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Indium-mediated mild and facile method for the synthesis of amides

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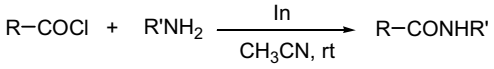
Abstract—Indium-mediated coupling reactions of acyl chlorides and amines for the synthesis of amide bonds are described. The reaction afforded high yields of the desired amides under mild and neutral conditions, and it was applicable also to the preparation of peptides without epimerization.

Amide bond formation can be accomplished by the reaction of carboxylic acids and amines in the presence of coupling reagents.[1] In the case of substrates having steric hindrance or low reactivity, however, the coupling reactions are encumbered.[2] Epimerization is also a serious problem in peptide synthesis with coupling reagents.[3] Therefore, there still is a great demand for a method using acyl chlorides for the synthesis of amide bonds.[3,4] The preparation of amides with acyl chlorides is commonly carried out in the presence of tertiary amines, but the use of amines causes problems in peptide synthesis such as epimerization or premature deblocking of protecting groups.[5] In this context, the development of a facile method for the synthesis of amide bonds under mild and neutral conditions is strongly desired.

Indium metal has recently drawn increasing attention owing to its unique properties such as low toxicity and stability in water and air compared with other metals.[6] Our interests in utilizing indium metal in organic synthesis have prompted us to investigate indium-promoted reactions for the preparation of amides.[7] Herein we report a mild and convenient methodology for the formation of amide bonds from acyl chlorides and amines by using indium metal as a promoter under neutral conditions (Scheme 1).

The reaction of *p*-anisoyl chloride with cyclohexylamine in the presence of indium metal at room temperature



Scheme 1.

resulted in the formation of the corresponding amide in 82% yield (Table 1, entry 1). The reactivity of acyl chlorides under the present conditions was examined and the results are summarized in Table 1. The acyl chloride reacted smoothly with an aliphatic secondary or aryl amine to afford the amides in high yields (Table 1, entries 2 and 3). Aromatic acyl chlorides with electron-withdrawing groups gave higher yields of the amides compared to those with electron-donating groups (Table 1, entry 1 vs 6). The reaction proceeded smoothly at room temperature. And there was no need to activate indium metal with pretreatment.[8] The commercially available indium metal was active enough to accomplish the reactions. The reaction could be carried out in aqueous acetonitrile (10% (v/v) H_2O) giving a 91% yield of the amide (Table 1, entry 5) but the reaction performed in water alone gave a mixture of an equal amount of the amide and carboxylic acid. It showed that anhydrous conditions are not essential for the present reaction.

With aliphatic acyl chlorides the reaction also proceeded smoothly giving high yields of the amides (Table 1, entries 7–17). It is noteworthy that carbon–carbon double bonds remained intact under the reaction conditions while the reaction performed under basic reaction conditions led to double bond isomerized products

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* Corresponding author. Present address: Department of Chemistry, Yonsei University, Wonju 220-710, South Korea. Tel.: +82-33-760-2261; fax: +82-33-760-2182; e-mail: dojang@dragon.yonsei.ac.kr

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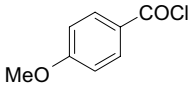
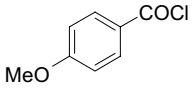
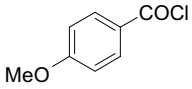
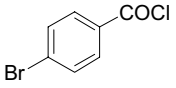
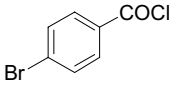
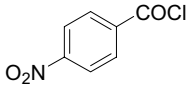
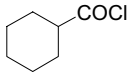
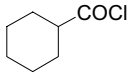
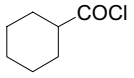
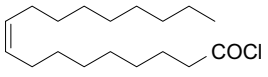
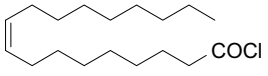
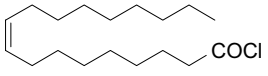
Table 1. Preparation of amides from acyl chlorides and amines by using indium metal at room temperature[a]

Entry	Acyl chloride	Amine	Time (h)	Yield (%)[b]
1		*c*-Hexylamine	4	82
2		Piperidine	4	80
3		Aniline	6	77
4		*c*-Hexylamine	3	87
5		*c*-Hexylamine	3	91[c]
6		*c*-Hexylamine	2	93
7		*c*-Hexylamine	3	80
8		Piperidine	3	84
9		Aniline	4	81
10		*c*-Hexylamine	3	90
11		Piperidine	3	95
12		Aniline	4	91
13	^{t}Bu-COCl	*c*-Hexylamine	3	86
14	^{t}Bu-COCl	Piperidine	3	85
15	^{t}Bu-COCl	Aniline	4	94
16	^{t}Bu-COCl	^{t}BuNH$_2$	6	48
17	^{t}Bu-COCl	^{t}BuNH$_2$	3	82[d]

[a] All the products were reported previously in the literature.
[b] Isolated yields.
[c] The reaction was carried out in aqueous media (H_2O:CH_3CN, 1:9).
[d] The reaction was performed at 40 °C.

(Table 1, entries 10–12).[9] The reaction proceeded efficiently even with highly sterically hindered pivaloyl chloride in high yields of the amides at ambient temperature (Table 1, entries 13–15). The reaction of pivaloyl chloride with sterically hindered ^{t}BuNH$_2$ required higher temperature (40 °C) to get the high yield of the amide (Table 1, entries 16 and 17). The same reaction except using zinc metal instead of indium metal was performed giving the amide in 43% yield.

With a mild and efficient method for the synthesis of amide bonds from acid chlorides and amines in our hands, we tested to see if it was applicable to the preparation of the peptide bonds with amino acids without epimerization during the reaction. The reaction of Fmoc-Ala-Cl with Leu-OMe in the presence of In at room temperature afforded the dipeptide, Fmoc-Ala-Leu-OMe in 81% yield (Table 2, entry 1). The reaction with more base sensitive Fmoc-Phg-Cl and Fmoc-D-Phg-Cl produced the corresponding dipeptides in high yields (Table 2, entries 2 and 3). There was no sign of epimerization or deblocking of the Fmoc group under the reaction conditions based on the analysis of the reaction mixture with NMR and HPLC analysis.

Table 2. Preparation of dipeptides from α-amino acids[a]

Entry	Acyl halide	Peptide	Time (h)	Yield (%)[b]
1	Fmoc-Ala-Cl	Leu-OMe	6	81
2	Fmoc-Phg-Cl	Phe-OMe	10	85
3	Fmoc-D-Phg-Cl	Phe-OMe	9	88
4	Fmoc-Phe-Cl	Leu-OMe	9	85
5	Fmoc-Pro-Cl	Pro-OMe	12	75

[a] All the products were reported previously in the literature.
[b] Isolated yields.

In summary, we have demonstrated a novel and facile method for the synthesis of amides by using indium metal as a promoter under mild and neutral reaction conditions. The reaction was used for the preparation of peptides with no epimerization and deblocking protecting groups detected during the reaction. The advantages of the present method include high yields of products, simple experimental procedure, nontoxicity of the reagent, no need for dry solvent and no pretreatment of metal promoter.

General procedure for preparation of amides (representive example): To a mixture of Fmoc-Ala-Cl (93 mg, 0.28 mmol) and In (32 mg, 0.28 mmol) in CH_3CN (1 mL) was added a solution of Leu-OMe (41 mg, 0.28 mmol) in CH_3CN (1 mL) under stirring at 20 °C. The reaction mixture was stirred for 6 h (monitored by TLC), filtered through a sintered glass packed with Celite. The solution was washed with water and dried over anhydrous $MgSO_4$. Evaporation of the solvent produced the crude product, which was purified with flash column chromatography on silica gel (CH_2Cl_2/MeOH, 12:1) to furnish the peptide Fmoc-Ala-Leu-OMe (100 mg, 81%), which is in full agreement with physical and spectral data of authentic sample. Fmoc-Ala-Leu-OMe: mp 123–126 °C (lit.[8a] 125–127 °C); $[\alpha]_D^{25}$ −25.2° (*c* 1, $CHCl_3$) (lit.[8a] $[\alpha]_D^{25}$ −28.6° (*c* 1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.91 (s, 6H), 1.41 (d, $J = 2.3$ Hz, 3H), 1.54 (m, 1H), 1.64 (m, 2H), 3.72 (s, 3H), 4.22 (t, $J = 2.4$ Hz, 1H), 4.29 (t, $J = 2.2$ Hz, 1H), 4.40 (d, $J = 2.3$ Hz, 2H), 4.61 (q, $J = 1.6$ Hz, 1H), 5.43 (br, 1H), 6.38 (br, 1H), 7.27–7.79 (m, 8H); ^{13}C NMR ($CDCl_3$) δ 18.8, 22.1, 23.0, 25.1, 41.8, 47.4, 51.1, 52.5, 67.4, 120.2, 125.3, 127.3, 128.0, 141.5, 144.0, 156.1, 172.2, 173.3.

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