Aluminum Chloride-Promoted Transamidation Reactions

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Summary: Aluminum chloride–amine complexes promote transamidation reactions of primary, secondary, and tertiary amides. Combining this method with the known activating effect of an electron-withdrawing group on the amide nitrogen allows transamidation reactions with hindered and aromatic amines.

Amide exchange (transamidation) represents a useful transformation in synthetic organic chemistry. Direct transamidation is, however, essentially limited to primary amines and lower carboxamides (e.g., DMF), and long reaction times are generally necessary.[1,2] The fusion of ammonium salts with amides is reported[3] to lead to rapid transamidation in high yield, but the method is only applicable to primary amines and amides. The base-catalyzed reaction of primary anilines with DMF has also been described.[4] In addition, a number of two-step methods have been developed which involve activation of primary and secondary carboxamides by the introduction of *N*-nitroso,[5] *N*-nitro,[6] *N*-(trifluoromethanesulfonyl),[7] or *N*-Boc[8,9] substituents, and in general, good results have been obtained in the reactions of these derivatives with primary, or in certain cases, nucleophilic secondary amines.

In the light of previous reports that acetamide–boron fluoride complex is a good acetylating agent for alcohols and amines[10] and that aluminum chloride ($AlCl_3$) activates lactones[11] and *N*-acyllactams[12] toward nucleophilic attack by amines, it seemed of interest to examine the activation of amides by complexation with this Lewis acid. The results obtained by reaction of a variety of primary and secondary amines with various acetamides and benzamides are shown in Table 1.[13] In general, as might be expected, primary amines gave higher yields than secondary amines (Table 1, entries 1 and 2, 3 and 4, 14 and 15), although excellent yields were obtained in reactions between aliphatic secondary amines and secondary amides, as shown by entries 9–11 and 13 in Table 1. It is noteworthy that in contrast with the known methods, better yields were obtained with secondary than with primary amides (Table 1, entries 1 and 5, 2 and 9); even unactivated tertiary amides such as *N*,*N*-dimethylacetamide reacted with benzylamine (Table 1, entry 19). It is also apparent that the benzoyl group is more difficult to transfer than the acetyl group (Table 1, entries 5 and 14, 9 and 15, 12 and 16), in accordance with the reactivity observed for *N*-acyllactams.[12] No reaction occurred in the case of aromatic or sterically hindered amines (Table 1, entries 6–8) or with amides bearing bulky substituents (Table 1, entries 17 and 18).

In an effort to develop a more general transamidation method, we investigated the reactivity of *N*-tosyl-, *N*-benzoyl-, and *N*-pivaloylamides toward $AlCl_3$–amine complexes (Table 2). The effectiveness of this double activation is illustrated by a comparison of entries 9 and 20 and 11 and 21 of Tables 1 and 2, which show that much milder reaction conditions are needed. The *N*-

Table 1. Transamidation of Unactivated Amides

entry	amide	amine	$AlCl_3$ (mol equiv)	time (h at 90 °C)	yield[a] (%)
1	CH_3CONH_2	$PhCH_2NH_2$	1.3	14	67
2	CH_3CONH_2	$PhCH_2NHCH_3$	1.3	17.5	28
3	$PhCONH_2$	$PhCH_2NH_2$	2.3	24	21
4	$PhCONH_2$	$PhCH_2NHCH_3$	2.3	24	traces
5	$CH_3CONHCH_3$	$PhCH_2NH_2$	1.3	3.5	97
6	$CH_3CONHCH_3$	*t*-$BuNH_2$	2.3	24	0
7	$CH_3CONHCH_3$	$PhNH_2$	2.3	27	0
8	$CH_3CONHCH_3$	$PhNHCH_3$	2.3	21	0
9	$CH_3CONHCH_3$	$PhCH_2NHCH_3$	1.3	3.5	97
10	$CH_3CONHCH_3$	THIQ[b]	1.3	3	95
11	$CH_3CONHCH_3$	Et_2NH	1.3	20	92
12	$CH_3CONHPh$	$PhCH_2NH_2$	1.3	16	98
13	$CH_3CONHPh$	$PhCH_2NHCH_3$	1.3	18.5	85
14	$PhCONHCH_3$	$PhCH_2NH_2$	2.3	15	55
15	$PhCONHCH_3$	$PhCH_2NHCH_3$	2.3	24.5	7
16	PhCONHPh	$PhCH_2NH_2$	2.3	5	24
17	CH_3CONH-*t*-Bu	$PhCH_2NH_2$	2.3	18.5	0
18	*t*-$BuCONHCH_3$	$PhCH_2NH_2$	2.3	15	0
19	$CH_3CON(CH_3)_2$	$PhCH_2NH_2$	2.3	24	44

[a] Yield, based on starting amide, of pure isolated product. [b] THIQ: 1,2,3,4-tetrahydroisoquinoline.

Table 2. Transamidation of Activated Amides

entry	amide	amine	$AlCl_3$ (mol equiv)	time (h at 25 °C)	yield[a] (%)
20	CH_3CONCH_3CO-*t*-Bu	$PhCH_2NHCH_3$	1.3	5.5	96
21	CH_3CONCH_3CO-*t*-Bu	Et_2NH	1.3	3.5	94
22	$PhCONCH_3Ts$	$PhCH_2NHCH_3$	2.3	16	65
23	CH_3CONCH_3COPh	*t*-$BuNH_2$	1.3	3	96
24	CH_3CONCH_3COPh	$PhNH_2$	1.3	2	97

[a] Yield, based on starting amide, of pure isolated product.

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(13) ***Experimental Procedure.*** In a typical experiment amide (1 equiv 11 mmol) and amine [2.5 equiv (or 3.5 equiv)] were added to a suspension of aluminum chloride [1.3 equiv (or 2.3 equiv)] in 1,2-dichloroethane (50 mL) at 0 °C. The mixture was stirred at rt, or if necessary at 90 °C, and monitored by IR or TLC. A mixture of ice and water was added. The organic layer was washed twice with brine and dried ($MgSO_4$). The products were separated by chromatography on silica gel using $CHCl_3$/MeOH as eluent. Physical and chemical constants of all products agreed with those reported in the literature.

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methylbenzamide activated by a tosyl group now reacts at room temperature with secondary aliphatic amines giving the desired product in good yield [Table 2, entries 15 (7%) and 22 (65%)]. The results obtained with *tert*-butylamine (Table 2, entry 23) and aniline (Table 2, entry 24) are particularly striking in comparison with entries 6 and 7 of Table 1.

Further work is in progress to optimize the nature of the activating group and to establish the scope of these $AlCl_3$–promoted transamidation reactions.