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[Tocco, G.; Laus, A., Caboni, P. "Mukaiyama Reagent: an Efficient Reaction Mediator for Rapid Synthesis of 1,2-Disubstituted-1H-benzo[d]imidazoles." Tetrahedron Letters, 104, 2022, 154045.

The publisher's version is available at:
https://doi.org/10.1016/j.tetlet.2022.154045

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Mukaiyama Reagent: an Efficient Reaction Mediator for Rapid Synthesis of 1,2-Disubstituted-1*H*-benzo[*d*]imidazoles.

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Abstract. Within the field of medicinal chemistry, 1,2-disubstituted benzimidazoles represent a privileged class of nitrogen-based heterocycles but, unlike 2-substitued derivatives, few synthetic methods have been reported. In this context, we developed a rapid, metal-free, and straightforward method to prepare a series of 1,2-disubstituted-1*H*-benzo[*d*]imidazoles starting from 1,2-phenylendiamines and various aromatic and aliphatic aldehydes in the presence of the Mukaiyama reagent. The reaction proceeded at room temperature with good product yields within few minutes.

Keywords Mukayiama reagent, 1,2-disubstituted-1*H*-benzo[*d*]imidazoles, metal-free synthesis, cyclization

Introduction

The history of 2-chloro-1-methylpyridinium iodide (CMPI) started in the middle of the 1970s when Teruaki Mukaiyama proposed its use for the activation of hydroxyl carboxylic groups in the synthesis of esters.[1] Since then, the CMPI is best known as the *Mukaiyama reagent* and it is extensively employed as efficient and versatile organic condensation agent[2,3] for ester[4] and amide[5,6] bond creation, particularly useful in macrolactonization,[7] β-lactam formation[8] and peptide synthesis.[6,9] Notably, CMPI is low toxic, stable at normal storage conditions, more cost-effective than other condensing agents and can be straightforwardly prepared from methyl iodide and 2-chloropyridine.[10]

The development of efficient protocols for C-N bond formation represents a significant step forward in the field of synthetic organic chemistry. In this regard, CMPI has been recently reported for its ability to activate aldehydic groups in the synthesis of dihydro quinazolinones.[11]

In continuation of our studies towards the synthesis of biologically active heterocycles,[12,13] herein we report the use of the Mukaiyama reagent in the formation of 1,2-disubstituted-1*H*-benzo[*d*]imidazoles.

The increasing demand for even more efficient synthetic approaches is justified by the ubiquitous presence of the 1,2-disubstituted benzimidazole framework in a variety of bioactive compounds as well as in many drugs placed on the market. Particularly, their chemical scaffold is found in a series of eminent antiviral (Zika Virus,[14] HIV-1,[15] RSV/CVB-5[16], HSV-1[17]), anti-bacterial[18], anti-tuberculosis[19,20] derivatives and hPreP function regulators[21]. (Figure 1)

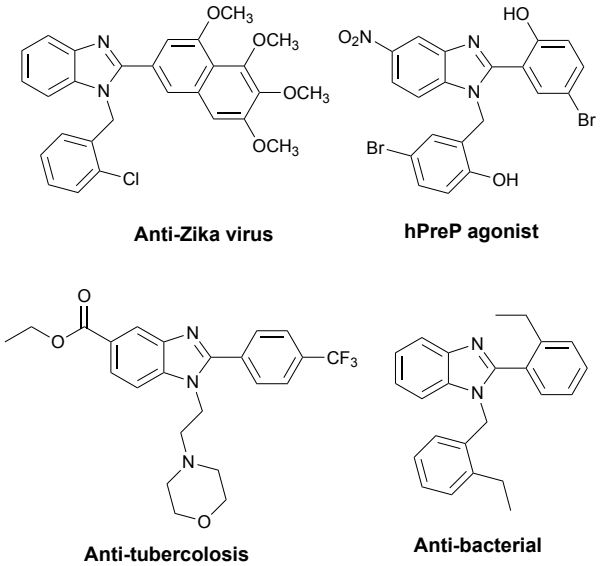


Fig.1 Typical examples of biologically active 1,2-disubstituted benzimidazoles

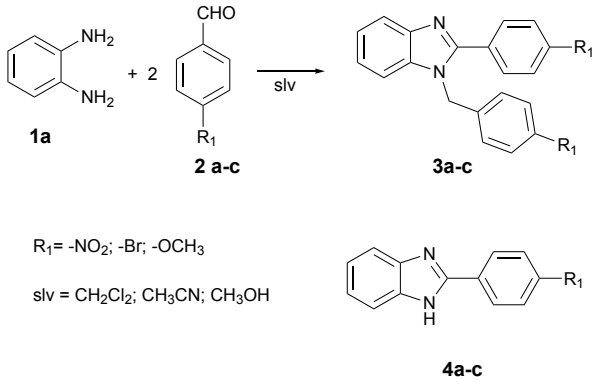
Oddly, although many approaches for the preparation of benzimidazoles have been reported, mostly are referable to 2-substituted derivatives and far fewer to compounds bearing substituents on both N-1 and C-2.[22] The published methodologies are ascribed to cyclocondensation of 2-phenylendiamines,[22,23-26] intra/intermolecular N-arylation catalyzed by transition-metals[22,27-31] and N-1 and/or C-2 functionalization of pre-built benzimidazoles.[22,32-35] Regretfully, apart from some interesting environmentally-friendly procedures,[36-39] many of the synthetic approaches are not devoid of some drawbacks (poor regioselectivity, drastic conditions, heating and long reaction times, use of hazardous acid or metal-containing catalysts). This underlines the need of new strategies for the development of more efficient protocols. Taking inspiration from the reported use of CMPI as carbonyl activator[11], here we propose, for the first time, the Mukaiyama reagent as an economic valuable adjuvant mediator to carry out a rapid and simple procedure for the selective synthesis of 1,2-disubstituted-1H-benzo[*d*]imidazoles.

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Electronic Supplementary Information (ESI) available: Experimental details, analytical data and copies of ^{1}HNMR, ^{13}CNMR spectra for the final products are provided.

Results and discussion

At the beginning of our study, to better define the optimal experimental conditions, the condensation of 1,2-phenylendiamine **1a** with three aromatic aldehydes of different reactivity was carried out.
The 4-nitrobenzaldehyde **2a**, 4-bromobenzaldehyde **2b** and 4-methoxybenzaldehyde **2c** were designated as model substrates and preliminary experiments were carried out at room temperature or under reflux in the absence of any catalyst. (Scheme 1 and Table 1)



Scheme 1. Reaction of **1a** with **2a-c** in the absence of CMPI

As expected, the reactions, followed by ESI-LC/MS, gave very poor results regardless of the nature of the aldehyde and of the solvent (Table 1), thereby, prompting us to examine the role of Mukaiyama reagent as reaction promoter.

Table 1. Results of reaction of **1a** with **2a-c** without Mukaiyama reagent

Aldehyde	Time (min)	Temperature (°C)	Yields 3/4 (%)[a]
2a	180	rt	0/ 10
		reflux	0/ 15
2b	180	rt	0
		reflux	0/ 10
2c	180	rt	0
		reflux	0

[a]GC Yields

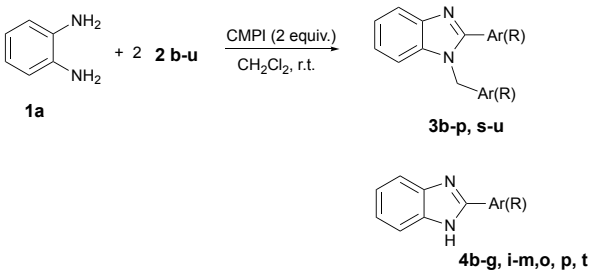
For conditions optimization, the reaction between **1a** and **2a**, selected as model experiment, was carried out in CH_2Cl_2 and in the presence of CMPI, also evaluating various Mukaiyama reagent loading, solvents, and temperature. (Table 2).

Table 2. Optimization of CMPI loading and reaction conditions

Entry	CMPI Loading	Temperature (°C)	Time (min)	Yields 3a/4a (%)[a]
1	0.3	rt	120	10/ 0
		reflux		20/ 0
2	0.5	rt	120	12/ 0
		reflux		22/ 0
3	1	rt	15	70/ 15
4	2	rt	4	87/ 10

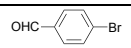
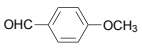
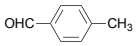
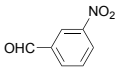
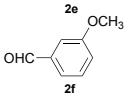
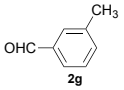
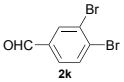
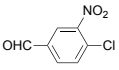
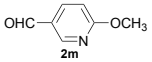
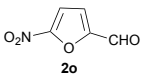
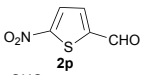
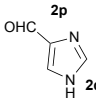
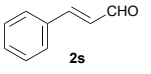
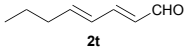
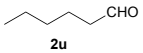
[a]GC Yields for entries 1 and 2. Isolated yields for entries 3 and 4.

Results reported in Table 2, highlight the role of CMPI as a reagent rather than a catalyst. In fact, the reaction proceeded rapidly at room temperature, affording 1,2-disubstituted product in good yields when Mukaiyama reagent was used in 1:1 or 1:2 ratio. Longer reaction times and/or higher CMPI loading did not increase reactions yields. First reaction attempts involving a slightly more than catalytic amounts of CMPI pointed out, however, its importance in the selective formation of 1,2-disubstituted derivatives. Interestingly, no substantial variations in terms of yields and selectivity were observed using acetonitrile, tetrahydrofuran, or methanol. Thus, dichloromethane was chosen as most suitable solvent for reaction work-up. Moreover, the experiment was carried in stochiometric amount of aldehyde observing reduced yields of compound **3a**. Hence, to further exploit Mukaiyama reagent applicability, cyclocondensation experiments were performed with a variety of aromatic and heteroaromatic aldehydes by means of the optimized reaction conditions. Predictably, best results from the standpoint of reaction times were observed with strongly deactivated aldehydes **2h, l, o, p**, due to the increased electrophilic character of the carbonyl carbon. Cinnamaldehyde **2s**, 2,4-octadienal **2u** and hexanal **2v**, were also employed to better investigate carbonyl group reactivity. No conjugated addition products were observed with α,β-unsaturated substrates. (Scheme 2 and Table 3)



Scheme 2. Synthesis of derivatives **3** and **4** by using optimized reaction conditions

Table 3. Results of reaction between **1a** and **2b-u**

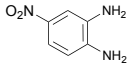
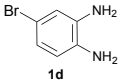
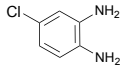
Entry	Aldehyde	Time (min) [a]	Yields 3/4 (%)[b]
1	 **2b**	15	82/10
2	 **2c**	25	79/10
3	 **2d**	20	80/11
4	 **2e**	9	87/10
5	 **2f**	20	80/12
6	 **2g**	10	82/10
7	 **2h**	6	86/ traces [c]
8	 **2i**	12	82/12
9	 **2j**	26	80/10
10	 **2k**	6	86/11
11	 **2l**	3	88/ 10
12	 **2m**	22	82/12
13	 **2n**	10	88/ traces [c]
14	 **2o**	5	87 /10
15	 **2p**	5	86/10
16	 **2q**	60	No reaction [c]
17	 **2r**	60	No reaction [c]
18	 **2s**	15	88/ traces [c]
19	 **2t**	15	86/11
20	 **2u**	20	87/ traces [c]

[a]GC determined. [b]Isolated yields. [c]Determined by GC/MS analysis

Interestingly, no steric hindrance effect was observed, and *ortho*-substituted aldehydes **2h-j** reacted smoothly with excellent product yields. Similarly, saturated and conjugated aldehydes **2s-u** efficiently reacted with **1a** to give 1,2-disubstituted benzimidazoles. Surprisingly, imidazole carboxaldehydes **2q** and **2r** were unreactive while reaction efficiently proceeded with furfural as well as with deactivated 5-nitro-2-furaldehyde **2o** and 5-nitro-2-thiophenecarboxaldehyde **2p**.

To extend the scope of the reaction, we also carried out the condensation between substituted *o*-phenylenediamines **1b-e** and the aromatic aldehyde **2l**. Results are summarized in Table 4.

Table 4. Results of reaction between **1b-e** and **2l**

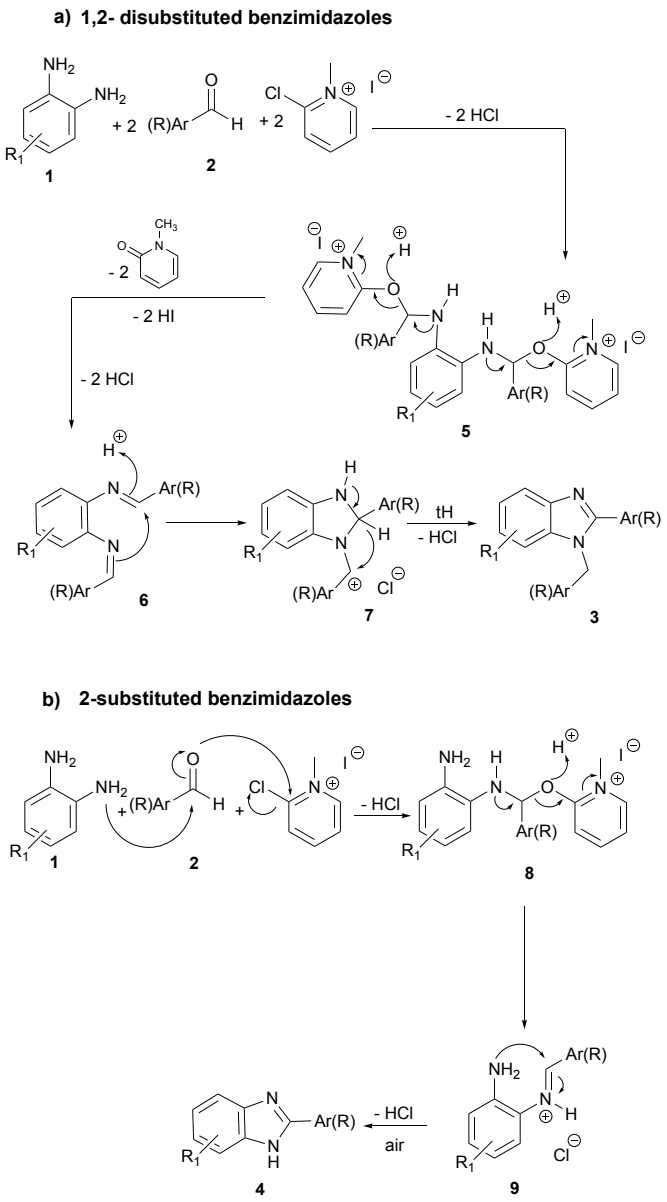
Entry	*o*-Phenylene diamine	Time (min) [a]	Yields 3/4 (%)[b]
1	 **1b**	30	traces [c] / 88
2	 **1c**	2	87/11
3	 **1d**	7	88/10
4	 **1e**	7	86/10

[a]GC determined. [b]Isolated yields. [c]Determined by GC/MS analysis

Electron-withdrawing substitutions affected the reaction rate. Particularly, the strong deactivating group at **1b** revealed a detrimental effect on both reaction time and product selectivity, leading only to the 2-substituted benzimidazole **4v**. Conversely, 3-methyl-*o*-phenylenediamine **1c** rapidly reacted to give 2-(4-chloro-3-nitrophenyl)-1-(3-chloro-4-nitrobenzyl)-4-methyl-1*H*-benzo[*d*]imidazole **3w**, regioselectively, as confirmed by 2D-Noesy experiment (see Electronic Supplementary Information).

Collectively, the experimental results might be suggestive of the reaction mechanism proposed in Scheme 3. We assume that each aldehydic carbonyl group, respectively activated by one equivalent of the electron deficient Mukaiyama reagent, is promptly attacked by 1,2-phenilendiamine. The nucleophilic additions give intermediate **5** and 2 equivalents of HCl that catalyze the formation of the double Schiff base **6** which, via intramolecular cyclization, generates 1,2-disubstituted benzimidazoles **3**. In a similar fashion, 2-subtituted benzimidazoles **4** are obtained.

As a confirmation, the reaction did not proceed if carried out in the presence of a K_2CO_3 (1:1 or 1:2).



Scheme 3. Proposed mechanism pathways

Conclusions

In conclusion, we developed a straightforward method for the synthesis of 1,2-disubstituted-1*H*-benzo[*d*]imidazoles, using the Mukaiyama reagent as a valid reaction mediator. All the experiments carried out at room temperature gave 1,2-disubstituted derivatives in good yields within few minutes. No conversion of **4** into **3** was observed also for prolonged times. Interestingly, reactions proceeded more promptly with electronrich diamines and deactivated aldehydes also not evidencing a steric hindrance effect with *ortho*-substituted aldehydes, regardless of the electronic nature of the substituent.

Acknowledgements

We acknowledge the CeSAR (Centro Servizi Ricerca d'Ateneo) core facility of the University of Cagliari and Dr. Sandrina Lampis and Dr. Giulio Ferino for assistance with the generation of NMR and HRMS data.

Author Contributions

G.T conceptualization, investigation, validation, writing-original draft, writing-review and editing. A.L. investigation, visualization, formal analysis. P.C. formal analysis, editing. All authors have given approval to the final version of the manuscript.

Declaration of competing interest

There are no conflicts to declare.

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