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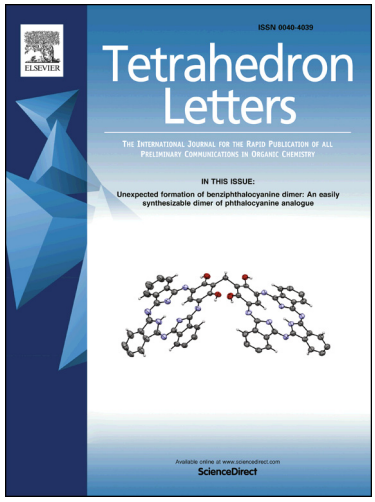

An expeditious synthetic protocol for chlorination of imidazole *N*-oxide: Synthesis of 2-chloroimidazoles

Mossaraf Hossain, Kiran Pradhan, Ashis Kumar Nanda

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An expeditious synthetic protocol for chlorination of imidazole *N*-oxide: Synthesis of 2-chloroimidazoles

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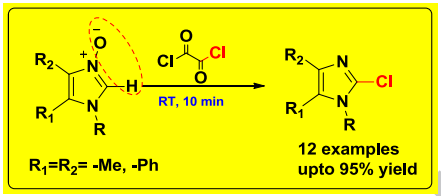
Mossaraf Hossain[a*], Kiran Pradhan[b] and Ashis Kumar Nanda[a]



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An expeditious synthetic protocol for chlorination of imidazole *N*-oxide: Synthesis of 2-chloroimidazoles

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ABSTRACT

An expeditious, one-pot and room temperature protocol is reported for the synthesis of 2-chloroimidazoles from imidazole *N*-oxide. Simple mixing of the imidazole *N*-oxide, derived easily from diacetyl monoxime via three-component reaction, with oxalyl chloride in an agate mortar and pestle in open air affords the desired products in excellent yields. In view of versatile applications of 2-chloroimidazoles and only two other methods are known in the literatures that suffer from certain drawbacks, the present protocol could be of importance.

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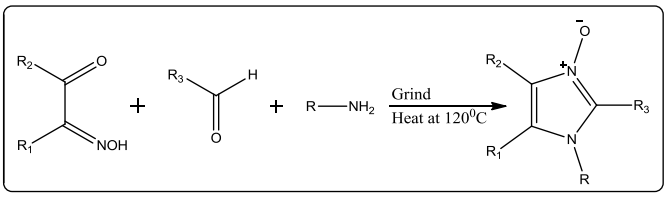
1. Introduction

Functionalized imidazoles are important scaffolds in many biologically active compounds.[1] For example, chloroimidazoles are subunits of different bioactive molecules exhibiting antifungal,[2] antibacterial,[3,4] antiprotozoal, anti-inflammatory,[5] antihypertensive,[6] and of late, anti-cancer medications.[7] Chloroimidazole moiety is often used as a building block in the development of new drugs.

Further applications of this moiety are found in coordination chemistry, organometallic chemistry and asymmetric synthesis.[9] 2-Chloroimidazole also represents a valuable synthetic precursor for further functionalizations under metal-free conditions. For example, simple nucleophilic substitution with thiolate anion leads to the formation of 2-sulfenylimidazole derivatives, which serve as important candidates as anti-inflammatory drugs.[10] A literature search for preparative methods for chlorination of imidazole reveals that the reaction could be achieved from imidazole *N*-oxide using $POCl_3$[11] or tosyl chloride.[12] However, both procedures suffer from one or more disadvantages from green chemistry point of views. While $POCl_3$ is toxic and expensive, use of tosyl chloride requires high temperature, refluxing in anhydrous solvents like $CHCl_3$ or THF. Therefore, the development of mild and greener conditions for regioselective chlorination of imidazoles is of importance.

We report herein an expeditious, one-pot and room temperature protocol under solvent-less for the synthesis of 2-chloroimidazoles from imidazole *N*-oxide in excellent yields. The starting compounds imidazole *N*-oxides are easily prepared following our previously reported protocol[13] (**Scheme 1**).



Scheme 1. Synthesis of substituted imidazole *N*-oxides.

The present procedure simply involves mixing of the imidazole *N*-oxide with oxalyl chloride (1:2 ratios) in an agate mortar and pestle in open air in the presence of triethylamine (1.5 equivalent of the starting *N*-oxide). It may be noted that oxalyl chloride has been used for chlorination of pyridine *N*-oxide.[14] Subsequently, isolating the desired product[15] by column chromatography. A comparison of previous synthetic protocols and our method are schematically shown in **Scheme 2**.

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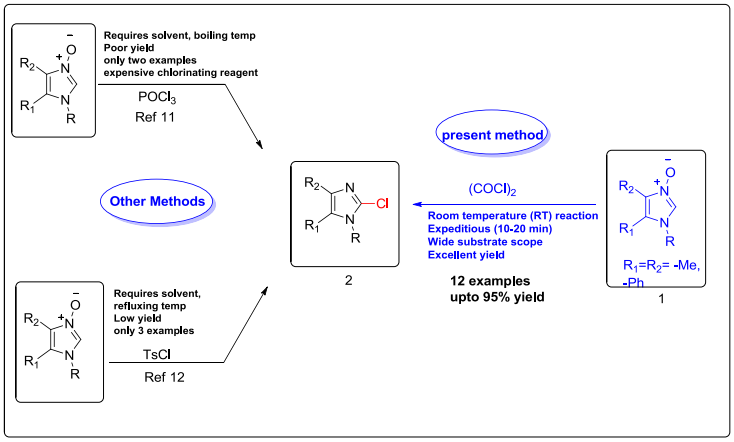


Scheme 2. Different routes of chlorination for the synthesis of 2-chloroimidazole derivative.

2. Results and discussion

We started optimization of the reaction conditions with a mixture of imidazole *N*-oxide and oxalyl chloride (1:1 ratios) in the presence triethylamine (1.5 equiv). After mixing in a mortar (15 min.), the TLC of the reaction mixture showed the presence of starting *N*-oxide. Further continuation for another 15 min. did not show much improvement. After column chromatography, we were able to isolate the desired product in 70% yield (Table 1, entry 1). Increasing the quantity of oxalyl chroride up to 2 equiv and stirring for only 10 min at room temperature showed complete disappearance of the starting *N*-oxide (on TLC) and isolated the 2-chloroimidazole in 95% yield (Table 1, entry 3). Changing the base with pyridine or without using any base afforded the product in relatively lower yields (Table 1, entries 4 and 5). It is evident that the best conversion (95% yields) is achieved with 2 equivalents of oxalyl chloride with respect to 1 equiv. of imidazole *N*-oxide in the presence of 1.5 equiv. of base, and stirring for 10 minutes at room temperatures. The presence of triethylamine promotes the reactions, since its absence the reaction proceeds with moderate yields (67%).

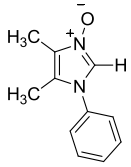
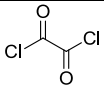
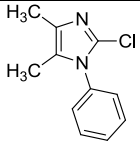
Table 1. Optimized conditions for chlorination of imidazole *N*-oxide[a] by oxalyl chloride

Entry	$(COCl)_2$ (mmol)	Base (1.5 equiv)	Temp (°C)	Time (min)	(2h)Yield (%)[b]
1	1	triethylamine	RT	30	70
2	1.5	-	RT	30	90
3	**2**	**-**	**RT**	**10**	**95[c]**
4	2	pyridine	RT	10	79
5	2	no base	RT	10	67

[a] Reactant (1mmol) [b] Isolated Yield [c] Optimized reaction condition

Based on the above optimization, a variety of 2-chloroimidazoles were synthesized using the solvent-free protocol (Table 2). It was observed that the presence of electron-donating groups such as –Me, –OMe, at various position of the *N*-phenyl ring afforded the product in 83-89% (Table 2, entries 2-4). On the other hand, the presence of electron-withdrawing groups such as –Cl, –Br, –COOH and $–NO_2$ gave slightly better yields and in the range of 91-95% yields (Table 2, entries 5-8). The results however could be explained on the basis of electrophilicity at the C-2 position of the imidazole ring system, which is increased by the presence of electron-withdrawing groups thereby facilitating attack by a nucleophile. We also carried out the reaction with imidazole *N*-oxide bearing a bulky naphthalene ring, which also afforded excellent conversion (Table 2, entry 9). Further extension of the protocol was examined with *n*-butyl group (an aliphatic substituent), which worked quite smoothly but afforded the desired product in relatively lower yield (85%; Table 2, entry 10). The reaction worked efficiently also from benzil monoxime yielding the desired 2-chloroimidazole with two phenyl groups at 4 and 5 positions (95%; Table 2, entry 11). However, glyoxal monoxime did not result in the formation of desired 2-chloroimidazole derivative (entry 12).

Table 2. Scope of various imidazole *N*-oxide in the synthesis of substituted 2-chloroimidazole[a] by varying time.

Entry	Imidazole N-oxide	Oxalyl Chloride	Temp (°C)	Time (min)	Product (2)	Yield (%)[b]
1			RT	15	 2a	93

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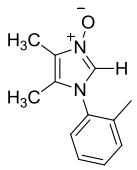
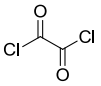
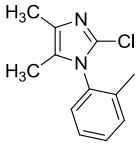
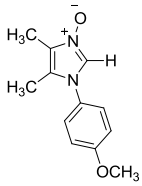
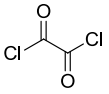
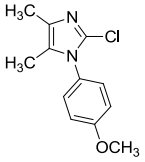
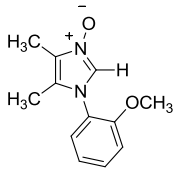
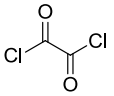
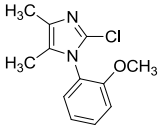
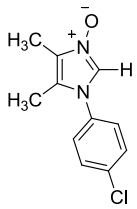
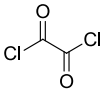
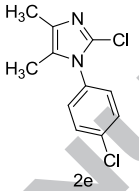
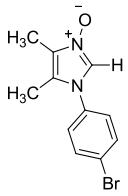
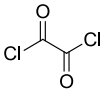
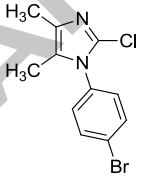
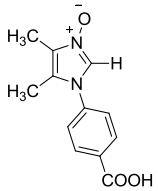
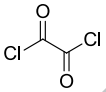
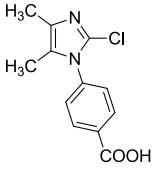
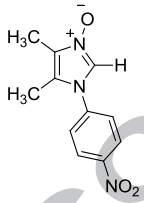
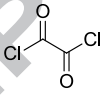
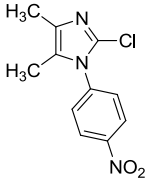
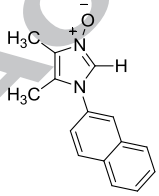
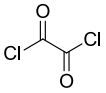
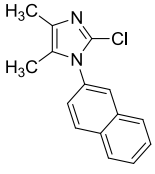
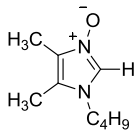
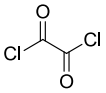
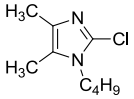
2			RT	20	 2b	83
3			RT	15	 2c	89
4			RT	20	 2d	85
5			RT	10	 2e	93
6			RT	10	 2f	91
7			RT	10	 2g	93
8			RT	10	 2h	95
9			RT	10	 2i	93
10			RT	20	 2j	85

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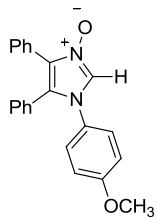
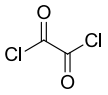
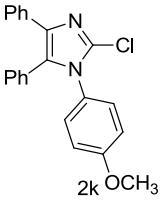
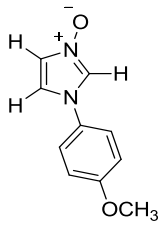
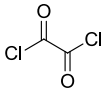
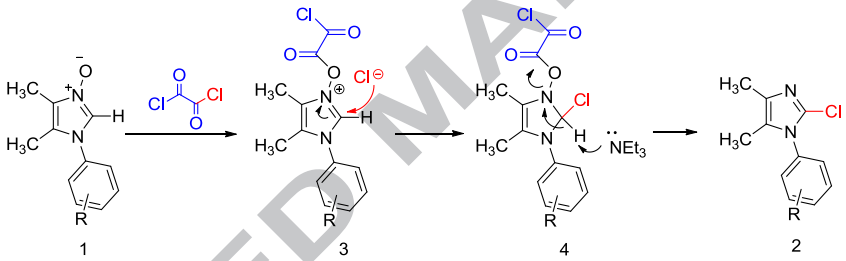
11			RT	15		95
12			RT	15	No desired product	-

[a]Imidazole *N*-oxide (1mmol), Oxalyl Chloride (2 mmol), Triethylamine (1.5 equiv) were ground and stirred at room temperature.

[b]Isolated yield from column chromatography.

On the basis of the experimental observations, a plausible mechanism of cine substitution,[12] is presumed to be operative (Scheme 3). Thus, initially the imidazole *N*-oxide (**1**) is activated by oxalyl chloride to form the imidazolium chloride (**3**), which is then converted to the intermediate (**4**). The hydrogen atom at the C-2 position, being now more acidic, is trapped by the base NEt_3 to yield the desired product **2**.



Scheme 3. Plausible mechanisms for solvent-free synthesis of substituted 2-chloroimidazole.

3. Conclusions

In summary, we have developed an expeditious and mild synthetic route for the chlorination at C-2 position of imidazole *N*-oxide under solvent-free conditions leading to the formation of 2-chloroimidazole. The protocol has been tested with diversely substituted *N*-phenyl group. In all cases, the yields are excellent, though the presence of electron-withdrawing groups favors the reaction over electron-donating substituents. 2-chlorinated imidazole derivatives are useful intermediates and subunits of several pharmacologically important compounds. This simple setup and facile method could be attractive to the synthetic chemists from academia and pharmaceutical industries. Further application of this protocol in other heterocyclic systems is underway in this laboratory.

Supporting information

The detailed experimental section, all other information such as melting point, FT-IR, NMR and Mass of all products are provided in the supporting information.

Acknowledgements

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References and notes

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15. **General experimental procedure for the chlorination of Imidazole N-oxides**: Imidazole *N*-oxide (1 mmol), oxalyl chloride (2 mmol) and triethylamine (1.5 mmol) were mixed intimately in an agate mortar and pestle for a period of 10-20 min under solvent-less condition. The reaction mixture was then dissolved in dichloromethane (2 mL), washed with water and finally dried over anhydrous $MgSO_4$. Evaporation of the solvent afforded the residue, which was chromatographed over silica gel column and elution with petroleum ether/ethyl acetate mixture to furnish the desired 2-chloroimidazole.

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Highlights

- Room temperature reaction.
- Expeditious, 10-20 mins.
- Wide substrate scope.
- Excellent yield.

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