amino-acids. They showed the usefulness of their methodology by illustrating a seven step solvent free procedure for the synthesis of Leu-enkephalin.[54] The same group reported the two step mechanosynthesis of the antiepileptic drug Phenytoin (Phenytek)[129] and a POLAG methodology for the synthesis of the anticonvulsant Ethotoin. [55]

A recurrent fragment in pharmaceutical compounds is the amide moiety.[130,131] Mechanochemical synthesis of amide group have been reported following several strategies.[132–137] The procedure reported by Lamaty in presence of *N,N'*-carbonyldiimidazole (CDI) as coupling reagent for the synthesis of amides is a representative methodology in total absence of organic solvent from the reaction to the recovery of the products (Scheme 20). The reaction proved to proceed faster than the corresponding solvent version and the product is recovered by simple filtration from water.[132]



Scheme 20 *Solvent-free CDI-mediated mechanosynthesis of amides*[132]

The high energy impact conditions occurring in ball milling were found to be compatible with the survival of enzymes. The first mechanoenzymatic transformation was documented by Hernandez and Bolm who described the activation and kinetic resolution of secondary alcohols by means of a lipase[138] (Scheme 21) and the formation of amide and peptide bonds by means of the protease enzyme papain[139] (Scheme 22).



Scheme 21 *Scheme acylative kinetic resolutions of secondary alcohols catalyzed by lipase B from Candida antarctica*[138]

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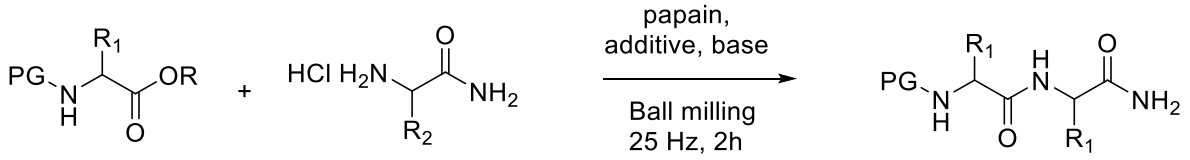

Scheme 22 *Scheme Amide bond formation catalysed by papain in the ball mill*[139]

As notable from literature, mechanochemistry offers several possibilities to organic synthesis and as suggested from the increasing number of publications, there is still a lot to explore in the field.

Chapter II An Environmentally Sustainable Mechanochemical Route to Hydroxamic Acid Derivatives

"An Environmentally Sustainable Mechanochemical Route to Hydroxamic Acid Derivatives"

Rita Mocci, Lidia De Luca, Francesco Delogu, and Andrea Porcheddu*

*Advanced Synthesis & Catalysis,***2016**, *358*, 3135-3144

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Introduction

Hydroxamic acids and their relevance

The hydroxamic acid moiety is a recurring structure in a consistent number of compounds of relevance in several fields of application.

When deprotonated to give hydroxamate, these molecules are able to coordinate metal ions as bidentate ligands. Their characteristic affinity for Iron II is so remarkable that nature developed a family of microbial siderophores hydroxamates as iron binding in bacteria and fungi which dissolve insoluble iron 3 compounds and transport them into the cell.[140–142]

This class of molecules is object of interest because of their wide spectrum of biological activity. The ability of some hydroxamic acids to inhibit various enzyme as matrix

metalloproteinases,[143,144] 5-lipoxygenase,[145,146] urease[147] or ribonucleotid reductase,[148] is responsible for their antibacterial, antifungal, antitumor and anti-inflammatory activities.

Hydroxamic acids derivatives were found to show inhibitory activities toward Histone deactylase (HDAC) enzyme, which is one of the main targets of anticancer drugs. These enzymes catalyse the removal of acetyl group from lysine residue on protein, including histone. It was observed that HDAC inhibitors (HDACHs) bind the active site and block the substrate access, with subsequently accumulation of acetylated histone. The effect of HDACHs is to induce tumour growth inhibition, cell differentiation, and programmed cell death.[149] As inhibitors of HDAC enzymes, some hydroxamic derivatives are used in anticancer therapy.

Vorinostat (rINN) (Figure 4), also known as suberanilohydroxamic acid (SAHA), was found to have inhibitory activity toward histone deactylase.[150] It is marketed under the name Zolinza by Merck and it is used for the treatment of cutaneous manifestations in patients with cutaneous T cell lymphoma (CTCL) when the disease persists, gets worse, or comes back during or after two systemic therapies.[151,152]

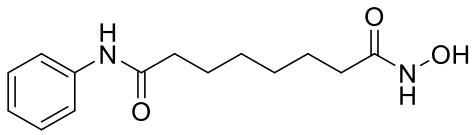


Figure 4 *Vorinostat*

Belinostat (trade name Beleodaq, previously known as PXD101) (Figure 5) was developed by Topotarget for the treatment of hematological malignancies and solid tumors.[153] It was approved in July 2014 by the US FDA to treat peripheral T-cell lymphoma.

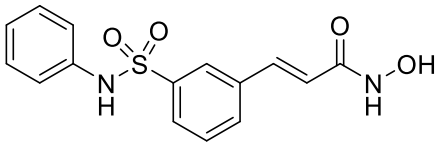


Figure 5 *Belinostat*

Novartis developed Panobinostat (trade name Farydak) (Figure 6) for the treatment of various cancers. It acts as a non-selective histone deacetylase inhibitor (pan-HDAC inhibitor).[154] Its use was approved in 2015 for treatment of patients with multiple myeloma.

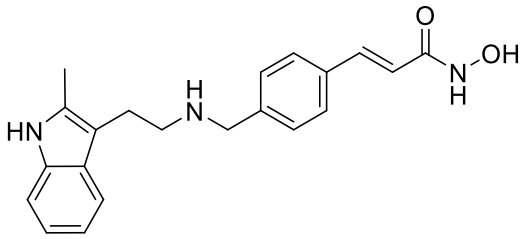
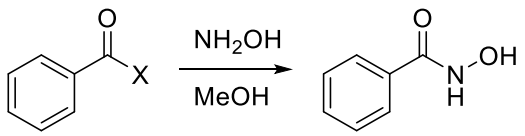


Figure 6 *Panobinostat*

Classical routes to Hydroxamic Acids

The chemistry literature of hydroxamic acids started in 1869, with the isolation of oxalohydroxamic acid by H. Lossen for reaction of hydroxylamine and etyloxalate.[155]

First reported synthesis of hydroxamic acids include reaction between a carboxylic acid derivative as chloride, esters, or amides and hydroxylamine hydrochloride liberated by a preventive treatment with a base (Scheme 23).[155,156]

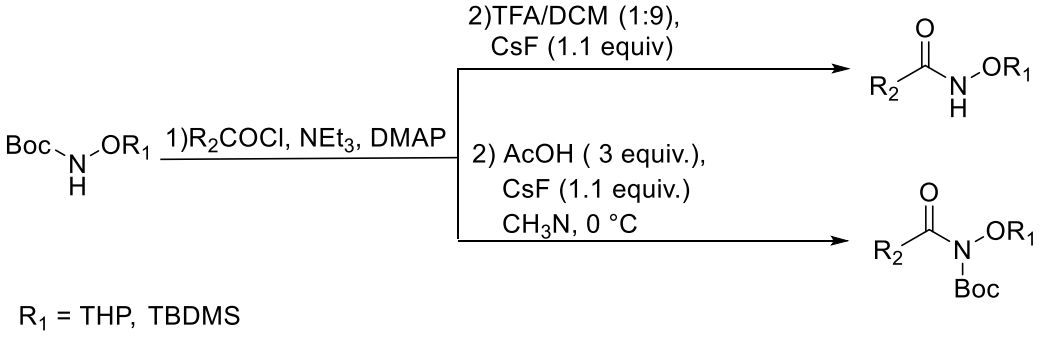


X = Cl, OR, NHR

Scheme 23 *Classical synthesis of Hydroxamic Acids*

One of the most serious problem associated with the preparation of these class of compounds is represented by the concomitant formation of complex mixture of *N*-, *O*- and di and triacylated compounds; besides, hydroxylamine hydrochloride is scarce soluble in common organic solvents. In order to overcome this issues, one possible approach is the reaction of *O/N*-protected hydroxylamine with activated carboxylic acids.

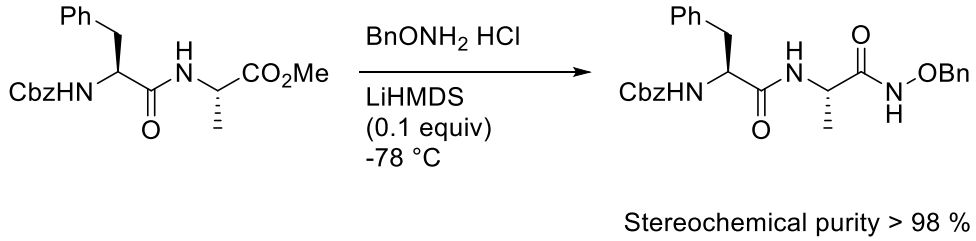
For instance, in 1992 Mioskowski reported the synthesis of *N,O*-bisprotected hydroxylamine derivatives by treatment of *N*-Boc protected hydroxylamines with either DHP (Dihydropyran) or with TBDMSCl (tert-Butyldimethylsilyl chloride), leading respectively to *N*-Boc-*O*-THP hydroxylamine or *N*-BOC-*O*-TBDMS hydroxylamine. Subsequent subjecting of either *N*-Boc-*O*-THP hydroxylamine or *N*-Boc-*O*-TBDMS hydroxylamine to reaction with various carboxylic acid chlorides in acetonitrile, at 0 °C, in the presence of triethylamine, led to the formation of *N,O*-bisprotected hydroxamic acids. Removal of the protecting groups under acidic conditions afforded the *N*-Boc protected or the free hydroxamic acids (Scheme 24)



Scheme 24 *Scheme synthesis of hydroxamic acids from hydroxylamines N-Boc protected derivatives*[157]

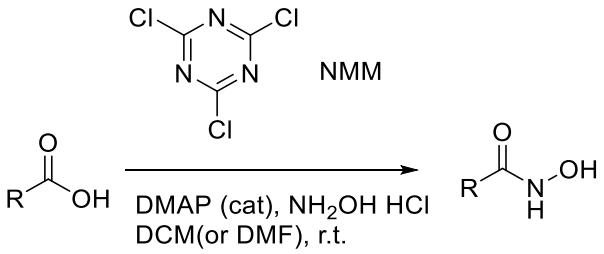
Economically convenient is the reaction of esters with hydroxylamine. To overcome the use of hazardous reagents as $AlMe_3$ necessary seen the poor electrophilicity of inactivated esters,[158] Gissot and Zanda developed a method for the synthesis of *O*-Bn hydroxamates in presence of lithium hexamethyldisilazide as base. The procedure was applicable even to enolizable esters,

R-amino acid esters, and peptide esters which were successfully reacted with no trace of racemization at the R carbon (Scheme 25).[159]



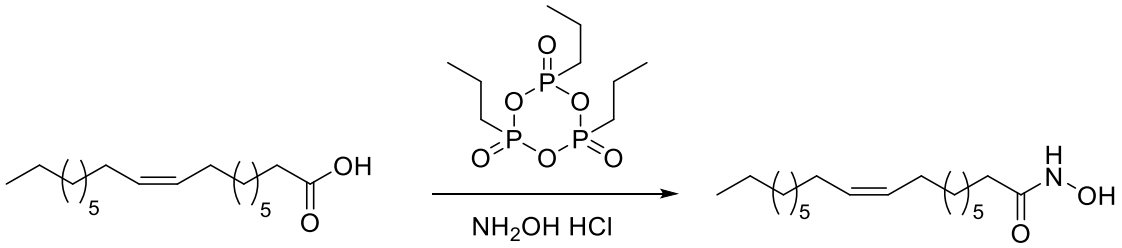
Scheme 25 *Synthesis of O-Bn hydroxamates from a range of inactivated esters and O-Bn hydroxylamine hydrochloride*[159]

Giacomelli and co-workers described a one-step conversion of carboxylic acids to hydroxamic acids under mild conditions in presence of 2,4,6-trichloro[1,3,5]-triazine (cyanuric chloride, TCT) as a coupling agent , *N*-methylmorpholine (NMM) , and dimethylamino pyridine (DMAP). This method gave access to enantiopure hydroxamate of R-amino acids and peptides using friendly reaction conditions and inexpensive reagents, and avoiding the use of *N*-protected hydroxylamine (Scheme 26).[160]



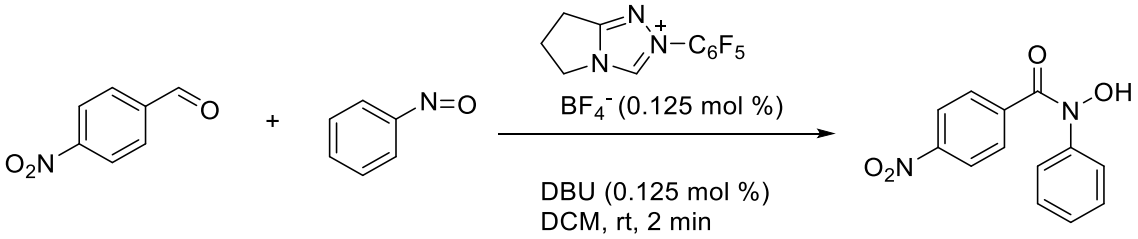
Scheme 26 *Synthesis of hydroxamic acids with TCT*[160]

To achieve a good chemoselectivity toward the formation of hydroxamic acids, Appendino and co-workers reported the *in situ* activation of carboxylic acids in presence of mixed phosphoric anhydrides and the air stable hydroxylamine hydrochloride. Advantages of this procedure rely as well in the possibility to avoid ex situ processes (derivatization of the acid, de-salification of hydroxylamine), and the absence of polyacylation without have recourse to an excess hydroxylamine or to its protection (Scheme 27).[161]



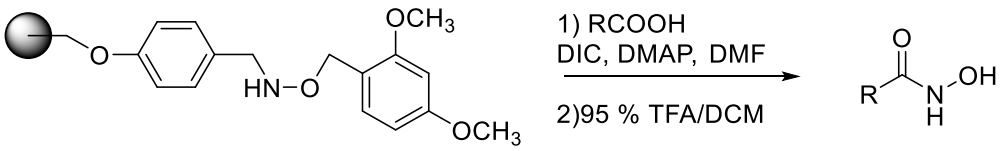
Scheme 27 *In situ activation of carboxylic acids in presence of mixed phosphoric anhydrides*[161]

N-arylhydroxamic acids can be prepared for amidation of aldehydes with nitroso compounds catalyzed by *N*-Heterocyclic Carbene (NHC).[162] The reaction proceeds *via* acyl anion addition to aryl nitroso compounds. The concentration of catalyst required is very low (0.125 mol %, Scheme 28) and the method was found to be applicable to the synthesis of chiral *N*-arylhydroxamic acids by kinetic resolution of R-branched aldehydes.



Scheme 28 *A amidation of aldehydes with nitroso compounds*

Yin *et al* reported a solid-phase synthesis of hydroxamic acids by using a modified Merrifield resin. The preparation of the resin was accomplished by conversion to PS-MB-CHO resin in presence of an acid labile aldehyde linker. The acid labile *O*-2,4-dimethoxylbenzyl(DMB) protected hydroxylamine was attached to resin using amino functionality via reductive amination in the presence of sodium cyanoborohydride to obtain the *N*-linked hydroxylamine resin as the one reported in Scheme 29. The usability of the so obtained resin was proved with the formation of hydroxamic acids by coupling Hydroxylamine resin with carboxylic acids under carbodiimide coupling condition. The subsequent acidolysis cleavage with trifluoroacetic provided the desired hydroxamic acids.[163]



Scheme 29 *Solid-Phase Synthesis of Hydroxamic Acids with N-Linked Hydroxylamine Resin*[163]

Alternative source of energy with respect to traditional means were used for the preparation of hydroxamic acid as microwave irradiation. Mordini and coworkers obtained the desired hydroxamic product within 6 minutes of MW irradiation at 80 °C of a methanolic solution of the opportune methylester, hydroxylamine hydrochloride, and potassium hydroxide. The protocol was found to be applicable to enantiomerically pure amino esters not leading to loss of enantiopurity.

Aim of the work

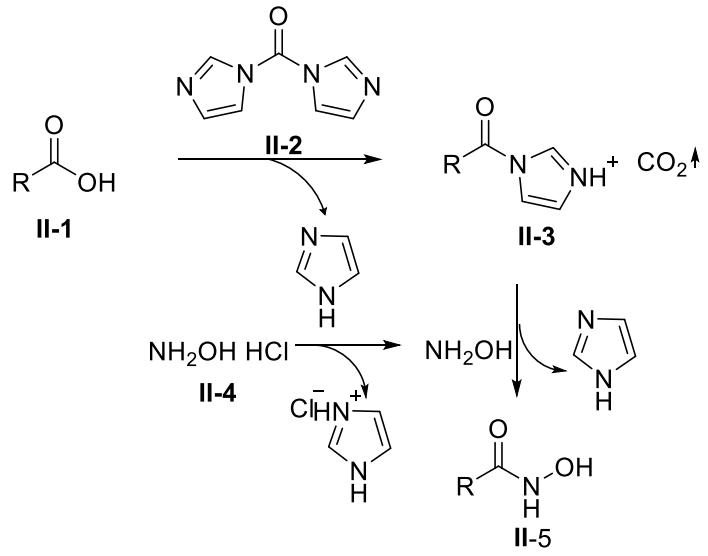
Despite the contribution to more efficient synthesis in the field, the necessity to develop more secure procedure which avoid the use as corrosive and polluting reagents represents a remaining challenge for the synthesis of these compounds. Besides, the insolubility of hydroxylamine hydrochloride in common organic solvents keeps constituting a not trivial problem for synthetic procedures. Furthermore, hydroxamic acids themselves present a very high polarity which render their purification processes challenging.

Seen all these factors, we envisioned the possibility to carry out the synthesis of hydroxamic acids with a ball milling approach. Besides the opportunity to conduct this preparation in a greener environment, providing conditions that do not require the presence of a solvent appears to be particularly desirable in the case of such substrate and product.

As a coupling reagent we choose to use *N*, *N*-carbonyldiimdazole (CDI)[164] which showed excellent results when used in combination with mechanochemistry.[165] DCI is a white crystalline solid which is stable under atmospheric conditions enough to avoid extreme precautions. It is available in kilogram scale, is cheap and its reactivity is accompanied by safe

by-product (imidazole and CO_2). Furthermore, it has been hypothesized that the low melting point of imidazole (mp 88−91 °C) favours the formation of eutectics. Formation of eutectics is, in some cases, claimed as beneficial for ball milling reaction because it may avoid reagents diffusion limitations that can arise during solvent-free ball milling. Moreover, the reactivity of CDI is lower with respect to other similar reagents (coupling reagents, isocyanate, chloroformates) and this can represent a drawback in solution protocols; in ball milling conditions instead, where high concentration could lead to the formation of undesired product, the poor reactivity of CDI can be an advantage.

Besides, the use of CDI is advantageous for an additional reason. In the first step of the reaction, *i.e.* the activation of the carboxylic acid, the liberation of a molecule of imidazole occurs. The presence of imidazole enables the activation of the nucleophilic hydroxylamine by an acid-base reaction with the chloridric acid, making unnecessary the presence of an additional base (Scheme 30).



Scheme 30 Synhtesis of Hydroxamic derivatives in presence of CDI

Results and discussion

Optimization of reaction conditions

As a model case for our investigation we explored the reaction of benzoic acid with CDI and hydroxylamine.

The experiments were performed in the mixer/mill SPEX 8000 into a hardened steel vial (45 mL) containing four 12 mm diameter steel balls, on a scale of 1 mmol of benzoic acid.

The transformation takes place in two separate steps in one-pot. The neat addition of CDI to the carboxylic acid resulted in a quite evident liberation of CO_2 prior to the grinding action. Milling for 5 minutes led to the complete consumption of starting material, detected by TLC.

Subsequent addition of one equivalent of hydroxylamine amine hydrochloride led to the formation of the final product with a 68 % of yield.

A slight variation of the stoichiometric ratio was applied in order to improve the performance of the reaction. 1.1 equivalent of CDI was used to ensure a complete conversion of the carboxylic acid, while the use of 2 equivalents of hydroxylamine hydrochloride was found to be beneficial for the final outcome of the transformation, leading to the recovering of the hydroxamic benzoic acid with a yield of 91 %.

The milling time was adjusted to 45 minutes, monitoring the consumption of the activated acid by TLC sampling the mixture every 15 minutes.

During this phase of the work contamination problems came to light. Indeed, we observed evident effect of the wearing of the jar as well as the grinding balls under the action of milling. Washing the jar after the reaction led to the recovering of turbid solution containing eye-visible metal particles (see Figure 7)

Figure 7 *Issue contaminations in hydroxamic acids synthesis*

In order to avoid the contaminations, we moved to a different material for the vessel and the grinding media, such as the agate. Considering possible variations in the energy outcome we performed the reaction by grinding the reagents under the optimized conditions in presence of 2, 4, and 8 agate balls of the diameter of 12.0 mm inside the agate vessel.

We found that 2 balls were not sufficient to provide an adequate amount of energy to the reaction, leading to an incomplete conversion of starting material in 45 minutes. Milling the reagents in presence of 4 agate balls led to comparable results to those previously observed.

Lastly, the use of 8 balls did not result in any considerable enhancement in the reaction performance both in terms of yield and time of conversion.

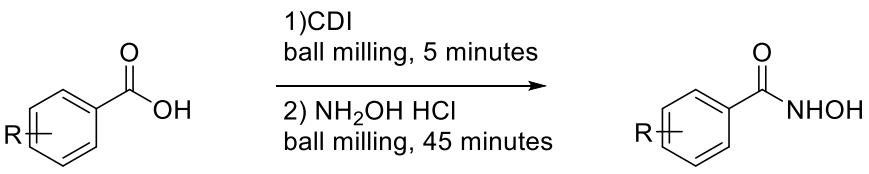
With the optimized conditions in hand, in accordance to the aim of our work to develop a synthetic procedure involving the minimal amount of hazardous waste such as solvents, we started to address our effort toward the development of an efficient purification method related to this transformation. The high polarity of hydroxamic acids render them soluble in water, which made us exclude the possibility to simply washing them with acidic aqueous solutions. We obtained instead the best results by recovering the mixture with a small amount of silica (350 mg of silica *per* 1 mmol of carboxylic acid) and loading it inside a column containing a short pad of silica, which was then eluted with heptane and ethylacetate. The efficiency of the purification step is simplified by the intrinsic cleanness of the reaction crude.

Then, we identify the best conditions for the mechanochemical synthesis of hydroxamic derivatives as follows: benzoic acid (1.0 equivalent) and CDI (1.1 equivalents) are loaded into an agate-milling beaker (45 ml) equipped with four balls (d = 10.0 mm) and milled in a Spex 8000M mixer/mill for 5 minutes, then hydroxylamine hydrochloride (2 equivalents) is added and the resulting mixture is ball milled for additional 45 minutes.

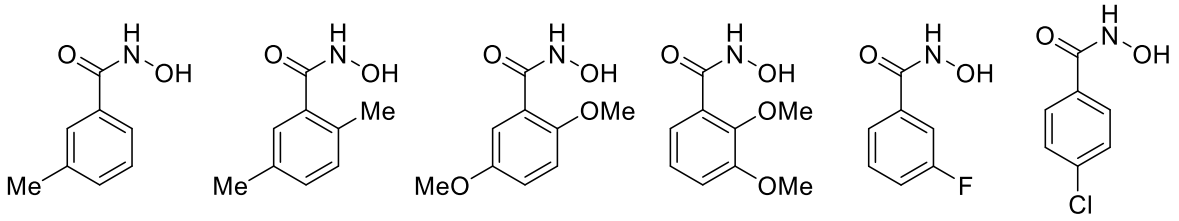
Scope of the reaction

The applicability of the method to aromatic and aliphatic carboxylic acids bearing different functionalities was evaluated. First, a series of aromatic carboxylic acids was subjected to the optimized conditions (Table 1)

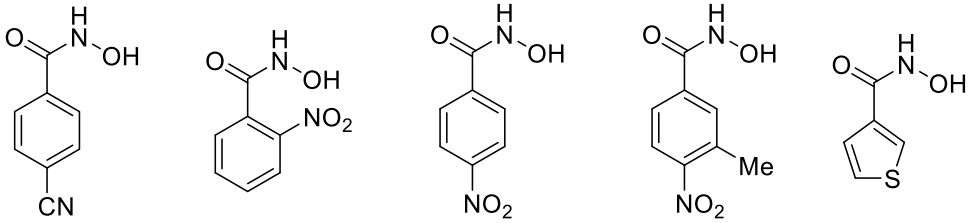
Table 1 Synthesis of hydroxamic acids starting from aromatic carboxylic acids[a][b]



II-1a-1k **II-5a-5k**



II-5a (84%) **II-5b (87%)** **II-5c (88%)** **II-5d (85%)** **II-5e (91%)** **II-5f (88%)**



II-5g (52%) **II-5h (nr)** **II-5i (nr%)** **II-5j (77%)** **II-5k (74%)**

[a] Reaction conditions: carboxylic acid (1.0 equiv, 1.0 mmol) and CDI (1.1 equiv., 1.1 mmol) are loaded into an agate-milling beaker (45 ml) equipped with four balls (d = 12.0 mm) of the same material and milled in a Spex 8000M mixer/mill for 5 minutes, then hydroxylamine hydrochloride (2 equivalents, 2 mmol) is added and the resulting mixture is ball milled for additional 45 minutes.
[b]Isolated yields reported

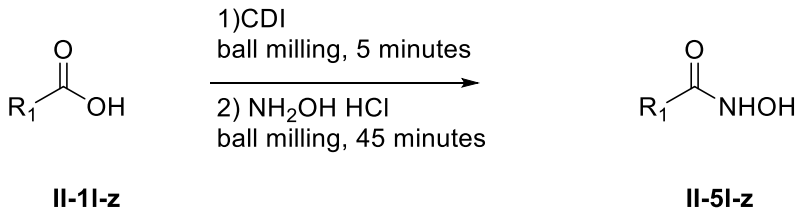
We found that the presence of substituents on the benzene ring was well tolerated, either for with-drawing (entries **II-5e**, **II-5f**, Table 1), either for electro-donating group (entries **II-5a**–**II-5d,** Table 1), giving the hydroxamic product in high yields. No considerable influence on the final yield was detected from the position of the substituent. The presence of a cyano-group appeared to affect significantly the yield of the reaction, leading to the formation of the hydroxamic derivative in 52 % of yield (entry **II-5g**, Table 1)

The presence of a nitro- substituent on the benzene strongly inhibit the formation of the desired product, which was not detected even after prolonged reaction time and addition of

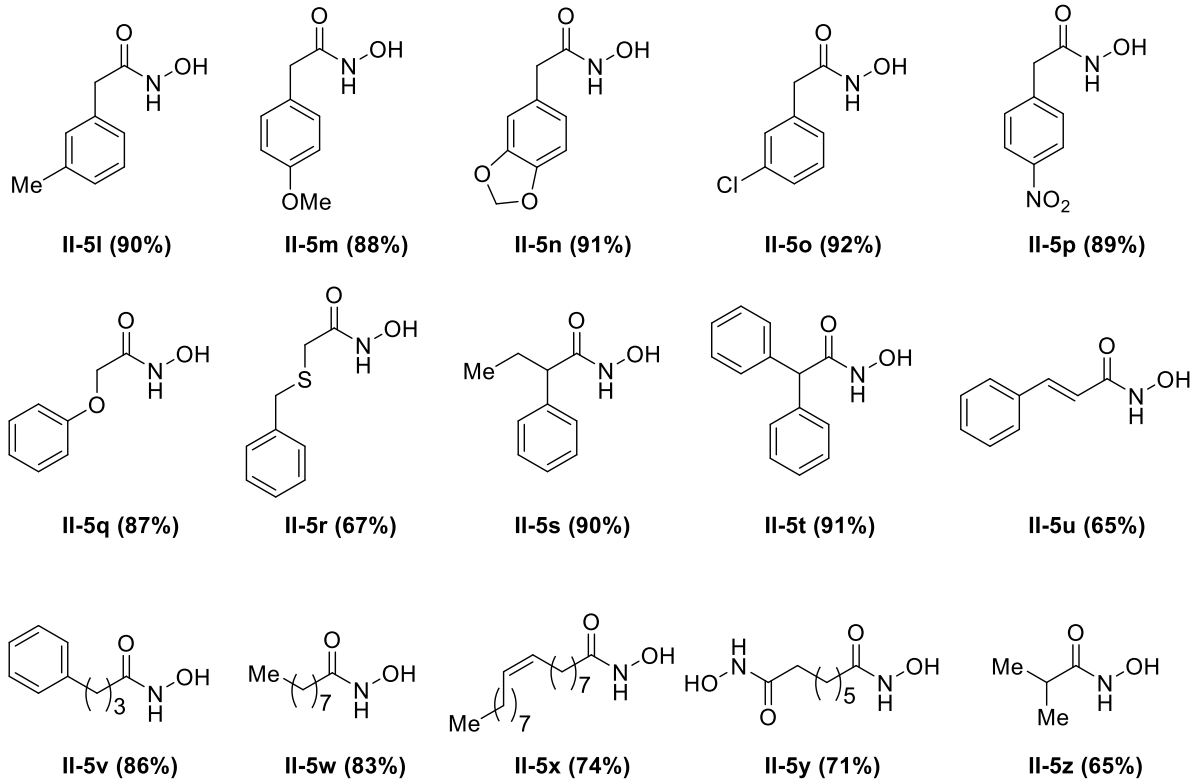
hydroxylamine. On the other hand, the 3-methyl-4-nitrobenzoic acid gave the corresponding hydroxamic acid in satisfactory yields (entry **II-5j**, Table 1). A carboxylic acid bearing a heteroaryl residual was reacted under the optimized conditions leading to the formation of the desired product in good yields (entry **II-5k**, Table 1).

In a second time, the scope of the methodology was expanded to wide number of carboxylic aliphatic acids. Even in this case the hydroxamic products were recovered with satisfying results. several acetic acid derivatives bearing different substituted ring were tested under the mechanochemical conditions. Either in the case of with-drawing substituent on the residual ring, either in the case of donating group the yield observed were good (Table 2). The presence of the nitro group in this case did not represent an obstacle for the good outcome of the reaction (Entry **II-5p**). The presence of the ether and thioether function were tolerated (Entries **II-5q**, **II-5r**, Table 2) as well as the substitution on the benzylic positions (Entry **II-5t**, Table 2) and the double bond (Entry **II-5u**, Table 2). Long chain aliphatic carboxylic acids were reacted with hydroxylamine providing the desired product with good yields and the oleic hydroxamic acid was usefully synthetized (entry **II-5w** and **II-5x,** Table 2). In the case of liquid starting material, such as butyric acid, a dispersion of the liquid in a small amount of silica gel was used (400 mg/mmol) (entry **II-5z**). Despite the slight decreasing in terms of yield, the cinnamic acid subjected to the reaction conditions led to the corresponding product without visible formation of the aza-Micheal potential by-product (entry **II-5u**).

Table 2 Synthesis of hydroxamic acids starting from aliphatic carboxylic acid[a][b]



II-1l-z **II-5l-z**



II-5l (90%) **II-5m (88%)** **II-5n (91%)** **II-5o (92%)** **II-5p (89%)**

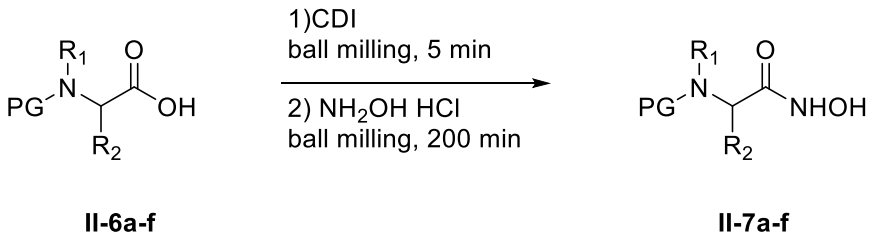
II-5q (87%) **II-5r (67%)** **II-5s (90%)** **II-5t (91%)** **II-5u (65%)**

II-5v (86%) **II-5w (83%)** **II-5x (74%)** **II-5y (71%)** **II-5z (65%)**

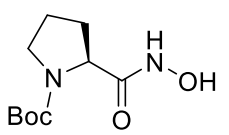
[a]Reaction conditions: carboxylic acid (1.0 equiv, 1 mmol) and CDI (1.1 equiv., 1.1 mmol) are loaded into an agate-milling beaker (45 ml) equipped with four balls (d = 12.0 mm) and milled in a Spex 8000M mixer/mill for 5 minutes, then hydroxylamine hydrochloride (2 equivalents, 2 mmol) is added and the resulting mixture is ball milled for additional 45 minutes.
[b]Isolated Yields reported

A number of *N*-protected aminoacids enantiomerically pure was then tested for this mechanochemical assisted preparation of hydroxamic acids. Such substrates demonstrated to require longer reaction times and two cycle of 100 minutes were found to be necessary for the complete conversion of the products. We registered a slight decrease of the yield if compared to other carboxylic acids even though the method was compatible with the presence of Boc, Cbz, Fmoc and Pht protecting group (Table 3).

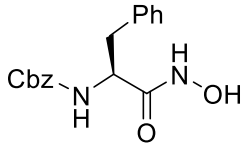
Table 3 *Synthesis of hydroxamic acids from aminoacids*[a][b]



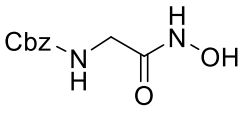
II-6a-f **II-7a-f**



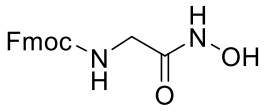
II-7a (56%)



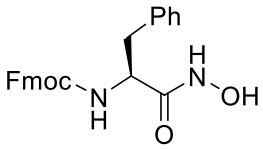
II-7b (61%)



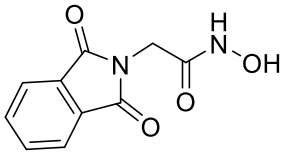
II-7c (48%)



II-7d (45%)



II-7e (54%)



II-7f (63%)

[a]Reaction conditions: aminoacid (1.0 equiv, 1 mmol) and CDI (1.1 equiv., 1.1 mmol) are loaded into an agate-milling beaker (45 ml) equipped with four balls (d = 12.0 mm) and milled in a Spex 8000M mixer/mill for 5 minutes, then hydroxylamine hydrochloride (2 equivalents, 2 mmol) is added and the resulting mixture is ball milled for additional 100 minutes.
[b]Isolated Yields reported

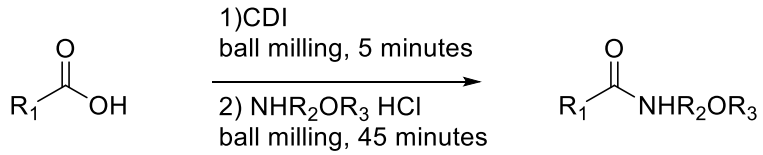
For these compounds was then verified the compatibility of the method with any loss of enantiopurity, by checking the enantiomeric purity by chiral HPLC.

Finally, a set of *O*- and *N, O*- substituted hydroxylamines was reacted with a range of carboxylic acids after the activation with CDI (Table 4). It was investigated the substitution on the oxygen atom by an aliphatic, a phenyl, and a benzyl residual. For these compounds the coupling with benzoic acids variously substituted led to the formation of the corresponding hydroxamate with a high yield even in the presence of electron-withdrawing group on the benzylic ring bound to the etheric function (entry **II-8g** and **II-8e**). *N*-Me-, *O*-Me substituted hydroxylamine were then reacted with a benzoic acid and an acetic acid bearing a substituted aryl residual, also in these cases the desired product was recovered in high yield (Table 4, entry **II-8b**). The aminoacidic

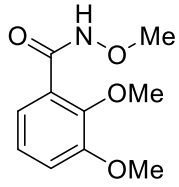
derivate Weinreib amide was then succefully prepared (entry **II-8h**, Table 4). As reported for the free hydroxamic aminoacidic derivatives, the retention of the chiral purity of the pure substrate during the mechanochemical transformation has been verified by chiral HPLC.

Unfortunately, we were not able to prepare the hydroxamic derivative (entry **II-8i**, Table 4) with our procedure

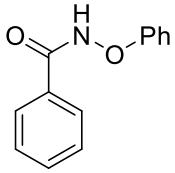
Table 4 *Synthesis of N,O- and O- substituted hydroxamates derivatives*[a][b]



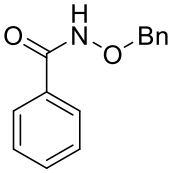
II-1,II-1d,II-1o II-7b **II-8a-i**



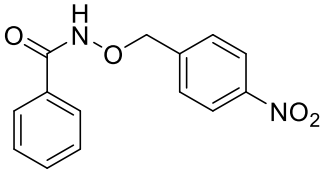
II-8a (82%)



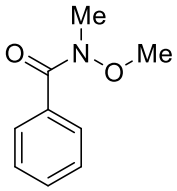
II-8b (90%)



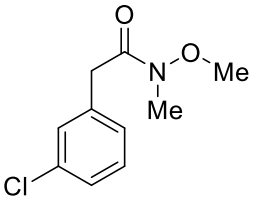
II-8c (92%)



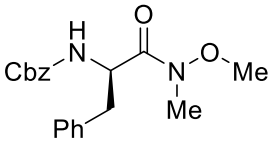
II-8e (85%)



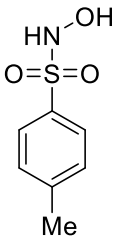
II-8f (88%)



II-8g (90%)



II-8h (87%)



II-8i (nr)

[a]Reaction conditions: aminoacid (1.0 equiv, 1 mmol) and CDI (1.1 equiv., 1.1 mmol) are loaded into an agate-milling beaker (45 ml) equipped with four balls (d = 12.0 mm) and milled in a Spex 8000M mixer/mill for 5 minutes, then the *N*, *O*- and *O*- substituted hydroxylamine hydrochloride (2 equivalents, 2 mmol) is added and the resulting mixture is ball milled for additional 45 minutes.
[b]Isolated yields reported

Scalability of the process

Lastly, the possibility to scale-up the process was investigated, transferring the condition founded for the mg scale (1 mmol) to a gram scale (2g, 16 mmol).

We observed no variations on the outcome of the reaction, which proceeded smoothly in the same time (5 minutes plus 45 minutes) with comparable yields (86 %) without need of further optimization experiments.

Thermal control experiments

To corroborate the value of the mechanochemical activation of the system, neat control experiments were carried out. We firstly excluded the formation of the desired product under prolonged time at room temperature. When the mixture was heated at 50 °C a complete conversion of reactants was observed after 4 hours but the formation of hydroxamic acid took place with lower yield (45 %) and was accompanied by side-product and decomposition.

Conclusions

In conclusion, the aim of developing an efficient and clean method for the synthesis of the hydroxamic acid mojety was accomplished. Besides the possibility to avoid the use of big amount of solvents in the reaction process; the purification procedure, made easier by the cleanness of the process itself, is convenient for the otherwise difficult recovering of the product.

We demonstrated as well that the process is robust and applicable to a wide range of substrate and the mechanochemical reaction conditions are tolerant toward the enantiomeric purity of product as L-aminoacids.

Experimental Section

General methods and material

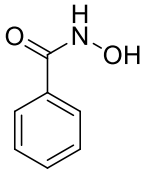
Commercially available reagents were purchased from Acros, Aldrich, Alfa-Aesar, TCI Europe and used as received. The solvents were purchased from Aldrich or VWR International in sure/sealedTM bottles over molecular sieves. Flash column chromatography was performed with Eco-ChromeMP Silica gel 60A, particle size 0.040–0.063 mm (230–400 mesh). All reactions were monitored by thin-layer chromatography (TLC) performed on glass-backed silica gel 60 F254, 0.2 mm plates (Merck), and compounds were visualized under UV light (254 nm) or using cerium ammonium molybdate solution with subsequent heating. The eluents were technical grade and distilled prior to use. An 8000M Mixer/Mill®, ball milling apparatus was used for all reactions. ^{1}H and ^{13}C liquid NMR spectra were recorded on a Varian 400 and 500 MHz NMR spectrometer at 25 °C and are calibrated using trimethylsylane (TMS). Proton chemical shifts are expressed in parts per million (ppm, d scale) and are referred to the residual hydrogen in the solvent ($CHCl_3$, d=7.27 ppm or DMSO-d_6 d=2.54 ppm). Data are represented as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet and/or multiple resonances, br s=broad singlet), coupling constant (*J*) in Hertz and integration. Carbon chemical shifts are expressed in parts per million (ppm, d scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, d=77.0 ppm or DMSO-d_6 d=39.5 ppm). Deuterated NMR solvents were obtained from Aldrich. High-resolution mass spectra (HR-MS) were recorded using an Electrospray Ionization (ESI) spectrometer. Infrared (IR) spectra were recorded on a NICOLET 5700 FT-IR spectrophotometer and reported in wavenumbers (cm^{-1}). Melting points were determined in an open capillary on a Büchi melting point apparatus and are uncorrected. Chiral HPLC analysis were determined by chiral stationary phase HPLC in a PerkinElmer Flexatm chromatograph using a column 5 mm, 4.6 x 250 mm (for racemization studies) coupled to a Perkin–Elmer UV-VIS detector. HPLC grade solvents were used for

HPLC analysis. All the experiments were carried out in duplicate to ensure reproducibility of the experimental data. Yields refer to pure isolated materials.

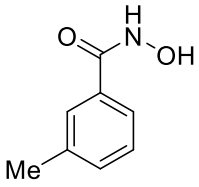
Synthesis of N-Hydroxybenzamide II-5; General Procedure for the Synthesis of Hydroxamic Derivatives

Benzoic acid (122 mg, 1.0 mmol) and CDI (178 mg, 1.1 mmol) were placed in an agate milling beaker (45 mL) equipped with four balls (d=12.0 mm) of the same material. The jar was sealed and ball milled for 5 min at room temperature. The progress of the reaction was monitored by TLC analysis (heptane/AcOEt: 1/1) on an aliquot of crude. Then, solid $HCl \cdot NH_2OH$ (139.0 mg, 2 mmol) was added and the mixture was subjected to grinding further for 45 min at room temperature. The ball milling operation was performed with an interval of 15 min followed by interval break of 5 min. The reaction was monitored every 15 min by TLC (hexane/AcOEt: 1/1) and stopped after complete consumption of the starting material. Upon completion of the ball milling process, the jar was opened, and silica gel (350 mg; 60–120 mesh) was added to the mixture reaction, the beaker sealed, and ball milled for additional 3 min. Once the milling balls were removed, the resulting crude product (adsorbed on silica gel) was easily transferred into a short chromatography column and eluted with a heptane/AcOEt/MeOH (7/2.9/0.1; v/v) mixed solvent system to give pure N-hydroxybenzamide **II-5** as a crystalline white solid;

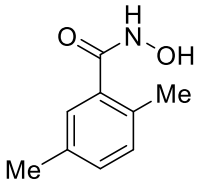
Summary of ^{1}H and ^{13}C NMR and HRMS data for Hydroxamic Derivatives II-5,II-5a-y, II-7a-f, II-8a-h.



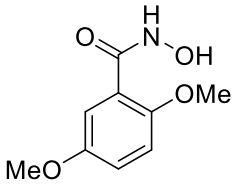
N-hydroxybenzamide II-5: yield: 125 mg (91%); mp 125–126 °C (Lit.[166] 126 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.21 (s, 1 H), 9.03 (s,1H), 7.74 (d, *J* = 8 Hz, 2H), 7.51 (t, *J* = 4 Hz, 1H), 7.44 (t, *J* = 8 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 164.0,132.8, 131.1, 128.4, 126.9. Spectroscopic data are in agreement with those reported earlier[167]



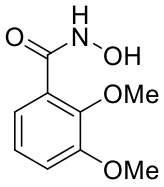
N-Hydroxy-3-methylbenzamide II-5a: Waxy solid; yield:127 mg (84%); mp 117–118 °C. ^{1}H NMR (400 MHz, DMSOd$_6$): δ =11.09 (s, 1 H), 8.93 (s, 1H), 7.51 (s, 1 H), 7.48 (bs,1H), 7.27 (bs, 2 H), 2.28 (s, 3H); ^{13}C NMR (101 MHz,DMSO-d$_6$): δ = 165.0, 138.3, 133.4, 132.3, 128.9, 128.1, 124.6, 21.6. Spectroscopic data are in agreement with those reported earlier.[168]



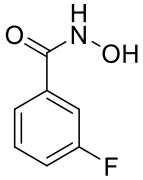
N-Hydroxy-2,5-dimethylbenzamide II-5b: White solid;yield:143 mg (87%); mp 132–133 °C. IR (KBr): ν = 3227, 3034, 2993, 2976, 2924, 1632, 1611, 1526, 1495, 1450, 1321, 1180, 1034, 881 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 10.75 (s, 1 H), 9.00 (s, 1 H), 7.17 (d, *J* = 7.7 Hz, 1 H), 7.06 (s, 1H), 7.02 (d, *J* = 7.9 Hz, 1 H), 2.31 (s, 3 H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d$_6$): δ = 166.9, 139.6, 136.3, 131.7, 128.0, 127.0, 126.6, 21.4, 19.9; HR-MS (ESI): m/z=166.0867, calcd. for $C_9H_{12}NO_2$: 166.0863 $[M+H]^+$.



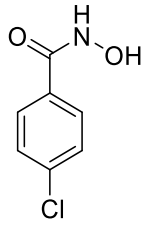
N-Hydroxy-2,5-dimethoxybenzamide II-5c: White solid; yield: 173 mg (88%); mp 119–120 °C. IR (KBr): ν = 3298,3132, 2970, 2839, 1632, 1607, 1585, 1499, 1441, 1412, 1489, 1319, 1258, 1221, 1180, 1159, 1034, 1051, 1022, 833 cm^{-1} ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 10.54 (s, 1 H), 9.03 (s, 1H), 7.07 (d, *J* = 2.9 Hz, 1 H), 6.96 (d, *J* = 4.1 Hz, 2 H), 3.72 (s, 3 H), 3.66 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d$_6$): δ = 163.3, 153.5, 151.3, 123.6, 117.5, 115.4, 113.8, 56.8, 56.2. Spectroscopic data are in agreement with those reported earlier.[169]



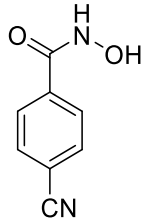
N-Hydroxy-2,3-dimethoxybenzamide II-5d: White solid; yield: 167 mg (85%); mp 130–131 °C. IR (KBr): ν =3346, 3321, 3294, 3144, 2924, 2874, 2864, 2841, 2830, 1630, 1576, 1508, 1477, 1456, 1427, 1314,1267, 1229, 1198, 1161, 1072, 1034, 995, 947 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 10.62 (s, 1 H), 9.02 (s, 1 H), 7.16–6.96 (m, 2 H), 6.98–6.82 (m,1H), 3.76 (s, 3 H), 3.70 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d$_6$): δ = 163.4, 152.4, 129.3, 123.9, 120.2, 114.4, 69.8,60.9, 55.8. Spectroscopic data are in agreement with those reported earlier.[168]



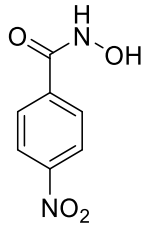
3-Fluoro-N-hydroxybenzamide II-5e: White solid; yield: 141 mg (91%); mp 147–148 °C. IR (KBr): ν =3300, 3090, 2762, 1661, 1626, 1584, 1568, 1508, 1487, 1456, 1423, 1331, 1229, 1271,893,827, 797 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.25 (s, 1 H), 9.11 (s, 1 H), 7.55 (d, *J* = 7.7 Hz, 1 H), 7.51–7.40 (m, 2 H), 7.30 (td, *J* = 8.5, 2.6 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): d=163.7, 163.4, 161.3, 135.7, 131.3, 131.2, 123.6, 118.8, 118.6, 114.4, 114.2. Spectroscopic data are in agreement with those reported earlier.[170]



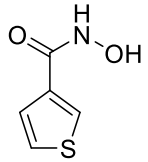
4-Chloro-N-hydroxybenzamide II-5f: White solid; yield: 151 mg (88%); mp 190–191 °C (Lit.[171] 193–194 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.24 (s, 1 H), 9.05 (s, 1 H), 7.71 (d, *J* = 8.0 Hz, 2 H), 7.46 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 163.1, 135.9, 131.5, 128.8, 128.5. Spectroscopic data are in agreement with those reported earlier.[166,172]



4-Cyano-N-hydroxybenzamide II-5f: White solid; yield: 84 mg (52%); mp 174–175 °C (Lit.[166] 173–174 °C). ^{1}H NMR (500 MHz, DMSO-d_6): δ = 11.45 (s, 1 H), 9.26 (s, 1 H), 8.00–7.84 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 167.7, 142.0, 137.7, 132.87, 123.4, 118.7. Spectroscopic data are in agreement with those reported earlier.[166]

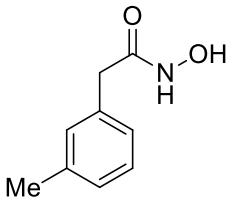


N-Hydroxy-3-methyl-4-nitrobenzamide II 5g : White solid; yield: 151 mg (77%); mp 154–155 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.10 (s, 1 H), 8.93 (s, 1 H), 7.52 (s, 1 H), 7.48 (t, *J* = 4.4 Hz, 1 H), 7.26 (d, *J* = 4.5 Hz, 1 H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 165.0, 138.3, 133.4, 132.3, 128.9, 128.1, 124.6, 21.6; HR-MS (ESI): m/z=197.0559, calcd. for $C_8H_9N_2O_4$: 197.0557 $[M+H]^+$.

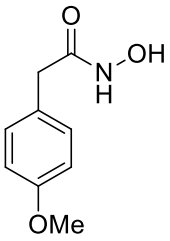


N-Hydroxythiophene-3-carboxamide II-5k: White solid; yield: 106 mg (74%); mp 133–134 °C. IR (KBr): ν =3283, 3115, 3098, 3049, 2926, 2758, 1657, 1611, 1570, 1516, 1416, 1395, 1136, 851, 808 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ =11.06 (s, 1 H), 9.12 (d, *J* = 75.9 Hz,

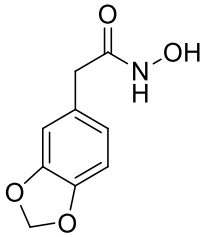
1 H), 8.04 (d, *J* = 2.9 Hz, 1 H), 7.58 (dd, *J* = 5.1, 2.9 Hz, 1 H), 7.43 (dd, *J* = 5.0, 1.2 Hz, 1H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 161.0, 135.9, 128.8, 127.5, 126.8; HR-MS (ESI): m/z=144.0115, calcd. for $C_5H_6NO_2$: 144.0114 $[M+H]^+$.



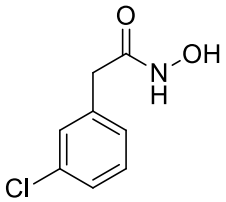
N-Hydroxy-2-(m-tolyl)acetamide II-5l: White solid; yield: 149 mg (90%); mp 151–152 °C. IR (KBr): ν = 3204, 3034, 2974, 2941, 2887, 1636, 1497, 1541, 1460, 1356, 1059, 974 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.59 (s, 1 H), 8.78 (s, 1 H), 7.22–7.14 (m, 1 H), 7.11 (dd, *J* = 7.8, 2.1 Hz, 3H), 3.30 (s, 2 H), 2.28 (s, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 167.6, 137.1, 135.2, 130.4 (2C), 127.2, 126.3, 37.5, 20.0; HR-MS (ESI): m/z=166.0867, calcd. For $C_9H_{12}NO_2$: 166.0863 $[M+H]^+$.



N-Hydroxy-2-(4-methoxyphenyl)acetamide II-5m (88%): White solid; yield: 159 mg (88%); mp 153–154 °C (Lit.[173] 154 °C).^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.57 (s, 1 H), 8.76 (s, 1H), 7.16 (d, J *J* = 8.2 Hz, 2 H), 6.85 (d, *J* = 8.3 Hz, 2 H), 3.72 (s, 3 H), 3.19 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 167.3, 157.9, 129.8, 127.9, 113.6, 54.9, 38.4. Spectroscopic data are in agreement with those reported earlier.[173]

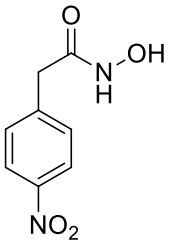


2-(Benzo[d][1,3]dioxol-5-yl)-N-hydroxyacetamide II-5n: White solid; yield: 178 mg (91%); mp 156–157 °C. IR (KBr): ν = 3204, 3024, 2943, 2901, 1636, 1547, 1503, 1489, 1447, 1418, 1377, 1360, 1250, 1202, 1190, 1055, 1038, 978, 926, 866 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.57 (s, 1 H), 8.78 (s, 1 H), 6.82 (d, *J* = 8.1 Hz, 2 H), 6.70 (d, *J* = 8.0 Hz, 1H), 5.97 (s, 2 H), 3.18 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 167.1, 147.0, 145.8, 129.6, 121.9, 109.3, 107.9, 100.7, 38.9; HR-MS (ESI): m/z=196.0607, calcd. for $C_9H_{10}NO_4$: 196.0604 $[M+H]^+$.

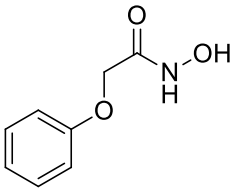


2-(3-Chlorophenyl)-N-hydroxyacetamide II-5o : White solid; yield: 170 mg (92%); mp 152–153 °C. IR (KBr): ν = 3190, 3013, 2903, 1638, 1599, 1574, 1543,1474, 1433, 1352, 1080, 1057,

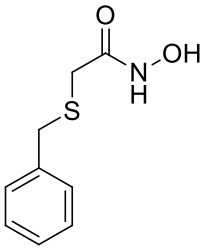
978, 866, 800, 764 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.66 (s, 1 H), 8.86 (s, 1H), 7.32 (dd, *J* = 7.3, 4.5 Hz, 3 H), 7.21 (d, *J* = 7.3 Hz, 1 H), 3.30 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 166.4, 138.5, 132.7, 130.0, 128.7, 127.6, 126.4, 34.9; HR-MS (ESI): m/z=186.0317, calcd. for $C_8H_9ClNO_2$: 186.0316 [M+H]+.



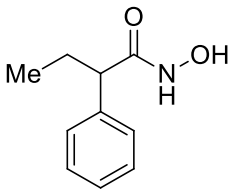
N-Hydroxy-2-(4-nitrophenyl)acetamide II-5p: White solid; yield: 174 mg (89%); mp 149–150 °C. IR (KBr): ν = 3364, 3335, 3209, 3069, 1663, 1626, 1609, 1524, 1497, 1541, 1387, 1310, 1354, 1111, 1045, 982 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.74 (s, 1 H), 8.92 (s, 1 H), 8.18 (d, *J* = 8.5 Hz, 2 H), 7.53 (d, *J* = 8.2 Hz, 2 H), 3.46 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 165.8, 146.3, 144.1, 130.2, 123.3, 38.9. Spectroscopic data are in agreement with those reported earlier.[174]



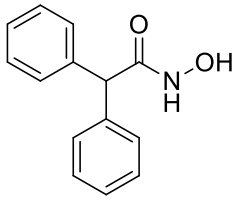
N-Hydroxy-2-phenoxyacetamide II-5q: White solid; yield: 145 mg (87%); mp 114–115 °C (Lit.[175] 115 °C). IR (KBr): ν = 3302, 2853, 1682, 1641, 1599, 1558, 1491, 1252, 1238, 1088,1067, 752 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.75 (s,1H), 8.90 (s, 1 H), 7.24 (t, *J* = 7.7 Hz, 2 H), 6.90 (t, *J* = 7.6 Hz, 3H), 4.39 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 164.3, 157.8, 129.4, 121.1, 114.6, 65.8. Spectroscopic data are in agreement with those reported earlier.[176]



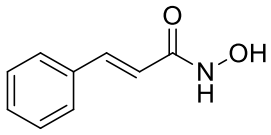
2-(Benzylthio)-N-hydroxyacetamide II-5r: White solid; yield: 132 mg (67%); mp 109–110 °C (Lit.[177] 111 °C). IR (KBr): ν = 3250, 3086, 3059, 3026, 2957, 2932, 2978, 1641, 1520, 1495, 1454, 1402, 1047, 980 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.56 (s, 1 H), 8.91 (s, 1 H), 7.44–7.13 (m, 5H), 3.83 (s, 2 H), 2.92 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 166.5, 138.6, 129.6, 129.0, 127.6, 36.3, 31.9; HR-MS (ESI): m/z=198.0585, calcd. for $C_9H_{12}NO_2S$: 198.0583 $[M+H]^+$. Spectroscopic data are in agreement with those reported earlier[177]



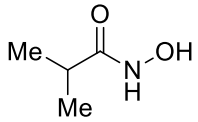
N-Hydroxy-2-phenylbutanamide II-5s : White solid; yield: 161 mg (90%); mp 112–113 °C. IR (KBr): ν = 3207, 3090, 3026, 2928, 2966, 2906, 2877, 1707, 1630, 1527, 1497, 1483, 1454, 1462, 1367, 1040, 986, 725, 696 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.58 (s, 1 H), 8.74 (s, 1 H), 7.25 (dd, *J* = 9.8, 6.9 Hz, 5 H), 3.09 (dd, *J* = 9.0, 6.2 Hz, 1 H), 1.97–1.83 (m, 1 H), 1.60 (m, 1 H), 0.76 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 170.2, 141.3, 128.8, 128.3, 127.2, 50.8, 26.5, 12.8; HR-MS (ESI): m/z=180.1022, calcd. for $C_{10}H_{14}NO_2$ 180.1019 $[M+H]^+$. Spectroscopic data are in agreement with those reported earlier.[178]



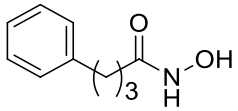
N-Hydroxy-2,2-diphenylacetamide II-5t: White solid; yield: 207 mg (91%); mp172–173 °C (Lit.[156] 172 °C). ^1H NMR (400 MHz, DMSO-d_6): δ = 10.91 (s, 1 H), 8.94 (s, 1H), 7.34–7.28 (m, 8 H), 7.24 (d, *J* = 6.4 Hz, 2H), 4.70 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.6, 140.6, 129.1, 128.9, 127.4, 54.0. Spectroscopic data are in agreement with those reported earlier.[179]



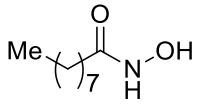
N-Hydroxycinnamamide II-5u: White solid; yield: 106 mg (65%); mp 136–137 °C (Lit.[180] 138–140 8C). ^1H NMR (400 MHz, DMSO-d_6): δ = 10.69 (s, 1 H), 8.98 (s, 1 H), 7.50 (d, *J* = 6.8 Hz, 2 H), 7.42 (d, *J* = 15.8 Hz, 1 H), 7.37–7.28 (m, 3H), 6.41 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (101 MHz, DMSOd_6): δ = 163.3, 139.0, 135.4, 130.1, 129.6, 128.1, 119.7. Spectroscopic data are in agreement with those reported earlier.[180]



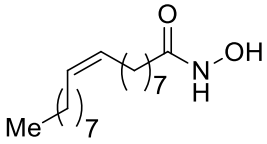
N-Hydroxyisobutyramide II-5z: White solid; yield: 53 mg (51%); mp 114–115 °C (Lit.[181] 114 °C). ^1H NMR (400 MHz, DMSO-d_6): δ = 10.29 (s, 1 H), 8.57 (s, 1 H), 2.17 (hept, *J* = 6.8 Hz, 1 H), 0.93 (d, *J* = 6.8 Hz, 6H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 173.1, 31.1, 19.4. Spectroscopic data are in agreement with those reported earlier.[180]



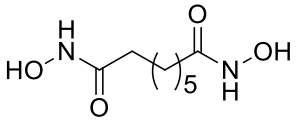
N-Hydroxy-4-phenylbutanamide II-5v White solid; yield: 154 mg (86%); mp 73–74 °C (Lit.[182] 71–72 °C). ^1H NMR 400 MHz, DMSO-d_6): δ = 10.32 (s, 1 H), 8.65 (s, 1 H), 7.24 (t, J=7.2 Hz, 2 H), 7.12 (d, *J* = 7.2 Hz, 3H), 2.49 (t, *J* = 7.7 Hz, 2 H), 1.92 (t, *J* = 7.4 Hz, 2 H), 1.72 (q, *J* = 7.4 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 168.9, 141.6,128.3, 125.8, 39.5, 34.6, 31.8, 26.9. Spectroscopic data are in agreement with those reported earlier.[182]



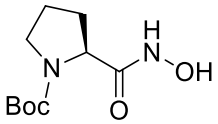
N-Hydroxydecanamide II-5w: White solid; yield: 155 mg (83%); mp 87–88 °C (Lit.[183] 88–89 °C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.26 (s, 1 H), 8.58 (s, 1 H), 1.86 (t, *J* = 7.4 Hz, 2 H), 1.41 (t, *J* = 7.1 Hz, 2H), 1.18 (m, 12H), 0.80 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 169.8,32.9, 31.9, 29.5, 29.4, 29.3, 29.2, 25.8, 22.7, 14.6; HR-MS(ESI): m/z=188.1646, calcd. for $C_{10}H_{22}NO_2$: 188.1645 $[M+H]^+$. Spectroscopic data are in agreement with those reported earlier.[183]



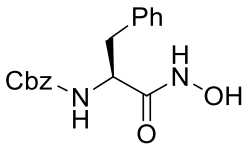
N-Hydroxyoleamide II-5x: White solid; yield: 220 mg (74%); mp 61–62 °C (Lit.[184] 62 °C). IR (KBr): ν = 3285, 3003,2918, 2872, 2851, 1665, 1624, 1568, 1560, 1466, 1427 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.25 (s, 1 H), 8.58 (s,1H), 5.27 (t, *J* = 4.9 Hz, 2 H), 1.91 (m, 5 H), 1.41 (m, 2 H), 1.19 (d, *J* = 11.2 Hz, 21H), 0.80 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 169.7, 130.2, 32.90, 32.00, 29.8, 29.5, 29.4, 29.3, 27.3, 25.8, 22.7, 14.5; HR-MS (ESI): m/z= 298.2746, calcd. for $C_{18}H_{36}NO_2$: 298.2741 $[M+H]^+$



N1,N8-Dihydroxyoctanediamide II-5y: White solid; yield: 144 mg (71%); mp 163–164 °C (Lit.[185] 164 8C). ^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.33 (s, 2 H), 8.66 (s, 2 H), 1.92 (t, *J* = 7.4 Hz, 4 H), 1.46 (t, *J* = 7.2 Hz, 4 H), 1.22 (m, 4H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 169.7, 32.9, 29.0, 25.7. Spectroscopic data are in agreement with those reported earlier.[185]

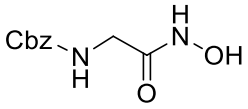


tert-Butyl 2-(hydroxycarbamoyl)pyrrolidine-1-carboxylate II-7a: The title compound was synthesized following the general procedure, but increasing the milling time up to 200 min. White solid; yield: 128 mg (56%); mp 152–153 °C; $[\alpha]_D^{25}$: −56.9 (c=1, methanol).[186] IR (KBr): ν=3217, 3036, 2988, 2957, 2914, 2882, 2891, 1690, 1666, 1545, 1481, 1449, 1414, 1366, 1350, 1279, 1258, 1207, 1159, 1128, 1032, 1049, 989, 854 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.81 (s, 1 H), 7.65 (s, 1 H), 4.23 (t, *J* = 5.2 Hz, 1 H), 3.33 (d, *J* = 29.1 Hz, 2H), 2.36 (s, 1 H), 2.07–1.79 (m, 3 H), 1.42 (s, 9H); ^{1}H NMR (400 MHz, DMSO-d_6, 50°C): δ = 10.39 (s, 1H), 8.65 (s, 1 H), 3.93 (s, 1 H), 3.44–3.08 (m, 3 H), 1.82 (d, J=40.4 Hz, 3 H), 1.35 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.9, 156.0, 57.2, 47.0, 28.4, 24.7, 14.2; ^{13}C NMR (101 MHz, DMSO-d_6, 50 °C): δ = 169.0, 153.0, 78.3, 57.3, 46.2, 29.9, 27.9, 23.8. The chiral integrity of the final compound was determined by HPLC using a Phenomenex Lux 5u Cellulose-1column [*n*hexane/ *i*-PrOH (90:10)]; flow rate 1.0 mLmin^{-1}]: t= 16.1 min (100%). Spectroscopic data are in agreement with those reported earlier.[187]

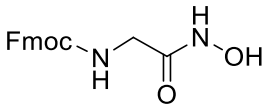


Benzyl (S)-(1-(hydroxyamino)-1-oxo-3-phenylpropan-2- yl)carbamate II-7b: The title compound was synthesized following the general procedure, but increasing the milling time up

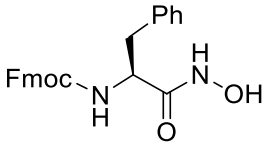
to 200 min. White solid; yield: 200 mg (61%); mp 91–92 °C (Lit.[188] 91–93 °C); $[\alpha]_D^{25}$: −38.5 (c=0.5, methanol).[171] IR (KBr): ν = 3329, 3154, 3061, 3032, 2945, 1734, 1655, 1699, 1668, 1605, 1497, 1539, 1439, 1454, 1385, 1364, 1263, 1211, 1022, 743 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.64 (s, 1 H), 8.80 (s, 1 H), 7.52 (d, *J* = 8.6 Hz, 1 H), 7.20 (s, 10 H), 4.88 (s, 2 H), 4.05 (s, 1 H), 2.88–2.64 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 168.7, 156.3, 138.6, 137.7, 129.8, 128.9, 128.7, 128.3, 128.1, 126.9, 65.8, 54.7, 38.3. The chiral integrity of the final compound was determined by HPLC using a CHIRALPAK AS-H column [*n*-hexane/*i*-PrOH (90:10)]; flow rate 1.0 $mLmin^{-1}$]: t = 19.4 min (100%). Spectroscopic data are in agreement with those reported earlier.[171]



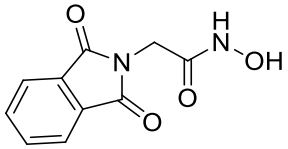
Benzyl [2-(hydroxyamino)-2-oxoethyl]carbamate II-7c: The title compound was synthesized following the general procedure, but increasing the milling time up to 200 min. White solid; yield: 107 mg (48%); mp 119–120 °C (Lit.[189]120– 122 °C). IR (KBr): ν = 3146, 3038, 3022, 3005, 2943, 2924, 2887, 1693, 1670, 1585, 1564, 1468, 1514, 1452, 1281, 1258, 1051, 729 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.50 (s, 1H), 8.78 (s, 1 H), 7.35 (s, 6 H), 5.02 (s, 2 H), 3.52 (d, *J* = 6.1 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 166.0, 156.4, 137.0, 128.3, 127.7, 127.7, 65.4, 41.4. Spectroscopic data are in agreement with those reported earlier.[190]



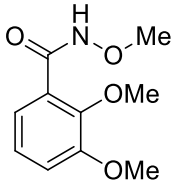
{[(9H-Fluoren-9-yl)methoxy]carbonyl}glycine II-7d (45%): The title compound was synthesized following the general procedure, but increasing the milling time up to 200 min. White solid; yield: 141 mg (45%); mp 95–96 °C (Lit.[191] 96 °C). ^1H NMR (400 MHz, DMSO-d_6): δ = 10.51 (s, 1 H), 8.79 (s, 1H), 7.89 (d, *J* = 7.5 Hz, 2 H), 7.72 (d, *J* = 7.3 Hz, 2 H), 7.54 (t, *J* = 5.4 Hz, 1 H), 7.42 (t, J=7.2 Hz, 2 H), 7.33 (t, J=7.8 Hz, 2 H), 4.24 (dt, *J* = 13.4, 6.8 Hz, 3 H), 3.52 (d, *J* = 5.7 Hz, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 166.0, 156.4, 143.8, 140.7, 127.6, 127.0, 125.2, 120.1, 65.7, 46.6, 41.3.
Spectroscopic data are in agreement with those reported earlier.[171,191]



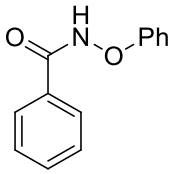
(9H-Fluoren-9-yl)methyl (S)-(1-(hydroxyamino)-1-oxo-3-phenylpropan-2-yl)carbamate II-7e : White solid; yield: 217 mg (54%): mp 172–173 °C. ^1H NMR (400 MHz, DMSOd_6): δ = 10.70 (s, 1 H), 8.86 (s, 1 H), 7.88 (d, *J* = 7.5 Hz, 2 H), 7.74–7.60 (m, 3H), 7.41 (td, *J* = 7.4, 3.8 Hz, 2 H), 7.28 (m, *J* = 7.6 Hz, 6 H), 7.18 (s, 1H), 4.13 (s, 4 H), 2.94–2.80 (m, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 168.0, 155.6, 143.8, 140.6, 137.9, 129.2, 128.0, 127.6, 127.0, 126.2, 125.3, 120.0, 65.7, 53.9, 46.1, 37.7; FT-IR (KBr): ν = 3315, 3260, 3061, 2922, 1684, 1641, 1531, 1450, 1384, 1265, 1039, 740 cm^{-1}. The chiral integrity of the final compound was determined by HPLC using a CHIRALPAK AS-H column [n-hexane/i-PrOH (90:10); flow rate 1.0 $mLmin^{-1}$: t=15.7 min (100%). Spectroscopic data are in agreement with those reported earlier[192]



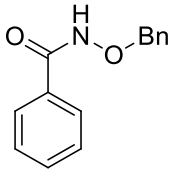
2-(1,3-Dioxoisoindolin-2-yl)-N-hydroxyacetamide II-7f : The title compound was synthesized following the general procedure, but increasing the milling time up to 200 min.White solid; yield: 138 mg (63%); mp 187–188 °C (Lit.[176] 189 °C). IR (KBr): ν = 3306, 3215, 3092, 3065, 3034, 2993, 2951, 2916, 1773, 1717, 1684, 1609, 1558, 1466, 1427, 1402, 1317, 1190, 1121, 1053, 955, 716 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.77 (s, 1 H), 8.92 (s, 1 H), 7.83 (dtt, *J* = 8.7, 5.5, 3.4 Hz, 4 H), 4.08 (s, 2H); ^{13}C NMR (101 MHz, DMSOd_6): δ = 168.1, 163.8, 135.2, 132.4, 123.8, 38.8; HR-MS (ESI): m/z=221.0558, calcd. for $C_{10}H_9N2O_4$: 221.0557 $[M+H]^+$. Spectroscopic data are in agreement with those reported earlier.[193]



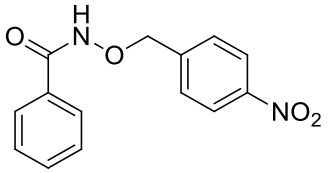
N,2,3-Trimethoxybenzamide II-8a : Colourless oil; yield: 173 mg (82%); IR (KBr): ν = 3217, 2970, 2939, 2837, 1668, 1580, 1477, 1458, 1427, 1314, 1267, 1231, 1192, 1171, 1074, 1040, 997, 826, 754 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.24 (s, 1 H), 7.17–6.90 (m, 3H), 3.87 (s, 3 H), 3.83 (s, 3 H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 152.6, 147.2, 138.3, 131.0, 124.9, 122.8, 116.0, 64.6, 61.6, 56.3; HR-MS (ESI): m/z=212.0920, calcd. for $C_{10}H1_4NO_4$: 212.0917 $[M+H]^+$.



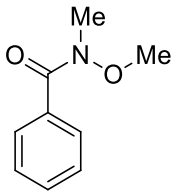
N-Phenoxybenzamide II-8b : White solid; yield: 192 mg (90%); mp 130–131 °C (Lit.[194] 131–133 8C). ^1H NMR (500 MHz, $CDCl_3$): δ = 9.14 (s, 1 H), 8.02–7.81 (m, 2 H), 7.61–7.42 (m, 3 H), 7.38–7.30 (m, 2 H), 7.18–7.04 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 159.5, 132.6, 129.5, 128.8,128.4, 127.3, 126.2, 123.1, 113.4. Spectroscopic data are in agreement with those reported earlier.[194]



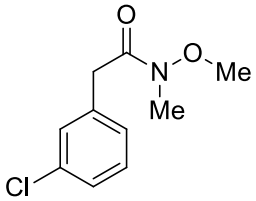
N-(Benzyloxy)benzamide II-8c : White solid; yield: 209 mg (92%); mp 102–103 °C (Lit.[159] 102–104 °C). ^1H NMR (400 MHz, DMSO-d_6): δ = 11.76 (s, 1 H), 7.75 (d, *J* = 7.6 Hz, 2H), 7.46 (m, 8 H), 4.93 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 164.4, 135.9, 132.3, 131.6, 128.9, 128.4 (2C), 128.3, 127.0, 76.9. Spectroscopic data are in agreement with those reported earlier.[194]



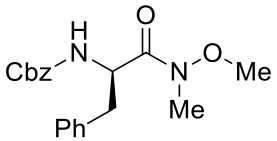
N-[(4-Nitrobenzyl)oxy]benzamide II-8e : White solid; yield: 167 mg (85%); mp 147–148 °C (Lit[195] 148–149 °C). IR (KBr): ν=3181, 3084, 2972, 2957, 2893, 2851, 1641, 1609, 1580, 1512, 1485, 1447, 1352, 1308, 1290, 1217, 1182, 1151, 1107, 1016, 980, 899, 866, 851, 826, 802, 745 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = (s, 1 H), 8.26 (d, *J* = 8.3 Hz, 2 H), 7.75 (t, *J* = 8.5 Hz, 4 H), 7.51 (dt, J=34.8, 7.3 Hz, 3 H), 5.09 (s, 2H); ^{13}C NMR (101 MHz, DMSO-d_6): δ = 157.0, 147.9, 144.5, 132.7, 132.4, 130.1, 129.1, 127.7, 124.1, 76.3. Spectroscopic data are in agreement with those reported earlier.[196]



N-Methoxy-N-methylbenzamide II-8f: Pale yellow oil; yield: 145 mg (88%). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69–7.57 (m, 2 H), 7.42–7.29 (m, 3 H), 3.49 (s, 3 H), 3.30 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 169.9, 134.0, 130.5, 128.0, 127.9, 60.9, 33.7. Spectroscopic data are in agreement with those reported earlier.[197]

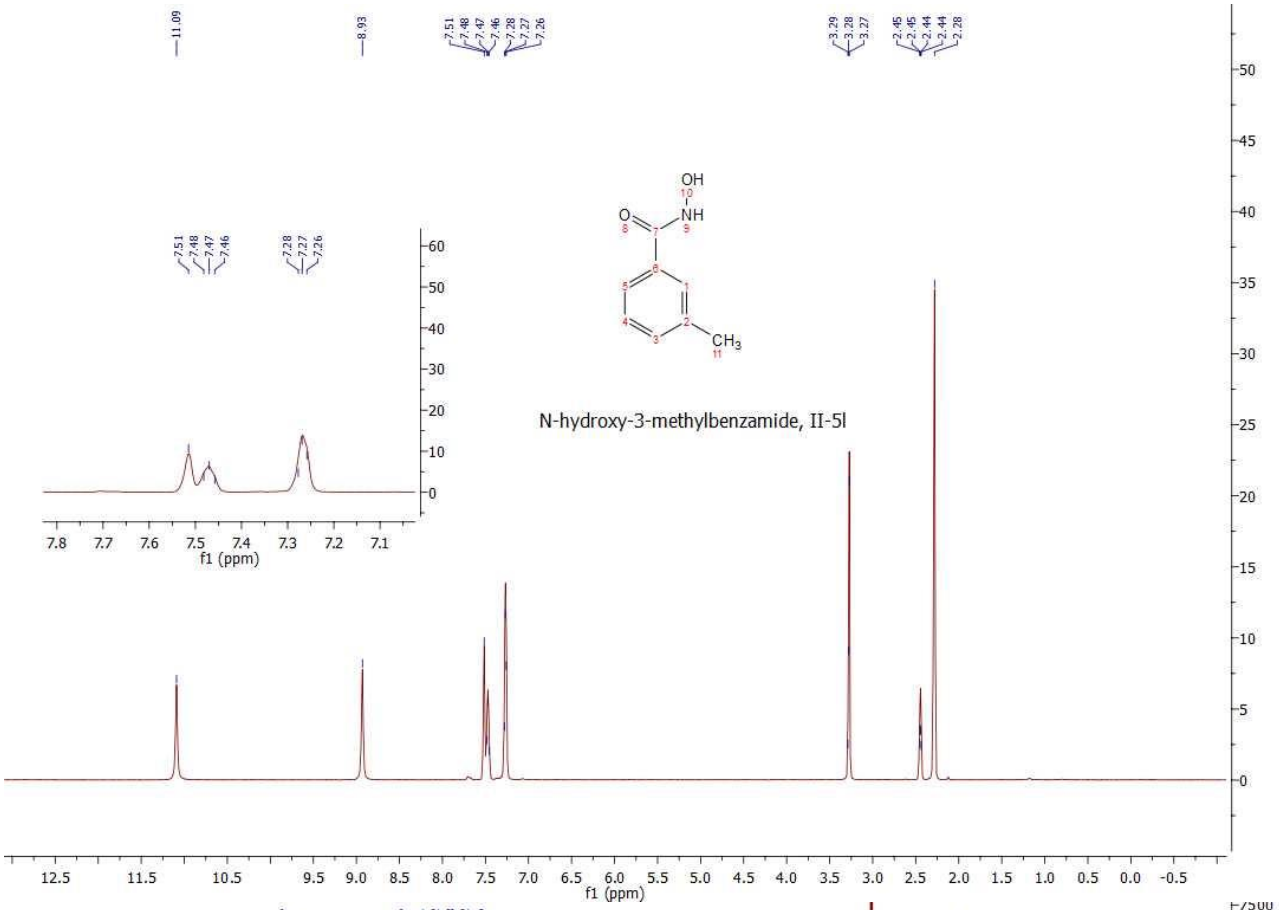


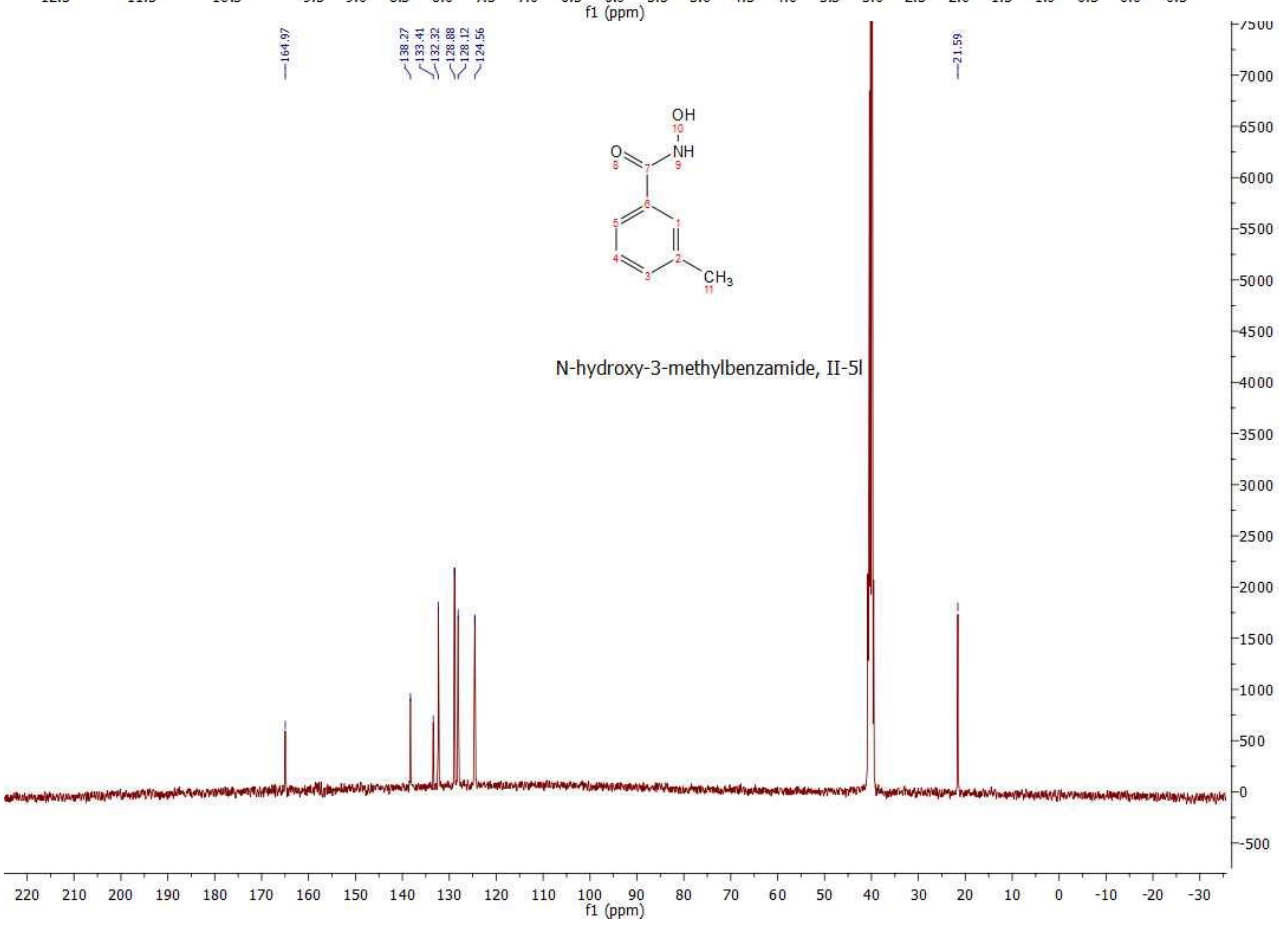
2-(3-Chlorophenyl)-N-methoxy-N-methylacetamide II-8g : Colourless oil; yield: 192 mg 90%). IR (KBr): ν = 3065, 2968, 2938, 2820, 1665, 1599, 1574, 1476, 1414, 1383, 1433, 1173, 1094, 1005, 1080, 768 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.29–7.05 (m, 4 H), 3.70 (s, 2 H), 3.59 (s, 3 H), 3.15 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 171.7, 137.0, 134.3, 129.8, 129.6, 127.8, 127.1, 61.5, 32.4; HR-MS (ESI): m/ z=214.0631, calcd. for $C_{10}H_{13}ClNO_2$: 214.0629 [M+H]+. Spectroscopic data are in agreement with those reported earlier.[198]

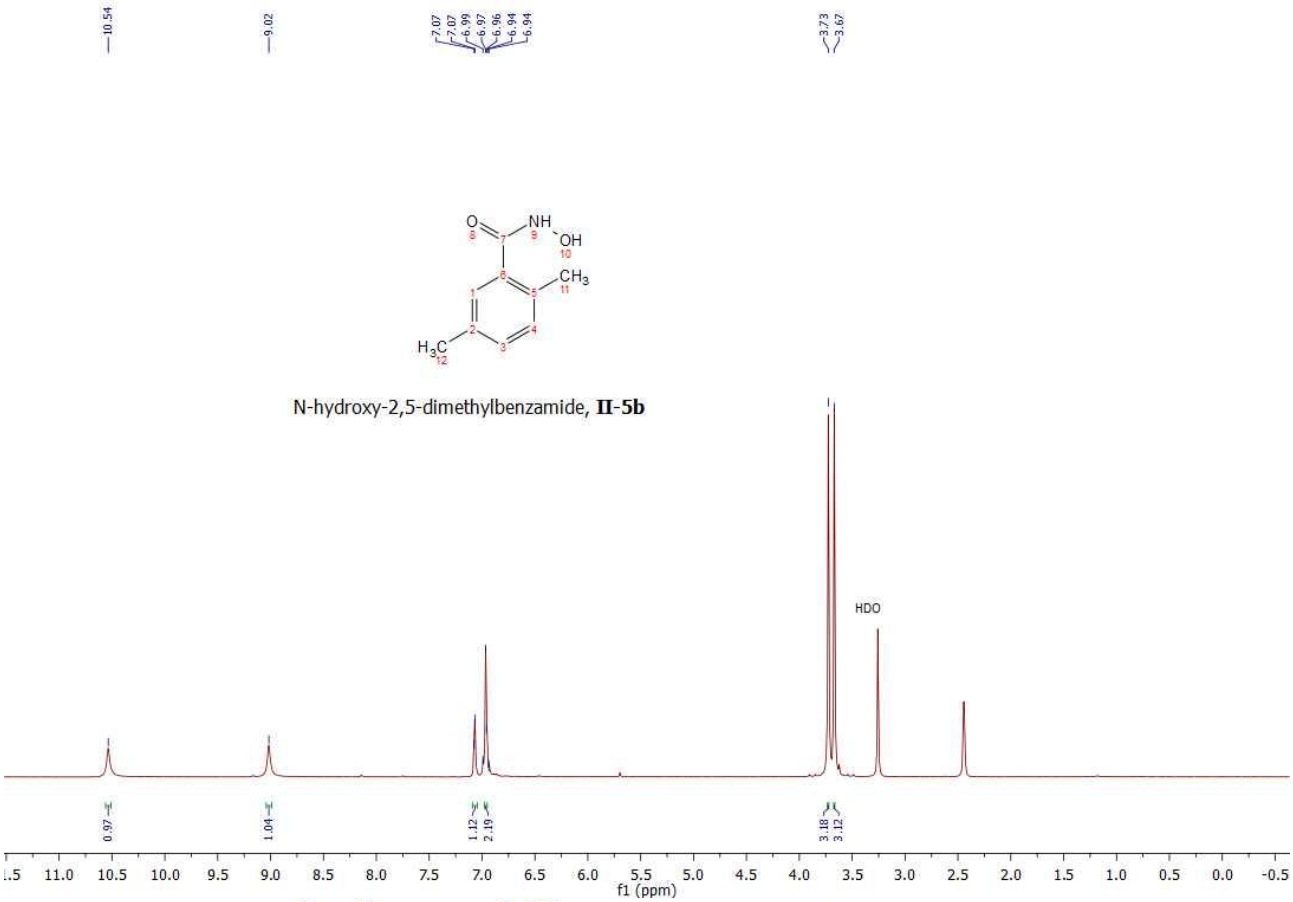


Benzyl (S)-{1-[methoxy(methyl)amino]-1-oxo-3-phenylpropan-2-yl}carbamate II-8h: White solid; yield: 298 mg (87%); mp 103–104 °C. FT-IR (KBr): ν = 3290, 3063, 3032, 2977, 2957, 2917, 1710, 1651, 1475, 1333, 1082, 981, 875 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 7.73 (d, J=8.4 Hz, 1 H), 7.47–7.08 (m, 10 H), 4.96 (s, 2 H), 4.66 (s, 1 H), 3.73 (s, 3 H), 3.11 (s, 3 H), 2.90 (dd, J=13.5, 3.9 Hz, 1 H), 2.83–2.69 (m, 1 H). ^{13}C NMR (101 MHz, DMSO-d_6): δ = 172.6, 156.6, 138.6, 137.6, 129.7, 128.9, 128.8, 128.4, 128.2, 127.1, 65.9, 61.8, 53.6, 37.1, 32.5. The chiral integrity of the final compound was determined by HPLC using a Phenomenex Lux 5u Cellulose-1 column [*n*-hexane/*i*-PrOH (98:2); flow rate 0.5 $mLmin^{-1}$: t=128.3 min (100%). Spectroscopic data are in agreement with those reported earlier.[199]

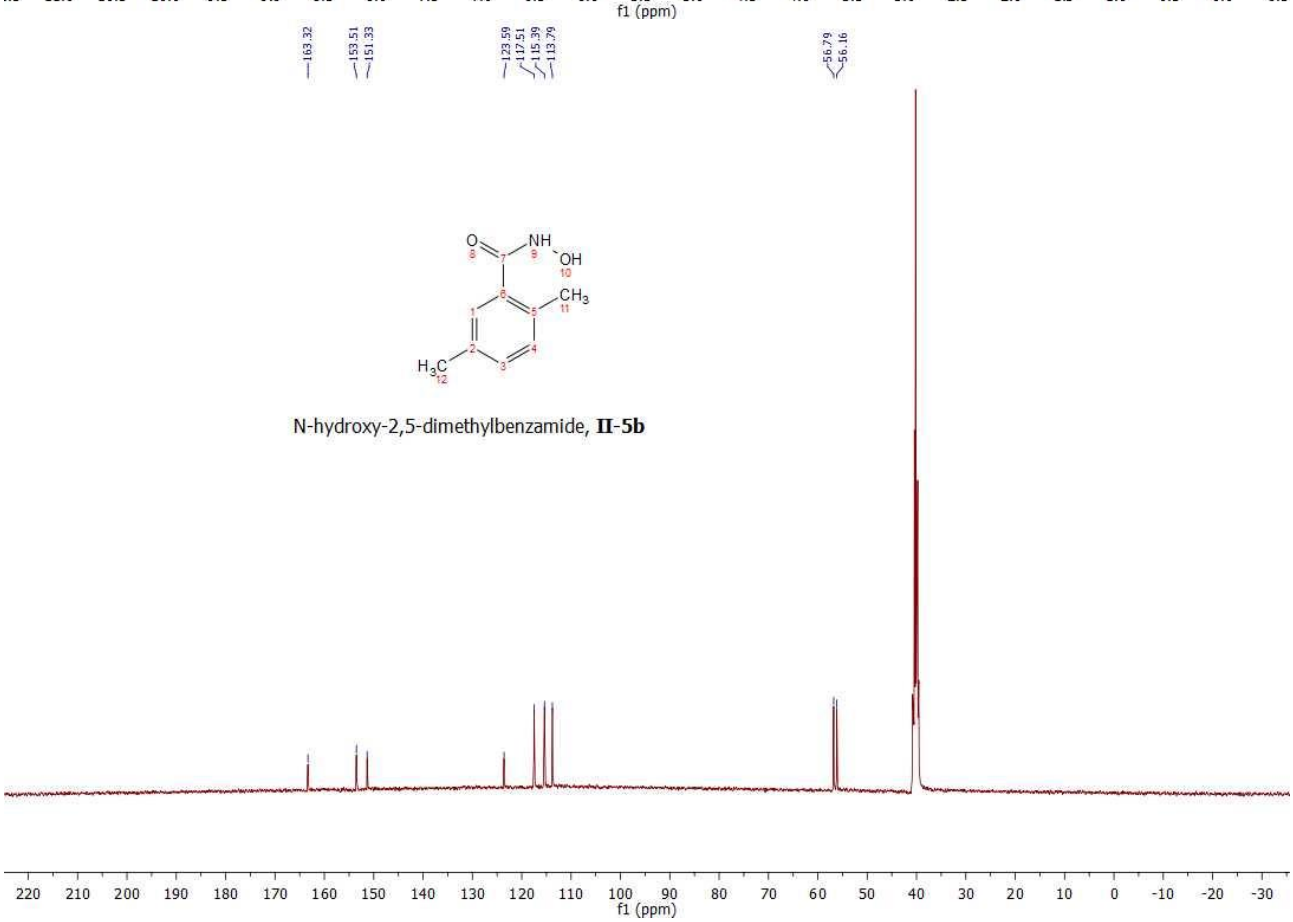
^{1}H and ^{13}C NMR spectra for Hydroxamic Derivatives II-5a-y, II-7a-f, II-8a-h.



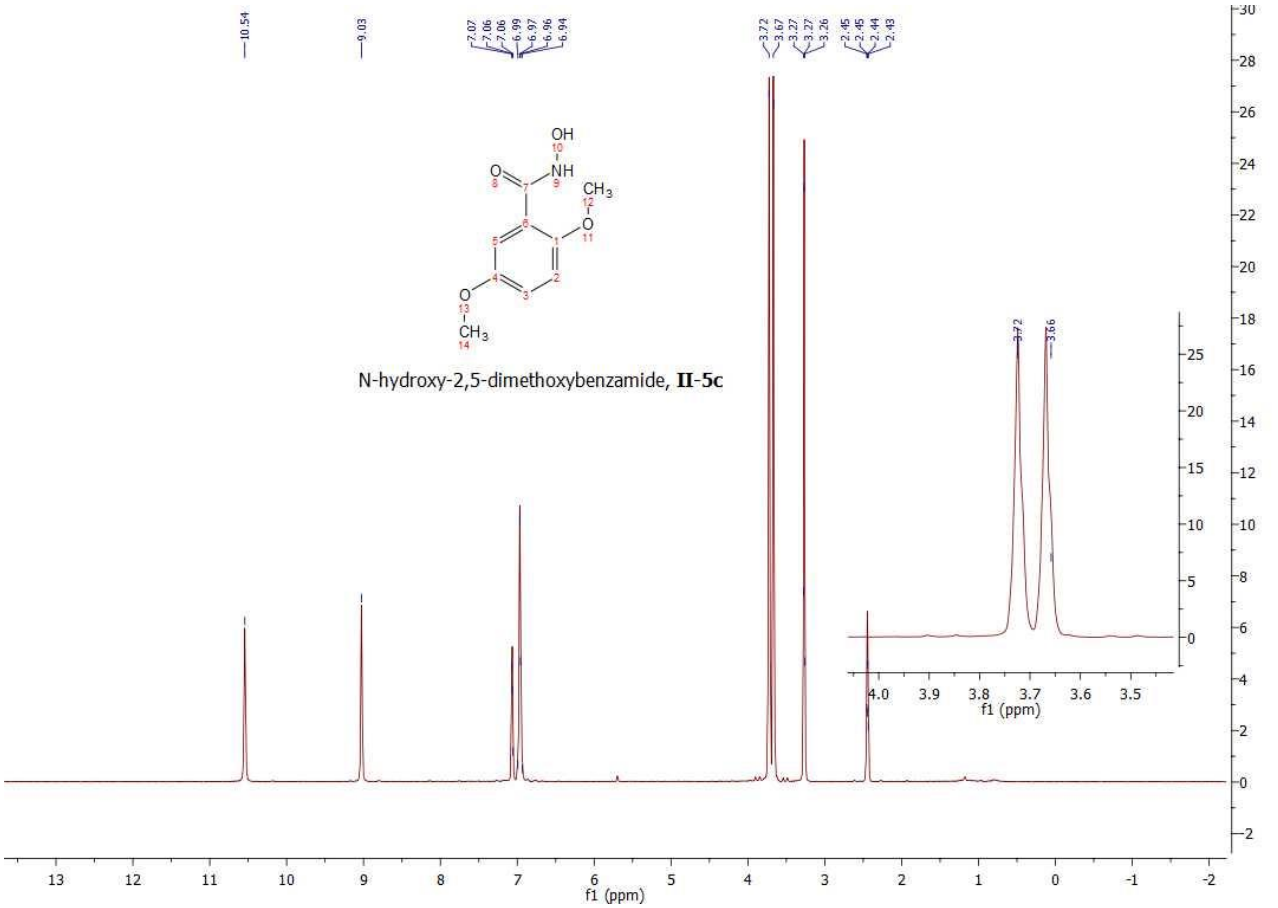




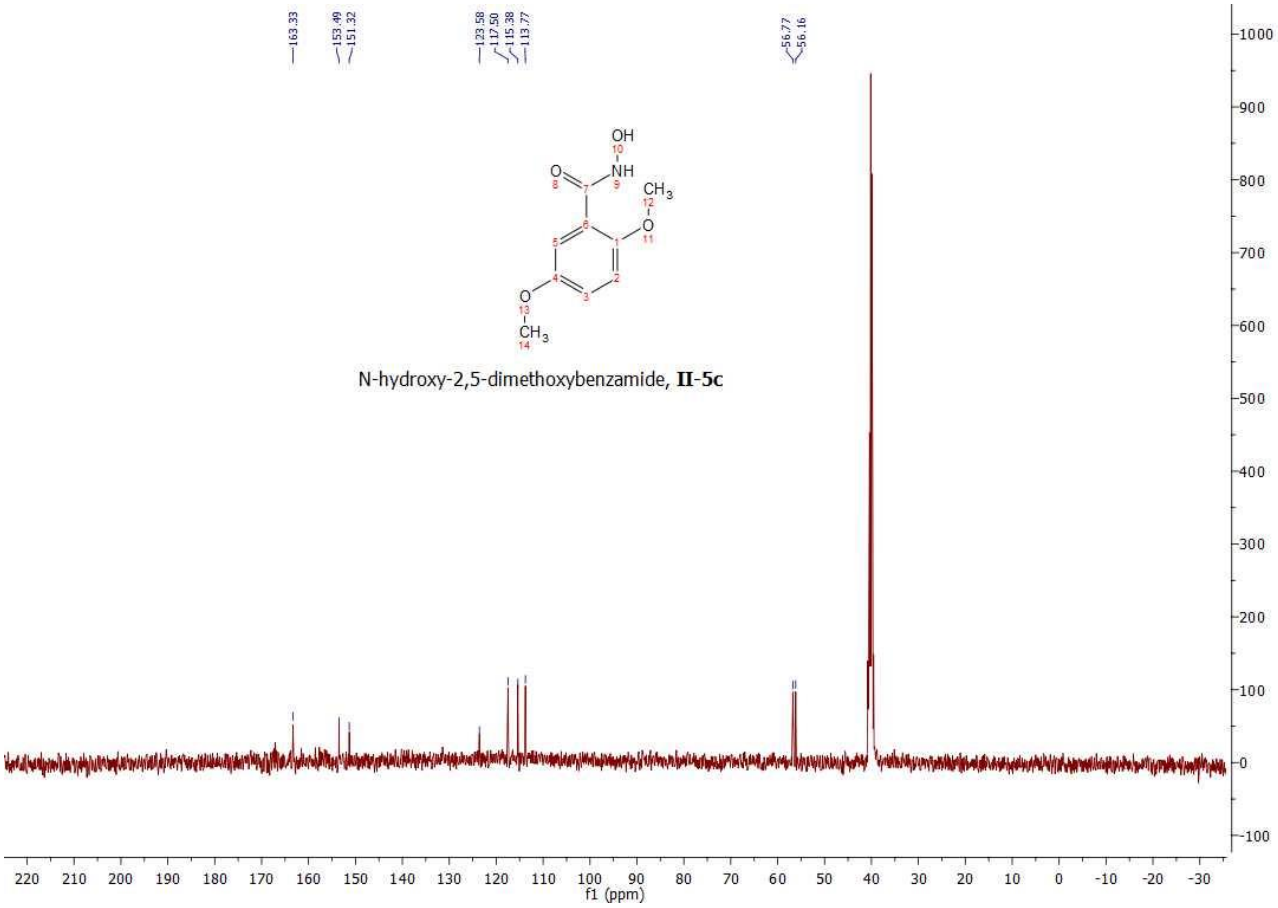
N-hydroxy-2,5-dimethylbenzamide, **II-5b**



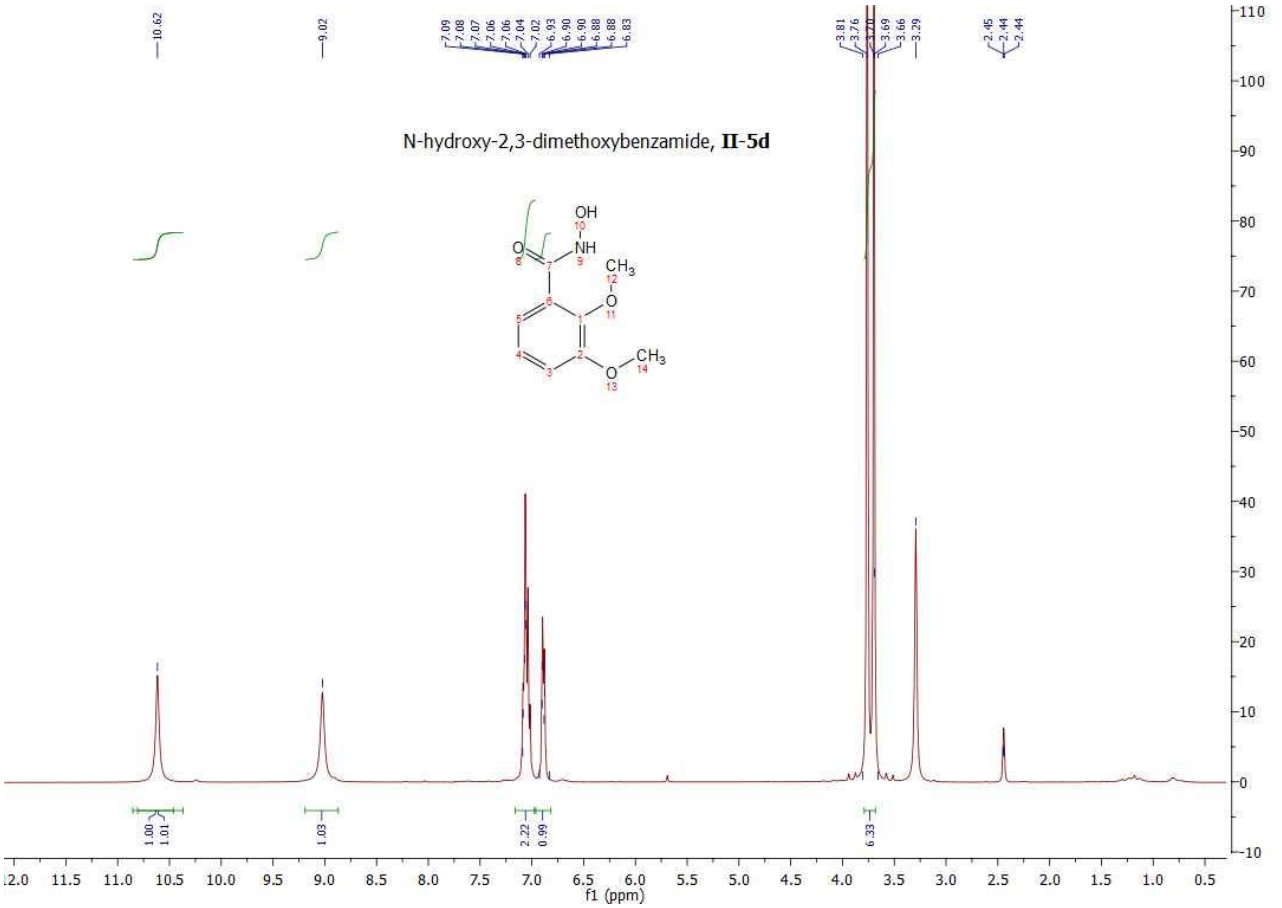
N-hydroxy-2,5-dimethylbenzamide, **II-5b**



N-hydroxy-2,5-dimethoxybenzamide, **II-5c**



N-hydroxy-2,5-dimethoxybenzamide, **II-5c**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7.08
7.07
7.06
7.06
7.04
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6.90
6.90
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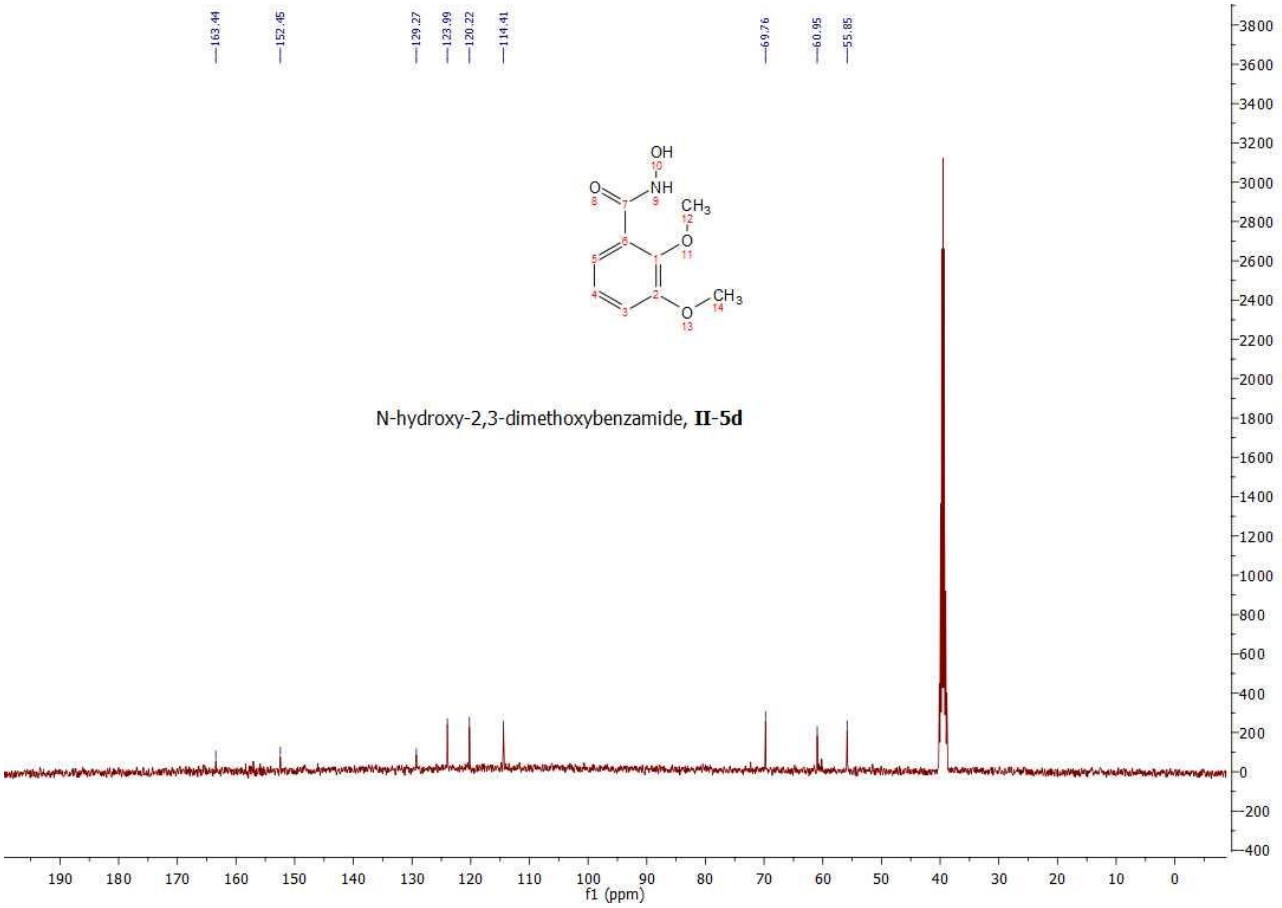
6.88
6.83
3.81
3.76
3.70
3.69
3.66
3.29
2.45
2.44
2.44
N-hydroxy-2,3-dimethoxybenzamide, II-5d
OH
10
O
8
NH
9
CH3
12
O
11
CH3
14
O
13
1.00
1.01
1.03
2.22
0.99
6.33
f1 (ppm)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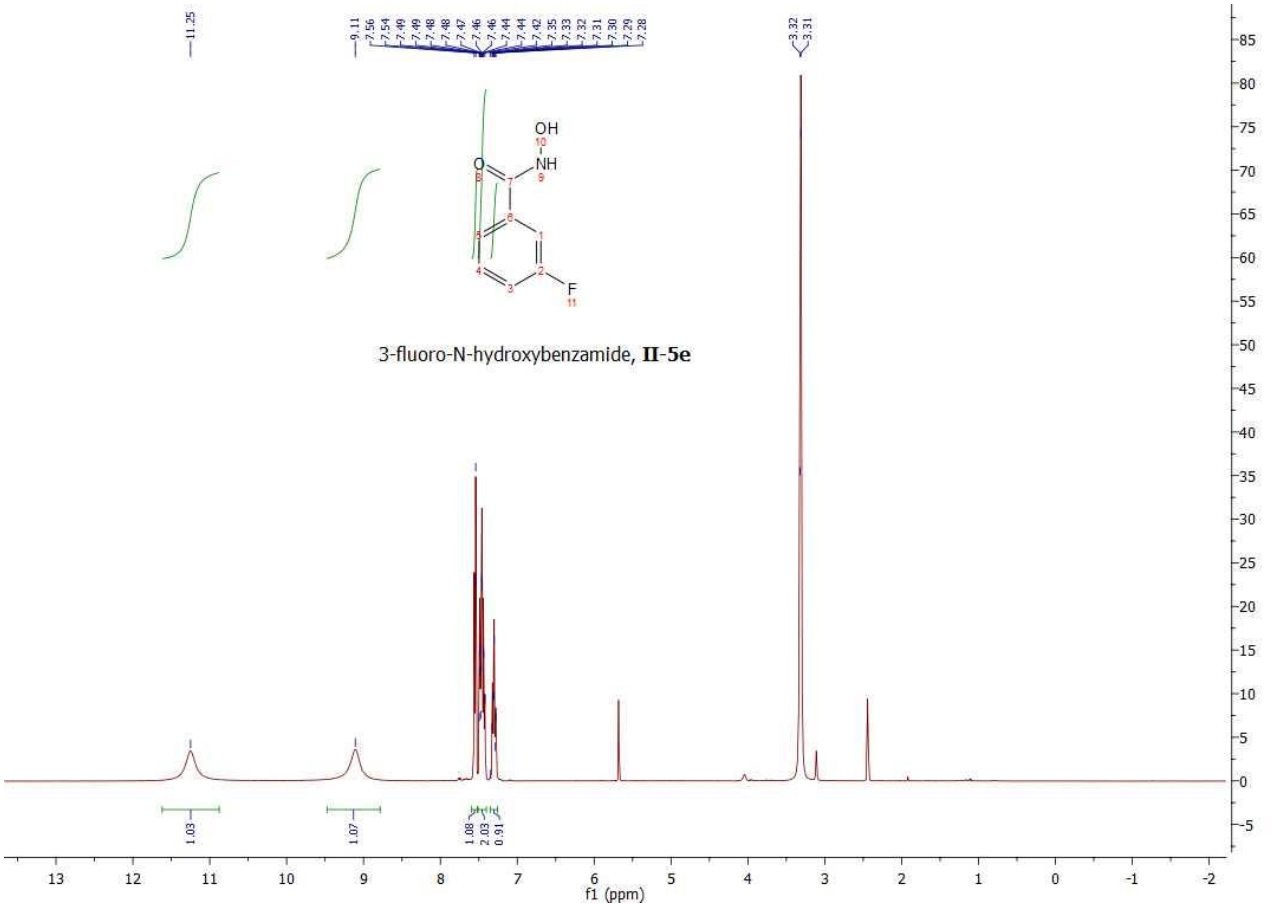
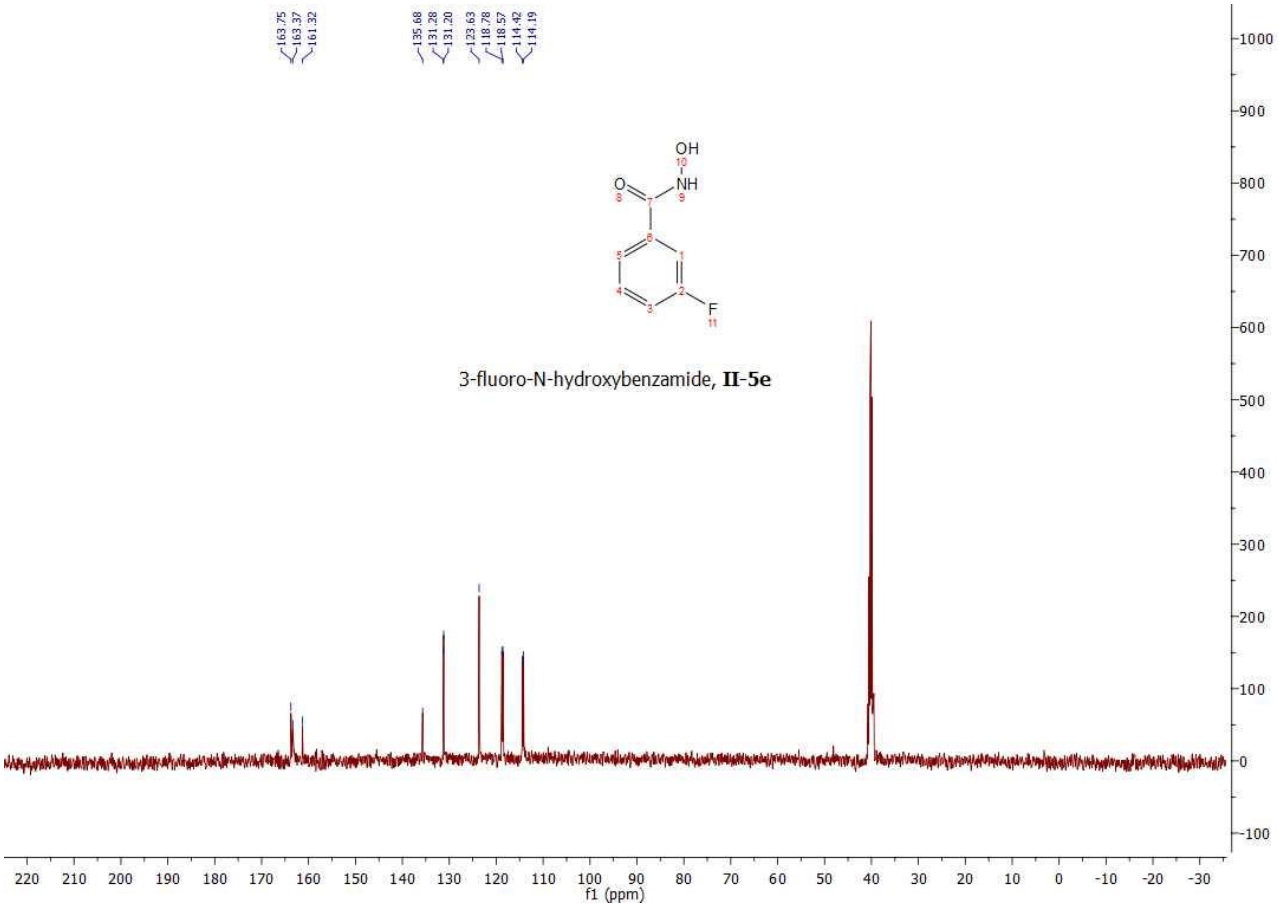
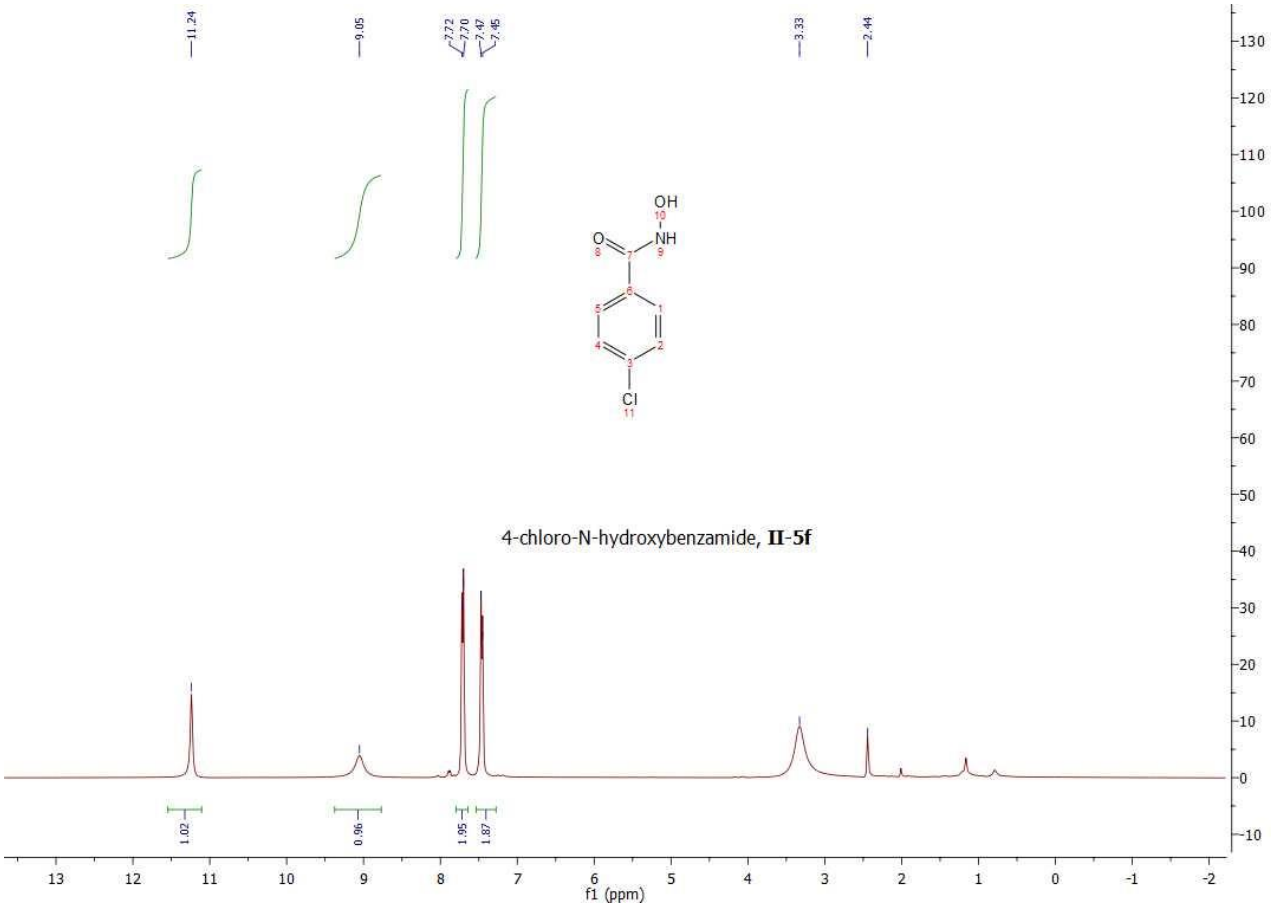
8
NH
9
CH3
12
O
11
CH3
14
O
13
N-hydroxy-2,3-dimethoxybenzamide, II-5d
f1 (ppm)



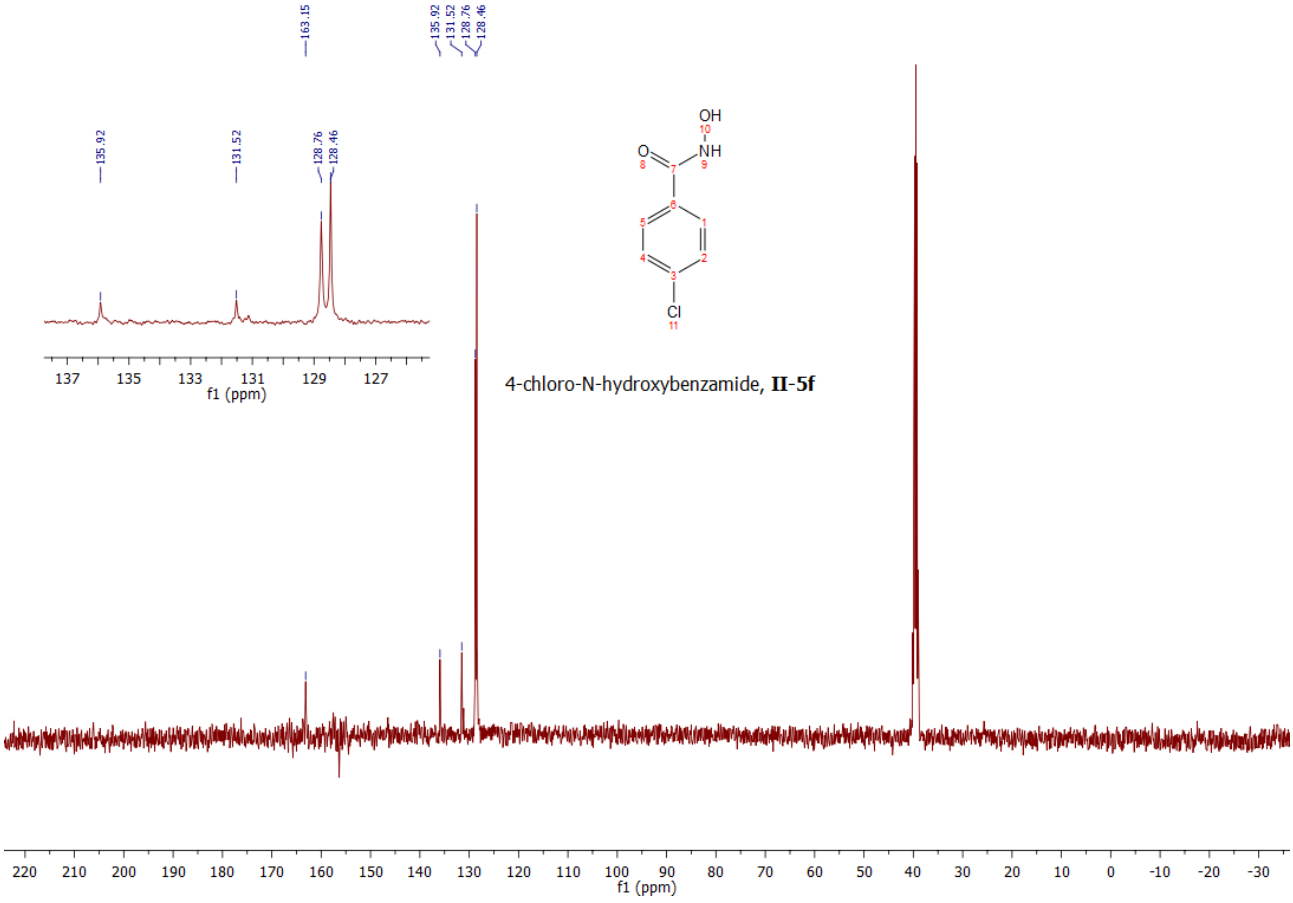
3-fluoro-N-hydroxybenzamide, **II-5e**



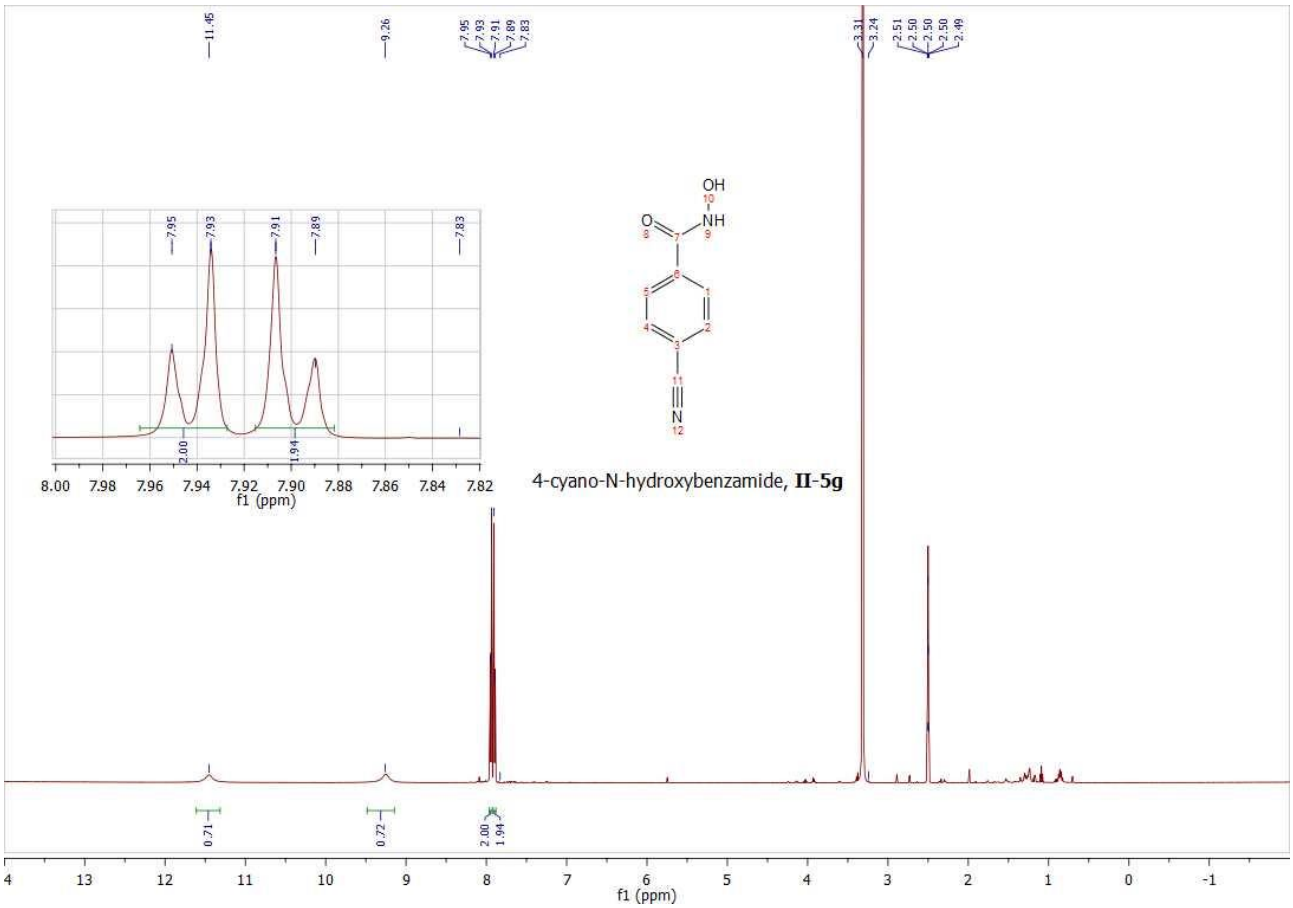
3-fluoro-N-hydroxybenzamide, **II-5e**

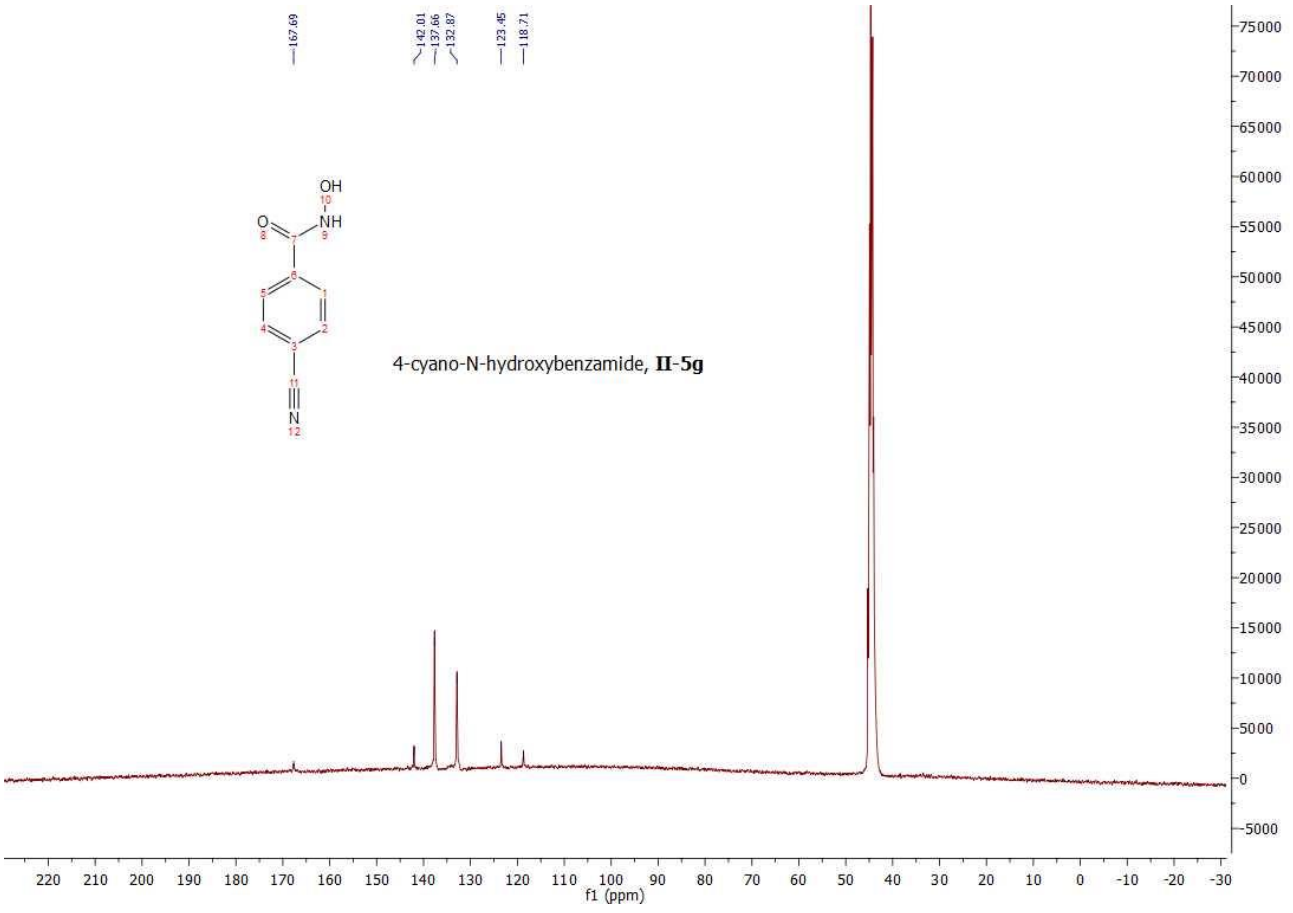


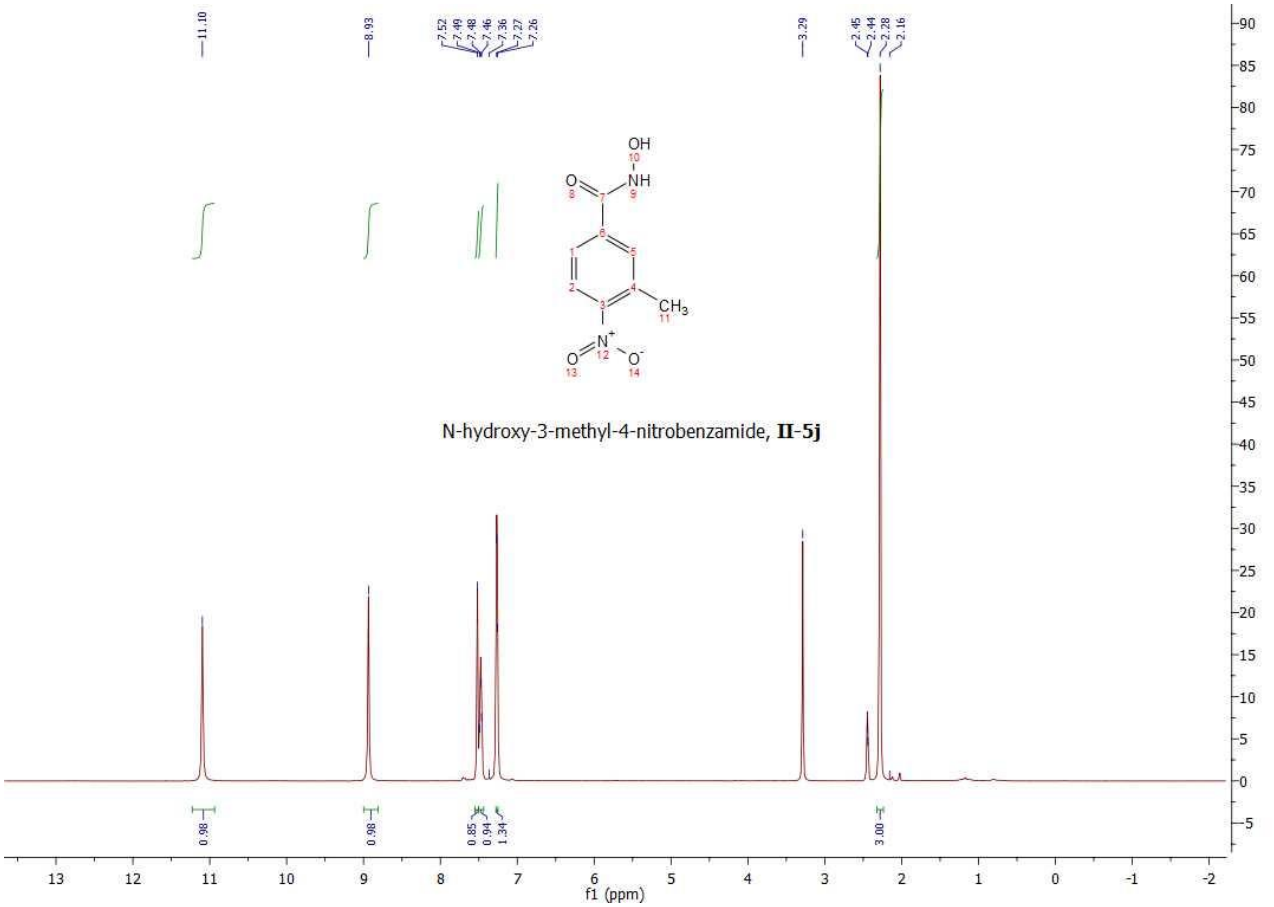
4-chloro-N-hydroxybenzamide, **II-5f**



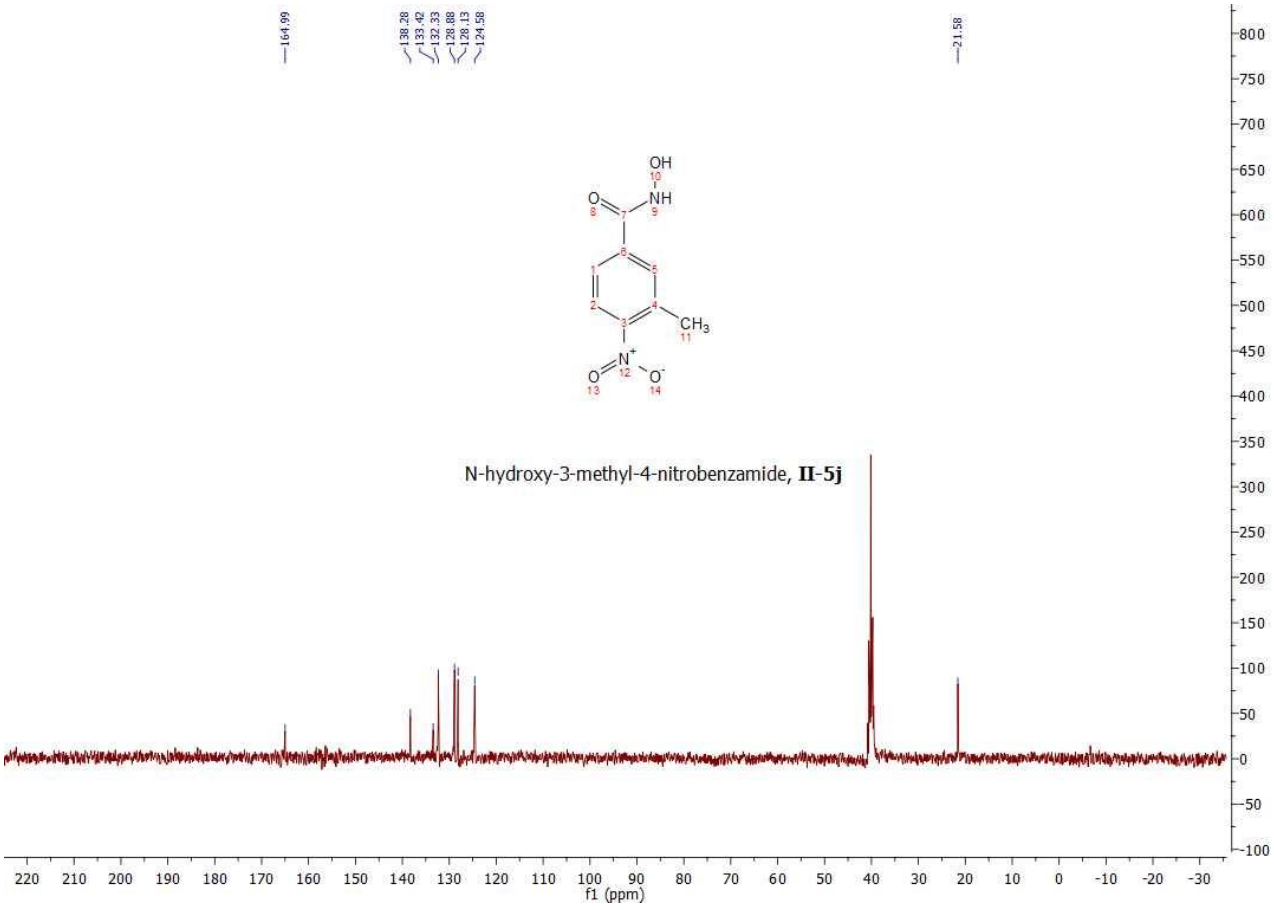
4-chloro-N-hydroxybenzamide, **II-5f**


11.45
9.26
7.95
7.93
7.91
7.89
7.83
3.31
3.24
2.51
2.50
2.50
2.50
2.49
4-cyano-N-hydroxybenzamide, II-5g
f1 (ppm)

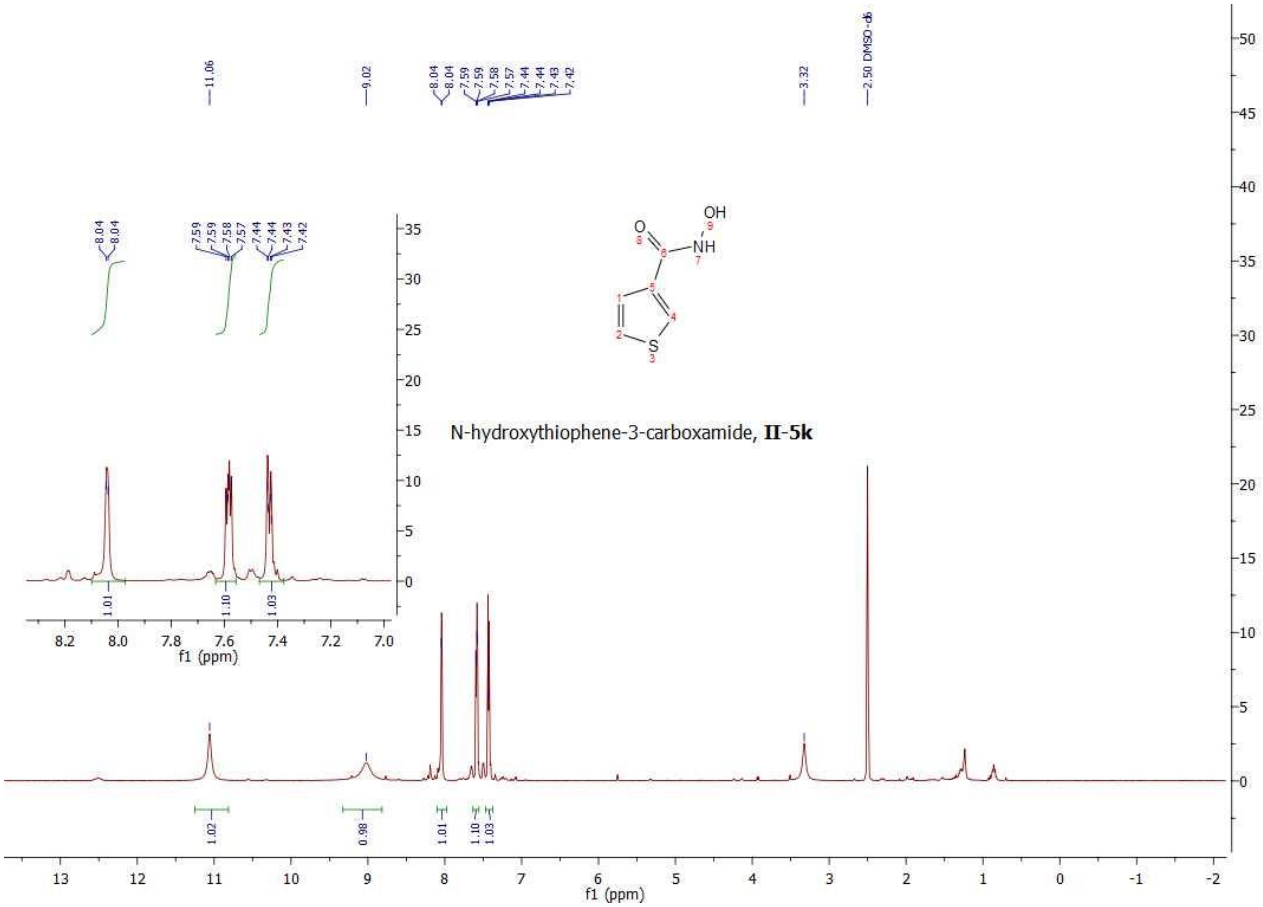

167.69
142.01
137.66
132.87
123.45
118.71
4-cyano-N-hydroxybenzamide, II-5g
f1 (ppm)

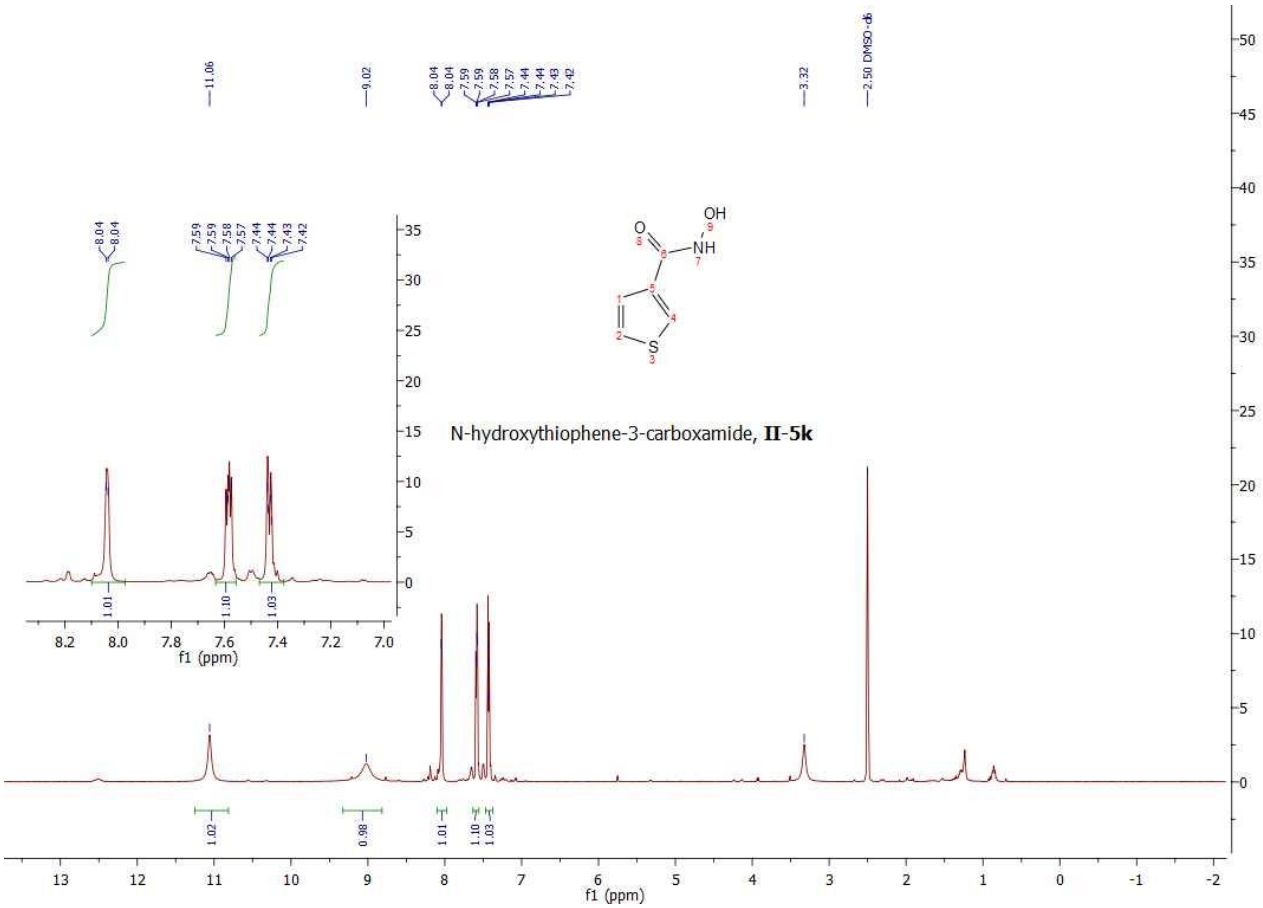


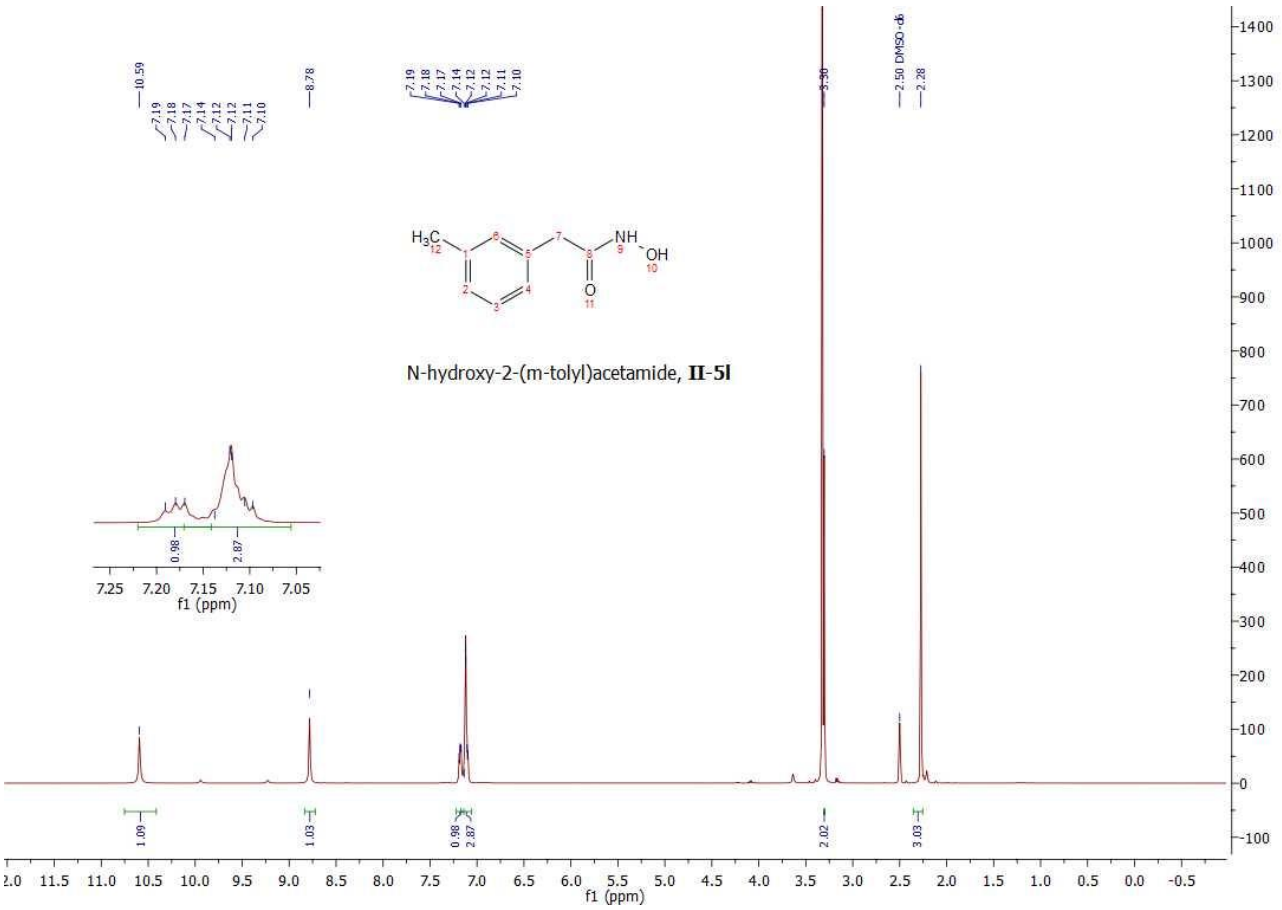
N-hydroxy-3-methyl-4-nitrobenzamide, **II-5j**

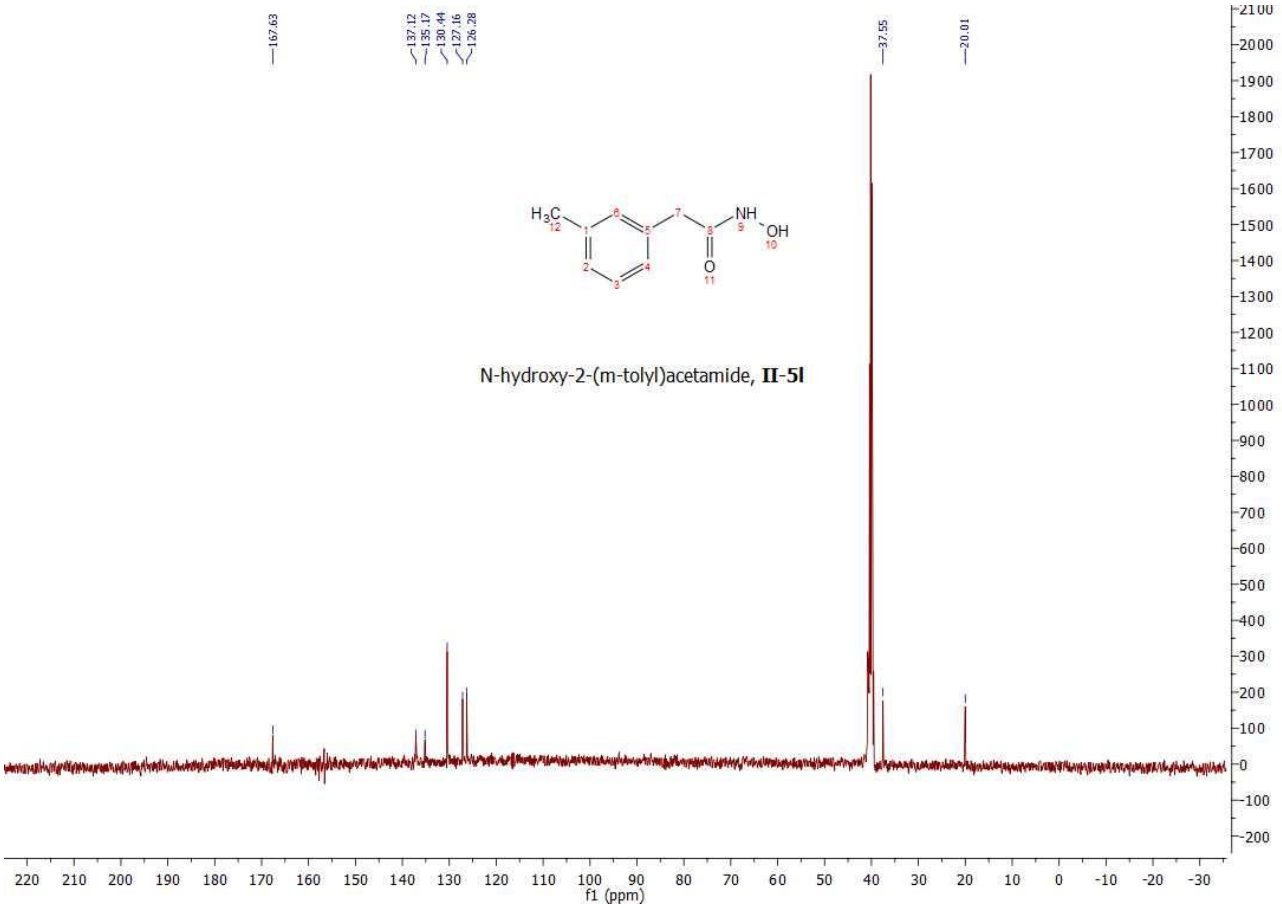


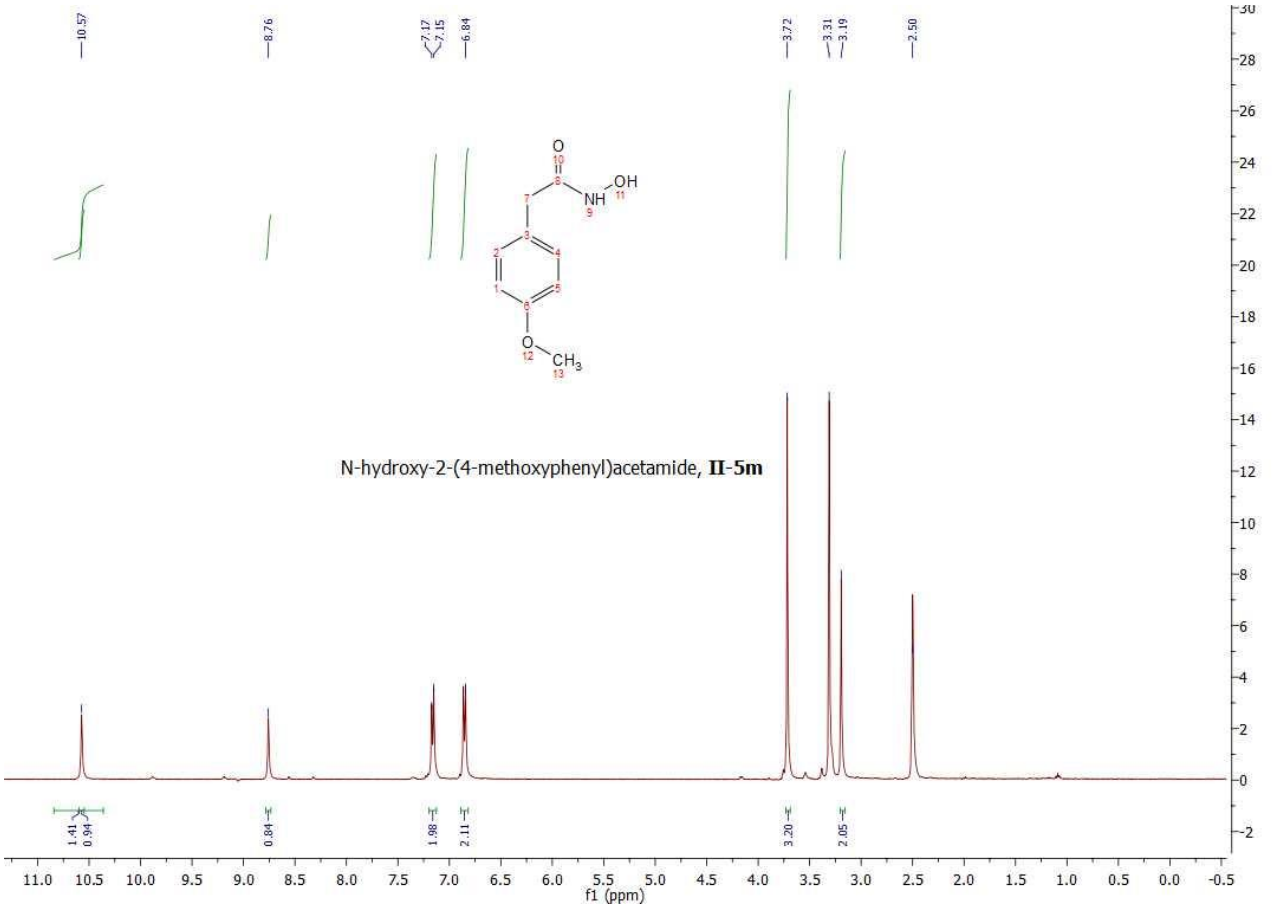
N-hydroxy-3-methyl-4-nitrobenzamide, **II-5j**

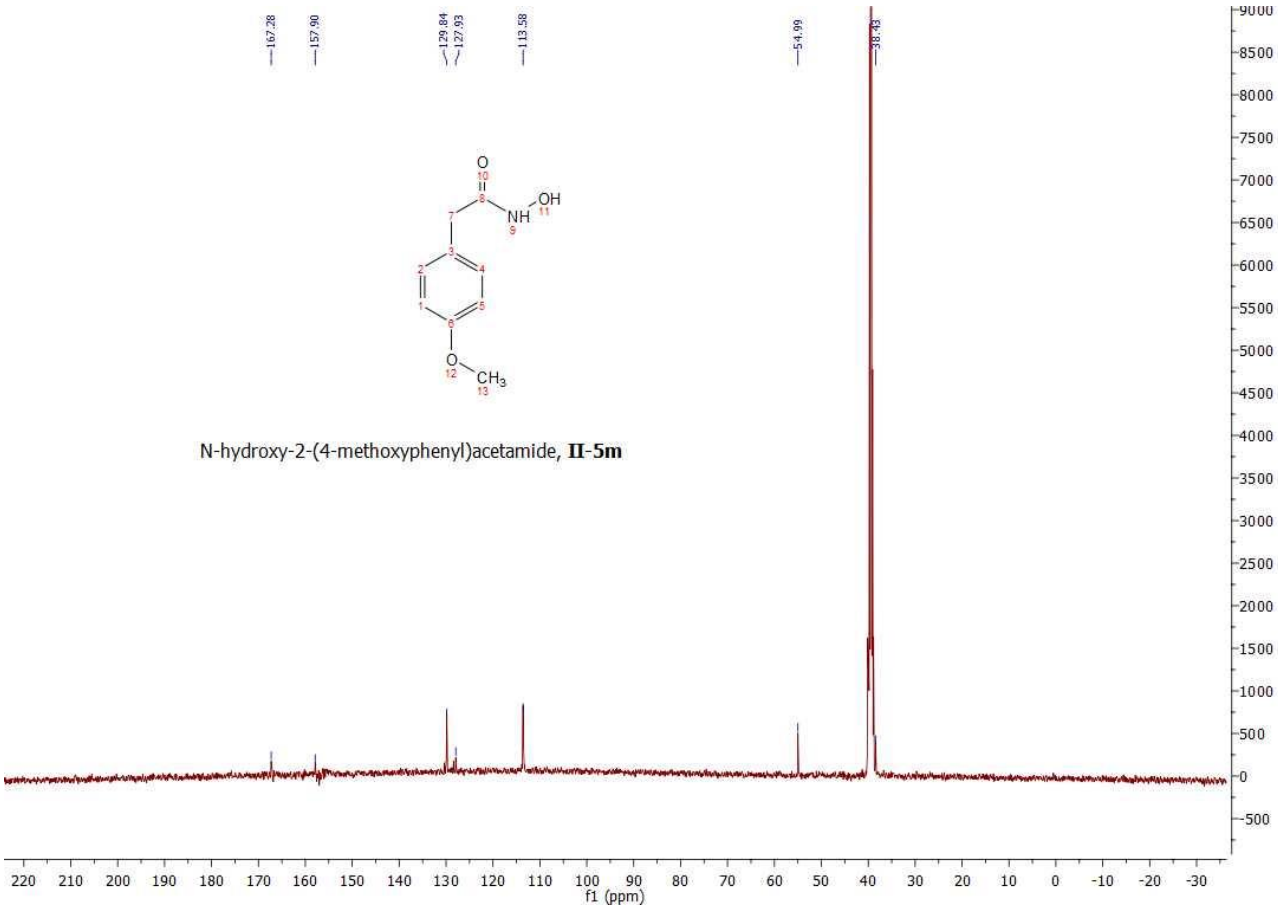

11.06
9.02
8.04
8.04
7.59
7.59
7.58
7.57
7.44
7.44
7.43
7.42
3.32
2.50 DMSO-d6
OH
O
NH
S
N-hydroxythiophene-3-carboxamide, II-5k
1.02
0.98
1.01
1.10
1.03
f1 (ppm)

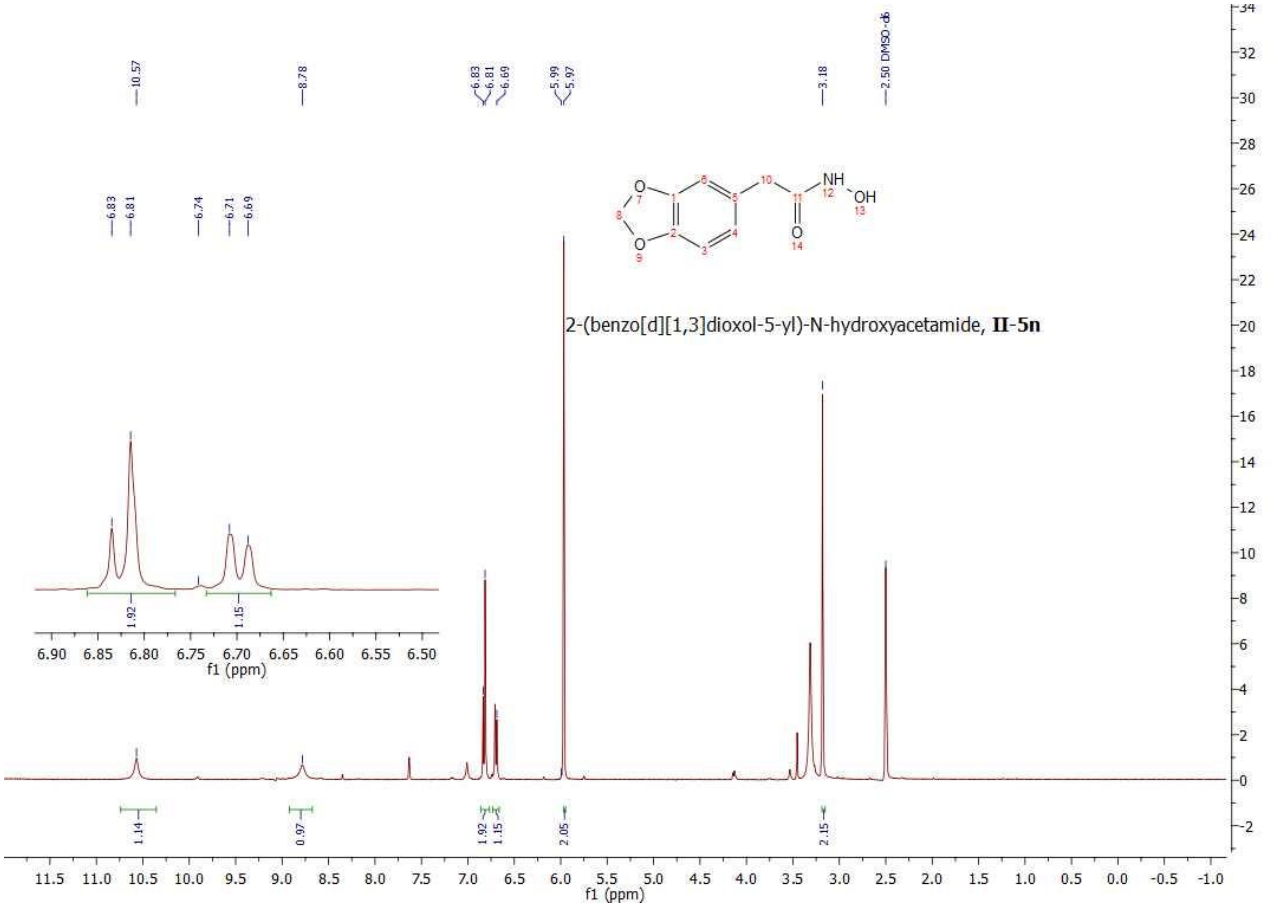

11.06
9.02
8.04
8.04
7.59
7.59
7.58
7.57
7.44
7.44
7.43
7.42
3.32
2.50 DMSO-d6
OH
O
NH
S
N-hydroxythiophene-3-carboxamide, II-5k
1.02
0.98
1.01
1.10
1.03
f1 (ppm)

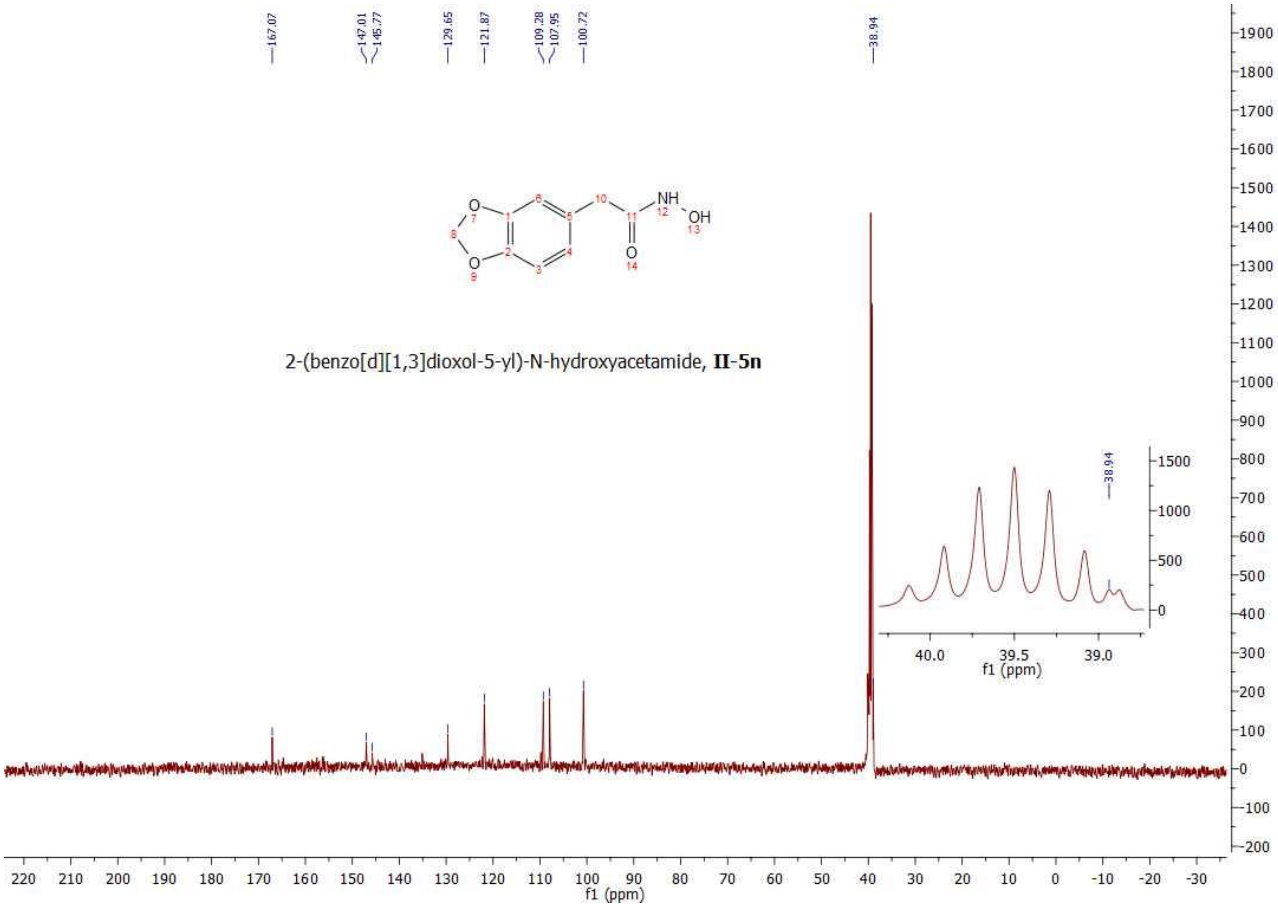

10.59
8.78
7.19
7.18
7.17
7.14
7.12
7.12
7.11
7.10
3.30
2.50 DMSO-d6
2.28
N-hydroxy-2-(m-tolyl)acetamide, II-5l
0.98
2.87
7.25 7.20 7.15 7.10 7.05
f1 (ppm)
1.09
1.03
0.98
2.87
2.02
3.03
f1 (ppm)

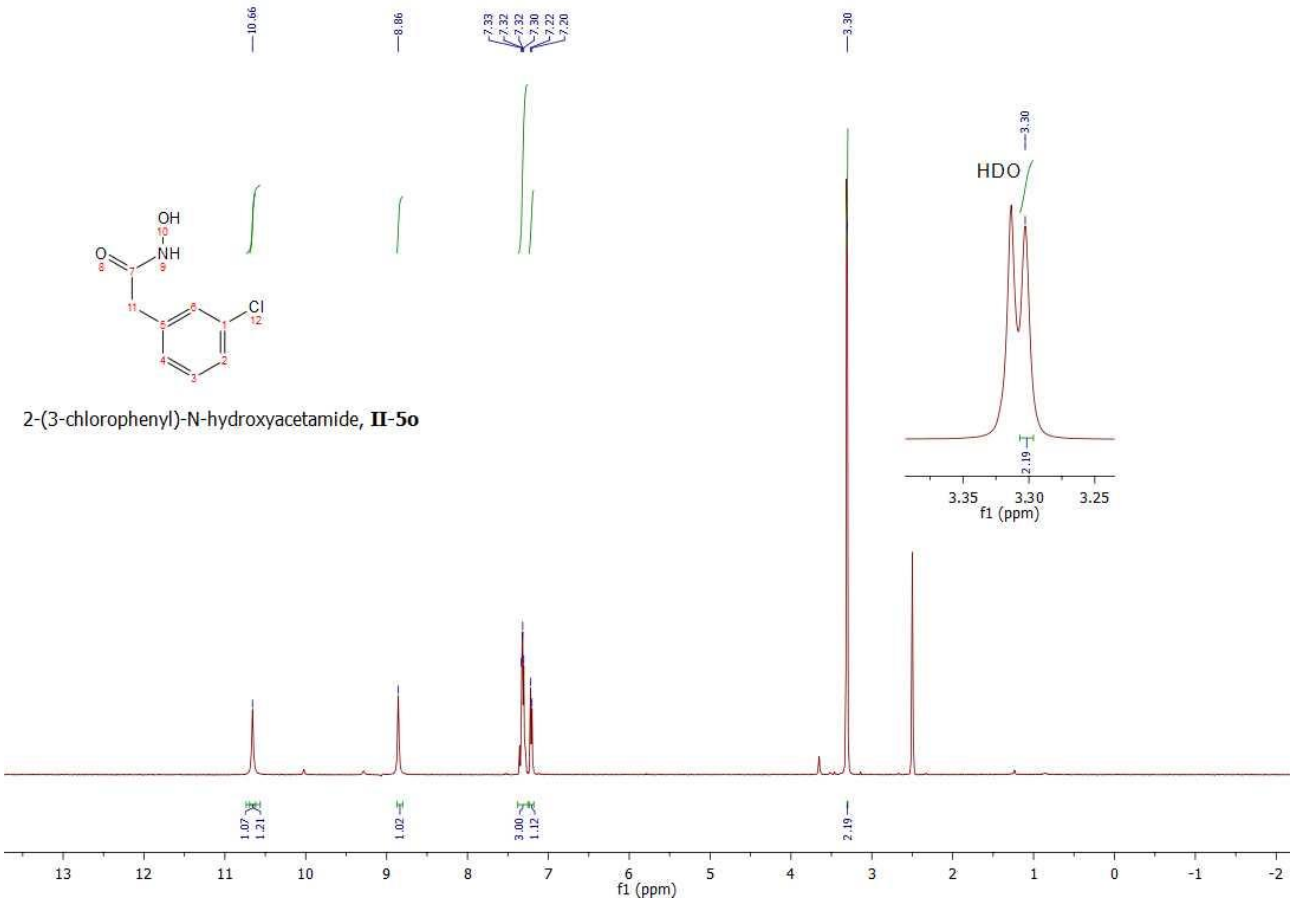

167.63
137.12
135.17
130.44
127.16
126.28
37.55
20.01
N-hydroxy-2-(m-tolyl)acetamide, II-5l
f1 (ppm)


10.57
8.76
7.17
7.15
6.84
3.72
3.31
3.19
2.50
N-hydroxy-2-(4-methoxyphenyl)acetamide, II-5m
1.41
0.94
0.84
1.98
2.11
3.20
2.05
f1 (ppm)

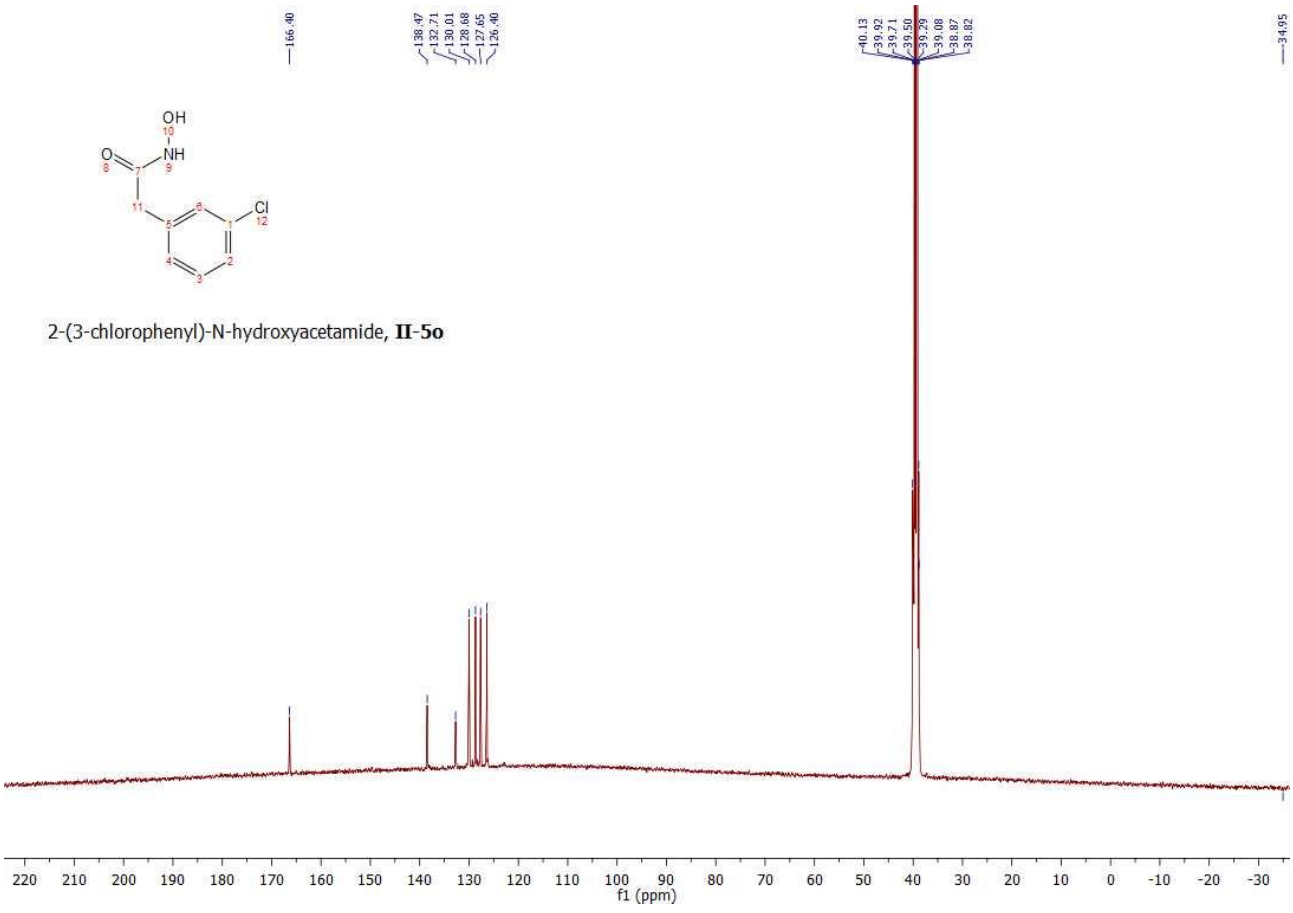

167.28
157.90
129.84
127.93
113.58
54.99
38.43
N-hydroxy-2-(4-methoxyphenyl)acetamide, II-5m
f1 (ppm)


10.57
8.78
6.83
6.81
6.69
5.99
5.97
3.18
2.50 DMSO-d6
6.83
6.81
6.74
6.71
6.69
NH
OH
2-(benzo[d][1,3]dioxol-5-yl)-N-hydroxyacetamide, II-5n
1.92
1.15
6.90 6.85 6.80 6.75 6.70 6.65 6.60 6.55 6.50
f1 (ppm)
1.14
0.97
1.92
1.15
2.05
2.15
11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)

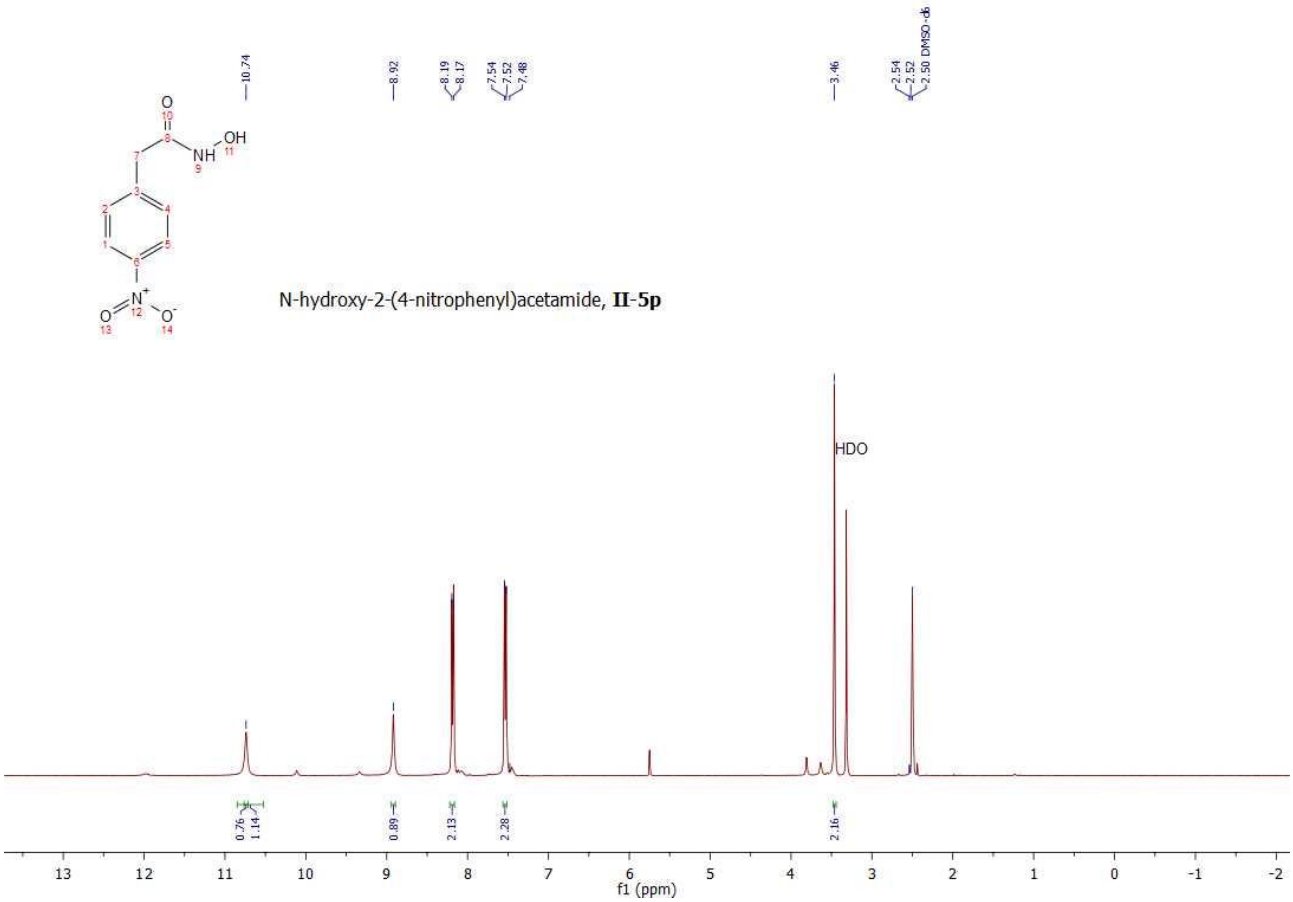

167.07
147.01
145.77
129.65
121.87
109.28
107.95
100.72
38.94
NH
OH
2-(benzo[d][1,3]dioxol-5-yl)-N-hydroxyacetamide, II-5n
38.94
40.0 39.5 39.0
f1 (ppm)
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20 -30
f1 (ppm)



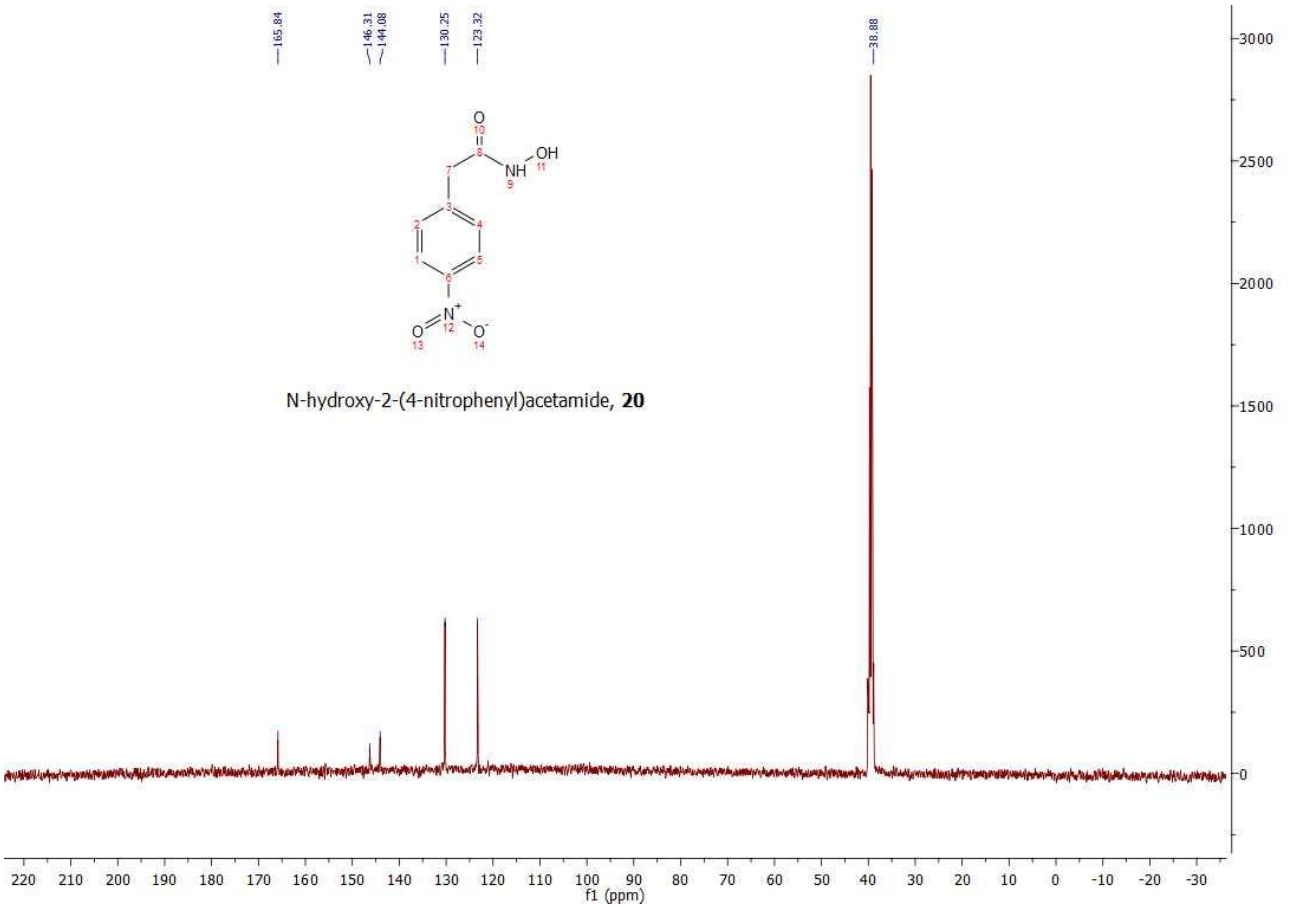
2-(3-chlorophenyl)-N-hydroxyacetamide, **II-5o**



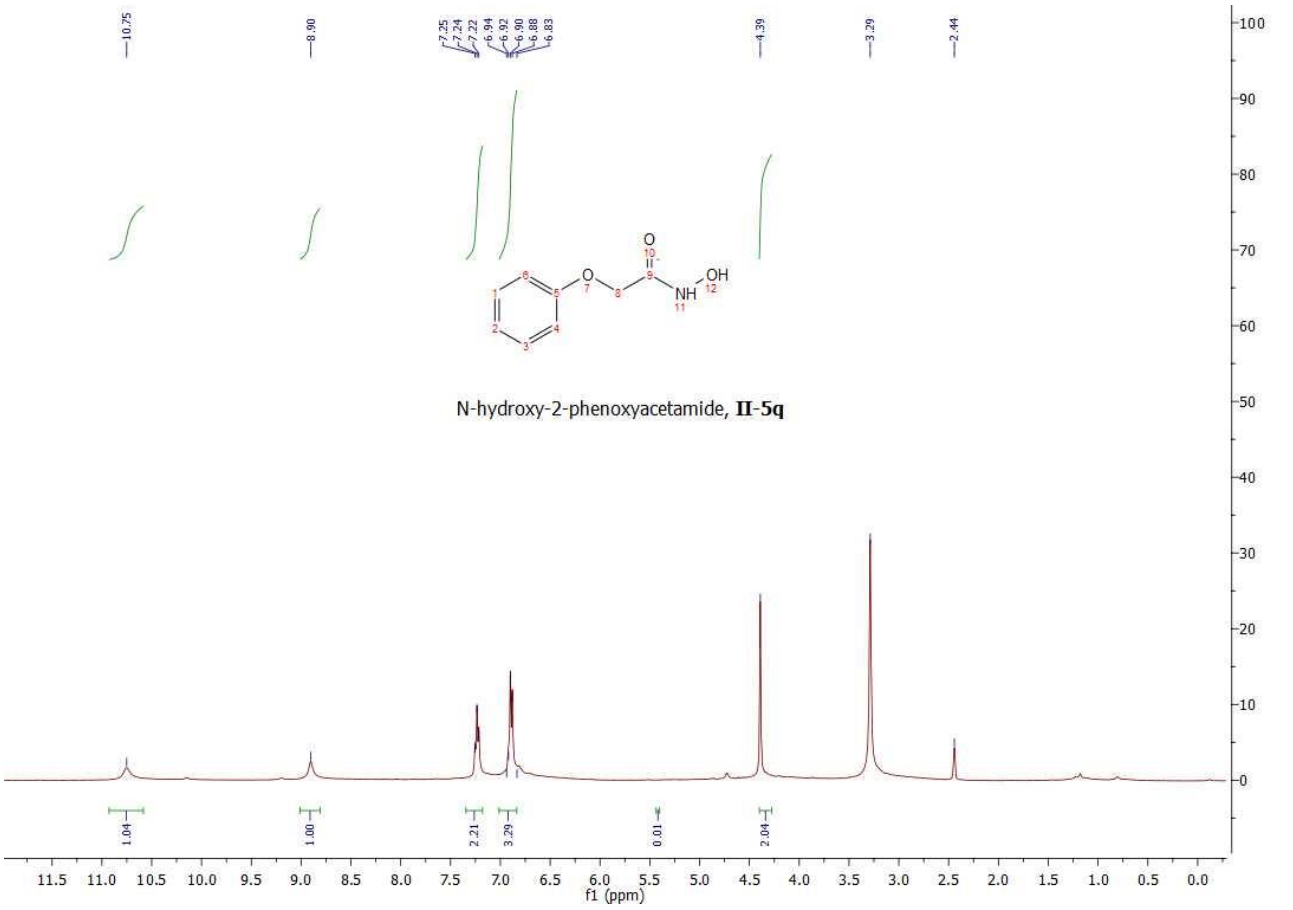
2-(3-chlorophenyl)-N-hydroxyacetamide, **II-5o**



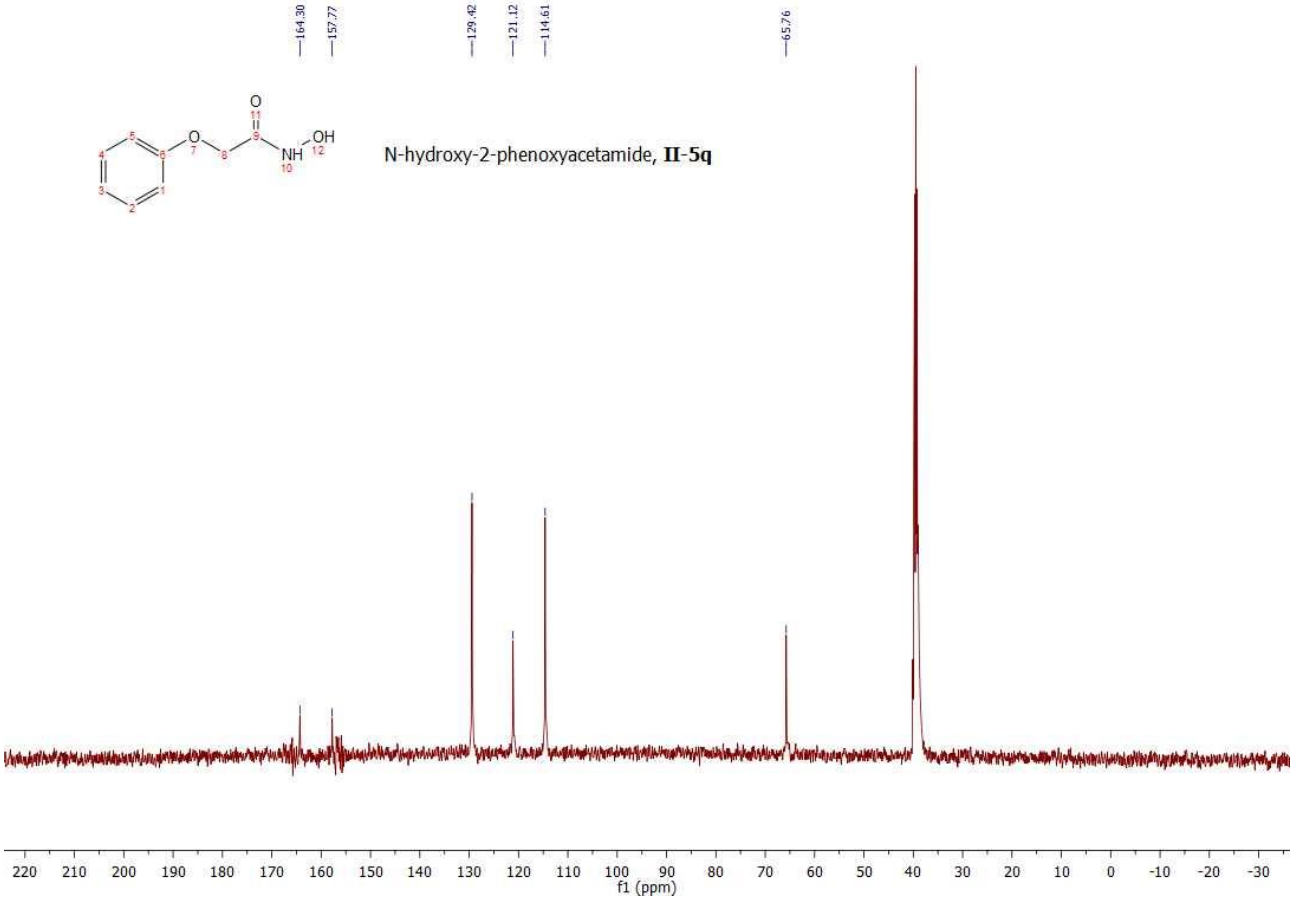
N-hydroxy-2-(4-nitrophenyl)acetamide, **II-5p**



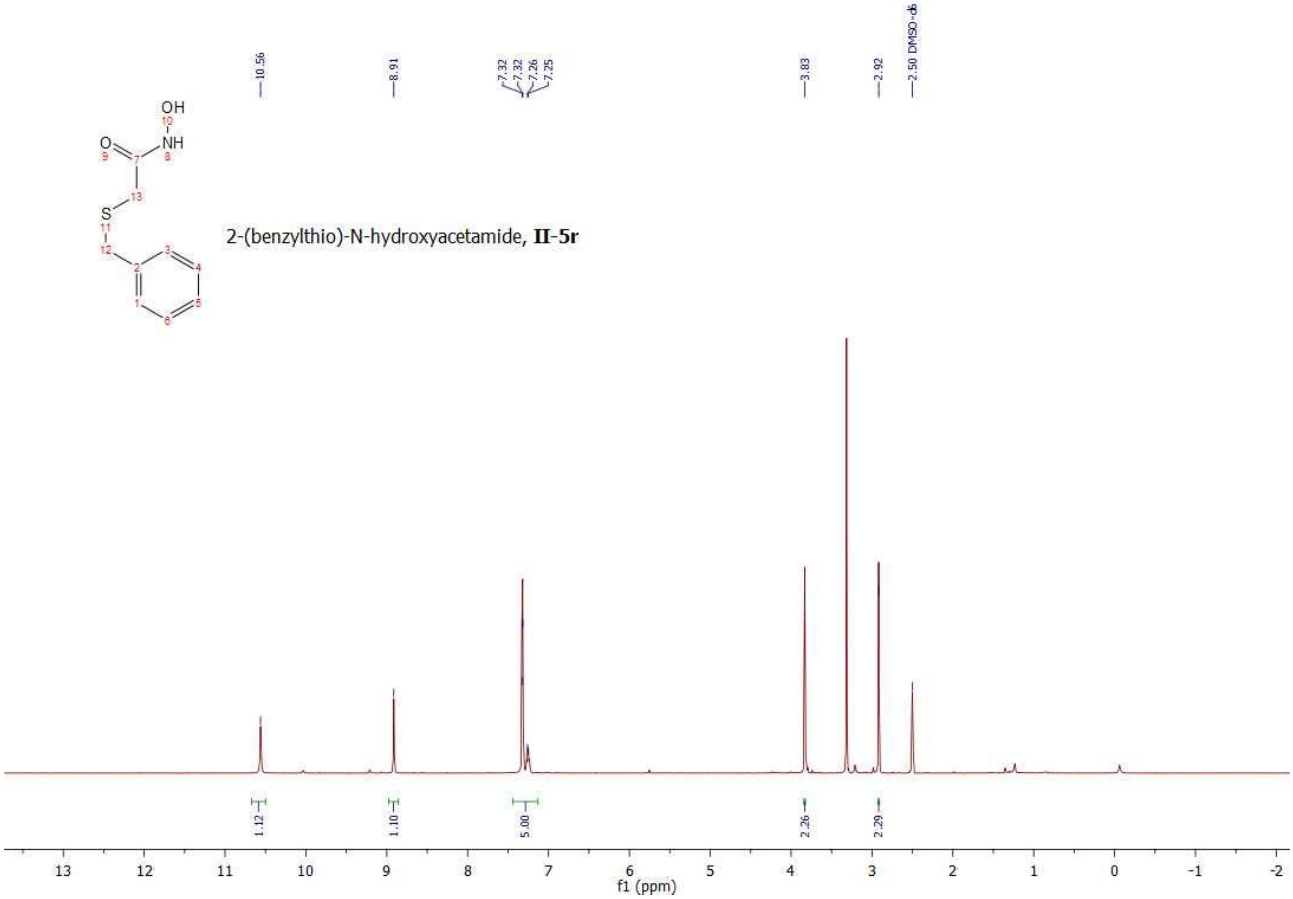
N-hydroxy-2-(4-nitrophenyl)acetamide, **20**

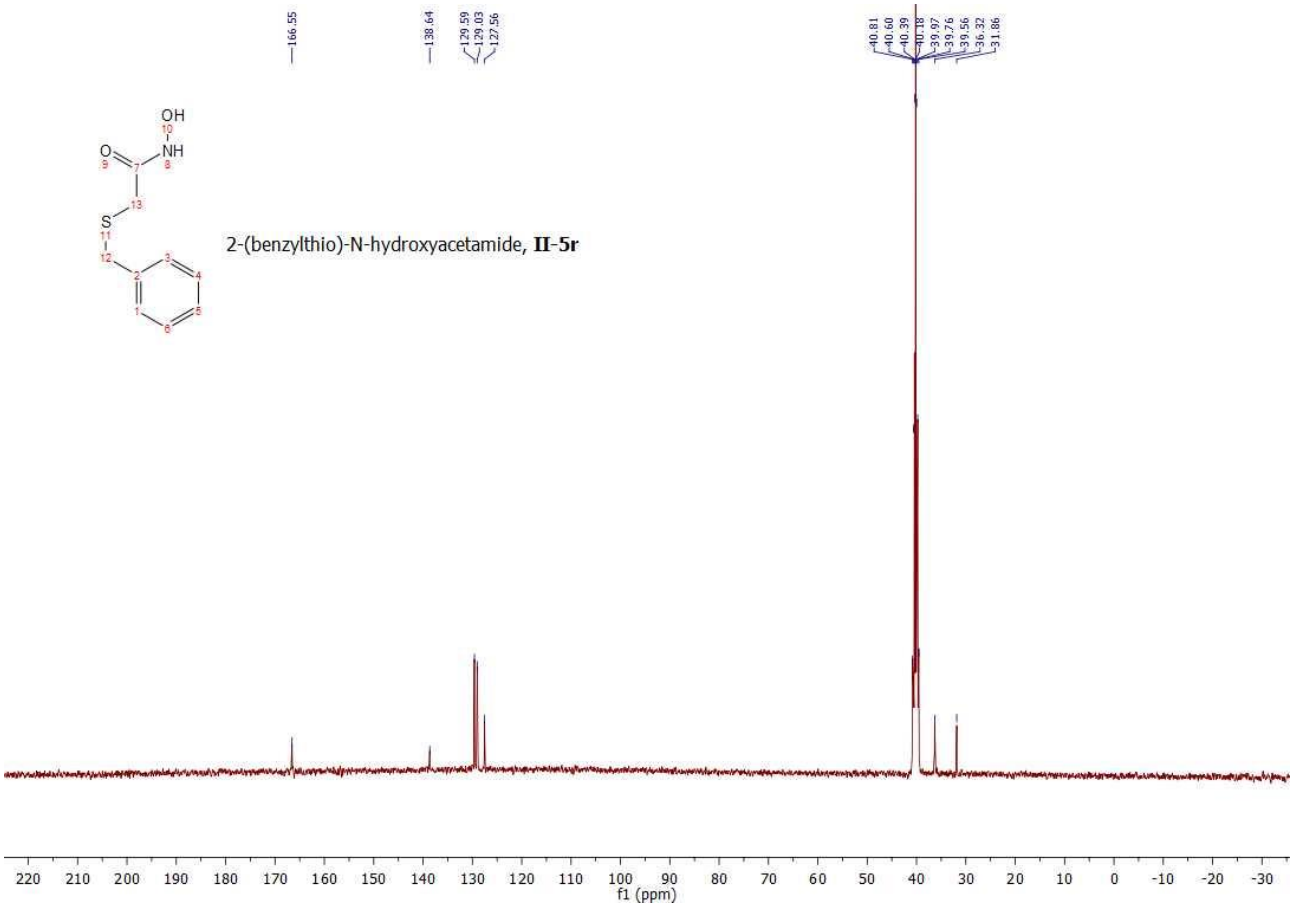


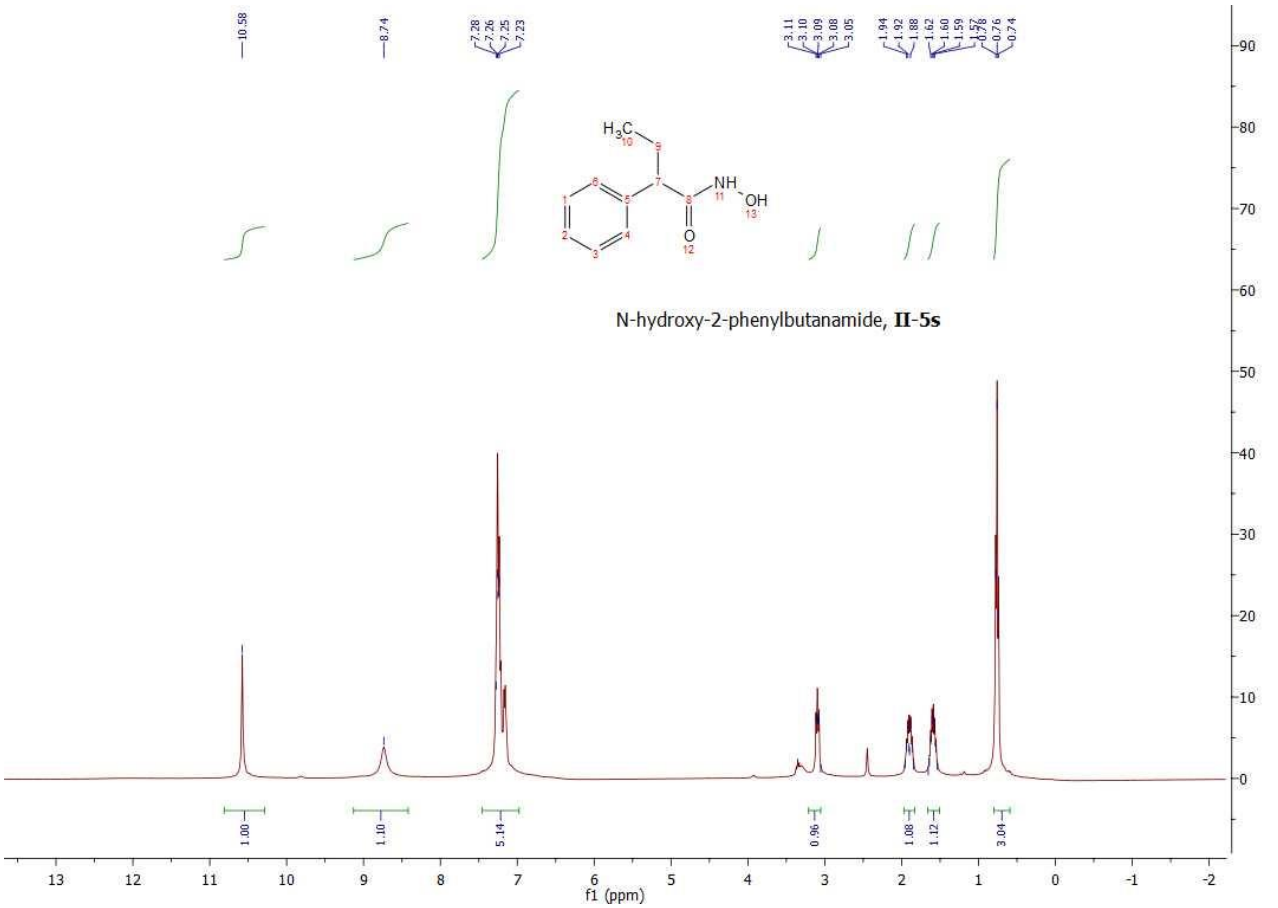
N-hydroxy-2-phenoxyacetamide, **II-5q**



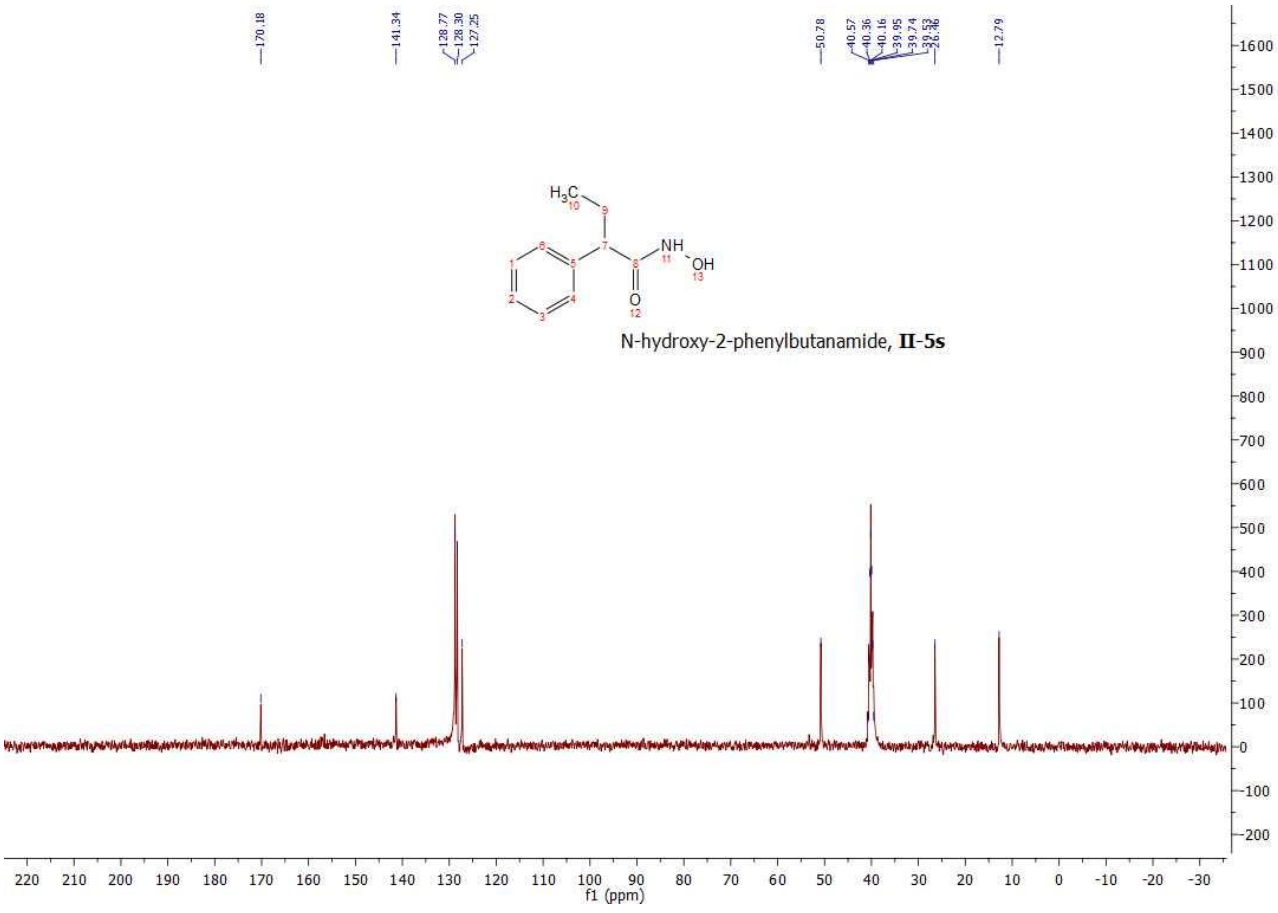
N-hydroxy-2-phenoxyacetamide, **II-5q**


10.56
8.91
7.32
7.32
7.26
7.25
3.83
2.92
2.50 DMSO-d6
OH
NH
O
S
2-(benzylthio)-N-hydroxyacetamide, II-5r
1.12
1.10
5.00
2.26
2.29
f1 (ppm)

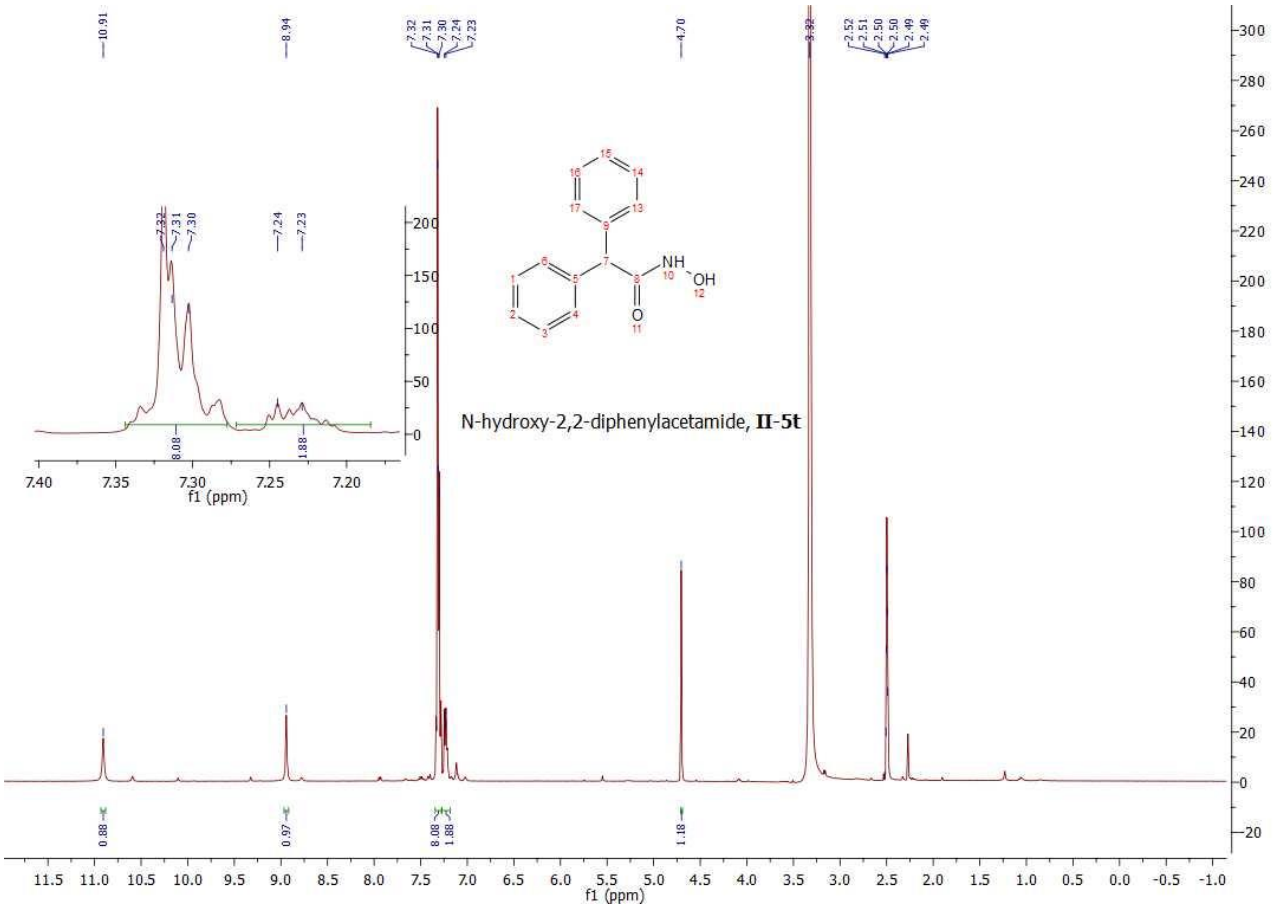

166.55
138.64
129.59
129.03
127.56
40.81
40.60
40.39
40.18
39.97
39.76
39.56
36.32
31.86
OH
NH
O
S
2-(benzylthio)-N-hydroxyacetamide, II-5r
f1 (ppm)

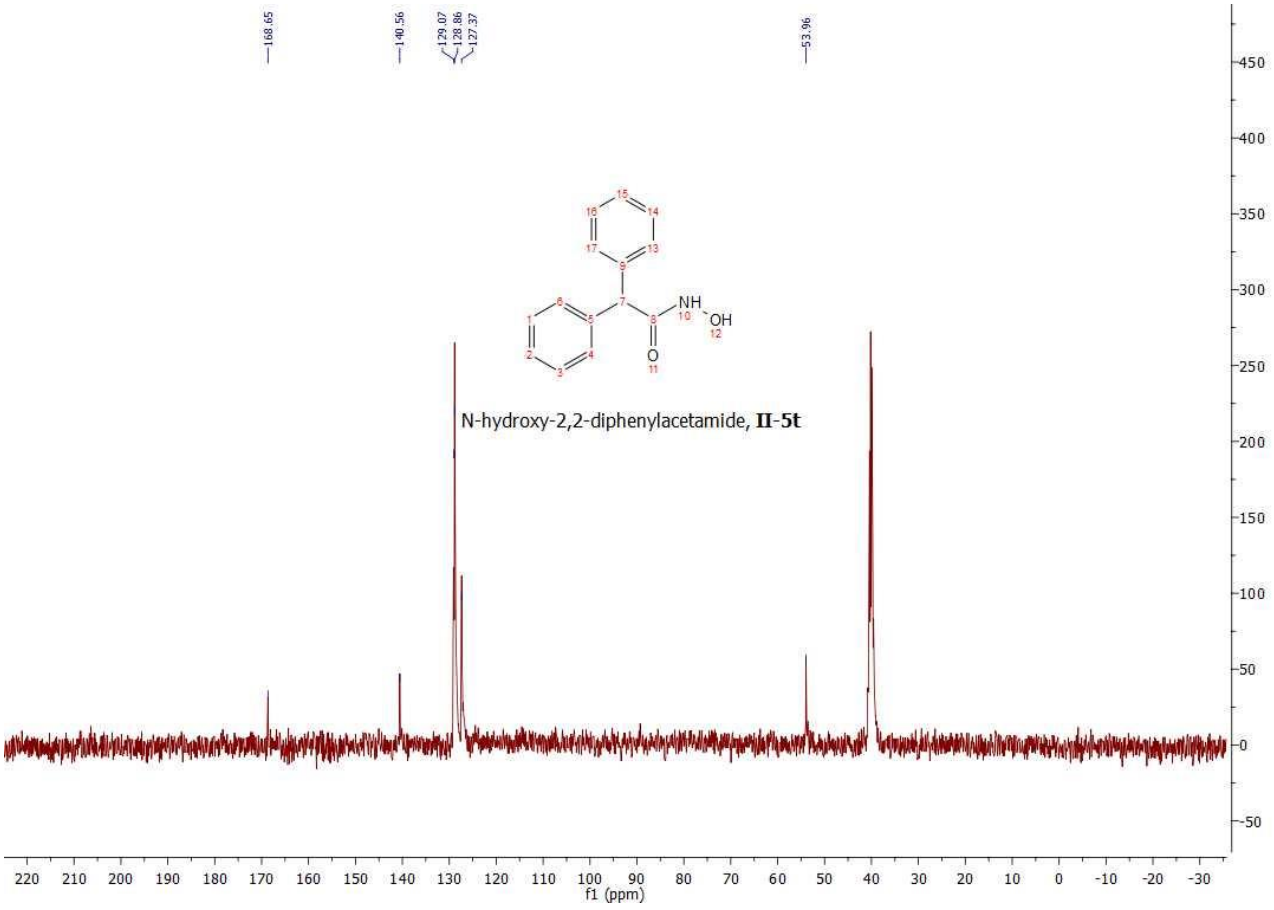


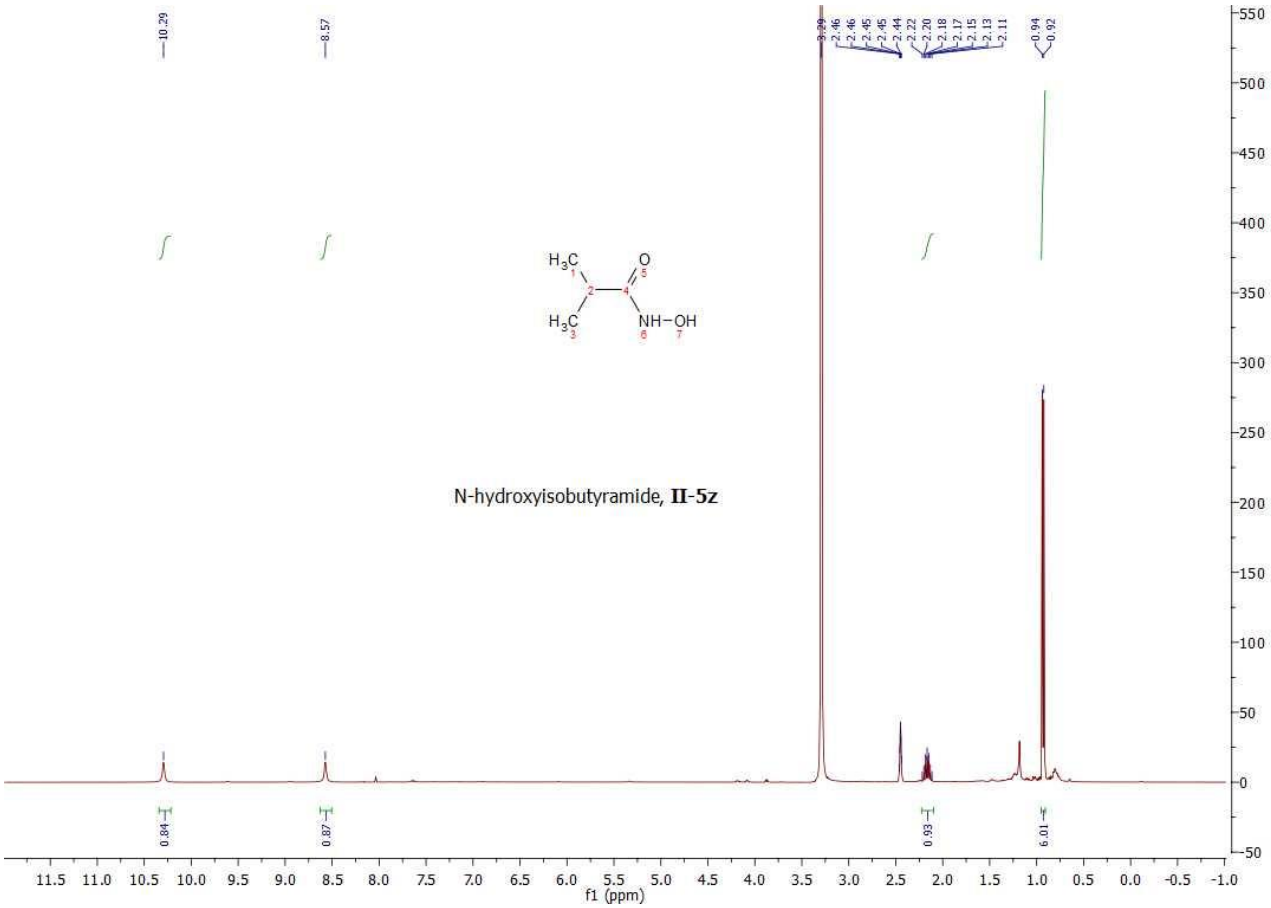
N-hydroxy-2-phenylbutanamide, **II-5s**



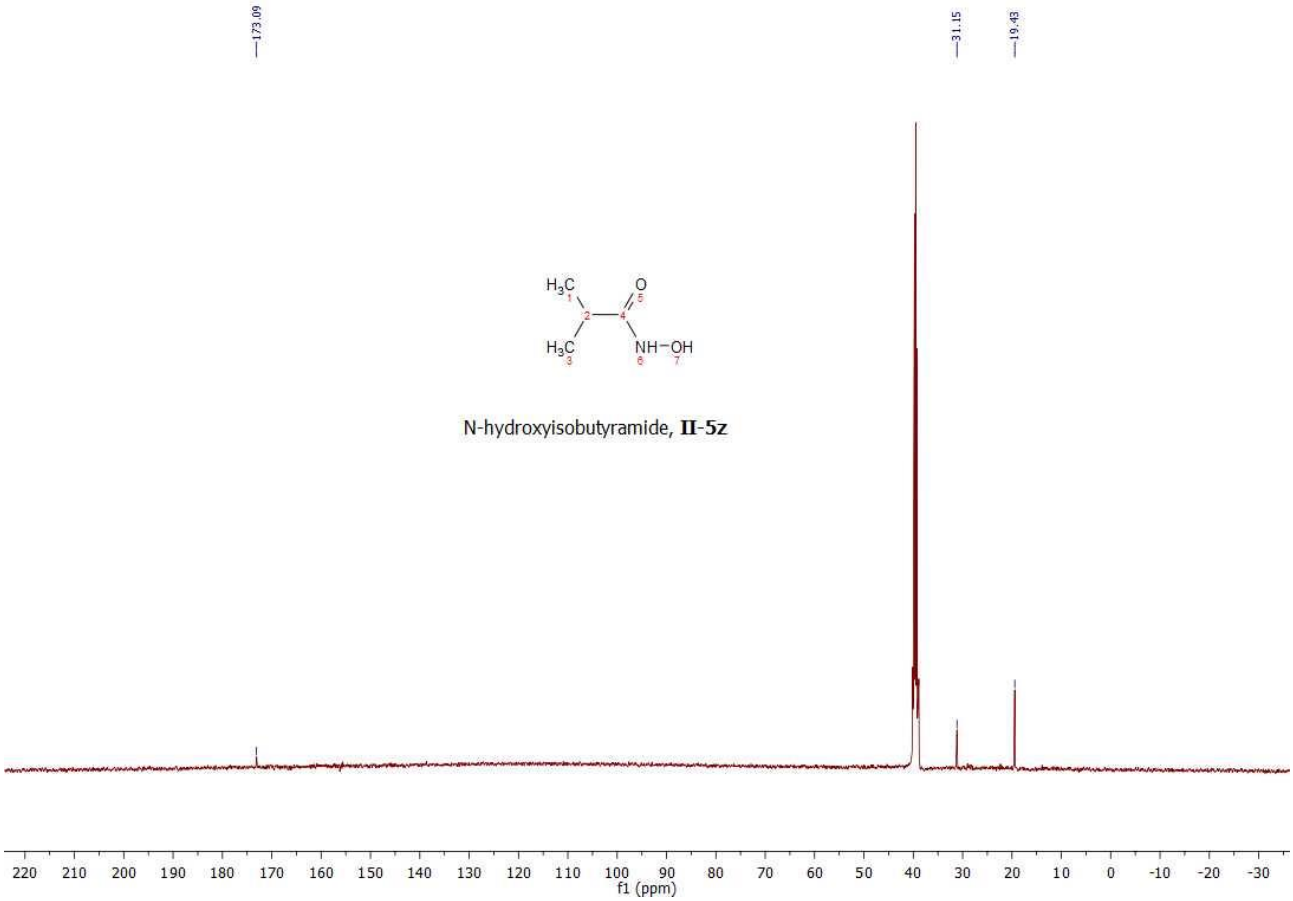
N-hydroxy-2-phenylbutanamide, **II-5s**


10.91
8.94
7.32
7.31
7.30
7.24
7.23
4.70
3.32
2.52
2.51
2.50
2.50
2.49
2.49
N-hydroxy-2,2-diphenylacetamide, II-5t
f1 (ppm)

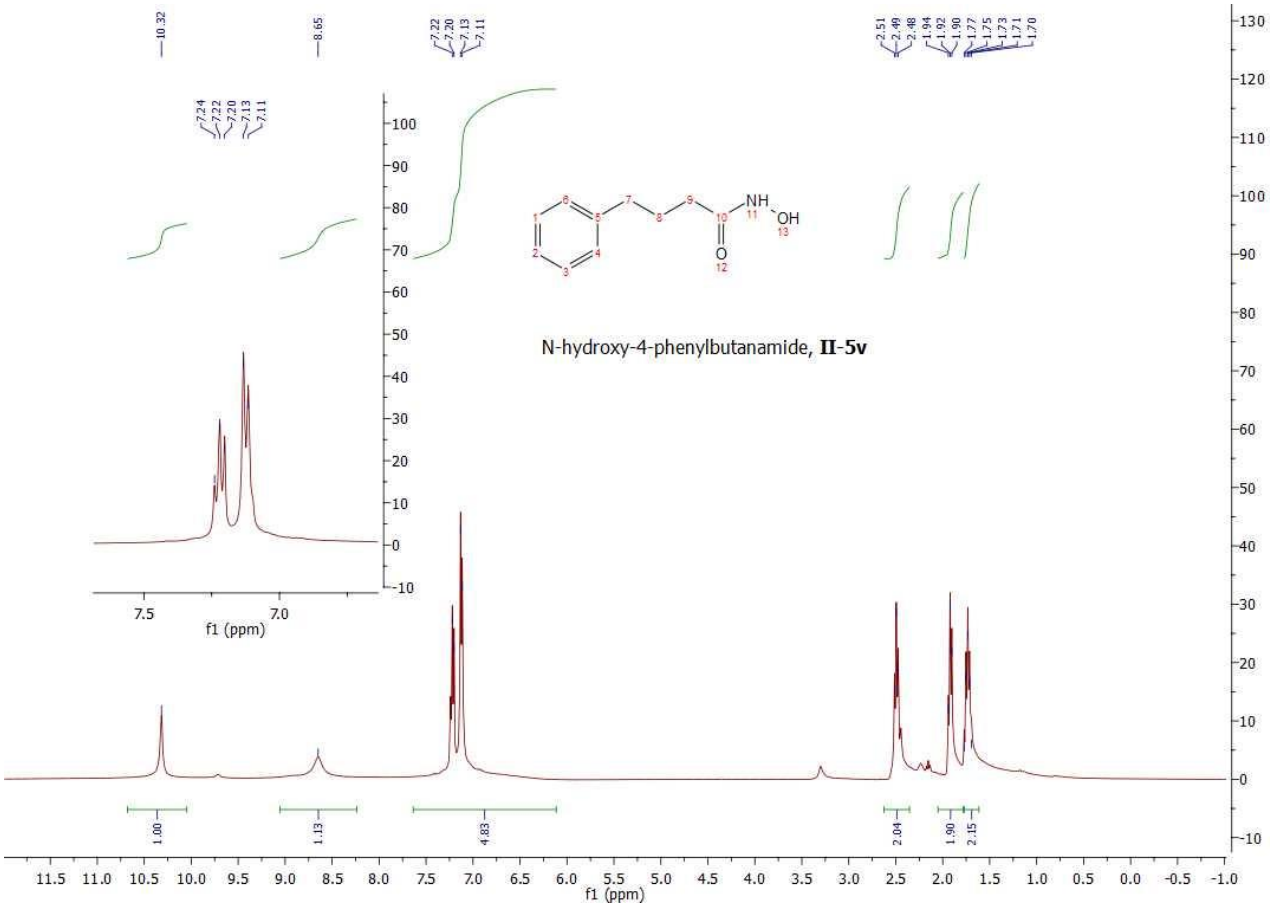

168.65
140.56
129.07
128.86
127.37
53.96
N-hydroxy-2,2-diphenylacetamide, II-5t
f1 (ppm)

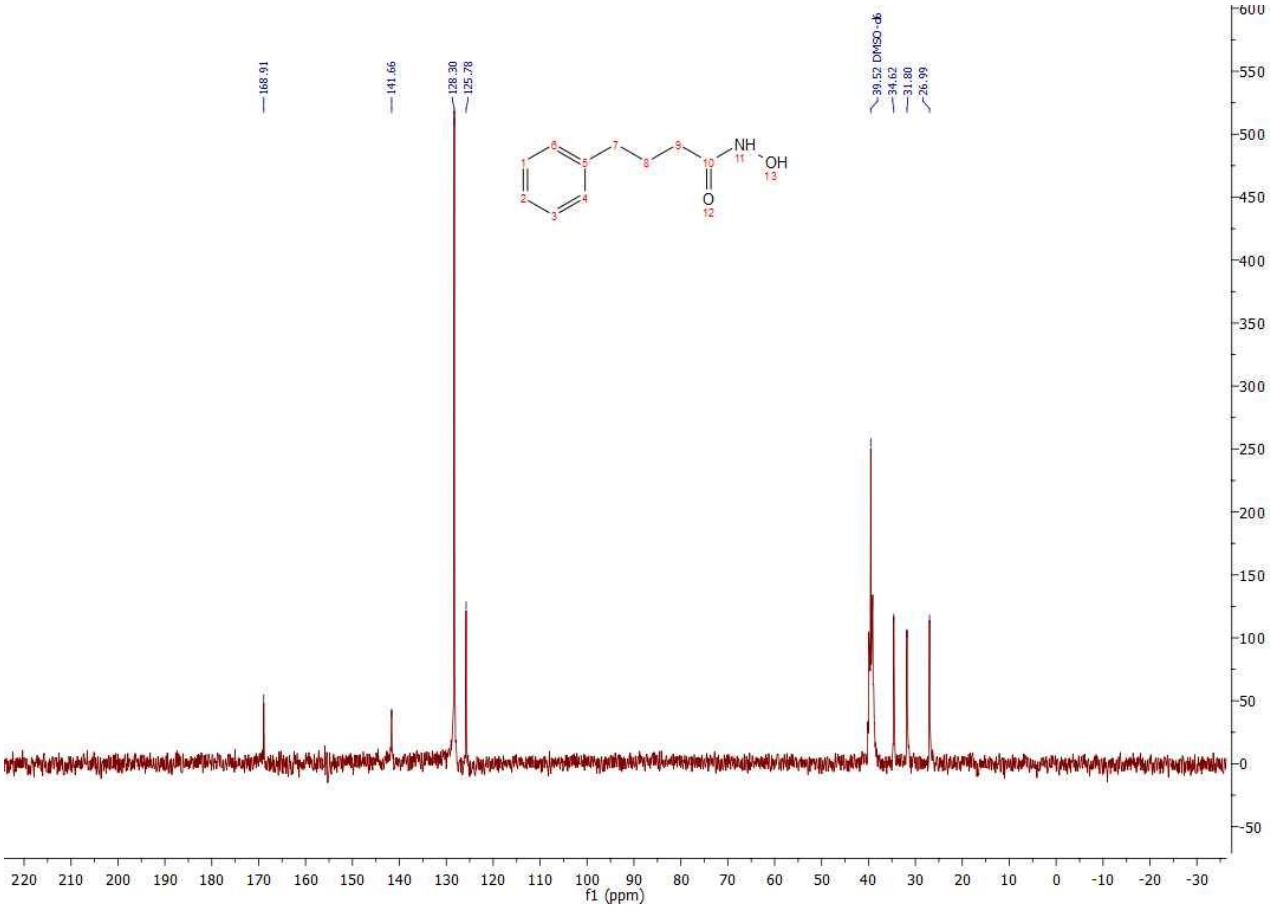


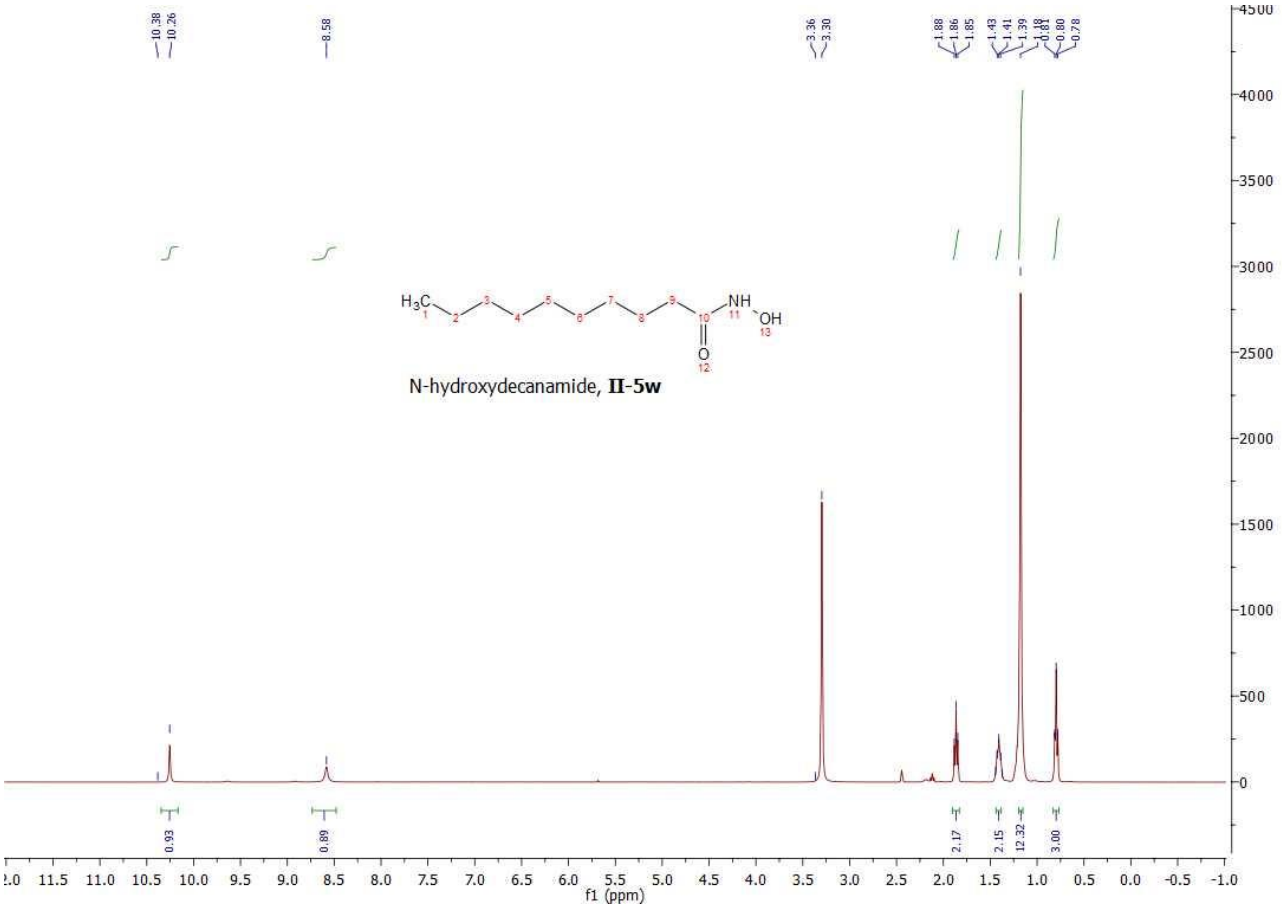
N-hydroxyisobutyramide, **II-5z**

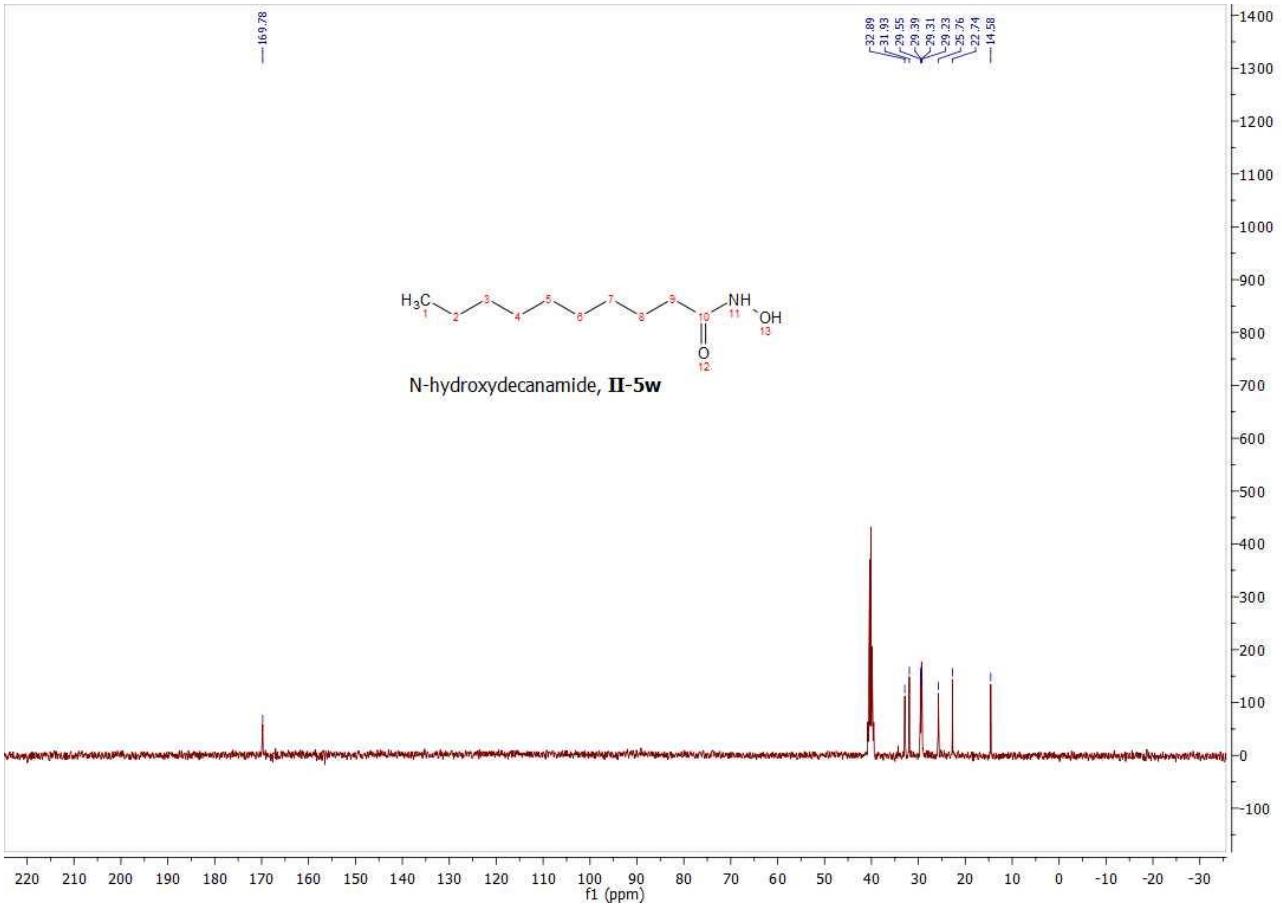


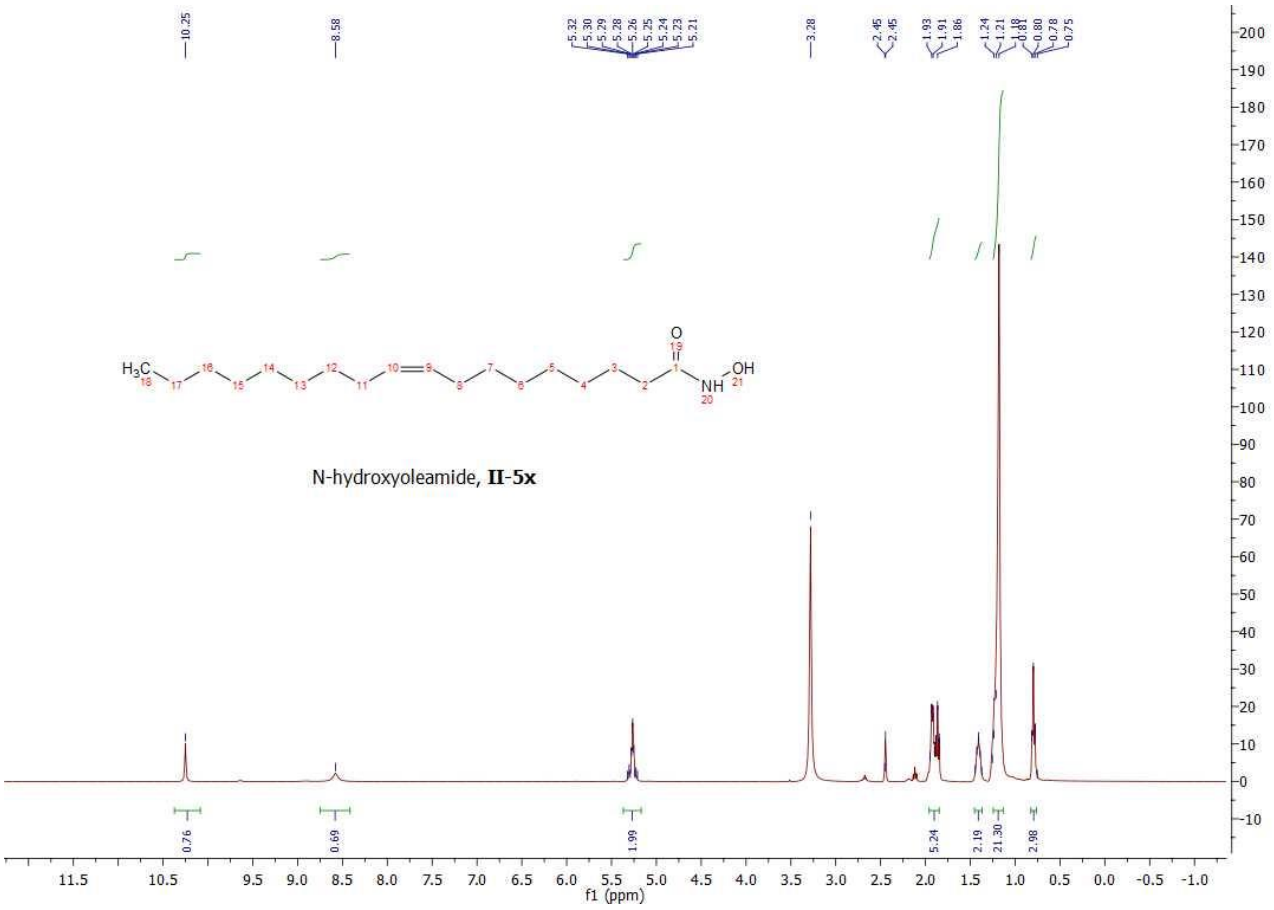
N-hydroxyisobutyramide, **II-5z**


10.32
8.65
7.22
7.20
7.13
7.11
2.51
2.49
2.48
1.94
1.92
1.90
1.77
1.75
1.73
1.71
1.70
7.24
7.22
7.20
7.13
7.11
NH
OH
O
N-hydroxy-4-phenylbutanamide, II-5v
f1 (ppm)
1.00
1.13
4.83
2.04
1.90
2.15
f1 (ppm)

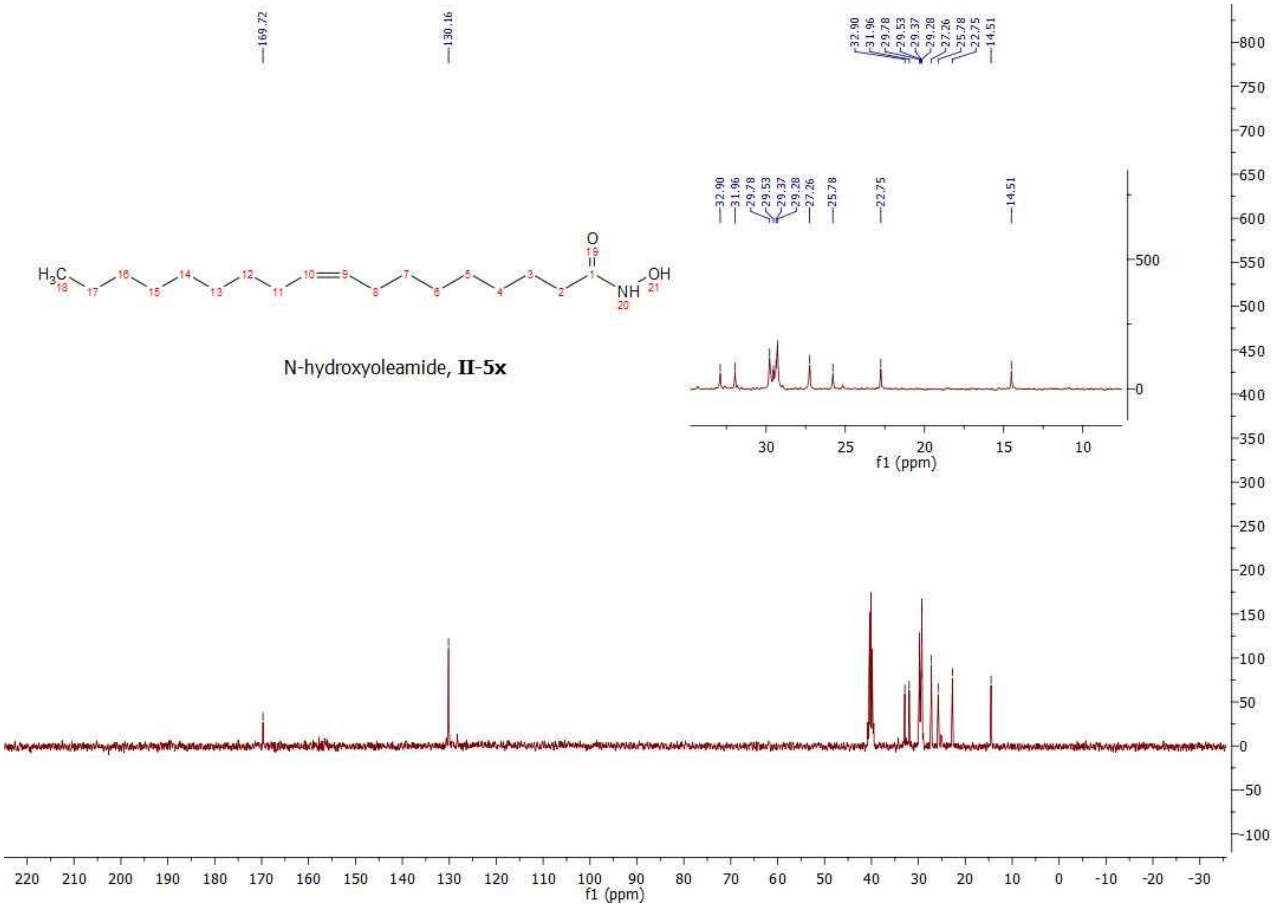

168.91
141.66
128.30
125.78
39.52 DMSO-d6
34.62
31.80
26.99
NH
OH
O
f1 (ppm)


10.38
10.26
8.58
3.36
3.30
1.88
1.86
1.85
1.43
1.41
1.39
0.88
0.80
0.78
N-hydroxydecanamide, II-5w
0.93
0.89
2.17
2.15
12.32
3.00
f1 (ppm)

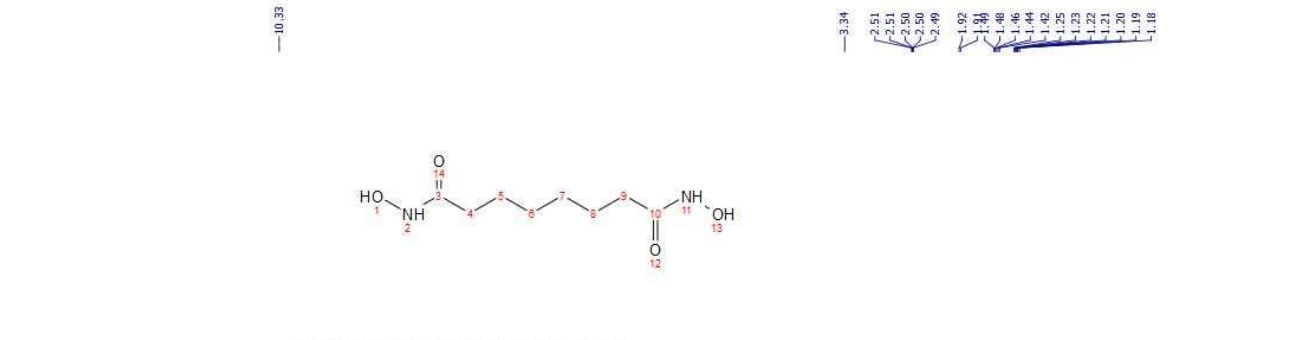

169.78
32.89
31.93
29.55
29.39
29.31
29.23
25.76
22.74
14.58
N-hydroxydecanamide, II-5w
f1 (ppm)



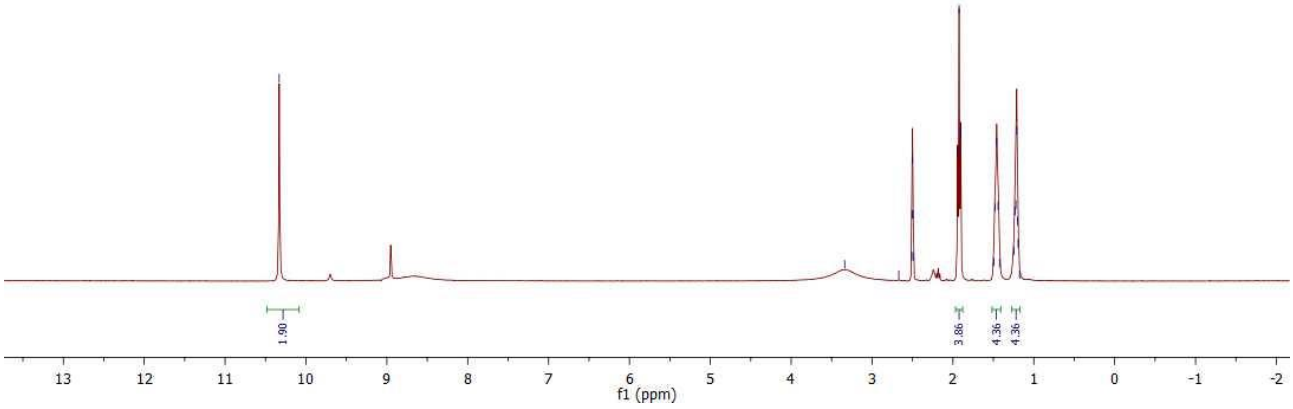
N-hydroxyoleamide, **II-5x**

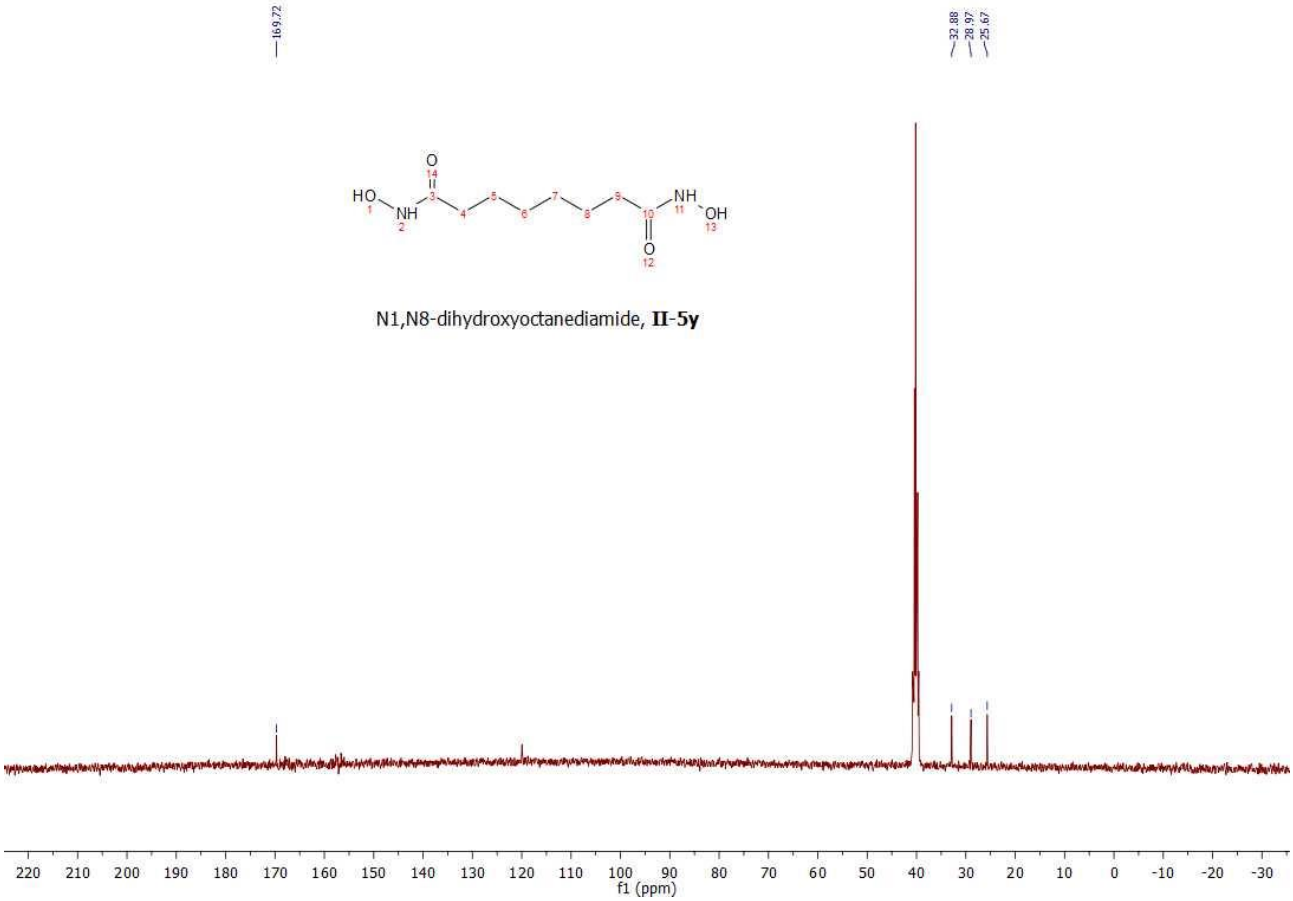


N-hydroxyoleamide, **II-5x**

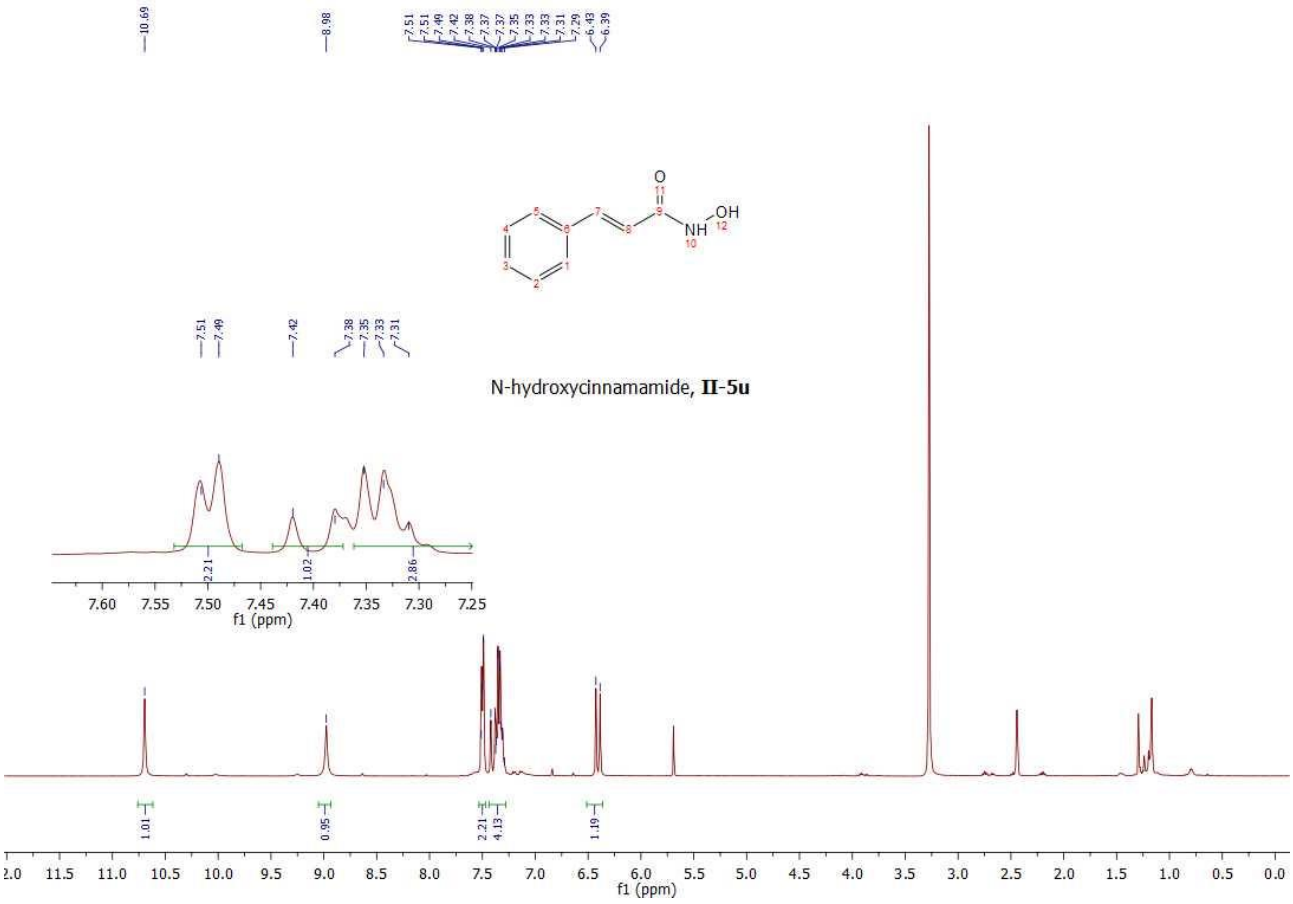


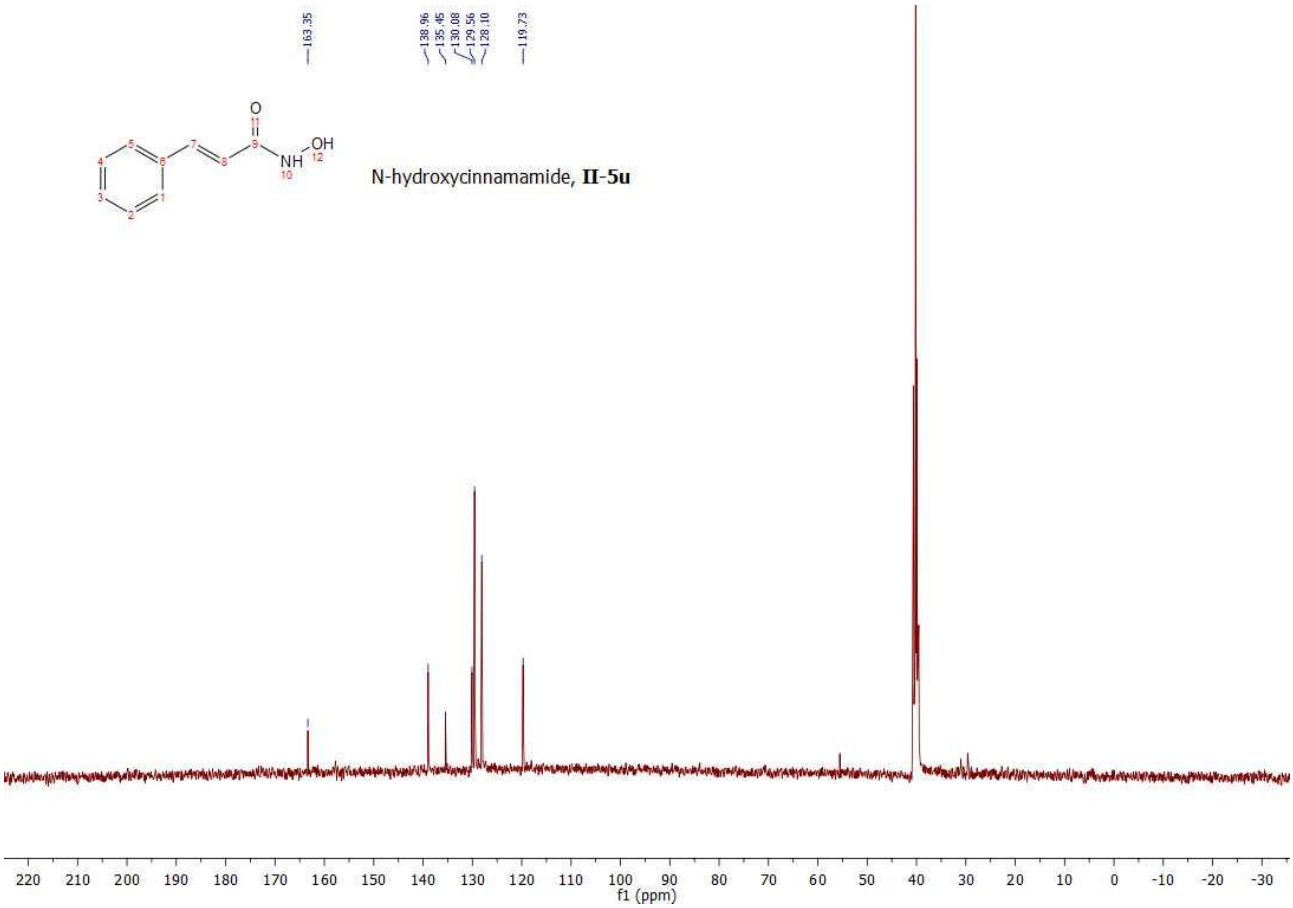
N1,N8-dihydroxyoctanediamide, **II_5y**

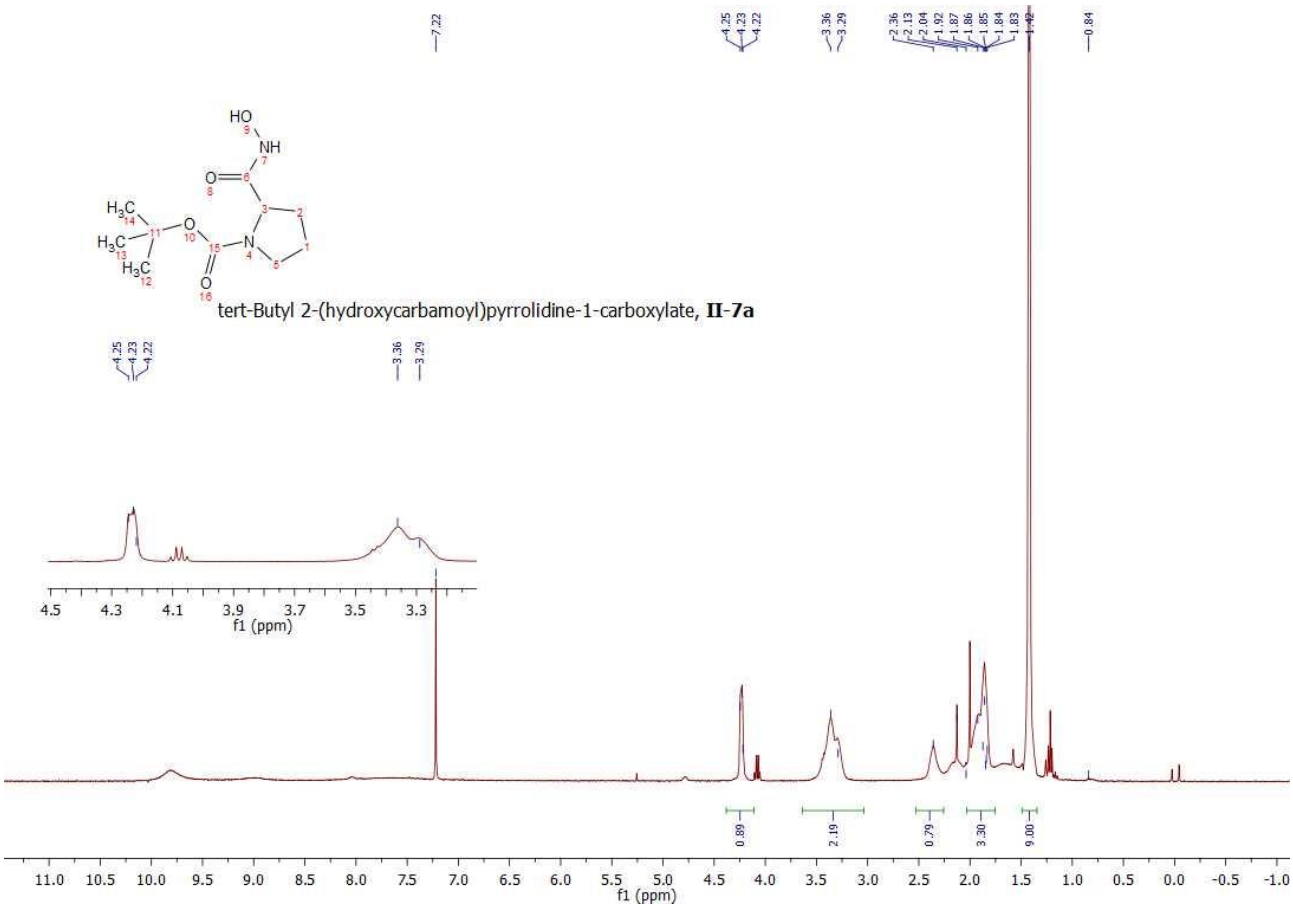


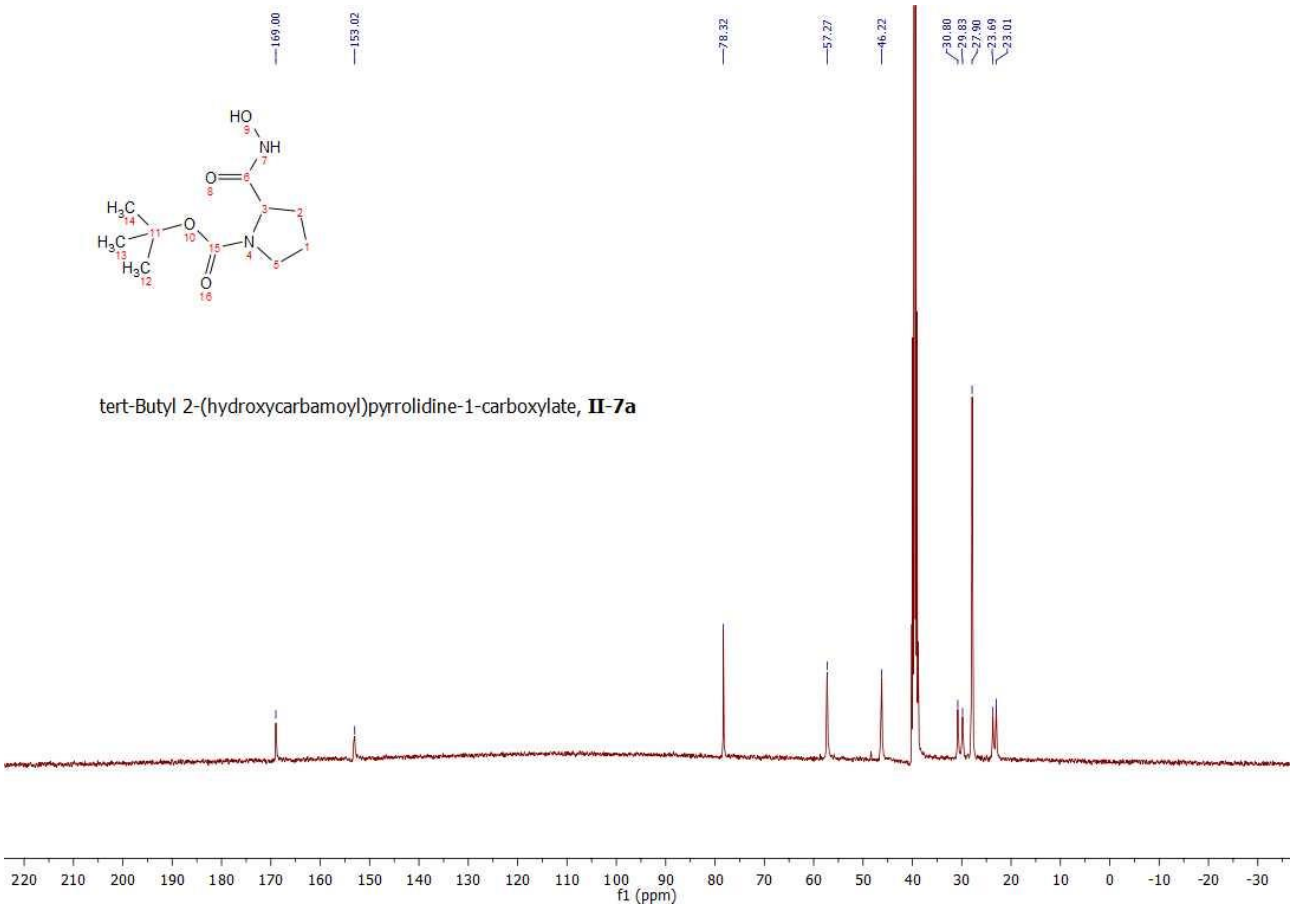


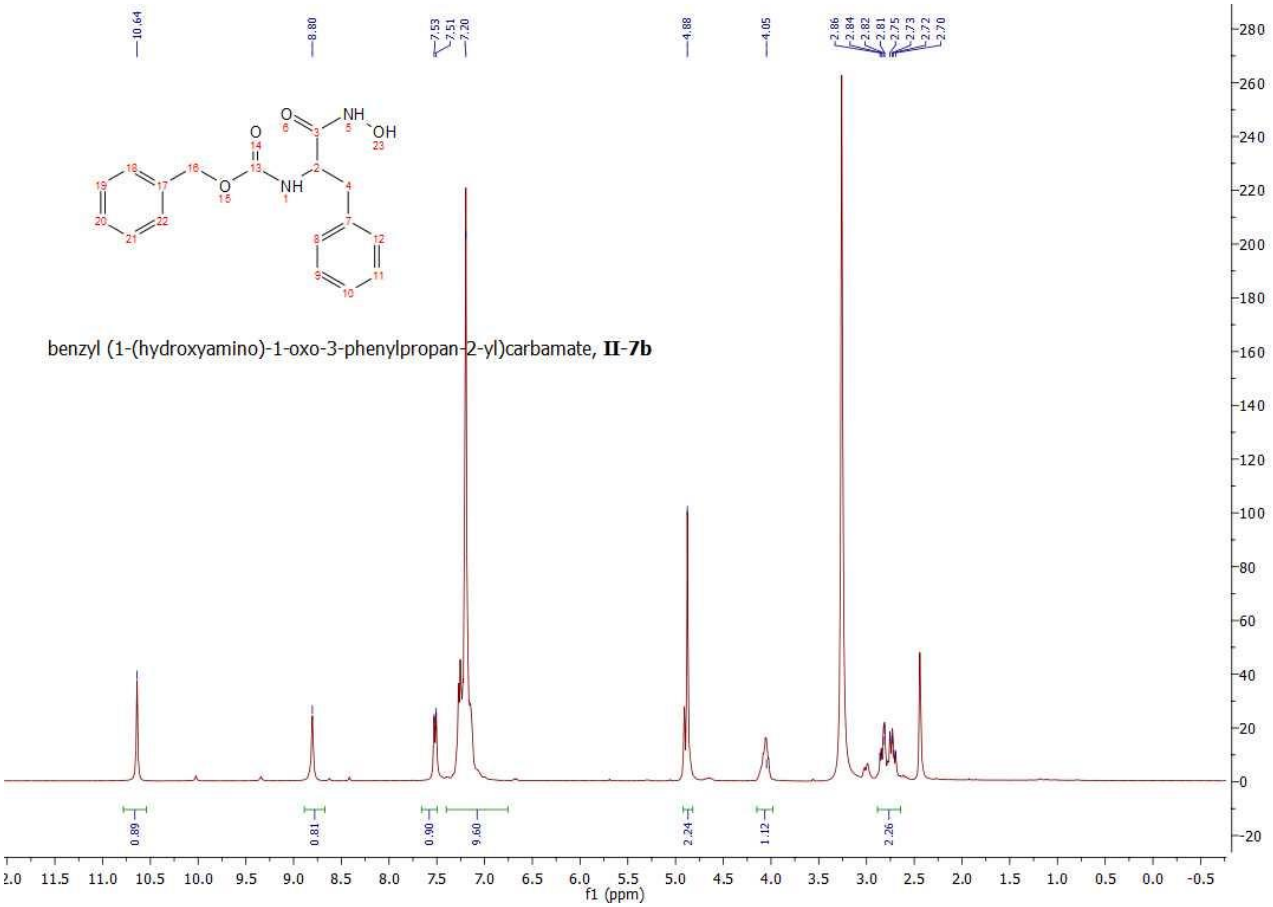
N1,N8-dihydroxyoctanediamide, **II-5y**

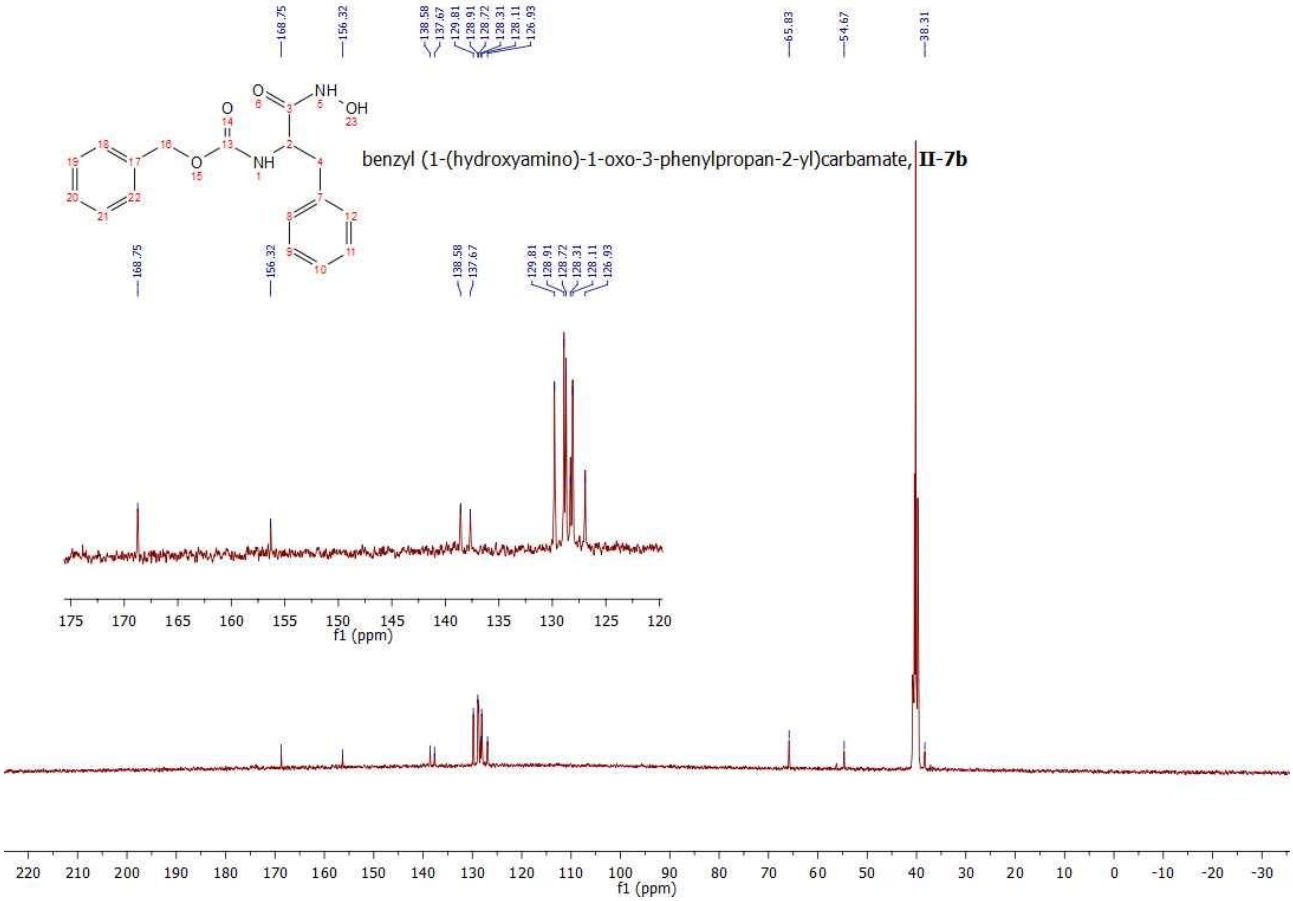

10.69
8.98
7.51
7.51
7.49
7.42
7.38
7.37
7.35
7.33
7.31
7.29
6.43
6.39
O
11
9
NH
10
OH
12
N-hydroxycinnamamide, II-5u
2.21
1.02
2.86
7.60 7.55 7.50 7.45 7.40 7.35 7.30 7.25
f1 (ppm)
1.01
0.95
2.21
4.13
1.19
f1 (ppm)

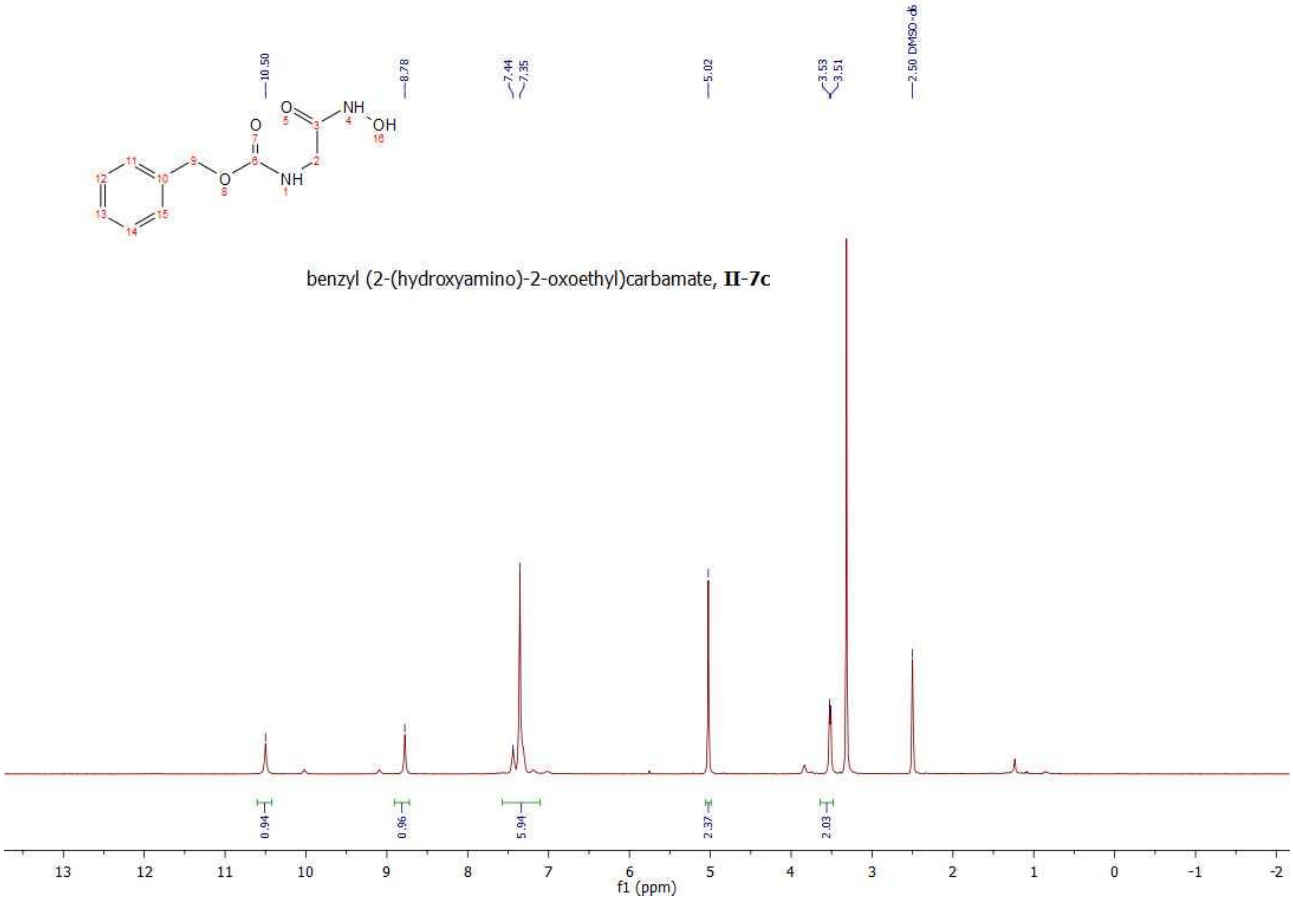

163.35
138.96
135.45
130.08
129.56
128.10
119.73
O
11
9
NH
10
OH
12
N-hydroxycinnamamide, II-5u
f1 (ppm)

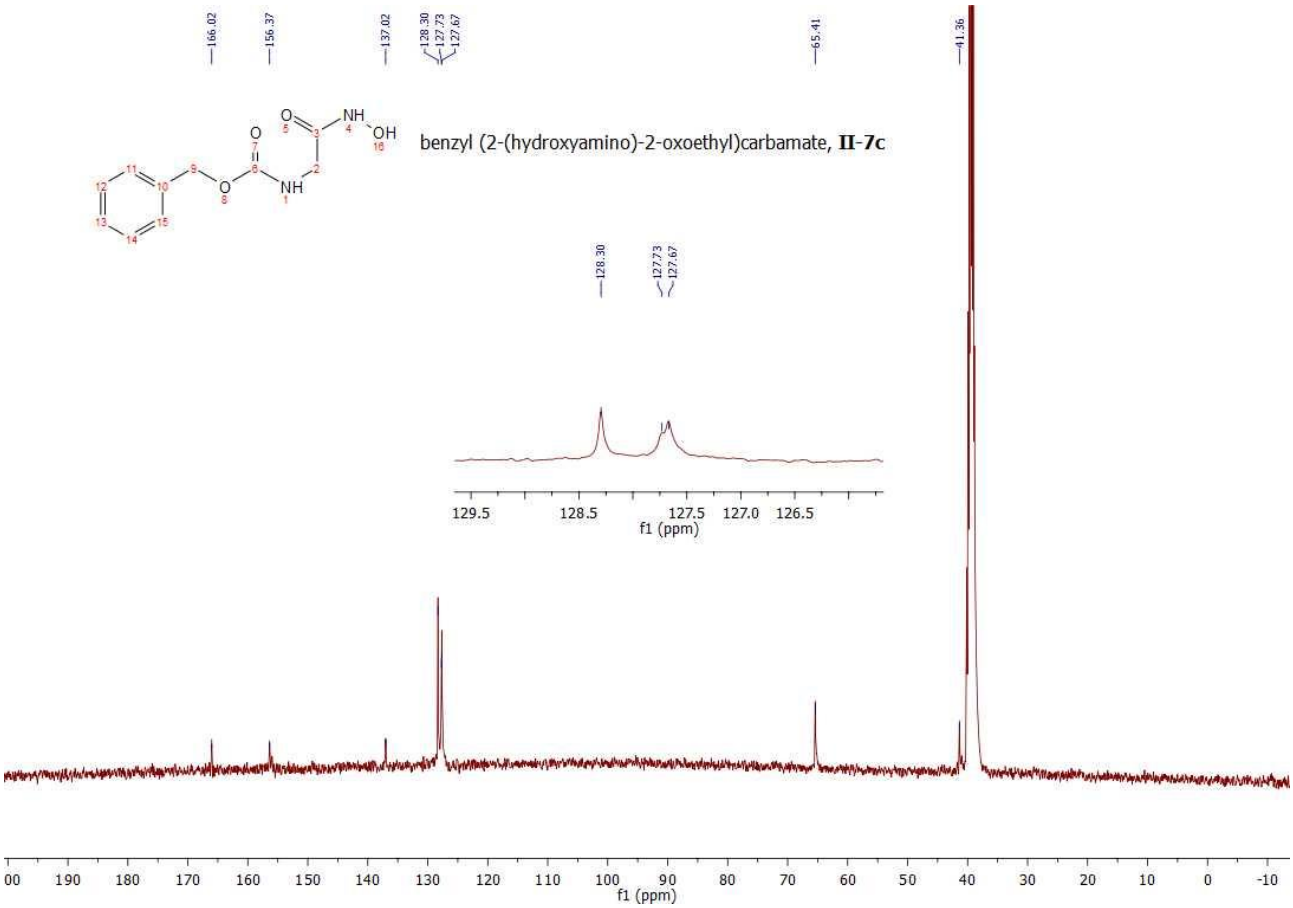

tert-Butyl 2-(hydroxycarbamoyl)pyrrolidine-1-carboxylate, II-7a
f1 (ppm)

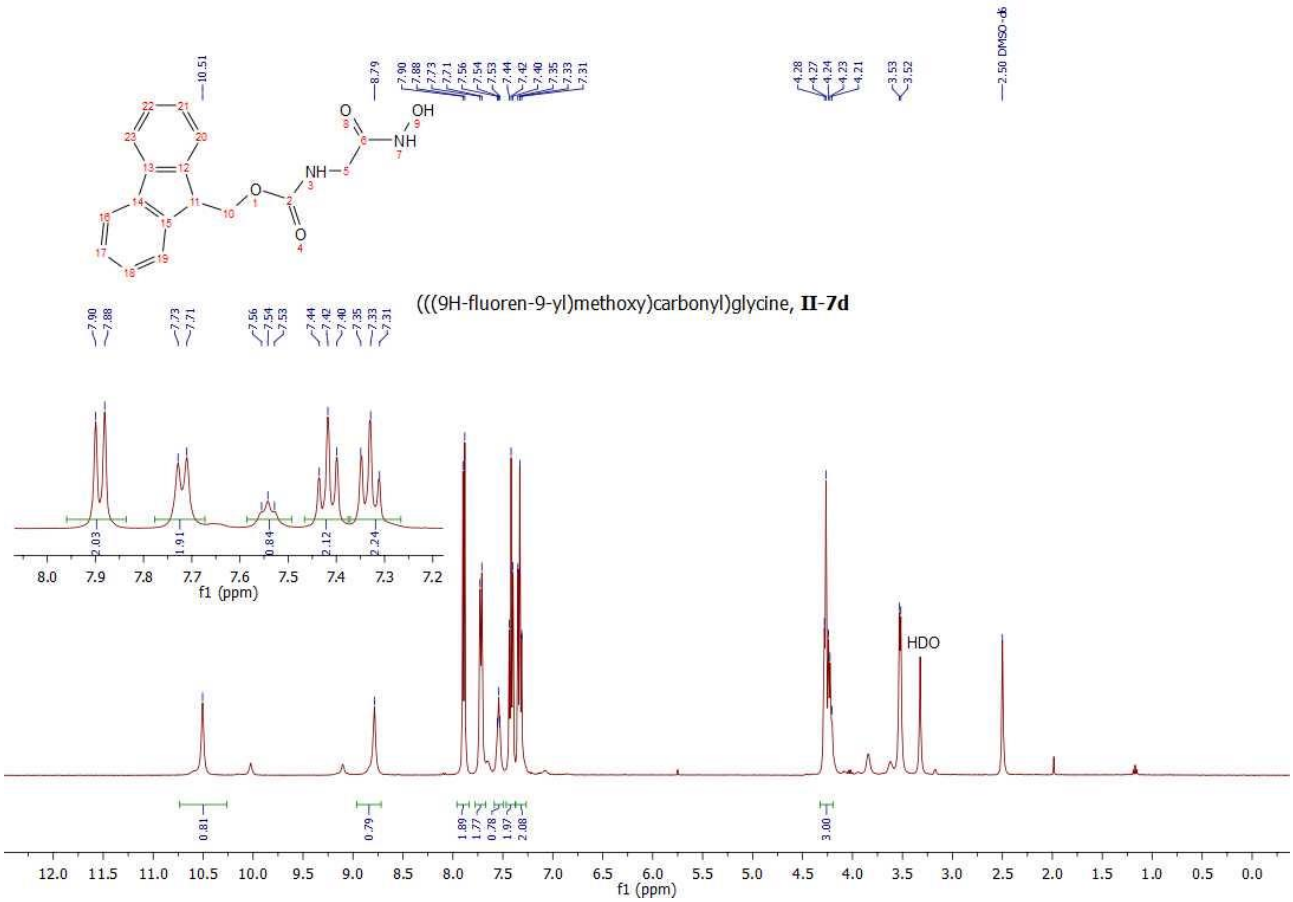

tert-Butyl 2-(hydroxycarbamoyl)pyrrolidine-1-carboxylate, II-7a
f1 (ppm)

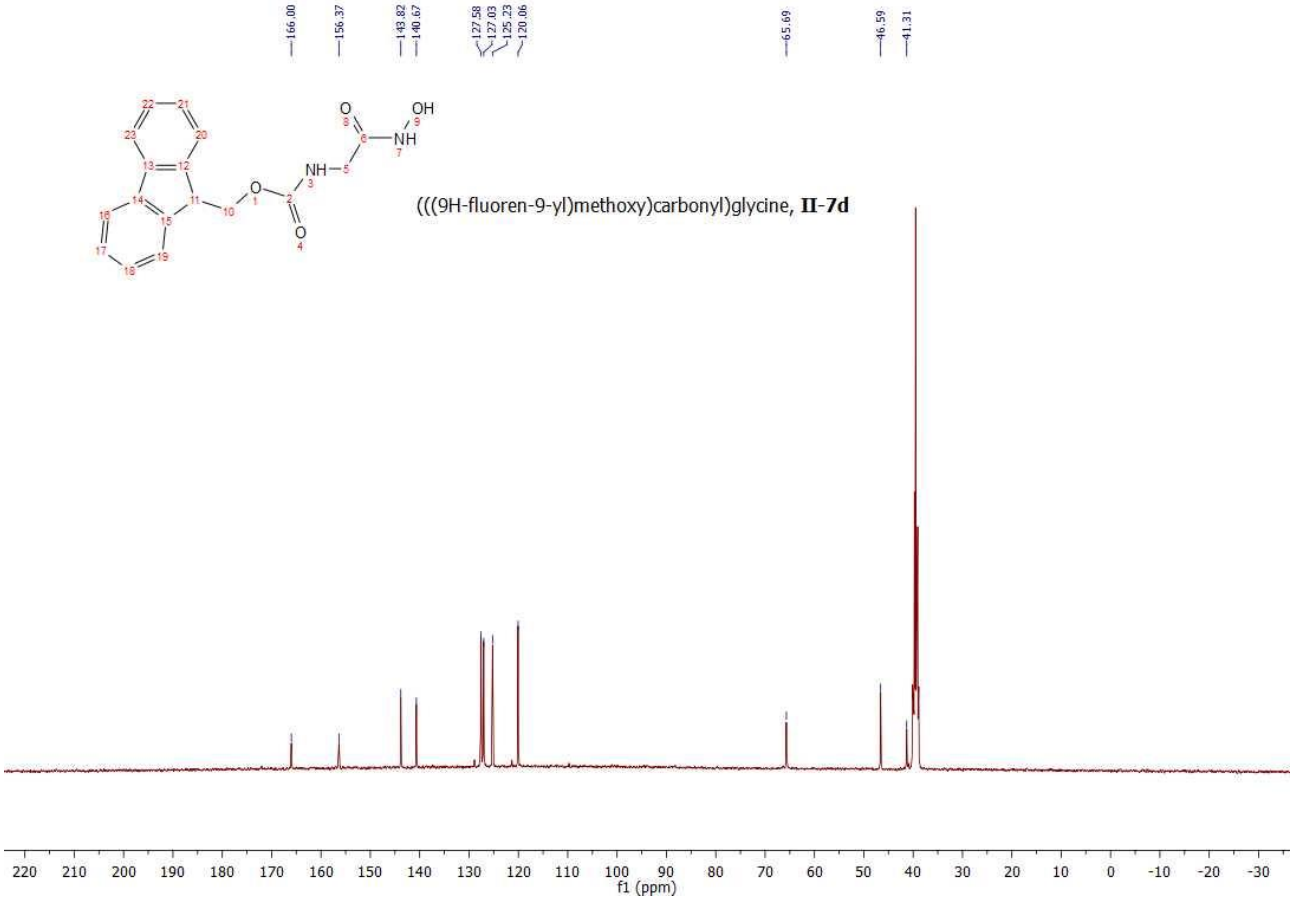

benzyl (1-(hydroxyamino)-1-oxo-3-phenylpropan-2-yl)carbamate, II-7b
f1 (ppm)

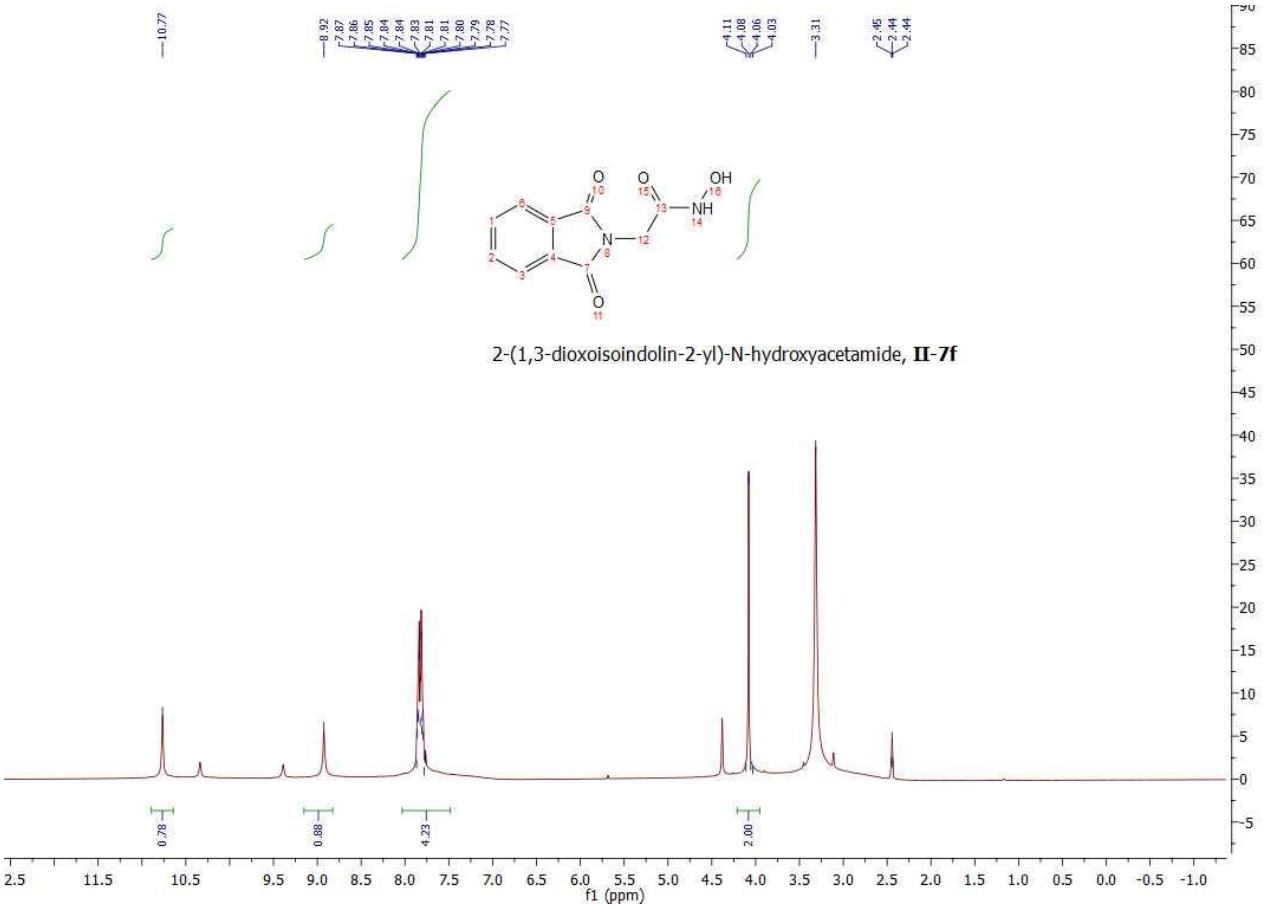

benzyl (1-(hydroxyamino)-1-oxo-3-phenylpropan-2-yl)carbamate, II-7b
f1 (ppm)
f1 (ppm)


benzyl (2-(hydroxyamino)-2-oxoethyl)carbamate, II-7c
f1 (ppm)

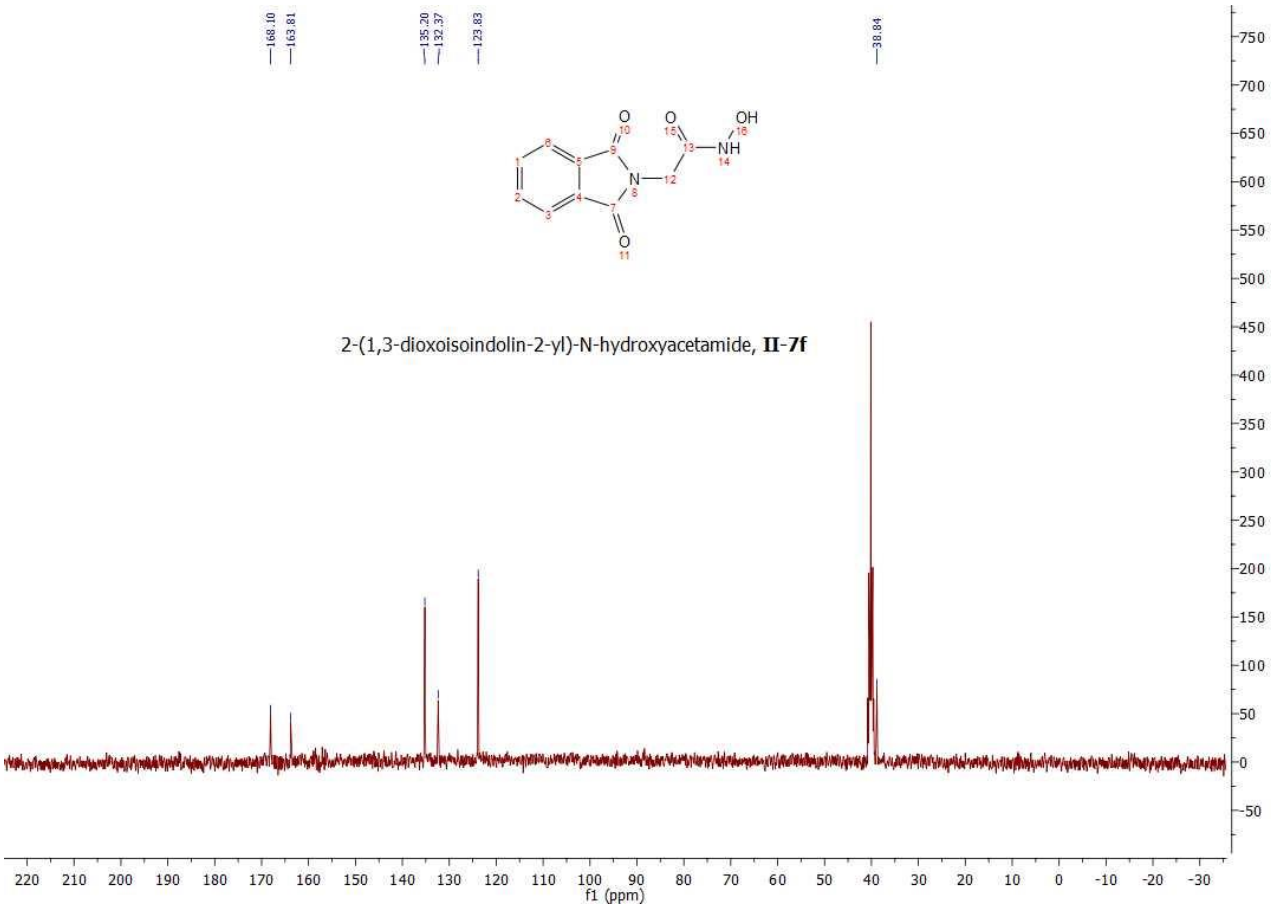

benzyl (2-(hydroxyamino)-2-oxoethyl)carbamate, II-7c
f1 (ppm)


(((9H-fluoren-9-yl)methoxy)carbonyl)glycine, II-7d
HDO
f1 (ppm)

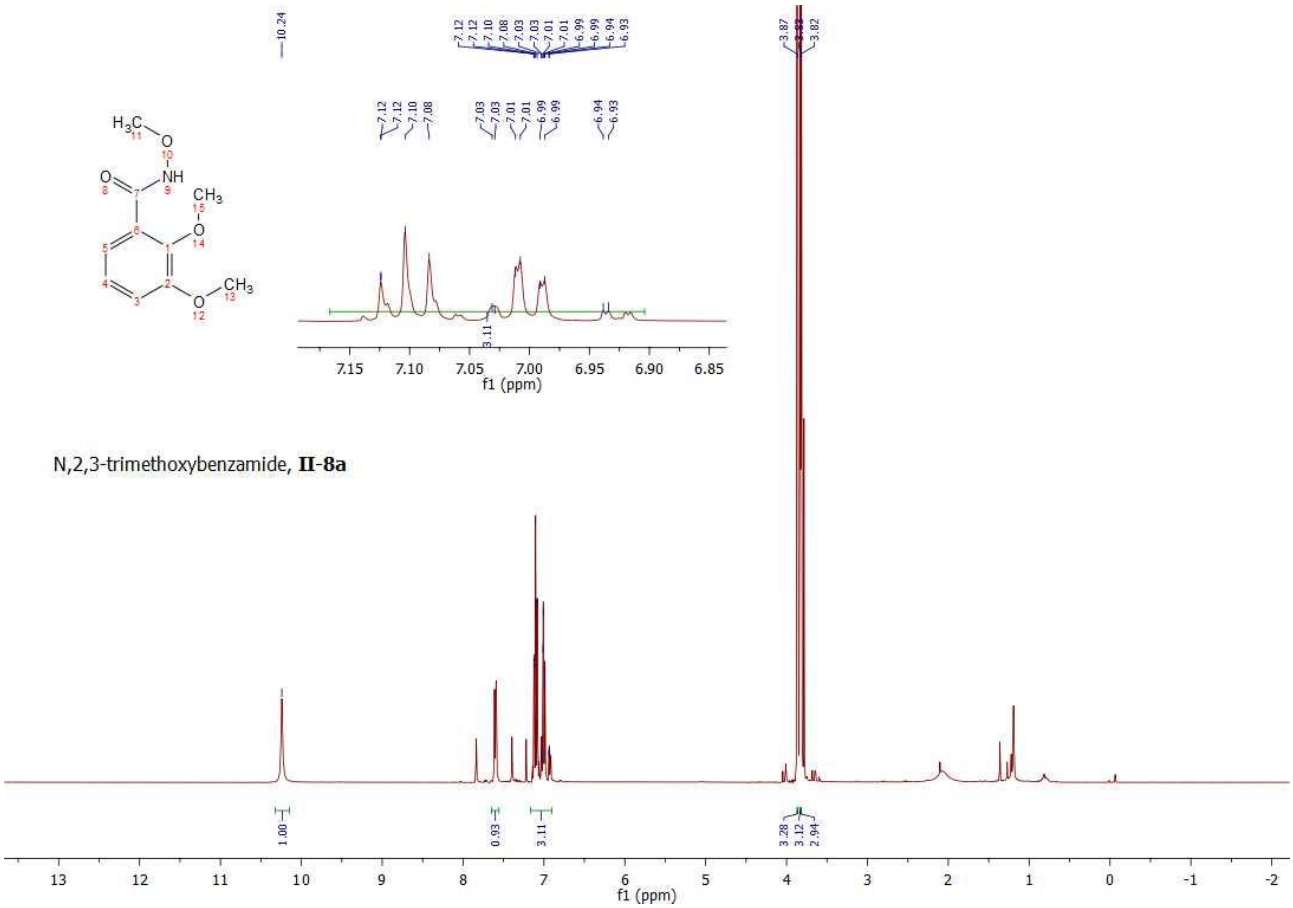

(((9H-fluoren-9-yl)methoxy)carbonyl)glycine, II-7d
f1 (ppm)

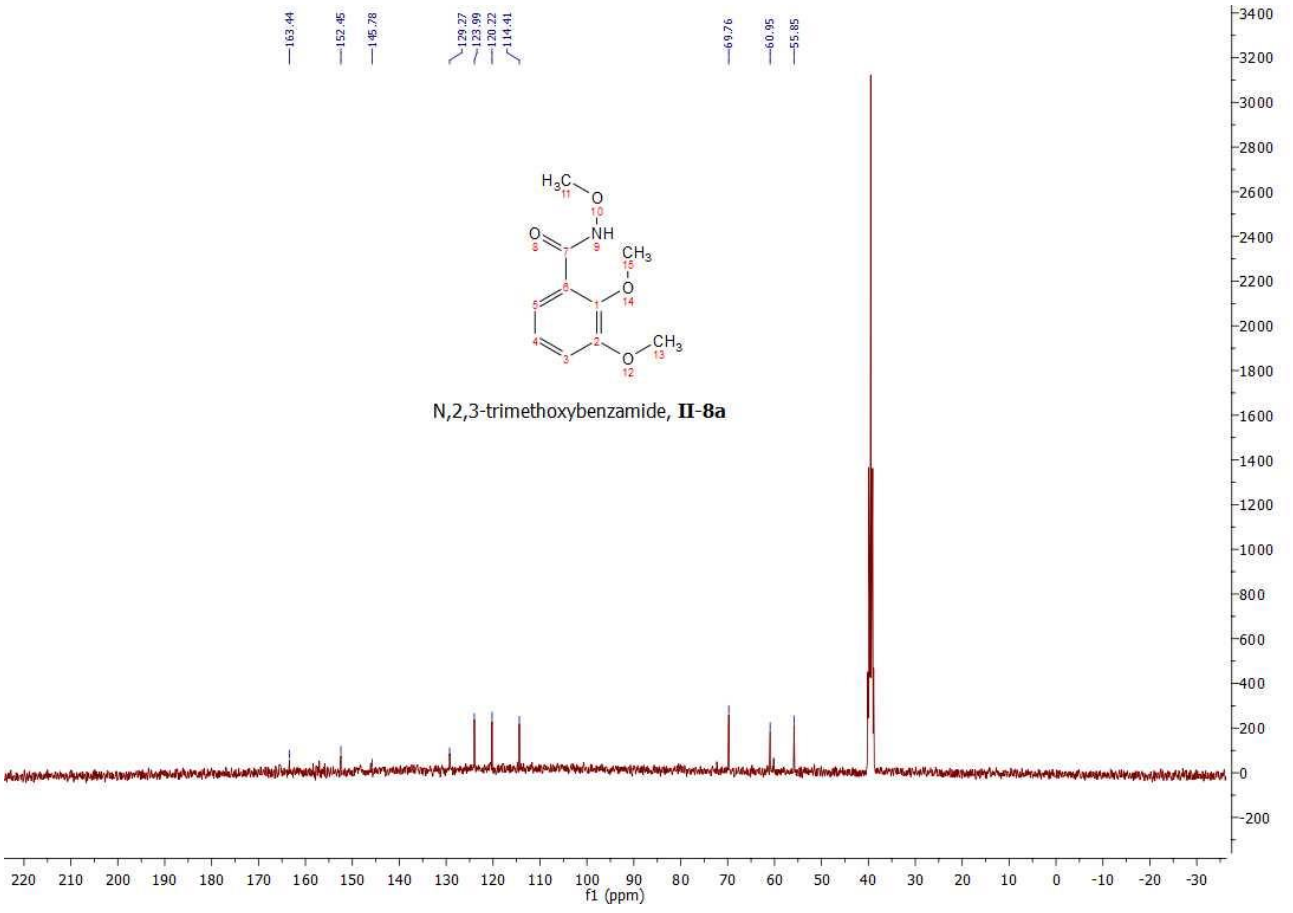


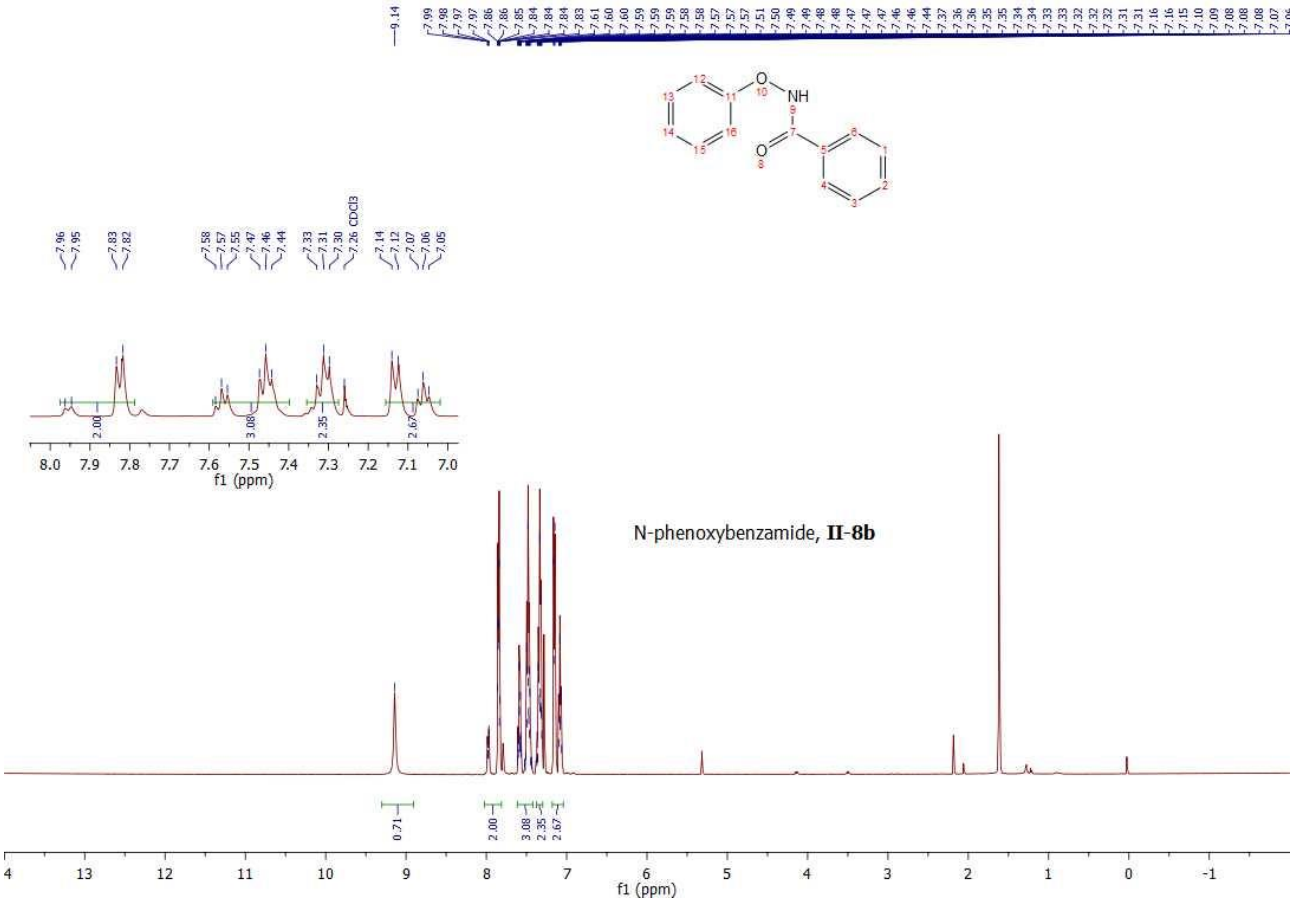
2-(1,3-dioxoisoindolin-2-yl)-N-hydroxyacetamide, **II-7f**



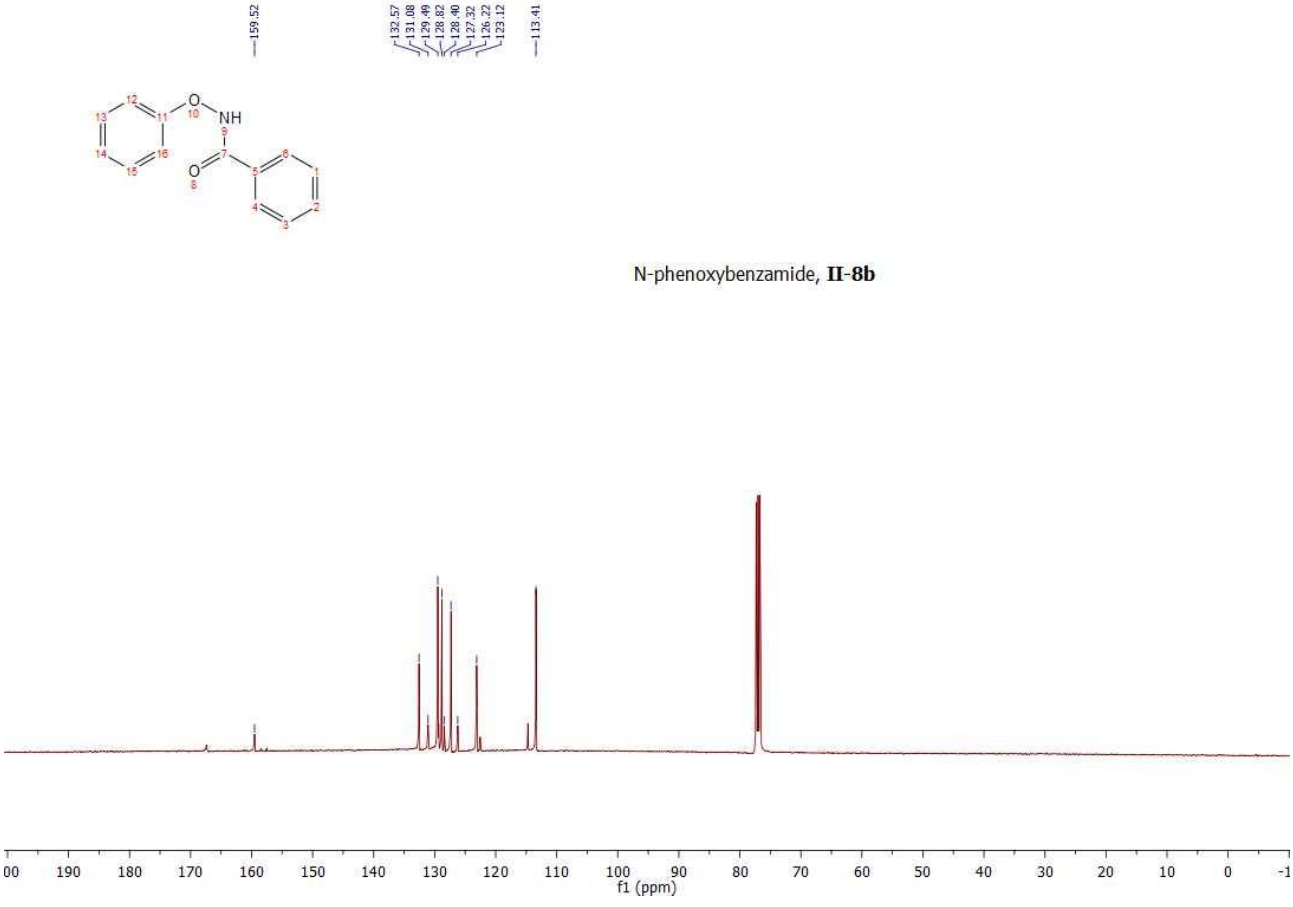
2-(1,3-dioxoisoindolin-2-yl)-N-hydroxyacetamide, **II-7f**


10.24
7.12
7.12
7.10
7.08
7.03
7.03
7.01
7.01
6.99
6.99
6.94
6.93
3.87
3.83
3.82
3.11
7.15
7.10
7.05
7.00
6.95
6.90
6.85
f1 (ppm)
N,2,3-trimethoxybenzamide, II-8a
1.00
0.93
3.11
3.28
3.12
2.94
13
12
11
10
9
8
7
6
5
4
3
2
1
0
-1
-2
f1 (ppm)

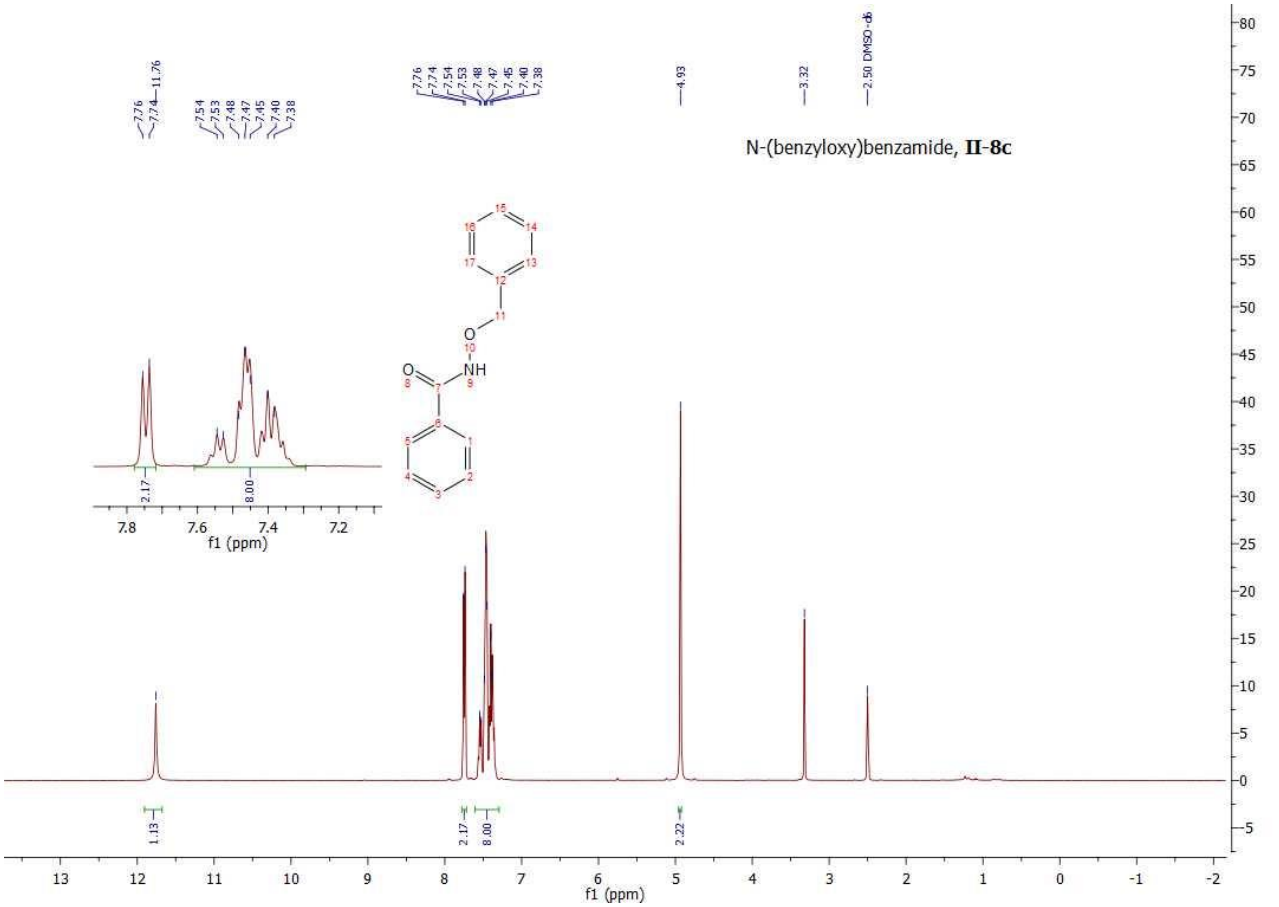

163.44
152.45
145.78
129.27
123.99
120.22
114.41
69.76
60.95
55.85
N,2,3-trimethoxybenzamide, II-8a
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
400
200
0
-200
220
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
-30
f1 (ppm)

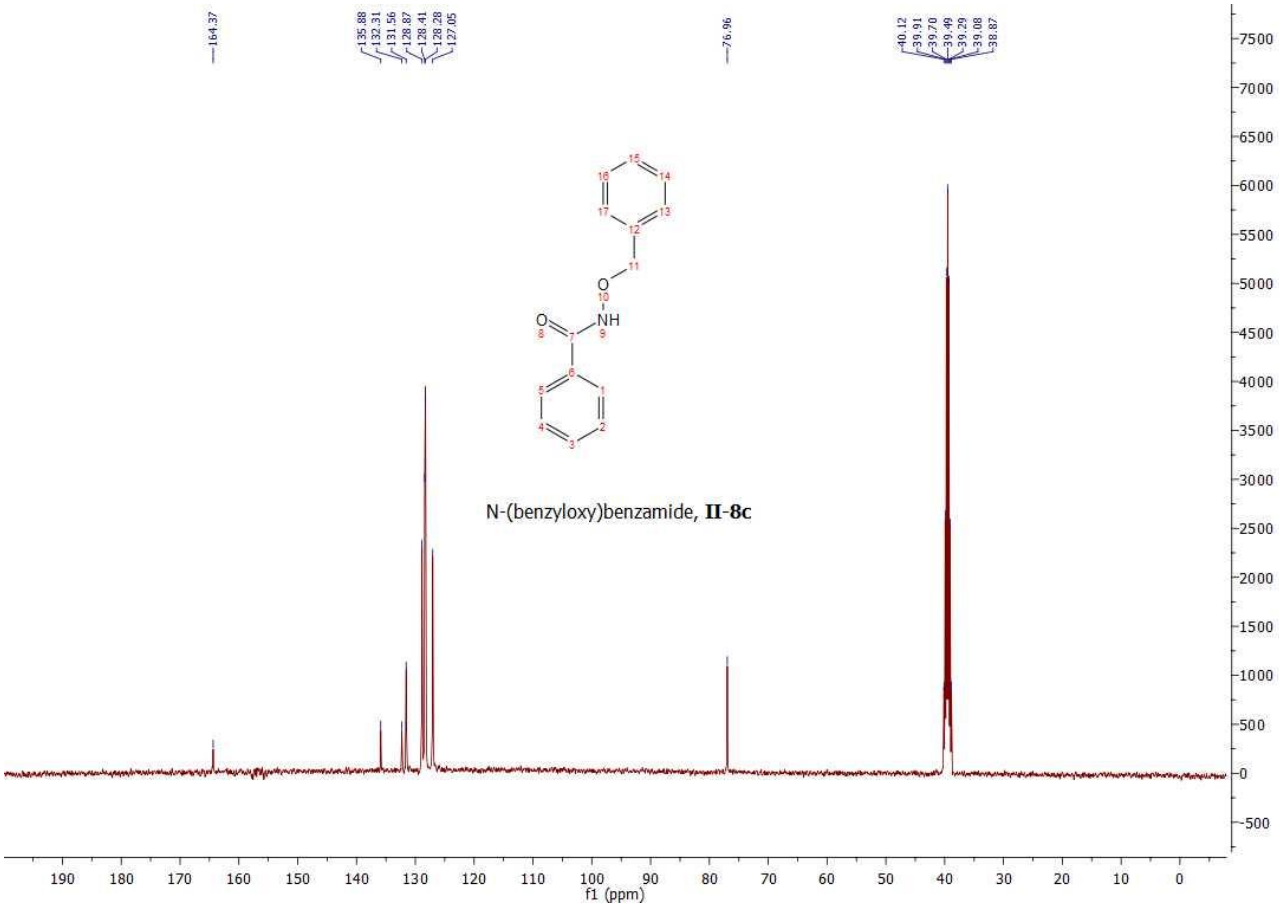


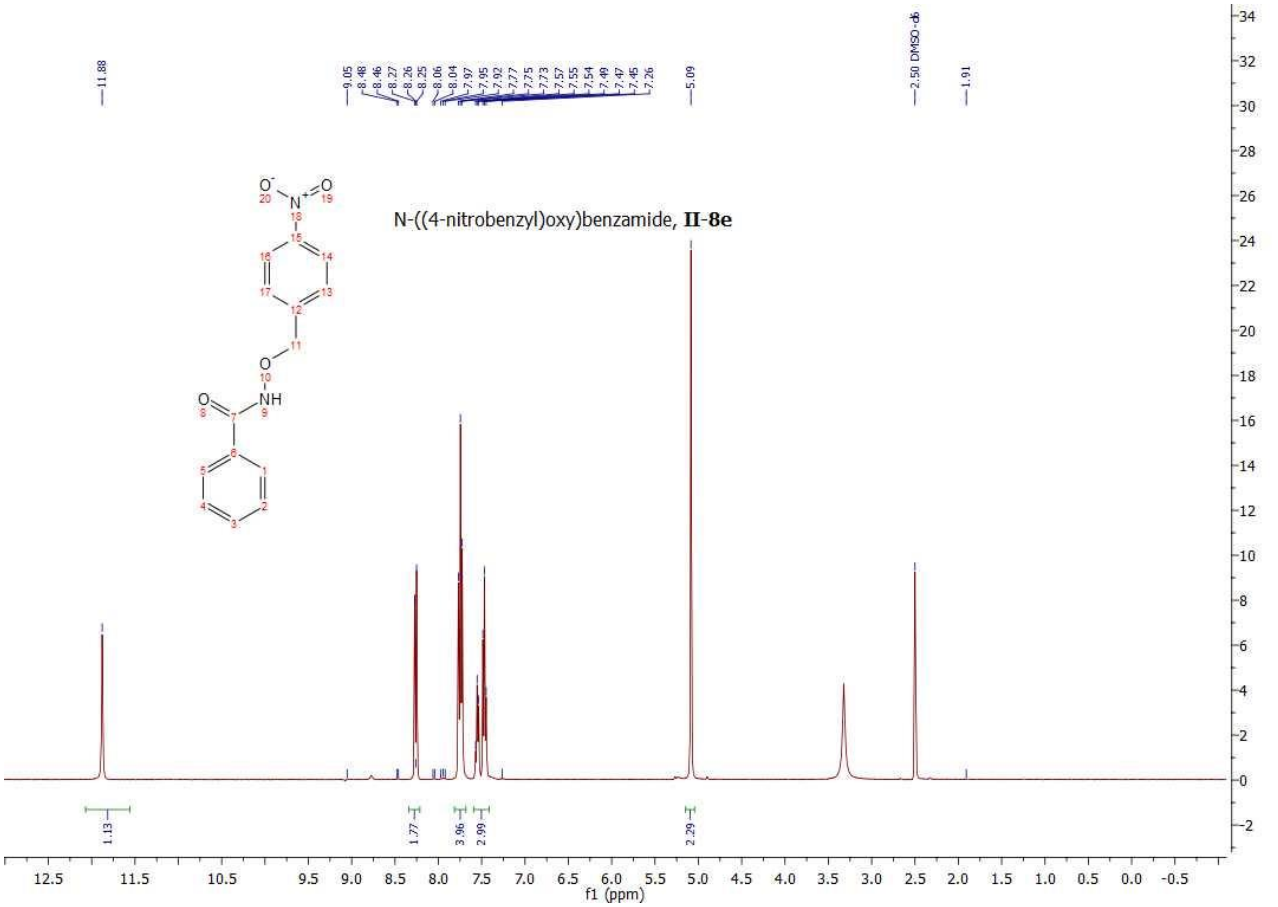
N-phenoxybenzamide, **II-8b**

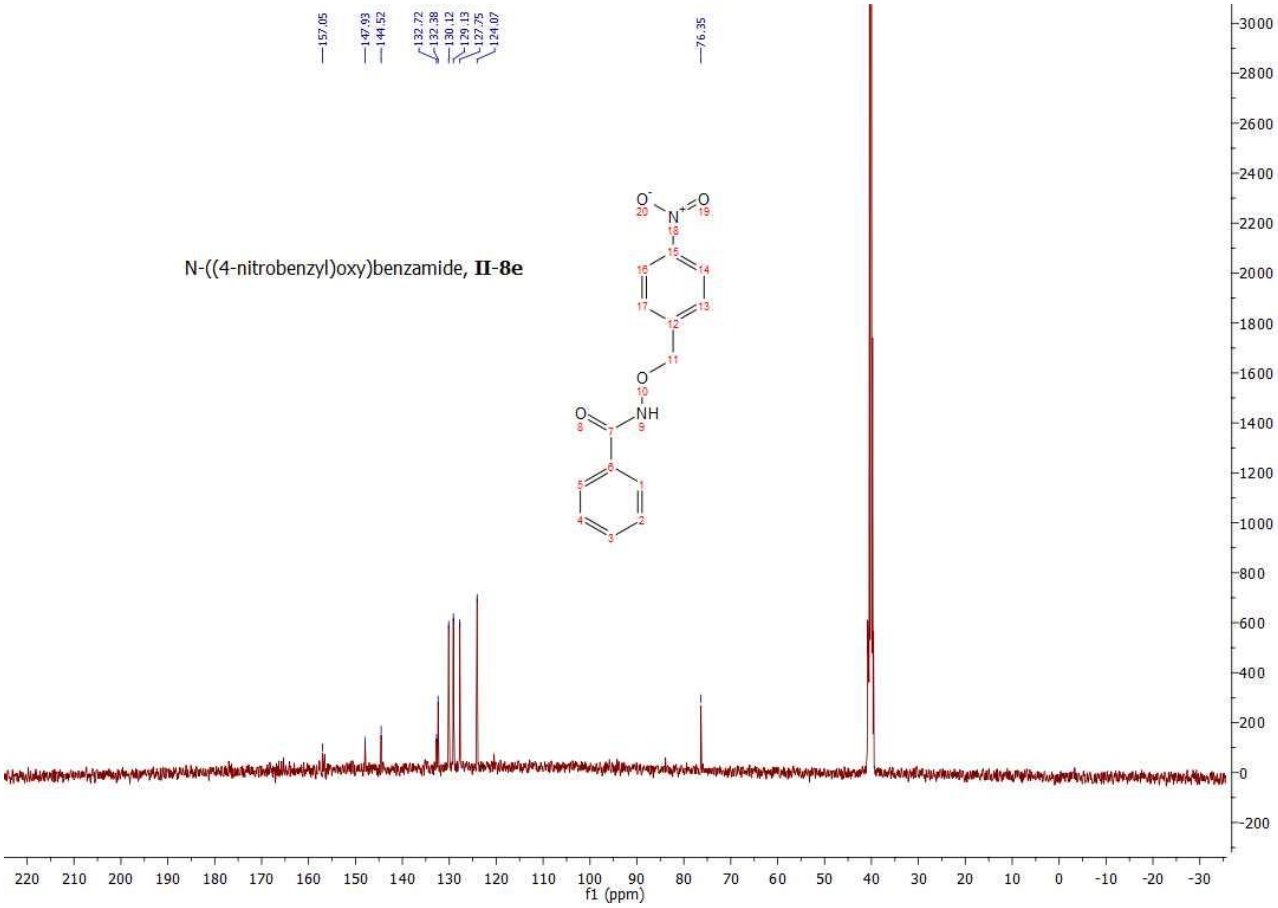


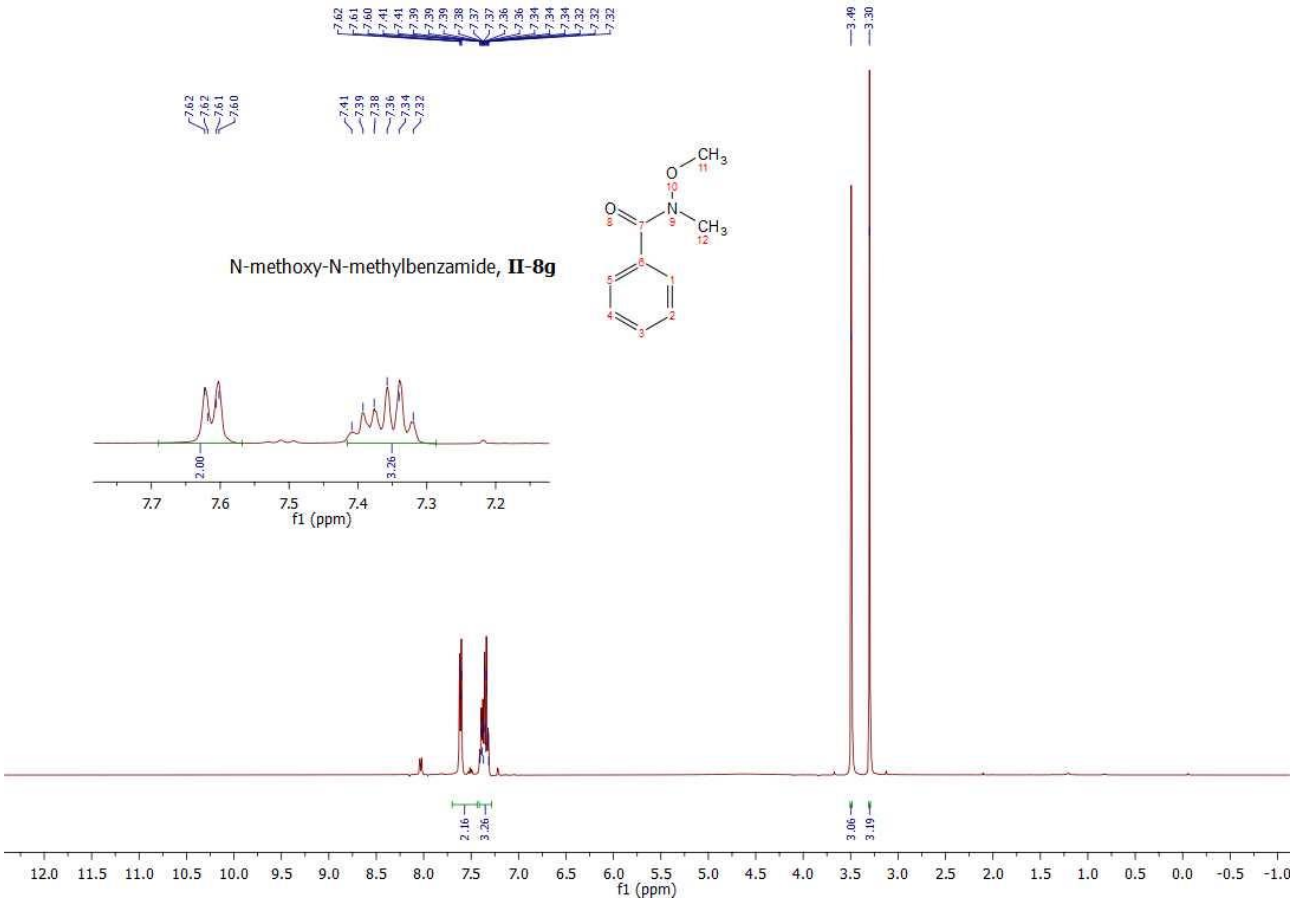
N-phenoxybenzamide, **II-8b**

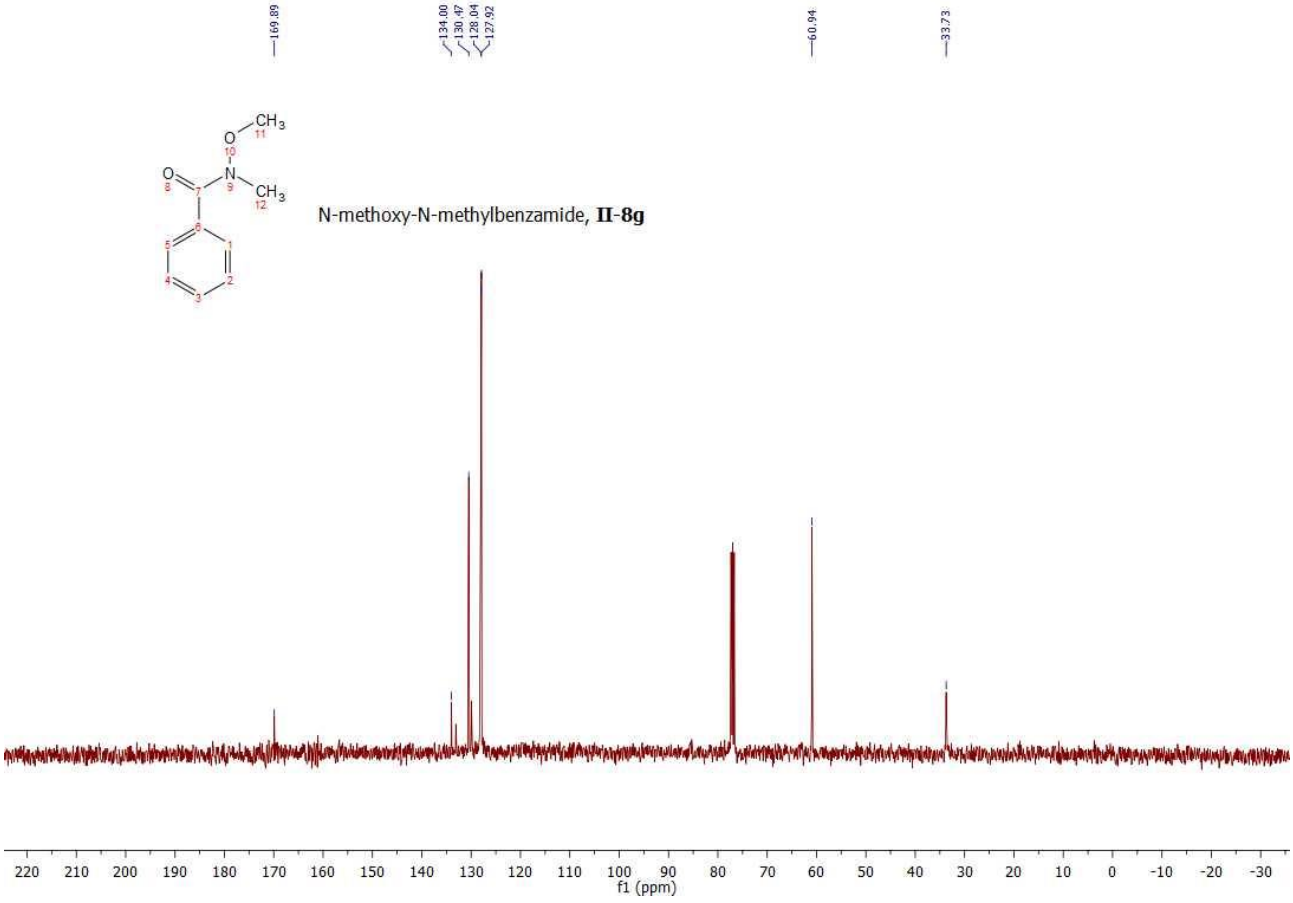

N-(benzyloxy)benzamide, II-8c
f1 (ppm)


N-(benzyloxy)benzamide, II-8c
f1 (ppm)


11.88
9.05
8.48
8.46
8.27
8.26
8.25
8.06
8.04
7.97
7.95
7.92
7.77
7.75
7.73
7.57
7.55
7.54
7.49
7.47
7.45
7.26
5.09
2.50 DMSO-d6
1.91
N-((4-nitrobenzyl)oxy)benzamide, II-8e
1.13
1.77
3.96
2.99
2.29
f1 (ppm)

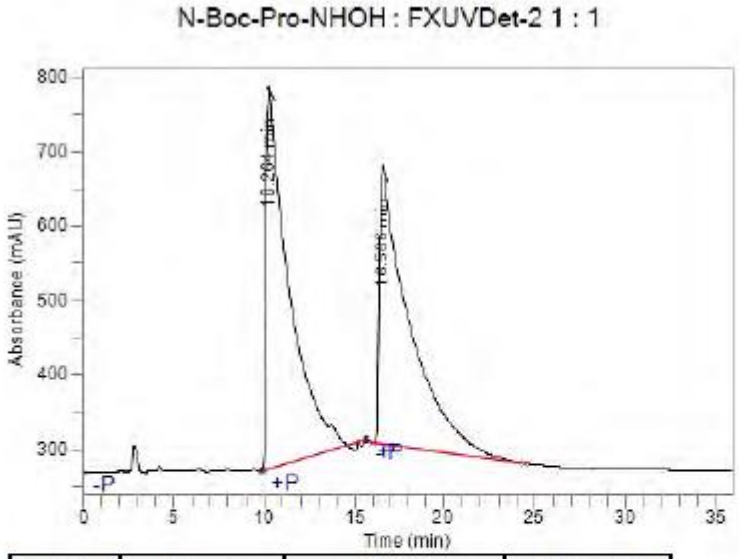

157.05
147.93
144.52
132.72
132.38
130.12
129.13
127.75
124.07
76.35
N-((4-nitrobenzyl)oxy)benzamide, II-8e
f1 (ppm)


N-methoxy-N-methylbenzamide, II-8g
f1 (ppm)


N-methoxy-N-methylbenzamide, II-8g
f1 (ppm)

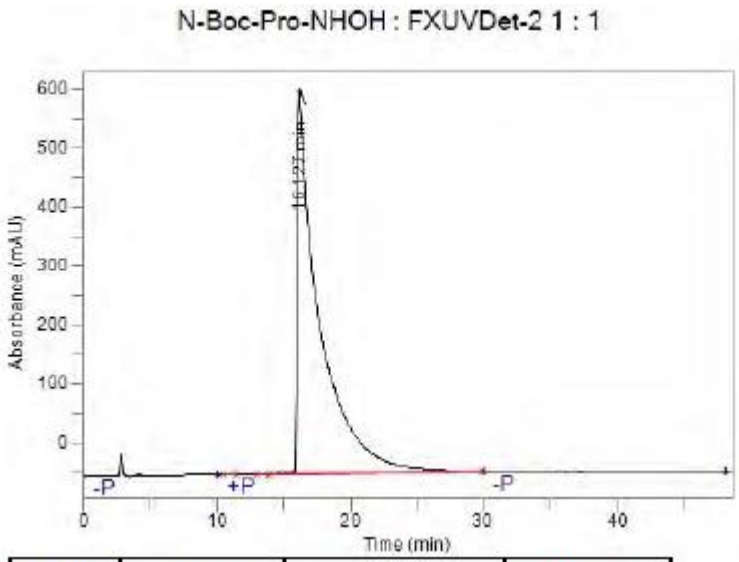
Chiral HPLC traces for hydroxamic acids II-7a, II-7b, II-7e and II-8h

Boc-DL-Pro-NHOH (II-7a), phenomenex Lux 5u Cellulose-1



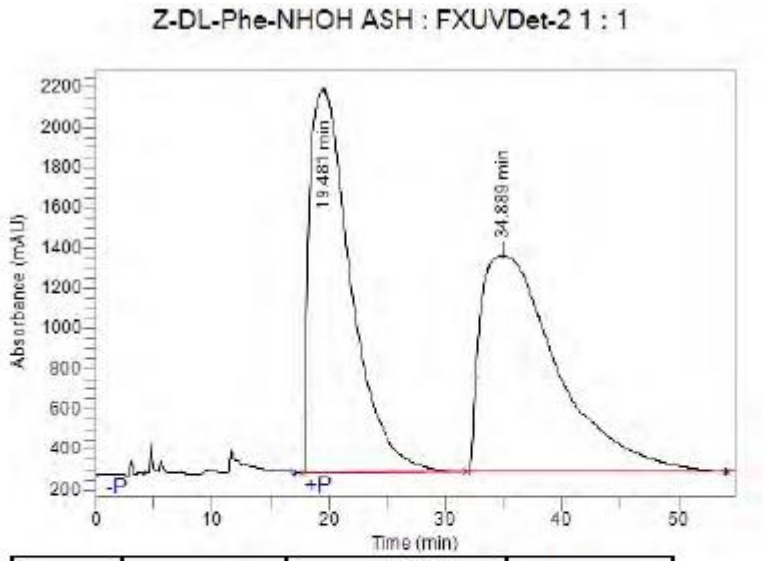
Peak #	Time	Area	Area %
1	10.264	45,121,459.1	50.36
2	16.566	44,477,629.1	49.64
Total		89,599,088.2	100.00

Boc-L-Pro-NHOH (II-7a), phenomenex Lux 5u Cellulose-1



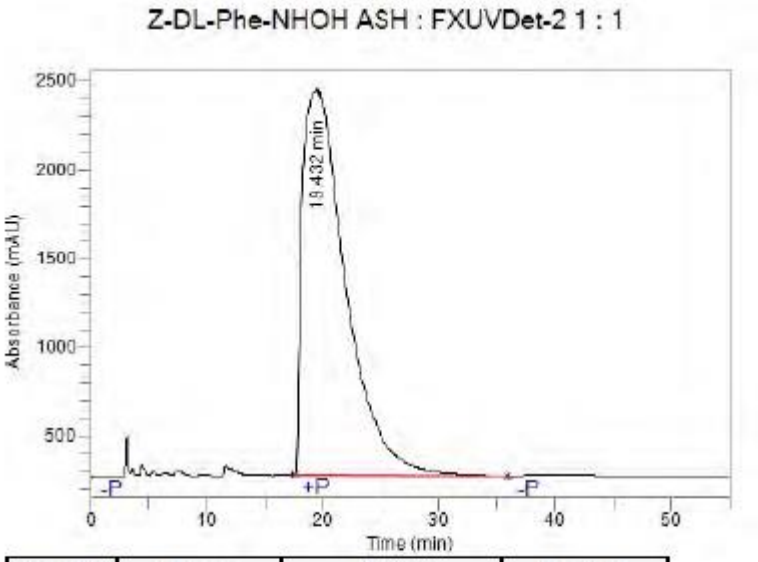
Peak #	Time	Area	Area %
1	10.710	20,591.3	0.03
2	13.545	4,453.8	0.01
3	15.115	282,568.4	0.39
4	16.127	73,074,962.6	99.58
Total		73,382,576.1	100.00

Cbz-DL-Phe-NHOH (II-7b), CHIRALPAK AS-H



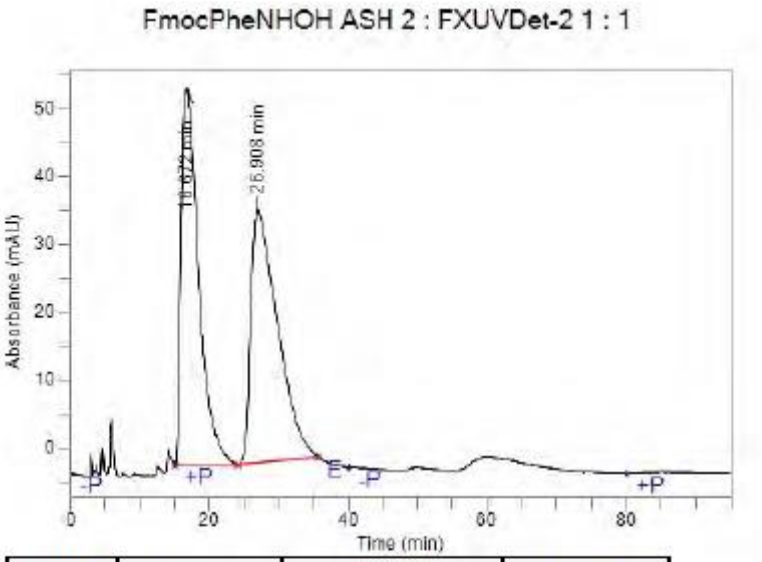
Peak #	Time	Area	Area %
1	19.481	464,505,176.9	48.68
2	34.889	489,759,997.3	51.32
Total		954,265,174.2	100.00

Cbz-L-Phe-NHOH (II-7b), CHIRALPAK AS-H



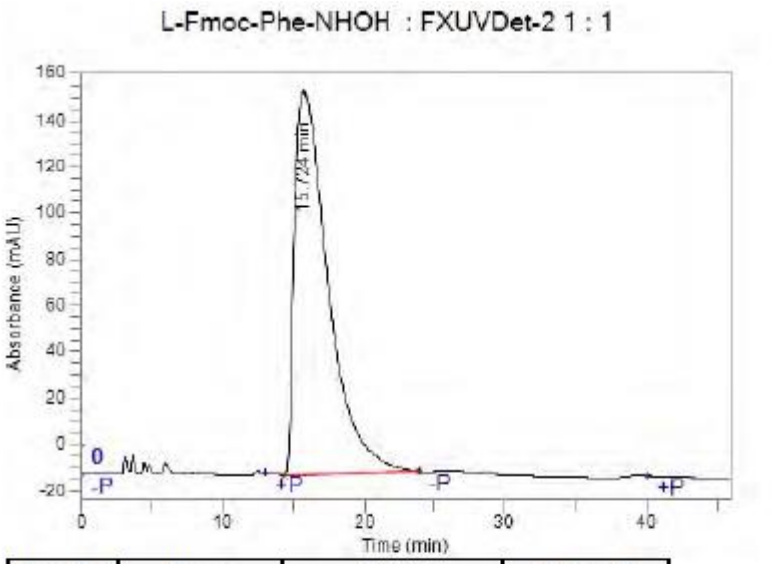
Peak #	Time	Area	Area %
1	19.432	559,023,349.5	100.00
Total		559,023,349.5	100.00

Fmoc-DL-Phe-NHOH (II-7e), CHIRALPAK AS-H



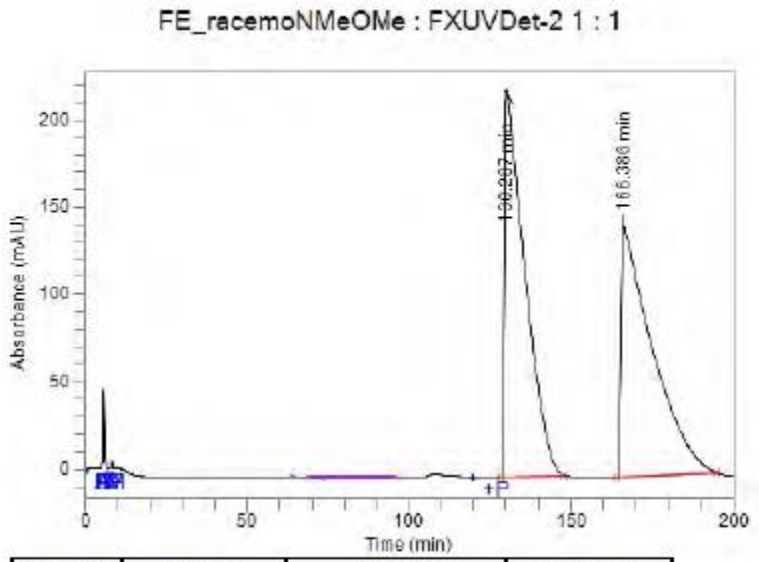
Peak #	Time	Area	Area %
1	16.672	9,635,729.9	49.42
2	26.908	9,861,475.7	50.58
Total		19,497,205.6	100.00

Fmoc-L-Phe-NHOH (7e), CHIRALPAK AS-H



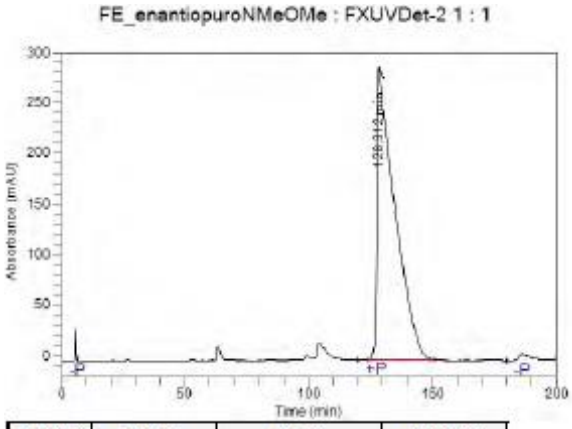
Peak #	Time	Area	Area %
1	15.724	27,306,659.1	100.00
Total		27,306,659.1	100.00

Cbz-DL-Phe-NMeOMe (II-8h), phenomenex Lux 5u Cellulose-1



Peak #	Time	Area	Area %
1	130.287	96,163,057.4	50.29
2	166.386	95,042,742.2	49.71
Total		191,205,799.6	100.00

Cbz-L-Phe-NMeOMe (II-8h), phenomenex Lux 5u Cellulose-1



Peak #	Time	Area	Area %
1	128.312	143,150,672.2	100.00
Total		143,150,672.2	100.00

Chapter III Ball-Milling and Cheap Reagents Breathe Green Life into the One Hundred-Year-Old Hofmann reaction

Rita Mocci, Sergio Murgia, Lidia De Luca, Evelina Colacino, Francesco Delogu and Andrea Porcheddu*

Ball-milling and cheap reagents breathe green life into the one hundred-year-old Hofmann reaction

Org. Chem. Front., 2018,***5***, 531-538

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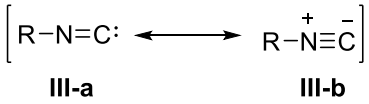
Introduction

Isocyanide: structure and reactivity

Isocyanides are a class of organic compound isomers of cyanide characterized by the presence of the group -N≡C. Their structure can be described by the two resonance forms between divalent carbon forms and zwitterions **III-a** and **III-b** (Scheme 31). The resonance structure **II**I-a reflects the carbene like reactivity of isocyanides, while the dipolar resonance structure **III-b** can explain the linear structure of isocyanides.

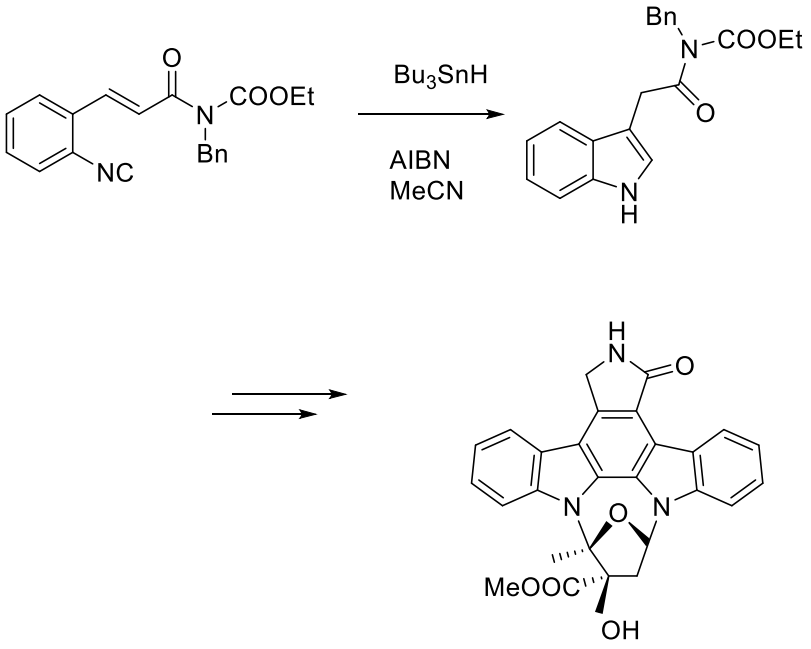


Scheme 31 *resonance structure of isocyanide*

Isocyanides are stable under basic treatment (they are often made under basic conditions), but they are quite sensitive to acids. In the presence of aqueous acidic solutions, isocyanides react to give the corresponding formamides, and acidic hydrolysis is a generally convenient method for removing the horrible smell of isocyanides.

Isocyanides are known to polymerize under Lewis acid catalysis to polyiminomethylenes with cylindrical helices structure.[200] Chemistry of isocyanide is characterized by three properties: the α acidity, the α addition and the easy formation of radicals.[123]

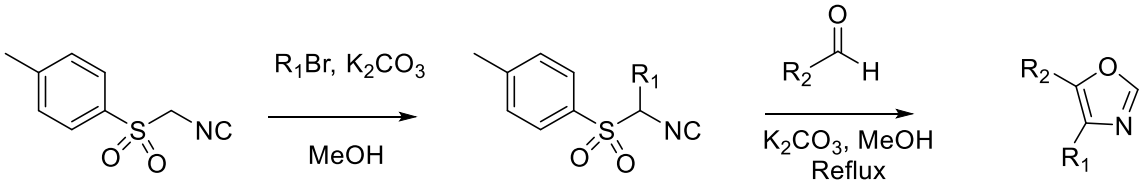
Isocyanides and specially phenylisocyanide undergo toward radical-induced cyclization. For instance, the *o*-isocyanocinnamic acid amides reported in the scheme 32 can be converted to the corresponding indole in a radical cyclization promoted by AIBN and Bu_3SnH which can be further transformed into the complex indole-containing natural product kinase inhibitor (+)-K252a.[201]



Scheme 32 *Scheme radical cyclization of o-isocyanocinnamic acid amides for the synthesis of kinase inhibitor (+)-K252a*[123]

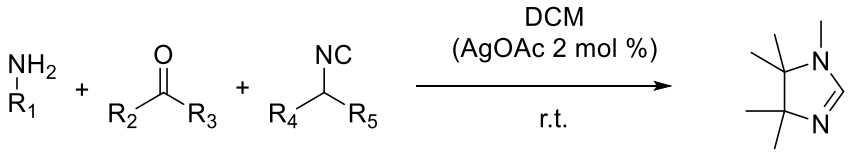
The synthesis of several heterocycles as oxazoles,[202] pyrroles,[203] triazoles, [204] can be achieved exploiting α acidity of isocyanides, increased by electron-withdrawing group such as carboxylic ester, nitriles and phosphonic ester or sulfonyl group.

For instance, Van Leusen originally reported the use of TosMIC (toluenesulfonylmethyl isocyanide) as a C-N=C synthon for the synthesis of various heterocycles, such as oxazoles, imidazoles, pyrroles, 1,2,4-triazoles and many more (Scheme 33).[202,204]



Scheme 33 *Van Leusen synthesis of oxazoles*

The employment of α acidic isocyanides was described by Orrù for the synthesis of 2-Imidazolines through a three-component reaction between R-acidic isonitriles, primary amines, and carbonyl compounds[205] (Scheme 34)



Scheme 34 *Multicomponent Synthesis of 2-Imidazolines*[205]

Remarkably, isocyanides are the only class of organic compounds which possess a formally divalent carbon and are stable. The most relevant feature of isocyanide from a synthetical point of view is their capability to react with electrophiles and nucleophiles at the isocyanide atom, leading to the formation of α-adducts. This is contrast with the major account of organic functional group that react with electrophiles and nucleophiles at different centres. This characteristic is the reason of parallelism of their chemistry with the one of carbene and carbon monoxide, that present similar properties.

The differences in reactivity between isocyanide an their corrispective isomers nitriles can be explained with a comparison of their frontiers orbitals:

In isocyanide, the orbital coefficient at the carbon atomin p star orbital is higher compared to the nitriles. This lead the nucleophilic attack to occur at the carbon atom. Electrophiles react with the sigma orbital on the homo 1 and therefore also with the carbon atom. On the other hand, nitriles are attacked by nucleophiles at the carbon atom (higher p* star coefficient) and by the electophiles at the nitrogen atom (higher p orbital coefficient)[123]

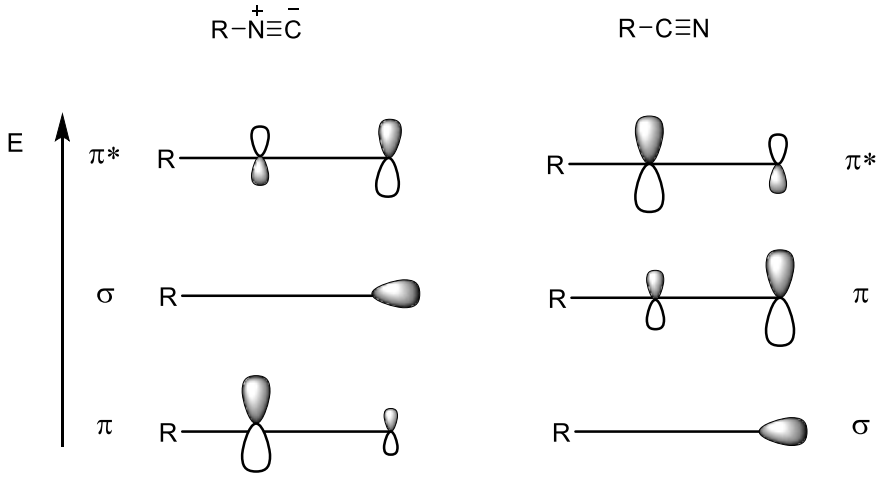
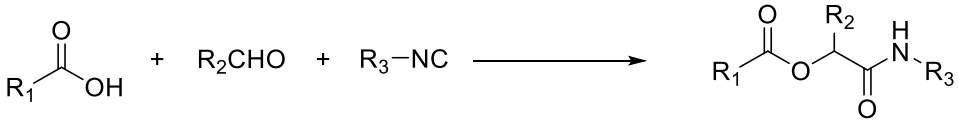


Figure 8 *Frontiers orbitals in isocyanides and cyanides*

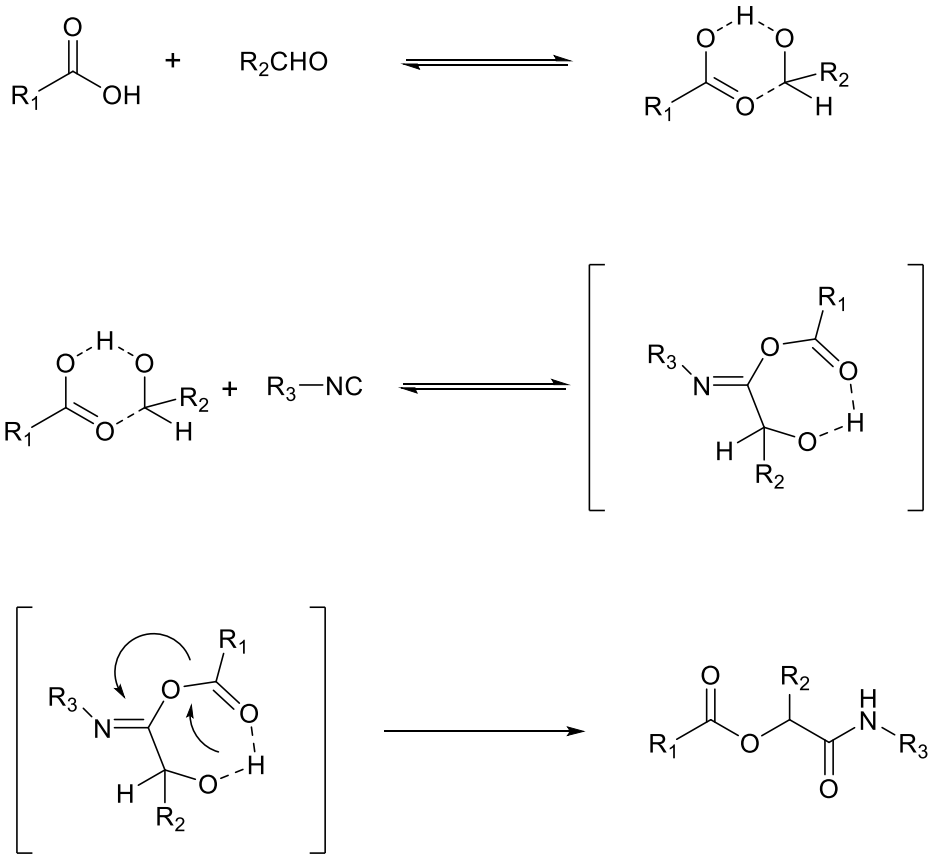
The most popular application of isocyanide is undubtely the multicomponent reactions, in particular Ugi reaction (U-4CR) and Passerini reaction (P-3CR).

The Passerini reaction, reported in 1921 is the first isocyanide based multicomponent reaction, in its classical version opens the access to α-acyloxycarboxamides in one step from carboxylic acids, oxocompunds and C-isocyanides (Scheme 35).[122,206,207]



Scheme 35 *Passerini reaction*

The mechanism of this transformation has been objected of several investigations. A nonionic mechanism is suggested by the fact that Passerini reaction is accelerated in aprotic solvents, unlike the Ugi reaction. Has been postuated according to experimental data that Passerini reaction proceeds through the formation of a loosely hydrogen-bond adduct from a carbonyl compound and a carboxylic acid. The subsequent α-addition of the electrophilic carbonyl carbon and the nucleophilic oxygen atom of the carboxylic acid to the isocyanide carbon lead to the cyclic transition state with all three parent compunds. The consequent intramolecular rearrangement gives the stable acyloxy carboxamide in a reaction of transacylation (Scheme 36). [123]

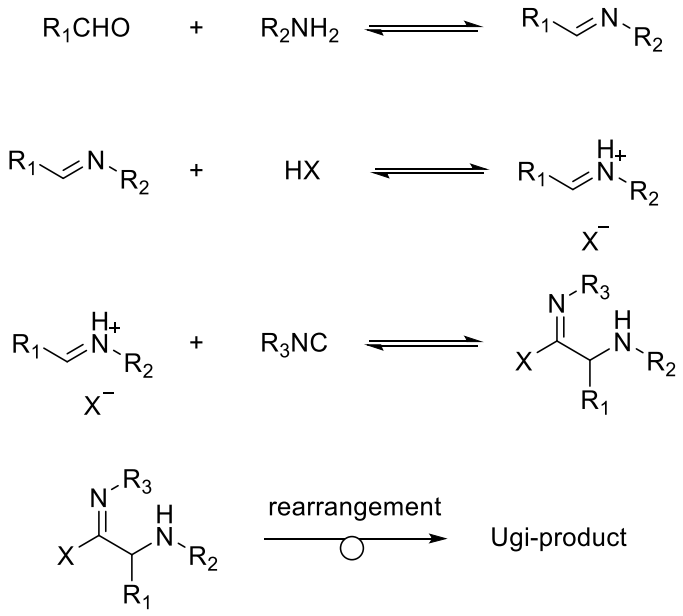


Scheme 36 *Proposed mechanism for Passerini*

A new era of isocyanide chemistry begun after 1958, when isocianides became generaly available by dehydration of formylamines[208–210]

One year later, Ugi introduced the four-component reaction of isocyanide. The educts of this reaction are amines (ammonia, mono- and disubstituted amines, hydroxylamine, hydrazine and

its suitable derivatives), carbonyl compounds, acid components and related compounds (water, thiosulfates, hydrogen selenide, hydrazoic acid, hydrogen cyanate and thiocyanate, aminocyanic acid, carboxylic acids and thioacids, alkoxycarboxylic acids and amines) and isocyanides.



Scheme 37 *Scheme: simplified mechanism of Ugi reaction*

A simplified mechnism is represented in the Scheme 37. The first step sees the condensation for the formation of the imine. The α-adduct is formed after the addition of elecrophilic iminium ion and the nucleophilic acid anion to the isocyanide carbon atom. Compound can be seen as a hetero analogue of an acid anhydride in wich an exo—oxygen atom is substituted by an NR group. Acid anhydrides are strong acylating agent, as their heteronalogues formed here, the intramolecular acylation lead to the hydroxylimine amide rearrangement gives the stable Ugi product, according to the originally described by Mumm.[211]

While all elementary steps in this transformation are equilibria, the driving force of the sequence relies on the oxidation of the isocyanide Cii atom to the amide Civ atom.

The U-4CR leads to the formation of one C-C bond and several heteroatom -C bonds are newly formed. The exceptionality of this transformation relies in the extraordinary heterogenicity of the product obtainable, as substituent and skeleton are highly variable.

In Figure 9 are reported 8 examples of how the variation of the amine and acid components can lead to several compounds of relevance.[208]

Seen the highly usefulness of the reaction it has been extensively studied[212] and several reviews collect the results obtained in the field of multicomponent reactions based on isocyanide, especially 3-PCR and 4-UCR.[123,213–217] They play a special role in combinatorial chemistry, synthesis of heterocycles, enantioselective transformation.

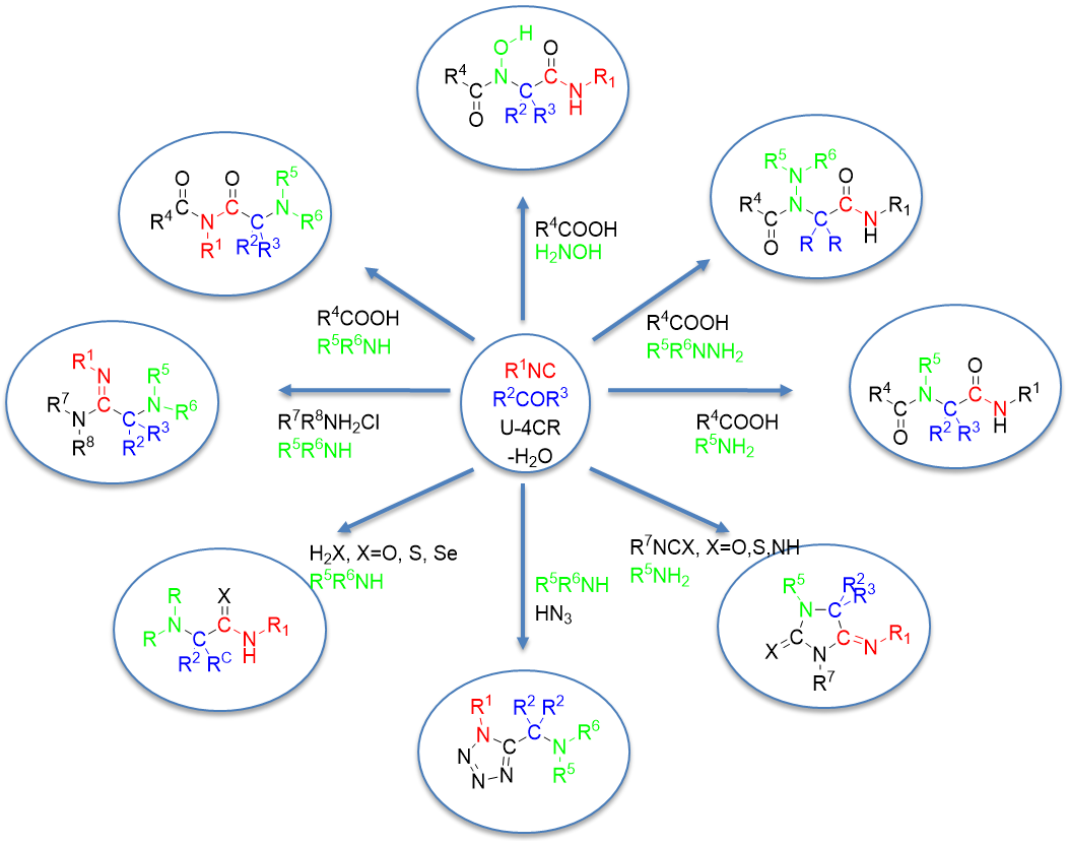
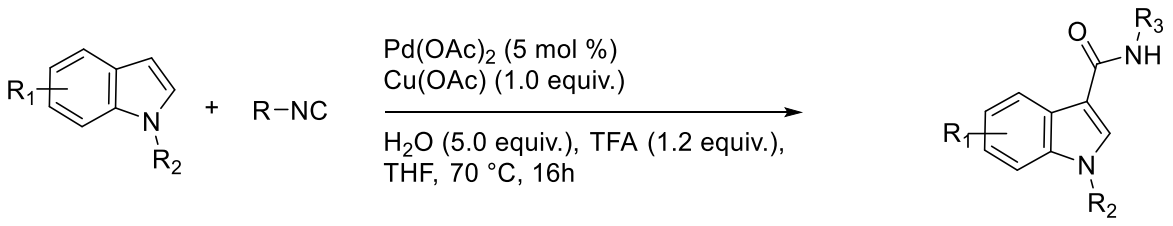


Figure 9 Isocyanide in multicomponent reactions

The synthetic relevance of isocyanide is as well connected to their ability to give insertion in transition metal catalyzed C-C bond formations, for instance in 2012 Zhu and coworkers reported the direct carboxamidation of indoles by palladium-catalyzed C–H activation and isocyanide insertion.[218]



Scheme 38 *Scheme direct carboxamidation of indoles by palladium-catalyzed C–H activation and isocyanide insertion*[218]

Relevance of isocyanide is as well related to the number of isocyano groups containing natural products that were isolated, in especial way from marine species. Besides, many natural isocyanide show a strong antibiotic, fungicidal, or antineoplastic effect [219–221]

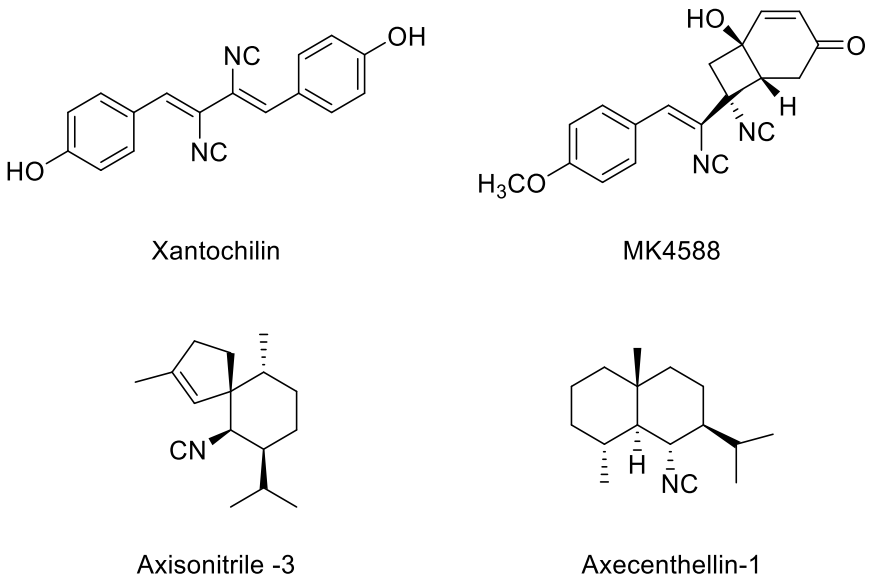


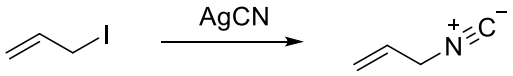
Figure 10 *Some examples of natural isocyanide*

Isocyanides are characterized by a strong odour, as Lieke[222] wrote "*Es besitzt einen penetranten, höchst unangenehmen Geruch; das Oeffnen eines Gefässes mit Cyanallyl reicht hin, die Luft eines Zimmers mehrere Tage lang zu verpesten, ...*" (It has a penetrating, extremely unpleasant odour; the opening of a flask of allyl [iso]cyanide is enough to foul up the air in a room for several days). The potent odor of isonitriles is the basis of a classic qualitative test for primary amines via conversion to the "carbylamine" by KOH/$CHCl_3$ (the Hofmann isonitrile synthesis)[223] They are sufficiently obnoxious to have been included in nonlethal weapons.[224]

The odour of isocyanide is so strong that in the past has been said that isocyanide chemistry development was affected from it: "*The development of the chemistry of isocyanides has probably suffered only little delay through the characteristic odor of volatile isonitriles, which has been described by Hofmann and Gautier as 'highly specific, almost overpowering', 'horrible', and 'extremely distressing'. It is true that many potential workers in this field have been turned away by the odour, but this is heavily outweighed by the fact that isonitriles can be detected even in traces, and that most of the routes leading to the formation of isonitriles were discovered through the odor of these compounds.*" [121]

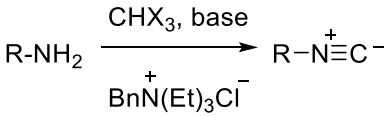
Synthesis of isocyanides

The first reported method for the synthesis of isocyanide goes back to 1859 and consists in the reaction between allyliodide and silver cyanide.[222]



Scheme 39 *Original synthesis of isocyanide*

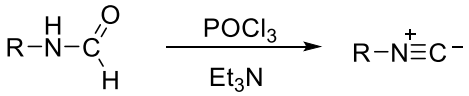
This method, as the thermal reduction of iso(thio)cyanate, and copper-catalyzed addition of hydrogen cyanide to tertiary olefin, is rarely used in organic synthesis.[123,186,225,226] In 1867 Hoffman described the formation of isocyanide via carbene formation in presence of chloroform and sodium hydroxide,[223,227] affected by low yield (up to 50 %) and reproducibility, the reaction was later improved by the introduction of a phase transfer catalyst (Scheme 40).[228,229]



Scheme 40 *Hoffman isocyanide synthesis with phase transfer catalysis*

The most used route for the preparation of isocyanide still remains the dehydration of formamides originally described by Ugi and Meyr,[121] who employed a combination of $POCl_3$

and triethylamine. Other methods involve the presence of a combination of triphenyphosphine, carbon tetrachloride and triethylamine [230] or for more labile substrates, Burgess's reagent is used. [231]

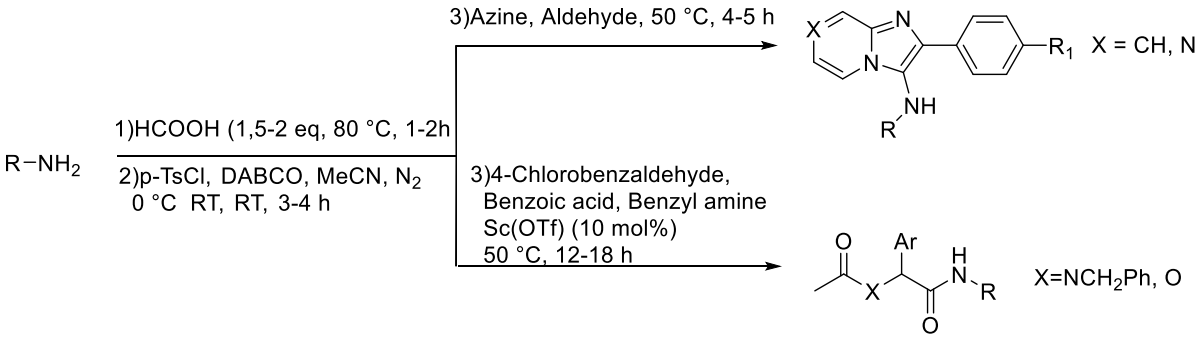


Scheme 41 *Scheme synthesis of isocyanide by formamide dehydration*

Several efforts have been done in order to avoid the use the hazardous substances as $POCl_3$, and the employment of a number of alternative dehydrating reagents were studied such as cyanuric chloride[232], triflic anhydride,[233] benzene-1,3-disulfonyl chloride, p-tosyl chloride and chlorophosphates[234] as well as diphosgene,[235] and triphosgene.[236]

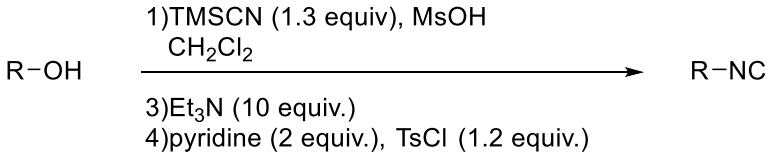
Kim *et al.* reported a continuous four-step in-line process (in situ generation, extraction, separation, and reaction of isocyanides) in an integrated microfluidic system using a solution of *N*-cyclohexylformamide in *N*,*N*-diisopropylethylamine and a solution of $POCl_3$ in toluene which were introduced into the capillary microreactor, then the biphasic stream leaving the extraction stage was separated into aqueous and organic streams with a microseparator.[237]

Some examples of one-pot synthesis of isocyanide directly starting from the corresponding amines have been reported. For instance, Guchhait *et al.* documented the use of DABCO as the tertiary base, together with formic acid and p-tosyl chloride.[238] Further transformations were carried out in Groebke-Blackburne-Bienaymé (GBB), Ugi, and Passerini type multicomponent reactions under different multicomponent conditions (Scheme 42) [238]



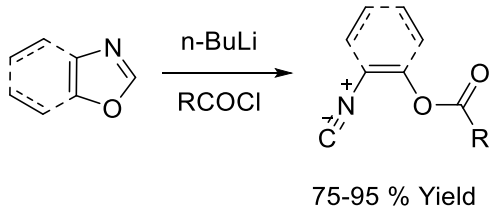
Scheme 42 *One-pot preparation of isocyanide from amines and their GBB and Ugi and Passerini MCRs*[238]

Another example of one-pot synthesis of isocyanide is the reaction of tertiary alcohols via modified Ritter reaction with trimethylsilyl cyanide and methansulphonic acid, followed by neutralization with triethylamine and dehydration with tosyl chloride and pyridine, reported by Kitano in 2011 (Scheme 43).[239,240]



Scheme 43 *Modified Ritter reaction for the synthesis of isocyanide*[239]

An interesting route to α-functionalized isocyanide was reported by Pirrung *et al.* for the synthesis of isocyanovinyl and 2-isocyanophenyl esters, which were found to be fragrant. The protocol sees the metalation of and oxazoles followed by acylation with the opportune acyl chloride (Scheme 44).[241]

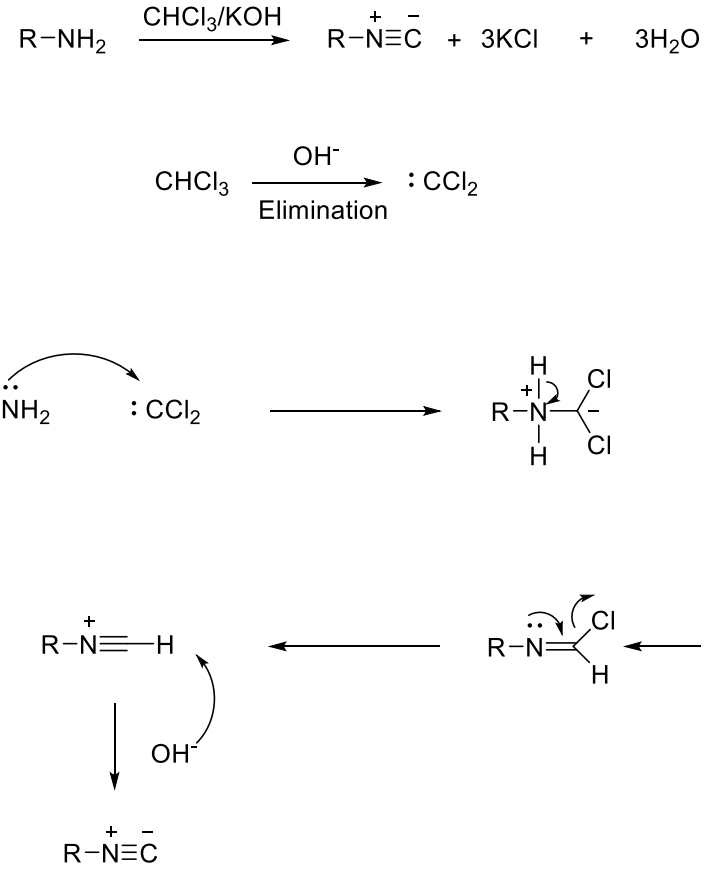


Scheme 44 *Synthesis of Unsaturated Isonitriles-esters from Oxazoles*[241]

Aim of the work

In line with our interest toward the exploiting of ball milling technology to develop more efficient and synthetic procedures in organic synthesis, we establish to reinvestigate the Hoffman carbylamines reaction in a more environmentally friendly view. Indeed, adopting the most common procedure of preparation of isocyanides, requires two reaction steps starting from the amine moiety; besides, despite the remarkable progress registered in the field, the use of dehydrating agents is often accompanied by a list of issue to them connected as their hazardous nature as well as the formation of not easily handling by-product.

Conversely, the reaction originally discovered by Hoffman is affected by very low yield, and requires the use of a phase transfer catalyst, working in a two-phase aqueous system. Furthermore, it involves the presence of chlorinated solvents, which should be avoided in line with the well-established guidelines. On the other side, this transformation formally led to the conversion of chloroform to a high valuable compound as isocyanide in one reaction step, with a formation of innocuous sodium chloride and water as by-product. The reaction proceeds via the formation of reactive carbene intermediate generated by the action of base on chloroform, successive base-mediated dehydrochlorination steps result in formation of the isocyanide (Scheme 45).



Scheme 45 *Putative mechanism of Hoffman carbylamines reaction*

We envisioned the possibility to revisit this reaction by including the presence of chloroform solely as a reagent, in absence of solvents and phase transfer catalyst, in order to simplify and improve a potential method for the preparation if isocyanides.

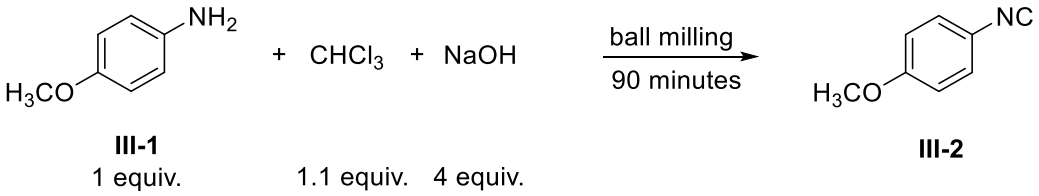
Results and discussion

Optimization experiments

We started our investigation using the aromatic primary aromatic amine anisidine as model substrate in a SPEX 8000 mixer/mill using a zirconia-milling beaker (45 ml) equipped with four balls (d = 10.0 mm) for a 5 mmol scale with respect to the amine. The amine was ball milled together with 1.2 equivalents of chloroform and 4 equivalents of NaOH. (The

stoichiometry of the reactions requires 3 equivalents with respect to amine). The analysis of the reaction outcome in the optimization experiments were performed by GC-MS and TLC.

Table 5 *Optimization experiment: effect of the adsorbent material*[a]



III-1 1 equiv. 1.1 equiv. 4 equiv. **III-2**

Entry	Additives	Conversion %
1	-	30
2	Na_2SO_4	39
3	$MgSO_4$	10
4	$CaSO_4$	12
5	K_2CO_3	31
6[b]	**Na_2SO_4**	**38**
7[c]	Na_2SO_4	31
8[d]	Na_2SO_4	39

[a] Reaction conditions: anisidine (5 mmol, 1.0 equiv), $CHCl_3$ (5.5 mmol, 1.1 equiv), NaOH (20 mmol, 4 equiv.), and the additive (3g) were continuously milled for 90 minutes in a Spex 8000M mixer/mill into a zirconia-milling beaker (45 ml) equipped with four balls (d = 10.0 mm) Substrate conversion and product selectivity were determined by GC-MS analysis.
[b] 1 g of Na_2SO_4 was used as additive
[c] 0.5 g of Na_2SO_4 were used as additive
[d] 5 g of Na_2SO_4 were used as additive

At this preliminary stage, we observed a very low conversion (entry 1, Table 5) even accompanied by the presence of consistent amount of a not identified by-products. not detectable by simple ^{1}HNMR.

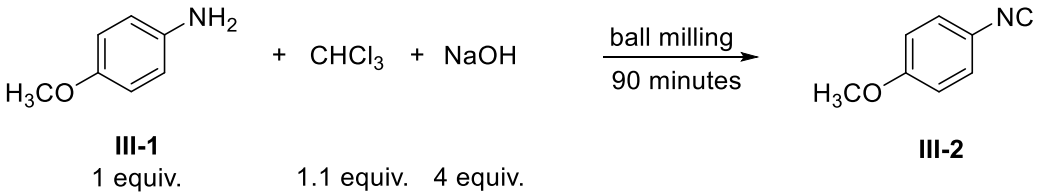
In order to lead the reaction to a major selective conversion toward the desired isocyanide we envisioned to use a solid scavenger for the water intrinsically formed during the process. The presence of the scavenger was thought to be useful as well to contrast the strong tendency of NaOH to incorporate water.

The results with respect to the dehydrating agent utilized are reported in Table 5. We found that the $MgSO_4$ affected in a negative way the outcome of the reaction (entry 3), while a beneficial effect was observed when sodium sulphate was used (entry 2) These experiments were carried out using the same amount in weight of adsorbent additive (3 g *per* 5 mmol), performing further experiments with sodium sulphate showed that also a lower amount of additive was enough to obtain similar results (entry 6) while increasing the amount up to 5 g did not result in any improvement (entry 8).

In the second stage, we were interest in discovering whether an alternative base could have given any improvement in the conversion and yield of the desired product

Then, we screened a series of bases. In the Table 6 are reported the results obtained when using NaOH, KOH, $Ca(OH)_2$, K_2CO3 and Cs_2CO_3. The best yields were achieved by carrying out the model reaction with alkaline hydroxides MOH.

Table 6 *Optimization experiment: effect of the base*[a]



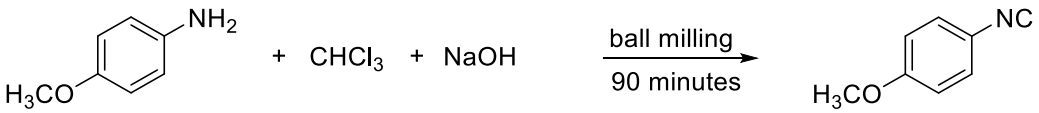
III-1 1 equiv. 1.1 equiv. 4 equiv. **III-2**

Entry	Base	Conversion %
1	**NaOH**	**39**
2	KOH	35
3	$Ca(OH)_2$	29
4	K_2CO_3	7
5	$CsCO_3$	9

[a] Reaction conditions: anisidine (5 mmol, 1.0 equiv), $CHCl_3$ (1 mmol, 1 equiv) the base (20 mmol, 4 equiv.), and 1g of Na_2SO_4 were continuously milled for 90 minutes in a Spex 8000M mixer/mill into a zirconia-milling beaker (45 ml) equipped with four balls (d = 10.0 mm) Substrate conversion and product selectivity were determined by GC-MS analysis.

After having chosen the best base we passed to explore the effect of the relative stoichiometric amounts of chloroform and sodium hydroxide on the isocyanide formation.

Table 7 *Optimization experiment: effect of the chloroform amount*[a]



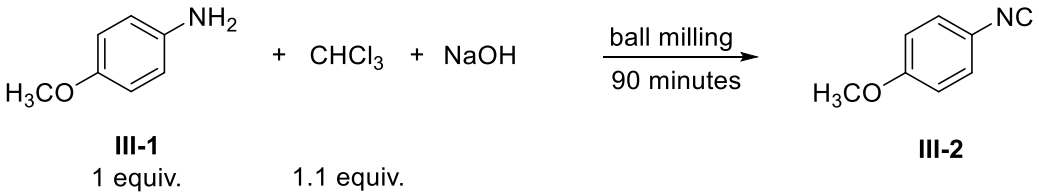
III-1 1 equiv. | 4 equiv. | **III-2**

Entry	Chloroform equiv.	Coversion %
1	**1.2**	**38**
3	1.5	38
5	2	38
6	2.4	40

[a]Reaction conditions: anisidine (5 mmol, 1.0 equiv), $CHCl_3$, NaOH (20 mmol, 4 equiv.), and 1g of Na_2SO_4 were continuously milled for 90 minutes in a Spex 8000M mixer/mill into a zirconia-milling beaker (45 ml) equipped with four balls (d = 10.0 mm) Substrate conversion and product selectivity were determined by GC-MS analysis

As visible in Table 7, the use of a strong excess of chloroform (up to 2.4 equiv.) did not lead to any significant improvement on the conversion of the anisidine to the desired product. Conversely, increasing the amount of base resulted in a consistent enhancement of the reaction performance. In particular, almost complete conversion of the anisidine was achieved when 12 equiv. of base were used (Table 8, entry 8).

Table 8 *Optimization experiment: effect of the NaOH amount*[a]



III-1 1 equiv. 1.1 equiv. **III-2**

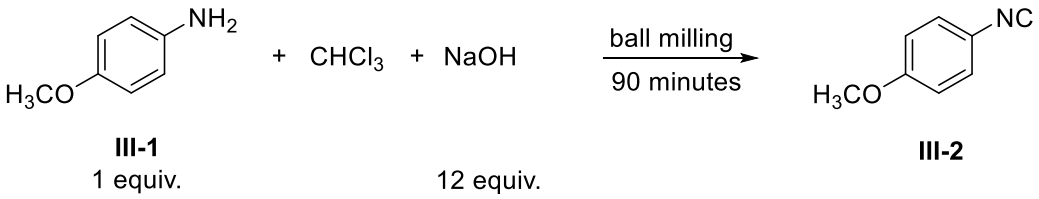
Entry	NaOH equiv.	Conversion %
1	5	45
2	6	51
3	7	59
4	8	66
5	9	72
6	10	79
7	11	85
8	**12**	**92**

[a]Reaction conditions: anisidine (5 mmol, 1.0 equiv), $CHCl_3$ (1.1 equiv.), NaOH, and 1g of Na_2SO_4 were continuously milled for 90 minutes in a Spex 8000M mixer/mill into a zirconia-milling beaker (45 ml) equipped with four balls (d = 10.0 mm) Substrate conversion and product selectivity were determined by GC-MS analysis

Finally, we wonder if an evaporation or decomposition of chloroform could have occurred during the milling period and we choose to separate addition of chloroform to see if this could bring any improvement to the reaction outcome, subsequently we performed a set of experiments at shorter reaction times in which additional amounts of chloroform were added to the previously milled reaction. By carrying out these experiments, we were also able to diminish the reaction times, in fact, a complete conversion of the anisidine to the corresponding isocyanide was observed even after two cycles of 15 minutes each (30 minutes in total), with the use of a total 12 equivalents of chloroform (Table 9, entry 3). Neither single cycles of 5,10 and 15, neither 2 cycles of 5 minutes and 10 minutes respectively were sufficient to bring the substrate to complete conversion (entries 1 and 2, Table 9). It is interesting to note that

performing the experiment with the same amount of chloroform and the same continuous milling time did not lead to the same results. (entry 4, Table 9)

Table 9 *Optimization experiment : time and way of addition*[a]



Entry	Chloroform equiv.	Times (min)	Conversion %
1	2x1.2	2x5	95
2	2x1.2	2x10	98
3	**2x1.2**	**2x15**	**>99**
4	2x1.2	30	84

[a]Reaction conditions anisidine (5 mmol, 1.0 equiv), $CHCl_3$, NaOH (60 mmol, 12 equiv), and 1g of Na_2SO_4 were continuously milled for the given time in a Spex 8000M mixer/mill into a zirconia-milling beaker (45 ml) equipped with four balls (d = 10.0 mm) Substrate conversion and product selectivity were determined by GC-MS analysis

After having identified best conditions, we addressed out attention to the tuning of efficient purification conditions. The instable nature of isocyanide renders this step challenging and the quantitative recovering of the product difficult to achieve.

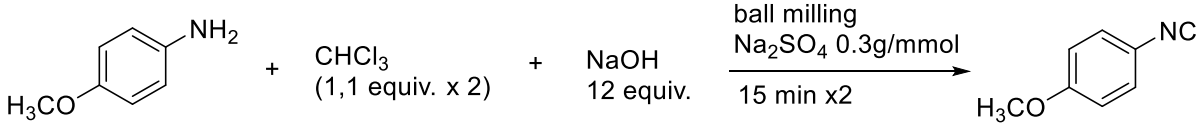
At a first instance, we thought to remove possible by-products treating the reaction mixture with a slightly aqueous acid solution, but the desired product was isolated in very low yields (9 %). Any attempt to distillate the product failed, leading to decomposition and scarce recovery of the product (5 % Yield). Isocyanide are quite sensitive compounds, and decomposition events can take place when a chromatographic column is performed. We found that loading the solid mixture obtained after the grinding procedure on a short pad of previously conditioned pad of silica gel, could allow a fast purification avoiding the contact of the isocyanide with

silica gel for too long time by eluting it with a mixture of heptane/ethylacetate. The potential decomposition of isocyanide during the purification process was further confirmed by allowing the isocyanide stirred overnight in presence of silica and observing its almost complete decomposition (just 6 % of the initial amount was recovered).

Moreover, the elution of the crude solid with 2-Me-THF provided a black tarry in which component could not be identified by simple ^{1}H-NMR spectroscopy analysis but separable from the crude mixture and the desired isocyanide product by simply washing with heptane and ether. Further analysis was performed on this black oil, more specifically we postulated the formation of a polymer, even though isocyanide is known to polymerize in acidic conditions.

This hypothesis was discarded by means of PGSTE (Pulsed-field Gradient STimulated Echo) ^{1}H NMRwhich allows to measure the self-diffusion coefficients of the analyzed compounds. The self diffusion coefficient *D,* as formally given by the Stokes-Einstein equation (D = kBT/6πηRh, where kB is the Boltzmann constant), depends by the viscosity of the solvent (η = 0.536 mPa s at 298 K for $CDCl_3$), the temperature (T) and, more importantly, by the hydrodynamic radius (Rh) of the spin-bearing molecule.[242] The analysis carried out led to a self diffusion coefficient measured in the range of 2.1 to 5.7 Å which belong to small molecules.

Once we explored the effect of different parameters on the reaction, we ended up with the optimized conditions reported in Scheme 46, which were applied to variously primary amines.



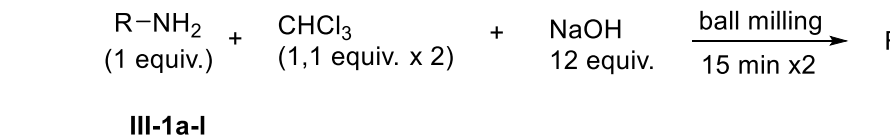
III-1 **III-2**

Scheme 46 *Optimized condition for the Hoffman mechanochemical reaction*

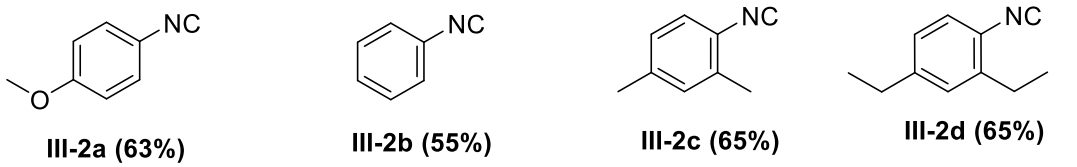
Scope of the reaction

Aromatic amines substitute in various positions were transformed to the corresponding isocyanide with satisfactory yields (Table 10). It was possible to carry out the reaction of formation of isocyanide in presence of several functional group as ethers (entries **III-2a**) thioether (**III-2g)**, carbonylic compound (**III-2m**) and other electron-withdrawing functionality as chloro- and trifluoromethyl- substituents (entries **III-2h** and **III-2i**). The presence of hydroxyl group seemed to affect the yield of the product which was anyway recovered with a 18 % of yield. Best results were obtained starting from the 2,4,6 trisubstitued aniline (entry **III-2e**)

Table 10 *Scheme scope of mechanochemical Hoffman reaction: aromatic amines*



III-1a-l **III-2a-l**

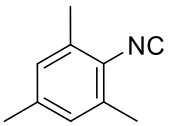


III-2a (63%)

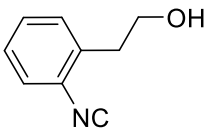
III-2b (55%)

III-2c (65%)

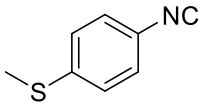
III-2d (65%)



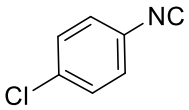
III-2e (70%)



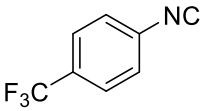
III-2f (18%)



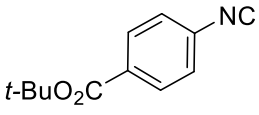
III-2g (51%)



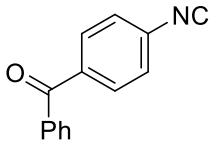
III-2h (50%)



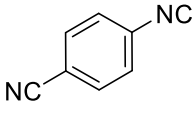
III-2i (45%)



III-l (49%)



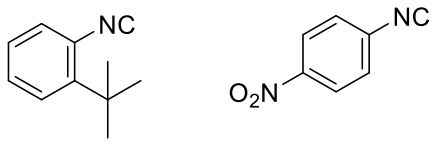
III-2m (43%)



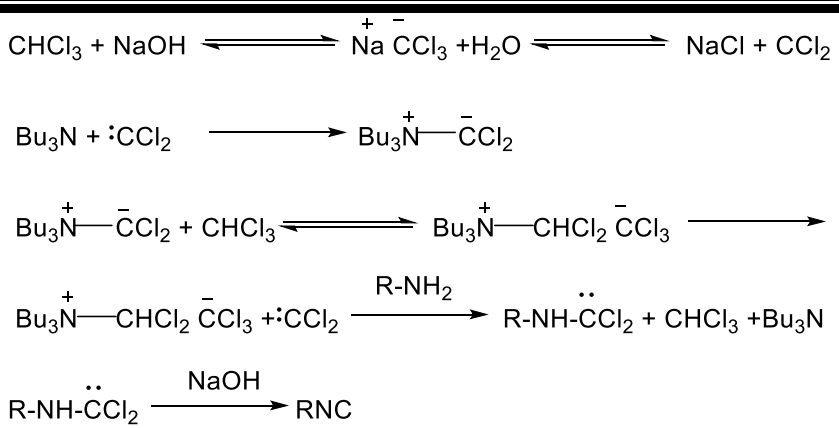
III-2n (29%)

[a] Reaction conditions aniline (5 mmol, 1.0 equiv), $CHCl_3$ (2x1.2), NaOH (60 mmol, 12 equiv), and 1g of Na_2SO_4 were continuously milled for the given time in a Spex 8000M mixer/mill into a zirconia-milling beaker (45 ml) equipped with four balls (d = 10.0 mm) Isolated yields

The presence of a *tert*-butyl group on the position 2 of the aniline ring was found to hinder the synthesis of the isocyanide. In this case we successfully adopt the use of 1 equivalent of a tertiary amine to the reaction mixture recovering the product that was not observed in previous conditions (entry **III-3a**). In this case the trialkylated amine plays a role which could be explained by the mechanism postulated by Makosza, reported in the Scheme 47.[243] The reaction between the chlorocarbene formed in presence of the base and the amine would result in an ammonium ylide specie, which would promote the transfer of the carbene specie to the aromatic hindered amine.



III-3a 19 % **III-3b 25 %**

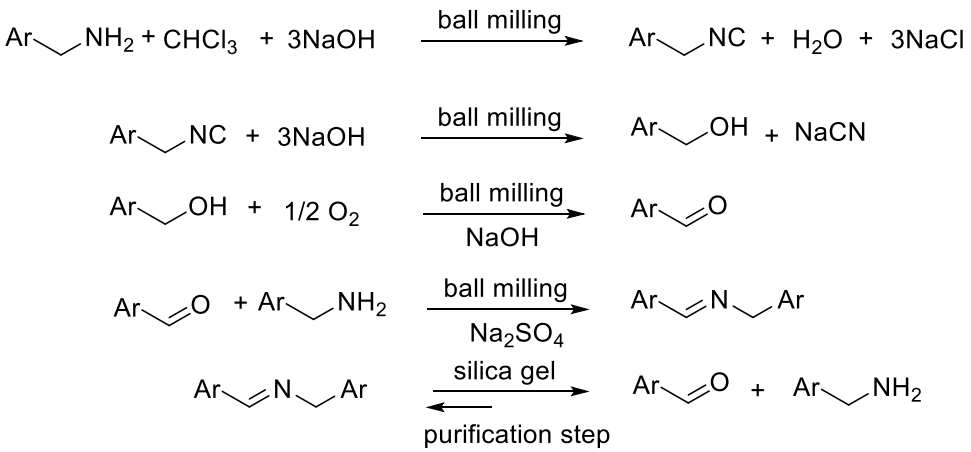


Scheme 47 *The use of trylkylamine for enhancing poor reactivity[a]*

Reaction conditions aniline (5 mmol, 1.0 equiv), $CHCl_3$ (2x1.2), NaOH (60 mmol, 12 equiv), 1g of Na_2SO_4 and tributylamine (5 mmol, 1 equiv.) were continuously milled for the given time in a Spex 8000M mixer/mill into a zirconia-milling beaker (45 ml) equipped with four balls (d = 10.0 mm) Isolated yields

The same approach was used to recover the otherwise not observed product deriving from the *p*-nitro-aniline (Entry **III-3b**, scheme 47).

The attempts to extend the method to benzylic amines provided us the unexpected information about the formation of the iminic corresponding product besides the desired isocyanide



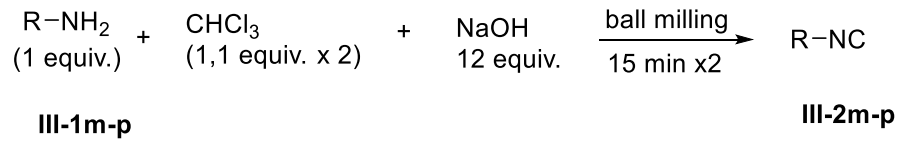
Scheme 48 *A possible pathway to the formation of carbonylic and imine by-product*

As a possible pathway leading to this function, we suggested the formation of the hydroxyl compound from the already formed isocyanide, which could, in presence of oxygen, the base and under mechanochemical conditions, undergo to oxidation. The resulting aldehydic derivative would then react with the amine present in the ambient reaction (scheme 48)[170]

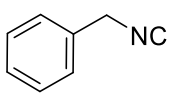
As a control experiment we reacted the benzylamine and the sodium hydroxide in absence of chloroform under mechanochemical conditions and we did not detect the formation of the imine or aldehyde. The benzyl isocyanide and the benzyl amine were as well grinded together without sodium hydroxide and also in this case we could not observe any trace of Schiff base.

On the other side carrying out the reaction between benzyl alcohol, benzylamine amine with sodium hydroxide led to the formation of the imine in good yield.

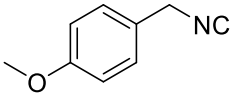
Table 11 *Scope of the reaction: benzylic amines*[a]



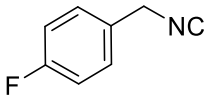
III-1m-p **III-2m-p**



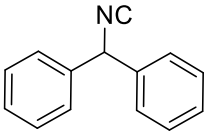
III-2m (56%)



III-2n (49%)



III-2o (49%)



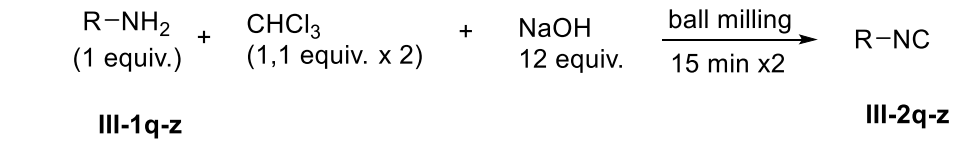
III-2p (49%)

[a]Reaction conditions amine (5 mmol, 1.0 equiv), $CHCl_3$ (2x1.2), NaOH (60 mmol, 12 equiv), and 1g of Na_2SO_4 were continuously milled for the given time in a Spex 8000M mixer/mill into a zirconia-milling beaker (45 ml) equipped with four balls (d = 10.0 mm) Isolated yields

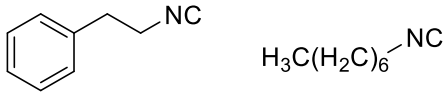
A series of benzylic isocyanide were succefully prepared with the method (Table 12). Electron-withdrawing (entry **III-2n**) and electron-donating (entry **III-2o**) group on the aryl ring did not influence in a considerable way the yield registered. The sterically hindered compound **III-2p** was prepared with satisfying yield.

The last part of our work was dedicated to validating the methodology to a wide number of aliphatic primary amines. We observed a general slight improvement in the yield with respect to the synthesized aromatic isocyanides (Table 12). Indeed, isocyanide with a medium long chain were usefully prepared and isolated (entry **III-2r**, **III-2s**, **III-2t**). The oleyl amine gave the desired product with satisfying yield and no isomerization on the double bond was observed (entry **III-2v**). Adamantyl-isocyanide was prepared with satisfying yield despite the sterical hindrance of the starting primary amine (**III-2w**).

Table 12 *Scope of the Hoffman mechanochemical reaction: aliphatic amines*[a]

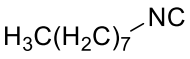


III-1q-z **III-2q-z**

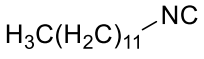


III-2q (52%)

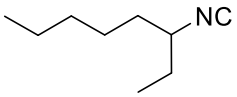
III-2r (63%)



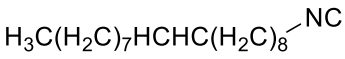
III-2s (71%)



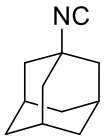
III-2t (69%)



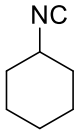
III-2u (54%)



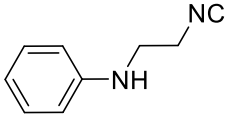
III-2v (61%)



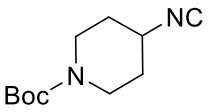
III-2w (58%)



III-2x (47%)



III-2y (25%)



III-2z (54%)

[a]Reaction conditions amine (5 mmol, 1.0 equiv), $CHCl_3$ (2x1.2), NaOH (60 mmol, 12 equiv), and 1g of Na_2SO_4 were continuously milled for the given time in a Spex 8000M mixer/mill into a zirconia-milling beaker (45 ml) equipped with four balls (d = 10.0 mm) Isolated yields

Conclusions

In conclusion, a mechanochemical approach to the classical Hoffman reaction for the synthesis of isocyanides has been developed. The reaction proceeds fast and the yields obtained are good if compared to the solution counterpart; besides, this transformation led to the isocyanide moiety directly from the primary amines and has been shown to be applicable to a wide class of compounds.

By means of ball milling we achieved to avoid the use of big amount of a toxic solvent such as chloroform and the necessity to use a phase transfer catalyst.

Experimental Section

General methods and material

Commercially available reagents were purchased from Acros, Aldrich, Strem Chemicals, Alfa Aesar, TCI Europe and used as received. The solvents were purchased from Aldrich or VWR International in sure/sealedTM bottles over molecular sieves. Filtration of the resulting brown crude isocyanide residue loaded onto a short bed of silica gel was performed by using EcoChromeTM MP Silica gel 60 Å, particle size 0.040–0.063 mm (230–400 mesh). All reactions were monitored by thin-layer chromatography (TLC) performed on glass-backed silica gel 60 F254, 0.2 mm plates (Merck), and compounds were visualized under UV light (254 nm) or using cerium ammonium molybdate solution with subsequent heating. The eluents were technical grade and distilled prior to use. A Spex 8000M Mixer/Mill®, ball-milling apparatus was used for all reactions. The reagents were milled using a zirconia-beaker (45 mL) equipped with balls (d = 10.0 mm) of the same material. ^{1}H and ^{13}C liquid NMR spectra were recorded on a Varian 400 and 500 MHz NMR spectrometer at 298 K and were calibrated using trimethylsylane (TMS). Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referred to the residual hydrogen in the solvent ($CHCl_3$, 7.27 ppm or DMSO 2.54 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br s = broad singlet), coupling constant (J) in Hertz and integration. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent (CDCl3, δ 77.0 ppm or δ DMSO-d6 δ 39.5 ppm). To remove any trace of heptane, all NMR samples were first dissolved in DCM (approximately 1 mL) and then concentrated under vacuum with a rotary evaporator. ^{1}H NMR self-diffusion measurements were performed in $CDCl_3$ at 298 K on a Bruker Avance 300 MHz (7.05 T) spectrometer. A Bruker DIFF30 probe supplied by a Bruker Great 1/40 amplifier was used to measure the self-diffusion coefficients, D. The NMR sequence

used was the Pulse-Gradient STimulated Echo (PGSTE). Experiments were performed varying the gradient strength (g) keeping, at the same time, the gradient pulse length (δ) and the gradient pulse intervals constant (Δ). D were extrapolated from the Stejskal-Tanner plot, i.e. the semi-logarithmic fitting of I/I0 vs q 2 t, where I and I0 are the signals intensities in the presence and absence of the applied field gradient respectively, q = γgδ is the scattering vector (γ being the gyromagnetic ratio of the observed nucleus), t = (Δ− δ/3) is the diffusion time.[1] Errors on the self-diffusion coefficients were estimated to be around 2 % on the basis of repeated measurements. Deuterated NMR solvents were obtained from Aldrich. High resolution mass spectra (HRMS) were recorded using an Electrospray Ionisation (ESI) spectrometer. Analysis of reaction mixture was determined by GC-MS (GC Agilent 6850, MS Agilent 5973) equipped with HP5 universal capillary column (30 m length and 0.20 mm diameter, 0.11 film thickness) and a flame ionization detector (FID). GC oven temperature was programmed from 80 °C to 250 °C at the rate of 10 °C/min. He gas was used as a carrier gas. Temperatures of injection port and FID were kept constant at 300 °C. Retention times of different compounds were determined by injecting pure compound under identical conditions. Melting points were determined in an open capillary on a Büchi melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a FT-IR Bruker Equinox-55 spectrophotometer and on a Bruker Tensor 27 spectrophotometer, equipped with a diamond-ATR accessory and a DTGS detector.

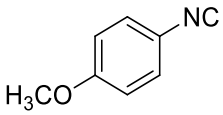
Synthesis of 1-Isocyano-4-methoxybenzene III-2a; general procedure for the synthesis of isocyanide II-2a-z

4-methoxy aniline (615 mg, 5.0 mmol), sodium hydroxide (2.4 g, 60.0 mmol), chloroform (716 mg, 484 µL, 6.0 mmol) and sodium sulfate (1.0 g, 7.0 mmol) were transferred into a zirconia-milling beaker (45 ml) equipped with four balls (d = 10.0 mm) of the same material. The jar was shaken at 18Hz for 15 minutes in a Spex 8000M Mixer/Mill. Then an additional aliquot of

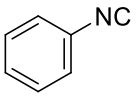
chloroform (716 mg, 484 µL 6.0 mmol) was added and the mixture was subjected to grinding further for 15 minutes. Upon completion of the ball milling process (monitored by TLC and GC), the resulting brown solid was scratched off from the jar, loaded onto a short bed of silica gel (1 g) and washed with heptane/ethyl acetate (97/3) solution (See picture Figure 11). The solvent was removed under reduced pressure, affording the desired product **III-2a** as yellow solid, (419 mg, 63% yield).

Figure 11 *Filtration of crude mixture on a short pad of silica*

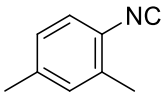
Summary of ^{1}H and ^{13}C NMR and HRMS data for isocyanide II-2a-z



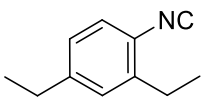
1-Isocyano-4-methoxybenzene III-2a. yellow solid, (419 mg, 63% yield). mp: 31–32 °C (Lit.:[232] 30 °C); Rf = 0.45 (9:1 Heptane/AcOEt); IR (KBr) ν = 2969, 2123, 1606, 1504, 1249, 1024, 831 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.31 (d, *J* = 8.8 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 3.82 (s, 3H); ^{13}C-NMR (126 MHz, $CDCl_3$): δ = 162.8 (t, J_{NC} = 5.2 Hz), 160.0, 128.0, 119.6 (t, J_{NC} = 13.5 Hz), 114.7, 55.7. Spectroscopic data are in agreement with those reported earlier.[232]



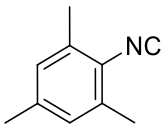
Isocyanobenzene III-2b. Yellow oil (284 mg, 55%); Rf = 0.57 (9:1 Heptane/AcOEt); IR (KBr) ν = 2972, 2123, 1611, 1512, 1261, 837 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ: = 7.41–7.36 (m, 5H); ^{13}C NMR (126 MHz, CDCl3): δ = 164.1 (t, J_{NC} = 5.2 Hz), 129.5, 129.5, 126.8 (t, J_{NC} = 13.5 Hz), 126.5. Spectroscopic data are in agreement with those reported earlier.[244]



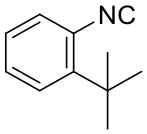
1-Isocyano-2,4-dimethylbenzene III-2c. Brown oil, (387 mg, 59%); Rf = 0.57 (9:1 Heptane/AcOEt); IR (KBr) ν = 2967, 2940, 2872, 2121, 1660, 1580, 1430, 801 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 7.8 Hz, 1H), 7.07 (s, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 2.38 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.9 (t, J_{NC} = 5.6 Hz), 139.6, 134.7, 131.2, 127.4, 126.4, 124.1 (t, J_{NC} = 13.2 Hz), 21.4, 18.6; HRMS (ESI): m/z calcd for $C_9H_{10}N$: 132.0813 $[M+H]^+$. Found: 132.0817.



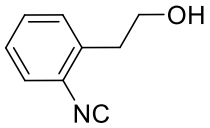
2**,4-Diethyl-1-isocyanobenzene III-2d.** Yellow oil, (517 mg, 65%); Rf = 0.53 (9:1 Heptane/AcOEt); IR (KBr) ν = 2970, 2942, 2880, 2120, 1667, 1585, 1459, 804 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.26 (t, *J* = 7.6 Hz, 1H), 7.12 (d, *J* = 7.6 Hz, 2H), 2.80 (q, *J* = 7.5 Hz, 4H), 1.27 (t, J = 7.5 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.9 (t, J_{NC} = 5.5 Hz), 140.9, 129.2, 126.3, 125.4, 25.9, 14.0; HRMS (ESI): m/z calcd for $C_{11}H_{14}N$: 160.1126 $[M+H]^+$. Found: 160.1130.



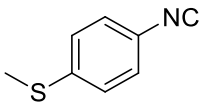
2-Isocyano-1,3,5-trimethylbenzene III-2e. Yellow oil (508 mg, 70 %); Rf = 0.51 (9:1 Heptane/AcOEt); IR (KBr) ν = 2970, 2942, 2880, 2120, 1667, 1585, 1459, 804 cm^{-1}; ^{1} H NMR (300 MHz, $CDCl_3$): δ = 6.90 (s, 2H), 2.36 (s, 6H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.8 (t, J_{NC} = 5.2 Hz), 138.9, 134.7, 128.5, 124.3 (t, J_{NC} = 12.5 Hz), 21.2, 18.9. Spectroscopic data are in agreement with those reported earlier.[245,246]



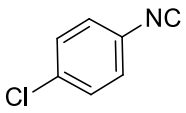
1-(tert-Butyl)-2-isocyanobenzene III-3a. Yellow oil (151 mg, 19%); Rf = 0.52 (9:1 Heptane/AcOEt); IR (KBr) ν = 2962, 2871, 2120, 1631, 749 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28 (d, *J* = 5.9 Hz, 1H), 7.08 (t, *J* = 6.1 Hz, 1H), 6.86–6.74 (m, 1H), 6.68 (d, *J* = 7.6 Hz, 1H), 1.47 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.2 (t, J_{NC} = 5.6 Hz), 145.7, 130.2, 129.5, 127.0, 126.9, 125.4 (t, J_{NC} = 12.4 Hz), 35.1, 29.3; HRMS (ESI): m/z calcd for $C_{11}H_{14}N$: 160.1126 $[M+H]^+$. Found: 160.1123.



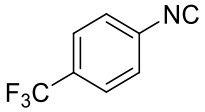
2-(2-Isocyanophenyl)ethan-1-ol III-2f. Colourless oil (132 mg, 18%); Rf = 0.52 (3:2 Heptane/AcOEt); IR (KBr) ν = 2962, 2932, 2844, 2863, 2142, 1667, 1465, 1380 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.45– 7.18 (m, 4H), 3.93 (t, J = 6.5 Hz, 2H), 3.04 (t, J = 6.5 Hz, 2H), 1.61 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.2, 135.5, 130.8, 129.6, 127.6, 127.2, 126.6 (t, J_{NC} = 12.4 Hz) 61.9, 35.7; HRMS (ESI): m/z calcd for $C_9H_{10}NO$: 148.0762 $[M+H]^+$. Found: 148.0759.



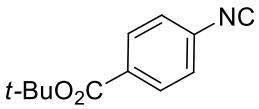
((4-Isocyanophenyl)(methyl)sulfane III-2g. Yellow oil (380 mg, 51%); Rf = 0.21 (9:1 Heptane/AcOEt). IR (KBr) ν = 2921, 2123, 1484, 1091, 812 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.28 (d, *J* = (8.6 Hz, 2H), 7.21 (d, *J* = 8.6 Hz, 2H), 2.49 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.2, 141.4, 126.7, 126.5, 123.2, (t, J_{NC} = 13.5 Hz) 15.4; HRMS (ESI): m/z calcd for C_8H_8NS: 150.0377 $[M+H]^+$, found: 150.0379.



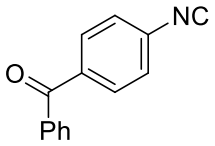
1-Chloro-4-isocyanobenzene III-2h. White solid (344 mg, 50%), m.p.: 71-72°C (Lit.:[247] 71 °C); Rf = 0.60 (9:1 Heptane/AcOEt). IR (KBr) ν = 2124, 1650, 1488, 1403, 1090, 1020, 828 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.38 (d, *J* = 8.8 Hz, 2H), 7.32 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 65.7, 135.6, 129.9, 127.8, 125.2 (t, J_{NC} = 13.5 Hz); Spectroscopic data are in agreement with those reported earlier.[248]



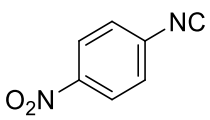
1-Isocyano-4-(trifluoromethyl)benzene III-2i. Brown oil (385 mg, 45%); Rf = 0.67 (9:1 Heptane/AcOEt); IR (KBr) ν: 3038, 2935, 2261, 1615, 1504, 1323, 1218, 1130, 827 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.1 Hz, 2H), 7.51 (d, *J* = 8.1 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 170.0, 134.3 (q, 2 J_{CF} = 33 Hz, C(Ar)-CF_3), 132.0 (t, J_{CN} = 15 Hz, C(Ar)-NC), 129.6, 129.4 (dd, J 1 = 7.6 Hz, J 2 = 3,8 Hz), 125 (q, 1 J_{CF} = 273 Hz). Spectroscopic data are in agreement with those reported earlier.[249]



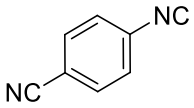
tert-Butyl 4-isocyanobenzoate III-l. Brown oil (498 mg, 49%), Rf = 0.42 (9:1 Heptane/AcOEt); IR (KBr) ν = 3001, 2978, 2126, 1719, 1604, 1290, 1100, 768 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.98 (d, *J* = 8.5 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 1.56 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.9, 164.0, 132.8, 130.6, 129.5, 126.2, 82.0, 28.1; HRMS (ESI): m/z calcd for $C_{12}H_{14}NO_2$: 204.1024 [M+H]+ , found: 204.1025



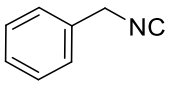
(4-Isocyanophenyl)(phenyl)methanone III-2m. White solid (445 mg, 43%), m.p.: 101–102 °C (Lit.:[250] 101 °C); Rf = 0.44 (9:1 Heptane/AcOEt); IR (KBr) ν : 3093, 3065, 2126, 1648, 1599, 1574, 1411, 1274, 694 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.84 (d, *J* = 7.4 Hz, 2H), 7.77 (d, *J* = 7.4 Hz, 2H), 7.63 (t, *J* = 7.0 Hz, 1H), 7.50 (t, *J* = 7.0 Hz, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): : = 195.0, 167.1, 138.3, 136.8, 133.2, 131.2, 130.1, 129.5, 128.7, 126.5. Spectroscopic data are in agreement with those reported earlier.[247]



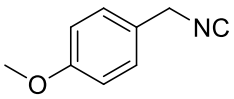
1-Isocyano-4-nitrobenzene III-3b. Yellow solid (185 mg, 25 %); m.p.: 109–110 °C (Lit.:[251] 110 °C); Rf = 0.53 (9:1 Heptane/AcOEt); IR (KBr) ν = 3067, 2132, 1545, 1354 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 8.31 (d, *J* = 8.9 Hz, 2H), 7.57 (d, *J* = 8.9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ: = 170.0 (t, J_{CN} = 10 Hz), 147.7, 131.4 (t, J_{CN} = 12.7 Hz), 127.7, 125.2. Spectroscopic data are in agreement with those reported earlier.[252]



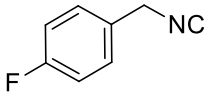
4-Isocyanobenzonitrile III-2n. White solid (186 mg, 29%), m.p.: 184-185 °C (Lit: [253] 180-185 °C); Rf = 0.53 (9:1 Heptane/AcOEt); IR (KBr) ν = 3093, 3045, 2235, 1607, 1501 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.73 (d, *J* = 8.6 Hz, 2H), 7.50 (d, *J* = 8.6 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 169.1, 133.6, 129.9 (t, J_{NC} = 13.5 Hz.), 127.4, 117.3, 113.6. Spectroscopic data are in agreement with those reported earlier.[254]



(Isocyanomethyl)benzene III-2m. Brown oil (328 mg, 56%); Rf = 0.54 (9:1 Heptane/AcOEt); IR (neat) ν = 3100, 2900, 2150, 1600, 1480, 1210, 690 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.42-7.34 (m, 5H), 4.65 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ = 157.8 (t, J_{NC} = 5.6 Hz), 132.4, 129.0, 128.4, 126.6, 45.5 (t, J_{NC} = 6.9 Hz). Spectroscopic data are in agreement with those reported earlier.[255]

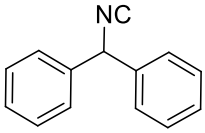


1-(Isocyanomethyl)-4-methoxybenzene III-2n. Yellow oil (361 mg, 49%); Rf = 0.30 (9:1 Heptane/AcOEt); IR (KBr) ν = 2939, 2838, 2148, 1681, 1510, 1247, 1029, 813 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.24 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.54 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz; $CDCl_3$) 159.7, 157.1 (t, J_{NC} = 5.1 Hz), 128.2, 124.6, 114.4, 55.4, 45.1 (t, J_{NC} = 6.7 Hz). Spectroscopic data are in agreement with those reported earlier.[256]

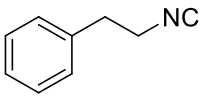


1-Fluoro-4-(isocyanomethyl)benzene III-2o. Yellow oil (304 mg, 45%); Rf = 0.39 (9:1 Heptane/AcOEt); IR (KBr) ν = 2932, 2262, 2153, 1607, 1507, 1222, 820 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ = 7.33 (dd, *J* = 8.6, 5.1 Hz, 2H), 7.10 (t, *J* = 8.6 Hz, 2H), 4.61 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 163.0 (d, 1 J_{CF} = 247 Hz, C(Ar)-F, 158.0 (t, 1 J_{CN} = 5 Hz), 128.6 (d,

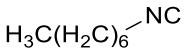
J_{CF} = 8.8 Hz), 128.51, 116.0 (d, J_{CF} = 23 Hz), 44.8 (t, J_{CN} = 6.3 Hz); HRMS (ESI): m/z calcd for C_8H_7FN: 136.0562 $[M+H]^+$ found: 136.0560. Spectroscopic data are in agreement with those reported earlier.[232]



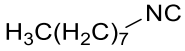
(Isocyanomethylene)dibenzene III-2p. White solid (396 mg, 41%), m.p.: 36–37 °C (Lit.:[254]35–36 °C); Rf = 0.50 (9:1 Heptane/AcOEt). IR (KBr) ν 3063, 3030, 2139, 1659, 1601, 1492, 1451, 1323, 700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.39–7.33 (m, 10 H), 5.91 (s, ^1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 158.43, 137.69, 129.09, 128.59, 126.70, 62.09 (t, J_{NC} = 6.4 Hz); HRMS (ESI): m/z calcd for $C_{14}H_{12}N$: 194.0970 [M+H]+ , found: 194.0967



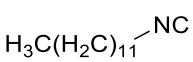
(2-Isocyanoethyl)benzene III-2q. Yellow oil (341 mg, 52%); Rf = 0.57 (9:1 Heptane/AcOEt); IR (neat) ν =3025, 2915, 2146, 1635, 1452, 696 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.34 (t, *J* = 7.3 Hz, 2H), 7.29–7.26 (m, 1H), 7.23 (d, *J* = 7.3 Hz, 2H), 3.61 (tt, *J* = 7.2, 2.1 Hz, 2H), 2.99 (tt, *J* = 5.2, 2.1 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.6 (t, J_{NC}= 6.3 Hz), 136.7, 128.8, 128.7, 127.2, 42.9 (t, J_{NC} = 6.9 Hz), 35.6. Spectroscopic data are in agreement with those reported earlier.[247,248]



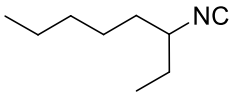
1-Isocyanoheptane III-2r. Yellow oil (394 mg, 63%); Rf = 0.7 (9:1 Heptane/AcOEt); IR (neat) ν = 2925, 2856, 2146, 1635, 1461, 1378, 725 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 3.37 (tt, *J* = 8.6, 3.8 Hz, 2H), 1.70–1.65 (m, 2H), 1.44–1.40 (m, 2H), 1.34–1.25 (m, 6H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ: = 155.8 (J_{NC} = 5.8 Hz), 41.7 (J_{NC} = 6.3 Hz), 31.7, 29.2, 28.5, 26.4, 22.6, 14.1; HRMS (ESI): m/z calcd for $C_8H_{16}N$: 126.1283 $[M+H]^+$, found: 126.1284. Spectroscopic data are in agreement with those reported earlier.[171]



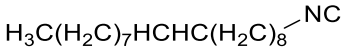
1-Isocyanooctane III-2s. Colourless oil (494 mg, 71%); Rf = 0.53 (9:1 Heptane/AcOEt); IR (KBr) ν = 2932, 2148, 1462 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.36 (tt, *J* 1 = 6Hz, *J* 2 = 3Hz, 2H), 1.70– 1.62 (m, 2H), 1.47–1.40 (m, 2H), 1.30–1.26 (m, 8H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3): δ = 155.7 (t, J_{NC} = 6.0 Hz), 41.7 (t, J_{NC} = 6.0 Hz), 31.8, 29.2, 29.1, 28.8, 26.4, 22.7, 14.2; HRMS (ESI): m/z calcd for $C_9H_{18}N$: 140.1439 [M+H]+ , found: 140.1437. Spectroscopic data are in agreement with those reported earlier. [257]



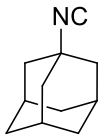
1-Isocyanododecane III-2t. Yellow oil (674 mg, 69%); Rf = 0.54 (9:1 Heptane/AcOEt); IR (KBr) ν = 3090, 2126, 1484, 1088, 823 cm^{-1}; ^{1}H NMR (300 MHz, CDCl3): δ = 3.39–3.34 (m, 2H), 1.69-1.64 (m, 2H), 1.45-1.40 (m, 2H), 1.32–1.26 (m, 16H), 0.87 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 155.7, (t, J_{NC} = 5.6 Hz), 41.6 (t, J_{NC} = 6.4 Hz), 32.0, 29.7 (2C), 29.6, 29.5, 29.4, 29.2, 28.8, 26.4, 22.8, 14.2. Spectroscopic data are in agreement with those reported earlier:[234]



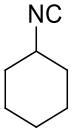
3-Isocyanooctane III-2u. Yellow oil (349 mg, 54%); Rf = 0.54 (9:1 Heptane/AcOEt); IR (KBr) ν = 3047, 2093, 2869, 2151, 1670, 1590, 1489, 1380, 1315, 752 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.34 (t, *J* = 4.0 Hz, 1H), 1.54–1.29 (m, 10 H), 0.90 (t, *J* = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156,2 (t, J_{NC} = 6.4 Hz), 44.6 (t, J_{NC} = 6.0 Hz), 39.0, 30.7, 28.8, 24.1, 22.9, 14.1, 10.9; HRMS (ESI): m/z calcd for $C_9H_{18}N$: 140.1439 $[M+H]^+$, found: 140.1435.



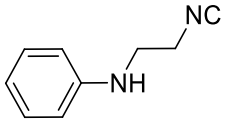
(Z)-1-isocyanoicos-9-ene III-2v. Yellow oil (708 mg, 51%); Rf = 0.48 (9:1 Heptane/AcOEt); IR (KBr) ν = 2927, 2854, 2146, 1635, 1465, 1350, 723 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.35 (dt, *J* = 8.0, 4.2 Hz, 2H), 3.39–3.36 (m, 2H), 2.06-1.98 (m, 2H), 1.69–1.66 (m, 2H), 1.45–1.42 (m, 2H), 1.27– 1.26 (m, 22H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.0 (t, J_{CN} = 5.0 Hz), 130.0, 129.7, 41.5 (t, J_{CN} = 6.3 Hz), 31.9, 29.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 28.7, 27.3, 27.2, 26.4, 22.7, 14.1; HRMS (ESI): m/z calcd for $C_{19}H_{36}N$: 278.2848 [M+H]+ , found: 278.2850.



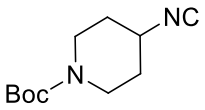
1-Adamantyl isocyanide III-2w. White solid (467 mg, 58%); m.p.: 189–190 °C, (Lit.:[234]190–191 °C); Rf = 0.62 (9:1 Heptane/AcOEt); IR (KBr) ν = 2916, 2858, 2123, 1454, 1354, 1309, 1108, 1076,831 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.10–2.02 (m, 3H), 2.02 (d, *J* = 3.1 Hz, 6H), 1.70–1.63 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 151.8 (t, J_{CN} = 5.0 Hz), 54.4 (t, J_{CN} = 6.3 Hz), 43.7, 35.6, 28.9. Spectroscopic data are in agreement with those reported earlier:[258]



Isocyanocyclohexane III-2x. Colourless oil (256 mg, 47%); Rf = 0.6 (9:1 Heptane/AcOEt); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.61–3.58 (m, 1H), 1.88–1.86 (s, 2H), 1.78–1.65 (m, 4H), 1.50–1.34 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.1 (t, J_{CN} = 5.0 Hz), 51.7 (t, J_{CN} = 6.3 Hz), 32.7, 25.0, 23.0. Spectroscopic data are in agreement with those reported earlier.[259]



N-(2-isocyanoethyl)aniline III-2y. Colourless oil (183 mg, 25%); Rf = 0.41 (9:1 Heptane/AcOEt); IR (KBr) ν = 2960, 2929, 2878, 2864, 2148, 1692, 1460, 1389 cm^{-1}; ^{1} H NMR (500 MHz, $CDCl_3$): δ = 7.22 (t, *J* = 7.8 Hz, 2H), 6.78 (t, *J* = 7.3 Hz, 1H), 6.64 (d, *J* = 9.4 Hz, 2H), 4.02 (bs, 1H), 3.60 (t, *J* = 5.9 Hz, 2H), 3.50 (t, *J* = 5.9 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 161.9, 147.9, 129.5, 118.0, 113.0, 43.8, 37.9; HRMS (ESI): m/z calcd for $C_9H_{11}N_2$: 147.0922 $[M+H]^+$, found: 147.0917.

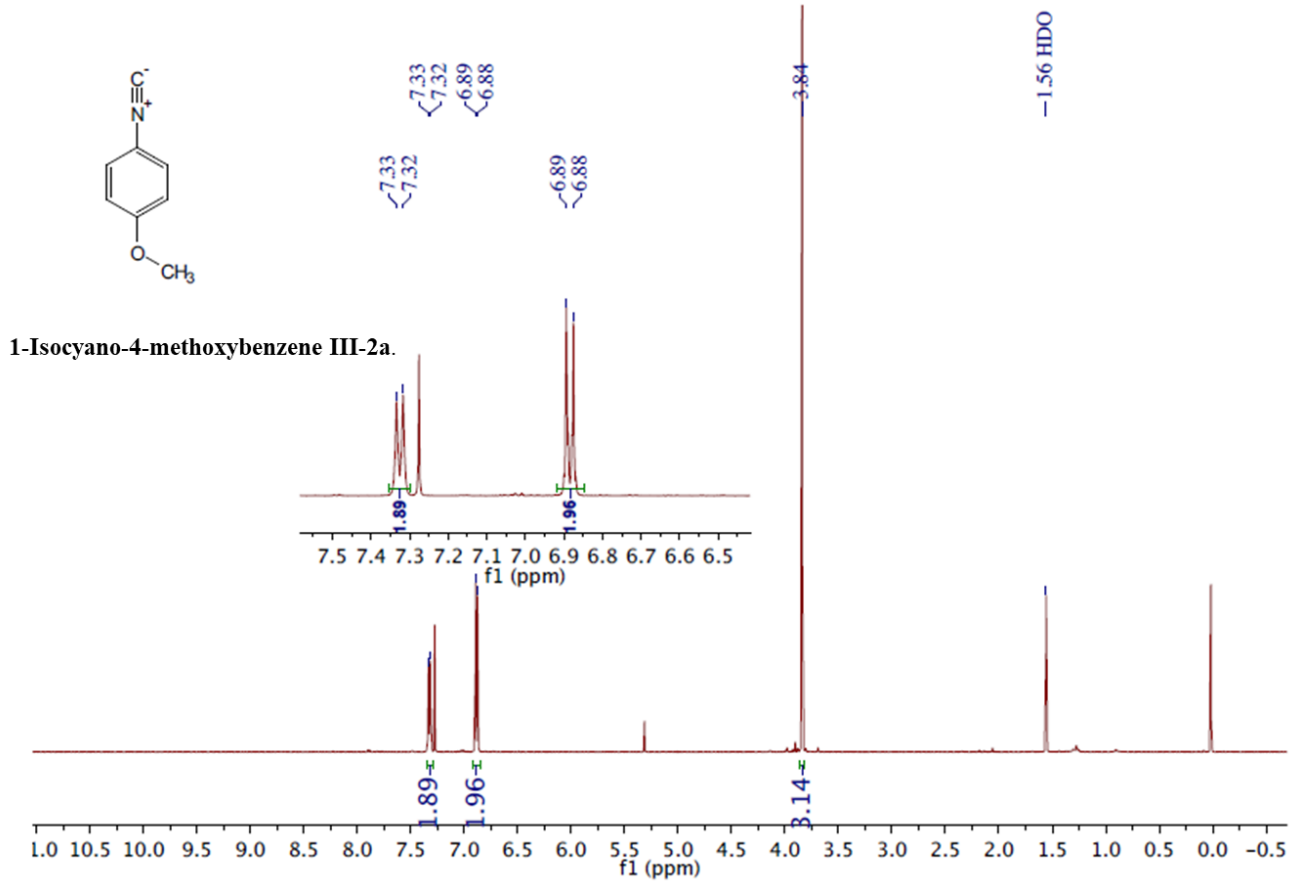


tert-Butyl 4-isocyanopiperidine-1-carboxylate III-2z. Colourless oil (568 mg, 54%); Rf = 0.3 (9:1 Heptane/AcOEt); IR (KBr) ν = 2974, 2931, 2862, 2140, 1678, 1423, 2236, 1129, 1033 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.84 (s, 1H), 3.63–3.55 (m, 2H), 3.45–3.40 (m, 2H), 1.90-1.79 (m, 2H), 1.82–1.79 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 156.7 (t, J_{CN} = 5.0 Hz), 154.5, 80.1, 49.7 (t, J_{CN} = 6.3 Hz), 40.0, 31.5, 28.5; HRMS (ESI): m/z calcd for: $C_{11}H_{19}N_2O_2$: 211.1446 [M+H]+ , found: 211.1450.

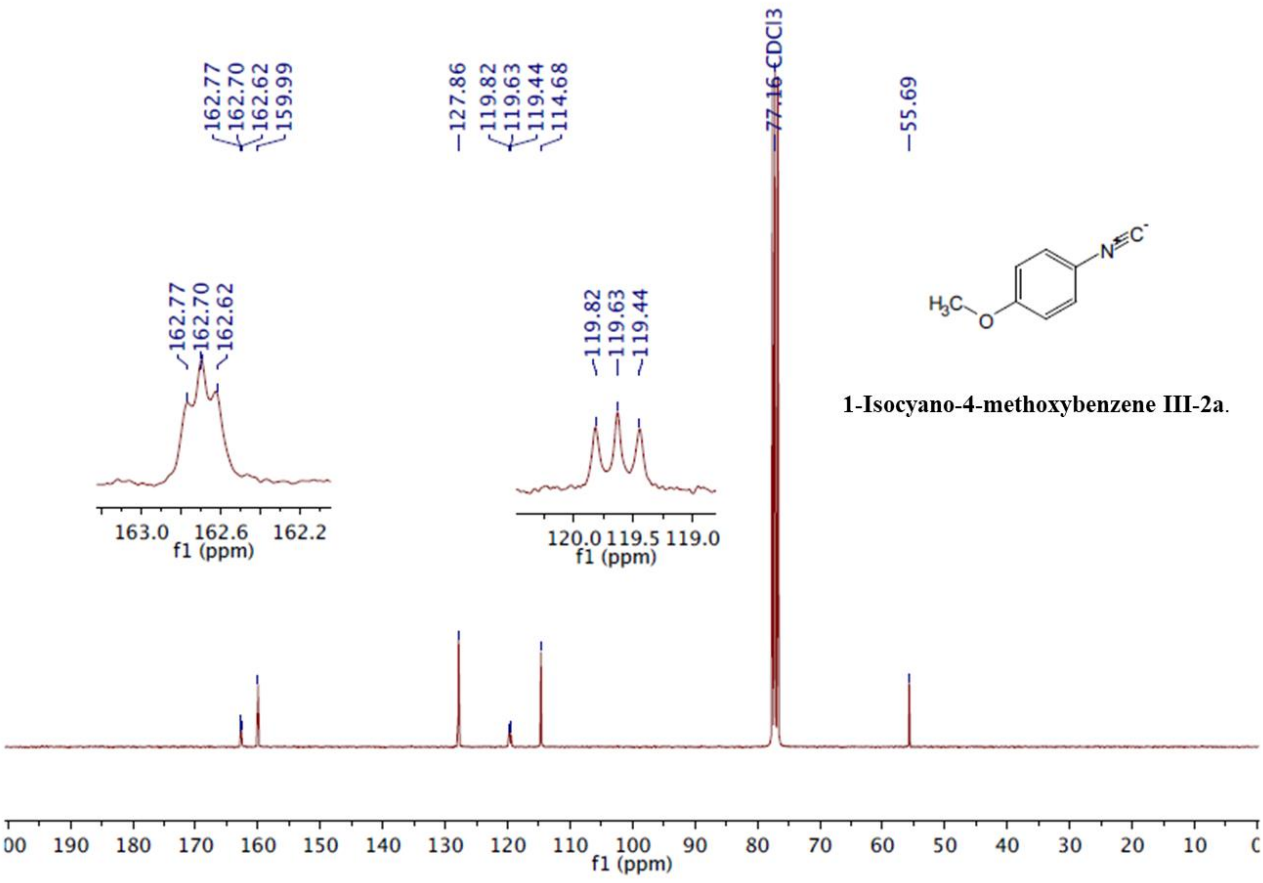
Table 13 *Self diffusion coefficients (D×109 m2 s−1) for all the signals in the 1H NMR spectrum of the by-products from reaction reported in Scheme 4 dissolved in CDCl3. ppm*

ppm	0.88	1.28	3.80	3.83	6.85	6.88	7.00	7.03	7.30	7.33	8.00	8.46
D	1.21	1.97	0.81	1.35	1.17	1.17	0.75	0.71	1.37	1.35	0.81	0.71

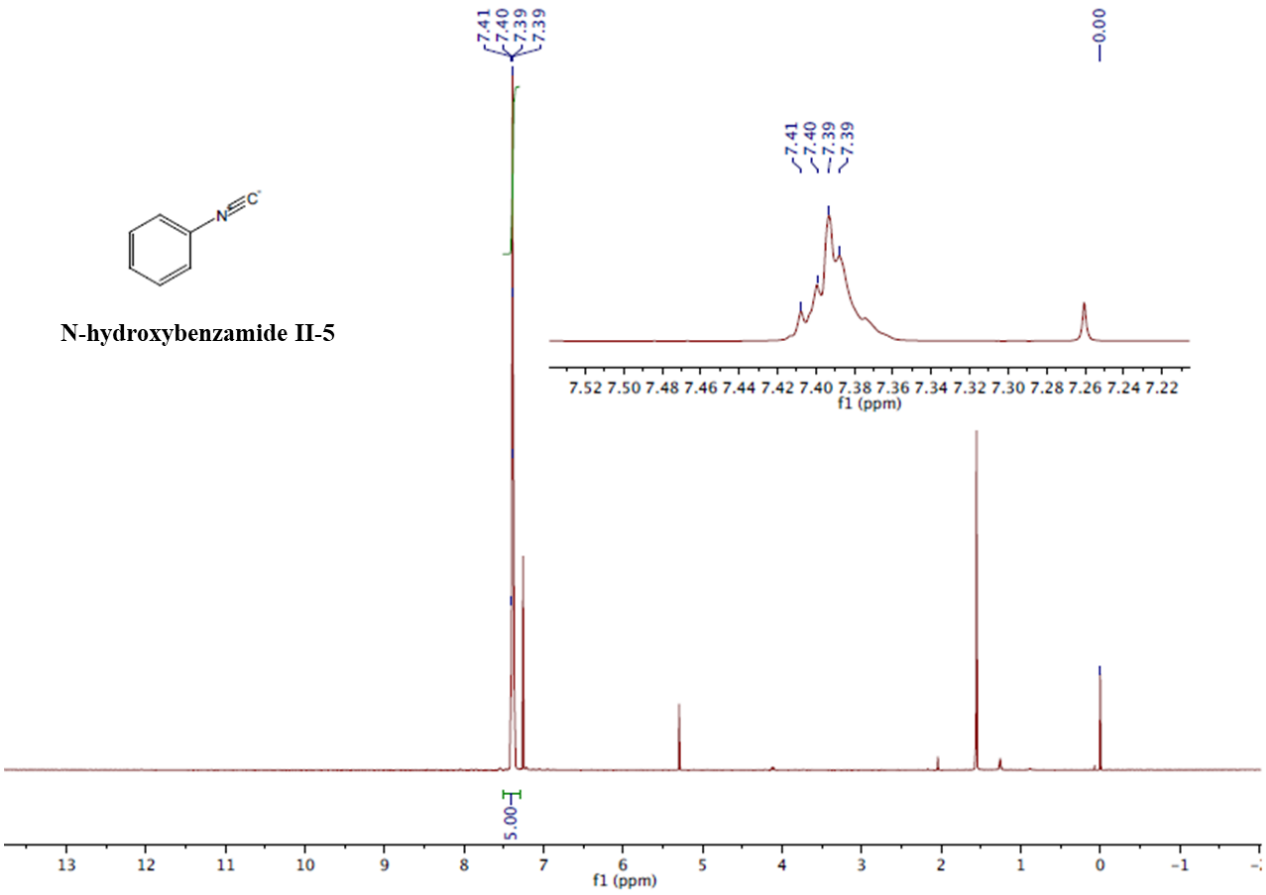
^{1}H NMR and ^{13}C NMR spectra for Isocyanide Derivatives III-2a-z**.**

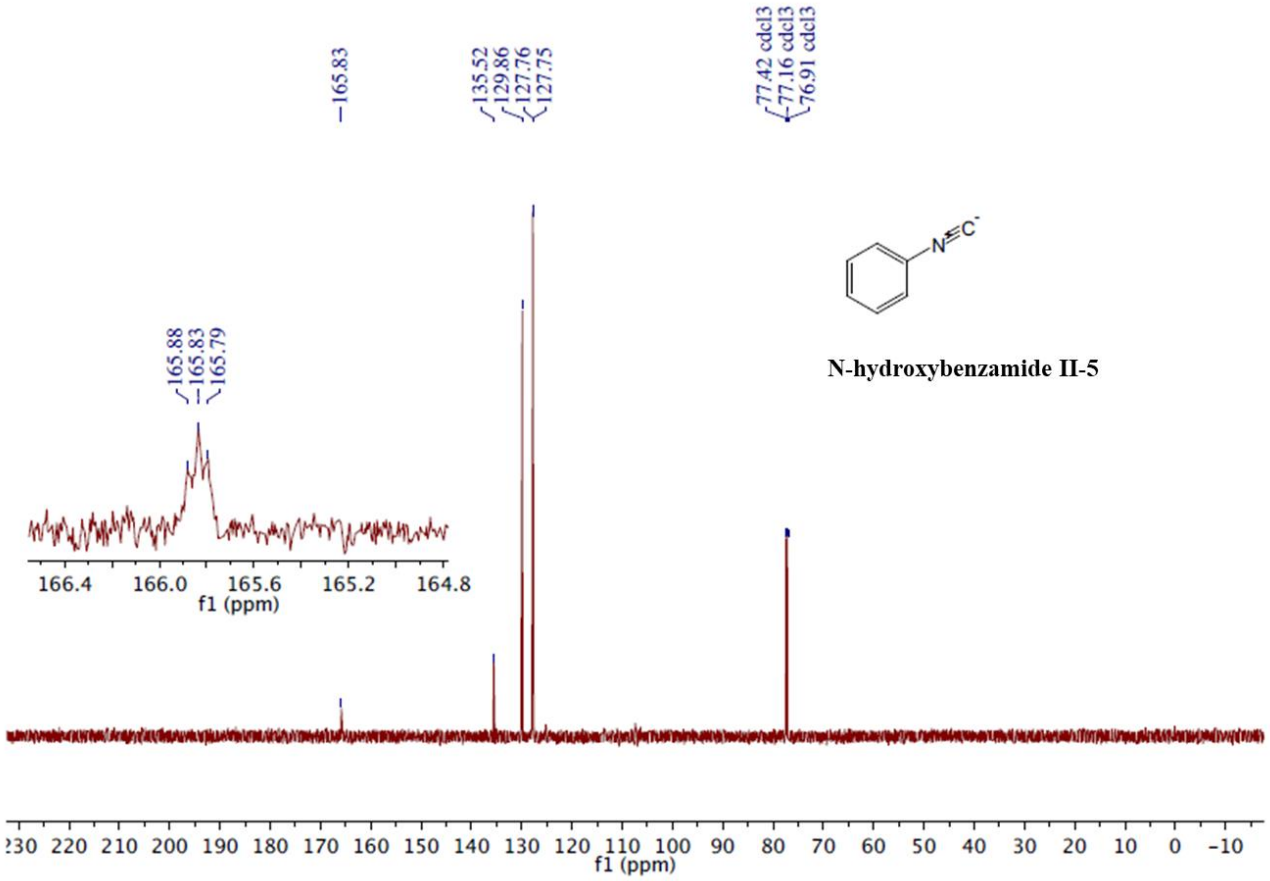


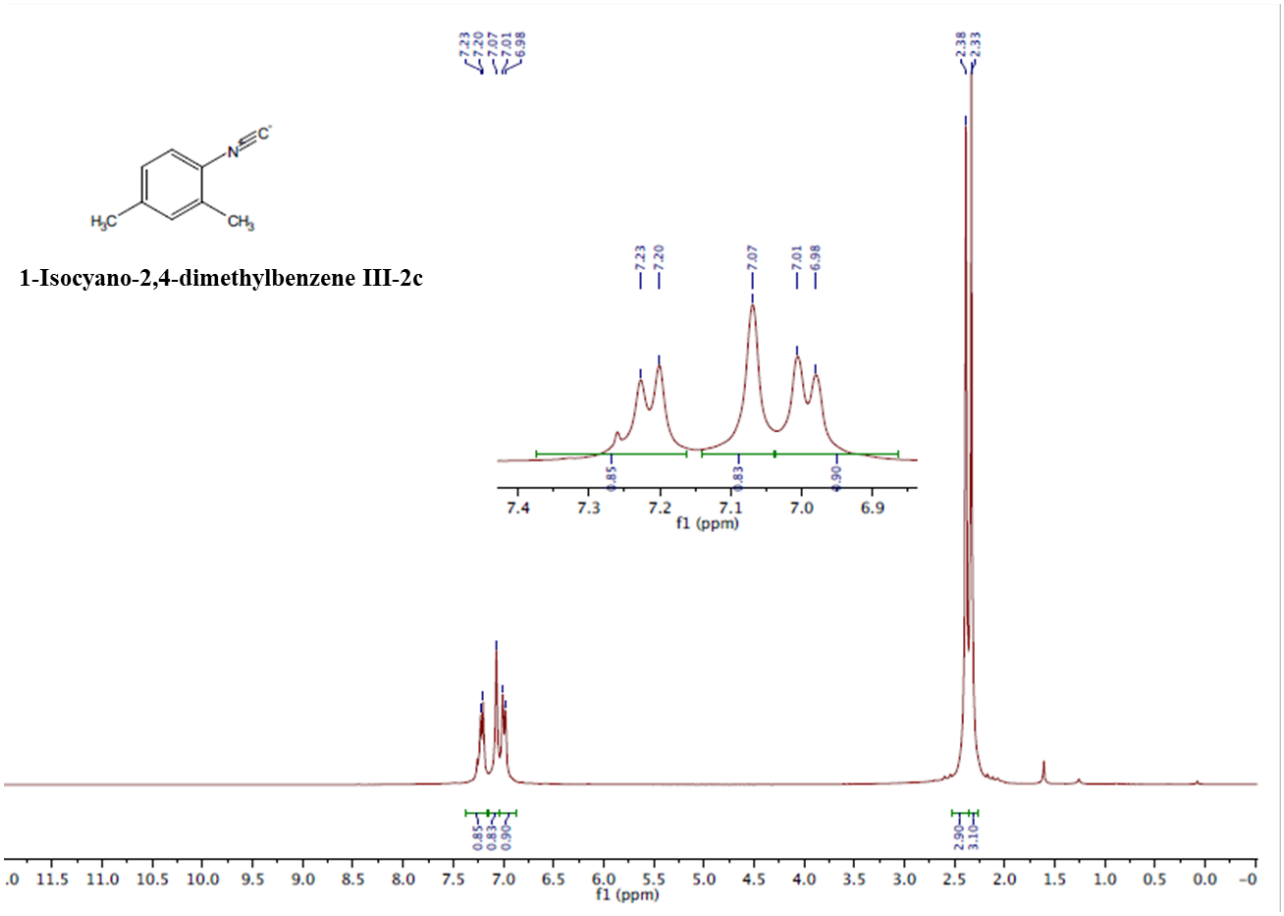
1-Isocyano-4-methoxybenzene III-2a.



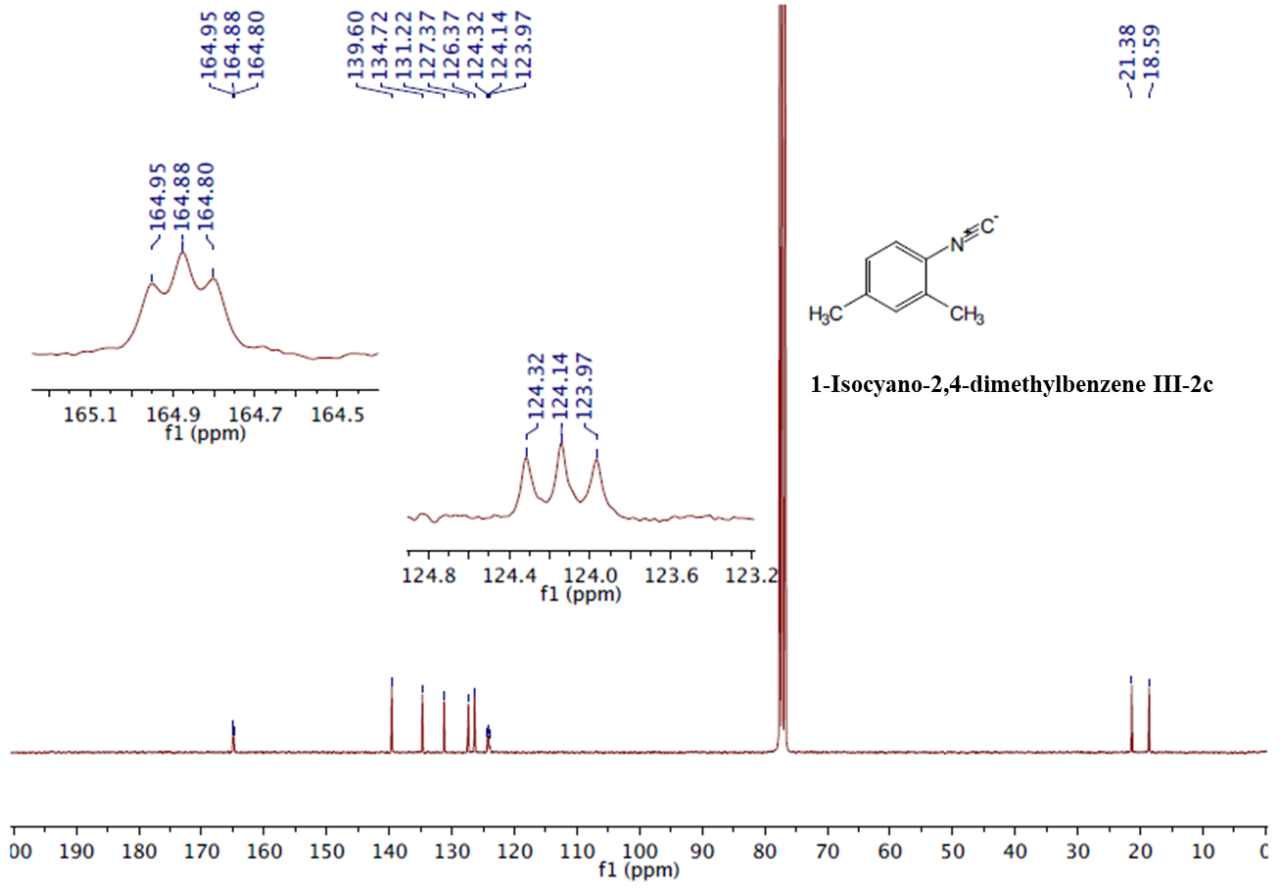
1-Isocyano-4-methoxybenzene III-2a.


7.41
7.40
7.39
7.39
0.00
N-hydroxybenzamide II-5
5.00
f1 (ppm)

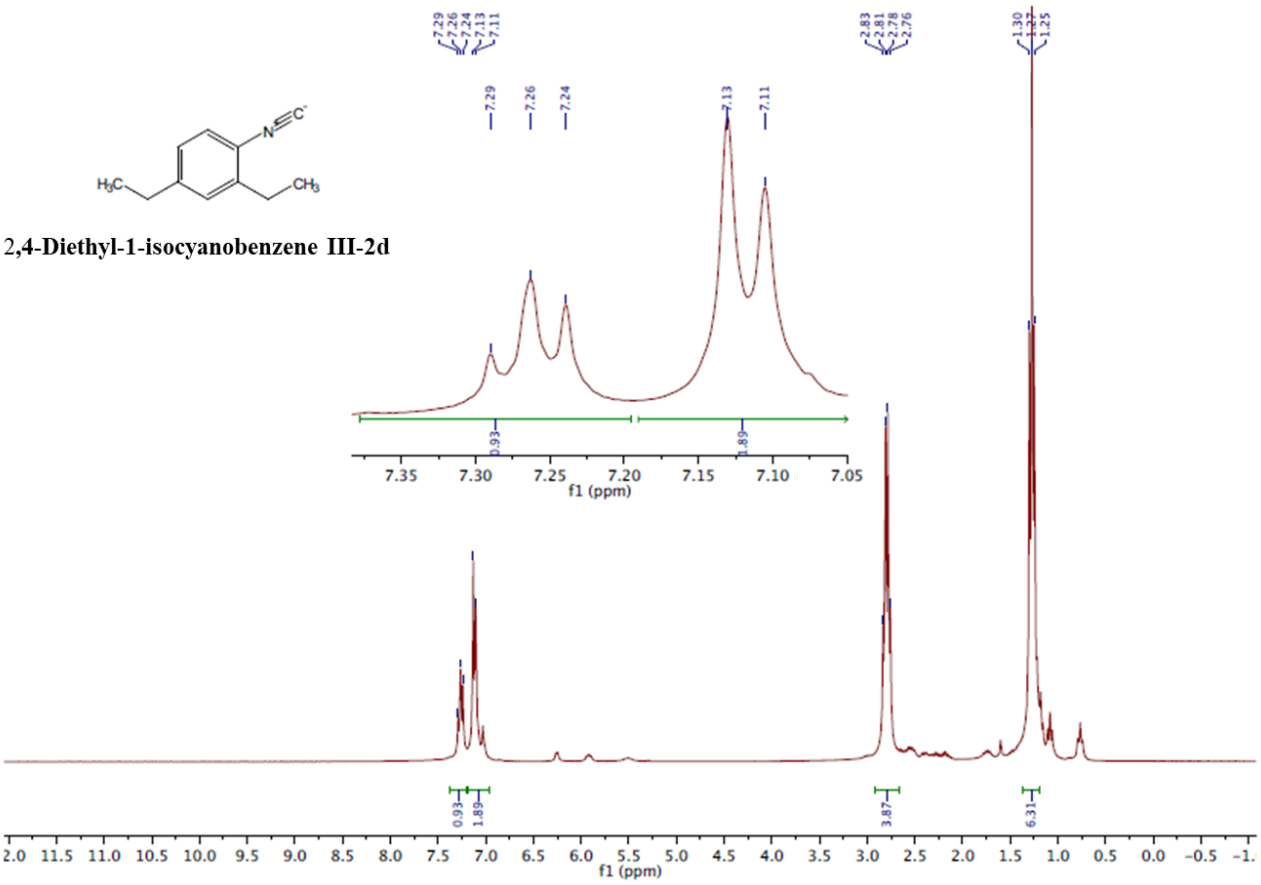

165.83
135.52
129.86
127.76
127.75
77.42 cdcl3
77.16 cdcl3
76.91 cdcl3
165.88
165.83
165.79
N-hydroxybenzamide II-5
f1 (ppm)



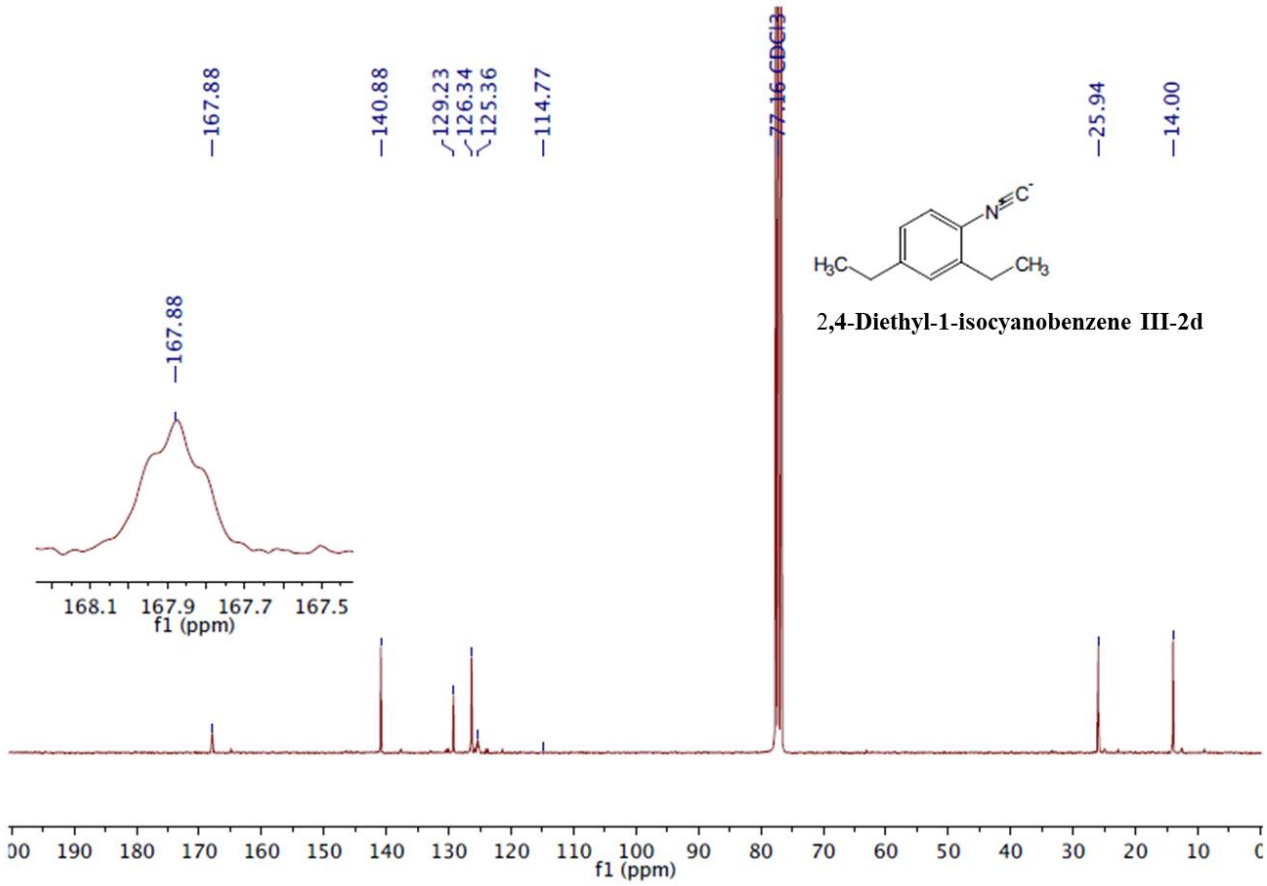
1-Isocyano-2,4-dimethylbenzene III-2c



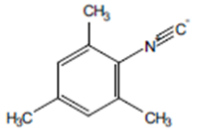
1-Isocyano-2,4-dimethylbenzene III-2c



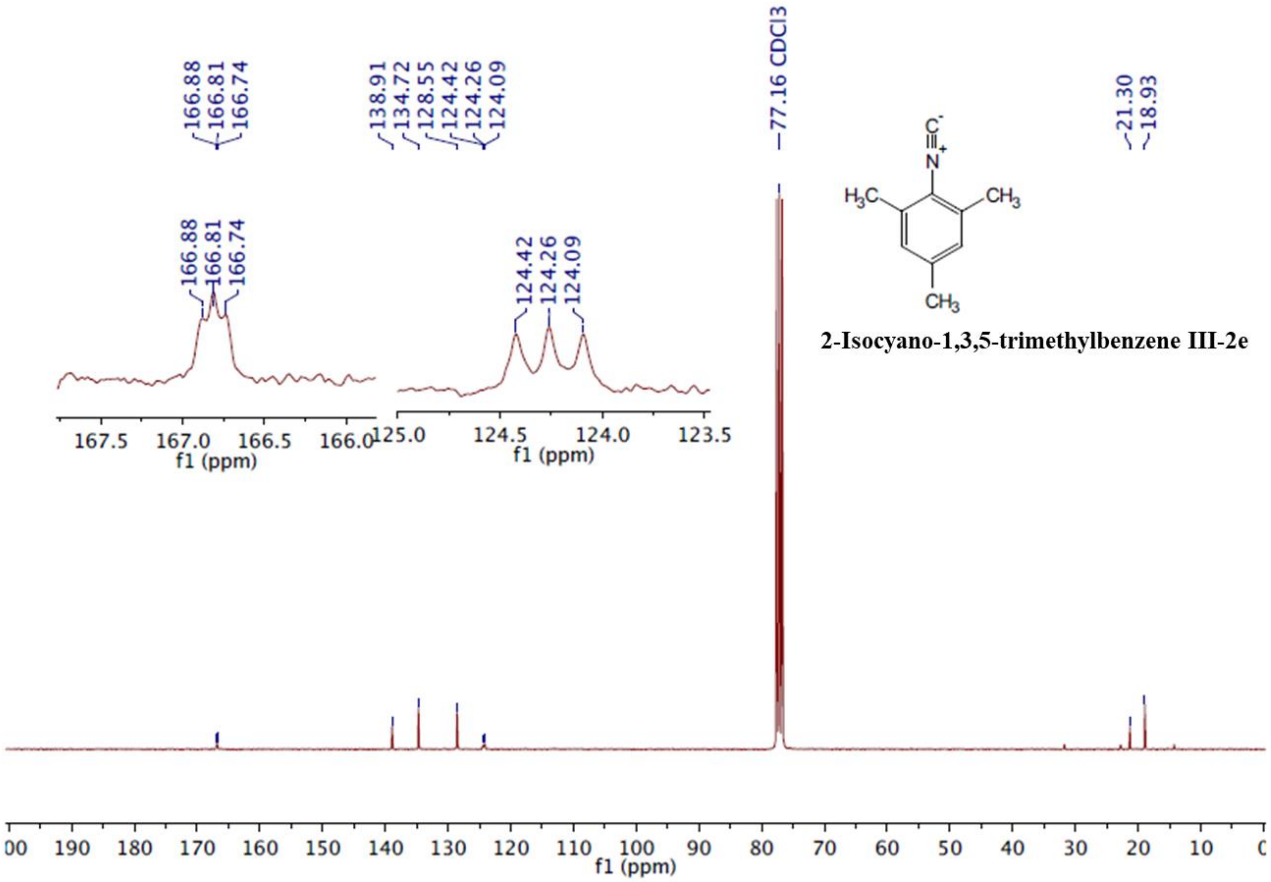
2,4-Diethyl-1-isocyanobenzene III-2d



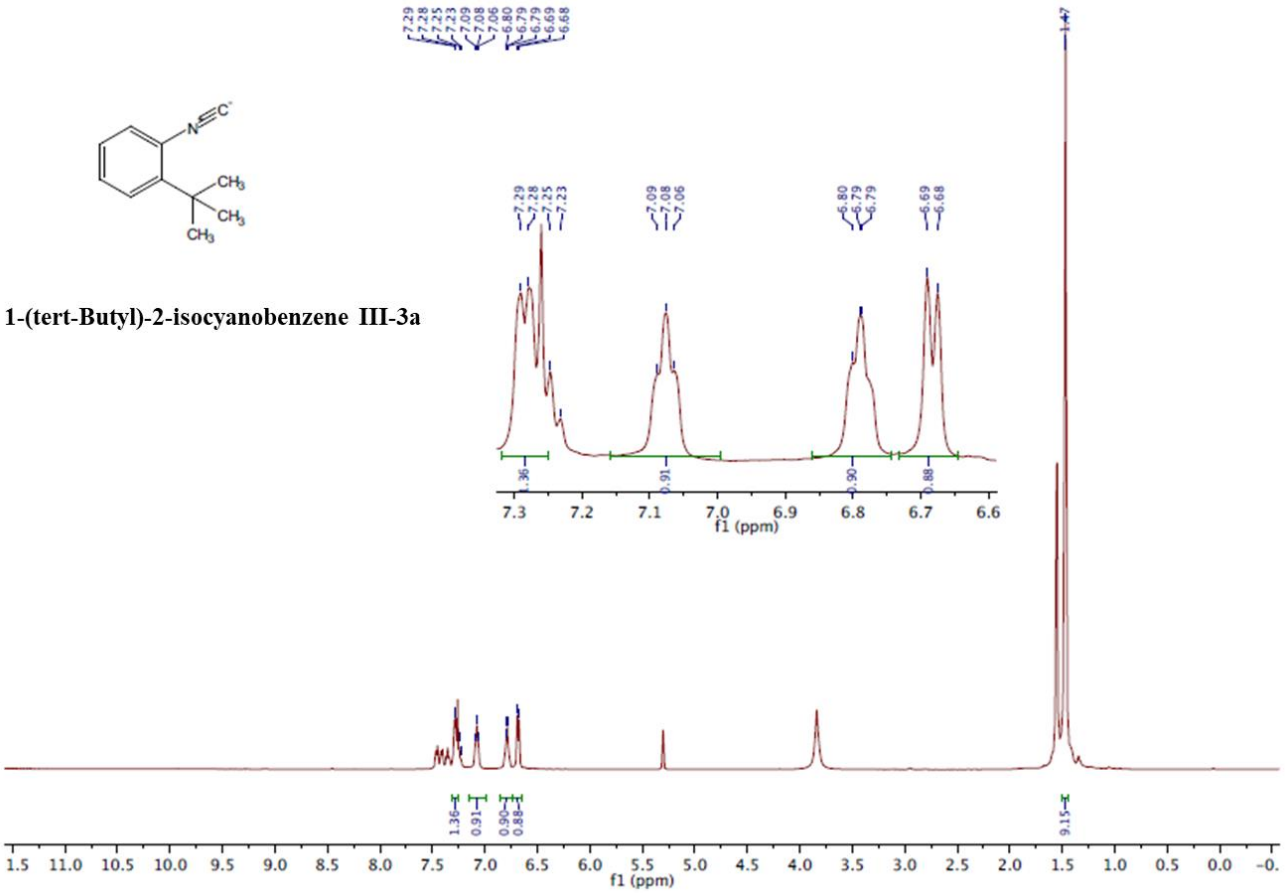
2,4-Diethyl-1-isocyanobenzene III-2d

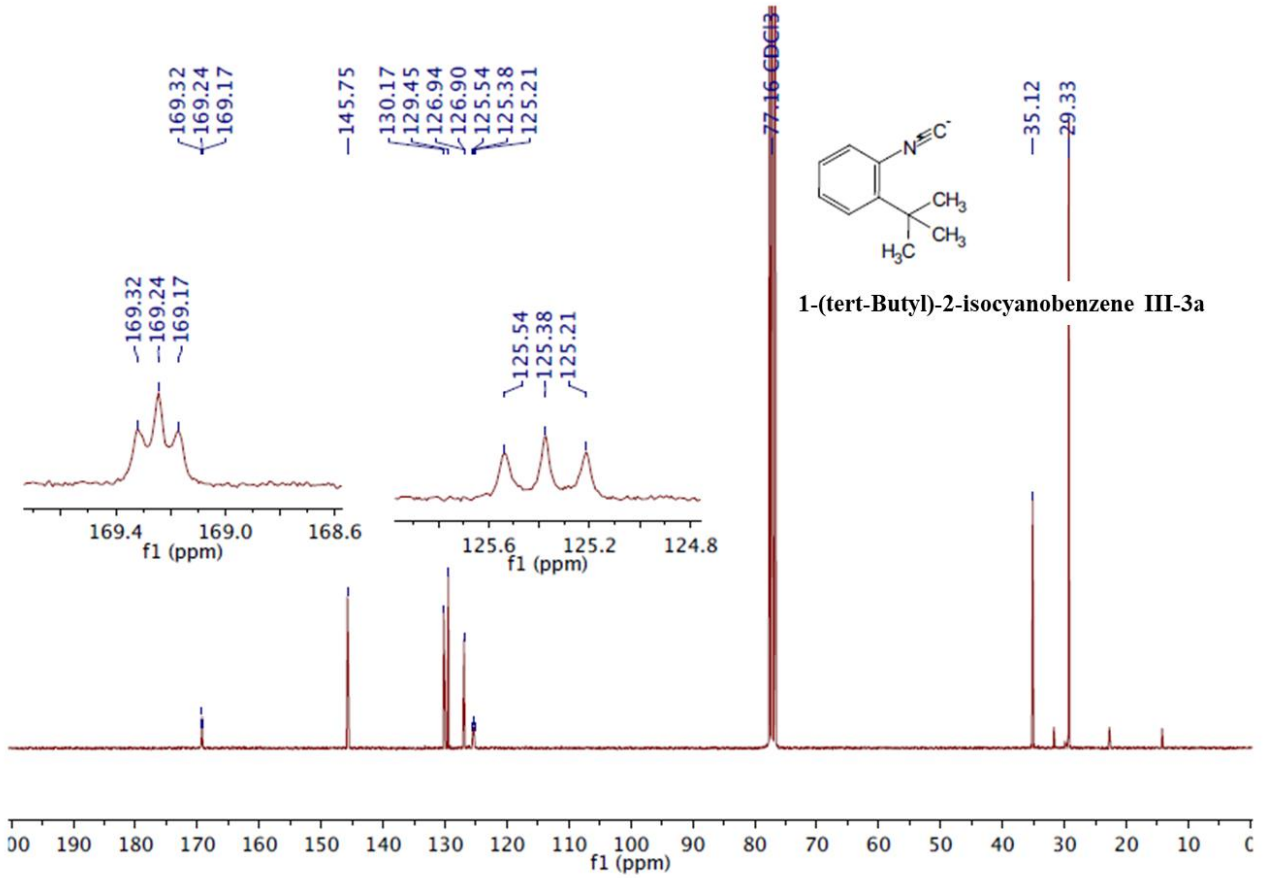


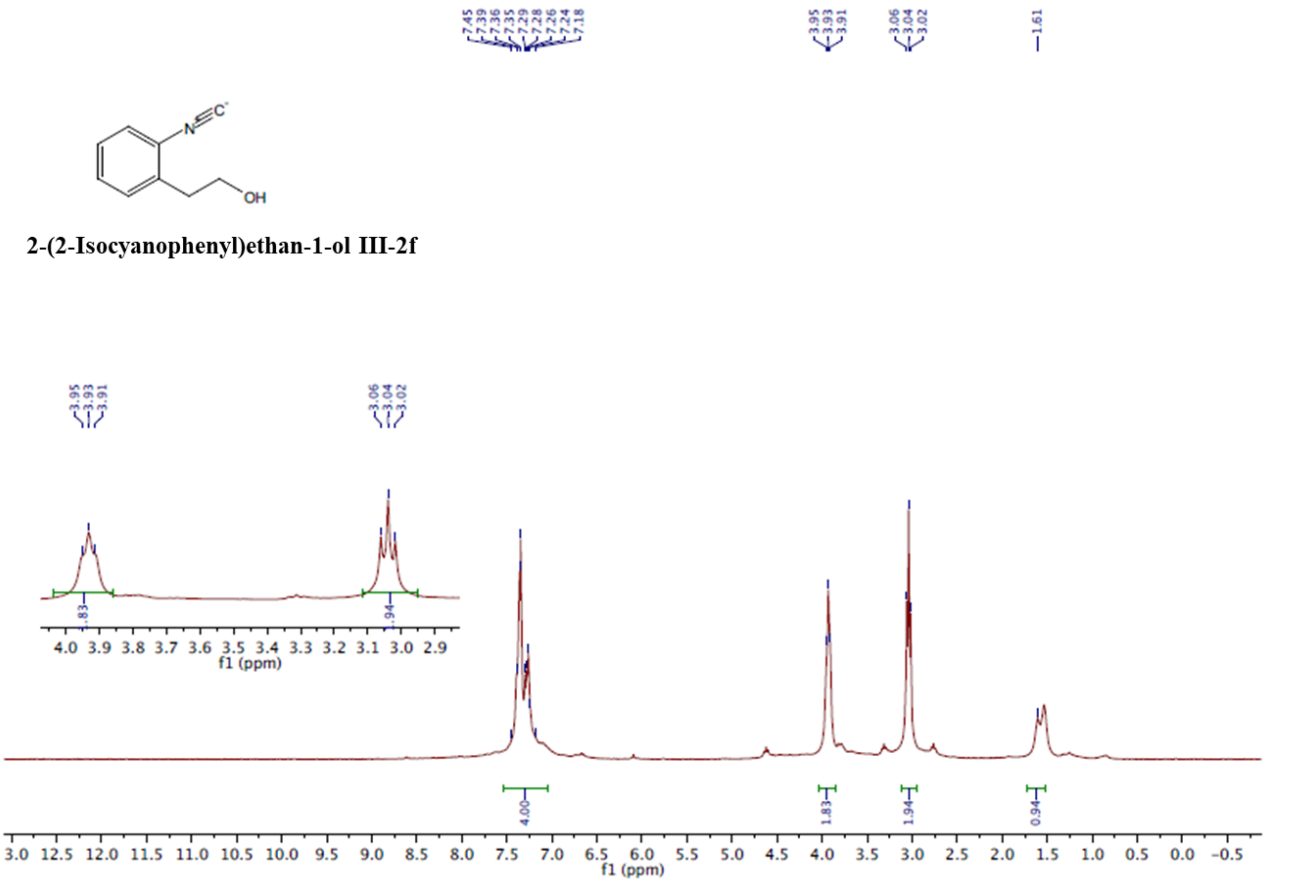
2-Isocyano-1,3,5-trimethylbenzene III-2e



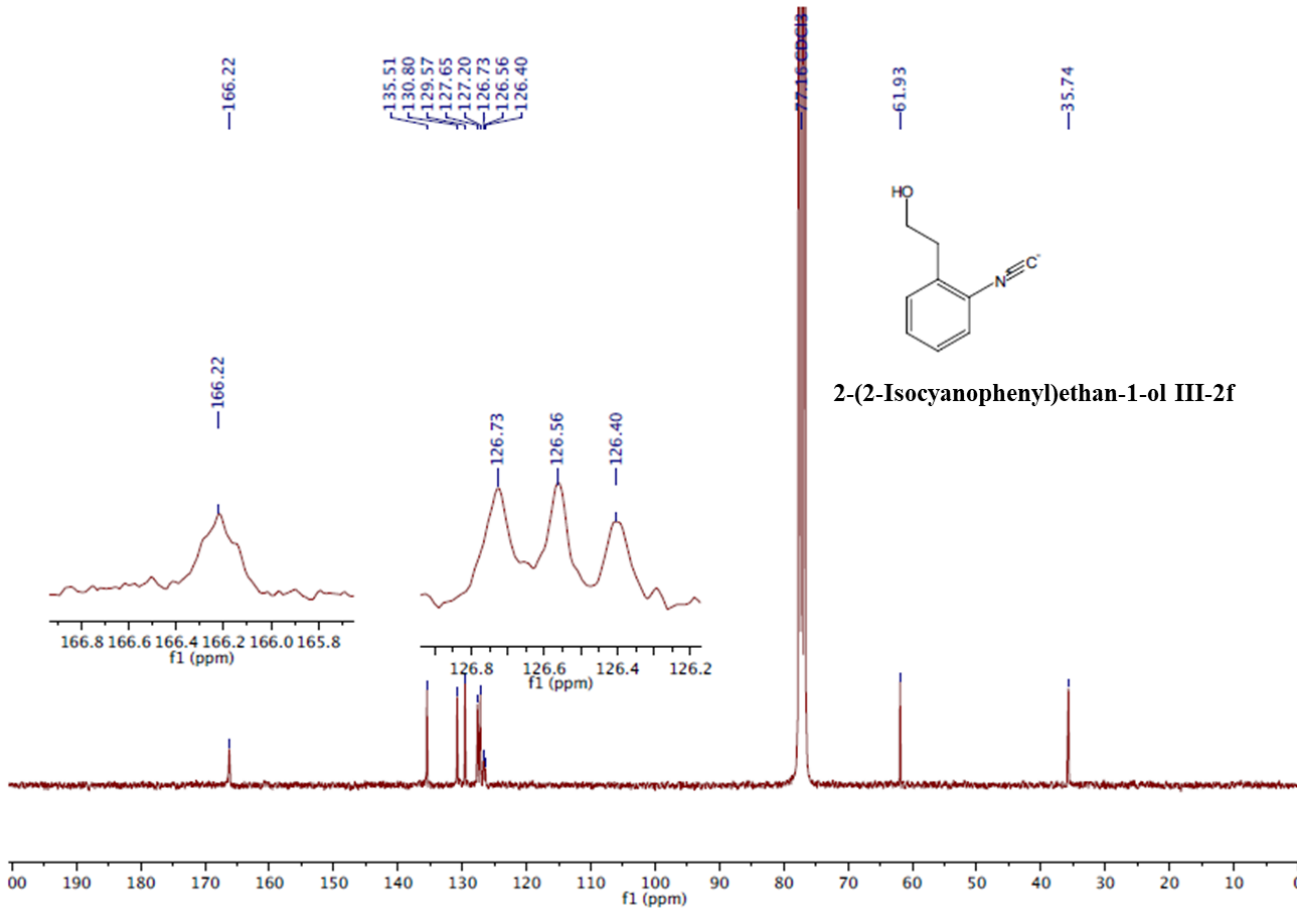
2-Isocyano-1,3,5-trimethylbenzene III-2e


1-(tert-Butyl)-2-isocyanobenzene III-3a
f1 (ppm)

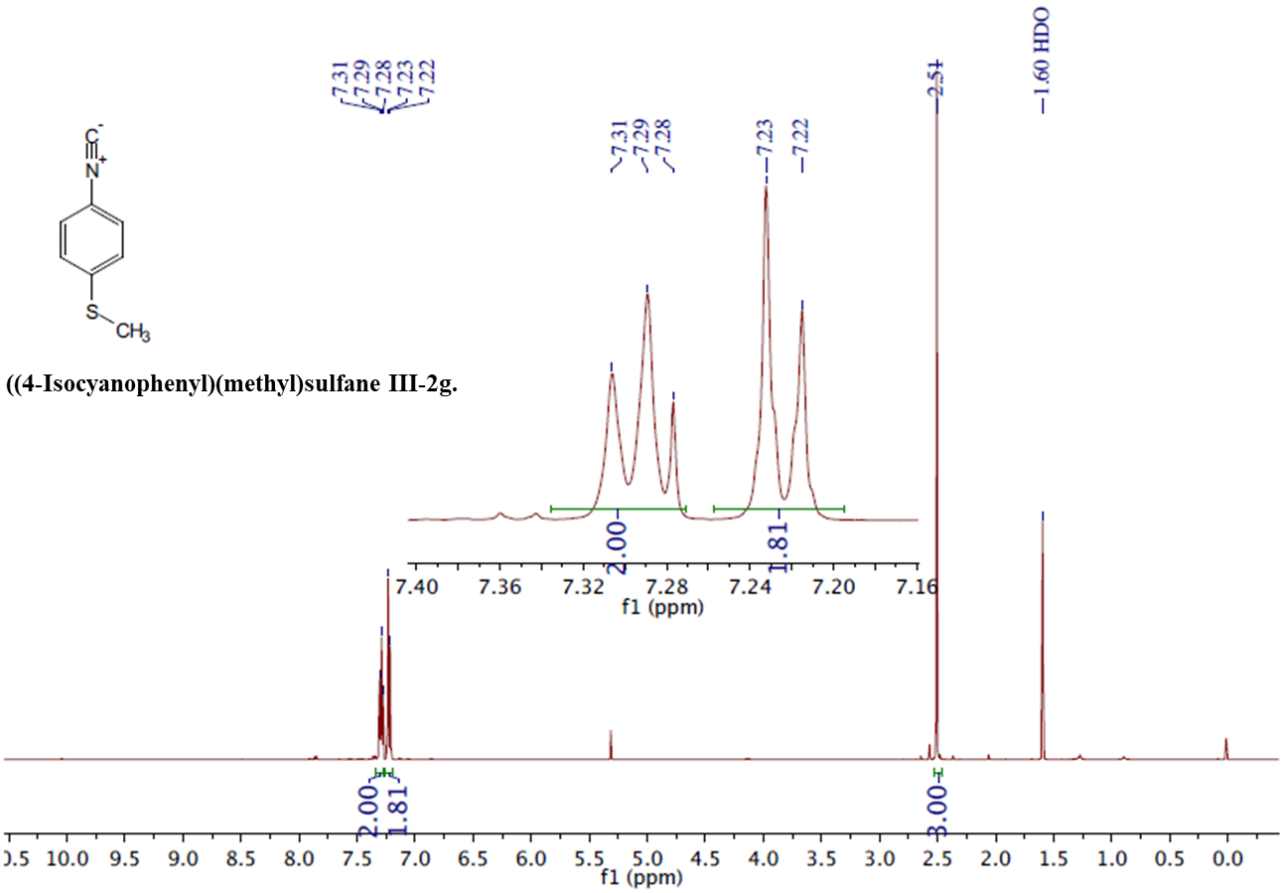

1-(tert-Butyl)-2-isocyanobenzene III-3a
f1 (ppm)



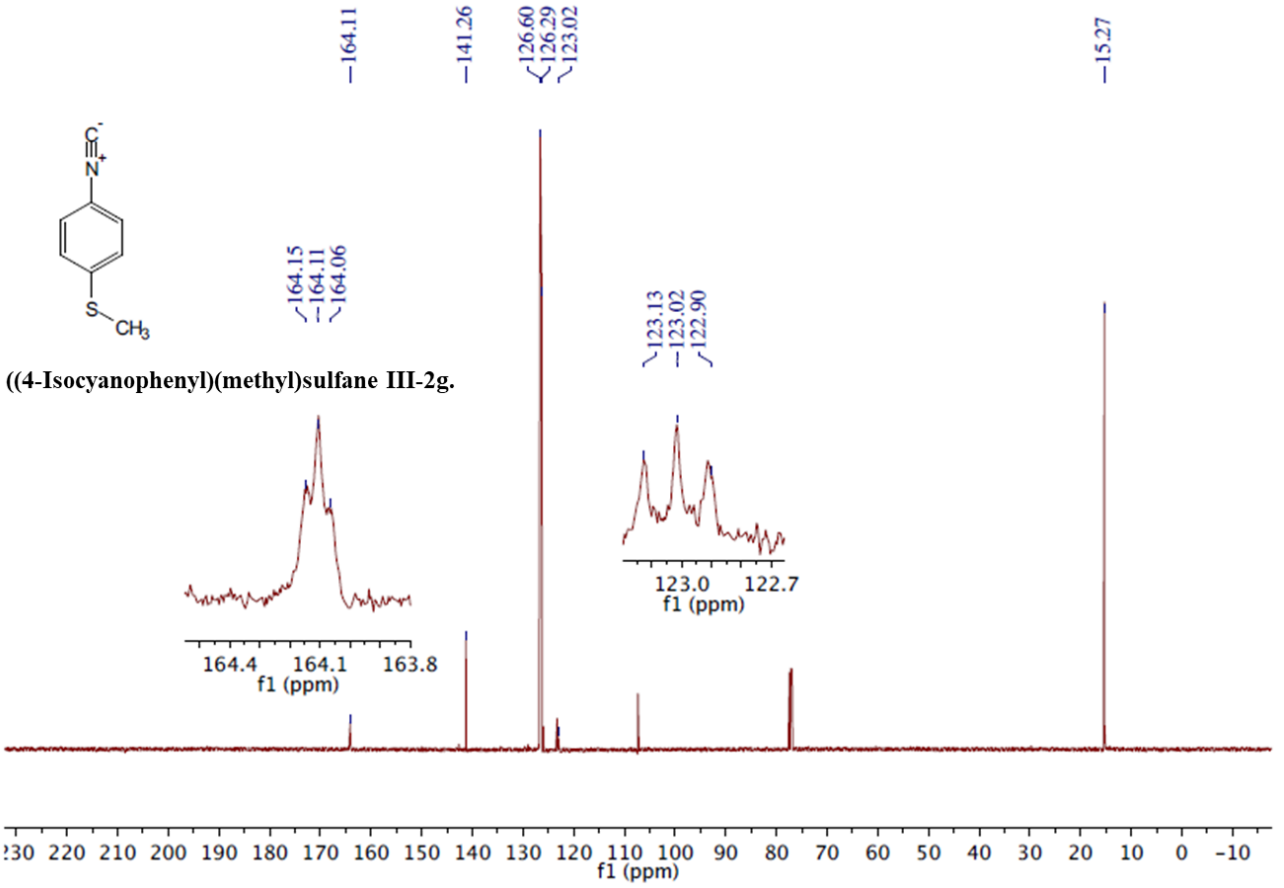
2-(2-Isocyanophenyl)ethan-1-ol III-2f



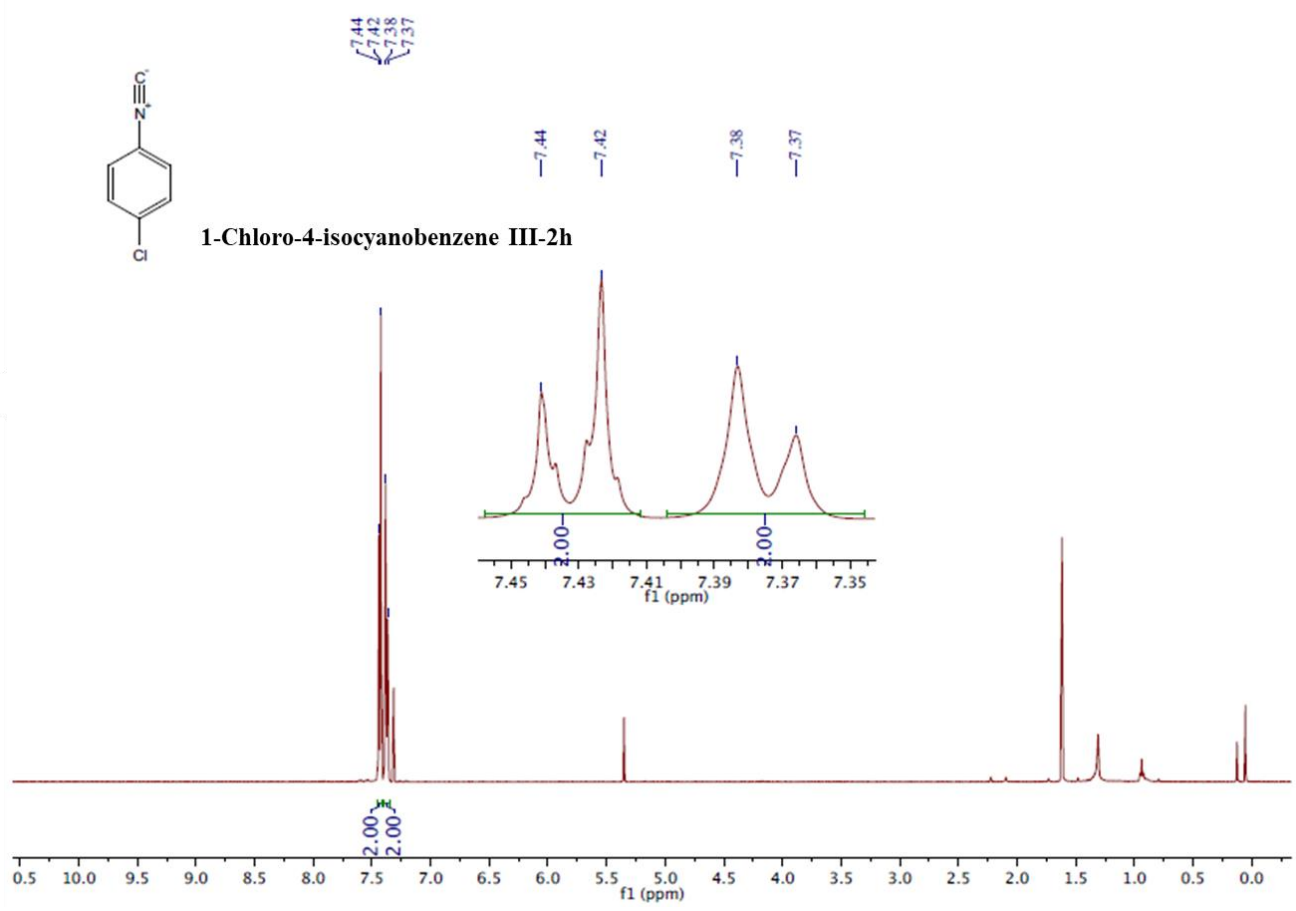
2-(2-Isocyanophenyl)ethan-1-ol III-2f

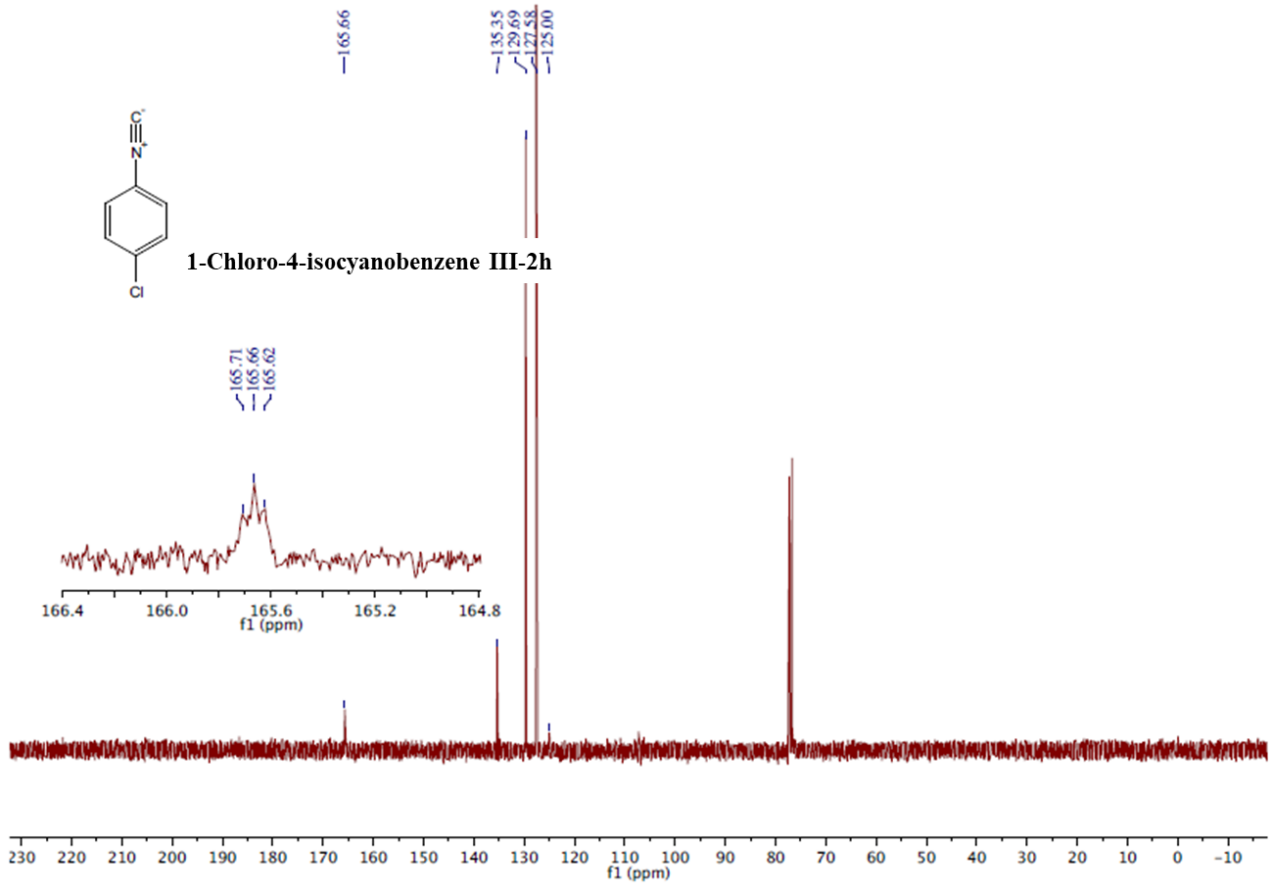


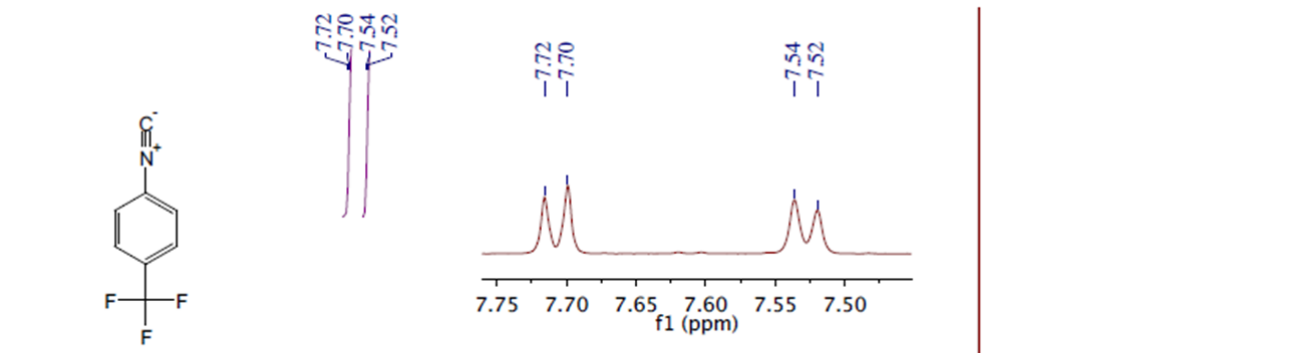
((4-Isocyanophenyl)(methyl)sulfane III-2g.



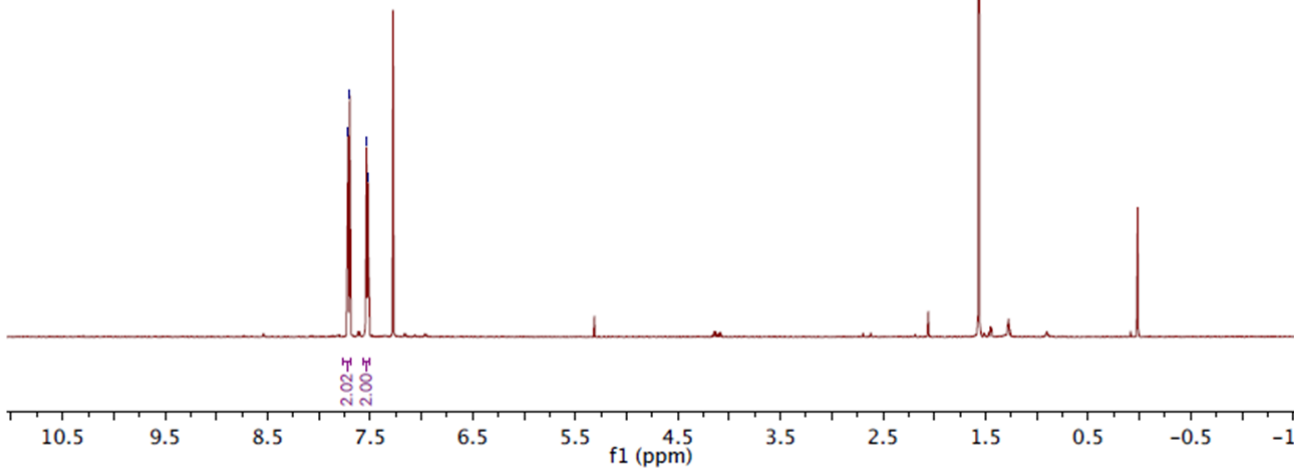
((4-Isocyanophenyl)(methyl)sulfane III-2g.

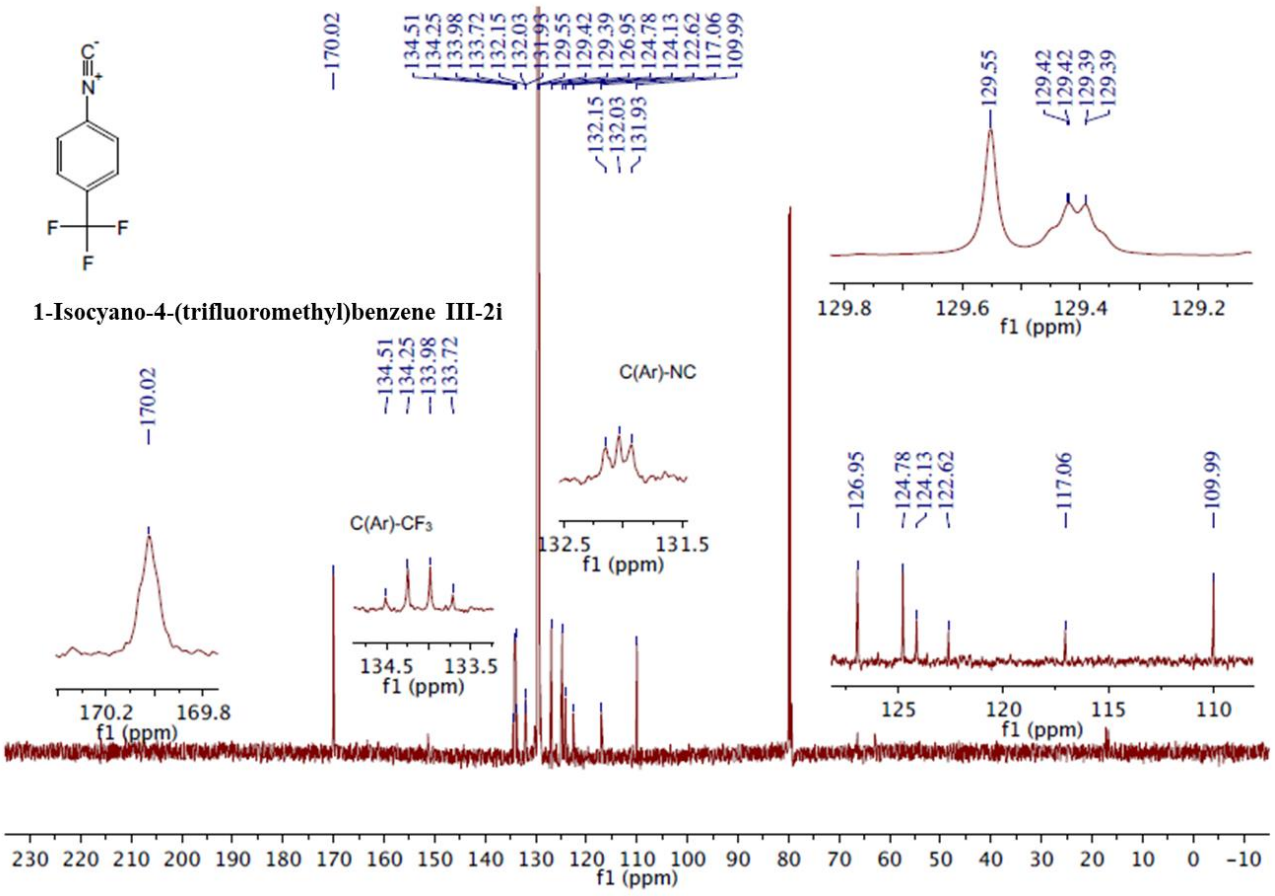

7.44
7.42
7.38
7.37
1-Chloro-4-isocyanobenzene III-2h
2.00
2.00
f1 (ppm)


165.66
135.35
129.69
127.58
125.00
1-Chloro-4-isocyanobenzene III-2h
165.71
165.66
165.62
f1 (ppm)

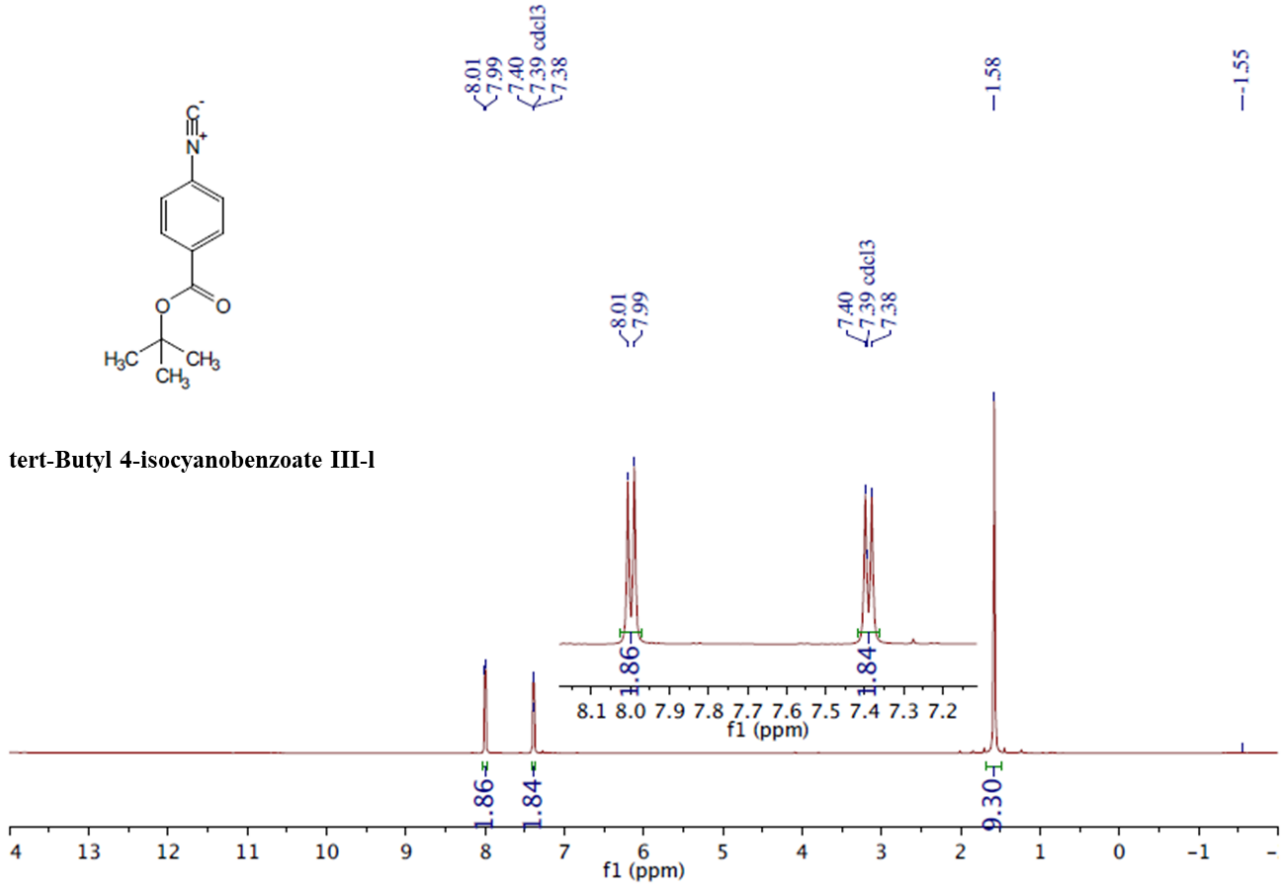


1-Isocyano-4-(trifluoromethyl)benzene III-2i

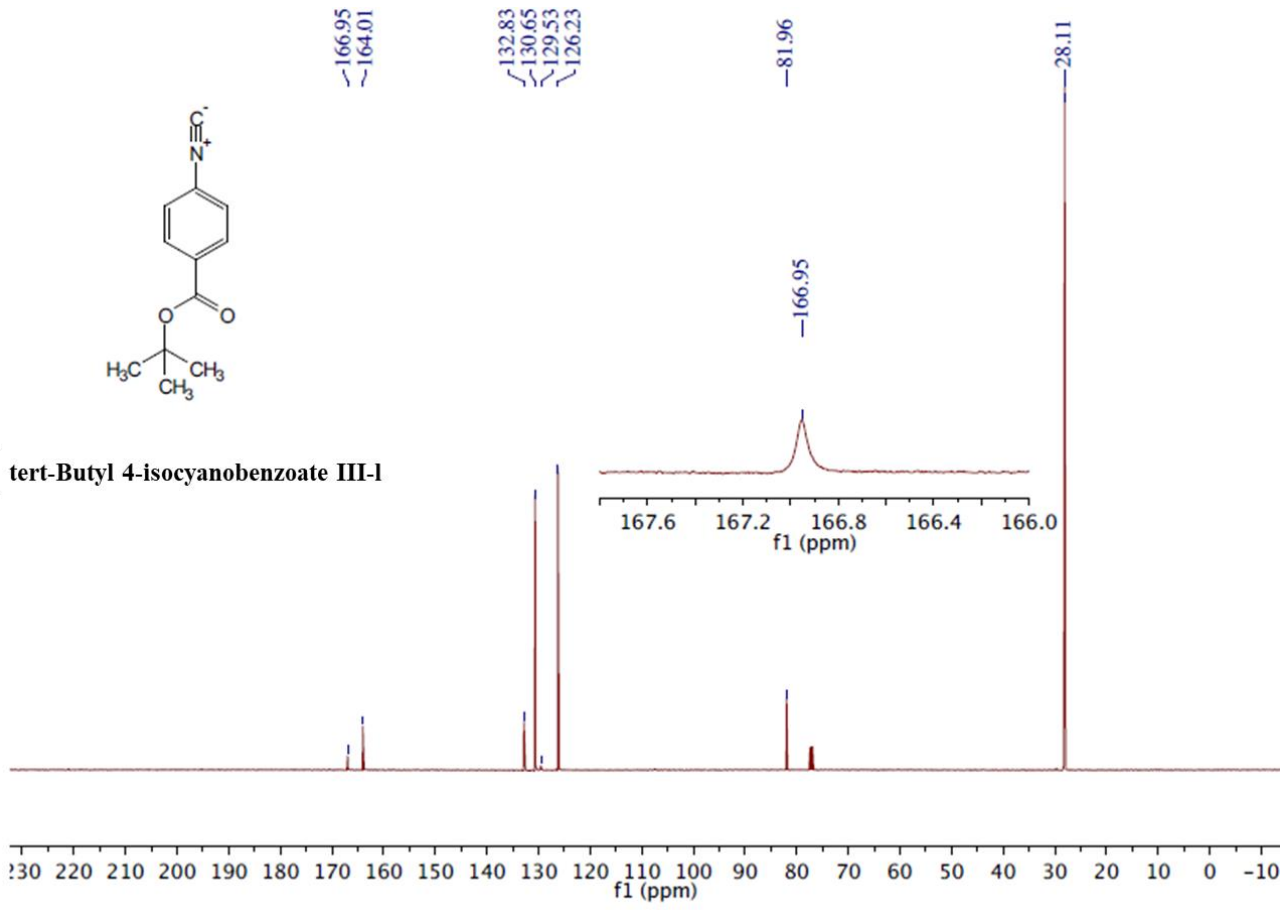




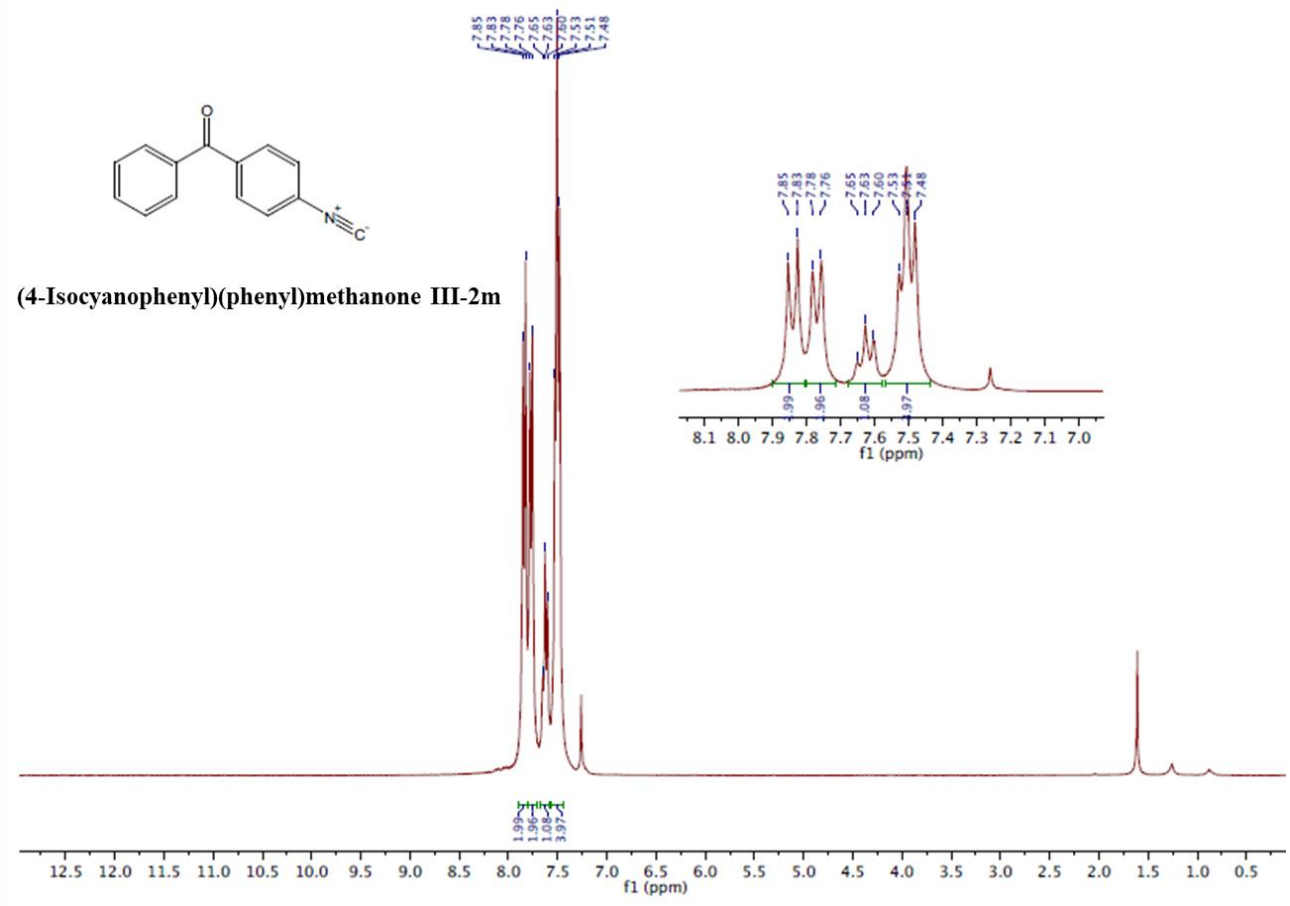
1-Isocyano-4-(trifluoromethyl)benzene III-2i

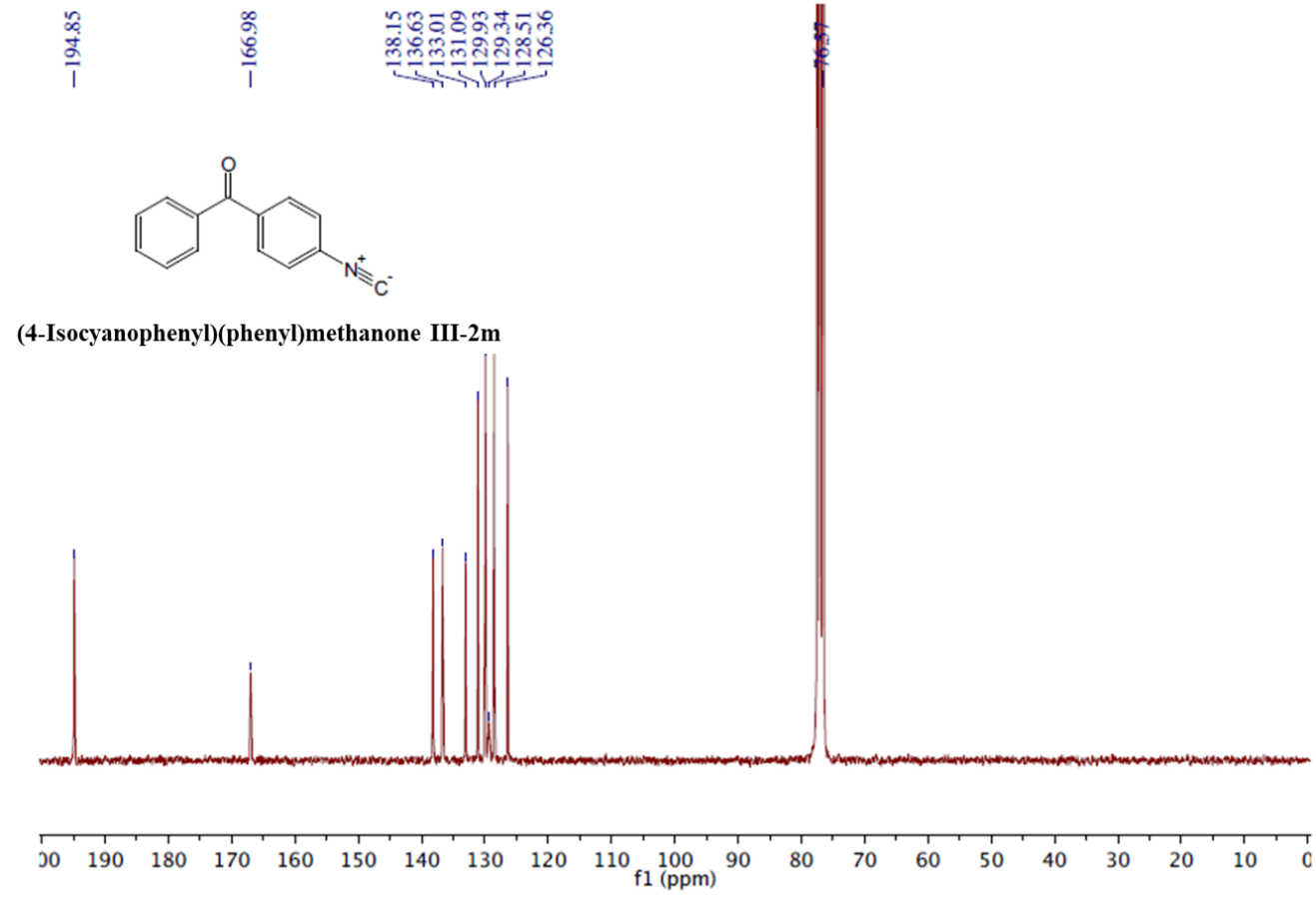


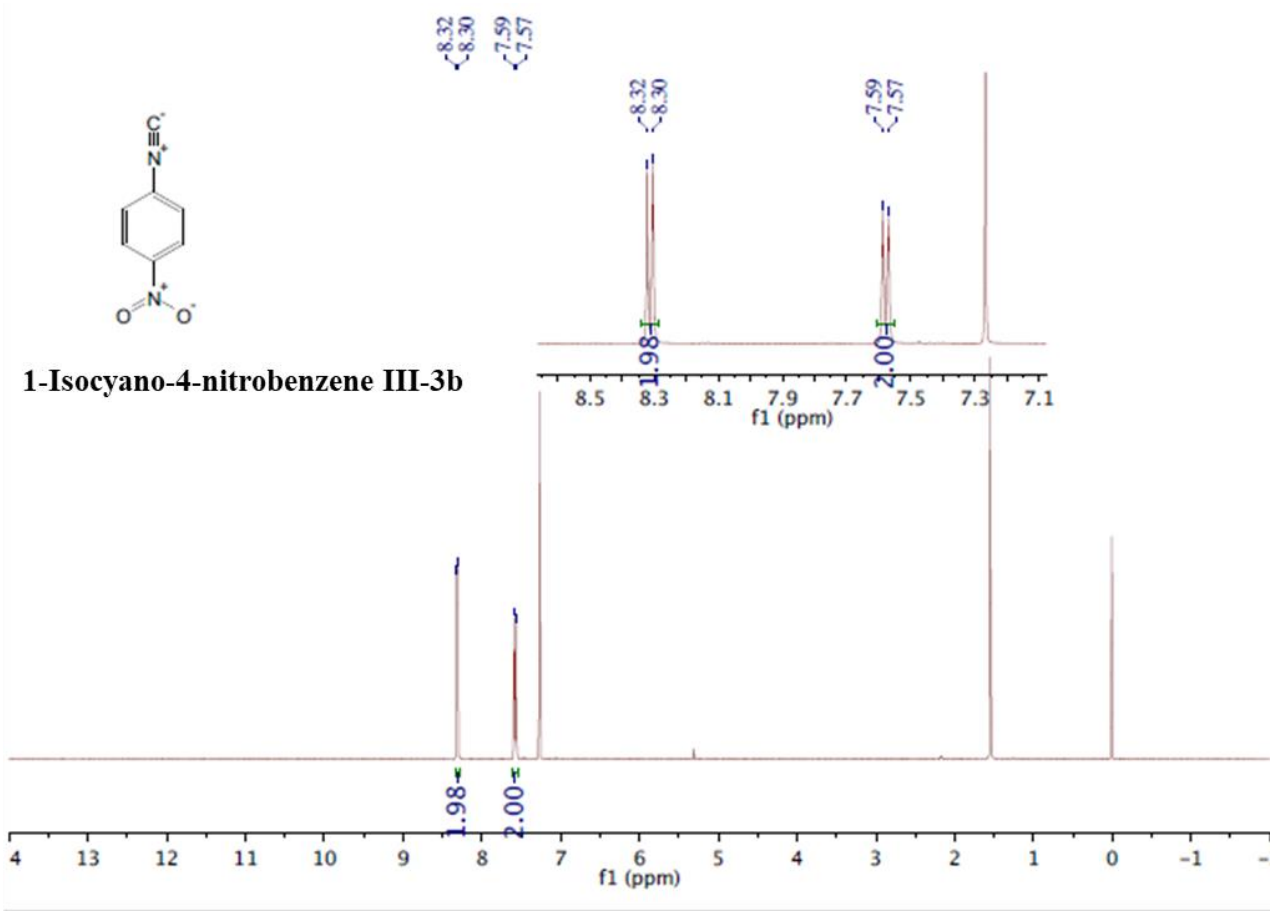
tert-Butyl 4-isocyanobenzoate III-l



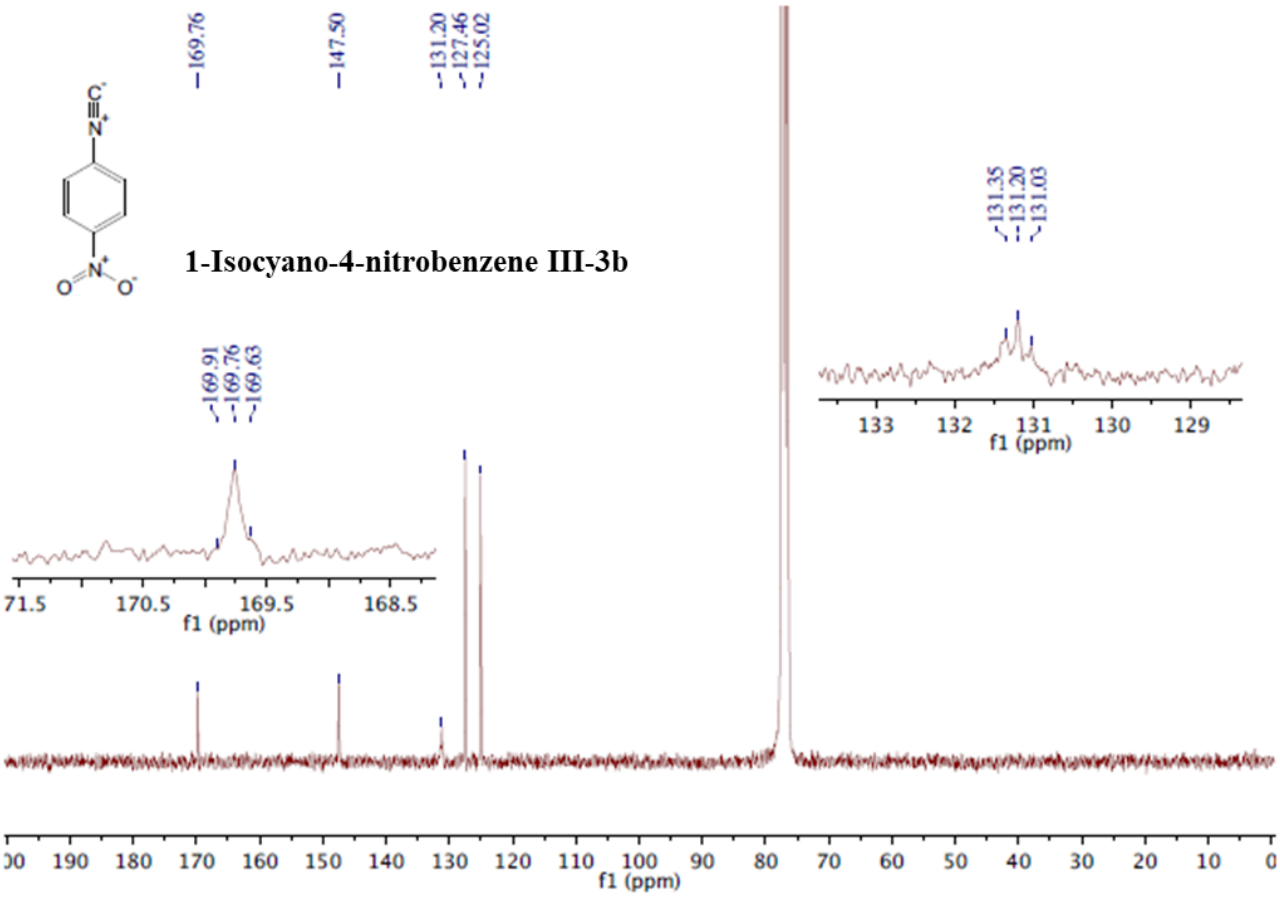
tert-Butyl 4-isocyanobenzoate III-l


(4-Isocyanophenyl)(phenyl)methanone III-2m
f1 (ppm)

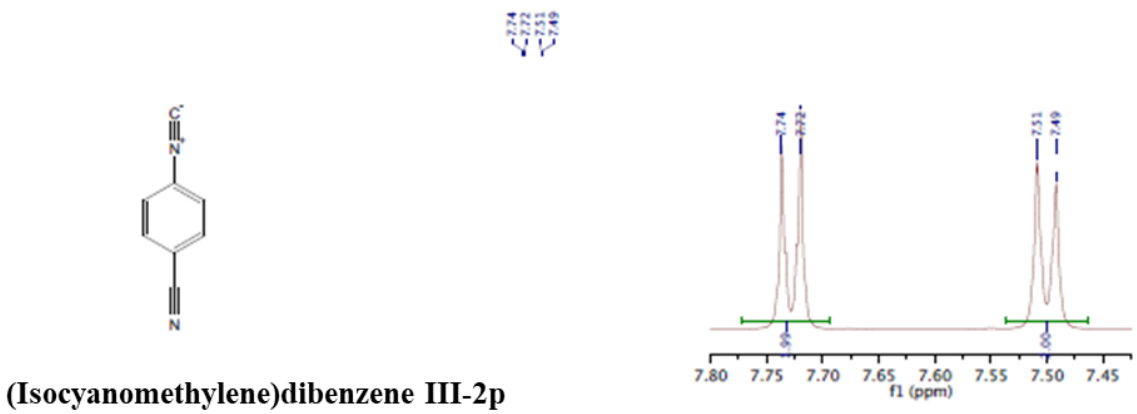

194.85
166.98
138.15
136.63
133.01
131.09
129.93
129.34
128.51
126.36
(4-Isocyanophenyl)(phenyl)methanone III-2m
f1 (ppm)



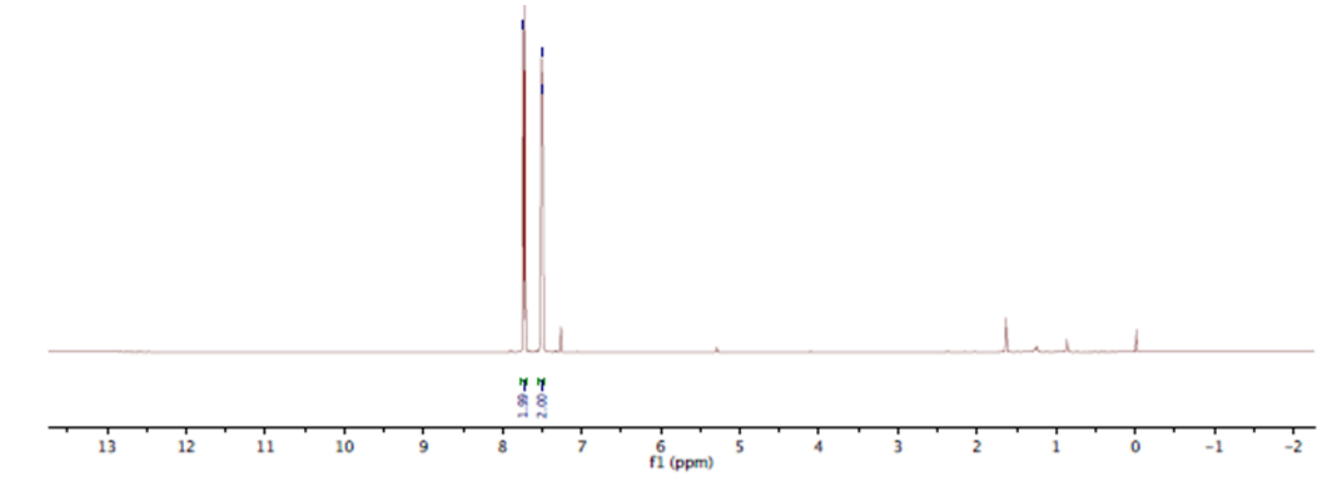
1-Isocyano-4-nitrobenzene III-3b

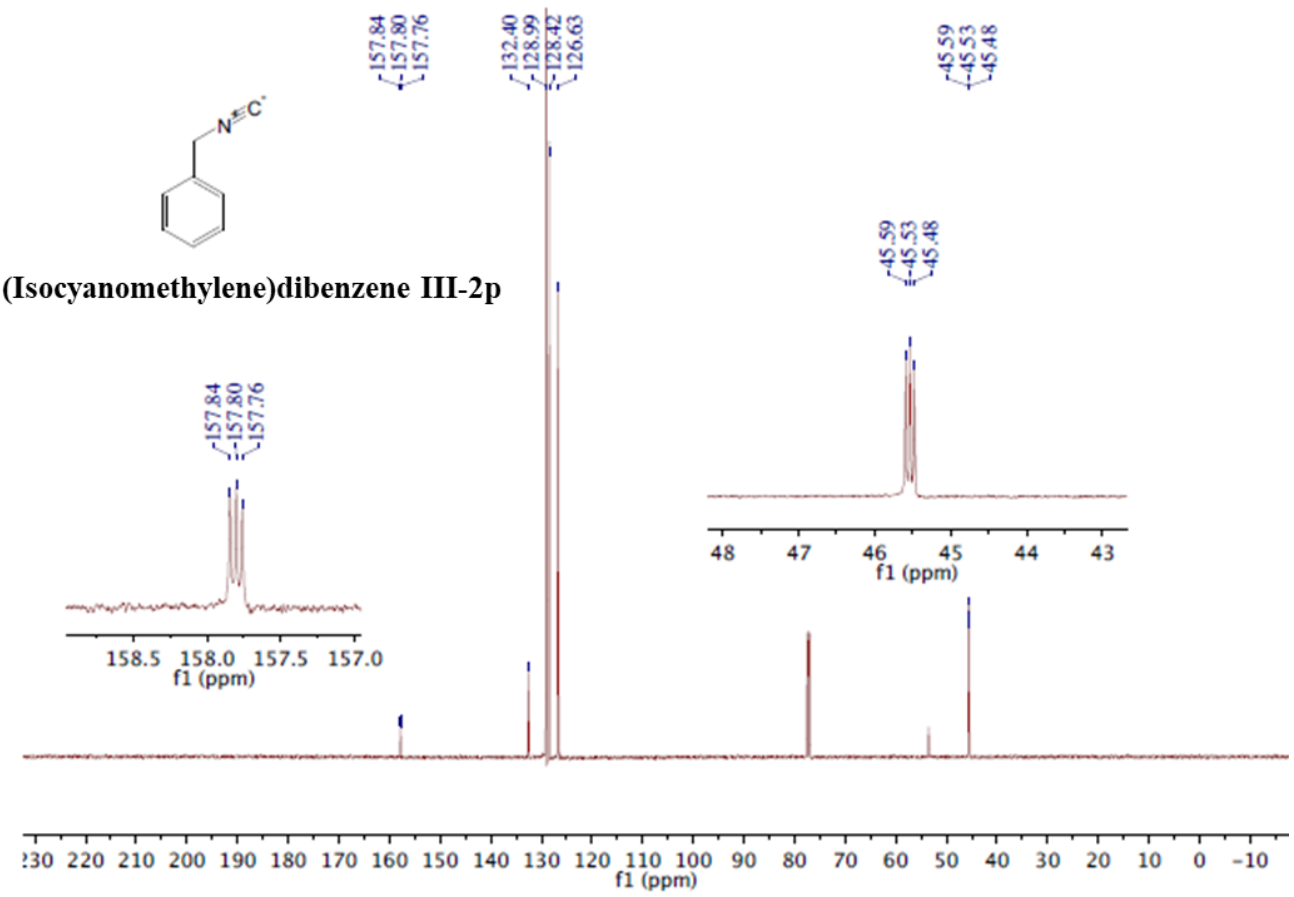


1-Isocyano-4-nitrobenzene III-3b

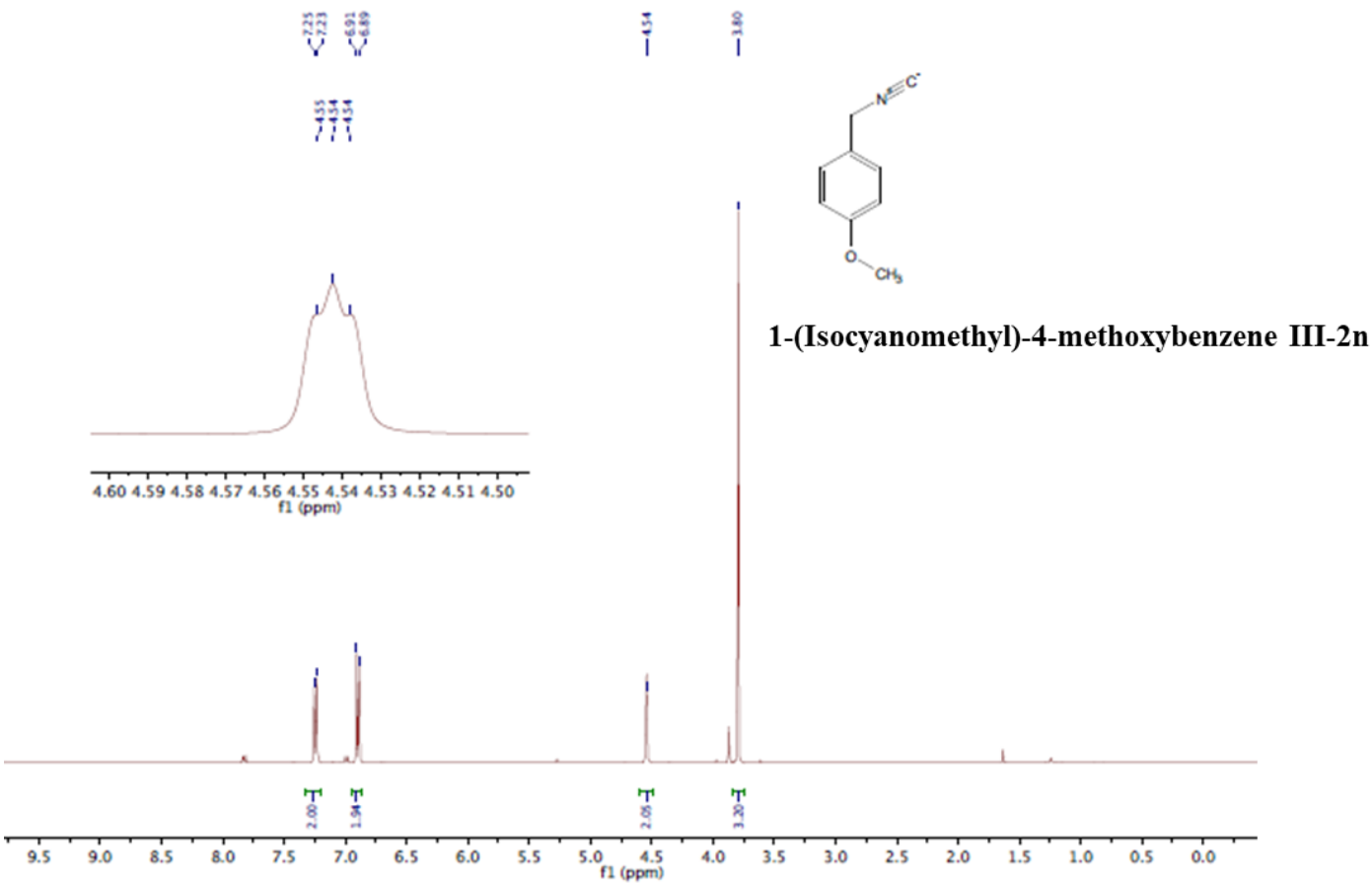


(Isocyanomethylene)dibenzene III-2p

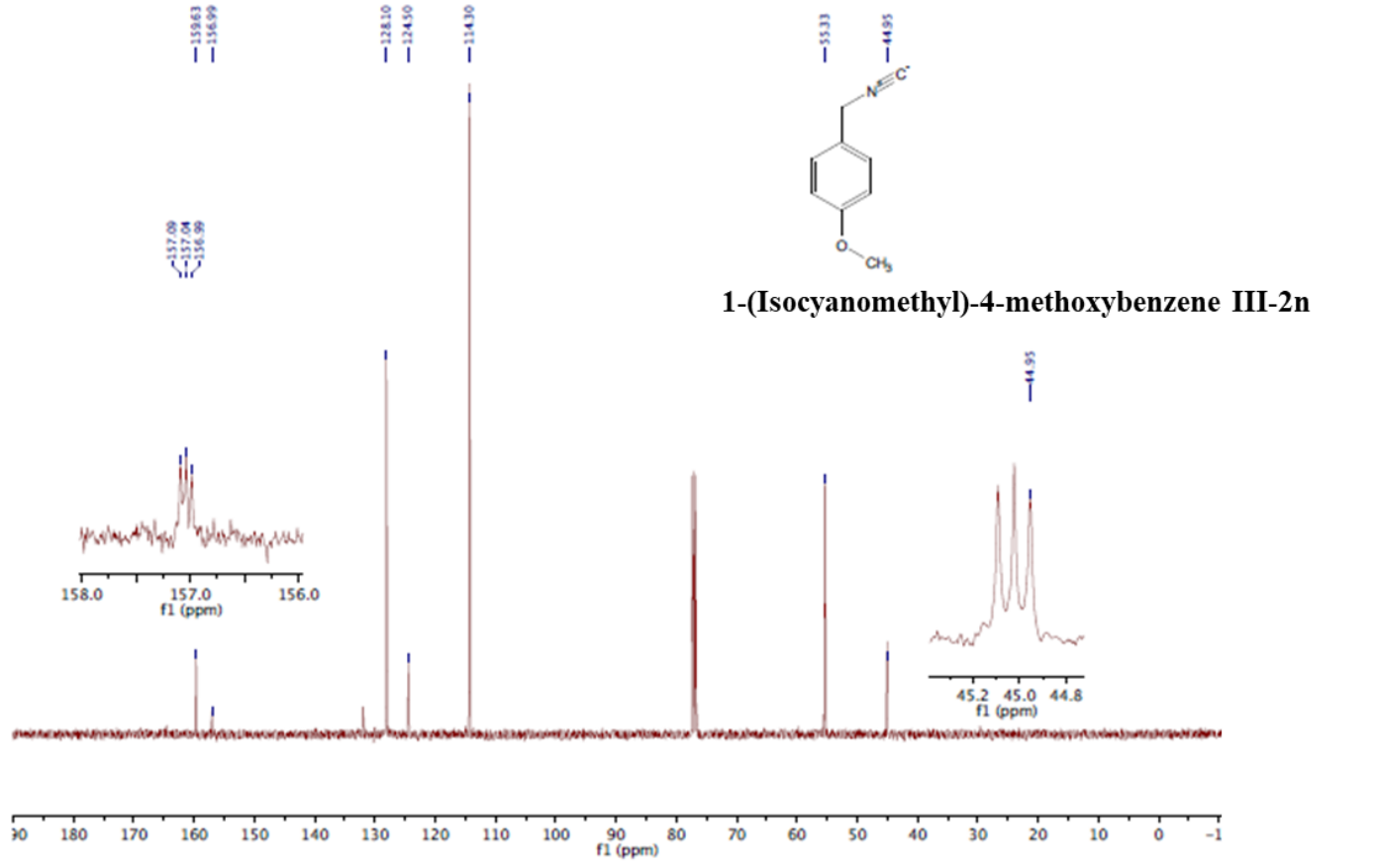




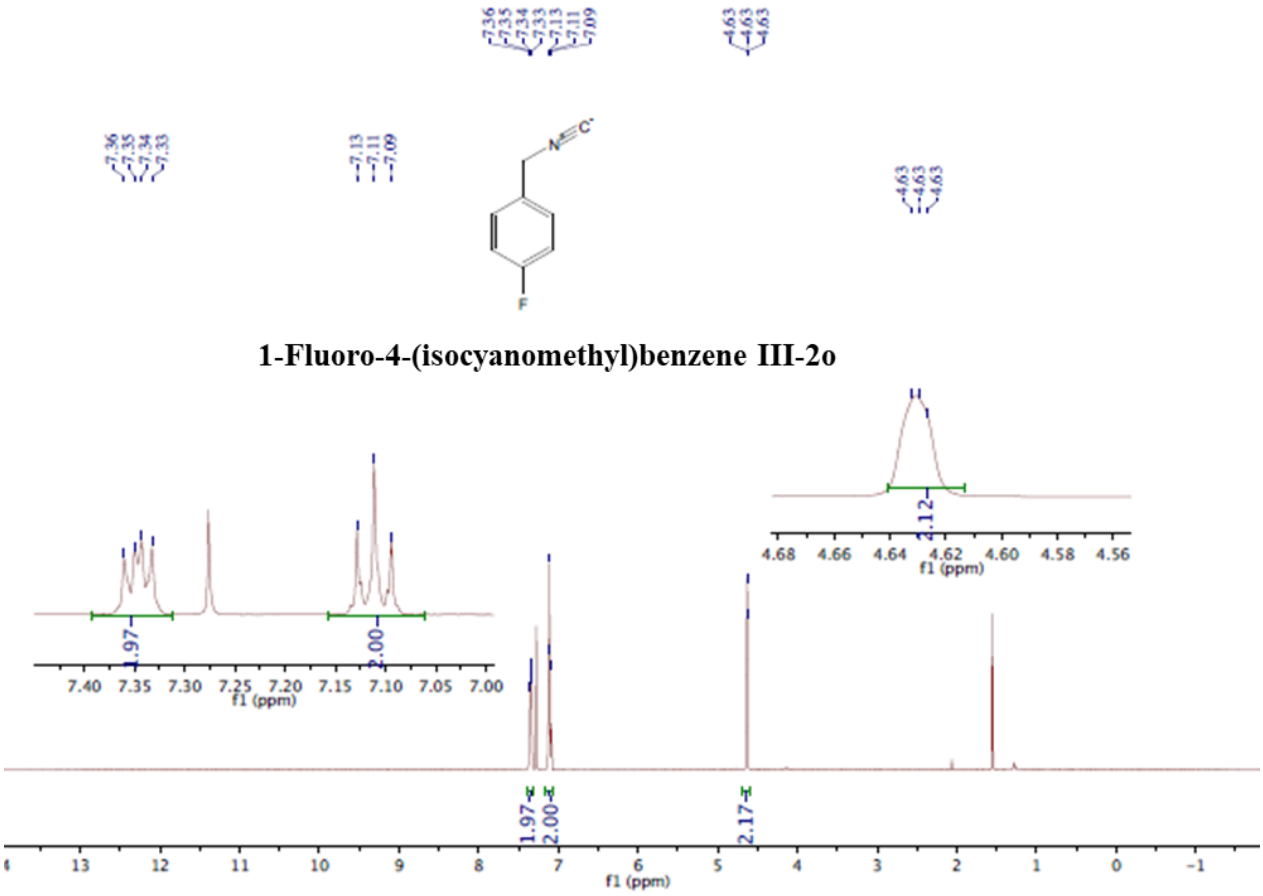
(Isocyanomethylene)dibenzene III-2p

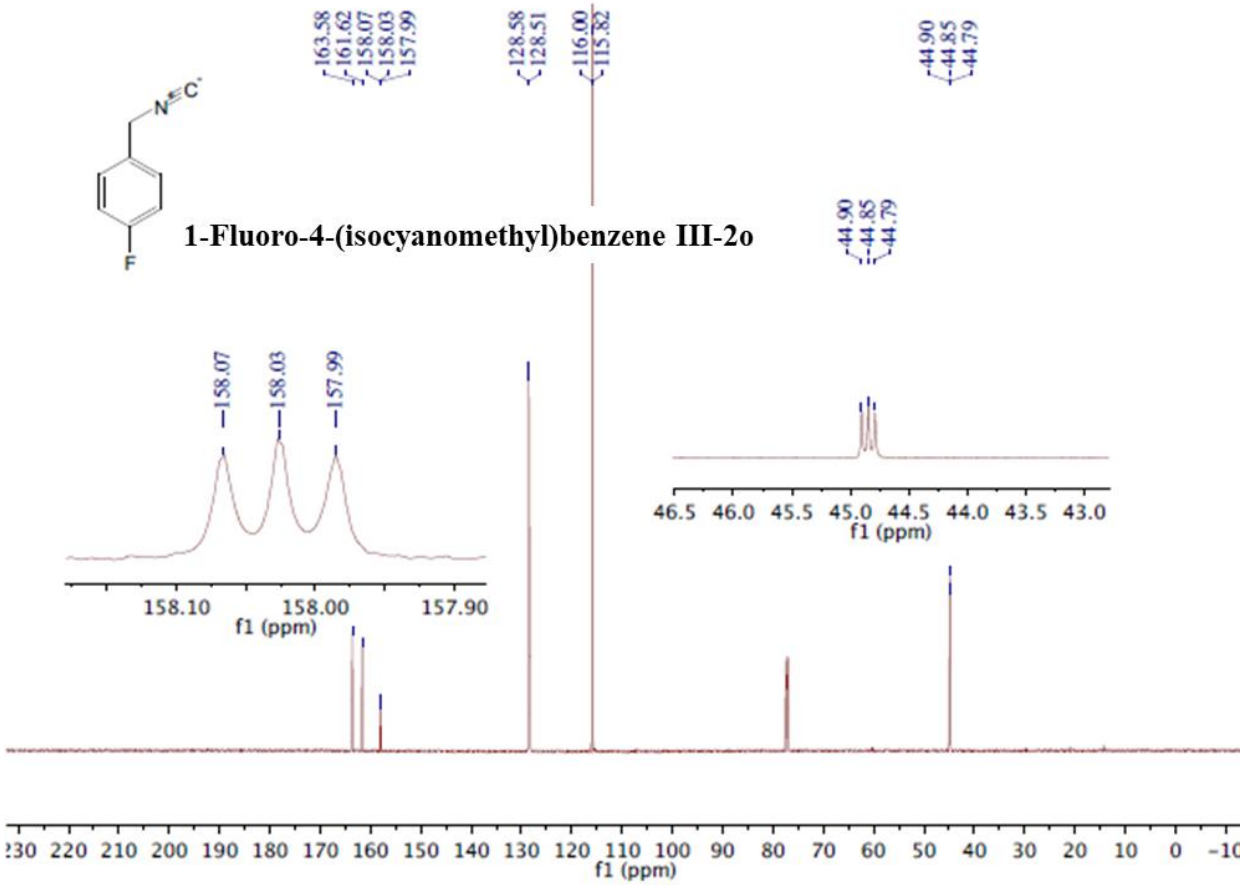


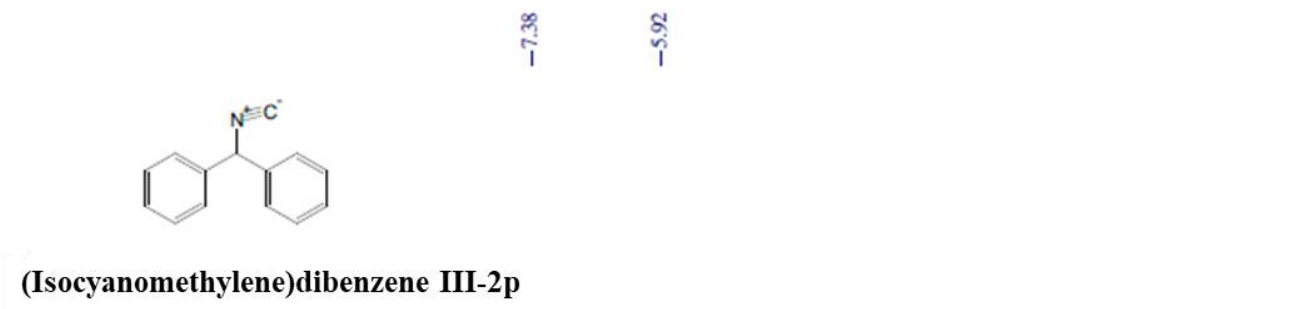
1-(Isocyanomethyl)-4-methoxybenzene III-2n



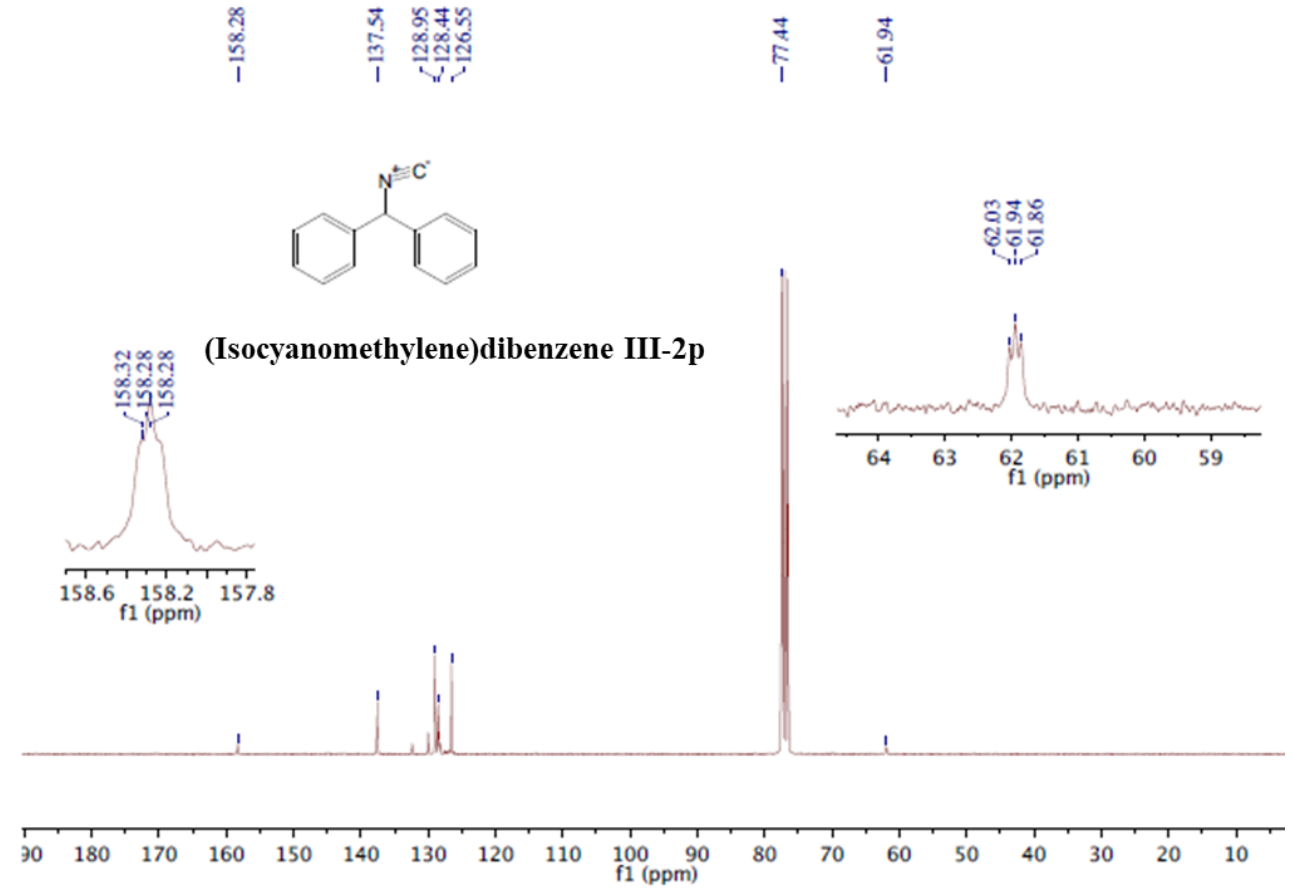
1-(Isocyanomethyl)-4-methoxybenzene III-2n


7.36
7.35
7.34
7.33
7.13
7.11
7.09
4.63
4.63
4.63
N
C
F
1-Fluoro-4-(isocyanomethyl)benzene III-2o
1.97
2.00
2.17
2.12
f1 (ppm)

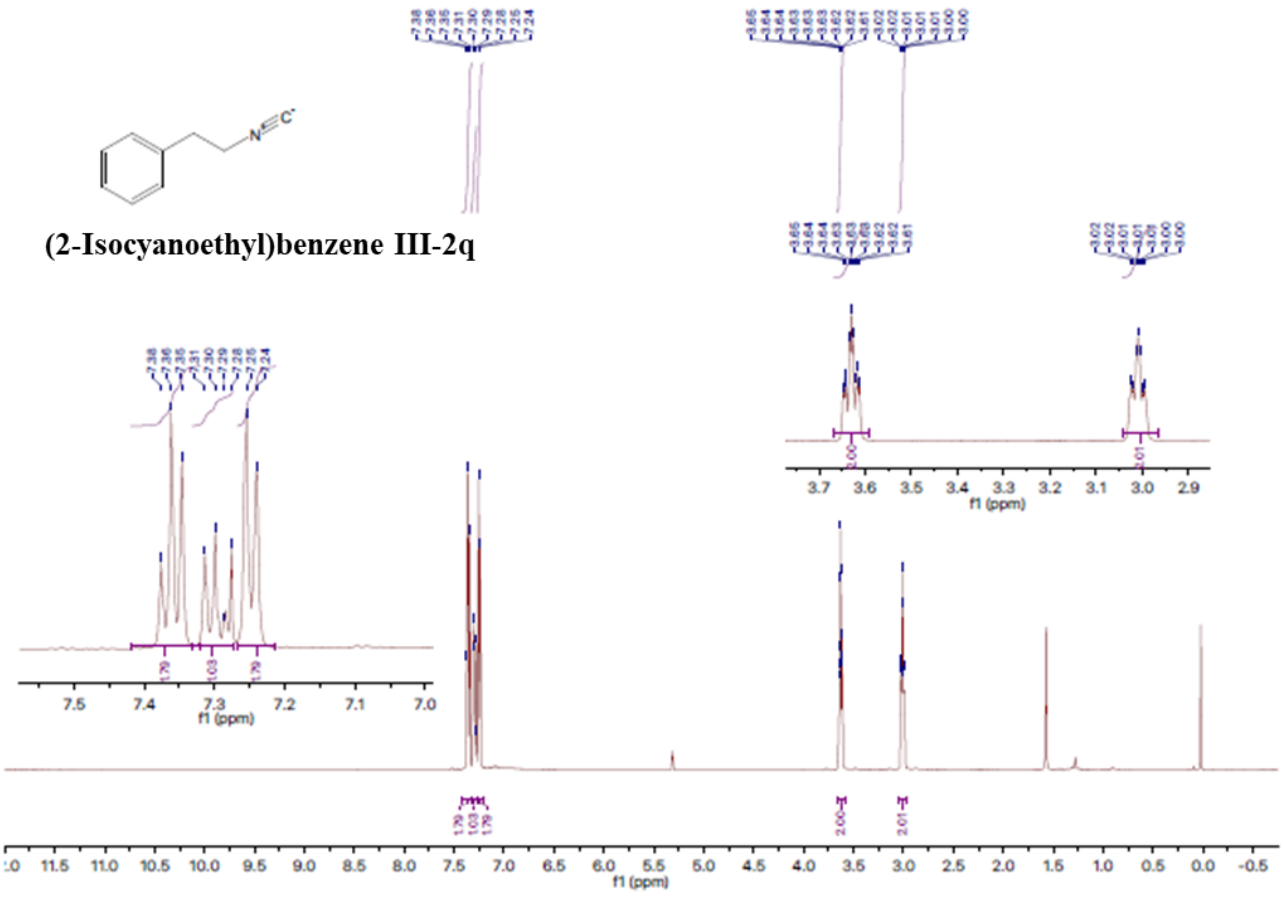

163.58
161.62
158.07
158.03
157.99
128.58
128.51
116.00
115.82
44.90
44.85
44.79
N
C
F
1-Fluoro-4-(isocyanomethyl)benzene III-2o
158.07
158.03
157.99
f1 (ppm)



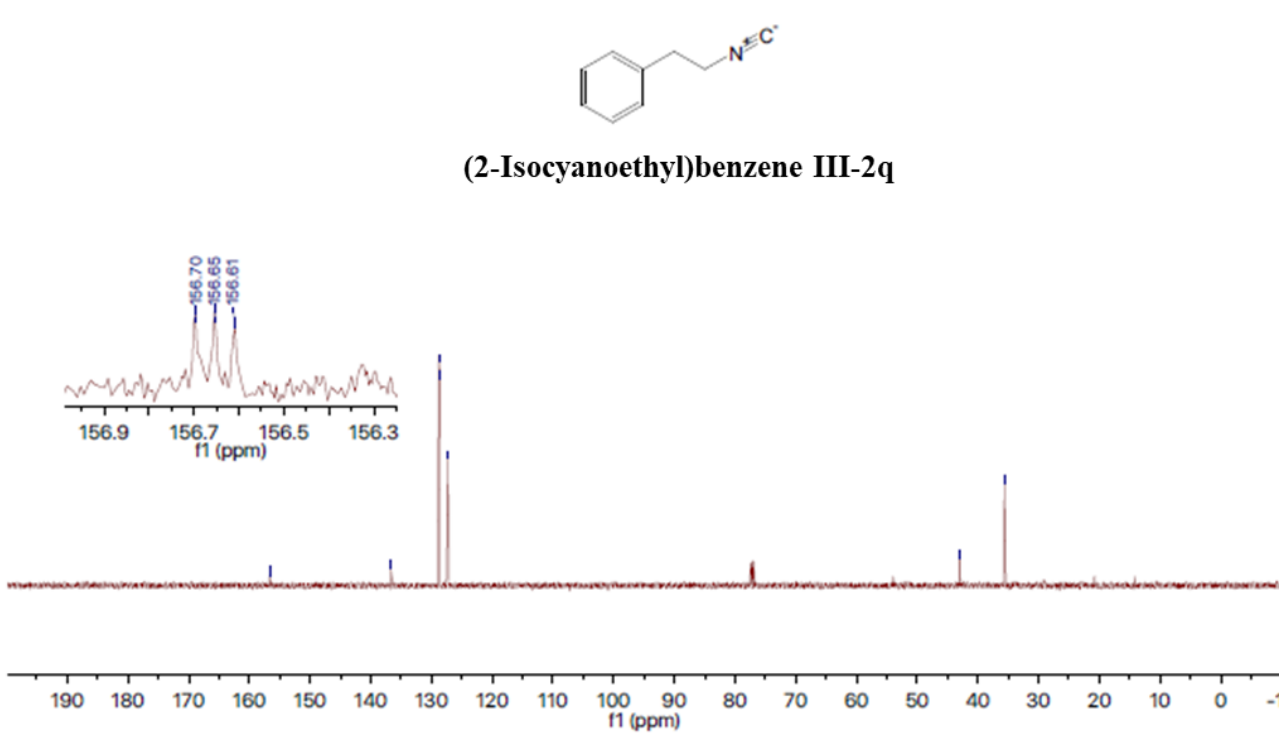
(Isocyanomethylene)dibenzene III-2p



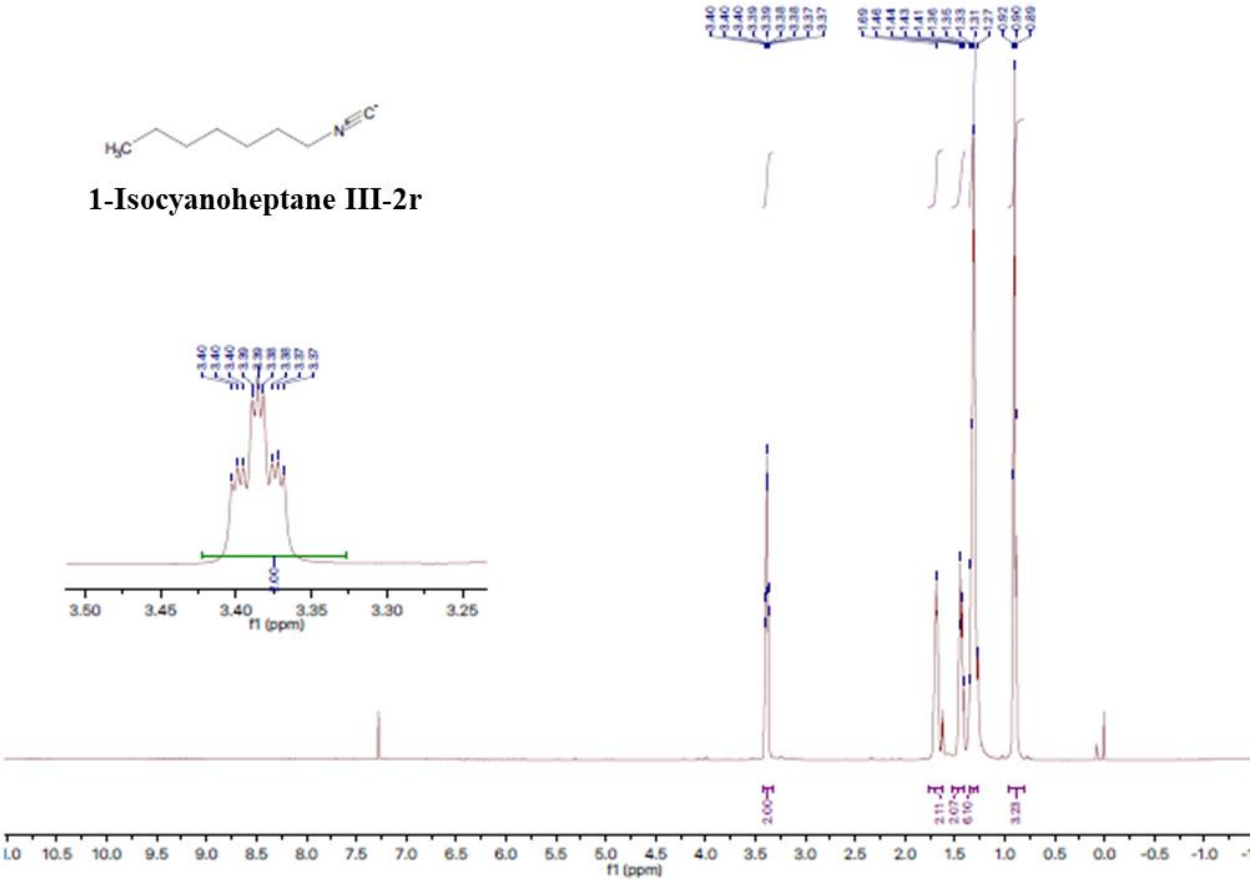
(Isocyanomethylene)dibenzene III-2p

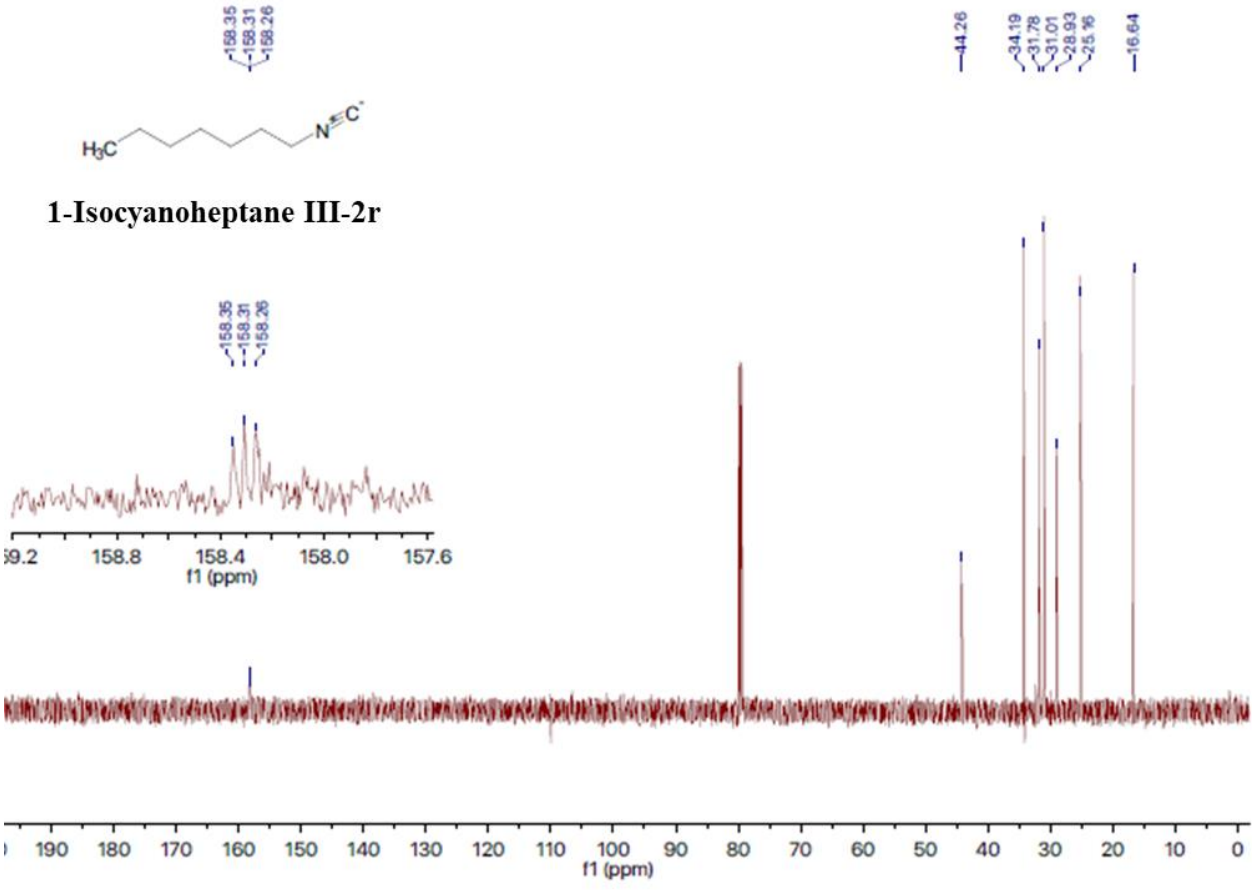


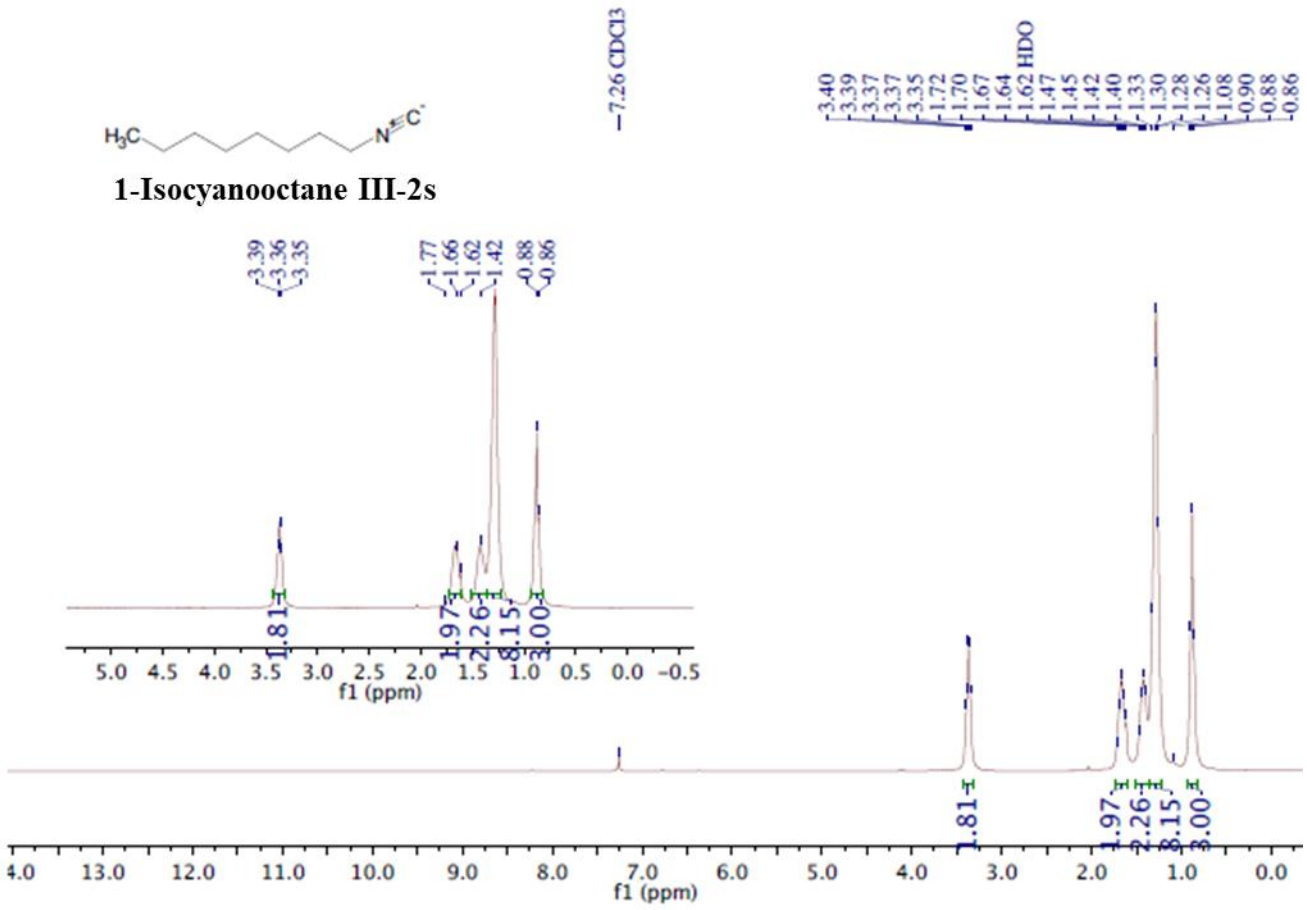
(2-Isocyanoethyl)benzene III-2q

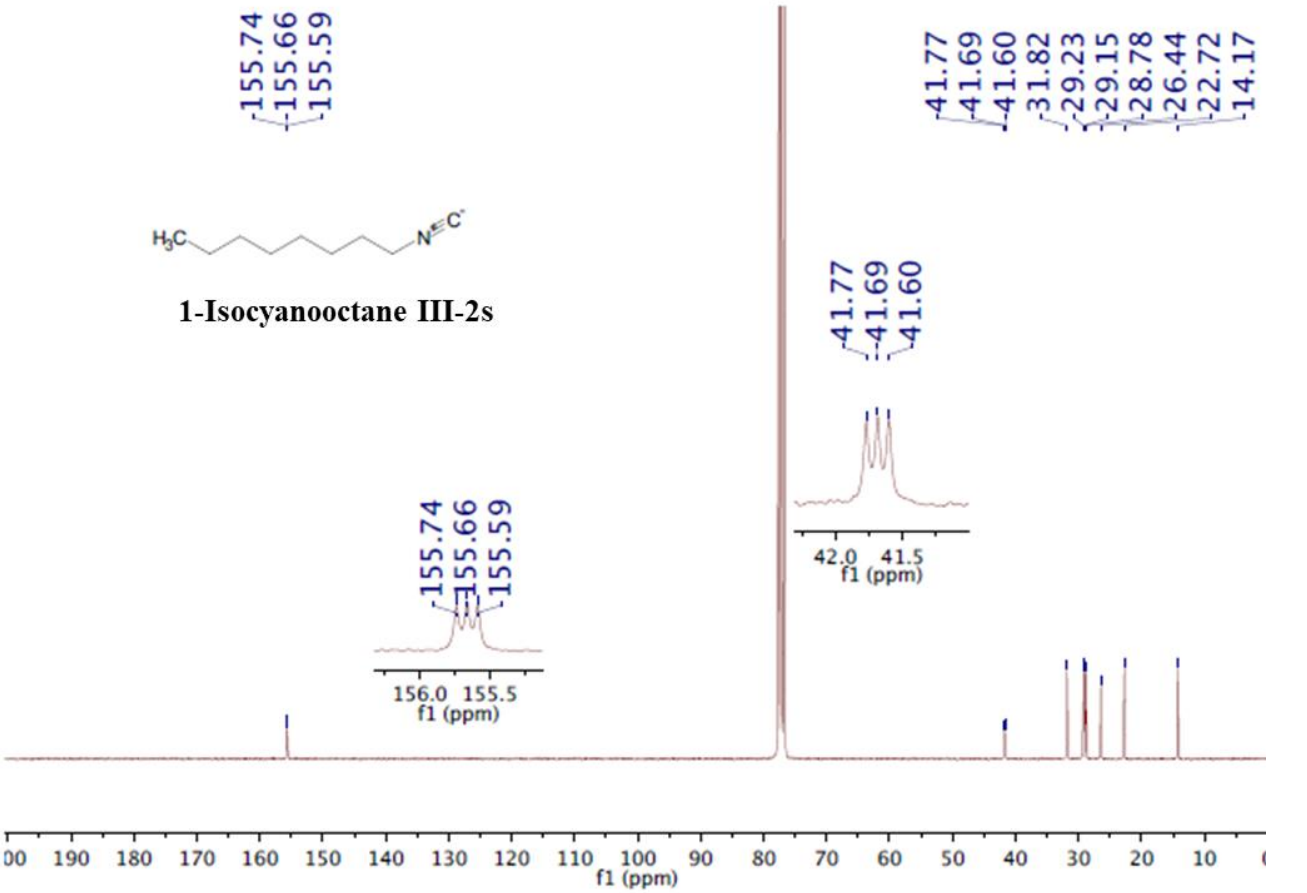


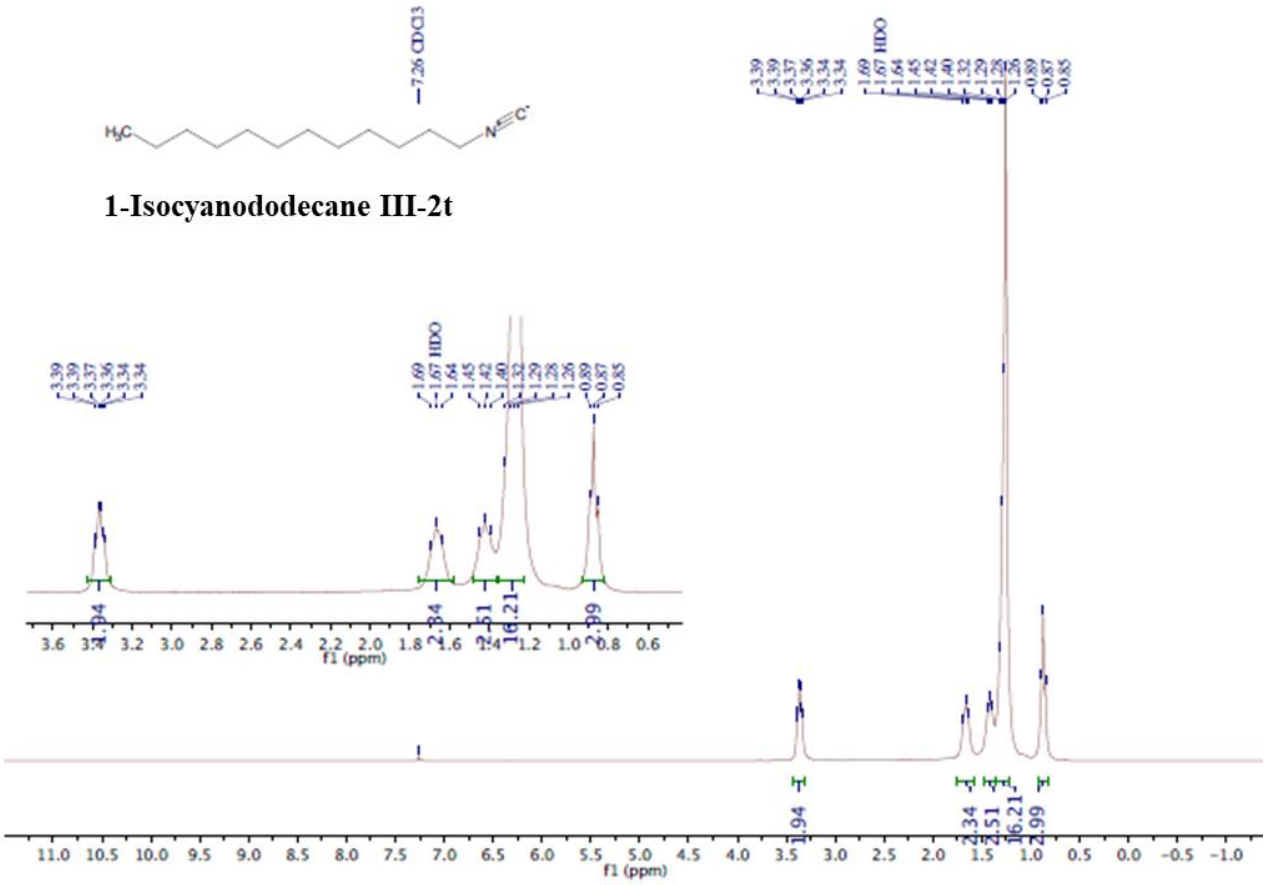
(2-Isocyanoethyl)benzene III-2q

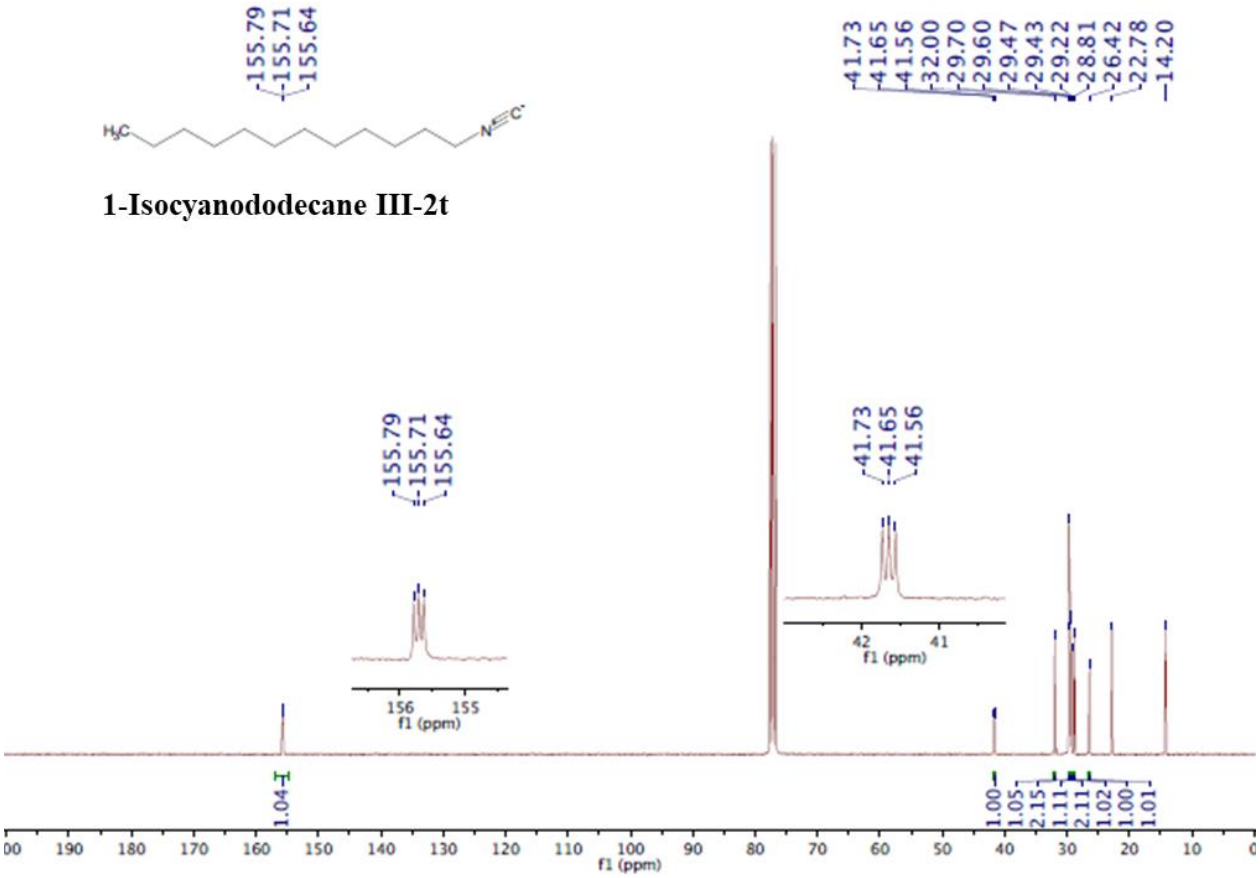

1-Isocyanoheptane III-2r
f1 (ppm)

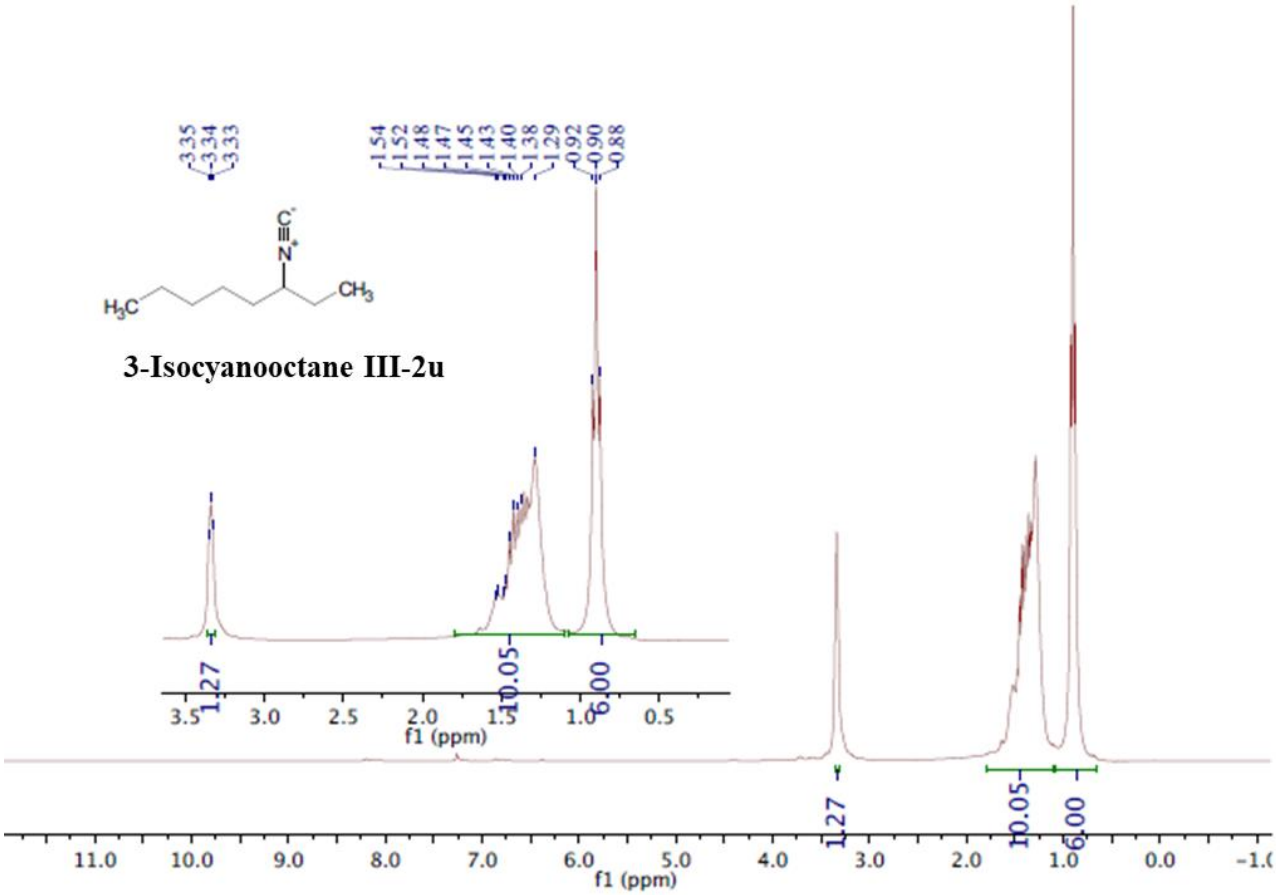

1-Isocyanoheptane III-2r
f1 (ppm)


1-Isocyanooctane III-2s
7.26 CDCl3
HDO
f1 (ppm)


1-Isocyanooctane III-2s
f1 (ppm)


7.26 CDCl3
H3C
N≡C
1-Isocyanododecane III-2t
3.39
3.39
3.37
3.36
3.34
3.34
1.69
1.67 HDO
1.64
1.45
1.42
1.40
1.32
1.29
1.26
0.89
0.87
0.85
1.94
2.34
2.51
16.21
2.99
f1 (ppm)


155.79
155.71
155.64
H3C
N≡C
1-Isocyanododecane III-2t
41.73
41.65
41.56
32.00
29.70
29.60
29.47
29.43
29.22
28.81
26.42
22.78
14.20
1.04
1.00
1.05
2.15
1.11
2.11
1.02
1.00
1.01
f1 (ppm)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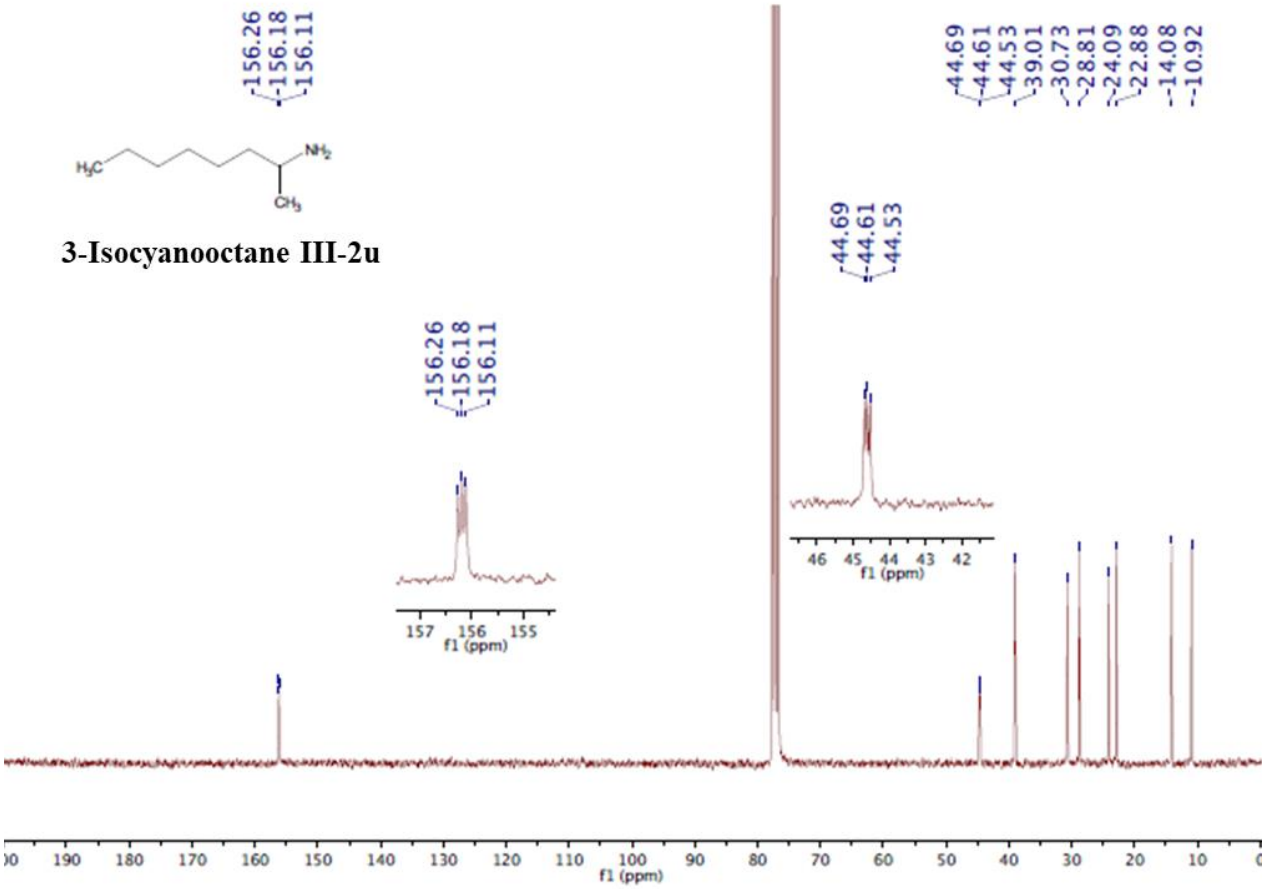
f1 (ppm)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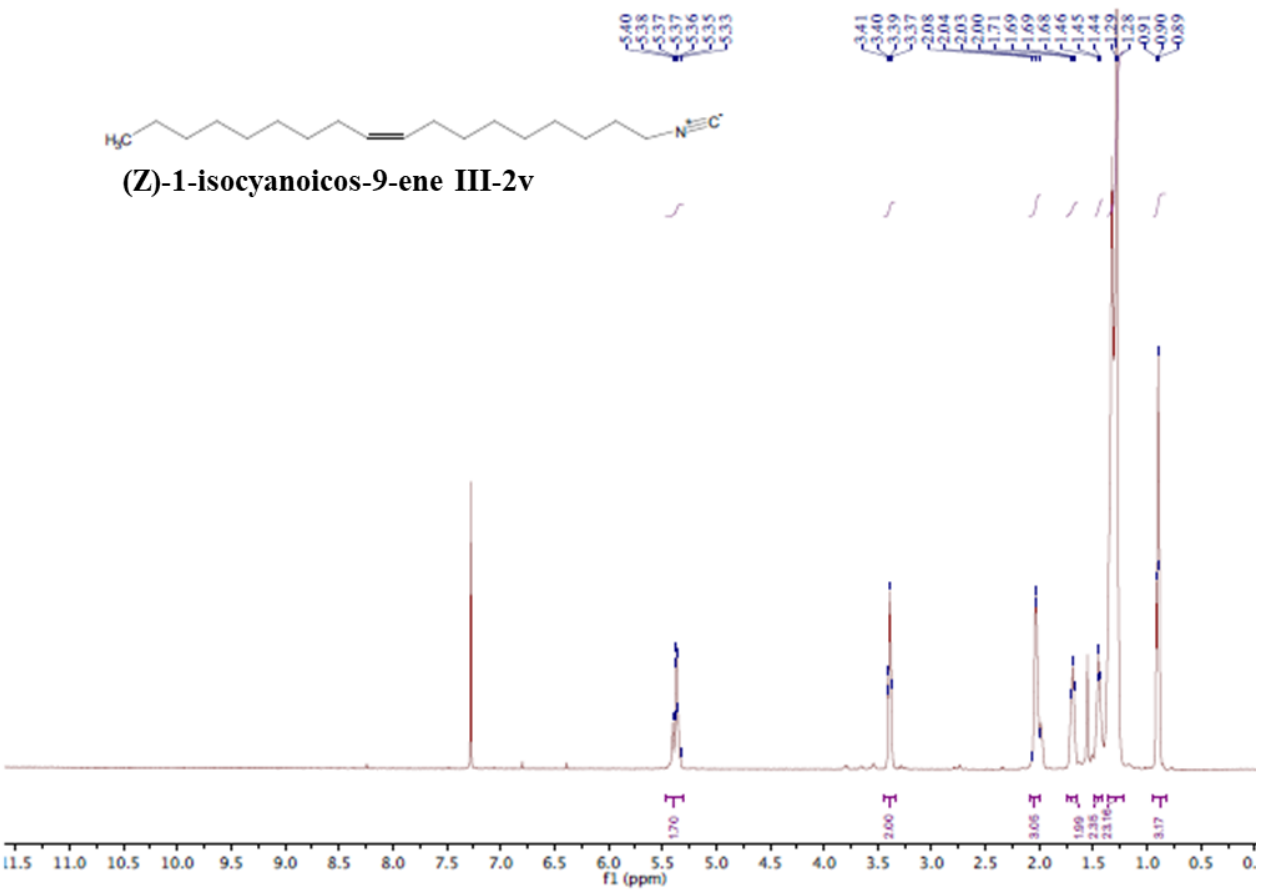
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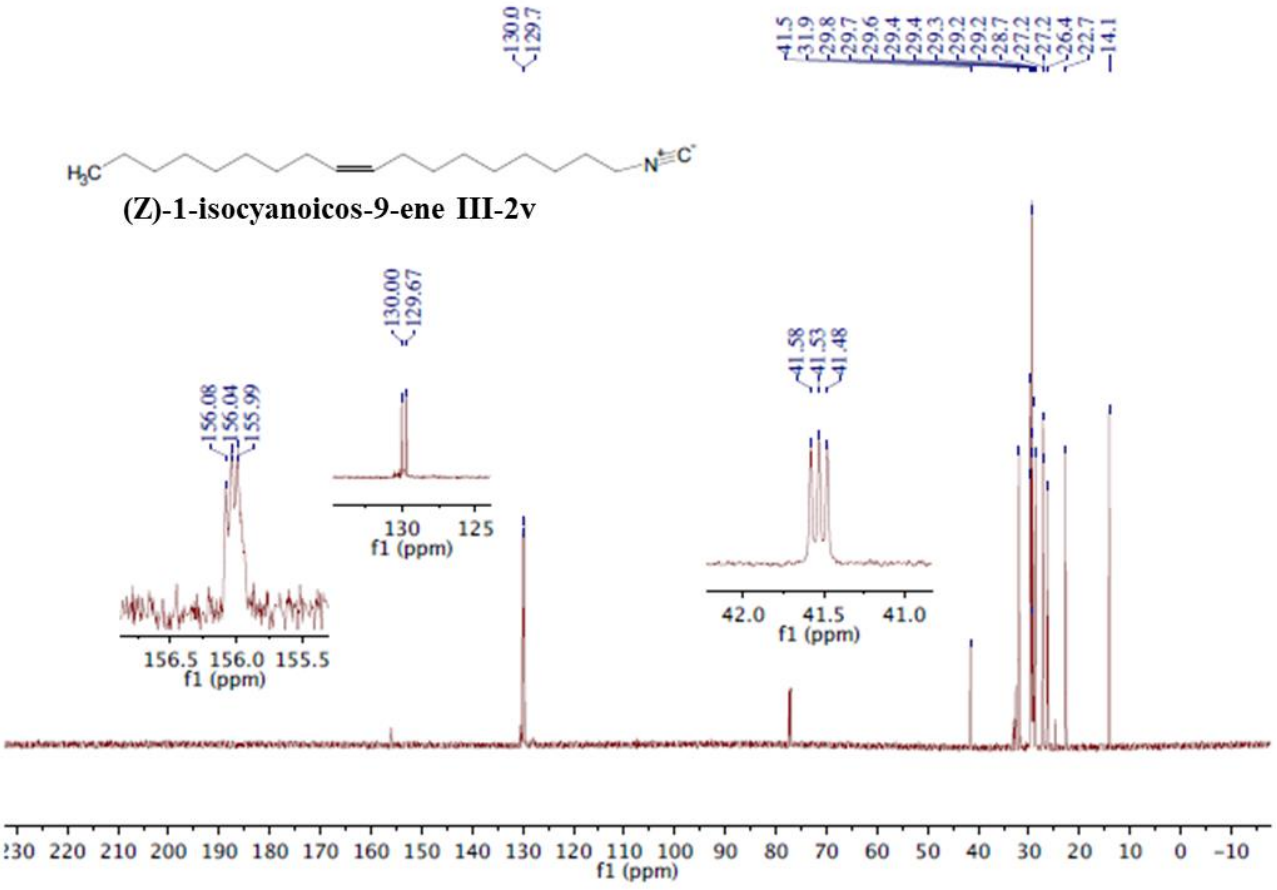
f1 (ppm)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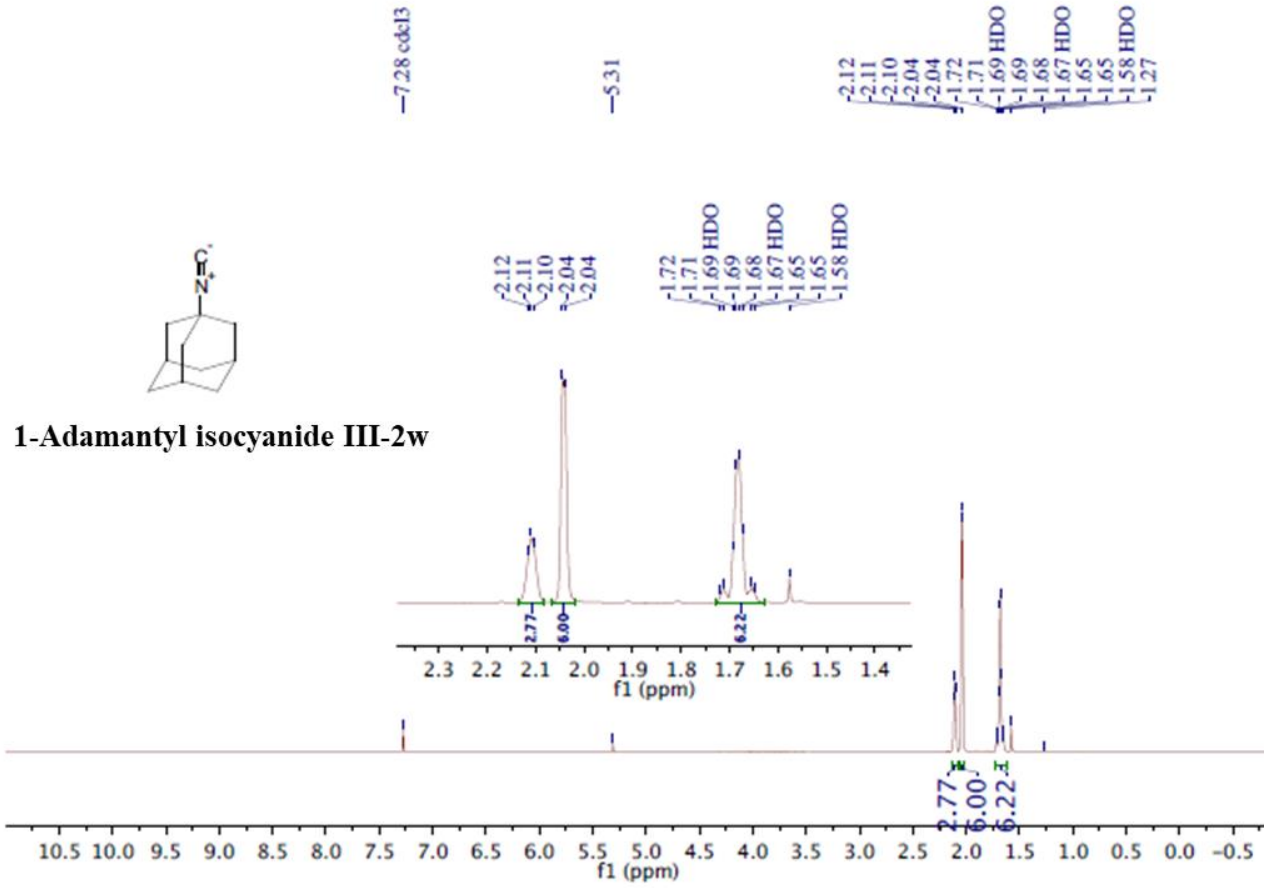
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5.31
2.12
2.11
2.10
2.04
2.04
1.72
1.71
1.69 HDO
1.69
1.68
1.67 HDO
1.65
1.65
1.58 HDO
1.27
1-Adamantyl isocyanide III-2w
2.77
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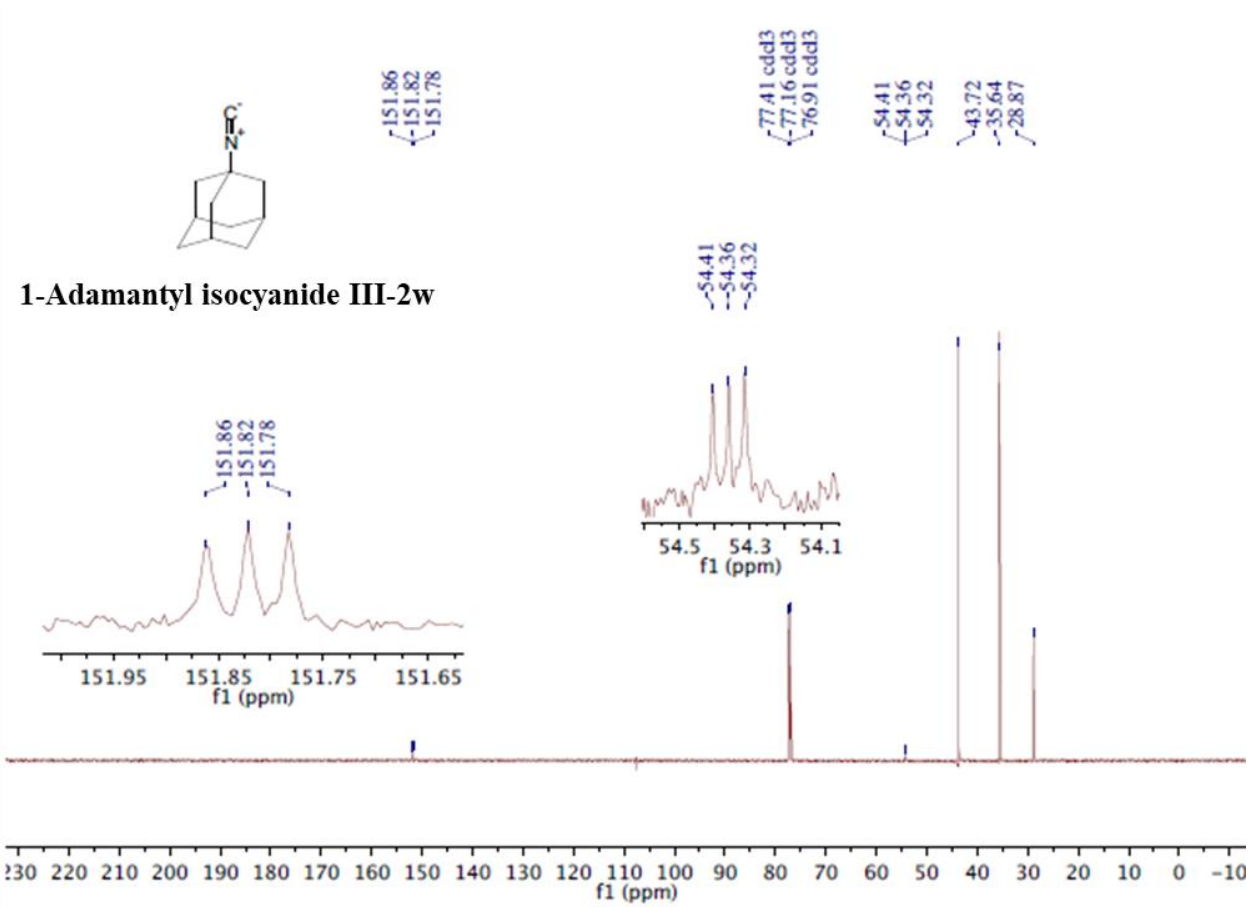
6.22
f1 (ppm)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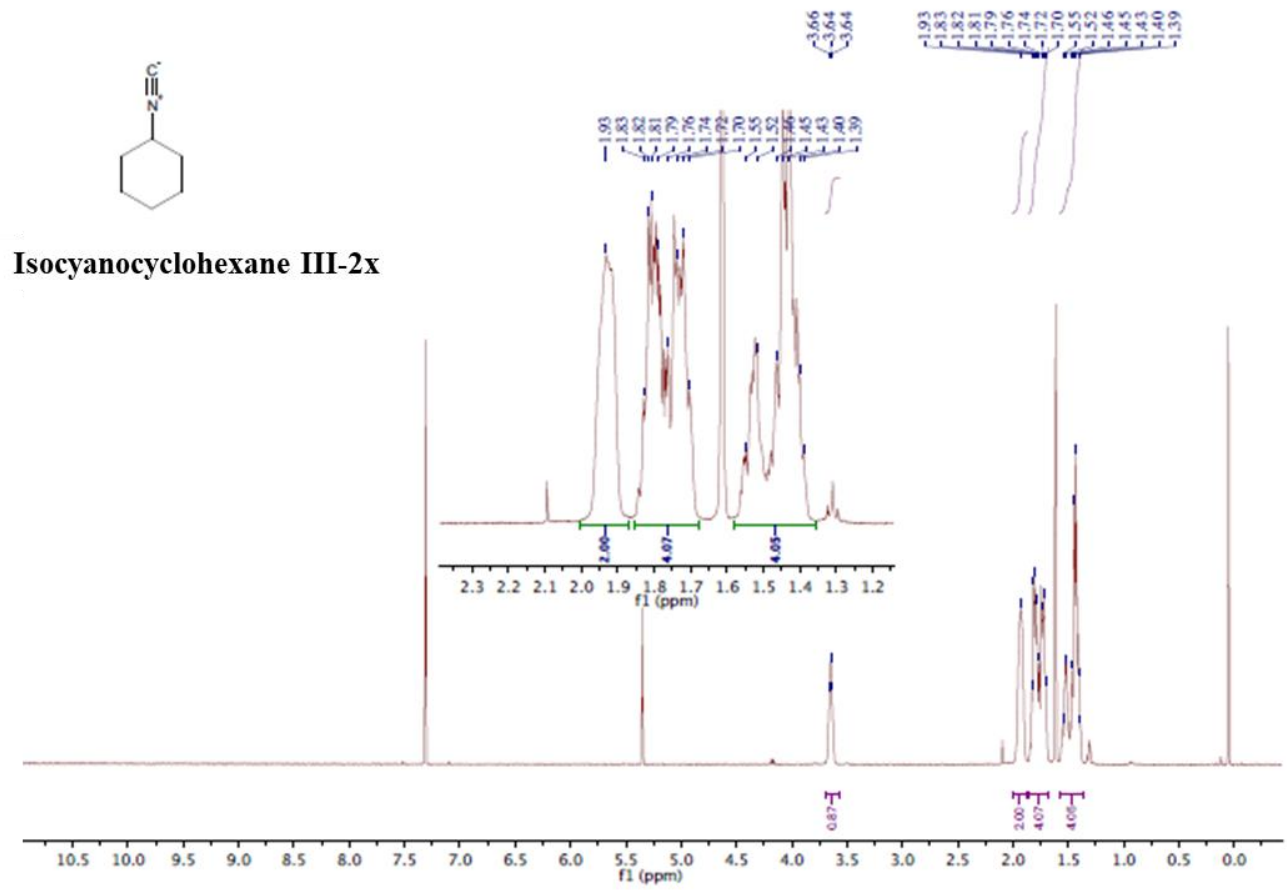
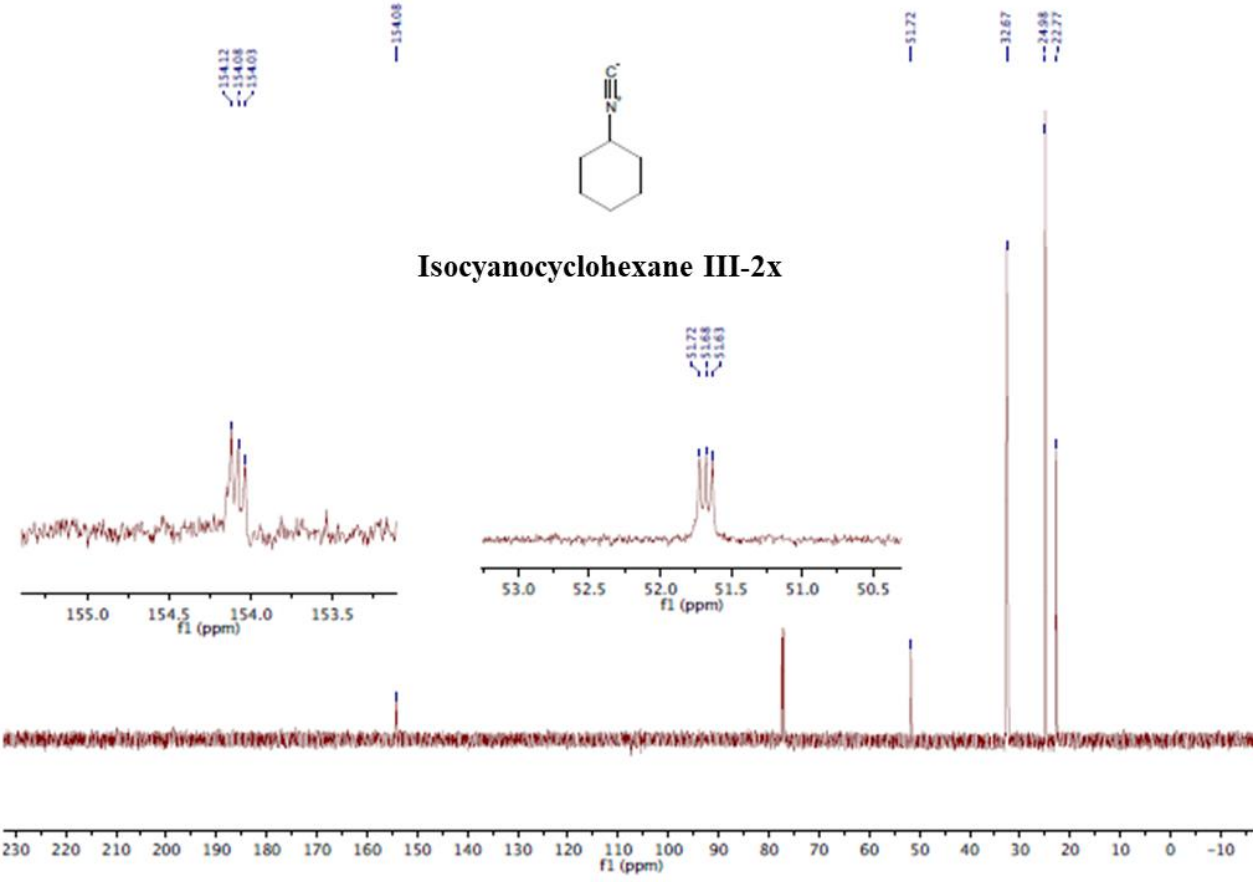
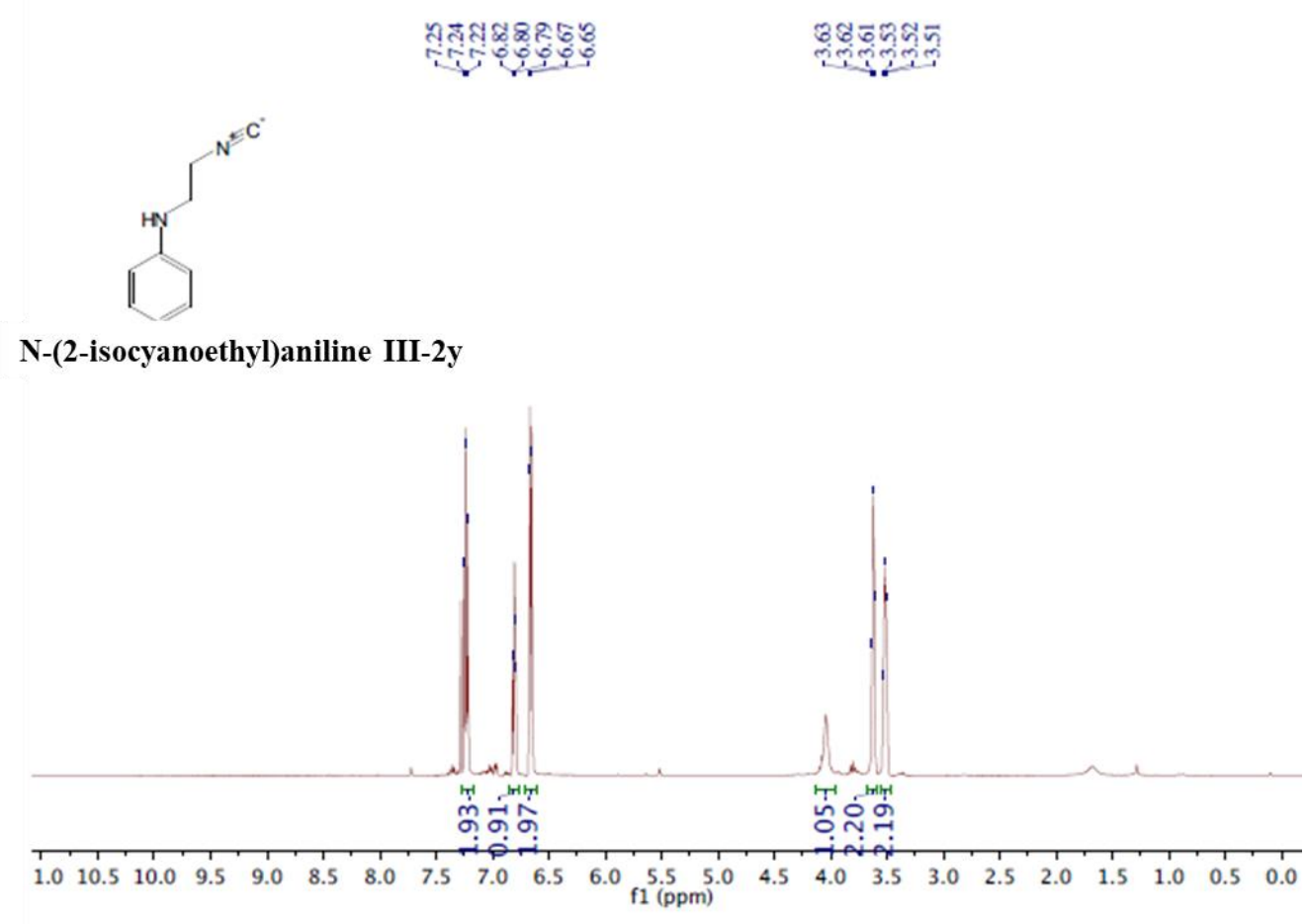
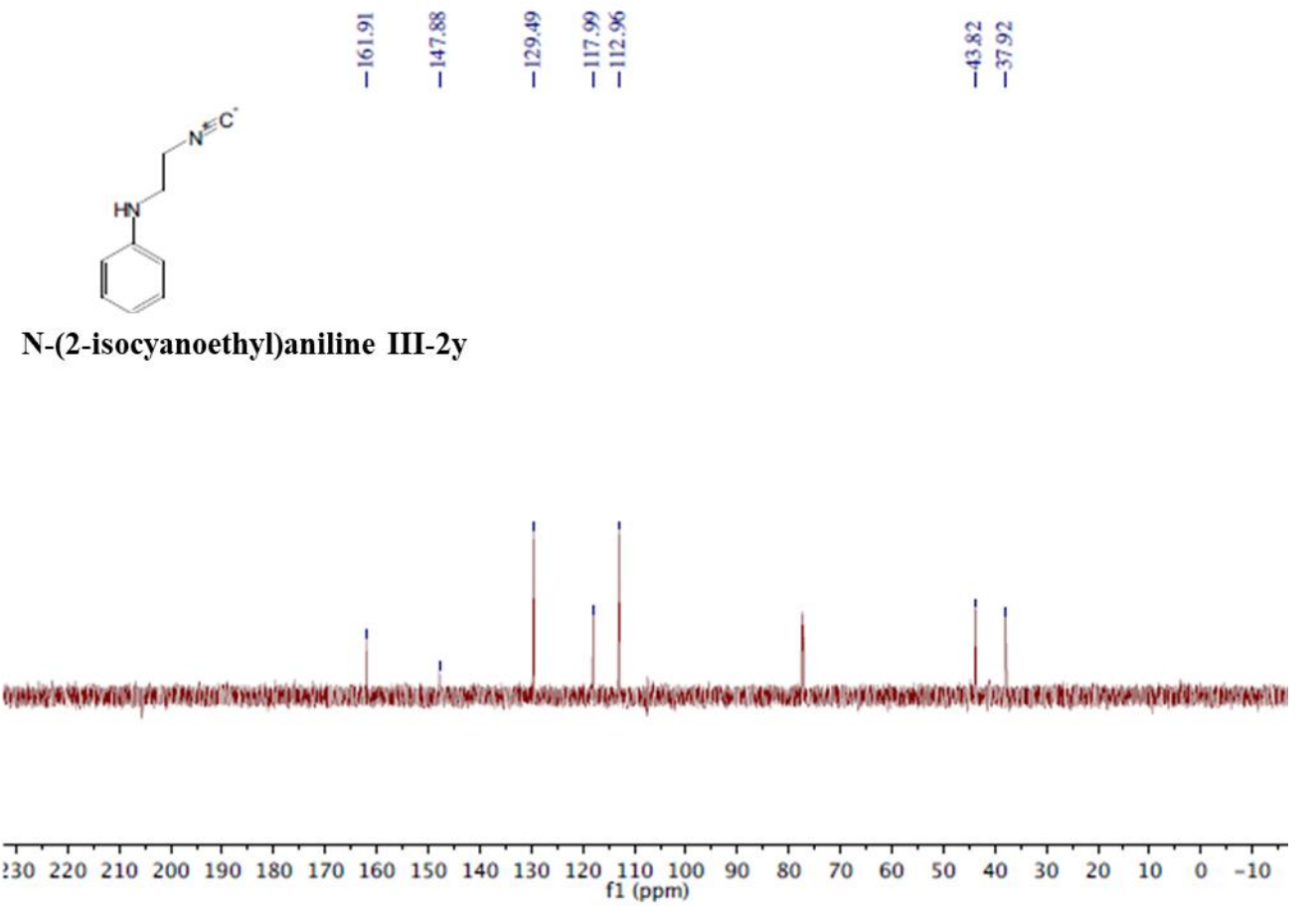
151.82
151.78
77.41 cdd3
77.16 cdd3
76.91 cdd3
54.41
54.36
54.32
43.72
35.64
28.87
1-Adamantyl isocyanide III-2w
f1 (ppm)


Isocyanocyclohexane III-2x
f1 (ppm)

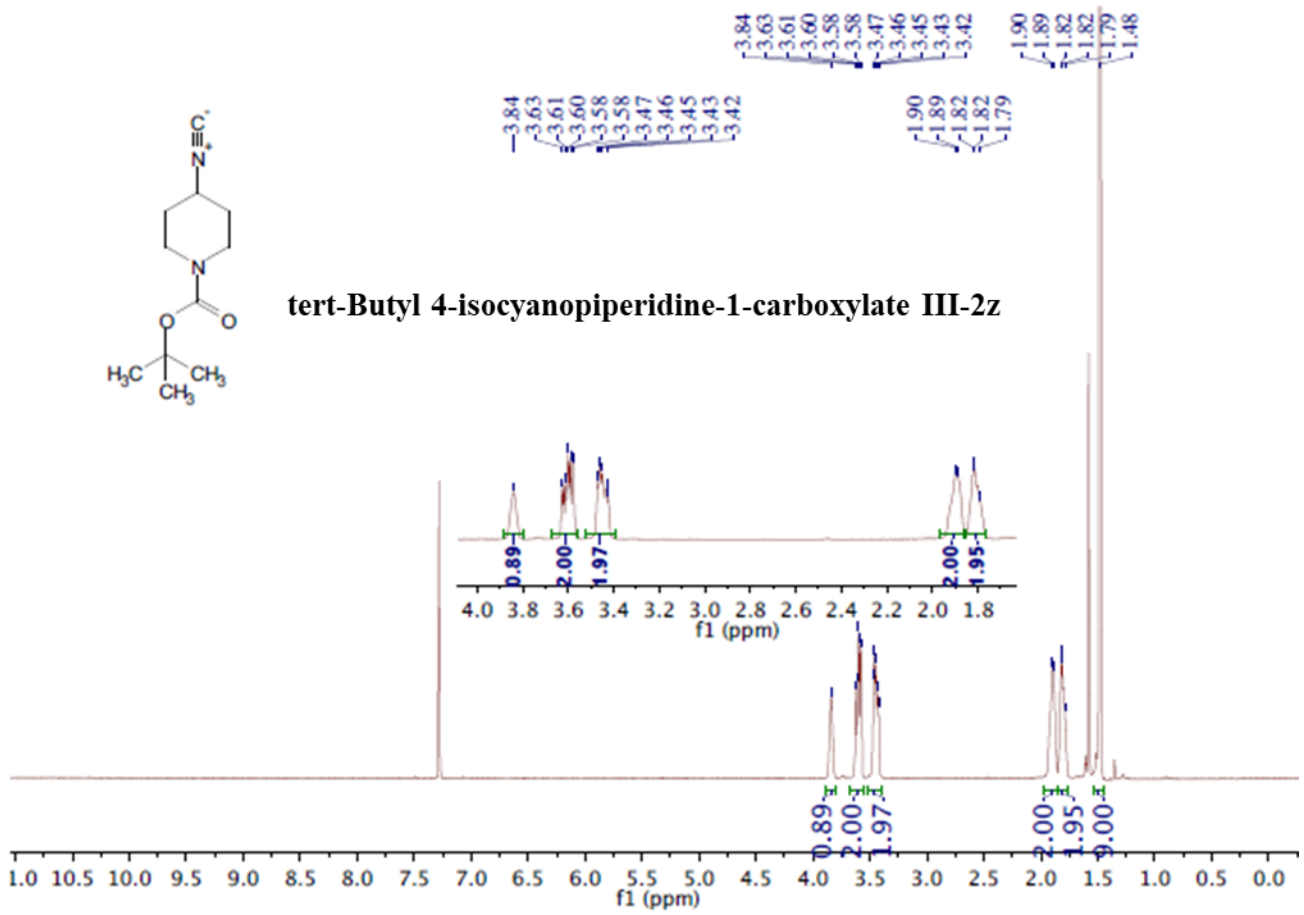

Isocyanocyclohexane III-2x
f1 (ppm)

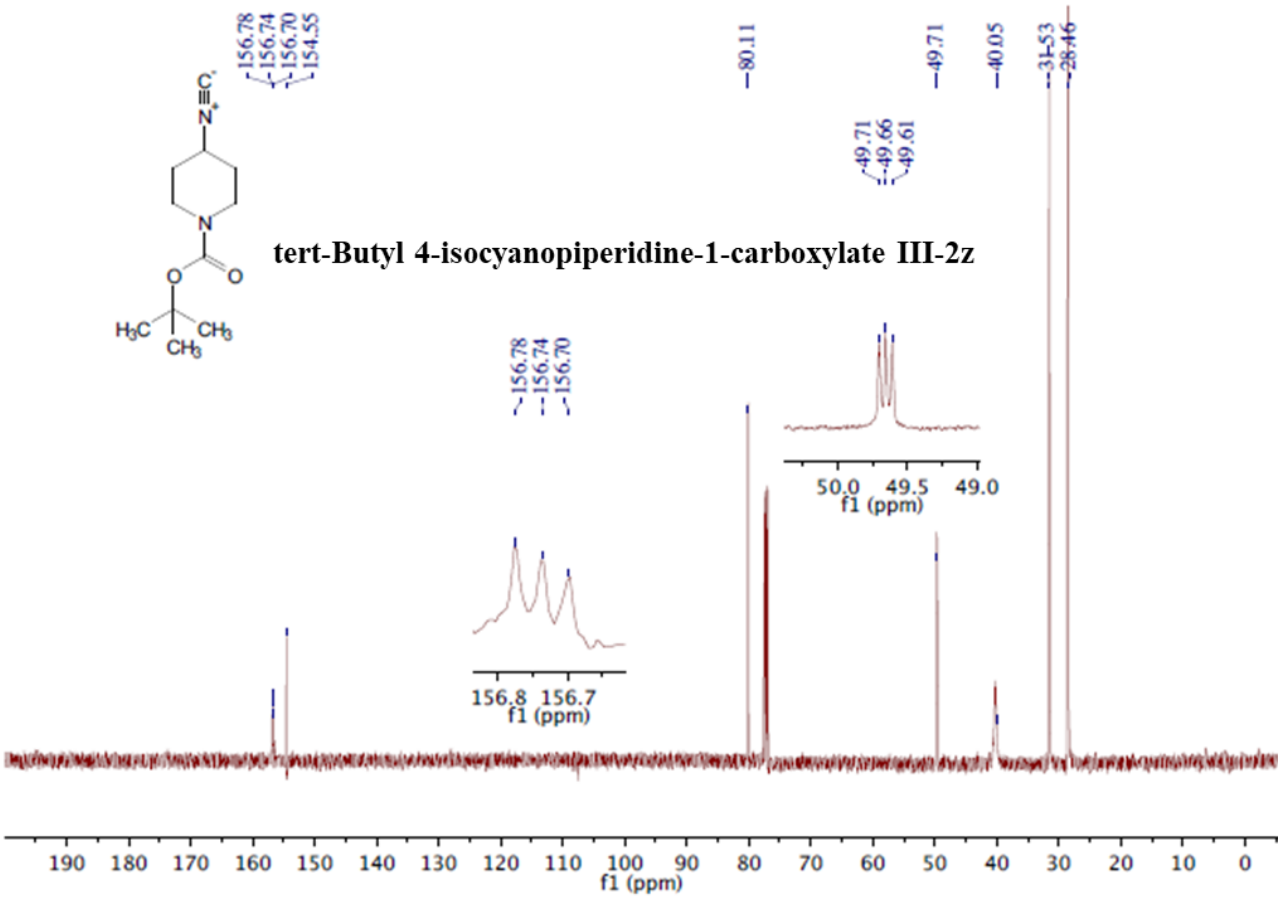


N-(2-isocyanoethyl)aniline III-2y



N-(2-isocyanoethyl)aniline III-2y


tert-Butyl 4-isocyanopiperidine-1-carboxylate III-2z
f1 (ppm)

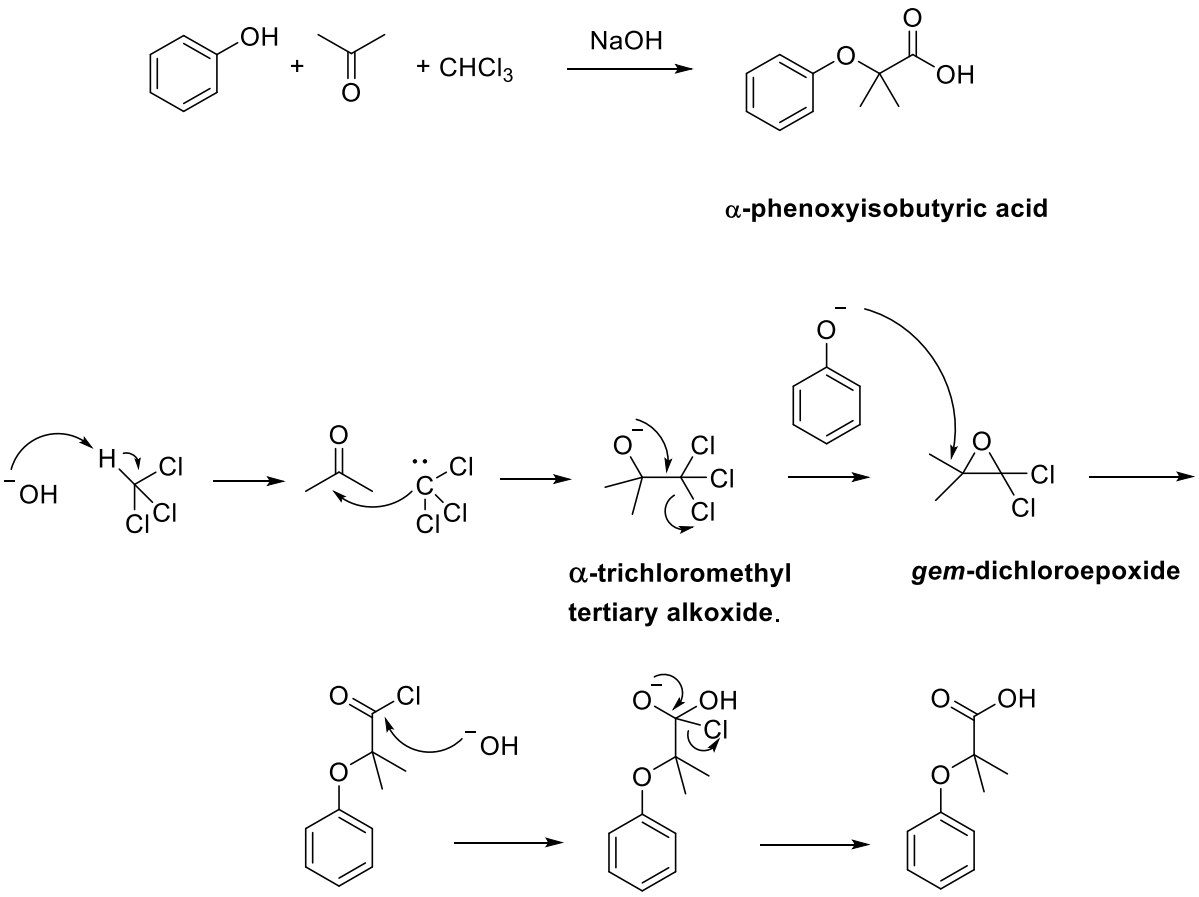

tert-Butyl 4-isocyanopiperidine-1-carboxylate III-2z
f1 (ppm)

Chapter IV-Isocyanide in modified Bargellini reaction: a direct route to 3-Carboxamido-isobutyric acids (3-CIAs) from primary amines

Introduction

The Bargellini reaction

The Bargellini reaction takes its name from the chemist Guido Bargellini.[260] The multicomponent reaction among phenol, chloroform, and acetone in the presence sodium hydroxide was already been published in a German patent of 1864,[261] but the product was not correctly identified. The credit of Bargellini was to recognize the α-phenoxyisobutyric acid derivative as the actual product of this transformation. The reaction proceeds through the addition of acetone to trichloromethide (formed by deprotonation of added chloroform with hydroxide) resulting in an α-trichloromethyl tertiary alkoxide. The alkoxide rapidly forms the highly reactive *gem*-dichloroepoxide. Regioselective attack of phenol to the dimethyl substituted carbon leads to the formation of the α-substituted carboxylic acid chloride, which is then hydrolyzed to the corresponding carboxylic acid (Scheme 49)



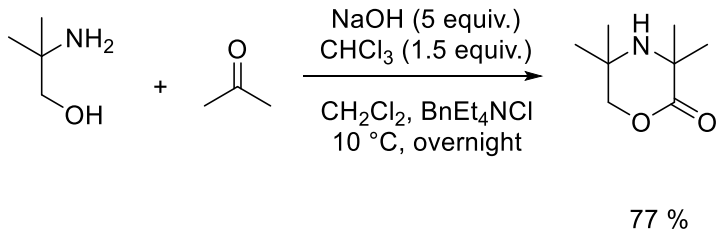
Scheme 49 *Bargellini reaction*

The potential of this synthetic route relies in different aspects. First, three distinct substitution reactions are involved in a one-pot process, (*i.e*. the intra-molecular substitution to give the reactive *gem*-dichloroepoxide intermediate, inter- or intramolecular nucleophilic substitution and chloride elimination to produce the acyl chloride derivative, nucleophilic substitution to afford the final product. Moreover, the transformation sees the formation of innocuous NaCl and water as by-products. The reaction conditions do not involve the required presence of strong Lewis or Brönsted acids for substitutions to occur, seen the intrinsic reactivity of the *gem*-dichloroepoxide intermediates. Thus, the procedure is applicable to a wide number of nucleophilic partners and is operational simple if compared to the conditions often required for nucleophilic substitution on epoxides.

Indeed, the replacement of the phenol with other suitable nucleophilic functions gives access to wide variety of α-substituted carboxylic acid derivatives. Fifty years after first reports of

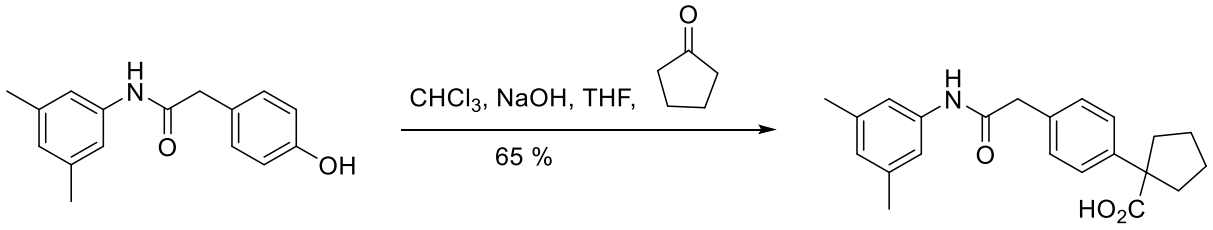
Bargellini, Galimberti and co-workers demonstrated the applicability of this transformation using thiophenols,[262] ureas and thioureas,[263,264] semicarbazides and thiosemicarbazides,[265] secondary alcohols, benzotriazoles, and guanidine[266,267] as nucleophilic partner in this transformation.

Several contributes were also given from Lai in the field of modified Bargellini reaction.[268–271] In 1980 he reported the use of diamines[271] and β-amino alcohols[272] (Scheme 50) as nucleophiles in an intramolecular Bargellini-type reaction in phase-transfer catalyzed reaction. The protocols give access to hindered morpholinones and piperazinones with two quaternary centers adjacent to the amine in a single step.



Scheme 50 *Intramolecular Bargellini reaction*[272]

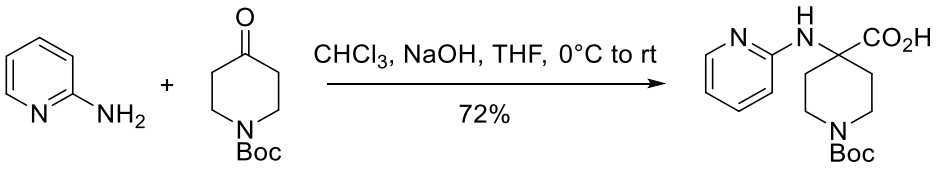
The transformation involving the addition to an intermediate *gem*-dichloroepoxide has attracted attention in pharmaceutical research, resulting in a wide number of applications in this field.[273] For instance, Abraham and coworkers applied a Bargellini reaction to a gram-scale synthesis of a known allosteric effector of hemoglobin (Hb) (Scheme 51).[274]



Scheme 51. *Synthesis of a Bioactive aminoacid precursor*[274]

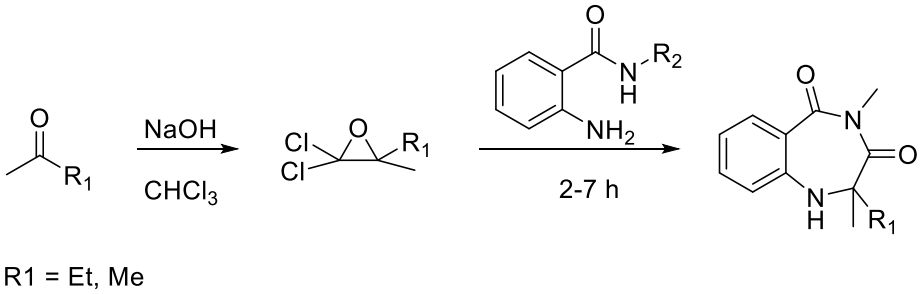
Another variation on the nucleophilic partner was reported by Butcher and Hurst, who demonstrated that weakly nucleophilic anilines and amine-substituted heterocycles can be used

in Bargellini reactions to prepare hindered α-amino acid derivatives in a single step (Scheme 52).[275]



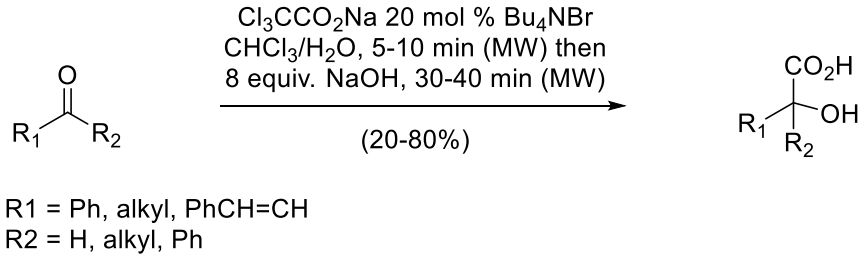
Scheme 52. *Hindered amino acid with an amino-heterocycle*[275,276]

Shafiee and co-workers showed that 2-aminobenzamides can react as efficient nucleophiles under Bargellini conditions to prepare potentially bioactive 1,4-benzodiazepine-3,5-dione derivative as the one reported in Scheme 53.[277]



Scheme 53*.-Aminobenzamides as nucleophiles in Bargellini raction*

Yu and coworkers used sodium trichloroacetate and catalytic tetrabutylammonium bromide in chloroform/water by 70 W microwave irradiation for the formation of thrichloromethyl carbinol as intermediate for the synthesis of α-hydroxy-acids (Scheme 54). [278]

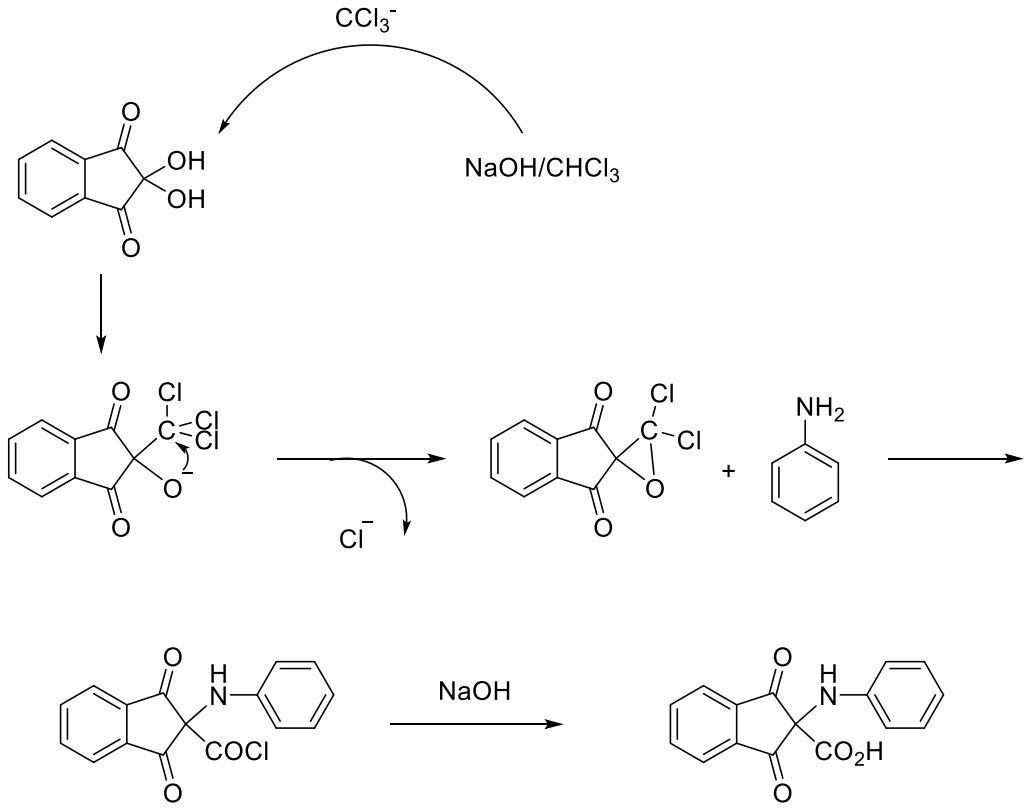


Scheme 54*. Synthesis of α-hydroxy-acids*[278]

Variation on the carbonylic group were also reported. Youseff used phenols as nucleophiles and cyclopentanone as the ketone for the preparation of intermediate in the synthesis of chiral

allosteric modifiers of Hemoglobin;[274] aniline and amine-substituted heterocycles were coupled with the *N*-*t*-butyloxycarbonyl-protected piperidinone by Butcher.[275]

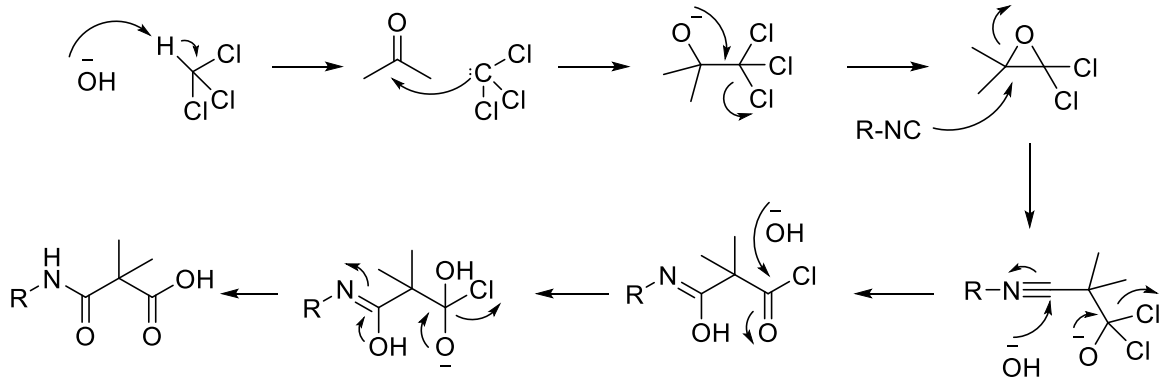
In 2016 Naeimi and coworkers reported the use of ninhydrin to synthesize a series of novel a-amino acids in presence of chloroform and NaOH and various substituted anilines as nucleophiles. The purposed mechanism, reported in Scheme 55, sees the deprotonation of chloroform followed by nucleophilic attack on the ninhydrin yielding dichloro epoxide. The nucleophilic aniline attack in turn the dichloro-epoxide to give the acid chloride, which undergo the hydrolysis.[279]



***Scheme 55**. Purposed mechanism for the Bargellini reaction in presence of ninidrin as carbonylic partner*[279]

In 2016 Giustiniano and co-workers published an interesting application of the Bargellini route for the one-pot synthesis of 3-Carboxamido-Isobutyric Acids using isocyanide, chloroform, acetone and sodium hydroxide.[280] They were able to synthesize a number of acids starting from either aromatic either aliphatic isocyanides. In the mechanism proposed (see Scheme 56), the

formation of the 2,2-dichloro-3,3-dimethyloxirane intermediate is followed by the attack from cyclohexylisocyanide in an S_N2 reaction with substantial S_N1 character.



***Scheme 56**. Bargellini reaction using isocyanide as nucleophile*[280]

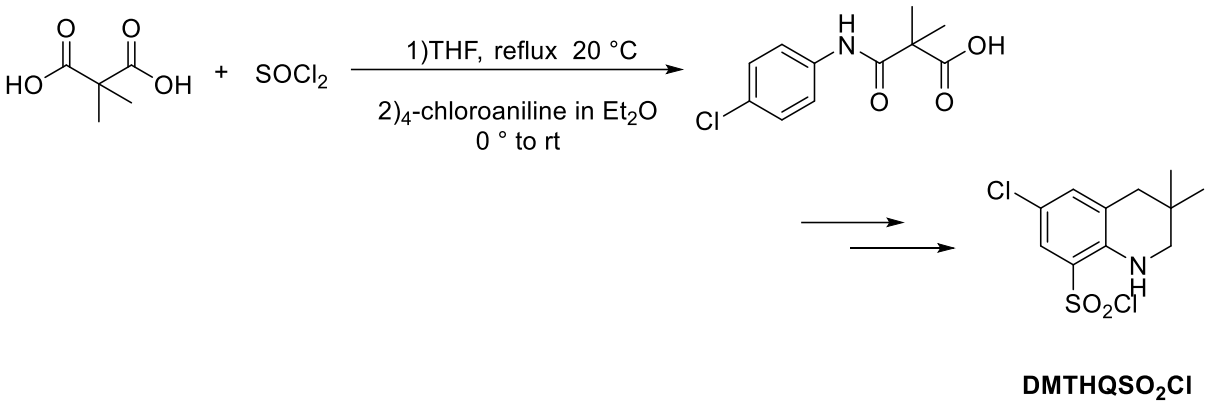
Afterwards the hydroxide ion attacks the nitrilium ion formed leading to the formation of iminol, which in turn tautomerizes to the more stable amide.

Under this basic reaction conditions, the acyl chloride is hydrolyzed to the carboxylate ion. The whole process is thermodynamically favored by the oxidation of isocyanide and chloroform carbon atom and by the energy released during the epoxide ring opening.[280]

3-Carboxamido hindered acids and their relevance.

3-Carboxamido hindered acids are key intermediate in several molecules of pharmaceutical relevance as confirmed by their application in several patents.[281–283]

The 4-chloro substituted carboxamido isobutyrric acid is used in the synthesis of 3,3-Dimethyl-6-chlorotetrahydroquinolinesulfonylChloride ($DMTHQSO_2Cl$), intermediate for the preparation of Thrombin Inhibitors of MD-805 Analogues.[284]

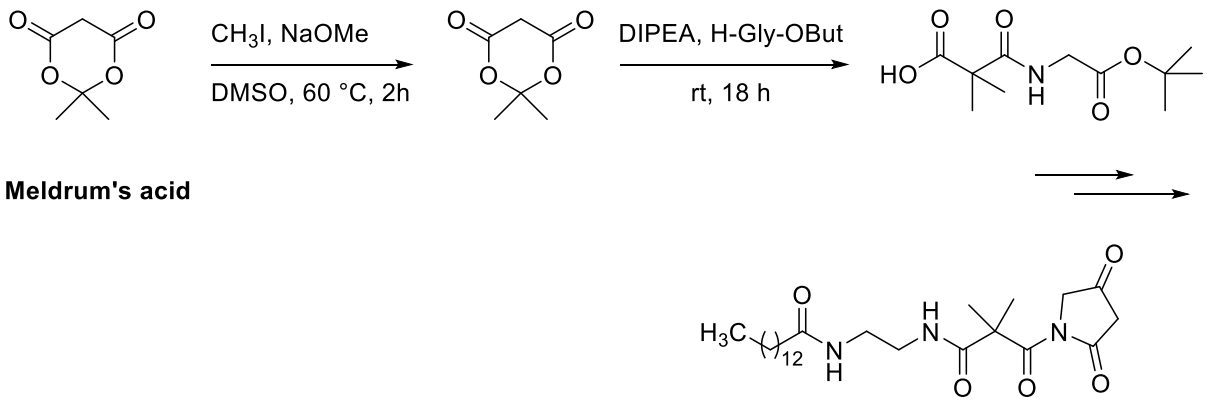


DMTHQSO$_2$Cl

Scheme 57*. Synthesis of the carboxamido isobutyrric acid derivatives as intermediate for the synthesis of DMTHQSO2Cl*[284]

The authors prepared the 3-Carboxamido hindered acid by reacting at room temperature 4-chloroaniline with dimethylmalonic acid previously reacted with $SOCl_2$ in THF at reflux, obtaining the corresponding 3-Carboxamido-isobutyrric acid with 33% of yield, as shown in Scheme 57.

Studies on Isomalyngamide A analogs as the one reported in Scheme 58 demonstrated its therapeutic potential against tumor cell migration *in vitro* at the level of nanomolar to micromolar ranges.[285] The key intermediate CIAs was prepared by addition of methyl iodide to Meldrum's acid reported in scheme followed by intermolecular condensation with H-Gly-OBut and elimination of the acetone (Scheme 58).



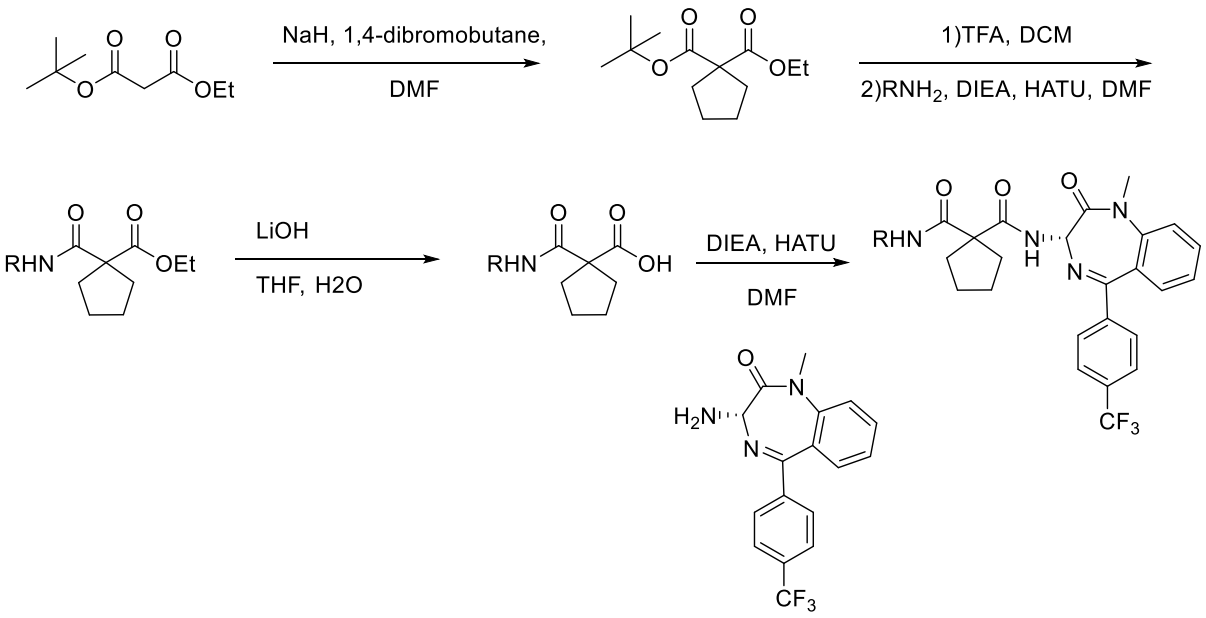
Meldrum's acid

isomalyngamide A analogue

Scheme 58. *Synthesis of CIA derivative with using Meldrum's acid for the synthesis of anisomalyngamide A analogue*[285]

The 3-Carboxamido acid derivative in scheme is a key intermediate for the formation of benzoazepinone-derived cyclic malonoamides, a potent gamma-secretase inhibitors.[286]

Its synthesis passes through the dialkylation of malonate with 1,4-dibromobutane to give the cyclic dicarboxylate. The *tert*-butyl group is removed to give the free acid which undergo toward coupling with the amine. Hydrolysis of the ester provides the carboxylic acid, which is coupled to the aminobenzodiazepinone to give the desired amides (Scheme 59)



Scheme 59*.Carboxamido acid derivative in the synthesis of benzoazepinone-derived cyclic malonoamides, a potent gamma-secretase inhibitors*

Result and Discussion

Aim of the work

Inspired by the work of Giustiniano, we thought to develop a method to further transform the isocyanide achieved by mechanochemical route. As highlighted above, the combination of ball milling technique with multicomponent approach revealed to be very useful for several transformation[116] including Ugi and Passerini mechanochemical reactions.[124]

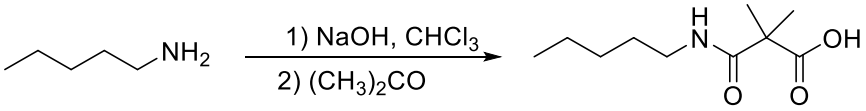
Our working hypothesis was to develop a one-pot procedure for preparing 3-Carboxamido hindered dialkyl acids directly from primary amine, exploiting the reactivity of *gem*- dichloro epoxide formed reacting the suitable ketone, chloroform and sodium hydroxide.

Screening of reaction conditions

For the first step of the reaction, we applied the mechanochemical conditions previously developed for the synthesis of isocyanide in a ball mill. 1-Pentylamine has been used as model substrate, while competition experiments were performed on a 1 mmol scale. The amine (1.0 equiv), $CHCl_3$ (2x1.2 equiv.), NaOH (12 equiv), and 0.3 g of Na_2SO_4 were continuously milled for the given time in a the Spex 8000M mixer/mill into a zirconia-milling beaker (45 ml) equipped with four balls (d = 10.0 mm). These conditions were kept fixed for all the following experiments, expect when specified.

For the next step, *i.e.* the formation of the 3-Carboxibutyrric acid, we started from the conditions reported by Giustiniano for the same reaction in homogeneous phase. In particular, we kept the stoichiometric ratio among the amine, the chloroform, the acetone and the sodium hydroxide, without keeping into account the preliminary presence of the excess of chloroform and sodium hydroxide. Besides, an additional amount of Na_2SO_4 (1.6 g) as adsorbent was introduced in the jar. Once the mechanochemical synthesis of isocyanide was complete, Acetone (5 equiv.), $CHCl_3$, (7 equiv.), NaOH (7 equiv.) and Na_2SO_4 (1.6 g) were introduced into the same reactor and the mixture ball milled for additional 45 minutes.

Table 14 *Optimization of conditions: effect of the stoichiometric ratio of $CHCl_3$ and $(CH_3)_2CO$* [a][b]



IV-1 **IV-2**

Entry	Equiv. of $(CH_3)_2CO$	Equiv. of $CHCl_3$	Time (min)	^{1}H-NMR Yield[c] %
1	5	7	45	29
2	2.5*2	3.5*2	25*2	traces
3	1.1	1.2	45	30
4	1.1*2	1.2*2	25*2	36
5	1.1*3	1.2*3	25*2	34
6	**0.8*2**	**1x2**	**25x2**	**48**
7	-	1x2	25x2	n.r.

[a]Reaction conditions: 1) pentanamine (1.0 mmol, 1.0 equiv), $CHCl_3$ (2x1.2), NaOH (12 mmol, 12 equiv), and 0.3 g of Na_2SO_4 were continuously milled for 2 cycles of 15 minutes in a Spex 8000M mixer/mill into a agate-milling beaker (45 ml) equipped with four balls (d = 10.0 mm) 2) Acetone and $CHCl_3$ in the given amounts, NaOH (7 equiv.) and Na_2SO_4 (1.6 g) were added and the mixture was ball milled for the given time
[b]Values in the table are referred to the amounts of reagents added in the second step of reaction.
[c] ^{1}H-NMR yield was determined using 2,5-Dimethylfuran as internal standard.

At the above conditions we recovered a very complex reaction mixture, in which the desired product was identified by the presence of the amide peak at 7.54 ppm. The aliphatic area was characterized by the presence of a wide number of peaks, rendering more difficult the integral measurement. The ^{1}H NMR spectrum is reported in Figure 12

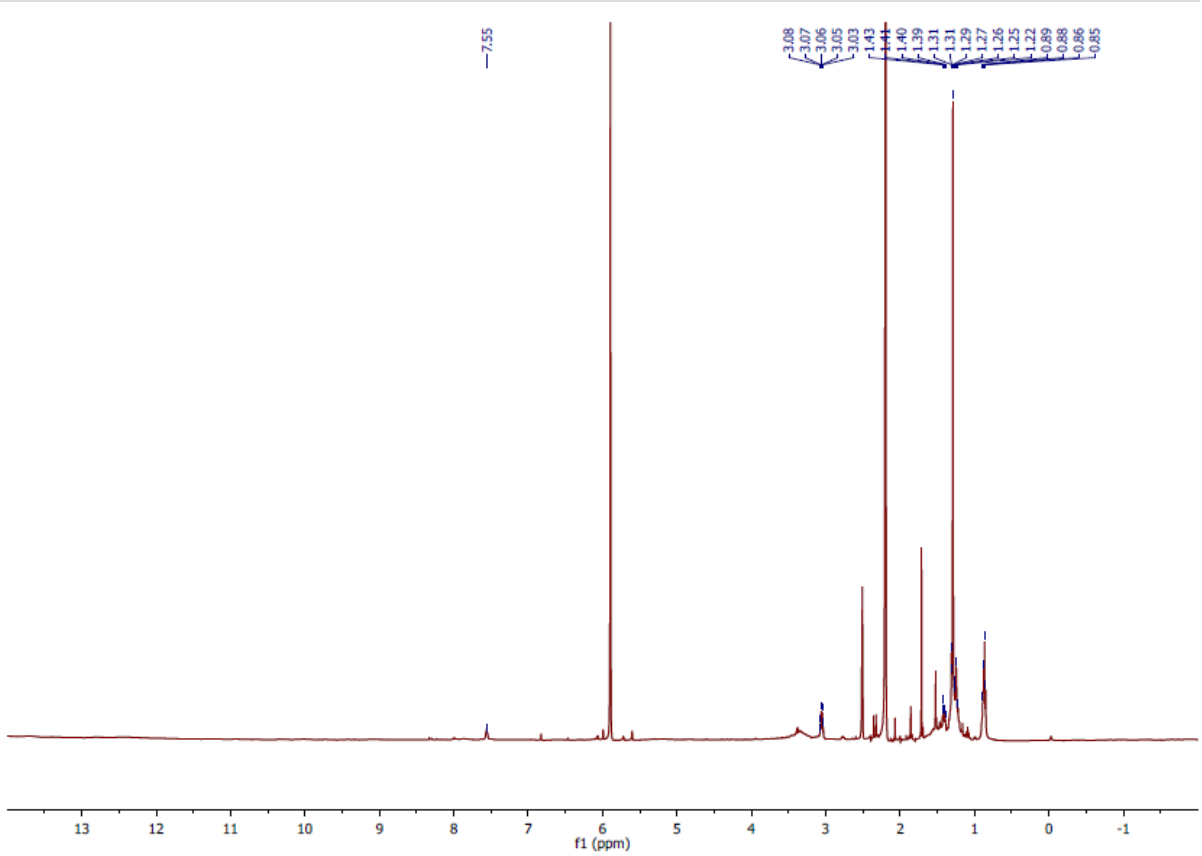


Figure 12 *Crude ^{1}H-NMR of complex reaction mixture (Entry 2)*

The calculated ^{1}H-NMR yield at these conditions was found to be 29 % (entry 1, Table 14). In order to improve the performance of the reaction and inspired by the results obtained with the isocyanides we thought to add the same equivalents of chloroform and acetone in two separate steps. In this case only traces of product were detected in a complex spectrum from which we were not able to isolate the single compounds (Entry 2, Table 14).

We then switched to use an almost stoichiometric amounts of chloroform and acetone. While the reaction mixture appears cleaner, no significant improvement in the ^{1}H-NMR yield was registered (entry 3, 30%,Table 14). Once again, we went back to the two-step addition strategy using increasing value of chloroform. A slight improvement in yield was observed when 1.1 equiv. of Acetone and 1.1 equiv. of chloroform were added twice (entry 4, Table 14). The addition of a third amount of chloroform and acetone was of no use (entry 5, Table 14))

In order to understand the nature of the by-product during the mechanochemical treatment of the reactants, we performed the reaction in the absence of the nucleophilic partner for the Bargellini reaction.

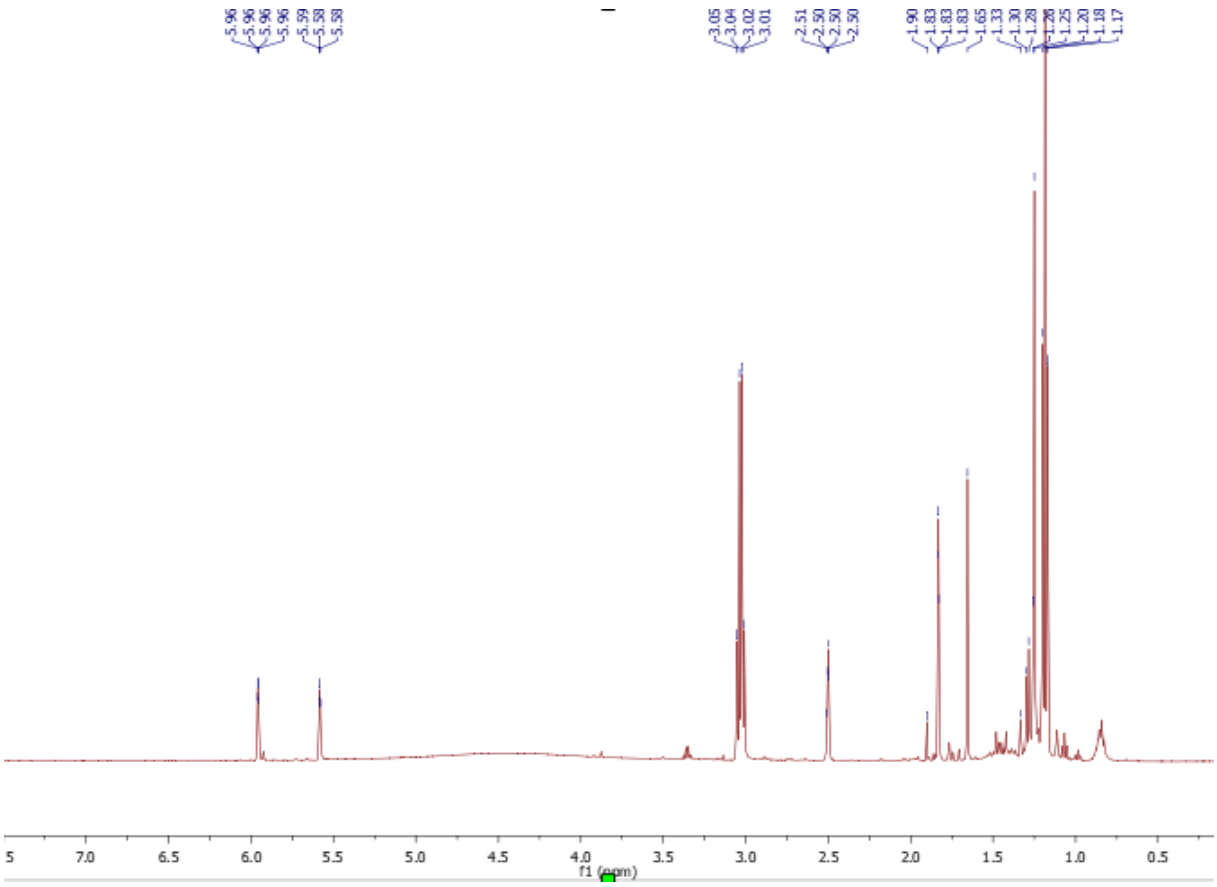


Figure 13 *^{1}H-NMR spectrum of reaction crude obtained with 2.5x2 equiv. of acetone and 3.5x2 equiv. of chloroform*

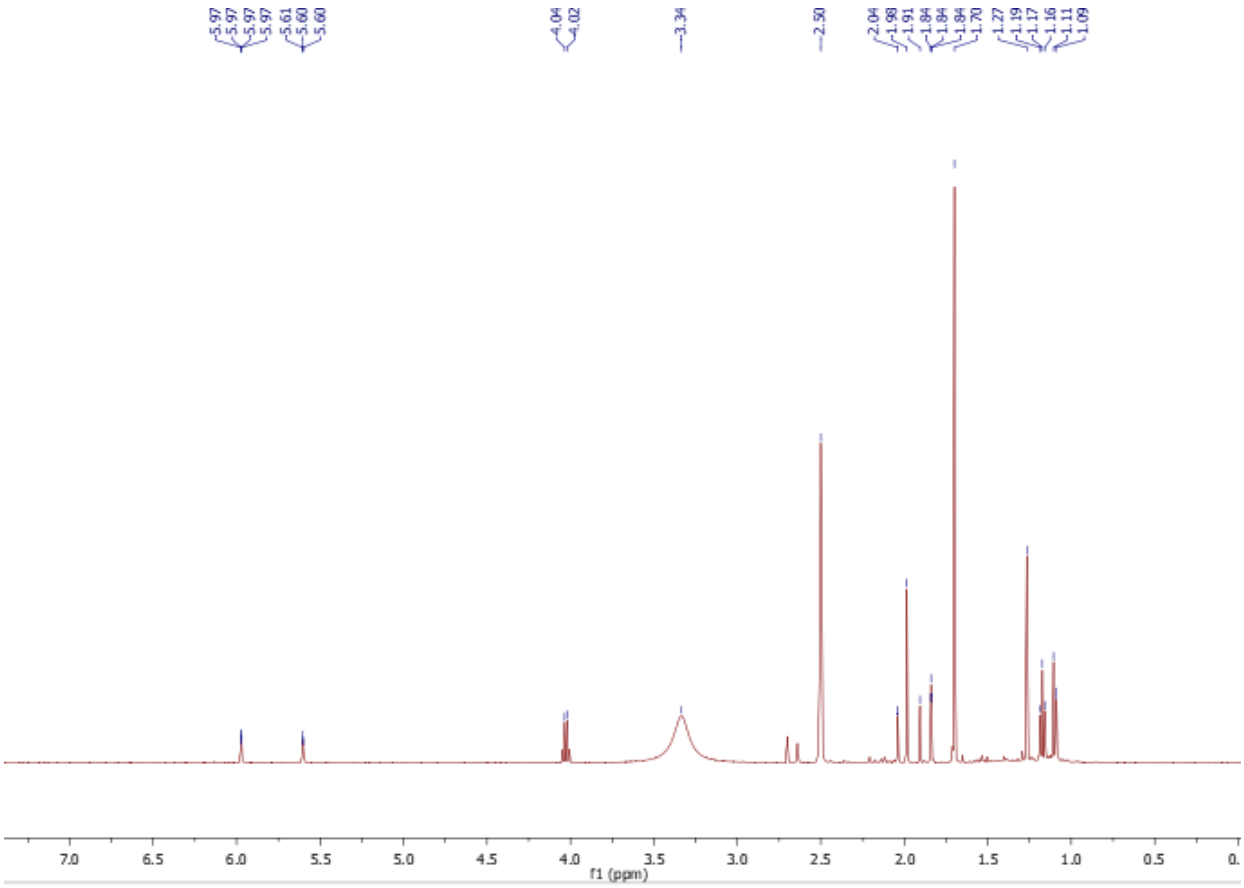


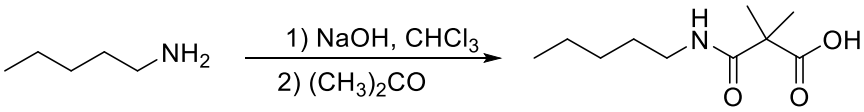
Figure 14 *[1]H-NMR spectrum of reaction crude obtained by milling NaOH, acetone and chloroform in presence of sodium sulfate*

The reaction crude [1]H- NMR (Figure 14) showed the presence of several peaks in common with the reaction crude obtained when 7 equiv. of chloroform and 6 equiv. of acetone were added in two steps (entry 2**,** Table 14) This promted us to reduce the amounts of the two reagents, which seems to convert in any case to undesired by-product.[278] Indeed, we recovered a much more clean reaction mixture when 0.8 equivalents of acetone and 1 equivalent of chloroform were added twice to the jar, and milled together after the preliminar formation of isocyanide. We finally arrived to a slight enhancement in the reaction performance achieving a 48 % of yield determined by [1]H-NMR (entry 6, Table 14) Lastly, the addition of an excess of chloroform resulted to be mandatory since no formation of the product was observed when acetone was added without the additional amount of chloroform (Table 14, entry 7)

Attempts to increase the overall yield of the reaction were made by changing the nature and the amounts of the adsorbent material. The use of dry or wet NaCl did not provide any additional

benefit for preparing the 3-Carboxamidobutyrric acid (Entry 2 and 3, Table 15) The use of NaCl further complicated the recovery effort of the solid mixture from the jar. Decreasing the quantity of Na_2SO_4 up to 0.8 g did not result in any considerable variation of the yield.

Table 15. *Optimization of conditions: effect of solid additive* [a][b



IV-1 **IV-2**

Entry	Additive (mg)	^{1}H-NMR Yield %[c]
1	Na_2SO_4 (1.2) g	48
2	NaCl	43
3[d]	NaCl	36
4	**Na_2SO_4 (0.8g)**	**46**

[a]Reaction conditions: 1) pentanamine (1.0 mmol, 1.0 equiv), $CHCl_3$ (2x1.2 equiv.), NaOH (12 mmol, 12 equiv), and 0.3 g of Na_2SO_4 were continuously milled for 2 cycles of 15 minutes in a Spex 8000M mixer/mill into a agate-milling beaker (45 ml) equipped with four balls (d = 10.0 mm) 2) Acetone (2x0.8 equiv.,2x0.8 mmol), $CHCl_3$ (2x1 equiv., 2x1 mmol), NaOH (7 equiv., 7 mmol) and given solid additive in given amounts were added and the mixture was ball milled for 2 cycles of 25 minutes

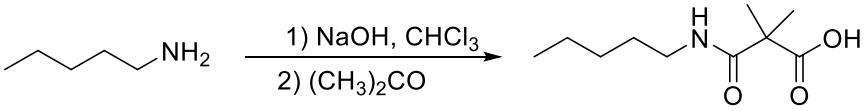
[b] Values in the table are referred to the amounts of reagents added in the first step of reaction.

[c] ^{1}H-NMR yield was determined using 2,5-Dimethylfuran as internal standard.

[d] dry NaCl was used

Increasing the loading of sodium hydroxide up to 8 equivalents did not result in any improvement in the reaction yield. We try to diminish the loading of sodium hydroxide with respect to the starting conditions (7 equiv. entry 2, Table 16) and we found out that 6 equivalents were necessary to keep the values of yield comparable to what previously obtained. Indeed, when 5 equivalents were used, the ^{1}H-NMR registered yield was found to be 30 % (entry 4, Table 15).

Table 16 *Optimization of conditions: effect of sodium hydroxide quantity* [a][b]



IV-1 **IV-2**

Entry	Equiv. of NaOH	Time (min)	NMR Yield%[c]
1	8	25*2	45
2	7	25*2	48
3	**6**	**25*2**	**46**
4	5	25*2	30

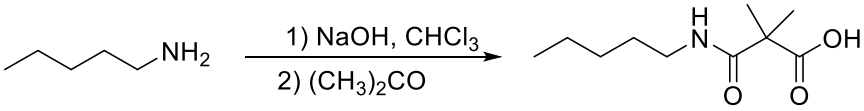
[a]Reaction conditions: 1) pentanamine (1.0 mmol, 1.0 equiv), $CHCl_3$ (2x1.2 equiv.), NaOH (12 mmol, 12 equiv), and 0.3 g of Na_2SO_4 were continuously milled for 2 cycles of 15 minutes in a Spex 8000M mixer/mill into a agate-milling beaker (45 ml) equipped with four balls (d = 10.0 mm) 2) Acetone (2x0.8 equiv.,2x0.8 mmol), $CHCl_3$ (2x1 equiv., 2x1 mmol), NaOH and Na_2SO_4 (0.8 g) were added and the mixture was ball milled for 2 cycles of 25 minutes

[b] Values in the table are referred to the amounts of reagents added in the first step of reaction.

[c] ^{1}H-NMR yield was determined using 2,5-Dimethylfuran as internal standard

In order to limit the conversion to undesired by-product we studied the effect of a time reduction.

Table 17 *Optimization of conditions effect of time* [a[b]]



IV-1 **IV-2**

Entry	Time (min)	^{1}H-NMR Yield (%)[c]
1	15*2	48
2	60*2	30
3	5*2	traces

[a]Reaction conditions: 1) pentanamine (1.0 mmol, 1.0 equiv), $CHCl_3$ (2x1.2 equiv.), NaOH (12 mmol, 12 equiv), and 0.3 g of Na_2SO_4 were continuously milled for 2 cycles of 15 minutes in a Spex 8000M mixer/mill into a agate-milling beaker (45 ml) equipped with four balls (d = 10.0 mm) 2) Acetone (2x0.8 equiv.,2x0.8 mmol), $CHCl_3$ (2x1 equiv., 2x1 mmol), NaOH (6mmol, 6 equiv.) and Na_2SO_4 (0.8 g) were added and the mixture was ball milled for the given time

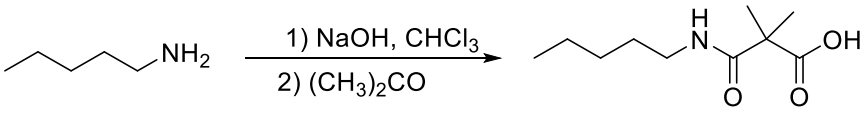
[b] Values in the table are referred to the amounts of reagents added in the first step of reaction.

[c] ^{1}H-NMR yield was determined using 2,5-Dimethylfuran as internal standard

Results obtained in two cycles of 15 minutes (entry 1, Table 17) are comparable to those obtained in two cycles of 30 minutes (entry 4, Table 17). Increasing (Entry 2, Table 17) or lowering (entry 3, Table 17) further the reaction time negatively affected the yield.

Lastly, alternative milling media, vessel material and different amount of balls were used. These experiments led to the conclusion that 4 ball were needed for the transfer of the adequate amount of energy and mixing (entry 2, Table 18). Besides, the use of stainless steel jars and balls was found to have a negative effect on the yield of the reaction (entries 5 and 6, Table 18)

Table 18 *Optimization of conditions: effect of the milling material*



IV-1 **IV-2**

Entry	Number of balls	Milling media and vessel material	NMR Yield %[c]
1	2	Agate	traces
2	**4**	**Agate**	**47**
3	6	Agate	49
4	8	Agate	50
5	4	Stainless steel	35
6	8	Stainless steel	25

[a]Reaction conditions: 1) pentanamine (1.0 mmol, 1.0 equiv), $CHCl_3$ (2x1.2 equiv.), NaOH (12 mmol, 12 equiv), and 0.3 g of Na_2SO_4 were continuously milled for 2 cycles of 15 minutes in a Spex 8000M mixer/mill into a-milling beaker of the given material(45 ml) equipped with the given number and type of balls 2) Acetone (2x0.8 equiv.,2x0.8 mmol), $CHCl_3$ (2x1 equiv., 2x1 mmol), NaOH (6mmol, 6 equiv.) and Na_2SO_4 (0.8 g) were added and the mixture was ball milled for the given time

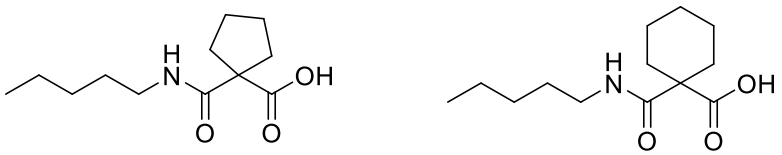
[b] Values in the table are referred to the amounts of reagents added in the first step of reaction.

[c] ^{1}H-NMR yield was determined using 2,5-Dimethylfuran as internal standard

Attempts of scope expansion

With the aim of extend the scope of the reaction with respect to the solution counterpart, we attempt to obtain the product of the multicomponent Bargellini-type reaction varying the

carbonylic partner. We were interested in the synthesis of the 3-Carboxamido derivatives **IV-3** and **IV-4** (Figure 15). The two starting ketones were found to be not reactive in solution in this kind of transformation.



IV-3 **IV-4**

Figure 15 *3-Carboxamido substituted derivatives from alternative carbonyl source*

Indeed, when reacting them under our best conditions, once again the reaction mixture was particularly complex. Nevertheless, we detected in the ^{1}H-NMR spectra of peaks which could be ascribed to the desired product. Unfortunately, we were not able to isolate them to provide further characterization.

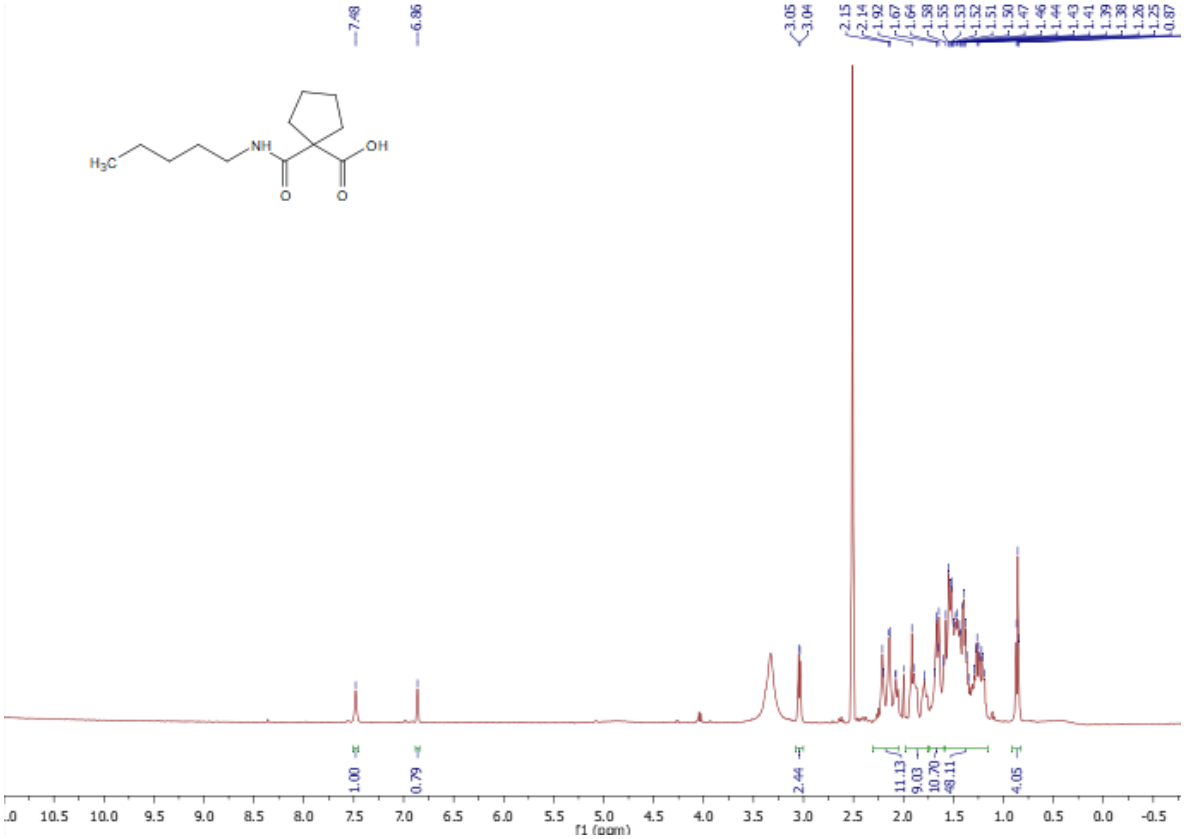


Figure 16 *Crude ^{1}H-NMR spectrum for the attempted synthesis of* ***IV-3***

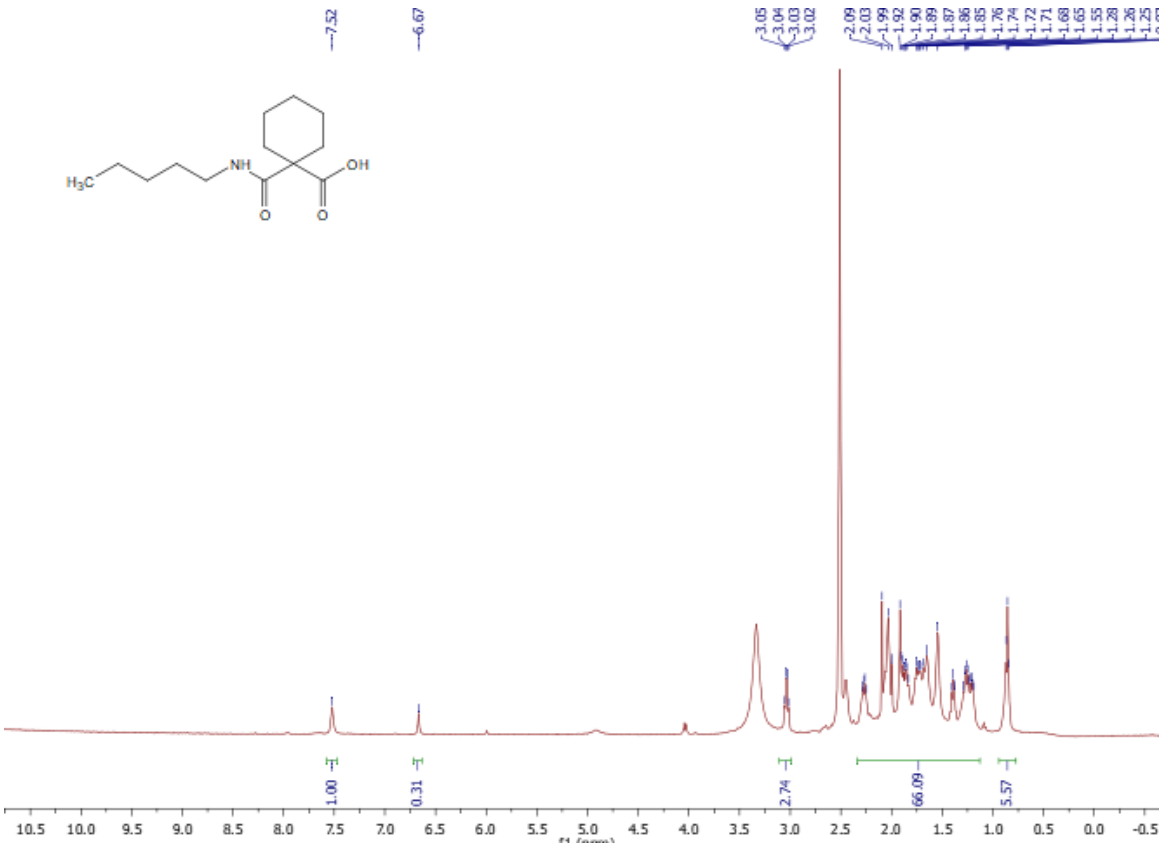


Figure 17 *Crude ^{1}H-NMR spectrum for the attempted synthesis of* ***IV-3***

Conclusions

Despite the scarce results in terms of yield, the possibility to directly convert an amine to a compound with added complexity as the carboxamide is of remarkable importance. Further experiments will be carried for better understanding and improve the reactivity of the system, such as a wider investigation in terms of alternative bases and experiments addressed to understand the nature of the by-products. Furthermore, object of the study will be the extension of the scope to different amines and especially to non-classically reactive carbonylic partners.

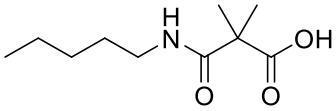
Experimental Section

General methods and material

Commercially available reagents were purchased from Acros, Aldrich, Strem Chemicals, AlfaAesar, TCI Europe and used as received. The solvents were purchased from Aldrich or VWR International in sure/sealedTM bottles over molecular sieves.). All reactions were monitored by thin-layer chromatography (TLC) performed on glass-backed silica gel 60 F254, 0.2 mm plates (Merck), and compounds were visualized under UV light (254 nm) or using cerium ammonium molybdate solution with subsequent heating. The eluents were technical grade and distilled prior to use. A Spex 8000M Mixer/Mill®, ball-milling apparatus was used for all reactions. The reagents were milled using a agata-beaker (45 mL) equipped with balls (d = 10.0 mm) of the same material. ^{1}H and ^{13}C liquid NMR spectra were recorded on a Varian 400 and 500 MHz NMR spectrometer at 298 K and were calibrated using trimethylsylane (TMS). Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referred to the residual hydrogen in the solvent ($CHCl_3$, 7.27 ppm or DMSO 2.54 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br s = broad singlet), coupling constant (J) in Hertz and integration. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, δ 77.0 ppm or δ DMSO-d_6 δ 39.5 ppm). To remove any trace of heptane, all NMR samples were first dissolved in DCM (approximately 1 mL) and then concentrated under vacuum with a rotary evaporator. 1 H NMR self-diffusion measurements were performed in $CDCl_3$ at 298 K on a Bruker Avance 300 MHz (7.05 T) spectrometer. Deuterated NMR solvents were obtained from Aldrich. Analysis of reaction mixture was determined by GC-MS (GC Agilent 6850, MS Agilent 5973) and equipped with HP5 universal capillary column (30 m length and 0.20 mm diameter, 0.11 film thickness) and a flame ionization detector (FID). GC oven temperature was programmed

from 80 °C to 250 °C at the rate of 10 °C/min. He gas was used as a carrier gas. Temperatures of injection port and FID were kept constant at 300 °C. Retention times of different compounds were determined by injecting pure compound under identical conditions. Melting points were determined in an open capillary on a Büchi melting point apparatus and are uncorrected.

Experimental procedure for the synthesis of 2,2-dimethyl-3-oxo-3-(pentylamino)propanoic acid IV-2



1-Pentylamine (1.0 mmol, 87 mg), $CHCl_3$ (2x1.mmol., 2x142 mg), NaOH (12 mmol, 480 mg), and 0.3 g of Na_2SO_4 were milled for 2 cycles of 15 minutes in a Spex 8000M mixer/mill into a into a agate-milling beaker (45 ml) equipped with four balls (d = 10.0 mm). Then, Acetone (2x0.8 mmol., 2x46 mg), $CHCl_3$ (2x1 mmol, 2x120 mg), NaOH (6mmol, 240 mg.) and Na_2SO_4 (0.8 g) were added and the mixture was ball milled for two cycles of 15 minutes. After completion of reaction the solid mixture was dissolved in water and the solution washed with ethylacetate three times. Then, the aqueous phase was acidified and extracted with ethylacetate three times. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The yellow oil obtained was recrystallized from heptane/ethylacetate. (Isolated yield: 40 %)

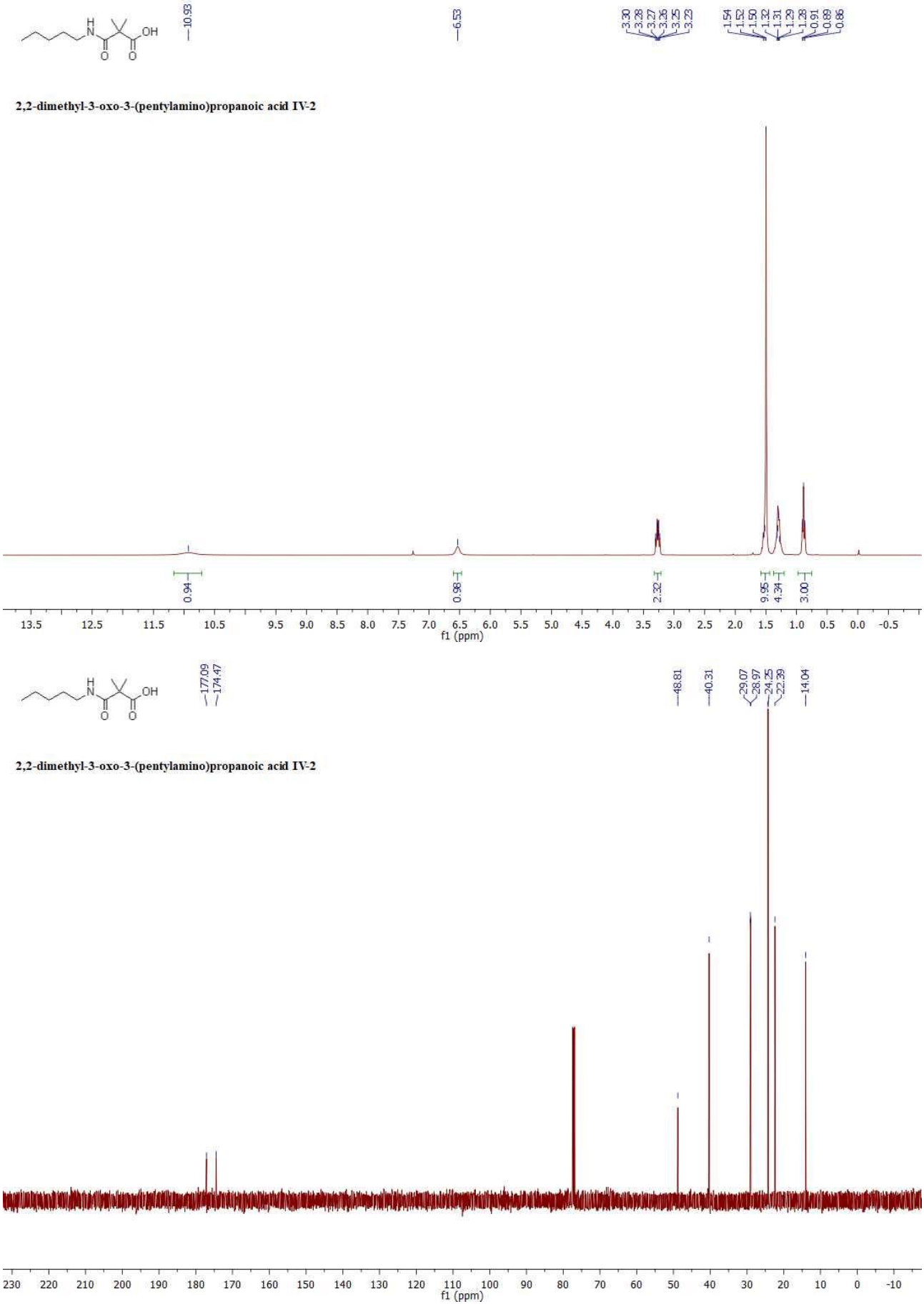
^{1}H NMR (300 MHz, $CDCl_3$): δ = 10.93 (s, 1H), 6.53 (s, 1H), 3.27 (td, *J* = 7.3, 5.7 Hz, 2H), 1.50 (s, 10H), 1.30 (q, *J* = 3.9, 3.5 Hz, 4H), 0.88 (t, *J* = 6.7 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$): δ = 177.09, 174.47, 48.81, 40.31, 29.07, 28.97, 24.25, 22.39, 14.04.

Spectroscopical data are in agreement with those reported in literature[280]

Work-up for the optimization experiments:

Crude reaction mixture was treated as follow prior analysis: when the reaction was over, the solid mixture was dissolved in water and acidified with HCl 2 M, then the water was extracted 3 times with ethyl acetate. The collected organic layers were dried over $MgSO_4$ and the solvent was evaporated, the crude was then analyzed by ^{1}H-NMR spectroscopy using 2,5-Dimethylfuran as internal standard.

^{1}H-NMR and ^{13}C-NMR spectrum of compound IV-2



Chapter V-Synthesis of secondary amines with borrowing hydrogen strategy at room temperature

Introduction

The role of amines

The value of amines is relevant either from an industrial either from a biological point of view. Aminoacids and nucleotides are essential building blocks and the amino group is recurring in several bioactive compound, such as vitamins, hormones, alkaloids, neurotransmitters, or natural toxics. Amines are extensively used in agrochemical, pharmaceutical and food industry. Synthetic amines are extensively applied for the synthesis of solvents, agrochemicals, pharmaceuticals, detergents, fabric softeners, flotation agents, corrosion inhibitors, antistatic additives, lubricants, polymers, varnishes, and dyes.[287,288]

Given their huge field of application, the development of an efficient method for their preparation has been object of continuous interest from the chemistry community and several approaches have been developed and used in the last century such as the classical Hofmann alkylation,[289] Buchwald–Hartwig[290–293] and Ullmann [294295,296]reactions, hydroamination,[192,297,298] hydroaminomethylation,[299] reduction of nitriles,[300] and nitro[301–303] compounds, or reductive amination[304,305]

Amination of alcohols: Borrowing Hydrogen strategy

The preparation of substituted amines by reacting ammonia with alcohols plays an important role in an industrial perspective. Indeed, the synthesis of amines is accompanied by the formation of a molecule of water, which represents a way less problematic waste then salts derived using halogen alkyl or aryl halide. Furthermore, alcohols represent a readily available starting material.

Conditions of amination can be very drastic; for instance, the alkylation of ammonia with methanol is performed at 350–500 °C and 15–30 bar in presence of an aluminum-based heterogeneous catalysts.[306]

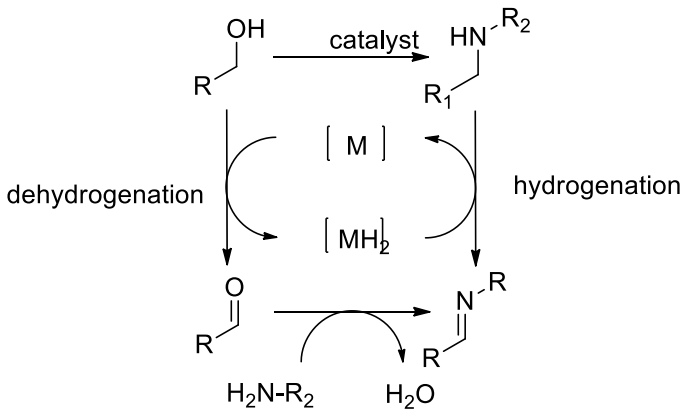
First examples of amine alkylation with alcohol are dated to 1901, when alkylation of aniline with sodium hydroxide has been described.[307] This kind of transformation takes place at very high temperature (>200 °C) or after prolonged time.[308,309] Acidic catalysis can also be employed for this reaction but usually they require benzylic, propargylic, or allylic alcohls.[310]

The so called *Borrowing Hydrogen* (BH) methodology, also known as the hydrogen auto transfer, represents an alternative pathway for the amine alkylation with alcohols.[311–313]

In this process, the metallic catalyst activates the alcohol by oxidizing it to aldehyde or ketone, which condenses with the nucleophilic amine to give the imine intermediate. Then the catalyst "gives back" the hydride formed in the precedent step reducing the imine and affording the substituted amine (Scheme 60).

Unlike other alkylation methods, borrowing hydrogen is advantageous for synthesis of secondary amines. Indeed, a primary amine can react more easily with an aldehyde, whereas the secondary amine is more reactive than the corresponding primary amine in substitution reaction with, for instance, alkyl halide.

In a view of atom economy, the process is convenient if compared to the process of hydrogen transfer for the reduction of an imine using an alcohol as a hydrogen donor, in this case the oxidized alcohol is a substrate and not a waste.

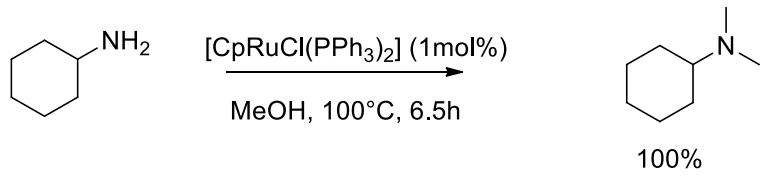


Scheme 60 *General mechanism of borrowing hydrogen synthesis of substituted amines*

In contrast to the reductive amination, the borrowing hydrogen process avoid side-reactions such as aldol condensation for instance, since the concentration of aldehyde is always very low and even more quickly it is consumed *in situ*. Preferential substrates for this methodology are primary alcohols, more reactive than the secondary. While heterogeneous catalysts for the alkylation of amines with alcohol have been known since the first half of the twentieth century,[314,315] the first homogeneous catalyst used for the *N*-alkylation with alcohols was reported in 1981 by Grigg and co-workers, who applied [$RhH(PPh_3)_4$] for the *N*-alkylation of pyrrolidine and primary amines with primary alcohols, demonstrating the efficacy of Ru and Ir based catalysts for this kind of transformation.[316] In the same year, Watanabe *et al*. reported the *N*-alkylation of anilines with simple alcohols, such as 1-propanol , using [$RuCl_2(PPh_3)_3$] as the catalyst, at temperature higher than 180 °C. Since then, *N*-alkylations of amines with alcohols have been extensively reported in the literature.[311,312,317]

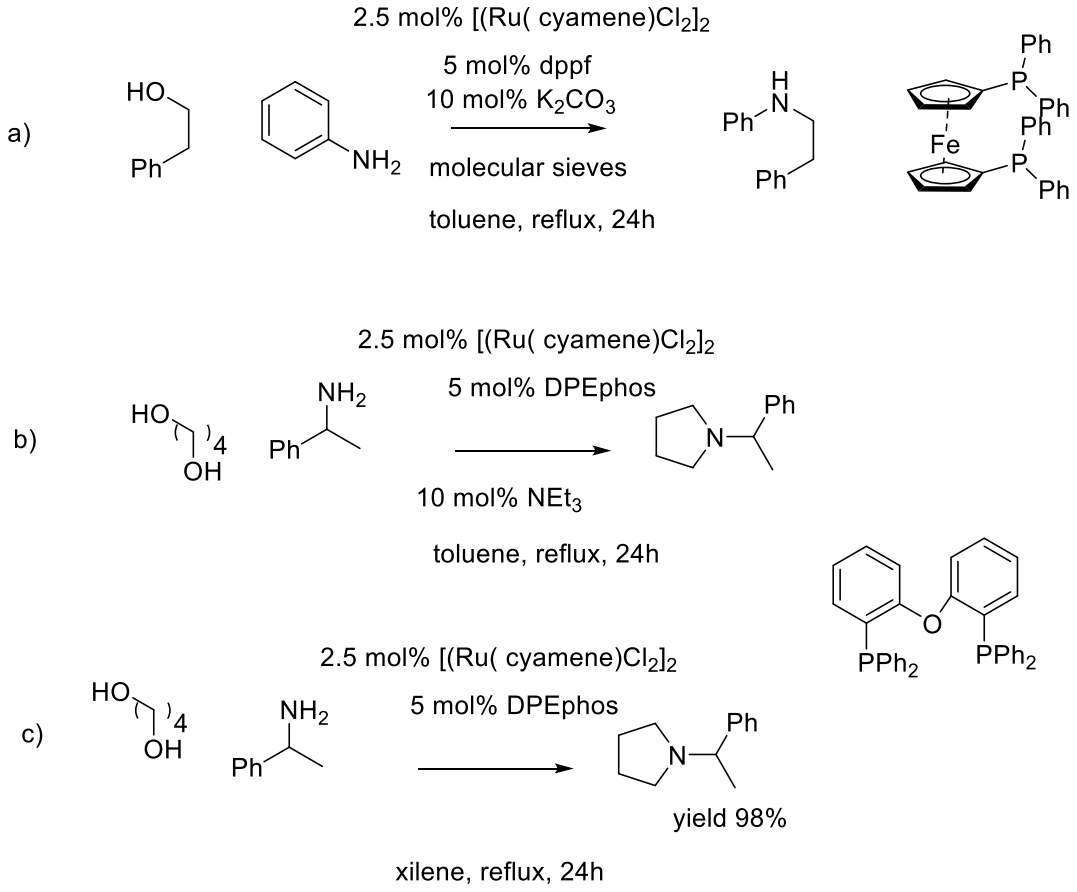
A dominant role in this area has been played by catalysts based on the two metals Iridium and Ruthenium, which showed the best performance until now.

In 2004 Del Zotto *et al.* published the *N*-methylation of amines with methanol promoted by a ruthenium (II) half-sandwich complex [CpRuCl(PPh_3)$_2$]. The method affords fast and quantitative conversion in relatively mild conditions since the reaction proceeds at 100 °C in 6.5 hours (Scheme 61). The scope of the method is limited to the *N*-alkylation of alkylamines.[318]



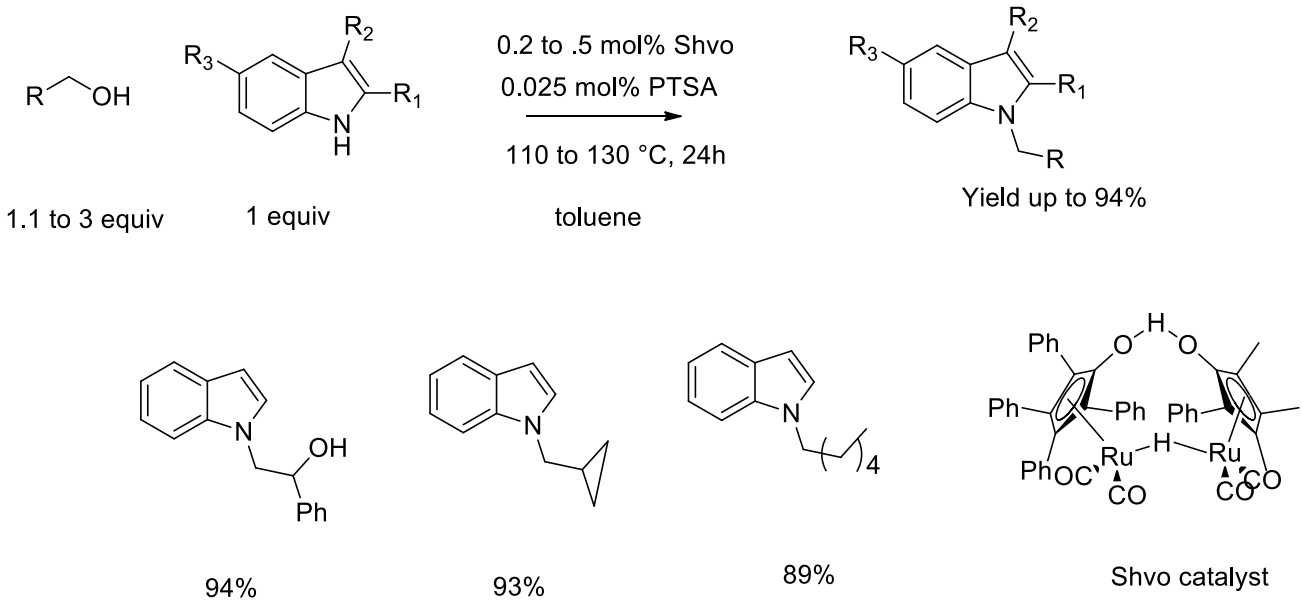
Scheme 61 *N-Methylation of amines with methanol [CpRuCl(PPh_3)$_2$] catalyzed*[311,318]

Williams and co-workers communicated that the combination of [Ru(p-cymene)Cl_2]$_2$ with bidentate phosphine as dppf (1,1'-Bis(diphenylphosphino)ferrocene) could be used for the alkylation of primary and secondary amines with primary alcohols (Scheme 62 a). [319,320] Later the same group developed a method which allows to expand the application of the system to the formation of tertiary amines from primary amines and diols, as well as *N*-alkylation of amines with secondary alcohols such as cyclohexanol[321] by using DPEphos (Oxydi-2,1-phenylene)bis(diphenylphosphine) as ligand (Scheme 62, b and c)



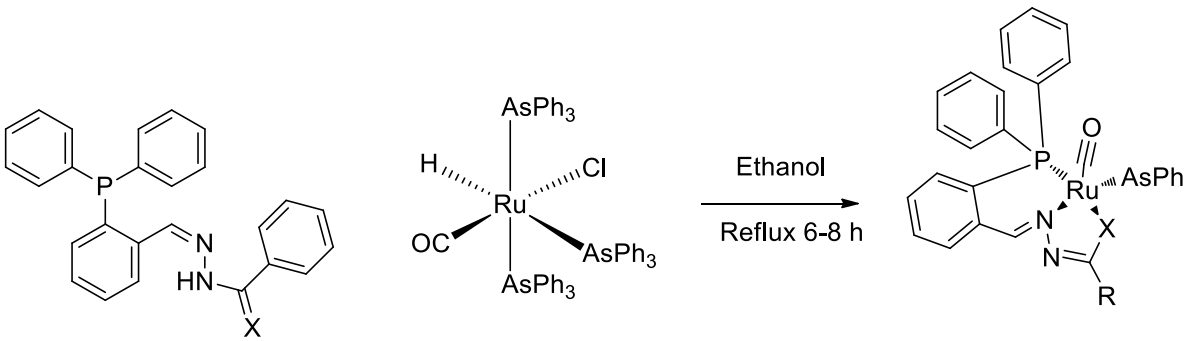
Scheme 62 *N-Alkylations with [Ru(p-cymene)Cl₂]₂ and bidentate phosphine ligands by William*[311,319–321]

In 2010, Beller and Williams published the first protocol for the *N*-alkylation of indoles with alcohols by homogeneous catalysis. This transformation is remarkable seen the poor nucleophilicity of the indole. In the presence of the Shvo catalyst, an *in situ* transfer hydrogenation of indole and the alcohol occurs, leading to the formation of indoline and aldehyde. The transfer hydrogenation reaction is followed by condensation of previous products which provides the *N*-alkylated indole by an intramolecular isomerization. Applying primary alcohols, *N*-alkylated products were obtained with excellent yield and selectivity (Scheme 63).[322]



Scheme 63 *N-alkylation of Indole using alcohls*[311,322]

Viswanathamurthi and co-workers described the synthesis and characterization of several Ru (II) carbonyl complexes bearing phosphine functionalized hydrazine/thiosemicarbazone ligands and triphenylarsine ligands (Scheme 64). Analysis showed that in all these catalysts Ru was coordinated by PNO/PNS donor atoms.[323] The catalyst bearing -R = $NH(CH_3)$ and X = S gave best results and was used in the reaction of heteroaromatic amines and diamines with substituted benzyl alcohols to afford the corresponding secondary amines.

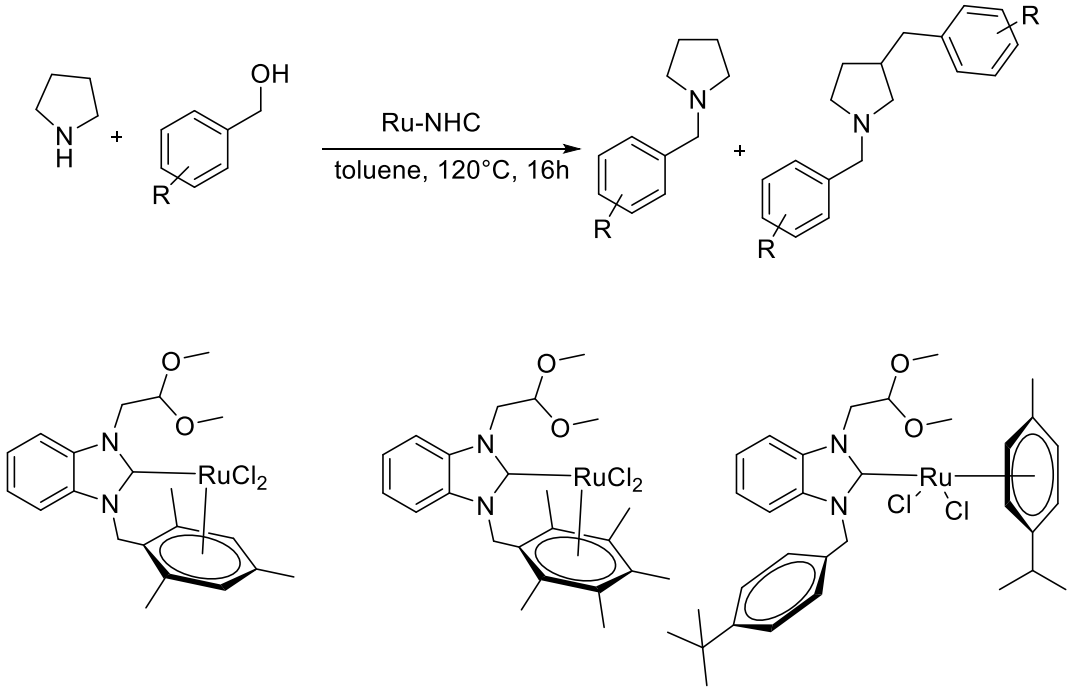


R= $-C_6H_5$ X=O (PNO-BHy)
R= $-C_6H_4N$ X=O (PNO-INHy)
R= $-C_5H_3O$ X=O (PNO-FHy)
R= $-NH(CH_3)$ X=S (PNS-EtTs)
R= $-NH(C_5H_{11})$ X=S (PNS-CyTs)

R= $-C_6H_5$ X=O
R= $-C_6H_4N$ X=O
R= $-C_5H_3O$ X=O
R= $-NH(CH_3)$ X=S
R= $-NH(C_5H_{11})$ X=S

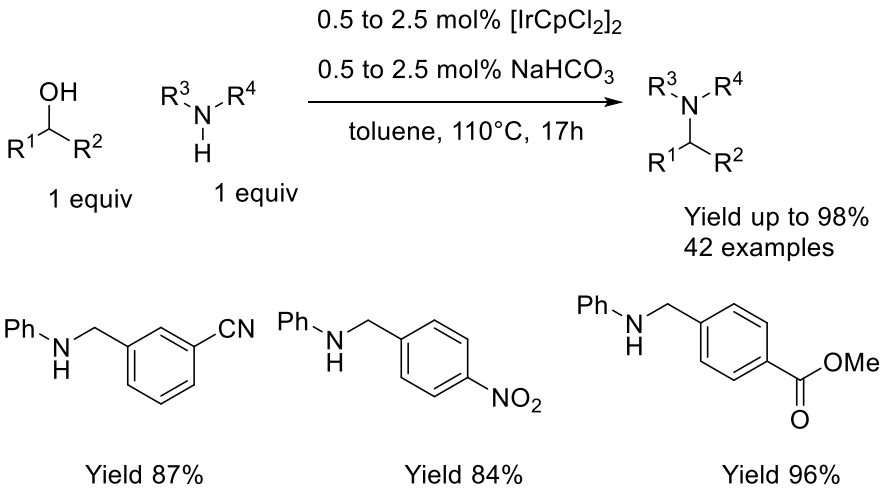
Scheme 64 *Synthesis arsine and PNO/PNS Ruthenium(II) carbonyl complexes as catalysts for N-alkylation of amines via hydrogen autotransfer process*[312,323]

Ru-NHC complexes were found to promote efficiently the catalytic *N* alkylation and *N*, *C* dialkylation of different cycloaliphatic amines like morpholine and pyrroldine with different benzylic alohols (Scheme 65).[324] The synthesis of the complexes was performed starting from 1,3-dialkylbenzimidazolium and $[RuCl_2(p\text{-cymene})]_2$ in presence of a base.



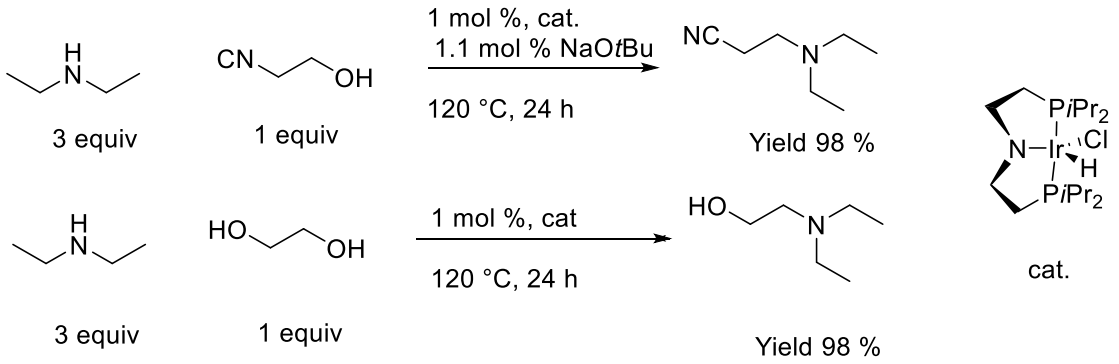
Scheme 65 *N-alkylation and N,C3 alkylation of Pyrrolidine with benzylalcohls derivatives*[312,325]

Besides Ru complexes, Iridium based counterparts are leading catalyst in this type of reactions. Fujita and co-workers originally reported in 2002 the combined use of $[IrCp^*Cl_2]_2$ and K_2CO_3 for the synthesis of Indoles, 1,2,3,4-Tetrahydroquinolines, and 2,3,4,5-Tetrahydro-1-benzazepine.[326] In 2008, the same group improved the protocol by changing the base to $NaHCO_3$;[327] they demonstrated that the method was applicable to primary and secondary amines with primary and secondary alcohols at a comparatively mild temperature of 110 °C (Scheme 66). The method resulted to be compatible with several functional groups, such as cyano, nitro, or methoxycarbonyl groups



Scheme 66 *$[IrCp^*Cl_2]_2$ catalysed N-alkylation of amines with alcohl in presence of $NaHCO_3$ as base*[311,327]

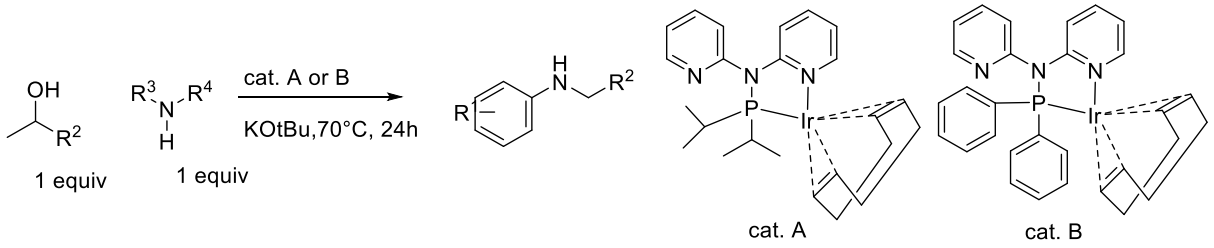
The iridium pincer complex reported in the Scheme 67 was used for the amination of alcohols and diols , the method was applied to ethylene glycol with secondary amines such as diethylamine with good to excellent yield [328]



Scheme 67 *N-alkylation of secondary amines with alcohls catalized by an Ir pincer complex*[311]

N-alkylation of several anilines was obtained in relatively mild conditions in presence of the iridium complexes of anionic P,N ligand represented in Scheme 68 with aliphatic and benzylic alcohols.[329]

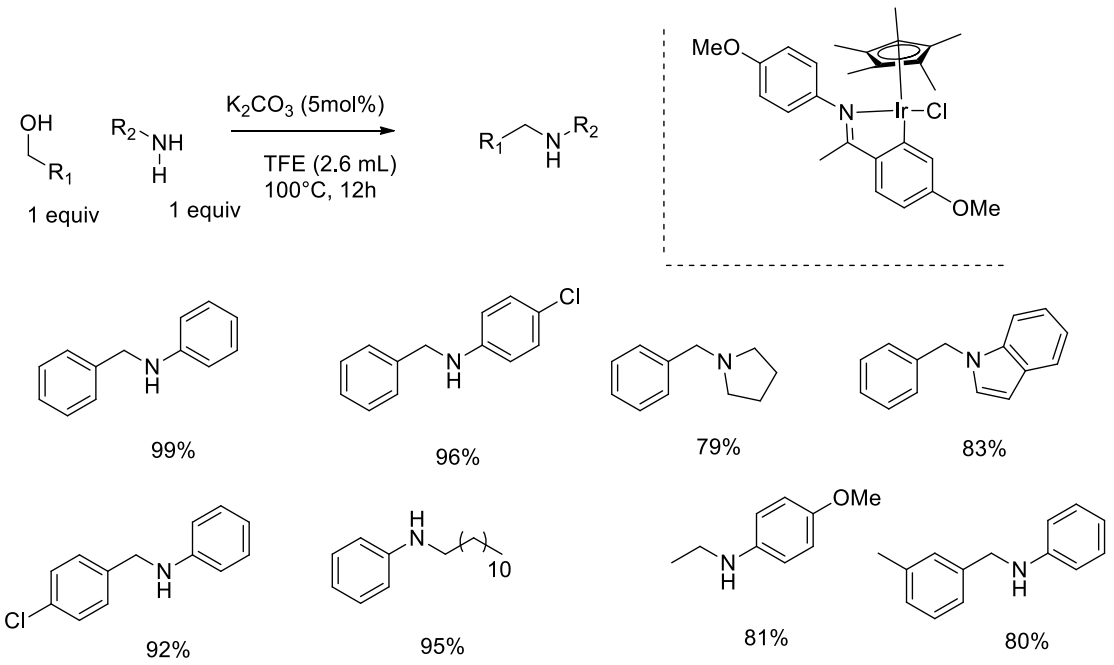
Almost complete conversion was registered at 70 °C with a low loading of catalyst (0.05 %mol). The authors demonstrated by kinetic experiment conduced in more than five days that the catalysts are characterized by good stability over time

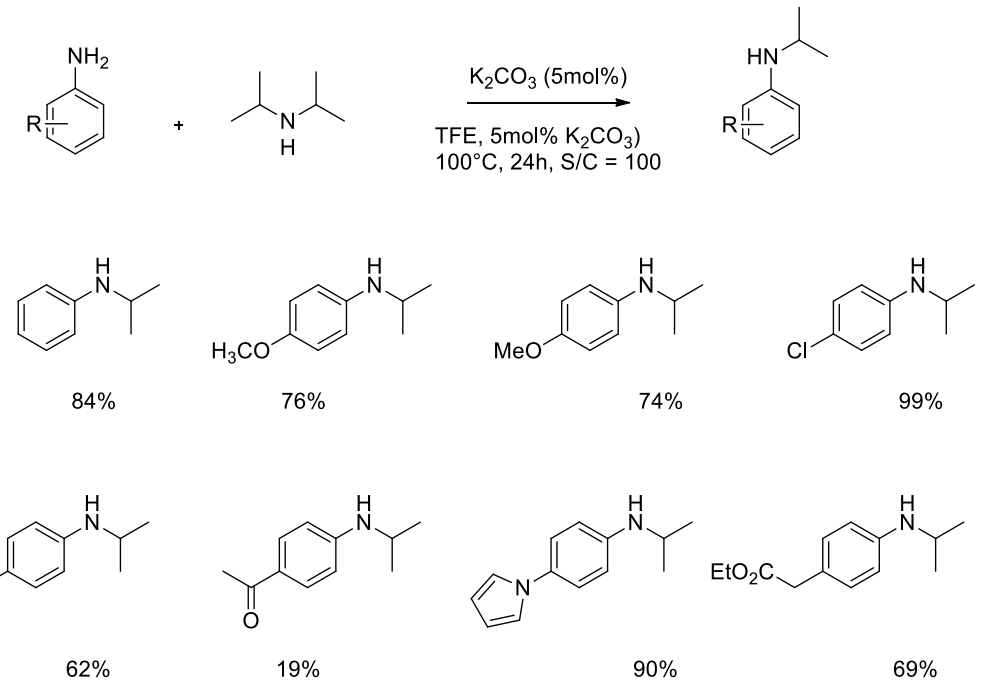


Scheme 68 *N-Alkylation of Anilines Derivatives with Primary Alcohols in the Presence of Iridium catalysts of the anionic P,N ligand*[312,329]

An exemplificative application for kilogram scale of the BH technology is the large scale synthesis of one inhibitor for the treatment of schizophrenia named PF-03463275 by means of a $(Cp^*IrCl_2)_2$ catalyst with a catalyst loading lower than 0.05 mol %.[330]

In 2015 Zhou *et al*. reported the application of a cyclometalated iridium complex to the synthesis of secondary and tertiary amines, the substrate scope was extended to synthesis of heterocycle from dioles, and MeOH was used as well as alkylating agent providing a green and selective *N*-methylation method. The procedure is affected by a strong dependence of solvent even if the catalyst presents remarkable activity. The iridium complex was used to synthesize a number of secondary amines starting from benzylic and aromatic primary amines with primary alcohols selectivity of the method can be tuned by adjusting the ratio of substrates, leading to both mono- and bis-alkylated amines. The method allows cross-coupling between amines which often requires more than 150 °C to take place (Scheme 69)[331]

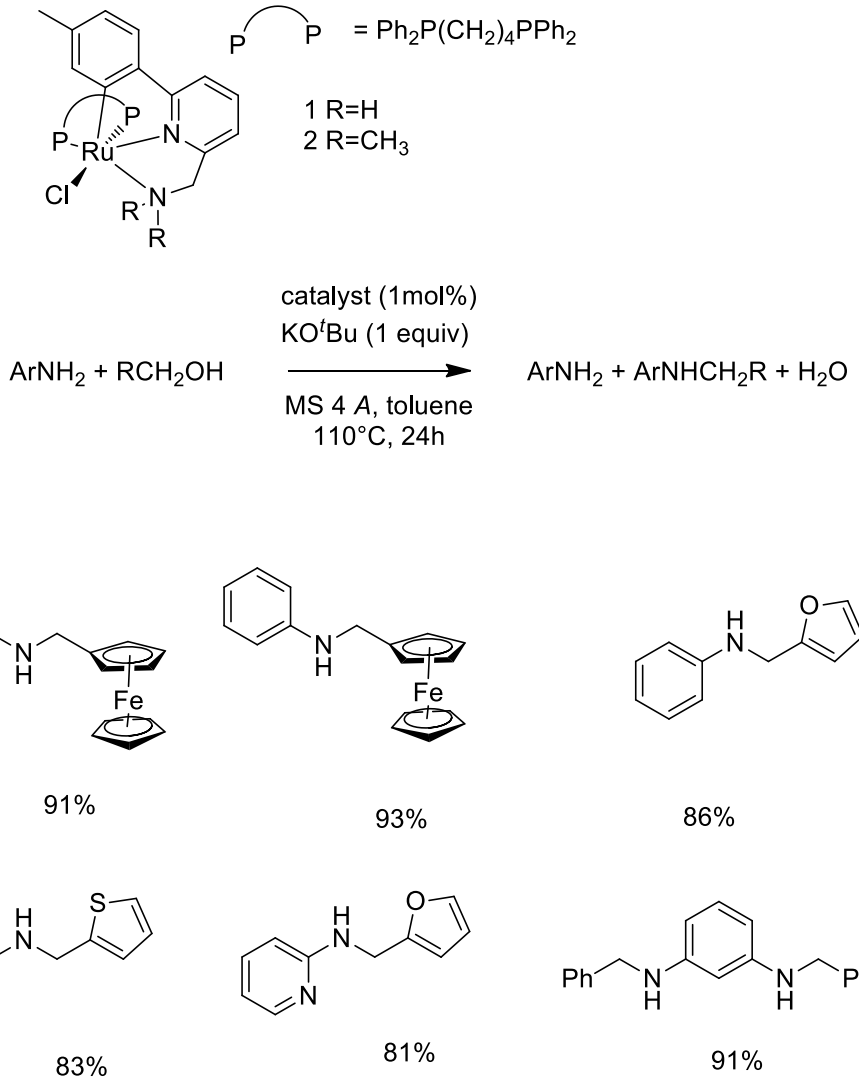




Scheme 69 *Cyclometalated iridium complex to the synthesis of secondary and tertiary amines*[312,331]

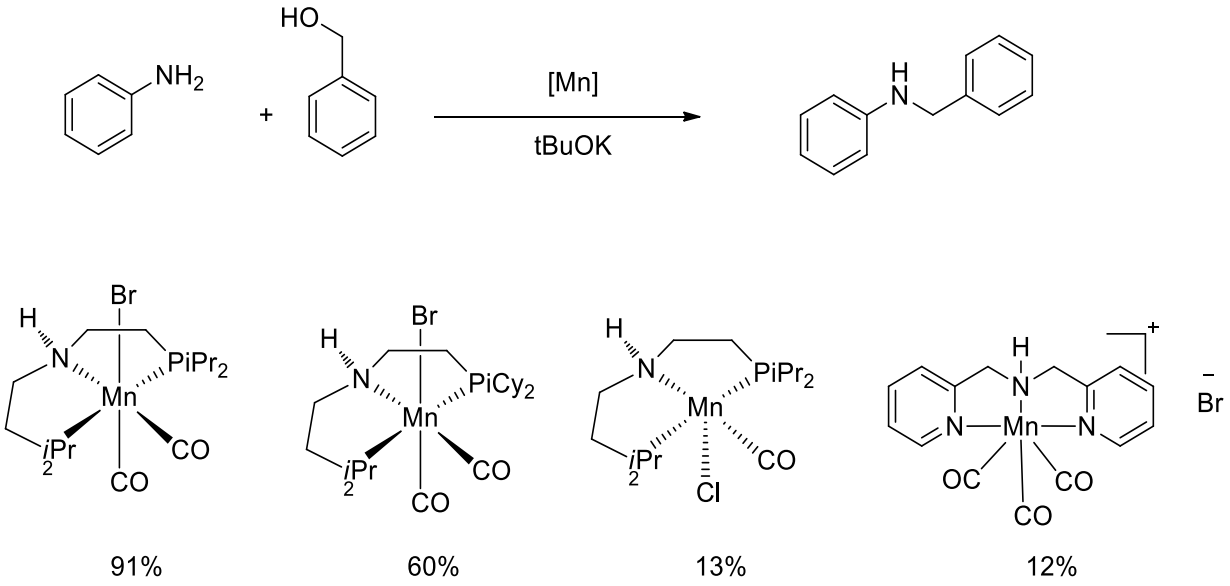
Ru and Ir pincer complexes application in Hydrogen borrowing synthetic methods have been extensively studied.[332,333] Following the work of Baratta for the reduction of ketones under hydrogen transfer conditions,[334,335] Martiń-Matute and co-workers reported that CNN Ru(II)

pincer complex reported in scheme catalyzes the selective synthesis of secondary amines from monoalkylation of aromatic and heteroaromatic amines by primary alcohols (Scheme 70).[336]



Scheme 70 *Alkylation of Primary arylamines catalysed by the a CNN Ru complex*[336]

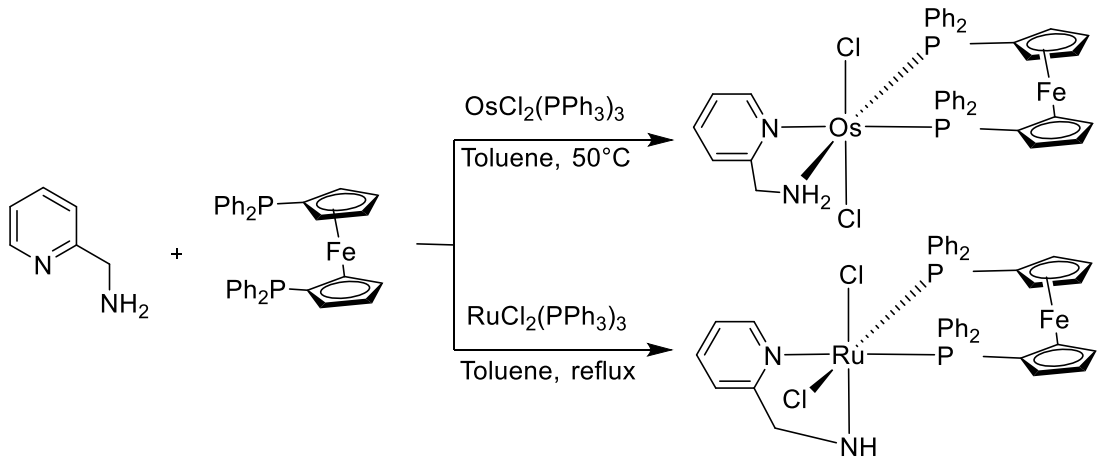
Despite the ubiquitous presence of Ru and Ir in metal catalysts for *N*-alkylation with alcohols, the use of other noble and non- noble metals appears to be promising .[312] A remarkable example has been given by Beller and co-workers, who for the first time reported the use of a manganese pincer complex as catalyst for the *N*-alkylation of aromatic amines and primary alcohol (Scheme 71).[337]

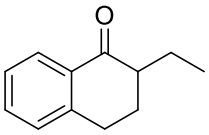
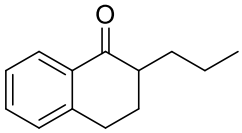
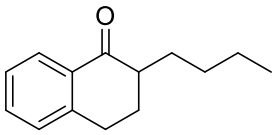


Scheme 71 *N-alkylation of aromatic amines and primary alcohol by a Mn pincer complex*[312,337]

Examples of use of Osmium in Hydrogen borrowing reactions are seldom.[332,338,339] Indeed, despite the large number of ruthenium complexes employed in BH processes, the use of osmium complexes is still extremely limited.

The first example of the use of an Osmium based catalyst in BH reactions was published by Baratta and co-workers.[340,341] The authors provided a comparative report on the applicability of the two osmium and ruthenium complexes reported in Scheme 72 − both incorporating the ligand 2-aminomethylpyridine − to a series of carbonyl compound/Alcohol Interconversion catalytic reactions; among which, the α-alkylation of α-tetralone with primary aliphatic alcohols. Interestingly, while needing higher temperature with respect to the related Ru complex, Os based catalyst provides better results in terms of TOF, leading to the formation of the product in respectively 1 h, 30 min, and 10 min



		[Ru]		[Os]	
Primary alcohol	alkylated α-tetrazole	Conv. %	TOF	Conv. %	TOF
EtOH		96	98	93	520
nPrOH		87	230	91	910
nBuOH		92	420	93	2800

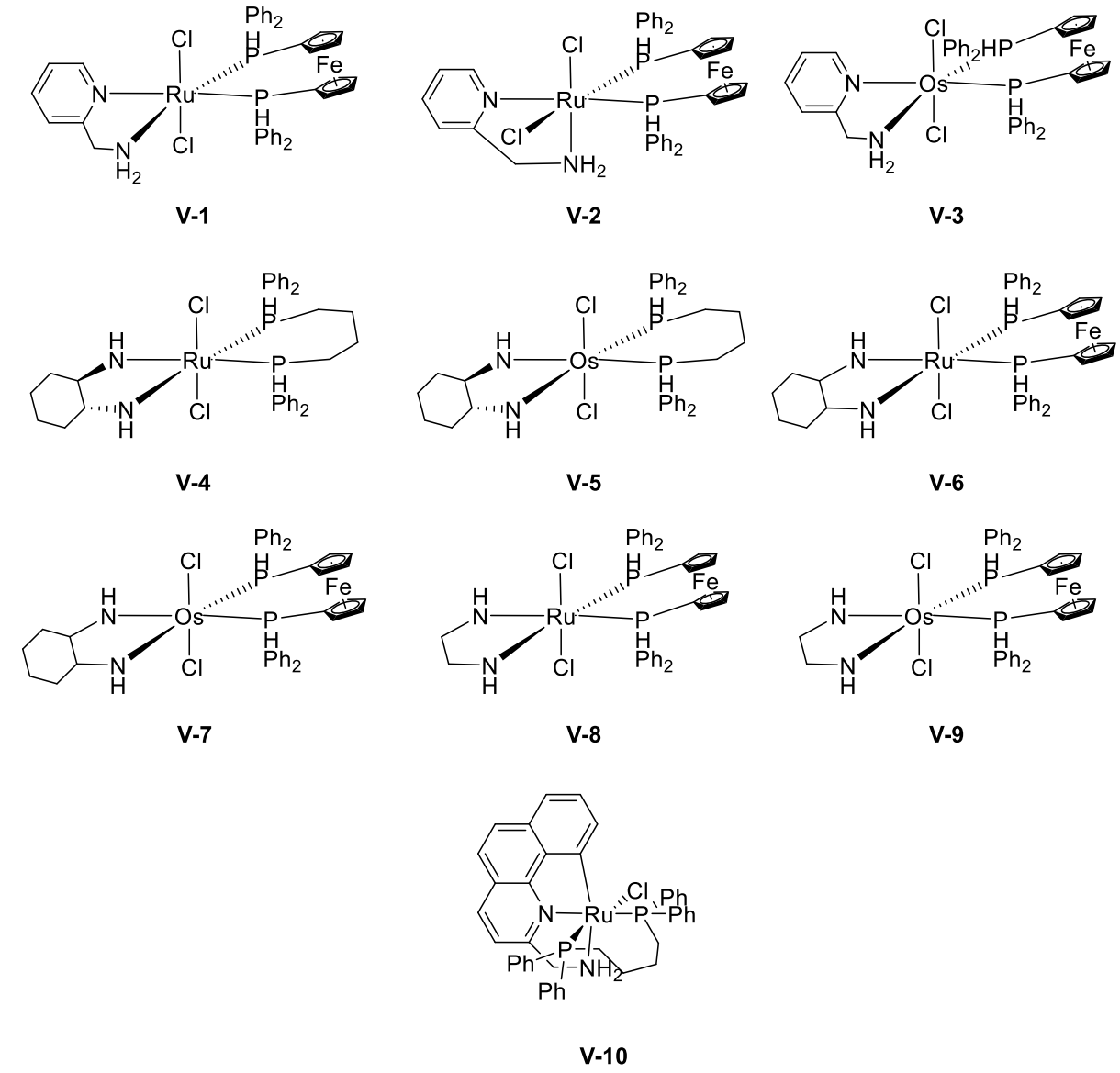
Scheme 72 *Synthesis of Os and Ru complexes with ligand 2-aminomethylpyridine and their application in alpha-alkylation of alpha-tetralone with primary aliphatic alcohols.* [340,341]

Discussion and results

Despite great accomplishments in the field of borrowing hydrogen strategy, methods for catalytic alkylation of amines with alcohol are often affected by the high temperatures involved. Remarkable progresses were registered, and milder reaction conditions have been found with respect to the pioneering work. However, to the best of our knowledge, only few examples of BH reaction for the synthesis of substituted amines at room temperature are reported,[342,343] sometimes even requiring expensive Ir NHC–phosphine complex catalyst.[344]

Benzo[h]quinoline-based ruthenium pincer complex **V-10** (Scheme 73) showed high catalytic activity in transfer hydrogenation of carbonyl compounds. Baratta and co-workers registered high reaction rates with a TOF up to 1.8 10^6 h^{-1} in presence of a low loading of catalyst (0.001 mol %). Derivatization of these complexes with chiral diphosphanes also provided catalysts able to promote the asymmetric TH of ketones with high enantioselectivity (95-98%).[345] In 2012 the same group reported that diphosphane complexes bearing a bidentate nitrogen ligand as the catalysts reported in the scheme, can promote the reaction of oxidation of alcohols by acceptorless dehydrogenation with low catalyst loading 0.8-0.04 mol % and at temperature between 130 -145 °C. [341]

We envisioned the possibility to test these arrays of catalysts in borrowing hydrogen reaction for the synthesis of *N*-alkylated secondary amines with alcohols. Within the frame of our interest toward the development of mechanochemical processes, we project to develop the solution method with the aim of modifying it and improve it with a mechanochemical solvent-less approach.

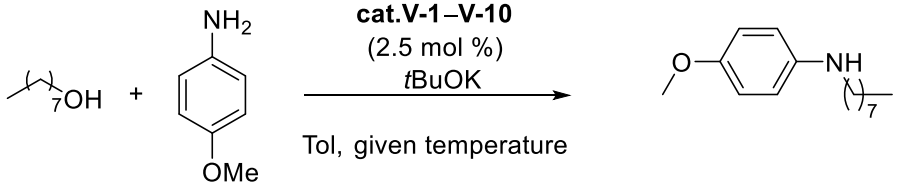


Scheme 73 *Os and Ru based catalysts active in transfer hydrogenation reactions*

Screening of catalysts

In the first stage, we performed a screening of the catalysts using 1-octanol and anisidine as model substrates in presence of potassium *tert*-butoxide, toluene, and 2 mol% of catalyst, letting them react for 12 hours. When the conversion of the anisidine was not complete at room temperature after 36 hours, we tested the catalysts at 50 °C and if necessary at 70°C. Results are showed in Table 19

Table 19 *Screening of catalysts*[a][b]



V-11a **V-12a** **V-13a**

Entry	cat	Temperature of complete conv.	Time (hs)
1	**V-1**	70 °C	12
2	**V-2**	rt	36
3	**V-3**	-	-
4	**V-4**	-	-
5	**V-5**	50 °C	24
6	**V-6**	rt	24
7	**V-7**	-	-
8	**V-8**	rt	24
9	**V-9**	-	-
10	**V-10**	rt	12

[a]Reaction conditions: Alcohol **V-11a** (1.1 mmol, 143 mg.), amine **V-12a** (1 mmol, 123 mg.) and potassium *tert*-butoxide were dissolved in 1 mL of toluene inside a 6 mL vial. The catalyst was added (0.025 mmol) and the reaction mixture was stirred for the given time and temperature.
[b] The conversion was evaluated by GC-MS

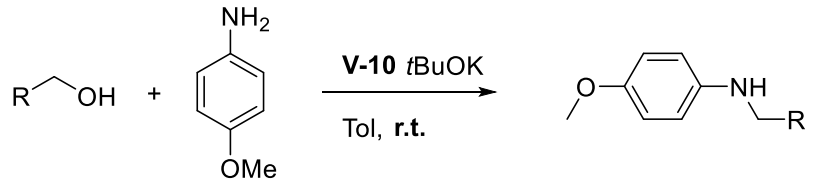
Os catalysts showed less activity compared to their Ru counterpart, indeed no Os based catalyst provided complete conversion at room temperature. The best results with Os based catalyst were obtained with the cat **V-5** which provided complete conversion of anisidine with a slight increase of the temperature (50 °C) in 24 h (entry 5, Table 19). Complex **V-1** afforded the quantitative conversion to the product solely at 70 °C after 24 h of reaction (Entry 1, Table 19).

Catalyst **V-6** and **V-8** gave excellent results promoting the complete formation of the secondary amine at room temperature in 24 hours (Entry 6 and 8, Table 19). We were pleased to observe that the complete conversion of anisidine to the secondary *N*-alkylated amine took place in only 12 hours at room temperature in presence of the catalyst **V-10** (Entry 10, Table 19)

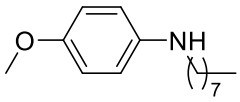
Preliminary studies on the scope expansion

Encouraged by these results, we addressed our effort to prove the general applicability of the method. Primary aliphatic alcohol with variable chain length were found to be good partners for this reaction. Compound **V-13a** was isolated and recovered in 84 % of yield (Table 20). The catalyst **V-10** revealed to promote efficiently at t.a. the alkylation of anisidine with 3-Phenyl-1-propanol in only 8 hours, providing the corresponding *N*-alkylated product in almost quantitively yield (94 %, Entry **V-13b**, Table 20). *N*-alkylation of anisidine with Cyclohexylmethanol provided the desired product in 74 % of yield (Entry **V-13c**). Lastly, the benzylic alcohol **V-11d**, was efficiently converted to disubstituted amine in satisfying yield (**V-13d**)

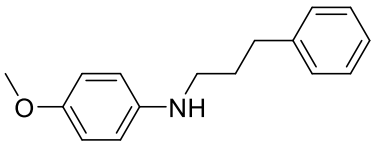
Table 20 *Isolation of N-alkyl secondary amines derived from aliphatic alcohol*[a]



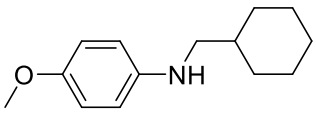
V-11a–d **V-12a** **V-13a–d**



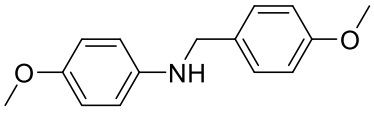
V-13a 84 % 12 h



V-13b 94 % 3 h



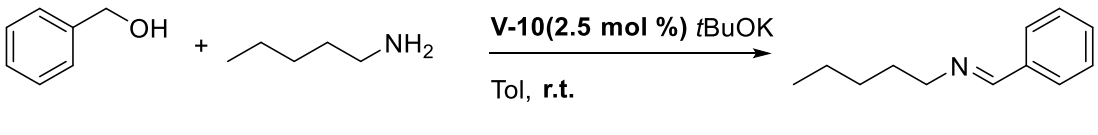
V-13c 74 % 24 h



V-13d 86 % 8 h

[a]Reaction conditions alcohol (1.1 mmol, 1.1 equiv.) anisidine (1mmol, 1 equiv.) and potassium *tert*-butoxide (1 mmol, 1equiv.) were dissolved in 1 mL of toluene inside a 6 mL vial The, catalyst was added, and the reaction mixture was stirred for the given time. Isolated yields

Afterward, the reaction was tested on aliphatic primary amines and benzylic alcohol Unfortunately we were not able to detect the formation of the product at the above conditions and only the formation of the imine was detected.

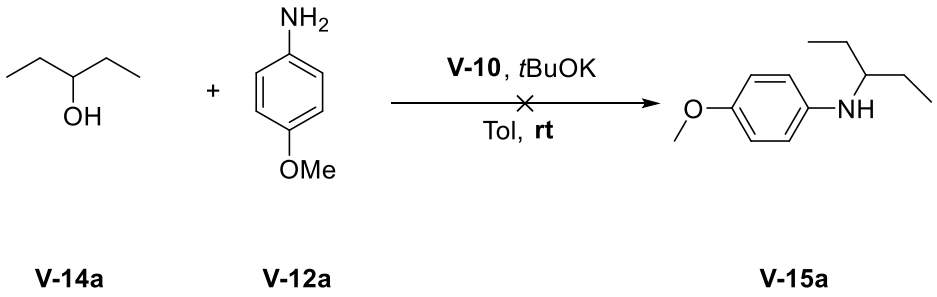


V-11d **V-12b** **V-14d**

Scheme 74 *Catalytic test on aliphatic amine*[a],[b]

[a]Reaction conditions: alcohol (1.1 mmol, 1.1 equiv.) pentylamine (1mmol, 1 equiv.) and potassium *tert*-butoxide(1 mmol, 1equiv.) were dissolved in 1 mL of toluene inside a 6 mL vial, the catalyst (2.5mol %) was added and the reaction mixture was stirred for the given time.
[b] Formation of imine was detected by GC-MS

The method proved to be selective for the *N*-alkylation of primary aromatic amine with primary alcohol. Indeed, it was not observed any reactivity of the secondary alcohol **VI-14a** at room temperature.



Scheme 75 *Attempted N-alkylation of secondary alcohols*

Outlook and conclusions

These preliminary studies on benzo[h]quinoline-based ruthenium complexes and diphosphane complexes bearing a bidentate nitrogen ligand gave promising results. They highlight a remarkable activity of the catalysts in BH reaction of primary amines and primary alcohols at room temperature. This represents a remarkable result in the field which suffer from a lack of methods with this characteristic.

More effort devoted to extending the methodology to a wider range of primary alcohols and aromatic amines are ongoing.

Furthermore, investigation on the Os based catalyst **V-5** will be performed.

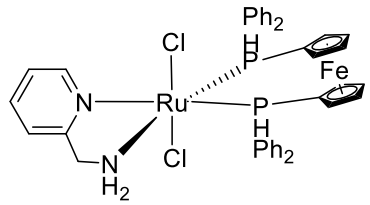
Lastly, we are studying for transfer the achievements accomplished in solution conditions to a mechanochemical approach.

Experimental Section

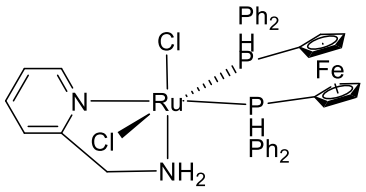
General methods and material

Commercially available reagents were purchased from Acros, Aldrich, Strem Chemicals, AlfaAesar, TCI Europe and used as received. The solvents were purchased from Aldrich or VWR International in sure/sealed^{TM} bottles over molecular sieves. Cromatographic columns were performed by using EcoChromeTM MP Silica gel 60 Å, particle size 0.040–0.063 mm (230–400 mesh). All reactions were monitored by thin-layer chromatography (TLC) performed on glass-backed silica gel 60 F254, 0.2 mm plates (Merck), and compounds were visualized under UV light (254 nm) or using cerium ammonium molybdate solution with subsequent heating. The eluents were technical grade and distilled prior to use. ^{1}H and ^{13}C liquid NMR spectra were recorded on a Varian 400 and 500 MHz NMR spectrometer at 298 K and were calibrated using trimethylsilane (TMS). Proton chemical shifts are expressed in parts per million (ppm, δ scale) and are referred to the residual hydrogen in the solvent ($CHCl_3$, 7.27 ppm or DMSO 2.54 ppm). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, br s = broad singlet), coupling constant (*J*) in Hertz and integration. Carbon chemical shifts are expressed in parts per million (ppm, δ scale) and are referenced to the carbon resonances of the NMR solvent ($CDCl_3$, δ 77.0 ppm or DMSO-d6 δ 39.5 ppm). To remove any trace of heptane, all NMR samples were first dissolved in DCM (approximately 1 mL) and then concentrated under vacuum with a rotary evaporator. Analysis of reaction mixture was determined by GC-MS (GC Agilent 6850, MS Agilent 5973) and equipped with HP5 universal capillary column (30 m length and 0.20 mm diameter, 0.11 film thickness) and a flame ionization detector (FID). GC oven temperature was programmed from 80 °C to 250 °C at the rate of 10 °C/min. He gas was used as a carrier gas. Temperatures of injection port and FID were kept constant at 300 °C. Retention times of different compounds were determined by injecting pure compound under identical conditions.

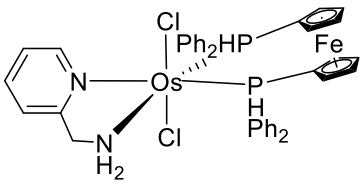
Catalysts List



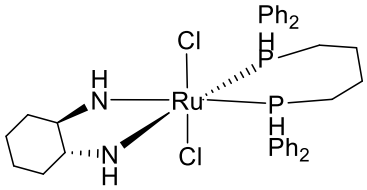
V-1



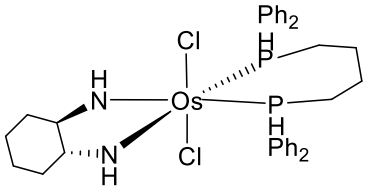
V-2



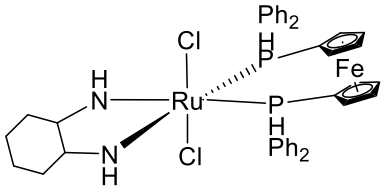
V-3



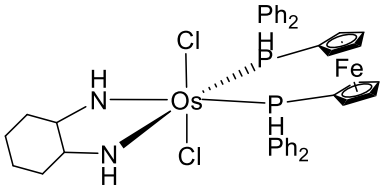
V-4



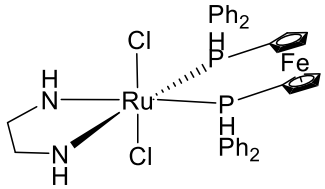
V-5



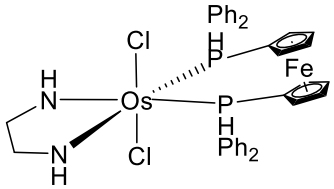
V-6



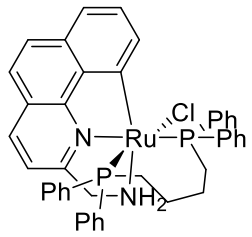
V-7



V-8



V-9



V-10

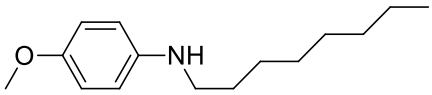
Catalysts **V-1**−**V-10** were prepared from Dr. Giorgio Chelucci and used as is unless otherwise noted.†[340,341,345]

Synthesis of N-4-Methoxy-N-octylaniline V-13a; General Procedure for the Synthesis of *N*-disustituted amines V-13a-d

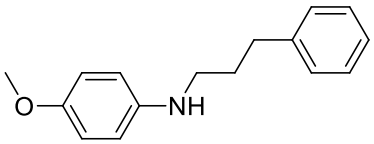
Alcohol **V-11a** (1.1 mmol, 143 mg.), amine **V-12a** (1 mmol, 123 mg.) and potassium *tert*-butoxide (1 mmol, 112 mg) were dissolved in 1 mL of toluene inside a 6 mL vial. The catalyst

V-10 (19 mg, 0.025 mmol) was added and the reaction mixture was stirred for 12 h at room temperature. The reaction solution was charged on a silica gel column and purified by flash cromathography (Hexane/AcOEt 9:1) to give compounds **V-13a** as a pale yellow oil.

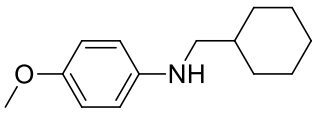
Summary of ^{1}H and ^{13}C NMR data for *N*-disustituted amines V-13a-d



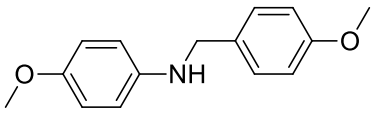
4-Methoxy-*N*-octylaniline V-13a. Reaction Time:12h. Pale yellow oil, (198 mg, 84% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.97–6.71 (m, 2H), 6.73– 6.48 (m, 2H), 3.75 (s, 2H), 3.06 (t, *J* = 7.1 Hz, 2H), 1.60 (dt, *J* = 14.6, 7.1 Hz, 2H), 1.44–1.18 (m, 10H), 0.89 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.7, 145.4, 117.6, 116.7, 79.9, 79.6, 79.4, 58.5, 47.7, 34.5, 32.3, 32.1, 31.9, 29.8, 25.29, 16.72. Spectroscopic data are in agreement with those reported earlier.[346]



4-Methoxy-*N*-(3-phenylpropyl)aniline V-13b . Reaction Time: 3h Yellow oil (226 mg, 94%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.44–7.29 (m, 1H), 7.25 – 7.15 (m, 1H), 6.80 (d, *J* = 8.9 Hz, 1H), 6.58 (d, *J* = 8.9 Hz, 1H), 3.77 (s, 1H), 3.14 (t, *J* = 7.0 Hz, 1H), 2.76 (t, *J* = 7.6 Hz, 1H), 2.06 – 1.84 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 154.7, 145.3, 144.4, 131.1, 131.2, 128.6, 117.6, 116.8, 79.9, 79.7, 79.4, 58.5, 47.1, 36.1, 33.9. Spectroscopic data are in agreement with those reported earlier.[347]

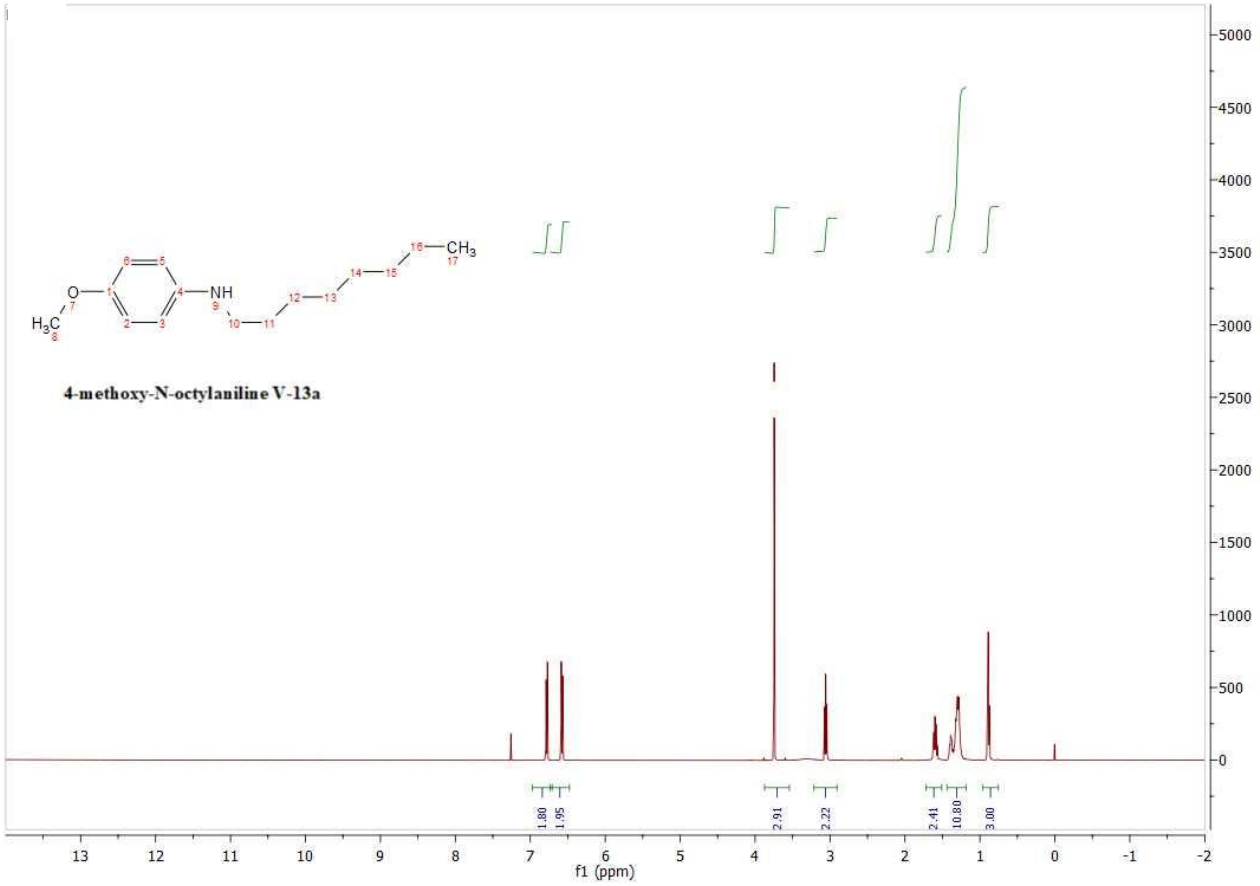


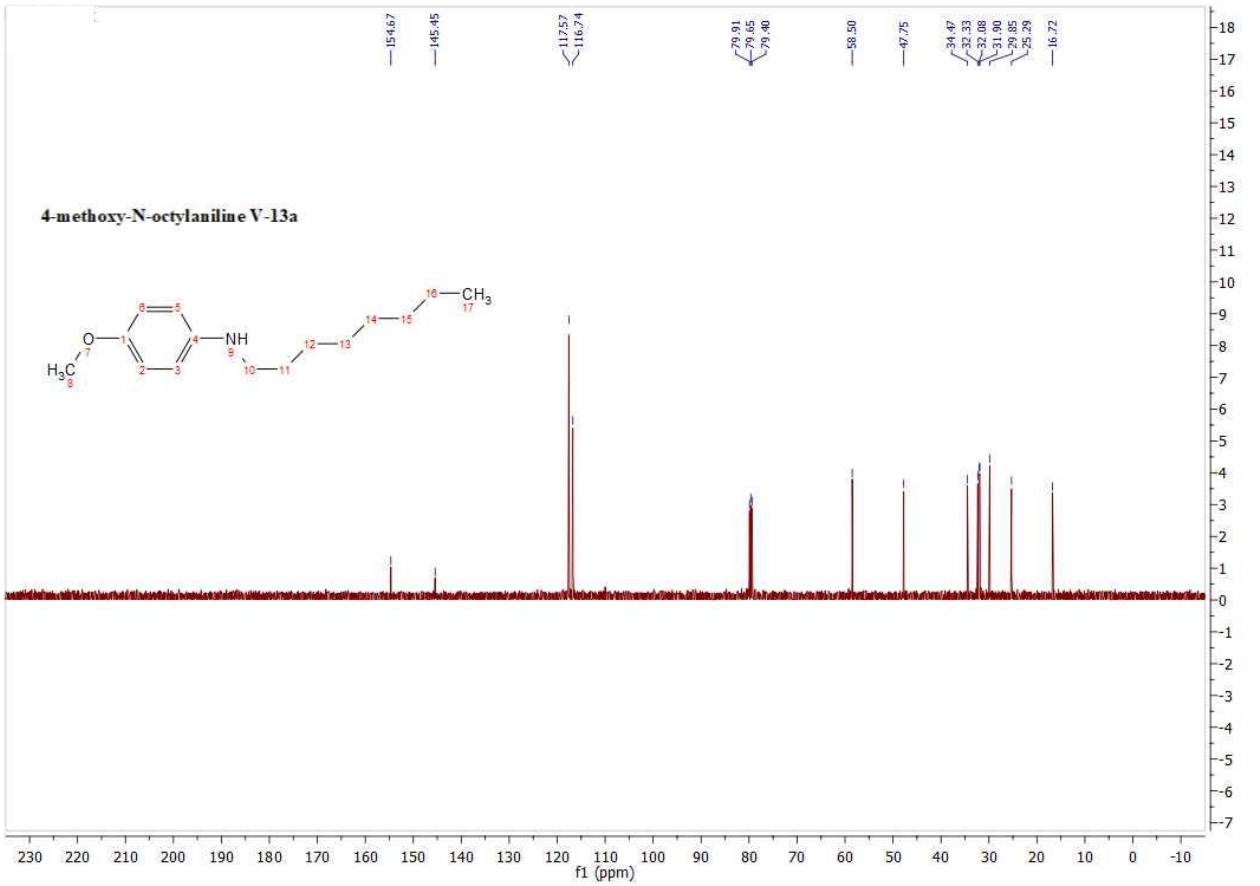
***N*-(Cyclohexylmethyl)-4-methoxyaniline V-13c.** Reaction Time: 24h Yellow oil, (162 mg, 74%); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.79 (d, *J* = 8.8 Hz, 2H), 6.60 (d, *J* = 8.5 Hz, 2H), 3.76 (s, 2H), 2.92 (d, *J* = 6.6 Hz, 3H), 1.83 (d, *J* = 12.7 Hz, 2H), 1.75 – 1.58 (m, 3H), 1.58 (ddd, *J* = 10.9, 7.5, 4.0 Hz, 1H), 1.39 – 1.11 (m, 4H), 1.09 – 0.82 (m, 2H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 117.6, 116.9, 58.5, 54.5, 40.2, 34.0, 29.2, 28.6. Spectroscopic data are in agreement with those reported earlier.[348]

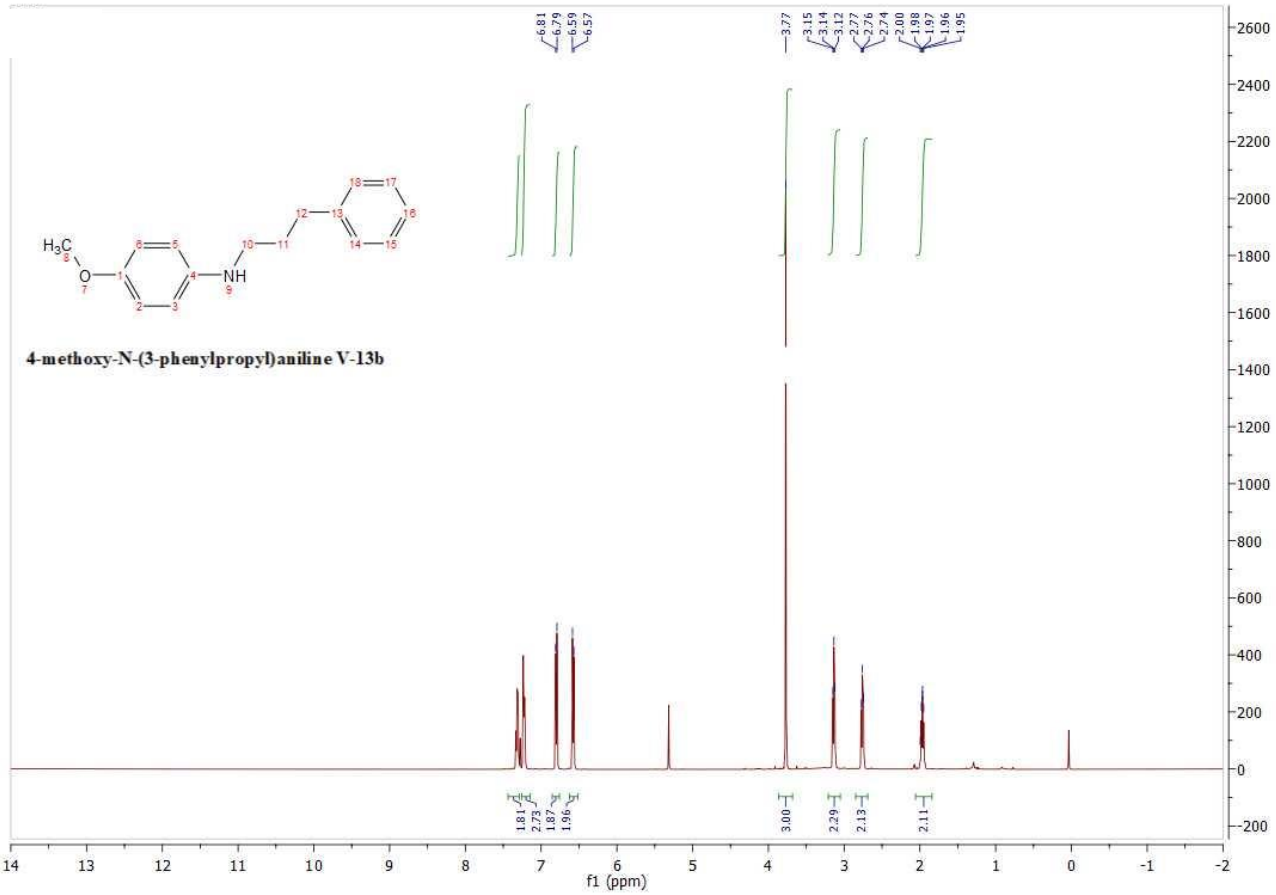


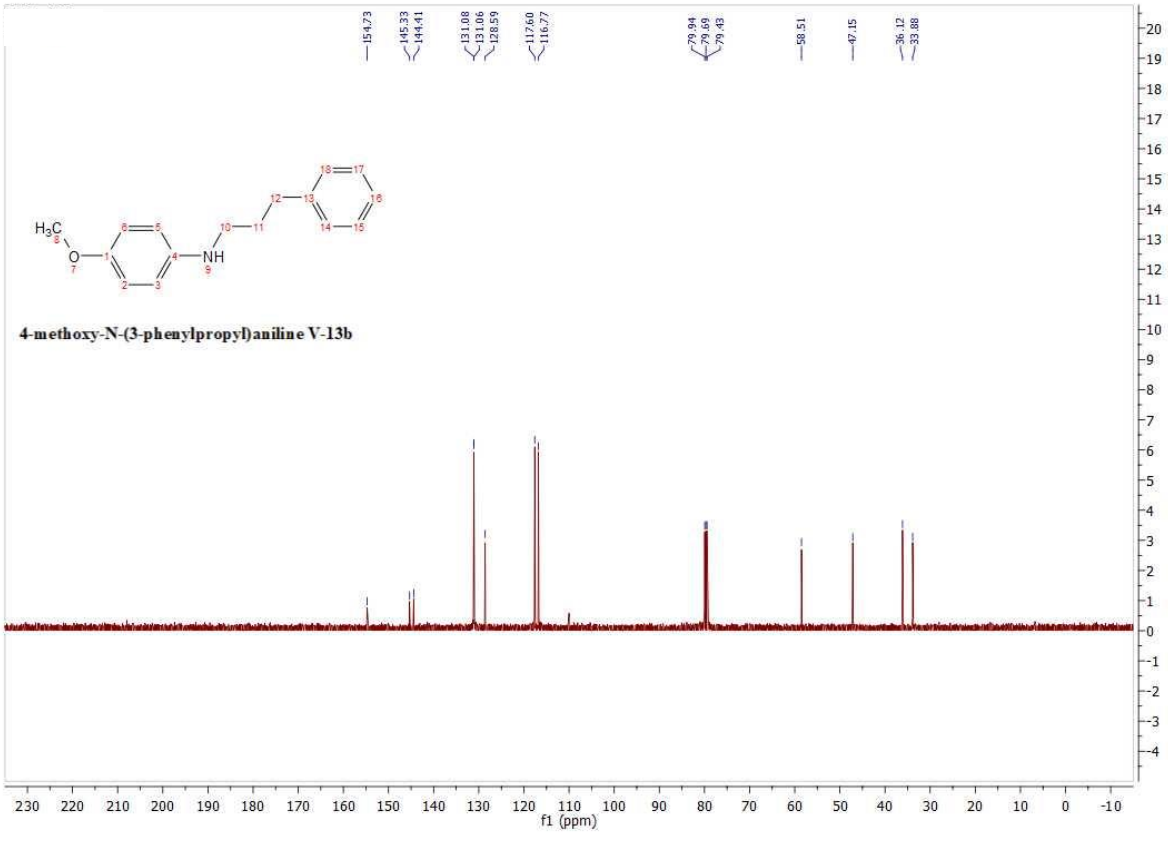
4-methoxy-N-(4-methoxybenzyl)aniline V-13d. Reaction Time:8h Yellow oil, (209 mg, 86%);^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.39 – 7.16 (m, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.83 – 6.71 (m, 2H), 6.67 (t, *J* = 6.1 Hz, 2H), 4.23 (s, 2H), 3.81 (s, 3H), 3.76 (s, 3H). ^{13}C NMR (126 MHz, $CDCl_3$): δ = 159.1, 152.8, 141.7, 131.2, 129.2, 115.1, 115.0, 114.1, 56.0, 55.4, 49.4. Spectroscopic data are in agreement with those reported earlier [7]

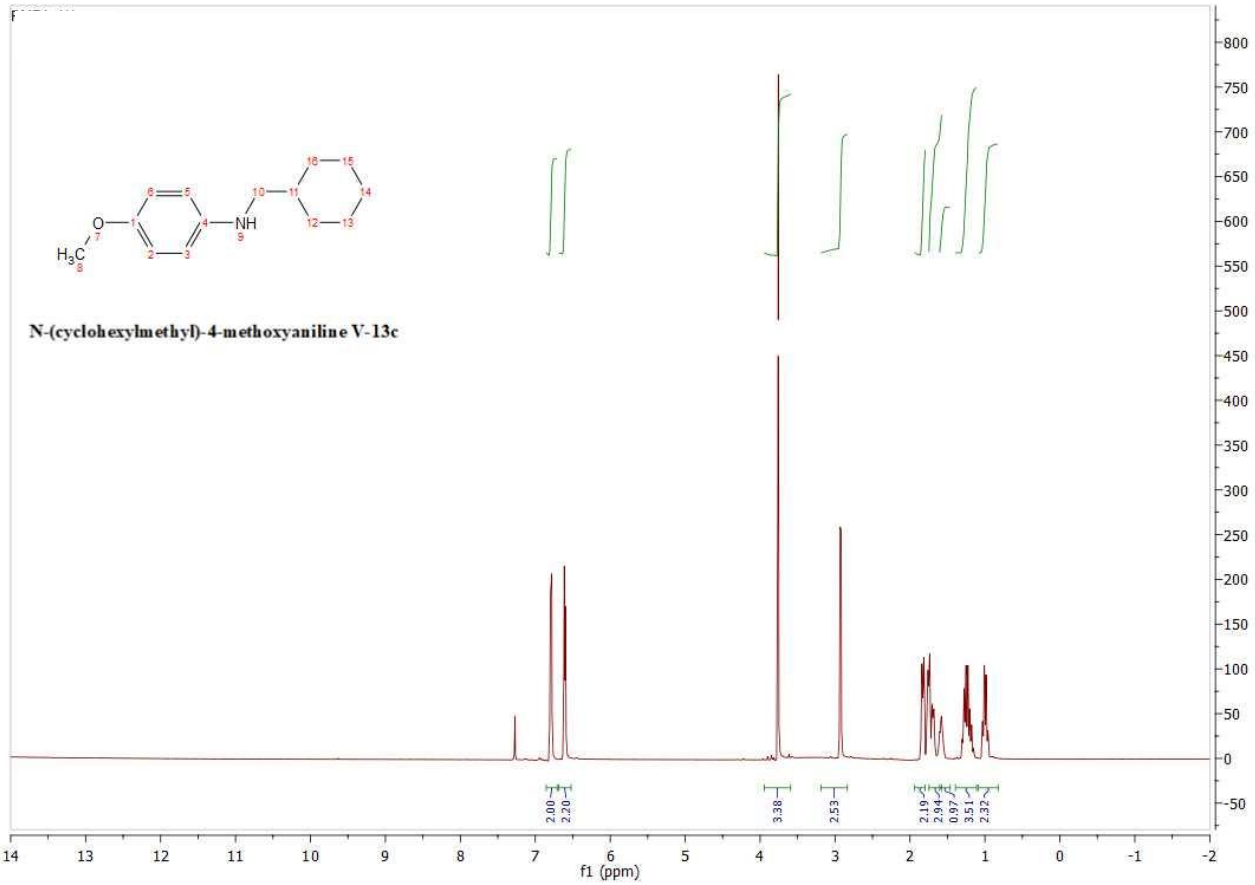
^{1}H-NMR and ^{13}C-NMR spectra of *N*-disustituted amines V-13a-d

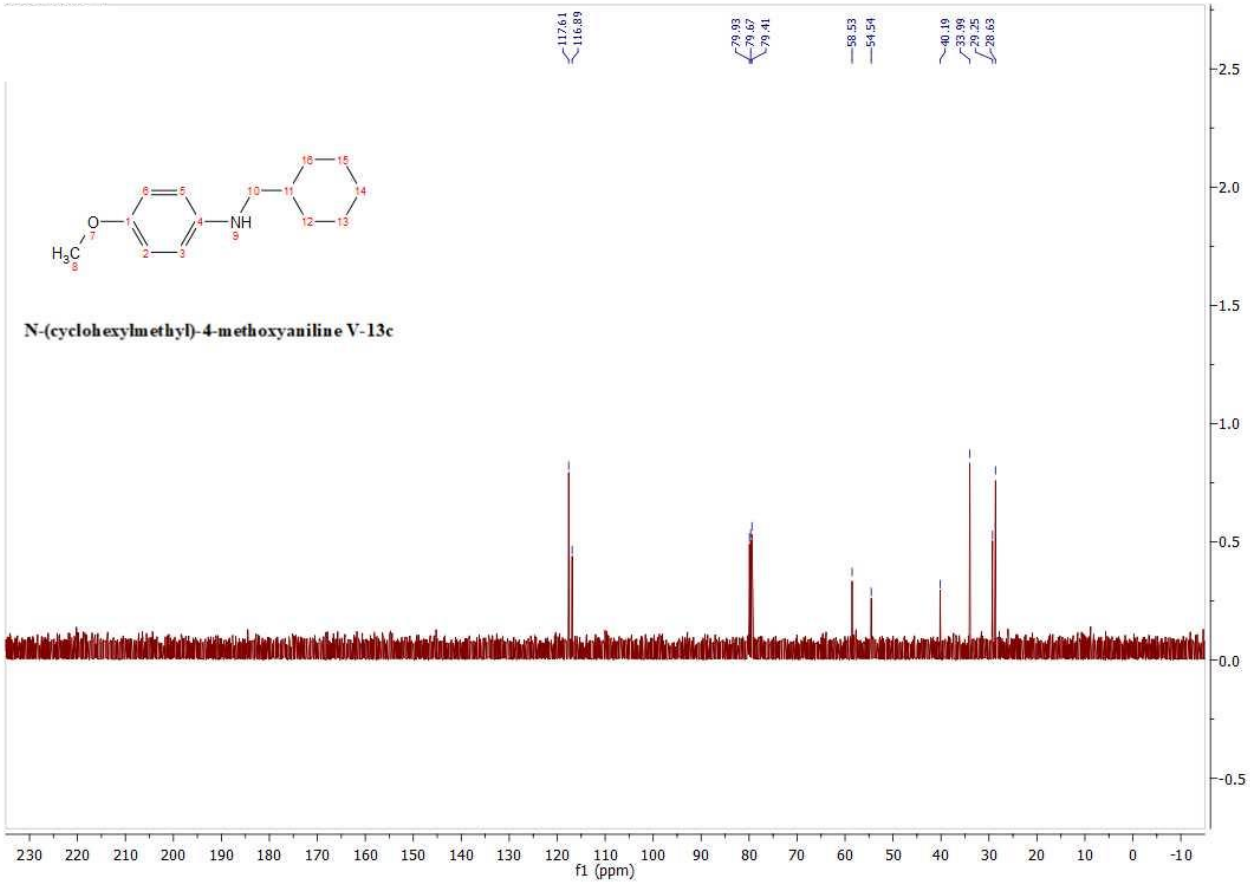


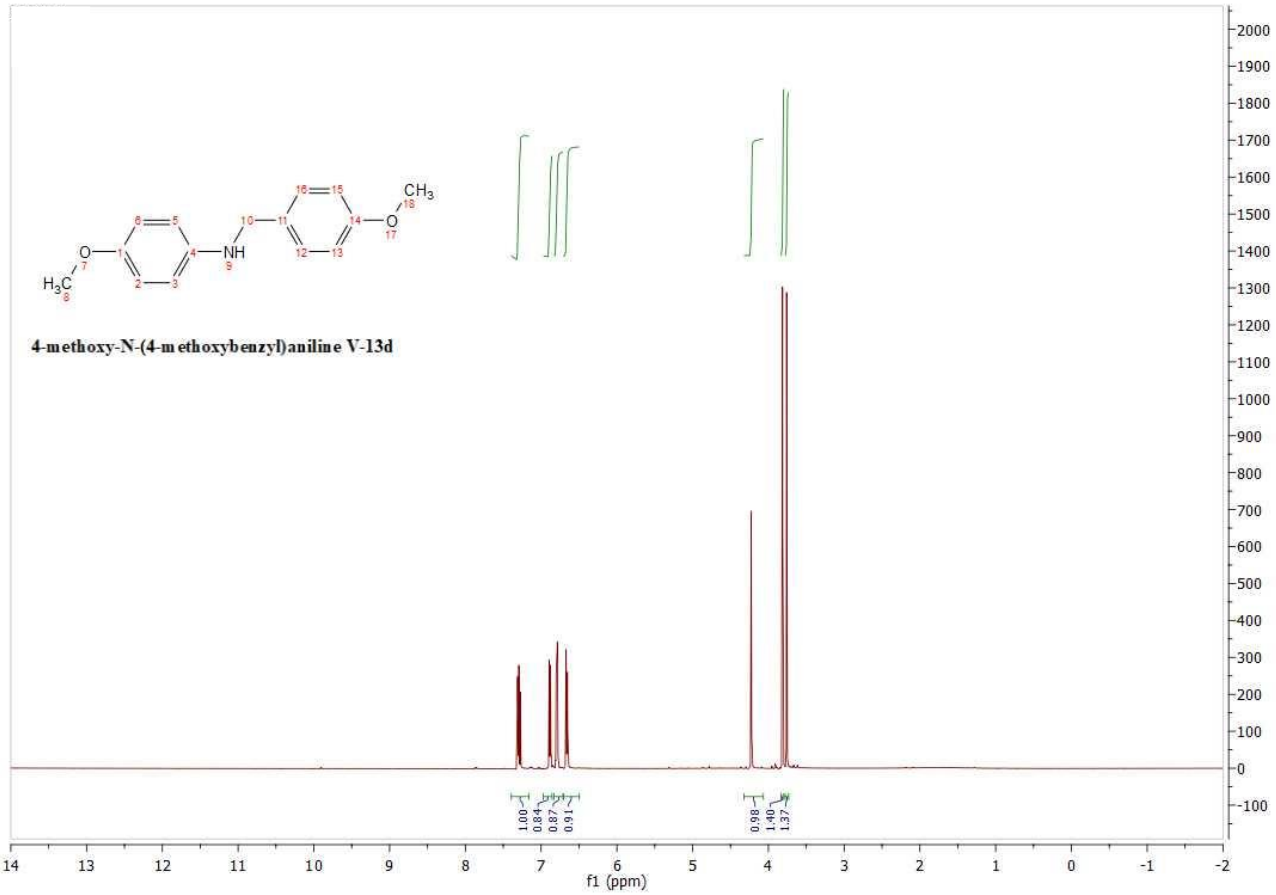


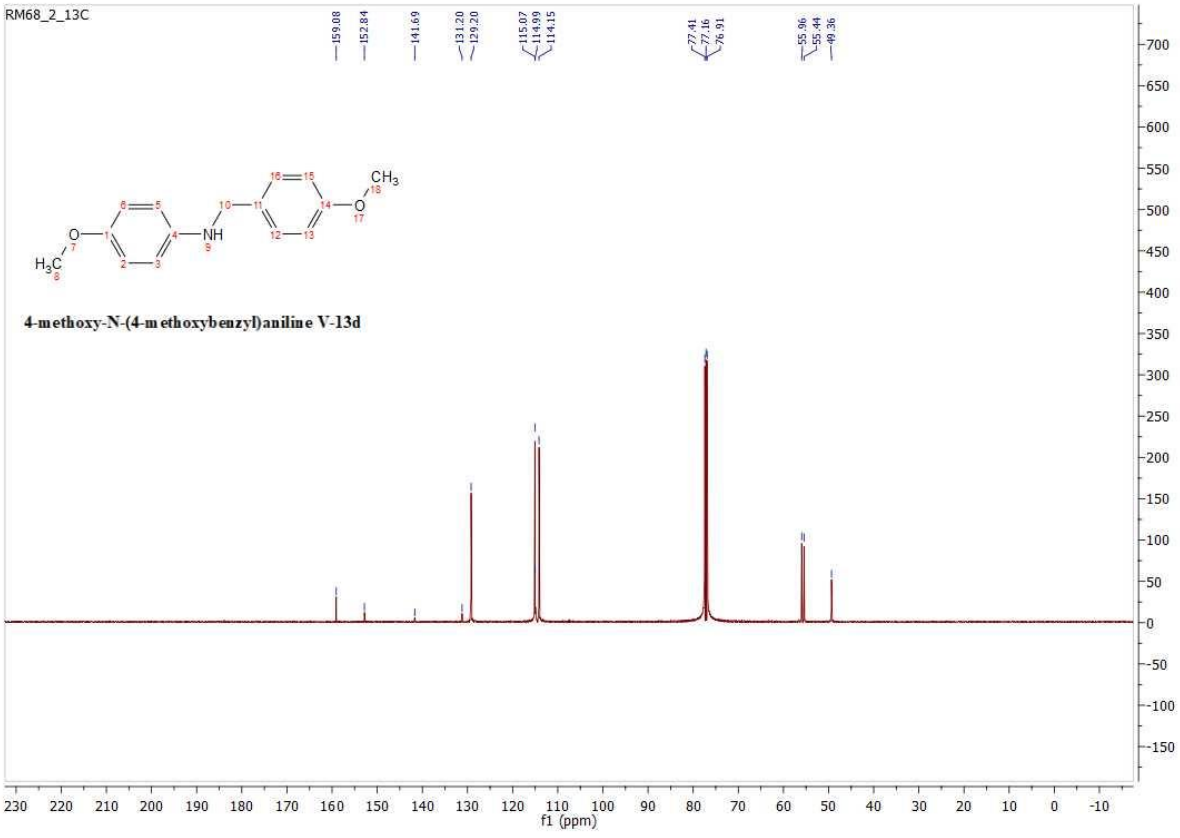

6.81
6.79
6.59
6.57
3.77
3.15
3.14
3.12
2.77
2.76
2.74
2.00
1.98
1.97
1.96
1.95
4-methoxy-N-(3-phenylpropyl)aniline V-13b
1.81
2.73
1.87
1.96
3.00
2.29
2.13
2.11
f1 (ppm)


154.73
145.33
144.41
131.08
131.06
128.59
117.60
116.77
79.94
79.69
79.43
58.51
47.15
36.12
33.88
4-methoxy-N-(3-phenylpropyl)aniline V-13b
f1 (ppm)


N-(cyclohexylmethyl)-4-methoxyaniline V-13c
f1 (ppm)


N-(cyclohexylmethyl)-4-methoxyaniline V-13c
f1 (ppm)


4-methoxy-N-(4-methoxybenzyl)aniline V-13d
1.00
0.84
0.87
0.91
0.98
1.40
1.37
f1 (ppm)


RM68_2_13C
159.08
152.84
141.69
131.20
129.20
115.07
114.99
114.15
77.41
77.16
76.91
55.96
55.44
40.36
4-methoxy-N-(4-methoxybenzyl)aniline V-13d
f1 (ppm)

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