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Mechanochemistry for Healthcare: Revealing the Nitroso Derivatives Genesis in the Solid State

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Nitroso derivatives with unique characteristics have been extensively studied in various fields, including biology and clinical research. Although there has been substantial investigation of "nitrosable" components in many drugs and commonly consumed nutrients, there is still a need for a higher awareness about their formation and characterization. This study demonstrates how these derivatives can be produced through a mechanochemical procedure under solid-state conditions. The results include synthesizing previously unknown compounds with potential biological and pharmaceutical applications, such as a nitrosamine derived from a Diclofenac-like structure.

Introduction

Organic compounds with heteroatoms linked to the nitroso moiety (**NO**) possess unique features exploitable in organic chemistry and photochemistry.[1] However, the same properties lead these compounds into toxicological scenarios (*e.g.*, drinking water, food, pharmaceuticals, and so forth).[2] For instance, in 2018, *N*-nitrosamines were reported as contaminants in the industrial production of sartans due to collateral reactivities occurring in quenching hydrazoic acid.[3] Consequently, the drug manufacturers recalled the involved batches, leading to a dramatic drug shortage in many affected products.[4] In the following years, quality controls on other medicines revealed the presence of *N*-nitrosamines, as in the case of Pioglitazone (2019). Therefore, the EMA and the other regulatory agencies implemented stringent guidelines for monitoring these impurities through pharmacovigilance studies (ICH M7 guidance, ALARA, and ALARP principles).[5] The issues related to nitroso compounds are mainly connected to their mutagenicity and carcinogenicity, divided by IARC into three categories based on the risk level.[6]

Nonetheless, the limited availability of information – especially in the case of API-like scaffolds – makes implementing a comprehensive database for the potential mutagenic properties of nitroso compounds somewhat challenging.[7] For instance, the only method for evaluating the carcinogenic features of nitrosamines is based on *in-vivo* metabolic activations, generating an electrophilic diazonium derivative able to interact with the DNA backbone. Such a bioactivation generally depends on several classes of p450 cytochromes. However, many other factors can affect their genesis in the human body (*e.g.*, bacteria, viruses, stress, smoking, or dietary habits).[8] On top of this, the different responsiveness of individuals further complicates an already intricate scenario according to their *genotype*, which implies discrepancies in the nitroso-related DNA repair processes and bioactive pathways.[8a,9] Analyzing complex *N*-nitrosamines and DNA repair processes is not trivial with *in-vitro* models.[10] Unfortunately, animal models bear some limits due to the prolonged administration of nitrosamines in doses much higher than humans would ever be exposed to.[8a]

To this array of issues related to biological assays, it must be added that supplies of and knowledge about these compounds are scarce. Commercially available substances are very limited, partly due to their high instability and partly to their potential toxicity. The only chance for investigating such compounds lies in their *ex novo* synthesis. A copious number of approaches have been suggested over time, but most rely on hazardous chemical agents, harmful organic solvents, or demanding reaction conditions, as shown in Scheme 1.

On second thoughts, hardly anyone would lean toward synthesizing *'potentially toxic compounds'* with even more hazardous or harsh procedures. To some extent, solvent-free techniques bring an unprecedented advantage in this direction, given the high costs and risks (fire hazards, explosions, human toxicity, environmental pollution, etc.) connected to organic solvent disposal.[11] Among all the emerging technologies, mechanochemistry has been proven to be the most efficient regarding cost, and environmental impact, enabling the processes to be performed under milder conditions, even on an industrial scale.[12]

Within this framework, we have focused on the mechanical activation of $NaNO_2$ and $NaHSO_4 \cdot H_2O$ for synthesizing nitroso compounds. $NaNO_2$ is often implemented in the meat industry[13] due to its action as a bacteriostatic[14] and its ability to inhibit lipid oxidation that leads to rancidity.[14c] $NaHSO_4$ plays an essential role in the food industry as an anti-browning agent[15] and a food additive in cakes.[3b] Moreover, the FDA

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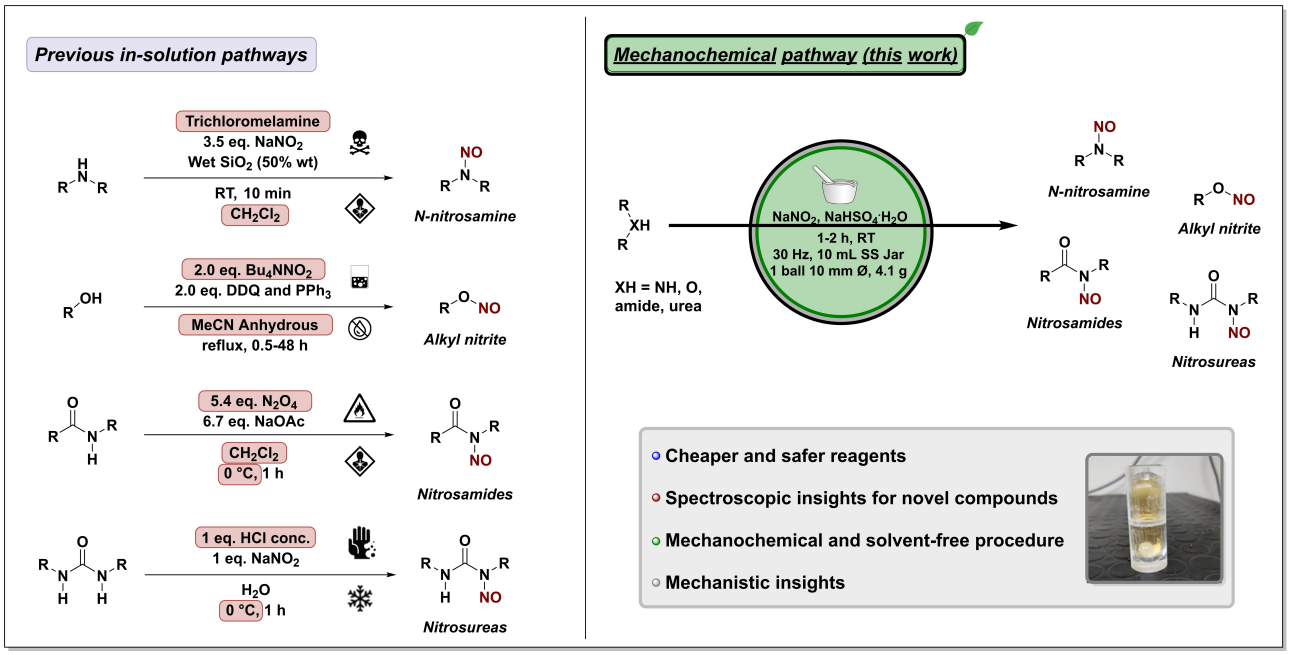
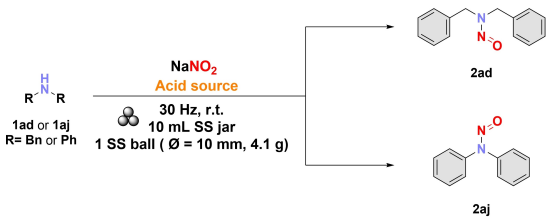


Scheme 1. Comparison between the existing procedures and this work.

considers it a GRAS (Generally Recognized As Safe) and has been listed on the EPA Safer Choice Safer Chemicals Ingredients List.[16] The physical state of these two solid inorganic salts enables the development of grinding procedures through the *in situ*-release of a '*nitrosating*' agent responsible for the '*nitrosation*' of alcohols and secondary amines, amides, and ureas.

Spending this improvement, we herein portray a solvent-free methodology for the '*nitrosation*' of different classes of organic compounds, allowing for a straightforward and efficient mechanochemical preparation of nitroso derivatives. Furthermore, investigating the effects of mechanical forces on this system may also shed light on the still unclear mechanisms involved in the collateral genesis of these compounds during the preparation of tablets and capsules in pharmaceutical industries.[17]

Table 1. Optimization of the reaction conditions for benzylic and aromatic amines.



Entry	Acid source	Acid (mmol)	Time (h)	Yield
1	$NaHSO_4 \cdot H_2O$	1.74	1	76%
2	$NaHSO_4 \cdot H_2O$	1.74	2	72%
3[a]	$NaHSO_4 \cdot H_2O$	2.61	1	97%
4[a,b]	$NaHSO_4 \cdot H_2O$	2.61	1	91%

[a] $NaNO_2$ (3.00 mmol). [b] **1 ad** used as substrate (2.00 mmol).

Results and Discussion

Our study for *N*-'nitrosation' commenced with diphenylamine (**1 aj**) and dibenzylamine (**1 ad**) as model substrates for aromatic and benzylic amines (Table 1). On our first trial, we milled a mixture of the aromatic **1 aj** (2.00 mmol), $NaNO_2$ (2.00 mmol), and $NaHSO_4 \cdot H_2O$ (1.74 mmol) in a stainless-steel jar (10 mL) with 1 ball (Ø = 10 mm, $mass_{tot}$ = 4.1 g) at 30 Hz and room temperature for 1 h. To our delight, the desired product **2 aj** was isolated in 76% yield (Table 1, entry 1). It followed then a comprehensive screening of different parameters (for further information, please see Supplementary Table 1 in the ESI file), culminating in the following optimum settings: **1 aj** (2.00 mmol), $NaNO_2$ (3.00 mmol), and $NaHSO_4 \cdot H_2O$ (2.61 mmol) under solvent-free ball-milling conditions for 1 h at a frequency of 30 Hz at room temperature (97% yield, Table 1, entry 3). The findings were equally suitable for the benzylic substrate **1 ad** (91% yield, Table 1, entry 4).

To test the reaction versatility, we then moved to aliphatic substrates. We chose piperidine **1 at** (2.00 mmol) as the model substrate and milled it with $NaNO_2$ (2.00 mmol) and $NaHSO_4 \cdot H_2O$ (1.74 mmol) in a stainless-steel jar (10 mL) at 30 Hz with 1 ball (Ø = 10 mm, $mass_{tot}$ = 4.1 g) at room temperature for 1 h. Regrettably, it was barely recovered the protonated starting material only (Table 2, entry 1). Considering the higher basicity of aliphatic amines, we doubled the *nitrosating* mixture to 4.00 mmol of $NaNO_2$ and 3.48 mmol of $NaHSO_4 \cdot H_2O$. Gladly, the yield of **2 at** steeply increased to 85% (Table 2, entry 2; for further details, please see Supplementary Table 2 in the ESI file). Upon closure of the screening, changes in frequency and jar

Table 2. Optimization of the reaction conditions for alkyl amines.

Entry	$NaHSO_4 \cdot H_2O$ (mmol)	Time (h)	Yield
1	1.74	1.0	0%
2[a]	3.48	1.0	85%
3[a,b]	2.61	1.0	70%
4[a,c]	3.48	1.0	84%

[a] $NaNO_2$ (4.00 mmol). [b] The reaction was run at 20 Hz. [c] A 10 mL ZrO_2 jar was used.

Table 3. Optimization of the reaction conditions for alcohols.

Entry	$NaHSO_4 \cdot H_2O$ (mmol)	Time (min)	NMR Conversion
1	1.74	60	80%
2	1.74	100	Traces
3[a]	4.35	60	90%
4[a,b]	4.35	60	15%
5[a,c]	4.35	60	73%

[a] $NaNO_2$ (5.00 mmol). [b] 0.10 mmol of 1,3,5-trimethoxybenzene were added. [c] 0.10 mmol of xylene were added.

materials were tested. In the former case, a lower frequency (20 Hz) permitted a conversion into **2at** in 70% yield (Table 2, entry 3). In the latter, the results obtained with the zirconia media were somewhat comparable to the ones obtained with stainless steel (Table 2, entry 4).

Once we set these optimized conditions, we explored the scope of this methodology (Scheme 2). Several alkyl substituents (**2aa–2ae, 2ah–2ai, 2ap–2aq, 2av**) and heterocycles (**2af–2ag, 2ao, 2as, 2au**) proved to be compatible with the '*nitrosative*' process. The procedure also displayed good functional group tolerance with EWGs groups (**2ak–2am**), halogens (**2an**), olefins (**2ar**), carboxylic acids (**2aw**), and esters (**2ax**). Predictably, substrates bearing bulky residues on the nitrogen atom (**2ay, 2az**) or an EWG on the aromatic ring (**2ba–2bc**) performed less. In addition, we decided to explore the formation of nitroso moieties in pharmaceutical products.[4,18] Although nitrosamine impurities have been acknowledged in specific drugs,[4] their presence in different APIs cannot be *a priori* ruled out. What makes these substrates labile are the vulnerability of ubiquitous secondary amine scaffolds and the occurrence of not-fully-elucidated processes.[19] Based on the process leading to *N*-nitrosamines from Valsartan,[17c,18c, 20] it was taken under consideration the '*nitrosative*' process of the substrates **1bd** and **1be**, which respectively resemble the Diclofenac and Indapamide scaffolds.[21] Lastly, we evaluated the selectivity of this *nitrosative* process by analising the reactivity of Synephrine (**1bf**), which presents reactive alcoholic and phenolic groups.[22] Moreover, its structure encloses the pharmacophore of SABAs and LABAs drugs, which are common bronchodilators.[23]

Alcohols were evaluated to explore further the substrate scope of the reaction (Table 3). After selecting *tert*-butanol (**3e**) as the model compound, its reactivity was analyzed in the presence of $NaNO_2$/$NaHSO_4 \cdot H_2O$. We began using a stoichiometric amount of these three reagents for 1.0 h at 30 Hz, and the outcomes were satisfactory, with an NMR calculated conversion of 80% (Table 3, entry 1).

However, with a prolonged reaction time of 100 minutes, the results were not as comparable as before, probably because of the lability of alkylnitrites (Table 3, entry 2). By having screened several parameters (see Supplementary Table 3 for further details), we then decided to increase the '*nitrosating*' mixture equivalents (Table 3, entry 3). These conditions gave the best results, converting **3e** into **4e** with a 90% NMR calculated conversion. Any attempt to use an *in situ*-internal standard for quantifying the reaction yield failed in this process, presumably due to interferences with the '*nitrosative*' process (Table 3, entries 4 and 5).

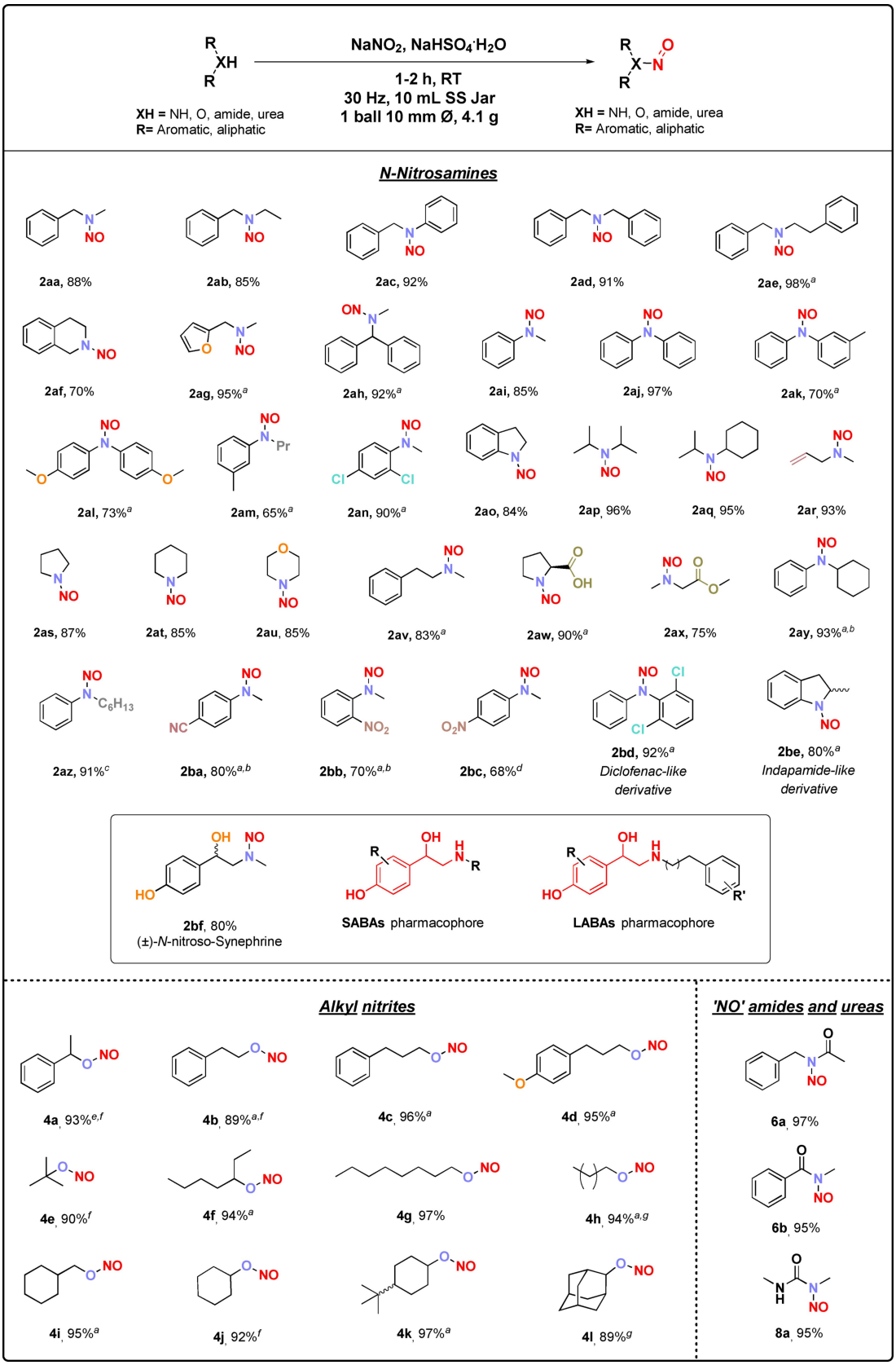
Once the reactivity of the reference substrate was widely clarified, the scope was extended to a broad range of alcohols, as reported in Scheme 2. The alkyl substrates **3a, 3c–d, 3f–g, 3i, and 3k** were quantitatively converted to the corresponding alkyl nitrites with an average yield of 94%, while **3b** (2-phenylethanol) and **3j** (cyclohexanol) still presented traces of starting material. Due to their poor nucleophilicity, the synthesis of **4h** and **4l** predictably required a longer reaction time.

We finally propose the mechanochemical synthesis of *N*-nitrosoamides and *N*-nitroureas (Scheme 2). *N*-nitrosamides **6a** and **6b** were quantitively obtained through 5 mmol of $NaNO_2$ and 4.34 mmol of $NaHSO_4 \cdot H_2O$ in 2 h. Regarding *N*-nitrosourea **8a**, its synthesis was accomplished in 2 h by employing 1 mmol of *N,N'*-dimethylurea **7a**, 2 mmol of $NaNO_2$, and 1.75 mmol of $NaHSO_4 \cdot H_2O$.

To assess the greenness of our mechanochemical procedure, chemical yield (CY), atom economy (AE), environmental factor (E-factor), and reaction mass efficiency (RME) for **2at** (Figure 1) were quantified and compared with a reported solvent-free methodology (see SI for further details).[24]

Spectroscopic and mechanistic insights

Two conformational isomers usually identify *N*-nitrosamines because the rotation around the **N–N** bond is slow on the NMR time scale.[25] A magnetic anisotropy of the NO group gives rise to the different chemical shifts of the protons being *syn* and *anti* to the nitroso oxygen (Figure 2a).[26] Not only does the



Scheme 2. *Nitrosation* scope. Reactions on amines and alcohols were performed on a 2 mmol scale, while those on amides and ureas were run on a 1 mmol scale. If not otherwise stated, the yields were calculated on isolated products. [a] Products never reported in the literature. [b] $NaNO_2$ (4.00 mmol) and $NaHSO_4 \cdot H_2O$ (3.48 mmol) were used. [c] Run for 2 h in the presence of $NaNO_2$ (5 mmol) and $NaHSO_4 \cdot H_2O$ (4.48 mmol). [d] Run for 2 h in the presence of $NaNO_2$ (6 mmol) and $NaHSO_4 \cdot H_2O$ (5.22 mmol). [e] 7 % of acetophenone was present. [f] Conversion NMR calculated. [g] The reaction was run for 1.5 h.

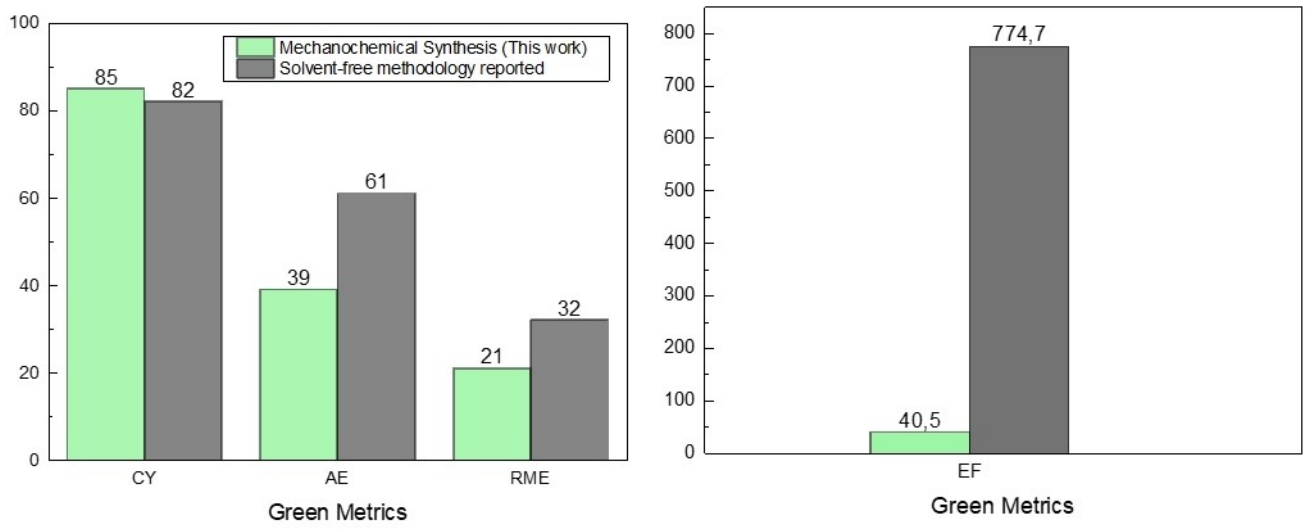


Figure 1. Comparative graphical plot of green chemistry metrics calculated for the synthesis of **2at**. Their values are depicted in green for the procedure reported in this article and gray for a process documented in the literature.[24]

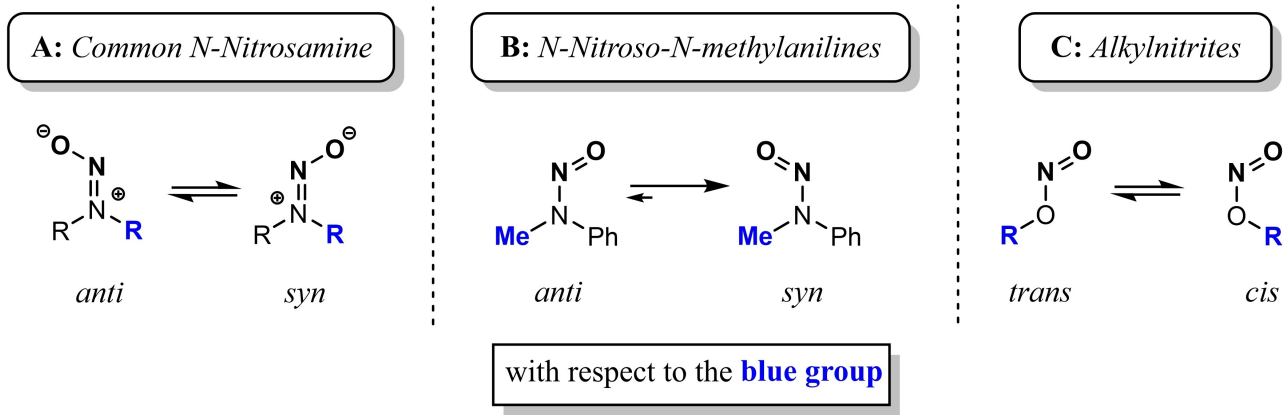


Figure 2. Conformations of nitroso derivatives.

presence of the N-NO moiety alter the chemical shift of the proximal nuclei,[27] but it also modifies the molecule's spatial conformation.[28] Therefore, we reported the different ratios of isomers for each *N*-nitrosamine synthesized (for further information, please see the ESI file). Interestingly, some products possess just one conformational isomer because they prefer a specific conformation. This is the case of the *N*-benzyl-*N*-nitroso aniline **2ac**, *N*-methyl-*N*-nitroso anilines **2ai**, **2ba**, **2bc**, and *N*-nitrosoindoline **2ao**. Despite the coexistence of both isomers, the steric hindrance prevents the stabile interaction between their π electrons, promoting only the formation of the *syn* isomer concerning the alkylic moiety (Figure 2b).[29] In the case of *ortho*-substituted *N*-methyl-*N*-nitrosaniline **2an**, and **2bb** and 2-substituted *N*-nitrosoindoline **2be**, both isomers were formed instead.

O-nitroso compounds, unlike *N*-nitrosamines, did not show any isomer in the NMR spectra. The typical pattern for primary alkyl nitrites is the loss of multiplicity of the protons in the α-position concerning the **O**–**NO** group (Figure 2c). Notably, this phenomenon was not observed for the secondary substrates, which partially displayed a multiplicity. For this reason, a ^{1}H COSY spectrum of several primary alkyl nitrites was done to confirm their structures. Such a behavior can be attributed to either the overlap of the *cis* and *trans* isomers or the impaired relaxation of the α-protons due to the nitroso moiety presence (Figure 2c). In the former case, it is worth speculating that the multiplicity is lost only on primary alkyl nitrites because they have a comparable ratio of the *cis* and *trans* isomers. In secondary alkyl nitrites, the major abundance of the *trans* isomer made it possible to grasp part of the multiplicity. All these speculations are strengthened by the IR spectra, where the presence of the isomers can be seen by looking at the doubling of the $\delta_{O\text{-}N\text{-}O}$ (~600 cm^{-1}), $\upsilon_{N\text{-}O}$ (800 cm^{-1}), $\upsilon_{C\text{-}O}$ (1000 cm^{-1}), and $\upsilon_{N=O}$ (1650 cm^{-1}) frequencies.[30] It must be highlighted that other possible conformations cannot be ruled out, so we opted for simplifying our system by considering the presence of only the *cis* and *trans* isomers.[30] Lastly, substrate **4k** deserves a specific analysis because the two diastereoisomers in the spectra embody the abovementioned behaviors (Figure 3). Considering that the *tert*-butyl group cannot be

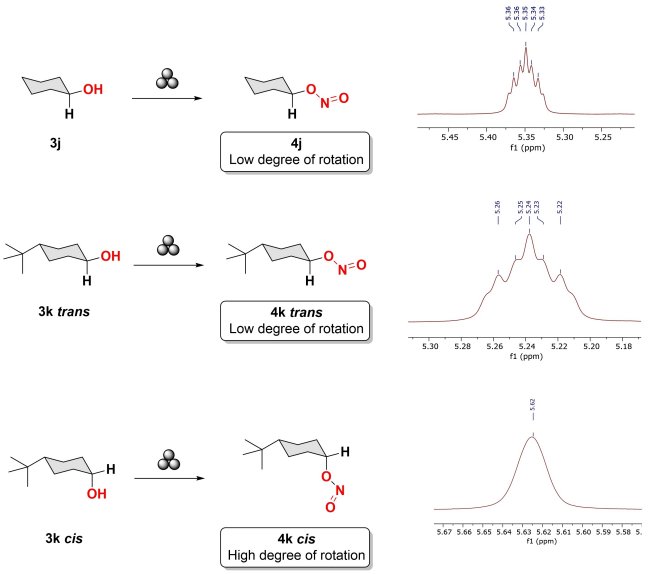


Figure 3. Comparison between **4j** and **4k** *cis* and *trans* diastereoisomers.

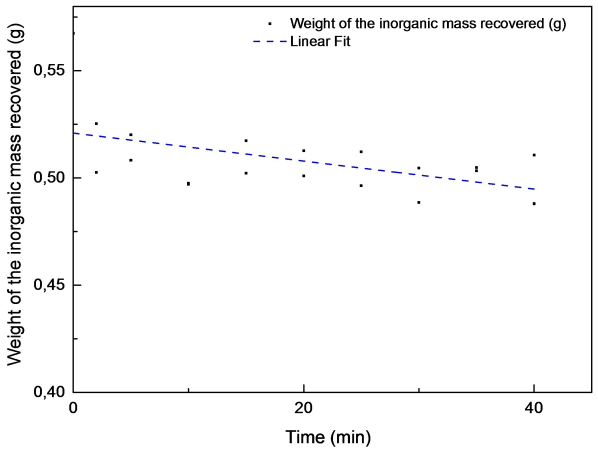
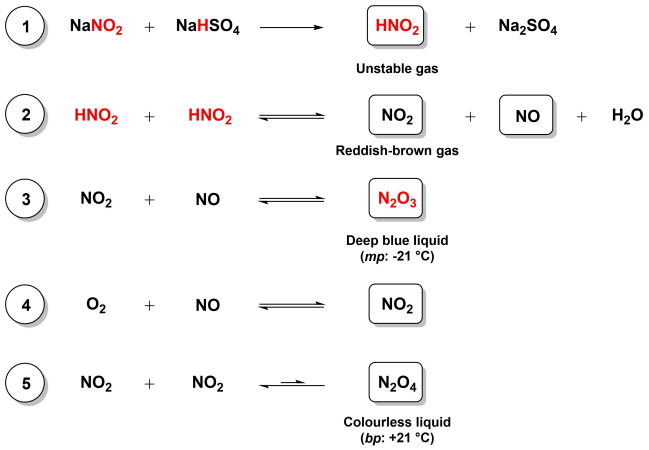


Figure 4. Inorganic mass recovered as a function of grinding time. The reaction conditions were set as follows: 3.00 mmol of $NaNO_2$, 2.61 mmol of $NaHSO_4 \cdot H_2O$ in a 10 mL ZrO_2 at a frequency of 30 Hz (see Supplementary Graph 1 for further details).

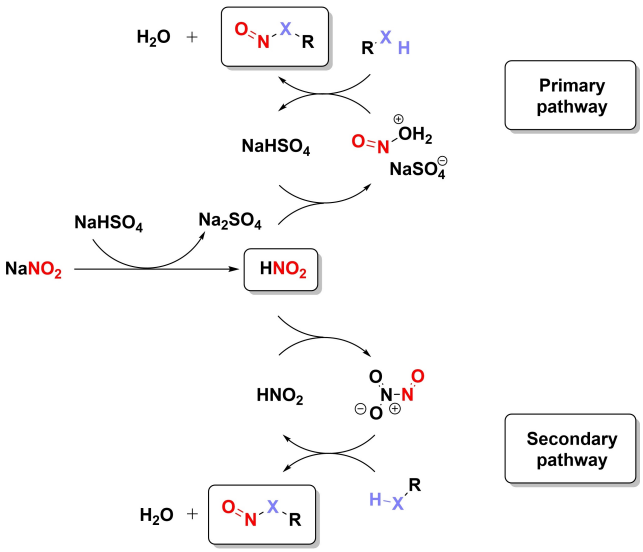
found in the axial position due to its dimension, the sole two supposed conformations are reported in Figure 3.[31] The α-proton can lose its multiplicity because of the **O–NO** position in the aliphatic ring, as the NMR spectra can reveal it. Although some speculations can be done by comparing the NMR pattern of **4k** with the one of cyclohexylnitrite **4j**, it cannot still be attributed a specific pattern to each conformation of the **O–NO** group. With the data collected up to this moment, it can be said that the absence of multiplicity might be attributed to the *cis* diastereoisomer and the appearance of multiplicity to the *trans* diastereoisomer based on their degree of movement. In the latter case, the possible presence of hyperconjugative effects between the **O–NO** group and the proton on the ring may further confirm our hypothesis.[29]

We investigated the reaction mechanism to give a comprehensive view of our system. Based on the previous literature, the '*nitrosating*' agent formed in the solvent-based procedures is surely gaseous.[32] In our case, the formation of a gaseous species during the grinding of $NaNO_2$ and $NaHSO_4 \cdot H_2O$ confirmed the aforementioned model (see the picture in Scheme 1). This is also supported by further experiments to evaluate the inorganic mass consumption after running the *nitrosating* species' release (Figure 4). Considering that various nitrogen derivatives are reported in the literature for this kind of processes,[33] we ran further experiments to prove which can be the most probable one. The first hint concerns the reddish-brown vapours released when $NaNO_2$ and $NaHSO_4 \cdot H_2O$ are ground together (Scheme 1). These vapours remind us of the presence of NO_2, a by-product of unstable nitrous acid solutions.[34] For confirming the presence of NO_2 from the decomposition of HNO_2 (Scheme 3, reactions 1 and 2), $NaNO_2$ and $NaHSO_4 \cdot H_2O$ were ground in a flask both under atmospheric conditions and an inert atmosphere (see the ESI file for further information). As the gas had been developed, both flasks were placed at −78 °C to see the possible formation of



Scheme 3. Nitrous acid decomposition pathways.

liquid N_2O_3 (Scheme 3, reaction 3). Supposing NO formation as a nitrosating agent instead of HNO_2, the presence of an inert atmosphere should not make the formation of N_2O_3 possible because NO cannot be oxidised to NO_2 by molecular oxygen (Scheme 3, reaction 4).[35] Remarkably, the deep blue colour associated with its formation proved that the gas released in both atmospheric and inert conditions contains a mixture of NO and NO_2.[36] Consequently, we strongly support the formation of the *nitrosating* species $NO^+/H_2NO_2^+$ from the decomposition of HNO_2 inside the jar as the principal pathway.[37] A supplementary proof of HNO_2 formation is given by the IR analysis of the gas generated by grinding $NaNO_2$ and $NaHSO_4 \cdot H_2O$ (see the ESI file for further information). Although the genesis of N_2O_3 under our reaction conditions should be relatively scarce, we cannot still completely exclude a less relevant secondary mechanism where this species acts as a nitrosonium donor. In conclusion, it is rather improbable that N_2O_4 has a role in this process[38] because it is highly favoured the presence of NO_2 at room temperature (Scheme 3, reaction 5).[39] Once the '*nitrosating*' agent is generated, the reaction should proceed with a



Scheme 4. Reaction mechanisms proposed.

nucleophilic attack and form the NO derivative, along with water and Na_2SO_4 as by-products (Scheme 4).

Conclusions

In conclusion, we have successfully developed a mechanochemical solvent-free synthesis of nitroso compounds from amines, alcohols, amides, and ureas by using the mixture $NaNO_2$/$NaHSO_4$ as a source of the '*nitrosating*' species. Affording a wide variety of nitroso derivatives in up to 98% yield at room temperature, the present protocol features mild reaction conditions, high reaction efficiency, and a sustainable route to diverse products of biological and pharmaceutical interest. Furthermore, it depicts a reliable chemical model for deeply analyzing the formation of nitroso derivatives in industrial processes. By having screened the different conditions that can bring their synthesis under mechanochemical conditions, we laid the ground for further studies that may even avoid any possible drug recall and, therefore, an interruption in the drug supply. Following this line, we presented some bioactive nitrosamines, such as **2aw** and **2ax**, and drug-like nitroso derivatives **2bd**, **2be**, and **2bf**. A plausible reaction mechanism supported by the reported literature is also proposed to explain the '*nitrosative*' process inside the jar, along with an extensive spectroscopic analysis of *N*-nitroso and *O*-nitroso compounds.

Experimental Section

Commercially available reagents were purchased from Acros, Aldrich, Strem Chemicals, Alfa-Aesar, and TCI Europe and used as received. 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). The eluents were technical grade. Mechanochemical reactions were carried out using a Retsch MM500 Vario apparatus. The reagents were milled using a stainless-steel grinding jar (10 mL) equipped with 1 ball (Ø = 10 mm, $Mass_{tot}$ = 4.1 g) of the same material. ^1H and ^{13}C liquid NMR spectra were recorded on a Varian 500 MHz and Bruker Avance III HD 600 MHz NMR spectrometer at 298 K and were calibrated using trimethylsylane (TMS). Deuterated NMR solvents were obtained from Aldrich. Samples were analyzed using an Agilent 5977B MS interfaced to the GC 7890B equipped with a DB-5 ms column (J & W), injector temperature at 230 °C, detector temperature at 280 °C, helium carrier gas flow rate of 1 ml/min. The GC oven temperature program was 60 °C initial temperature with 4 min hold time and ramping at 15 °C/min to a final temperature of 270 °C with 7 min hold time. 1 μL of each sample was injected in split (1:20) mode. After a solvent delay of 3 minutes, mass spectra were acquired in full scan mode using 2.28 scans/s with a mass range of 50–500 Amu. Retention times of different compounds were determined by injecting pure compound under identical conditions. All the experiments were carried out in duplicate to ensure reproducibility of the experimental data. Yields refer to pure isolated materials when feasible. Otherwise, only the conversion ratio has been reported.

General procedure for nitrosamine synthesis

A 10 mL stainless steel jar equipped with one stainless steel milling ball (10 mm diameter) was filled with amine **1aa**–**1bf** (2.00 mmol), $NaNO_2$ (3.00 mmol or 4.00 mmol) and $NaHSO_4 \cdot H_2O$ (2.61 mmol or 3.48 mmol). The vessel was then closed and the mechanochemical reaction was conducted for 60 or 120 min at 30 Hz. At the end of the reaction, the crude was recovered as a solid in a beaker, dissolved in ethyl acetate or in ethanol (8 mL), and filtered on paper. Lastly, the solvent was removed under reduced pressure to afford the pure nitrosamines **2aa**–**2bf**.

General procedure for alkyl nitrites synthesis

A 10 mL stainless steel jar equipped with one stainless steel milling ball (10 mm diameter) was filled with alcohol **3a**–**3l** (2.00 mmol), $NaNO_2$ (5.00 mmol), and $NaHSO_4 \cdot H_2O$ (4.34 mmol). The vessel was then closed and the mechanochemical reaction was conducted for 60 min or 90 min at a frequency of 30 Hz. At the end of the reaction, the crude was recovered as a solid in a beaker, dissolved in ethyl acetate or in ethanol (8 mL), and filtered on paper. Lastly, the solvent was removed under reduced pressure to afford the desired alkylnitrite compound **4a**–**4l**.

General procedure for nitroso amide synthesis

A 10 mL stainless steel jar equipped with one stainless steel milling ball (10 mm diameter) was filled with amide **5a**–**5b** (1.00 mmol), $NaNO_2$ (5.00 mmol) and $NaHSO_4 \cdot H_2O$ (4.34 mmol). The vessel was then closed and the mechanochemical reaction was conducted for 120 min at a frequency of 30 Hz. At the end of the reaction, the crude was recovered as a solid in a beaker and dissolved in ethyl acetate (4 mL). Lastly, the solvent was removed under reduced pressure to afford the pure nitroso amide compound **6a**–**6b**.

General procedure for nitrosourea synthesis

A 10 mL stainless steel jar equipped with one stainless steel milling ball (10 mm diameter) was filled with the urea **7a** (1.00 mmol), $NaNO_2$ (2.00 mmol), and $NaHSO_4 \cdot H_2O$ (1.75 mmol). The vessel was then closed and the mechanochemical reaction was conducted for 120 min at a frequency of 30 Hz. At the end of the reaction, the crude was recovered as a solid in a beaker and dissolved in ethanol (4 mL). Lastly, the solvent was removed under reduced pressure to afford the pure nitrosourea compound **8a**.

Supporting Information

The authors have cited additional references [60,76] within the Supporting Information.

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: Nitrosamines · mechanochemistry · solvent free · healthcare · industry

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