Communications

Mild and Efficient Cooper (II) Oxide-Catalyzed Acylation of Amines and Alcohols

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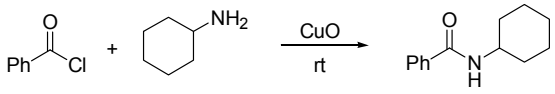
The formation of amide bonds is one of the most important process in the synthesis of pharmaceuticals[1] and agrochemicals.[2] Amide bonds are prepared by various coupling or dehydration reactions of carboxylic acids and amines,[3-7] or reactions of carboxylic acid derivatives such as acid chlorides and acid anhydrides with amines in the presence of a base.[8] These methods suffered from their own limitations for substrates with high steric hinderance.[9] Moreover, tertiary amines often used to scavenge the liberated HCl may cause epimerization during the amide bond formation with chiral acid chloride or premature deblocking of protecting groups.[10] Therefore, the development of a mild and efficient method for the synthesis of amide bonds in the absence of a base is strongly desired. In this communication, we report on a new and efficient method for the synthesis of amides from corresponding acyl chlorides and amines using a catalytic amount of cooper (II) oxide (CuO). To the best of our knowledge, this is the first demonstration of CuO-catalyzed acylation of amines and alcohols.

Initially, we chose benzoyl chloride and cyclohexylamine as model compounds. When benzoyl chloride was treated with cyclohexylamine (1 equiv) and CuO (1 equiv) in CH_3CN at room temperature for 1 h, cyclohexylbenzamide was afforded in 94% yield (Table 1, entry 1). To establish optimal reaction conditions, we carried out several experiments under various reaction conditions. The reaction turned out to be effective with a catalytic amount of CuO without diminishing the yield of the desired product (entries 2-4). The reaction performed in boiling CH_3CN made the reaction time shorten (entry 5). The reaction without CuO did not proceed efficiently (entry 6). The solvent effects on the reaction were also examined. The reactions in CH_2Cl_2, $ClCH_2CH_2Cl$, THF, Et_2O, EtOAc, and DMF afforded high yields of cyclohexylbenzamide (entries 7-12). The reactions performed in acetone and benzene gave

Table 1. Optimizing reaction conditions



Entry	CuO (equiv)	Solvent	Time (h)	Isolated yield (%)
1	1.0	CH_3CN	1	94
2	0.5	CH_3CN	2	93
3	0.25	CH_3CN	3	94
4	0.1	CH_3CN	3	94
5[a]	0.1	CH_3CN	1	94
6	0	CH_3CN	10	41
7	0.1	CH_2Cl_2	3	86
8	0.1	$ClCH_2CH_2Cl$	3	85
9	0.1	THF	3	75
10	0.1	Et_2O	3	83
11	0.1	EtOAc	3	80
12	0.1	DMF	3	86
13	0.1	acetone	3	62
14	0.1	benzene	3	58

[a]At reflux.

Table 2. Synthesis of amides from acyl chlorides and amines in the presence of CuO at room temperature

Entry	Acid chloride	Amine	Time (h)	Yield (%)[a]
1	4-MeO-Ph-C(O)Cl	cyclohexylamine	4	85
2	4-Br-Ph-C(O)Cl	cyclohexylamine	4	83
3	4-^{t}Bu-Ph-C(O)Cl	cyclohexylamine	3	85
4	4-NO_2-Ph-C(O)Cl	cyclohexylamine	2	96
5	4-NC-Ph-C(O)Cl	cyclohexylamine	3	90
6	cinnamoyl chloride	cyclohexylamine	3	82
7	oleoyl chloride	cyclohexylamine	3	89
8	octanoyl chloride	cyclohexylamine	3	85
9	^{t}BuC(O)Cl	cyclohexylamine	3	89
10	4-MeO-Ph-C(O)Cl	piperidine	4	82
11	4-MeO-Ph-C(O)Cl	aniline	5	83
12	^{t}BuC(O)Cl	piperidine	3	81
13	^{t}BuC(O)Cl	aniline	4	90
14	^{t}BuC(O)Cl	^{t}BuNH$_2$	7	62
15[b]	^{t}BuC(O)Cl	^{t}BuNH$_2$	3	85
16	Fmoc-Ala-Cl	Leu-OMe	5	83
17	Fmoc-Phg-Cl	Phe-OMe	6	85

[a]Isolated yield. [b]The reaction was carried out in boiling CH_3CN.

Table 3. Synthesis of esters from acyl chlorides and alcohols in the presence of CuO at room temperature

Entry	Acid chloride	Alcohol	Time (h)	Yield of ester[a] (%)
1	Ph-C(O)Cl	^{n}BuOH	6	84
2	Ph-C(O)Cl	cyclohexanol	8	78
3	4-MeO-Ph-C(O)Cl	cyclohexanol	12	73
4	4-NO_2-Ph-C(O)Cl	cyclohexanol	5	85
5	cinnamoyl chloride	cyclohexanol	9	79
6	oleoyl chloride	cyclohexanol	9	78
7	Ph-C(O)Cl	(+)-menthol	8	81
8	4-NO_2-Ph-C(O)Cl	(+)-menthol	4	87
9	Ph-C(O)Cl	phenol	8	81
10	4-NO_2-Ph-C(O)Cl	phenol	5	88
11	Ph-C(O)Cl	^{t}BuOH	12	52
12	4-NO_2-Ph-C(O)Cl	^{t}BuOH	12	77

[a]Isolated yield.

somewhat lower yields (entries 13-14). These findings led us to conclude that the reaction conditions were optimal when the reaction was performed in the presence of CuO (0.1 equiv) in CH_3CN at room temperature.

We applied the optimal reaction conditions to preparing a wide range of amides. The results are presented in Table 2. The reaction shows the generality for a wide range of acyl chlorides and amines. Aromatic and aliphatic acyl chlorides afforded the corresponding amides in high isolated yields. Compared with electron-rich aromatic acyl chlorides, electron-deficient aromatic acyl chlorides gave the products in higher yields (entries 1-5). The reaction with aliphatic acyl chlorides also proceeded smoothly at room temperature (entries 6-9). It is noteworthy that the carbon-carbon double bond remained intact under conditions. The reaction performed under basic conditions led to a double bond isomerization product.[11] The reaction with a secondary amine worked well under the same conditions (entry 10). The reaction with less nucleophilic aniline also afforded the amide in high yield (entry 11). Sterically hindered acyl chlorides such as pivaloyl chloride were also converted smoothly into the corresponding amides in high yields (entries 12-13). The reaction of pivaloyl chloride with a sterically hindered amine, $^{t}BuNH_2$, required high temperature to get high yield of the amide (entries 14-15). The synthesis of peptides employing Fmoc-amino acid chlorides in the presence of CuO produced the corresponding peptides in high yields (entries 16-17). On the base of ^{1}H NMR analysis of the reaction mixture, there was no sign of epimerization or deblocking of the Fmoc group under the reaction conditions.[12]

Formation of ester is valuable in organic and biological chemistry.[13] Therefore, we expanded this new protocol to the synthesis of esters from acid chlorides and alcohols.[14] As expected, primary and secondary alcohols worked well with aromatic and aliphatic acyl chlorides affording the corresponding esters in high yields (Table 3). The reaction with a sterically hindered tertiary alcohol afforded relatively lower yields (entry 11). An acyl chloride with an electron-withdrawing group gave a higher yield of the amide (entry 12).

In conclusion, we have developed a simple, mild and efficient catalytic method for synthesizing amides and esters from acyl chlorides. The method shows the generality for a wide range of substrates including less necleophilic and sterically hindered amines and alcohols.

General procedure: To a suspension of CuO (16 mg, 0.20 mmol) and benzoyl chloride (0.26 mL, 2.0 mmol) in CH_3CN (2 mL) was added cyclohexylamine (0.23 mL, 2.0 mmol) dropwise for 5 min at room temperature under argon. The reaction mixture was stirred for 3 h at room temperature. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic layer was dried over anhydrous $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure. The residue was purified with column chromatography on silica gel (hexanes/EtOAc, 2 : 1) to give cyclohexylbenzamide (0.38 g, 94%).

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