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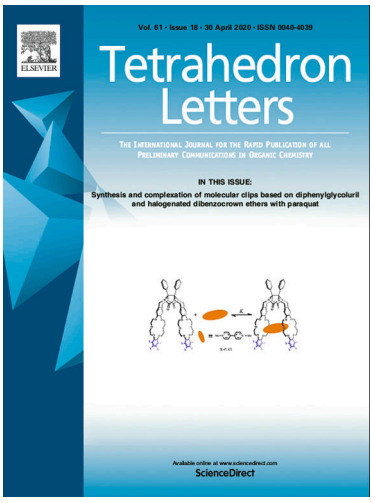


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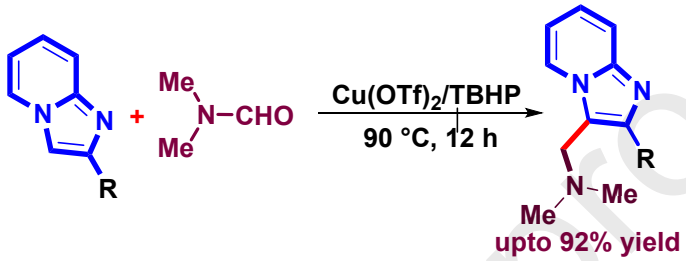

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# Aminomethylation of Imidazopyridines using *N,N*-Dimethylformamide as an Aminomethylating Reagent under Cu(II)-Catalysis

Payel Ghosh, Sadhanendu Samanta, Sumit Ghosh, Sourav Jana, and Alakananda Hajra*
[a] *Department of Chemistry; Visva-Bharati (A Central University), Santiniketan 731235, India*

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ABSTRACT

*N,N*-Dimethylformamide has been explored as an aminomethylating reagent in the functionalization of imidazopyridine under Cu(II)-catalysis. A library of aminomethylated imidazopyridines with broad functionalities was synthesized in good yields.



*N,N*-Dimethylformamide (DMF) is a readily available high boiling polar solvent. The solvent properties of DMF are attractive due to its high dielectric constant and aprotic in nature. Moreover, apart from solvent property in various reactions DMF have been explored as different building block units such as CO, CN, $NMe_2$, $CONMe_2$, Me, CHO, $CH_2$, $NH_2$ *etc* (Figure 1).[1] Recently, DMF has gained considerable attention to introduce as methylene[2] and also dimethylamino[3] groups.

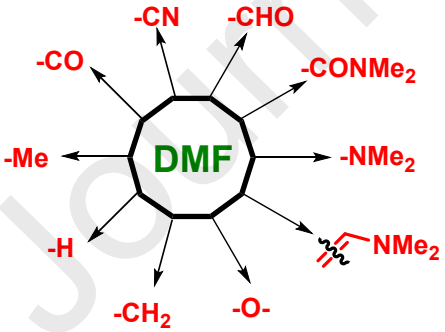



**Figure 1:** *N,N*-Dimethylformamide as building block.

Imidazo[1,2-*a*]pyridine is an important class of heterocyclic scaffold.[4] This scaffold has been found in a number of biologically active pharmaceutical products[5] and material sciences.[6] Several bioactive compounds such as necopidem (**I**), saripidem (**II**) and alpidem (**III**) work as an anxiolytic agent. Moreover, zolpidem (**IV**) is used in the treatment of insomnia and GSK812397 (**V**) is used for the treatment of HIV infection.[4,5] Many of these compounds contain 3-alkyl amine substituted imidazo[1,2-*a*]pyridine moiety as the core structure (Figure 2). The pharmacological activity of this moiety is dependent on its substituent. Therefore, there is a continuous efforts of chemist for the construction of functionalized imidazo[1,2-*a*]pyridines.[7,8]

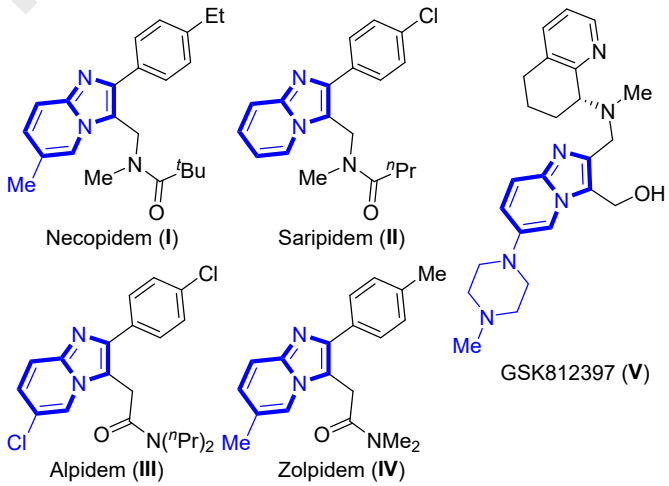
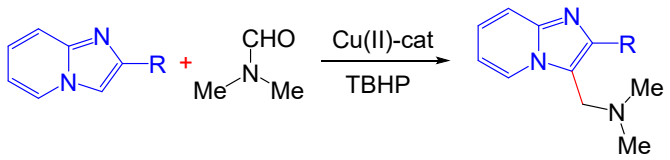



**Figure 2:** Imidazo[1,2-*a*]pyridine containing bioactive molecules.

On the other hand, amines are interesting organic compounds in synthetic and pharmaceutical chemistry.[9] Moreover, tertiary *N,N*-dimethylamines have been also used as ligands for the preparation of metallic complexes, buffers in the sequential analysis of proteins and peptides, modifiers for reversed-phase chromatography, dehydrating agent and reducing agent.[10] So, the synthesis of tertiary amines becomes an important area in pure and applied chemistry.[3,11] Thus development of easy protocol for the synthesis of tertiary amines has gained much attention from the synthetic chemists. In continuation of our research on synthesis[12] and functionalization[13] of imidazo[1,2-*a*]pyridines, herein we report a synthesis of trisubstituted amines *via* aminomethylation of imidazopyridine using DMF in presence of Cu(II)-salt and TBHP (Scheme 1). To the best of our knowledge

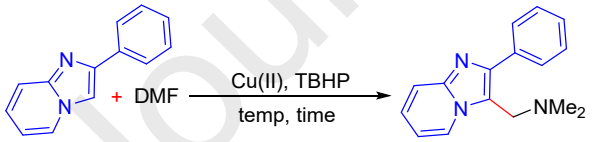
the dimethylformamide as a synthon.




**Scheme 1.** Aminomethylation of imidazopyridines.

We commenced our study reacting 2-phenylimidazo[1,2-*a*]pyridine (**1a**) with *N,N*-dimethylformamide (**2a**) in the presence of 10 mol% $Cu(OTf)_2$, and 3 equiv TBHP, and the reaction mixture was stirred at 25 °C for 5 min. Then the temperature was increased at 90 °C and stirred for 12 h (Table 1, entry 1). Interestingly, the aminomethylated product **3aa** was isolated in 29% yield after 12 h. To determine the optimal reaction conditions, the amount of oxidant was increased from 3 equiv to 6 equiv. The yield of **3aa** was improved to 81% (Table 1, entry 2). An almost similar result was obtained with 9 equiv of TBHP (Table 1, entry 3). Other common Cu salts like $CuCl_2$, $CuBr_2$, CuI and $Cu(OAc)_2.H_2O$ were employed as the catalyst, but these were not so effective like $Cu(OTf)_2$ (Table 1, entries 4-7). However, the amiomethylated product was not obtained in absence of $Cu(OTf)_2$ or TBHP (Table 1, entries 8 and 9) which implies the necessity of both in this transformation. Common Lewis acid like $FeCl_3$ and oxidant like DTBP were also tested but they did not produce any aminomethylated product (Table 1, entries 10 and 11). Further the reaction was screened with several common solvents like 1,2-DCB, xylene, DMA and $H_2O$ (Table 1, entries 12-15) in the presence of 10 equiv of DMF and all these cases the desired product was not formed. However, significant decrease of the yield was observed on decreasing the catalyst loading. Moreover increment of the catalyst loading from 10 mol% to 15 mol% did not improve yield of the reaction (Table 1, entries 16 and 17). With decreasing the reaction temperature to 80 °C, much lower yield was obtained (Table 1, entry 18). Furthermore, at higher temperature (100 °C), no observable change was noticed (Table 1, entry 19). Thus, a combination of 10 mol% $Cu(OTf)_2$, 6 equiv of TBHP at 90 °C for 12 h was found to represent the optimized reaction conditions affording 81% yield of the aminomethylated product (Table 1, entry 2).

**Table 1.** Evaluation of the reaction conditions[a,b]



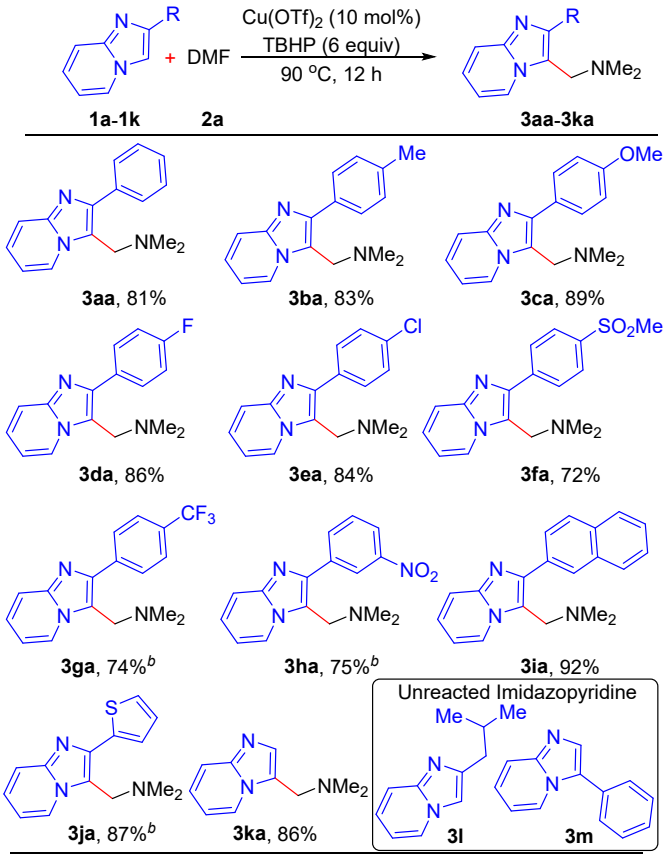

**1a** **2a** **3aa**

| entry | catalyst (mol%) | oxidant (equiv) | solvent | temp (°C) | yield (%) |
|---|---|---|---|---|---|
| 1 | $Cu(OTf)_2$ (10) | TBHP (3) | DMF | 90 | 29 |
| **2** | **$Cu(OTf)_2$ (10)** | **TBHP (6)** | **DMF** | **90** | **81** |
| 3 | $Cu(OTf)_2$ (10) | TBHP (9) | DMF | 90 | 81 |
| 4 | $CuCl_2$ (10) | TBHP (6) | DMF | 90 | 32 |
| 5 | $CuBr_2$ (10) | TBHP (6) | DMF | 90 | 37 |
| 6 | CuI(10) | TBHP (6) | DMF | 90 | 21 |
| 7 | $Cu(OAc)_2.H_2O$ (10) | TBHP (6) | DMF | 90 | nr |
| 8 | --- | TBHP (6) | DMF | 90 | nr |
| 9 | $Cu(OTf)_2$ (10) | --- | DMF | 90 | nr |
| 10 | $FeCl_3$ (10) | TBHP (6) | DMF | 90 | nr |
| 11 | $Cu(OTf)_2$ (10) | DTBP (6) | DMF | 90 | nr |
| 13 | $Cu(OTf)_2$ (10) | TBHP (6) | xylene | 90 | nr[c] |
| 14 | $Cu(OTf)_2$ (10) | TBHP (6) | DMA | 90 | nr[c] |
| 15 | $Cu(OTf)_2$ (10) | TBHP (6) | H2O | 90 | 16[c] |
| 16 | $Cu(OTf)_2$ (5) | TBHP (6) | DMF | 90 | 52 |
| 17 | $Cu(OTf)_2$ (15) | TBHP (6) | DMF | 90 | 82 |
| 18 | $Cu(OTf)_2$ (10) | TBHP (6) | DMF | 80 | 64 |
| 19 | $Cu(OTf)_2$ (10) | TBHP (6) | DMF | 100 | 80 |

[a]Reaction conditions: **1a** (0.2 mmol), $Cu(OTf)_2$ (7.2 mg, 10 mol%) in DMF (**2a**, 1.5 mL) with 6 equiv of TBHP solution (5.5-6.0 M in decane) at 25 °C for 5 min, then the temperature was increased at 90 °C and stirred for 12 h. [b]Isolated yields. [c]10 Equiv of DMF was added. nr = No reaction.

After getting the optimized reaction conditions, various substituted imidazo[1,2-*a*]pyridines were introduced to prove the general applicability of this protocol. At first, the effect of the substituent on phenyl ring of imidazopyridine was studied and the results are summarized in Table 2. Electron donating like -Me, -OMe substituted imidazopyridines gave the desired products in excellent yields (**3ba** and **3ca**). Halogen substituted imidazopyridines were also well tolerated under the present reaction conditions (**3da** and **3ea**). Interestingly commercially available drug zolimidine was also aminomethylated under the present reaction conditions with 72% yield (**3fa**). Imidazo[1,2-*a*]pyridine with strong electron-withdrawing $-CF_3$ and $-NO_2$ groups reacted well to give the corresponding products **3ga** and **3ha** in 74% and 75% yields respectively. 2-Naphthyl and heteroaryl like 2-thiophenyl substituted imidazo[1,2-*a*]pyridines also produced the desired aminomethylated products in good yields (**3ia** and **3ja**). But, 2-pyridyl substituted imidazo[1,2-*a*]pyridine produced an inseparable mixture of products. Moreover, unsubstituted imidazo[1,2-*a*]pyridine regioselectively produced 3-aminomethylated product in 86% yield (**3ka**). However, aliphatic substituted as well as C-3 substituted imidazo[1,2-*a*]pyridines (**1l** and **1m**) were unreacted under the present reaction conditions. This observation illustrated that the reaction selectively took place at the C-3 position because of being more electron rich center.

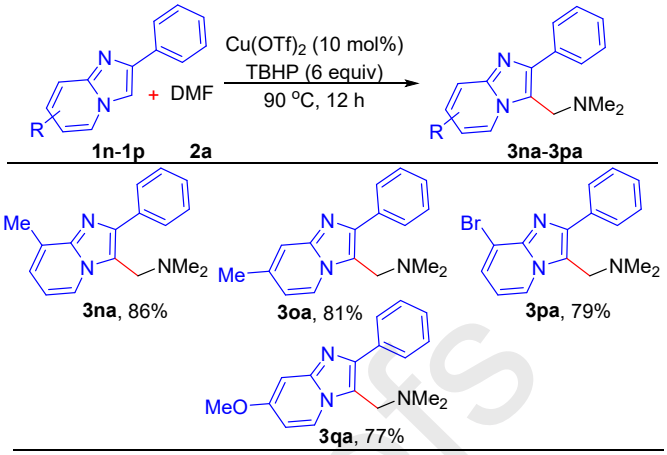
**Table 2.** Substrate scope: Variation of C-2 substituents on imidazo[1,2-*a*]pyridines[a]




[a]Reaction conditions: **1** (0.2 mmol), $Cu(OTf)_2$ (10 mol%) in DMF (**2a**, 1.5 mL) with 6 equiv of TBHP solution (5.5-6.0 M in decane) at 25 °C for 5 min, then the temperature was increased at 90 °C and stirred for 12 h. [b]Reaction time 18 h.

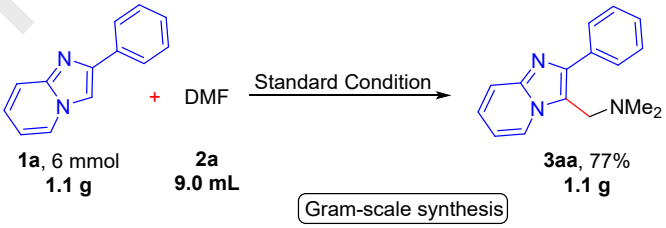
Next the effects of substituents present on the pyridine ring of imidazo[1,2-*a*]pyridine were examined and the results are summarized in Table 3. Imidazopyridines containing methyl substituent at different position of pyridine ring and bromo substituted derivative were successfully afforded the corresponding aminomethylated products with good to excellent yields (**3na**, **3oa** and **3pa**). 7-methoxy-2-phenylimidazo[1,2-*a*]pyridine (**1q**) also well tolerable for this transformation and produced 1-(7-methoxy-2-phenylimidazo[1,2-*a*]pyridin-3-yl)-N,N-dimethylmethanamine (**3qa**) in 77% yields.

imidazo[1,2-*a*]pyridine at pyridine ring[a]



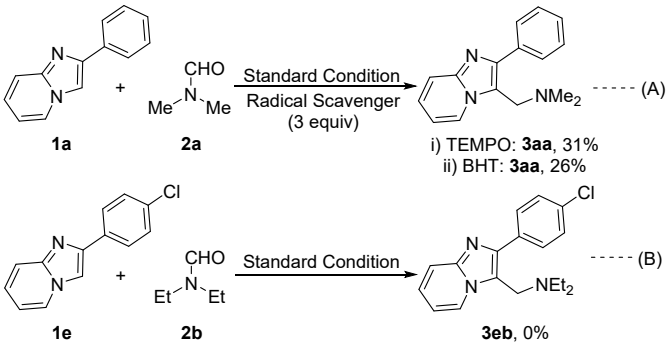

[a]Reaction conditions: **1** (0.2 mmol), $Cu(OTf)_2$ (10 mol%) in DMF (**2a**, 1.5 mL) with 6 equiv of TBHP solution (5.5-6.0 M in decane) at 25 °C for 5 min, then the temperature was increased at 90 °C and stirred for 12 h.

The gram-scale reaction was also performed to show the practical applicability of the present protocol and the result are summarized in Scheme 2. The reaction between 2-phenylimidazo[1,2-*a*]pyridine (**1a**) and *N,N*-dimethylformamide (**2a**) was carried out and the desired product, *N,N*-dimethyl-1-(2-phenylimidazo[1,2-*a*]pyridin-3-yl)methanamine was obtained in 77% yield (1.116 g, **3aa**).

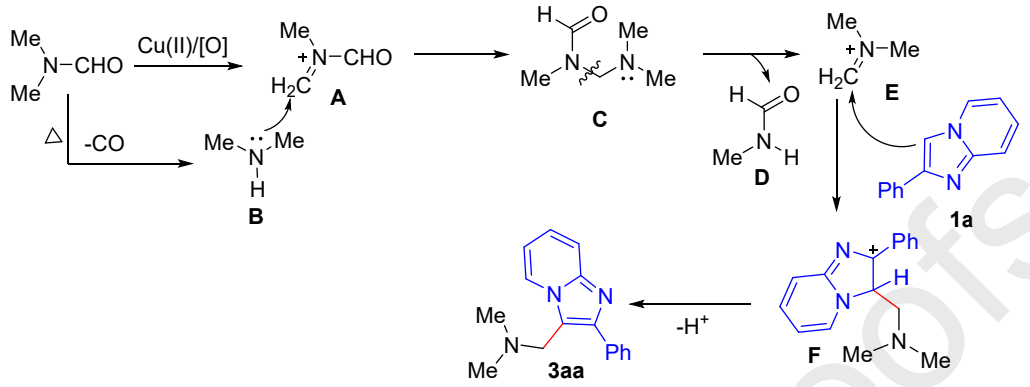



**Scheme 2.** Gram-scale reaction.

Few control experiments were performed to understand the plausible reaction mechanism (Scheme 3). At first the reactions were carried out in presence of radical scavengers such as 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and butylated hydroxytoluene (BHT). The yield of **3aa** decreased that signifies the reaction possibly proceeds through the radical pathway (Scheme 3, eq A). However, *N,N*-diethylformamide (**2b**) did not respond to this reaction (Scheme 3, eq B).



On the basis of literature reports[14] and our previous experiences,[15] the probable mechanism for this transformation is outlined in Scheme 4. In the presence of Cu(II) and oxidant, possibly DMF is oxidized to produce the reactive iminium few intermediates as proposed by Ge[3b] and Lin.[3c] Then, the aromatic electrophilic substitution occurs with electron rich imidazopyridine to form intermediate **F**. Finally, deprotonation of intermediate **F** affords the desired aminomethylated product **3aa**.




**Scheme 4.** Probable mechanistic pathway.

In summary, we have successfully explored DMF as an aminomethylating agent in the synthesis of aminomethylated imidazopyridines through Cu(II)-catalyzed coupling between DMF and imidazo[1,2-*a*]pyridine. To the best of our knowledge, this is the first report for the use of DMF as an aminomethylenating reagent in the synthesis of functionalized imidazoheterocycles. We believe that the present finding of aminomethylation using DMF will gain useful applications in pharmaceuticals and material sciences.

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