Cu(OTf)₂-catalyzed synthesis of highly substituted 1-methoxy imidazoles via (3 + 2) cycloaddition between imino carbenoids and nitriles

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ABSTRACT
A Cu(OTf)₂-catalyzed simple synthetic approach for highly substituted 1-alkoxy imidazole has been described. This protocol involves (3 + 2) cycloaddition of oximino carbenoids with organo nitriles. This method has wide substrate scope and tolerates alkyl, aryl, substituted aryl, vinyl, and ester nitriles.

GRAPHICAL ABSTRACT

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Introduction
Imidazole is an important heterocycles present in many biologically active molecules and natural products. It also possesses the unique property to form stable carbenes known as N-heterocyclic carbenes (NHC) and ionic liquids. 1-Hydroxy imidazoles and their derivatives have received interest in recent years because of their important biological antiviral, antihypertensive, bacteriostatic, and insecticidal properties. In spite of their promising biological properties, only a few derivatives had been synthesized and studied, mainly due to limited methods to access them. The most convenient method involves the three-component coupling of α-hydroxy imino ketone, aldehydes, and ammonium acetate [Eq. (1), Fig. 1]. Furthermore, derivatization of N-alkoxy imidazoles at the cyclic carbon (C-5) via directed lithiation has been described. The accessibility to α-hydroxy imino ketones limits the substrate scope of this method. Hence, the search for a simple protocol to achieve readily derivatizable highly substituted 1-hydroxy imidazole is desirable.
α-Diazo compounds have versatile functionalities in organic chemistry and undergo a wide variety of organic transformations such as insertion, cycloaddition, and rearrangement. Their nitrogen analogs, i.e., α-diazo oxime ethers, have recently been stereoselectively synthesized via diazo transfer reaction and have been demonstrated as precursors for N-alkoxy pyrroles. In this article, we report the synthesis of highly substituted 1-methoxy imidazoles from α-diazo oxime ethers via (3 + 2) cycloaddition.

Results and discussion

In continuation of our work on the reactions of α-diazo oximino ethers to get N-heteroatom substituted heterocycles, we envisaged that (3 + 2) cycloaddition between imino carbenoids and nitriles could serve as the simplest method to access diversified N-alkoxy imidazole derivatives [Eq. (2), Fig. 1]. As expected, the α-diazo imine 1a reacts with acetonitrile in the presence of copper(II) trifluoromethanesulfonate (Cu(OTf)₂) as a catalyst in CH₂Cl₂ to give highly substituted N-methoxy imidazole 3a in good yield (Scheme 1).

To optimize the reaction conditions, we screened several rhodium and copper salts as catalysts in different solvents and results are given in Table 1. As can be seen, Cu(OTf)₂ gave better yield as compared to Rh₂(OAc)₄ and palladium salts. In the case of Rh₂(OAc)₄, full conversion was observed within 2 h while palladium salts failed to give full conversion even after 5 h. The decrease in the yield may be attributed
to the decomposition of diazo compounds, forming self-coupled dimers. Among the solvents, chlorinated solvents were found to be good while ethers gave poor yields. Diazo compound was found to be stable at 50 °C (using Cu(OTf)$_2$ as catalyst) while an increase in the temperature to 90 °C resulted in decomposition. The optimum catalyst loading was fixed to be 5 mol% based on the results. Among the copper catalysts, Cu(OTf)$_2$ gave the maximum yield while Cu(hfacac)$_2$ gave moderate yield. Cul failed completely to give the desired product.

The substrate scope of this methodology was studied by subjecting various diazo imines and nitriles to this reaction condition and results are given in Table 2.

From these results, it is evident that not only the simple aliphatic nitrile but also bulkier benzonitrile undergoes (3 + 2) cycloaddition to give the desired product with appreciable yield. The reaction of imino carbenoids with acrylonitrile was expected to follow three different reaction pathways, i.e., (3 + 2) cycloaddition, (3 + 4) cycloaddition, and cyclopropanation with double bond. Surprisingly, we observed only (3 + 2) cycloaddition products, i.e., 2-vinyl 1-alkoxy imidazoles (3d and 3j), rather than (3 + 4) cycloaddition and cyclopropanation products. Both the aliphatic and aromatic nitriles with electron-withdrawing groups also underwent (3 + 2) cycloaddition readily to give the desired products (3f, 3g, and 3k).

Mechanistically, the metal carbenoid A formed from diazo compound is attacked by nitriles to give intermediates B and C, which undergo cyclization to give imidazole (path 1).$^{[9,10]}$ It may also be expected to proceed through azirine D formation followed by ring expansion (path 2). However, we have not isolated any azirine intermediate along with imidazole. Thus, we presume that the path 1 is favored over path 2.

### Table 1. Catalyst and solvent screening.$^a$

| No. | Catalyst | Solvent       | Yield (%)$^b$ |
|-----|----------|---------------|---------------|
| 1   | Cu(hfacac)$_2$ | CH$_2$Cl$_2$ | 56            |
| 2   | CuOTf    | CH$_2$Cl$_2$ | 62            |
| 3   | Cu(OTf)$_2$ | CH$_2$Cl$_2$ | 89            |
| 4   | Cul      | CH$_2$Cl$_2$ | Trace$^c$     |
| 5   | Pd(OAc)$_2$ | CH$_2$Cl$_2$ | 48            |
| 6   | PdCl$_2$  | CH$_2$Cl$_2$ | 31            |
| 7   | Rh$_2$(OAc)$_4$ | CH$_2$Cl$_2$ | 78            |
| 8   | Cu(OTf)$_2$ | THF          | 55            |
| 9   | Cu(OTf)$_2$ | CHCl$_2$     | 74 (32)$^f$   |
| 10  | Cu(OTf)$_2$ | CHCl$_3$     | 71            |
| 11  | Cu(OTf)$_2$ | Et$_2$O      | 43            |

$^a$Reaction conditions: α-diazo oxime ether (2 mmol), nitrile (2 mmol), solvent (6 mL/1 mmol), refluxed for 2 h.

$^b$Yield corresponding to the isolated product by column chromatography.

$^c$Vacuum dried at 60 °C.

$^d$Observed by HPLC.

$^e$Yield at 90 °C using dichloroethane as solvent.
Conclusion

In conclusion, we have described a simple method to get 1-methoxy imidazoles via Cu (OTf)2-catalyzed (3 + 2) cycloaddition of α-diazo imines with organic nitriles. They are highly substituted and can be easily derivatized to get their derivatives. Further, these compounds may be explored for the synthesis of new class of ionic liquids by N-alkylation.

Experimental

General procedure for the synthesis of 1-methoxy imidazole

A solution of α-diazo oximino ester (1 eq.) in dry CH2Cl2 was charged with 5 mol% Cu (OTf)2 catalyst followed by the addition of organo nitrile (1 eq.). The reaction mixture was refluxed for 2 h. After the completion of the reaction as indicated by the thin-layer chromatography (TLC), the mixture was washed with water and brine, extracted with ethyl acetate, and dried over anhydrous Na2SO4. The organic layer was concentrated under reduced pressure to get the crude product, which was purified by column chromatography using petroleum ether / ethyl acetate (7:3) to obtain pure 1-methoxy imidazole.

Table 2. Substrate scope of (3 + 2) cycloaddition.a

| No. | Diazo oxime ether | Nitrile | Product (3a–m) | Yieldb (%) |
|-----|-------------------|---------|----------------|------------|
| 1   | ![Diazo oxime ether](image1) | ![Nitrile](image2) | ![Product (3a–m)](image3) | 3a R1 = CH3; 89% |
| 2   | ![Diazo oxime ether](image4) | ![Nitrile](image5) | ![Product (3a–m)](image6) | 3b R1 = C2H5; 77% |
| 3   | ![Diazo oxime ether](image7) | ![Nitrile](image8) | ![Product (3a–m)](image9) | 3c R1 = C3H7; 78% |
| 4   | ![Diazo oxime ether](image10) | ![Nitrile](image11) | ![Product (3a–m)](image12) | 3d R1 = CH=CH2; 75% |
| 5   | ![Diazo oxime ether](image13) | ![Nitrile](image14) | ![Product (3a–m)](image15) | 3e R1 = C6H5; 76% |
| 6   | ![Diazo oxime ether](image16) | ![Nitrile](image17) | ![Product (3a–m)](image18) | 3f R1 = C6H5-2-Cl; 77% |
| 7   | ![Diazo oxime ether](image19) | ![Nitrile](image20) | ![Product (3a–m)](image21) | 3g R1 = C6H5-p-CHO; 78% |
| 8   | ![Diazo oxime ether](image22) | ![Nitrile](image23) | ![Product (3a–m)](image24) | 3h R1 = CH3; 77% |
| 9   | ![Diazo oxime ether](image25) | ![Nitrile](image26) | ![Product (3a–m)](image27) | 3i R1 = CH3; 74% |
| 10  | ![Diazo oxime ether](image28) | ![Nitrile](image29) | ![Product (3a–m)](image30) | 3j R1 = C2H5; 76% |
| 11  | ![Diazo oxime ether](image31) | ![Nitrile](image32) | ![Product (3a–m)](image33) | 3k R1 = CH=CH2; 76% |
| 12  | ![Diazo oxime ether](image34) | ![Nitrile](image35) | ![Product (3a–m)](image36) | 3l R1 = C6H5; 70% |
| 13  | ![Diazo oxime ether](image37) | ![Nitrile](image38) | ![Product (3a–m)](image39) | 3m R1 = CH2CO2Et; 76% |

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a Reaction conditions: α-diazo oxime ether (1 mmol), nitrile (1 mmol), CH2Cl2 (3 mL/1 mmol), refluxed for 2 h.
b Yield corresponding to the isolated product by column chromatography.
**Ethyl 1-methoxy-2,5-dimethyl-1H-imidazole-4-carboxylate (3a)**

The title compound was prepared according to the general procedure and the product was obtained as pale yellow gum. Yield: 89% (0.201 g); $^1$H NMR (400 MHz, CDCl$_3$) δ 4.13 (q, $J = 7.1$ Hz, 2H), 3.79 (s, 3H), 1.30 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 164.93, 142.97, 138.13, 126.87, 70.23, 60.70, 12.76, 12.53, 11.52. MS (EI) m/z [M+H]$^+$: calcd. for C$_9$H$_{14}$N$_2$O$_3$: 198.2190; found: 198.2194.

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