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Indium-catalyzed reaction for the synthesis of carbamates and carbonates: selective protection of amino groups

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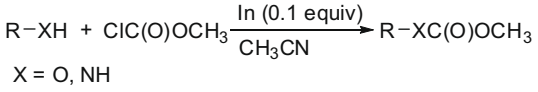
ABSTRACT

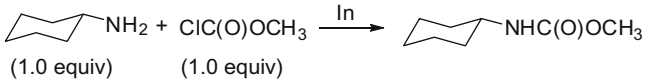
We developed a simple, efficient, and selective method for preparing organic carbamates and carbonates using a catalytic amount of indium. A wide range of carbamates and carbonates were synthesized in high yields. The method is also applicable to the selective protection of amino groups under mild conditions.

Organic carbamates and carbonates play an important role in organic synthesis. They have been used as protecting groups of amines and alcohols,[1] respectively, or as intermediates[2] in organic synthesis. In addition, the carbamates and carbonates are frequently encountered subunits of biologically active compounds in pharmaceuticals and agrochemicals.[3] Accordingly, simple and efficient methods for the synthesis of carbamates and carbonates are of great interest. A number of methods have been employed for preparing carbamates and carbonates including the Hofmann rearrangement of amides,[4] the reductive carbonylation of nitroaromatics,[5] the carbonylation of amines,[6] the reaction of alcohols with isocyanate,[7] and the carbon dioxide alkylation.[8] Although use of phosgene[9] or phosgene derivatives,[10] however, is generally regarded as the common methods for preparing carbamates and carbonates, they have some drawbacks in terms of availability, reactivity, selectivity, and difficulty in purification of the product. Alkyl chloroformates,[1,11] which are readily available, are the most frequently used reagents for the preparation of carbamates and carbonates. However, these reagents also have some drawbacks: a large excess of a base and a long reaction time are required to attain a high level of efficiency of the reaction. The reactions using excess reagents are not suitable for the synthesis of poly-functionalized molecules in which the chemoselectivity is critical. The most



Scheme 1.

Table 1
Reaction of cyclohexylamine with methyl chloroformate in the presence of In



Entry	In (equiv)	Solvent	Temp	Time (h)	Isolated yield (%)
1	1.0	CH_3CN	rt	5	89
2	0.5	CH_3CN	rt	7	88
3	0.1	*CH_3CN*	*rt*	10	90
4	0.1	CH_3CN	Reflux	3	92
5	0	CH_3CN	rt	10	40
6[a]	1.0	CH_3CN	rt	5	37
7	0.1	CH_2Cl_2	rt	10	82
8	0.1	Et_2O	rt	10	83
9	0.1	THF	rt	10	87
10	0.1	EtOAc	rt	10	85
11	0.1	DMF	rt	10	90
12	0.1	Acetone	rt	10	70
13	0.1	CH_3CN:H_2O (9:1)	rt	10	84

[a] $InCl_3$ was used instead of In.

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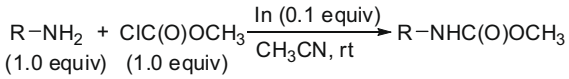
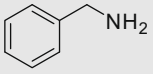
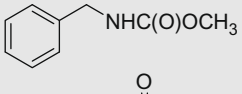
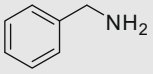
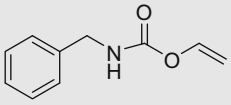
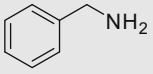
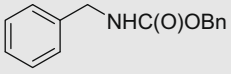
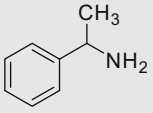
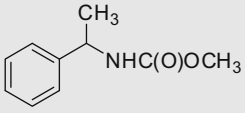
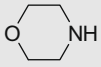
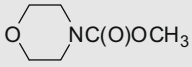
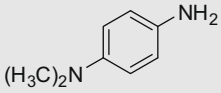
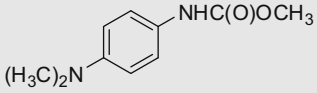
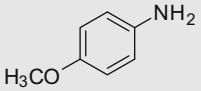
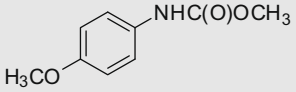
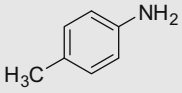
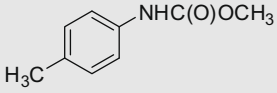
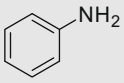
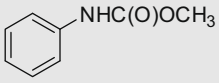
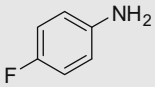
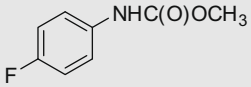
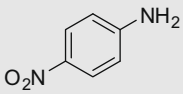
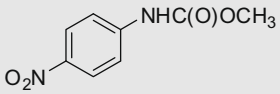
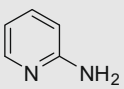
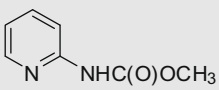
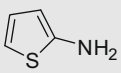
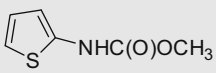
Table 2
Synthesis of carbamates from amines in the presence of In



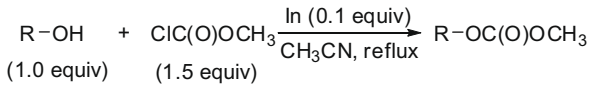
Entry	Amine	Product	Time (h)	Isolated yield (%)
1	$CH_3(CH_2)_5NH_2$	$CH_3(CH_2)_5NHC(O)CH_3$	7	91
2[a]	$H_2N(CH_2)_6NH_2$	$H_3CO(O)CHN(CH_2)_6NHC(O)CH_3$	8	89
3			8	86
4[b]			8	87
5[c]			8	90
6			10	83
7			10	86
8			10	84
9			7	91
10			10	84
11			10	82
12			10	82
13			10	81
14			12	77
15			10	73
16			10	81

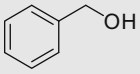
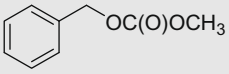
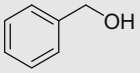
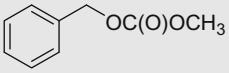
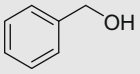
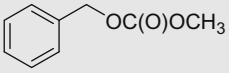
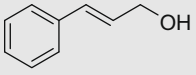
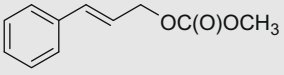
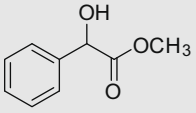
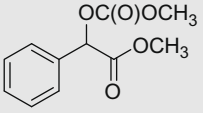
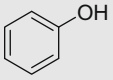
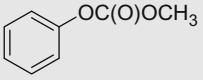
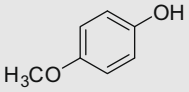
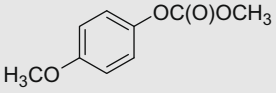
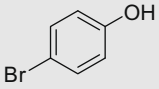
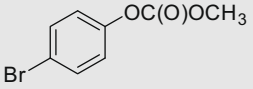
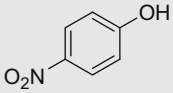
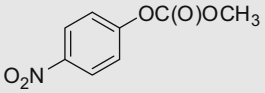
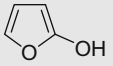
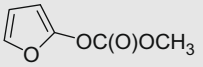
[a] 2.0 equiv of methyl chloroformate and 0.2 equiv of In were used.
[b] Vinyl chlorocarbonate was used.
[c] Benzyl chlorocarbonate was used.

promising method for preparing carbamates and carbonates is using a catalytic promoter.[12]

Recently, indium-mediated reactions have gained considerable attention because of its high reactivity and unique properties including non-toxicity and inertness toward air and water.[13] Moreover, pretreatment is unnecessary to activate indium metal. These inherited merits of indium prompted us to investigate indium-mediated reactions.[14] Herein we report a simple, efficient, and selective method for preparing organic carbamates and carbonates using a catalytic amount of indium (Scheme 1).

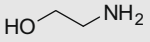
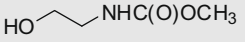
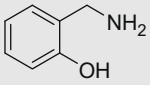
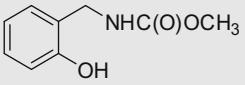
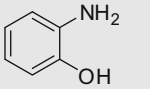
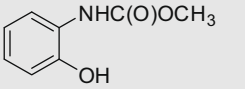
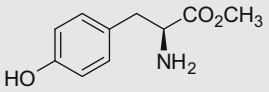
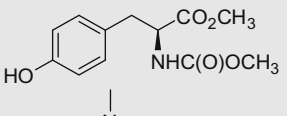
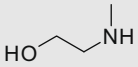
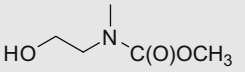
Table 3
Synthesis of carbonates from alcohols in the presence of In



Entry	Alcohol	Product	Time (h)	Isolated yield (%)
1[a]			14	13
2			12	80
3[b]			8	83
4	$CH_3(CH_2)_6CH_2OH$	$CH_3(CH_2)_6CH_2OC(O)OCH_3$	10	85
5			10	82
6			15	79
7			14	81
8			12	83
9			12	82
10			16	72
11			14	80
12	^{t}Bu–OH	^{t}Bu–OC(O)OCH$_3$	24	41
13[c]	^{t}Bu–OH	^{t}Bu–OC(O)OCH$_3$	14	70

[a] At room temperature.
[b] The reaction was carried out with 1.0 equiv of In.
[c] In DMF at 120 °C.

Table 4
Chemoselective protection of amino groups with methyl chloroformate at room temperature in the presence of In (0.1 equiv)

Entry	Substrate	Product	Time (h)	Isolated yield (%)
1			10	87
2			10	91
3			10	89
4			12	86
5			10	85

We started our studies with the reaction of methyl chloroformate (1.0 equiv) with cyclohexylamine (1.0 equiv) in the presence of indium (1.0 equiv) at room temperature for examining the feasibility of the reaction. The reaction proceeded smoothly affording the corresponding carbamate in 89% yield (Table 1, entry 1). A number of experiments were attempted with variations in equivalents of indium and reaction temperatures. The amount of indium powder could be reduced to 0.1 equiv without decreasing the yield of the carbamate, implying that indium plays a role as a catalytic promoter in the reaction (entry 3). The reaction went to completion in 3 h in boiling CH_3CN (entry 4). A blank experiment was performed under the same reaction conditions (entry 3) except with the absence of In, resulting in incompletion of the reaction with a low yield of the amide (entry 5). $InCl_3$ was not as efficient as indium metal (entry 6). The solvent effects on the reaction were also investigated. The reaction could be carried out in common organic solvents affording the carbamate in good yields (entries 7–12). The reaction proceeded even in aqueous CH_3CN without affecting the yield of the carbamate (entry 13).

Structurally diverse amines were subjected to the optimal reaction conditions. The results are summarized in Table 2. The reaction shows the generality for a wide range of amines. Aliphatic and aromatic amines gave the corresponding carbamates in good to high isolated yields. As expected, the reaction with a primary amine proceeded smoothly affording the carbamate in high yield (entry 1). A primary diamine was also converted into the corresponding dicarbamate without cyclic urea formation (entry 2). When vinyl or benzyl chloroformate was treated with benzylamine in the presence of indium, the corresponding carbamates were obtained in high yields (entries 4 and 5). There was no discernable difference between primary and secondary amines in terms of efficiency (entries 6–8). Reactions with less reactive aromatic amines than aliphatic amines produced the corresponding carbamates in good yields (entries 9–13). In the case of an aromatic amine having a strongly electron-withdrawing group, somewhat lower yield of the product was afforded (entry 14). Heteroaromatic amines such as pyridine-2-amine and thiophen-2-amine were also converted into the corresponding carbamates in good yields (entries 15 and 16).

We applied the reaction to the synthesis of carbonates from alcohols. The results are presented in Table 3. The reaction was sluggish at room temperature (entry 1). However, when the reaction was carried out in boiling CH_3CN, the corresponding carbonate was formed in high yield (entry 2). Employing a stoichiometric amount of indium did not improve the yield of the product (entry 3). Structurally diverse alcohols were subjected to the present reaction conditions. A wide range of alcohols were converted efficiently into the corresponding carbonates (entries 4–11). It appears that the steric bulkiness of substrates has a dramatic effect on the rate of the reaction. In the case of sterically hindered tertiary alcohol, the reaction did not go to completion, and only 41% yield of the carbonate was obtained even after a prolonged reaction time (entry 12). The reaction required heating to 120 °C in DMF to achieve the acceptable rate and efficiency of reaction (entry 13).

Finally, we applied our process to the selective protection of amino functional groups in amino alcohols (Table 4). The reaction with amino alcohols proceeded smoothly without forming either the carbonates or the cyclic carbamates, affording high yields of amino group protected products (entries 1–5). These results demonstrate that the present method might be very useful for the selective protection of amino groups in poly-functionalized molecules in a multi-step synthesis.

In conclusion, we have developed a simple, efficient, and selective method for synthesizing carbamates and carbonates from amines and alcohols, respectively. The method shows the generality for a wide range of sterically diverse amines and alcohols. The method is also applicable to the selective protection of amino groups under mild conditions.

Typical experimental procedure: A solution of L-tyrosine methyl ester (390 mg, 2.0 mmol), methyl chloroformate (155 μL, 2.0 mmol), indium powder (23 mg, 0.2 mmol) in CH_3CN (5 mL) was stirred at room temperature under argon for 12 h. After evaporation of volatiles, the residue was diluted with CH_2Cl_2 (10 mL) and washed with saturated $NaHCO_3$. The organic layer was dried over anhydrous $MgSO_4$. After filtration, the solvent was removed, and the residue was purified with column chromatography on silica gel (hexanes/EtOAc, 5:1) to give 435 mg (86%) of *N*-methoxycarbonyl-L-tyrosine methyl ester.[12c] ^1H NMR ($CDCl_3$) δ 3.10 (m, 2H), 3.75 (s, 3H), 4.20 (s, 3H), 4.74 (s, 1H), 5.20 (m, 1H), 6.90 (s, 1H), 7.01–7.50 (m, 4H); $[\alpha]_D^{25}$ −5.9 (*c* 1.0, $CHCl_3$).

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