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# Copper-Catalyzed α-Methylenation of Benzylpyridines Using Dimethylacetamide as One-Carbon Source

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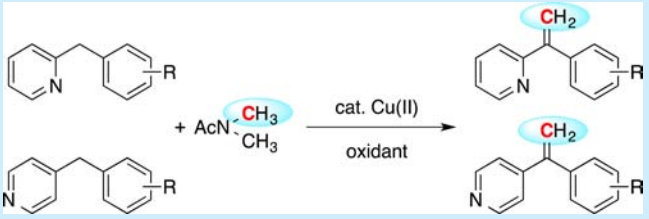
Supporting Information

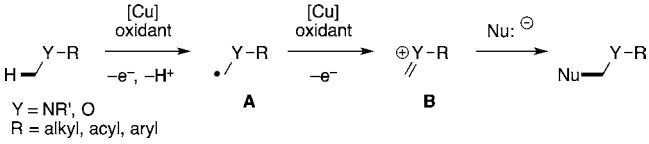
**ABSTRACT:** The direct α-methylenation of benzylpyridines was achieved using *N*,*N*-dimethylacetamide (DMA) as a one-carbon source under copper catalysis. An intermediary species was detected at an early stage, and a possible mechanism was proposed. Additionally, α-oxygenation and dimerization of benzylpyridines could also be performed efficiently.




Variously substituted pyridines can be seen in synthesized and naturally occurring bioactive compounds as well as in organic materials and ligands for transition metals.[1] Among the potential derivatives are 2-α-styrylpyridines and their analogues, which have recently attracted attention in the field of medicinal chemistry because of their unique biological properties such as inhibition of the tubulin assembly and cytotoxic activity.[2] They are also important precursors to be converted into other fine chemicals through hydroformylation and hydroaminomethylation.[3] However, synthetic approaches to such promising compounds are so far limited. Most of the currently available methods rely on the transition-metal-catalyzed cross-coupling[4] between substrates prepared through complicated multisteps using labile and/or toxic reagents or conventional condensation with low substituent tolerance. To explore further application of the class of compounds including medicinal screening, development of new, effective processes leading to them with simple starting materials by simple procedures is desired.

Meanwhile, transition-metal-catalyzed C−H functionalization reactions have recently been recognized as atom- and step-economical synthetic tools because of the needlessness of preactivation steps for substrates such as halogenation or metalation.[5,6] By using these processes, synthetic routes to various complex molecules can be simplified. Among them, copper-catalyzed $sp^3$ carbon functionalization of amines as well as ethers at the α C−H bonds has been known to be one of leading transformations with a relatively long history and wide exploration.[6] This type of reaction is often carried out in the presence of an oxidant including peroxides or molecular oxygen together with a copper catalyst. Under such oxidative conditions, radical (**A** in Scheme 1) and iminium cation (**B**) intermediates are formed via stepwise one-electron oxidations. The latter intermediate is known to react with various nucleophiles such as terminal alkynes, enols, electron-rich heteroarenes, and arylboronic acids to form a variety of oxidative coupling products.[7]

**Scheme 1. Copper-Catalyzed or Mediated α C−H Functionalization of Amines and Ethers**




As a recent intriguing example, Chang and co-workers reported that an iminium cation generated from *N*,*N*-dimethylformamide (DMF) in the presence of a stoichiometric amount of copper salt under $O_2$ couples with arylmetal reagents and ammonium iodide to form aromatic nitriles, in which a cyano carbon comes from DMF.[8] While DMF is widely recognized as a common solvent, it may also be employed as a cheap, readily available one-carbon source in synthetic reactions such as the Vilsmeier−Haack reaction.[9] *N*,*N*-Dimethylacetamide (DMA) is similarly popular as solvent to DMF. However, DMA is chemically stable compared to DMF, and therefore, the use of DMA as a one-carbon source has been less explored. In the course of our studies of transition-metal-catalyzed C−H functionalization,[10] we found that DMA effectively undergoes dehydrogenative $sp^3$ C−H/$sp^3$ C−H cross-coupling on treatment with 2-benzylpyridines under copper catalysis to give 2-α-styrylpyridine derivatives as α-methylenation products.[11] While iron-catalyzed α-methylenations of 3-substituted 2-methylquinoxalines and -quinolines have been recently reported,[12,13] these procedures could not be applied to simple pyridine systems. Moreover, other 1-(hetero)aryl-1-heteroarylmethanes also underwent methylenation with various *N*,*N*-dimethylamides to produce the corresponding 1-(hetero)aryl-1-heteroarylethenes. Besides methylenation, relevant α-oxygenation[14]

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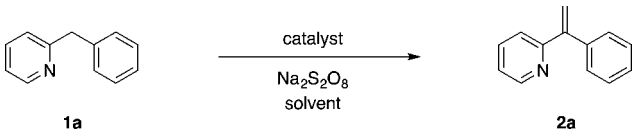
and dimerization could be realized. These new findings are described herein.

In an initial attempt, 2-benzylpyridine (**1a**) (0.5 mmol) was treated in the presence of $Cu(OAc)_2·H_2O$ (0.05 mmol) and $Na_2S_2O_8$ (1 mmol) in DMA (2.5 mL) at 120 °C for 4 h under $N_2$. As the $\alpha$-methylenation product, 2-(1-phenylethenyl)-pyridine (**2a**) was obtained selectively in 79% yield (entry 1 in Table 1). Decreasing and increasing the amount of $Na_2S_2O_8$ (0.5 and 1.5 mmol) slightly reduced the product yield (entries 2 and 3). Without the copper catalyst, the reaction did not proceed at all (entry 4). $Cu(OTf)_2$ showed high activity (entry 5), while $CuBr_2$ was less effective (entry 6). In addition, $FeCl_3·6H_2O$, which was employed for the methylenation of other substrates,[12] was found to be less effective than copper species (entry 7). Both at 140 and 90 °C, the yield of **2a** somewhat decreased (entries 8 and 9). As the methylene carbon source, DMF and *N*,*N*-dimethylpropanamide could also be employed. Thus, in these solvents, **2a** was obtained in 57 and 56% yields, respectively (entries 10 and 11). In NMP and DMSO, **2a** was not formed at all (entries 12 and 13).

**Table 1. $\alpha$-Methylenation of 2-Benzylpyridine (1a)[a]**




**1a** **2a**

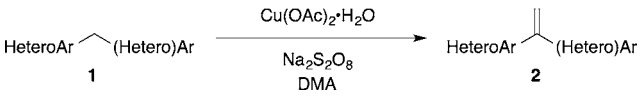
| entry | catalyst | solvent | temp (°C) | yield of **2a**[b] (%) |
|---|---|---|---|---|
| 1 | $Cu(OAc)_2·H_2O$ | DMA | 120 | 79 (70) |
| 2[c] | $Cu(OAc)_2·H_2O$ | DMA | 120 | 67 |
| 3[d] | $Cu(OAc)_2·H_2O$ | DMA | 120 | 65 |
| 4 | | DMA | 120 | 0 |
| 5 | $Cu(OTf)_2$ | DMA | 120 | 85 |
| 6 | $CuBr_2$ | DMA | 120 | 66 |
| 7 | $FeCl_3·6H_2O$ | DMA | 120 | 41 |
| 8 | $Cu(OAc)_2·H_2O$ | DMA | 140 | 60 |
| 9[e] | $Cu(OAc)_2·H_2O$ | DMA | 90 | 39 |
| 10 | $Cu(OAc)_2·H_2O$ | DMF | 120 | 57 |
| 11 | $Cu(OAc)_2·H_2O$ | $EtCONMe_2$ | 120 | 56 |
| 12 | $Cu(OAc)_2·H_2O$ | NMP | 120 | 0 |
| 13 | $Cu(OAc)_2·H_2O$ | DMSO | 120 | 0 |

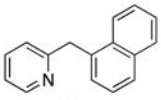
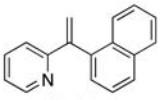
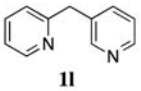
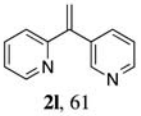
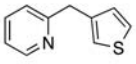
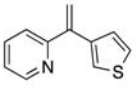
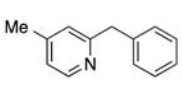
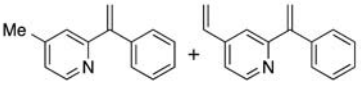
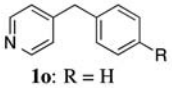
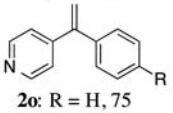
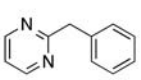
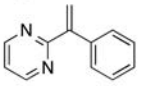
[a]Reaction conditions: **1a** (0.5 mmol), catalyst (0.05 mmol), $Na_2S_2O_8$ (1 mmol) in solvent (2.5 mL) under $N_2$ for 4 h. [b]GC yield based on the amount of **1a** used. Value in parentheses indicates yield after purification. [c]With $Na_2S_2O_8$ (0.5 mmol). [d]With $Na_2S_2O_8$ (1.5 mmol). [e]For 8 h.

Under conditions using $Cu(OAc)_2·H_2O$ and $Na_2S_2O_8$ as catalyst and oxidant, respectively, in DMA, the methylenation reactions of variously substituted 2-benzylpyridines were next examined. A series of 2-(*p*-substituted benzyl)pyridines **1b–f** underwent the reaction to afford the corresponding methylenation products **2b–f** (entries 1–5 in Table 2). The reactions of substrates possessing electron-donating groups (entries 1 and 2) gave **2** in relatively lower yields than those with electron-withdrawing groups (entries 3–5). 2-(*m*- or *o*-substituted benzyl)pyridines **1g–j** could also be employed for the reaction to give **2g–j** in 61–76% yields (entries 6–9). While 1-(1-naphthyl)-1-(2-pyridyl)methane (**1k**) and 1-(2-pyridyl)-1-(3-pyridyl)methane (**1l**) were transformed to the corresponding methylenation products **2k** and **2l** smoothly (entries 10 and 11), treatment of 1-(2-pyridyl)-1-(3-thienyl)-methane (**1l**) gave **2m** in a lower yield (entry 12). In the reaction of 2-benzyl-4-methylpyridine (**1n**), the methylenation took place not only on a benzylic *methylene* carbon but also on a *methyl* carbon to give a mixture of mono- and dimethylenation products **2n** and **2n′** (entry 13). Treatment of 2- and 4-picolines gave only trace amounts of methylenation products (not shown); the products seem to be labile under the present reaction conditions. 4-Benzylpyridines **1o** and **1p** also underwent the methylenation to give **2o** and **2p** in 75 and 56% yields, respectively (entries 14 and 15). Under the same conditions, 3-benzylpyridine was recovered almost completely (not shown). In addition to benzylpyridines, 2-benzylpyrimidine (**1q**) could be used for the reaction (entry 16).

A number of control experiments were conducted to obtain mechanistic insight for the methylenation of **1** (Scheme 2).

**Table 2. $\alpha$-Methylenation of 1-(Hetero)aryl-1-heteroarylmethanes 1[a]**




| entry | 1 | product(s), % yield[b] |
|---|---|---|
| 1 | **1b**: R = 4-Me | **2b**: R = 4-Me, 55 |
| 2 | **1c**: R = 4-OMe | **2c**: R = 4-OMe, 24 |
| 3 | **1d**: R = 4-Cl | **2d**: R = 4-Cl, 81 |
| 4 | **1e**: R = 4-$CF_3$ | **2e**: R = 4-$CF_3$, 83 |
| 5 | **1f**: R = 4-CN | **2f**: R = 4-CN, 75 |
| 6 | **1g**: R = 3-$CF_3$ | **2g**: R = 3-$CF_3$, 67 |
| 7 | **1h**: R = 2-Me | **2h**: R = 2-Me, 69 |
| 8 | **1i**: R = 2-F | **2i**: R = 2-F, 76 |
| 9 | **1j**: R = 2-Br | **2j**: R = 2-Br, 61 |
| 10 |  **1k** |  **2k**, 65 |
| 11 |  **1l** |  **2l**, 61 |
| 12 |  **1m** |  **2m**, 16 |
| 13 |  **1n** |  **2n+2n'**, 52 (4:1) |
| 14 |  **1o**: R = H |  **2o**: R = H, 75 |
| 15[c] | **1p**: R = Cl | **2p**: R = Cl, 56 |
| 16 |  **1q** |  **2q**, 65 |

[a]Reaction conditions: **1a** (0.5 mmol), $Cu(OAc)_2·H_2O$ (0.05 mmol), $Na_2S_2O_8$ (1 mmol) in DMA (2.5 mL) under $N_2$ at 120 °C for 4 h. [b]Isolated yield. [c]At 100 °C.



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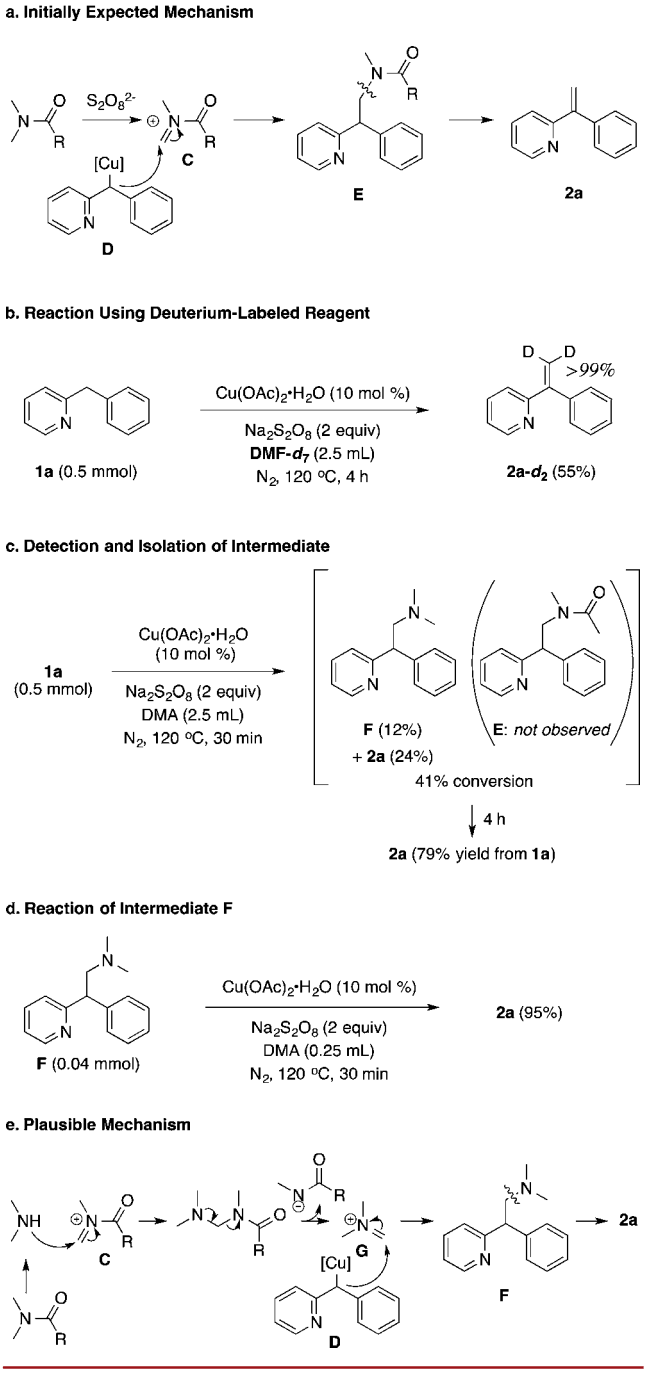
**Scheme 2. Investigation for Mechanistic Insights**

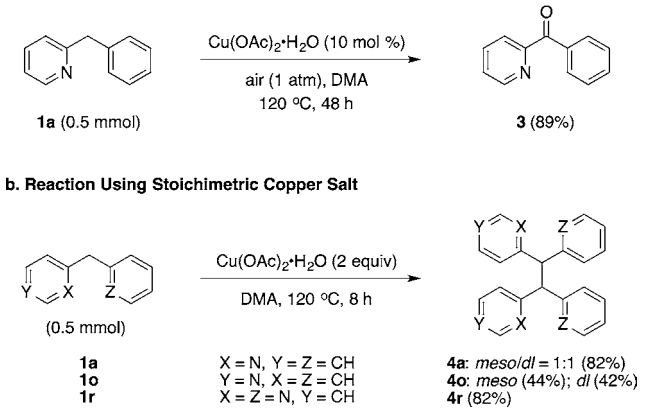



Initially, this reaction was expected to proceed via initial generation of iminium cation **C** by the oxidation with $Cu(OAc)_2·H_2O$ and $Na_2S_2O_8$, subsequent nucleophilic addition by a benzylcopper species **D** generated in situ, and final dehydroamidation[15] to form a methylenation product, as shown in Scheme 2a.

It was confirmed that the methylene unit in the produced **2** is from the *N*-methyl group of *N*,*N*-dimethylamides. Thus, the reaction of **1a** in DMF-$d_7$ gave **2a**-$d_2$ in 55% yield (Scheme 2b). In this case, partial deuteration at the $\alpha$-position of recovered **1a** (35% recovery, **1a**-$d_0$:**1a**-$d_1$:**1a**-$d_2$ = 39:49:12) was observed. This indicates that formation of **D** shown in Scheme 2a is reversible. At an early stage (30 min) of the reaction of **1a** in DMA under standard conditions, a small amount (12%) of intermediate **F**, rather than **E**, was unexpectedly detected along with **2a** (24%) by GC−MS analysis of the reaction mixture. Once formed, **F** disappeared during the progress of reaction. Fortunately, **F** could be isolated from the mixture, and the structure was unambiguously confirmed by NMR. Treatment of **F** under standard conditions gave **2a** in 95% yield (Scheme 2d). In contrast, treatment of separately prepared **E** under same conditions gave only a trace amount of **2a**, most of **E** being recovered (94%) (see the Supporting Information). These results indicate that the present reaction proceeds involving intermediary formation of **F** through nucleophilic addition of **D** to an iminium cation **G** (Scheme 2e),[16] which seems to be generated from dimethylamine and **C**.[17] Dimethylamine may be formed by hydration[18] of *N*,*N*-dimethylamides. In spite of these considerations, other possible pathways including a radical process through the coupling of **A** (Scheme 1) with 1-phenyl-1-pyridylmethyl radical cannot be excluded.

In the absence of the oxidant $Na_2S_2O_8$, **1** could be converted into other products. Treatment of **1a** (0.5 mmol) in the presence of $Cu(OAc)_2·H_2O$ (0.05 mmol) under air in DMA (2.5 mL) at 120 °C for 48 h led to oxygenation at the $\alpha$-position to produce phenyl pyridyl ketone (**3**) in 89% yield (Scheme 3a). On the other hand, the use of a stoichiometric amount of $Cu(OAc)_2·H_2O$ in the reaction of **1a** brought about exclusive formation of dimerization product **4a** in 82% yield as a mixture of diastereomers (*meso*/*dl* = 1:1) (Scheme 3b). Treatment of **1o** under same conditions gave a separable mixture of diastereomers of **4o**. Expectedly, the reaction of symmetrical **1r** gave **4r** as a single product in 82% yield.

**Scheme 3. Oxygenation and Dimerization of 1**




In summary, we have demonstrated that the copper-catalyzed $\alpha$-methylenation and $\alpha$-oxygenation as well as copper-mediated dimerization of benzylpyridines can be realized efficiently. In the methylenation, an *N*-methyl group of DMA or DMF was incorporated as the one-carbon source to produce $\alpha$-styrylpyridine derivatives, which are of interest for their unique biological properties.

## ■ ASSOCIATED CONTENT

### Supporting Information

Experimental procedures, additional results, and characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.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### Notes

The authors declare no competing financial interest.

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