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Copper-Catalyzed *N*-Methylation of Amides and *O*-Methylation of Carboxylic Acids by Using Peroxides as the Methylating Reagents

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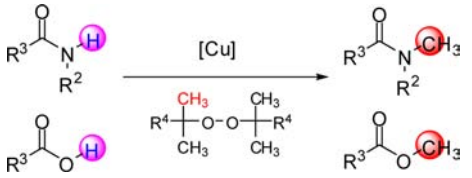
ABSTRACT



The copper-catalyzed *N*-methylation of amides and *O*-methylation of carboxylic acids by using peroxides as the methylating reagent are described. Various amides and carboxylic acids were methylated affording *N*-substituted amides and esters. Tentative mechanistic studies suggest that this reaction is likely to involve a radical process.

Amides are present in many natural organic compounds and medicinally relevant compounds.[1] *N*-Alkylation of amides is an efficient way to prepare more substituted analogues. Typical approaches to *N*-substituted amides generally involve nucleophilic substitution with alkyl halides under basic conditions[2] which suffers from the use of alkyl halides and strong bases. Recently, direct amidation of sp^3 C−H bonds has emerged as an attractive alternative for *N*-alkylation of amides.[3] This strategy is an important method for the synthesis of valuable amide derivatives without the need for prefunctionalized starting materials (Scheme 1a). However, only specific sp^3 C−H bonds such as benzylic C−H bonds were suitable for the direct amidation.

In the past decade, organic peroxides were widely used in sp^3 C−H bond activation processes, especially in the cross-dehydrogenative coupling (CDC) reactions.[4] In these reactions, organic peroxides were usually used as H-acceptors to activate C−H bonds. Herein, we report Cu-catalyzed *N*-methylation of amides in which organic peroxide serves as the methylating reagent, thus offering a new convenient pathway for the synthesis of various *N*-substituted amides (Scheme 1b). Compared with nucleophilic substitution, the new method was carried out under neutral conditions and the overalkylation of primary amides could be suppressed.

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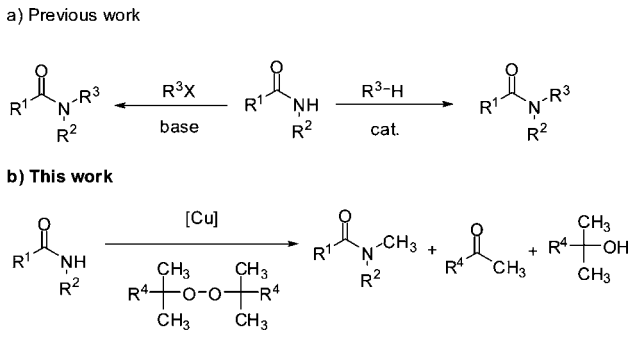
Scheme 1. *N*-Alkylation of Amides

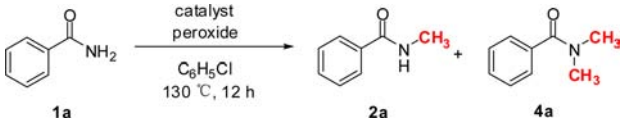


In a study of *N*-alkylation of amides with sp^3 C−H bonds using peroxide as the oxidant,[5] we occasionally observed the formation of the *N*-methylation product as an insignificant amount of byproduct. This inspired us to further investigate the reaction of benzamide (**1a**) with di-*tert*-butyl peroxide (DTBP) in chlorobenzene in the presence of CuCl. When the reaction was carried out at 130 °C for 12 h, *N*-methylbenzamide (**2a**) was obtained in 72% yield together with a trace amount of *N*,*N*-dimethylbenzamide (**4a**) (Table 1, entry 1). Obviously, the methyl group originates from the decomposition of peroxide. Actually, Li et al. reported the Pd-catalyzed directed methylation of 2-phenylpyridine through aryl C−H bond activation by using peroxides.[6] Further investigation indicated that other copper salts are also active regardless of their oxidation states but show lower catalytic efficiency than CuCl (entries 2−7). However, when $FeCl_2$ and $Pd(OAc)_2$ were used as the catalysts, no product was observed (entries 8 and 9). In addition, no *N*-methylation occurred in the absence of a Cu-catalyst (entry 10). Therefore, a Cu-catalyst is crucial for this transformation. We also found that other organic peroxides such as *tert*-butyl perbenzoate (TBPB) showed lower reactivity than DTBP (entry 11). The reaction did not proceed when *tert*-butyl hydroperoxide (TBHP) was used (entry 12). Among the peroxides tested, dicumyl peroxide (DCP) provided relatively higher yields of the product; the *N*-methylated product was isolated in 90% yield (entry 13). In addition, 2-phenylpropan-2-ol and acetophenone were simultaneously isolated in 78% and 73% yields, respectively. A lower loading of CuCl or DCP led to decreased yields (entries 14 and 15). The reaction could proceed in air, but the yield is slightly lower (entry 16). When we decreased the temperature to 110 °C, the yield was decreased to 81% (entry 17). A further decrease of the temperature to 80 °C resulted in no reaction indicating that the decomposition of peroxides requires a higher temperature (entry 18).

With the above optimized reaction conditions, a variety of primary amides were tested (Scheme 2). In all the reactions, only trace amounts of double methylation products were obtained. The reaction of 4-methylbenzamide afforded the desired product in 83% yield (**2b**). The reaction of 4-*tert*-butylbenzamide also proceeded well giving the coupling product in 81% yield (**2c**). Substrates bearing strong electron-donating substituents worked well under the standard conditions (**2d** and **2e**). Halogen substituents could be well tolerated, and 4-halobenzoamides were isolated in good yields (**2f**−**2h**). Moreover, benzamides bearing strong electron-withdrawing groups also display high activities (**2i** and **2j**). The results implied that the electronic effect is not critical for this transformation. *N*-Methylation of 2,6-difluorobenzamide afforded a slightly lower yield compared to benzamide (**2k**). The hydroxy group was well tolerated under the oxidation conditions (**2l**). Heteroaryl amides could also be transformed to *N*-methylated amides in good yields (**2m** and **2n**). Furthermore, cinnamamide was also a compatible substrate for this transformation and gave the desired product in good yield (**2o**).

We found that double methylation of primary aromatic amides to *N*,*N*-dimethylamides was hard under the optimized conditions. *N*-Methyl- and *N*-phenylbenzamide showed relatively lower activity compared to benzamide (Scheme 3, **4a** and **4b**). However, the secondary amides derived from aliphatic acids could be smoothly transformed into their corresponding products. As listed in Scheme 3, *N*-phenylacetamide worked well under the standard

Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	peroxide	yield of **2a** (%)[b]
1	CuCl	DTBP	72
2	CuBr	DTBP	29
3	CuI	DTBP	64
4	$Cu(OTf)_2$	DTBP	41
5	$Cu(OAc)_2 \cdot H_2O$	DTBP	63
6	$CuSO_4 \cdot 5H_2O$	DTBP	19
7	$CuCl_2 \cdot 2H_2O$	DTBP	57
8	$FeCl_2$	DTBP	–
9	$Pd(OAc)_2$	DTBP	–
10	–	DTBP	–
11	CuCl	TBPB	48
12	CuCl	TBHP	–
13	**CuCl**	**DCP**	**90**
14	CuCl	DCP	63[c]
15	CuCl	DCP	82[d]
16	CuCl	DCP	82[e]
17	CuCl	DCP	81[f]
18	CuCl	DCP	–[g]

[a] Reaction conditions: benzamide (0.5 mmol), peroxide (1.0 mmol), catalyst (0.05 mmol), C_6H_5Cl (1.0 mL), 130 °C, 12 h, under N_2. [b] Yield of isolated product. [c] CuCl (0.025 mmol). [d] DCP (0.75 mmol). [e] Under air. [f] The reaction was carried out at 110 °C. [g] The reaction was carried out at 80 °C.

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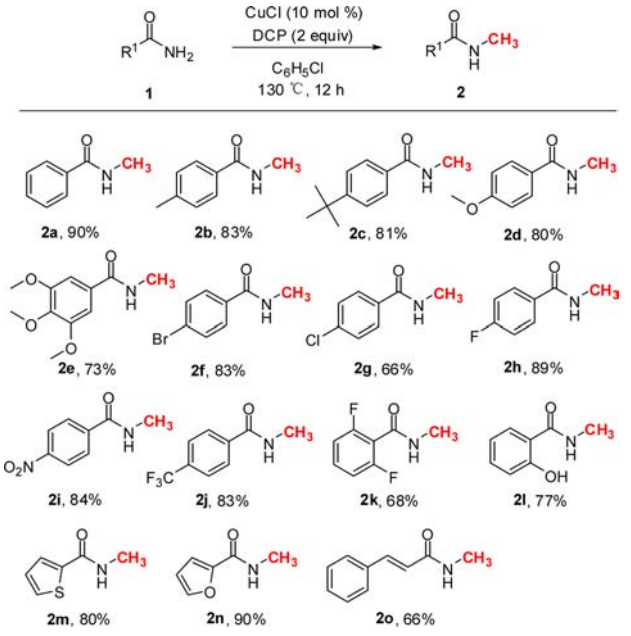
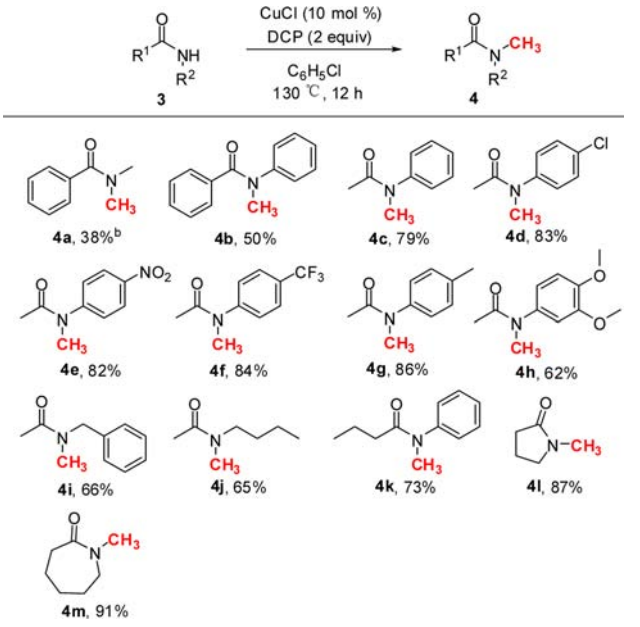
Scheme 2. *N*-Methylation of Various Primary Amides[a]



[a] Reaction conditions: **1** (0.5 mmol), DCP (1.0 mmol), CuCl (0.05 mmol), C_6H_5Cl (1.0 mL), 130 °C, 12 h, under N_2.

Scheme 3. *N*-Methylation of Various Secondary Amides[a]



[a] Reaction conditions: **3** (0.5 mmol), DCP (1.0 mmol), CuCl (0.05 mmol), C_6H_5Cl (1.0 mL), 130 °C, 12 h, under N_2. [b] 24 h.

conditions (**4c**). A halogen group such as Cl is also well tolerated, which offers further possibility for additional functionalization through cross-coupling reactions (**4d**). In general, the amides bearing both electron-donating and -withdrawing substituents could be methylated under the oxidation conditions. The strong electron-donating groups slightly decrease the yields (**4e**−**4h**). The reactions of *N*-benzyl- and *N*-butylacetamide produced the corresponding products in 66% and 65% yield, respectively (**4i** and **4j**). *N*-Phenylpropionamide could also be methylated in good yield similar to acetamides (**4k**). Moreover, the lactams could also be methylated and showed relatively higher reactivity than linear amides (**4l** and **4m**).

The present methylation reaction is not suitable for the methylation of phenols under the oxidation conditions. However, the methylation of a variety of carboxylic acids could proceed smoothly affording the corresponding esters. Both DTBP and DCP were good methylating reagents, and they reacted with various acids giving esters in similar yields. The results by using DTBP were summarized in Scheme 4. Methyl benzoate could be easily obtained in 76% yield (**6a**). Again, the halogen group is well tolerated (**6b** and **6c**). Unlike amides, strong electron-withdrawing substituents at the para-position significantly lower the yields (**6d** and **6e**). However, benzoic acids having electron-withdrawing substituents at the ortho-positions showed even higher activity compared to unsubstituted benzoic acid (**6f** and **6g**), where it seems that steric hindrance has little effect on the reaction. Electron-donating groups such as methyl, *tert*-butyl, and methoxy substituents of benzoic acids survived, and the desired products were obtained in good yields (**6h**, **6i**, and **6j**). 4-Biphenylcarboxylic acid and 1-naphthoic acid were suitable for this transformation giving the corresponding products (**6k** and **6l**) in 63% and 76% yields, respectively. A moderate yield was obtained when cinnamic acid was served as the substrate (**6m**). Most importantly, alkyl acids could also be methylated and the desired esters were isolated in good yields (**6n** and **6o**).

Esters are one of the most important intermediates in chemical and pharmaceutical industries and have been widely used in the production of valuable compounds such as polymers, fragrances, or fatty acids.[7] Esterification is one of the fundamental reactions in organic synthesis.[8] Traditionally, esters are prepared from carboxylic acids and alcohols catalyzed by Bronsted or Lewis acids. Other attractive approaches include transition-metal-catalyzed oxidative esterification of aldehydes[9] and direct C−H functionalization.[10] The present protocol provides an alternative route for the synthesis of methyl esters.

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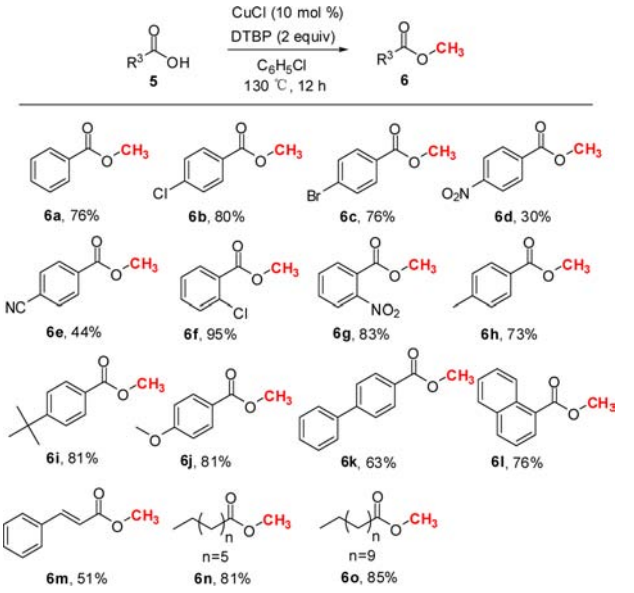
Scheme 4. *O*-Methylation of Various Carboxylic Acids[a]



[a] Reaction conditions: **5** (0.5 mmol), DTBP (1.0 mmol), CuCl (0.05 mmol), C_6H_5Cl (1.0 mL), 130 °C, 12 h, under N_2.

Although a metal insertion mechanism was proposed for the Pd-catalyzed C-methylation of 2-phenylpyridine,[6] the present *N*- and *O*-methylation was assumed to proceed via a radical mechanism. We observed that in both *N*- and *O*-methylation reactions, with the addition of the 2,2,6,6-tetramethylpiperidine-1-oxyl radical (TEMPO), a radical-trapping reagent, the formation of the desired products was completely suppressed under the standard reaction conditions and 1-methoxy-2,2,6,6-tetramethylpiperidine (**7**) was detected (Scheme 5). Furthermore, the reaction of TEMPO with DCP even without CuCl gave **7** in 87% yield. In the absence of a copper salt, 2-phenylpropan-2-ol and acetophenone could also be isolated. The results suggest that the reaction might proceed via the methyl radical. In addition, the generation of the methyl radical from DCP does not require copper.

Based on previous reports[3e,h,6,11] and the above results, a proposed reaction pathway is depicted in Scheme 6. Initially, the reaction between [Cu^I] and dialkyl peroxide would give copper(II) alkoxide **A** and alkoxy radical **B**. Metathesis of **A** in the presence of amides or carboxylic acids would then form intermediate **C** and alcohol **D**. Thermal β-methyl elimination from alkoxy radical **B** would generate ketone **E** and a methyl radical which can be quantitatively trapped by a TEMPO. Both alcohol **D** and ketone **E** have been isolated in stoichiometric amounts and determined by NMR. Finally, the methyl radical

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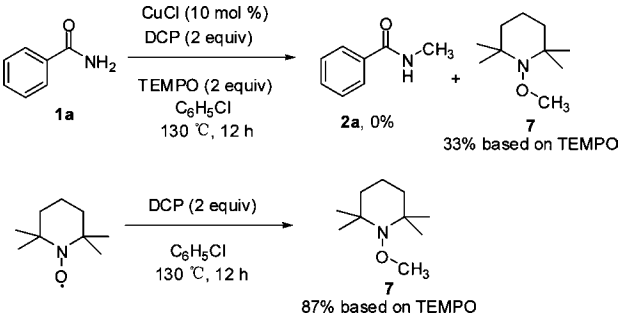
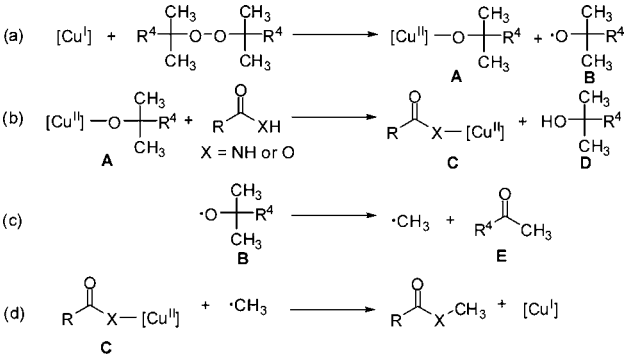
Scheme 5. Radical Trapping Experiment



Scheme 6. Proposed Mechanism



would reduce the [Cu^{II}] intermediate **C** to [Cu^I] and simultaneously afford the *N*- or *O*-methylation product.

In summary, the Cu-catalyzed *N*-methylation of amides and *O*-methylation of carboxylic acids by using peroxides as the methylating reagents have been developed. A variety of amides and carboxylic acids were suitable substrates for the reaction. This transformation provides a new and effective protocol toward the synthesis of *N*-substituted amides and esters. Tentative mechanistic studies suggest that this reaction is likely to involve a radical process. Further studies on the mechanistic details and expansion of the scope of the reaction are currently underway in our laboratory.

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Supporting Information Available. Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.