Trimethylaluminium-Facilitated Direct Amidation of Carboxylic Acids

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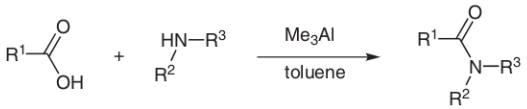
Abstract: Free carboxylic acids are converted into amides in moderate to high yields in the presence of a stoichiometric amount of trimethylaluminium and amines at 90 °C after 1 hour.

Key words: amide, amidation, trimethylaluminium, carboxylic acid, Lewis acid

Trimethylaluminium (Me_3Al) is a widely used Lewis acid that facilitates a variety of reactions often via activation of electronegative atoms and promotion of subsequent nucleophilic substitution on adjacent carbon atoms.[1] Of particular interest to the work reported here is the amidation of carboxilic esters facilitated by Me_3Al under mild conditions.[2] Herein we wish to report the use of Me_3Al to facilitate direct amidation of free carboxylic acids.[3]

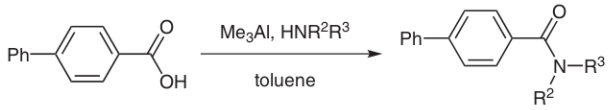
While investigating the chemistry of carboxylic acids in the presence of Lewis acid catalysts upon microwave heating,[4] we observed amidation of free carboxylic acids facilitated by Me_3Al. Subsequently, we examined this transformation under conventional heating. This led to the observation of amidation of free carboxylic acids in the presence of a stoichiometric amount of Me_3Al under conventional heating in moderate to high yields in toluene (Scheme 1).

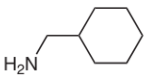
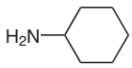
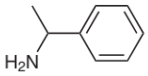
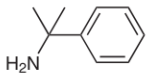
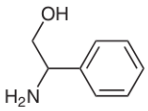
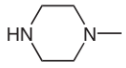
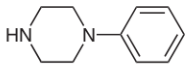
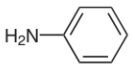
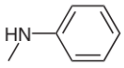
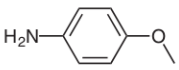
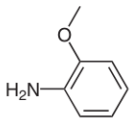


Scheme 1 Trimethylaluminium-facilitated amidation

Listed in Table 1 are the results of amidation of 4-biphenyl carboxylic acid with various amines.[5] For example, when a mixture of 1.0 mmol of cyclohexylmethyl amine and 1.0 mmol of 4-biphenylcarboxylic acid was treated with 1.0 mmol of Me_3Al in toluene at room temperature followed by heating at 90 °C for 1 hour, the corresponding amide product was formed in 80% yield according to LC-MS evaporative light scattering detection (ELSD).[6] Upon workup and purification, the pure product was isolated in 79% yield (entry 1).[7] The presence of Me_3Al is essential for amide coupling, as a control experiment of cyclohexylmethyl amine and 4-biphenylcarboxylic acid without Me_3Al resulted in no product formation. This transformation appears to be compatible with a variety of different amines. Primary amines (entries 1–5), including sterically hindered α,α-dimethyl benzylamine (entry 4) and β-hydroxylated amine (entry 5), all furnished amide products in moderate to high yields (64–86%). Secondary amines

Table 1 Amidation of 4-Biphenyl Carboxylic Acid with Amines



Entry	Amine	Yield (%)
1		80(79)
2		75
3		86
4		64
5		78
6		75
7		95
8		78
9		89
10		85
11		68
12		85
13		90

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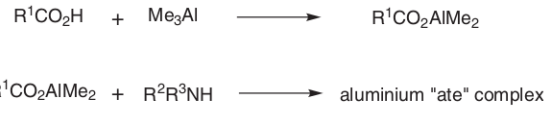
(entries 6–9) also underwent smooth transformation to generate amides in yields comparable to the primary amines (75–95%). Morpholine (entry 7, 95%) and piperizines (entries 8 and 9, 78% and 89%, respectively) are tolerated in this transformation. Anilines are compatible with this transformation as well (entries 10–13), with yields ranging from 85% for aniline, 68% for *N*-methylaniline, 85% and 90% for *p*- and *o*-methoxyanilines, respectively. Not surprisingly, anilines with ester or nitrile substitution did not furnish any desired product due to competing reactivity (not shown).

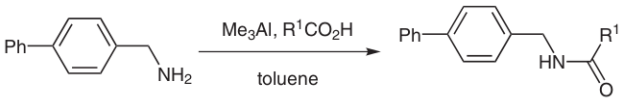
Listed in Table 2 are the results of this amidation reaction of 4-phenylbenzylamine with various aliphatic and aromatic carboxylic acids. For aliphatic acids, the yield ranged from 58% to 78%. Similar to the amine nucleophiles, sterically hindered aliphatic acids appear to furnish decent yield under the same conditions. For example, α,α-dimethyl propionic acid (entry 3) and α-methyl-α-phenyl propionic acid (entry 5) furnished the amide products in 78% and 65% yield, respectively. Aliphatic acids without α-substitution appeared to furnish the products in lower yield, as the amidation of propionic acid (entry 1) and phenyl acetic acid (entry 4) both proceeded in 58% yield; suggesting that the steric size of the carboxylic acid plays a less critical role in the reaction progression; rather, the presence of acidic α-protons in carboxylic acids probably interferes with the reaction. In these cases, increasing the amount of trimethylaluminium did not improve yield. For α,β-unsaturated carboxylic acids, both 3,3-dimethylacrylic acid and *trans*-cinnamic acid furnished amide products in moderate yield (entries 6 and 7, 71% and 63%). In either case, no trace amount of the Michael addition product was observed. Aromatic acids (entries 8–11) appeared to undergo this transformation more robustly, with benzoic acid furnishing the product in 94% yield (entry 8), 4-methoxybenzoic acid 70% (entry 9), 2-methoxybenzoic acid 80% (entry 10), and 4-[(dimethylamino)carbonyl] benzoic acid 80% (entry 11). Primary amide and urea functional groups seem to be less tolerated in this reaction (entries 12 and 13). This transformation appears to be compatible with phthalimide-protected amino acids, as phthalimidoalanine furnished the desired amide product in 76% yield (entry 14).

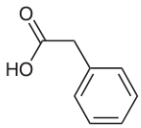
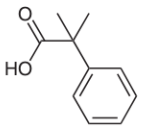
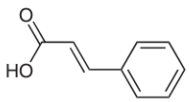
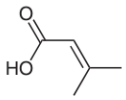
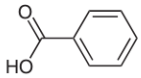
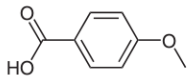
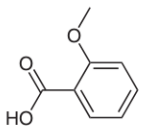
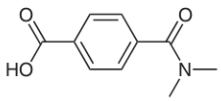
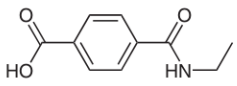
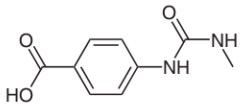
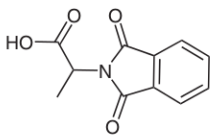
Similar to the boric acid and boronic acid facilitated catalytic amidation,[8] amidation effected by Me_3Al may be rationalized through the formation of an aluminium 'ate' complex (Scheme 2). The aluminium atom effectively brings into close proximity the carboxyl carbon and the amine nitrogen, thus setting up a favorable environment for rearrangement to the amide.



Scheme 2 Proposed reaction intermediate

Table 2 Amidation of 4-Phenylbenzylamine with Carboxylic Acids



Entry	Acid	Yield (%)
1		77
2		76
3		78
4		58
5		73
6		71
7		63
8		94
9		70
10		80
11		80
12		<40
13		<40
14		76

In summary, we report here an amidation of free carboxylic acids effected by Me_3Al directly with moderate to high yields. This one-pot transformation obviates the need for preparation of acid chlorides or use of organic coupling reagent (DCC, EDCI, HBTU, etc.), which lead to organic byproducts and complicates product isolation. The scope and limitation of this reaction are similar to the Weinreb amidation. The simplicity of this protocol is examplified by entry 1 of Table 1, where analytically pure product was obtained in 79% yield after dilution of the reaction mixture with aqueous NH_4OH and extraction with dichloromethane.

Acknowledgment

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References and Notes

(1) (a) Bracher, F. *J. Prakt. Chem.* **1999**, *341*, 88. (b) Suzuki, K.; Nagasawa, T. In *Encyclopedia of Reagents for Organic Synthesis*, Vol. 7; Paquette, L. A., Ed.; John Wiley and Sons: Sussex / UK, **1995**, 5186–5189. (c) Maruoka, K. In *Lewis Acid Reagents: A Practical Approach*; Yamamoto, H., Ed.; Oxford University Press: Oxford / UK, **1999**, Chap. 2.

(2) (a) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *48*, 4171. (b) Hirabayashi, T.; Itoh, K.; Sakai, S.; Ishii, Y. *J. Organomet. Chem.* **1970**, *25*, 33.

(3) Direct amide formation under thermal alone condition goes back to 1858. See: (a) Arnold, K.; Davies, B.; Giles, R. L.; Grosjean, C.; Smith, G. E.; Whiting, A. *Adv. Synth. Catal.* **2006**, *348*, 813; and references cited therein; also see ref. 8 below. Reviews of general amidation: (b) Benz, G. In *Comprehensive Organic Synthesis*, Vol. 6; Trost, B. M.; Fleming, I.; Heathcock, C. H., Eds.; Pergamon Press: New York, **1991**, Chap. 2.3. (c) Ziegler, T. *Science of Synthesis*, Vol. 21; Thieme: Stuttgart, **2005**, 43–75. (d) Although not cited in any reviews of amidation, we did uncover an isolated report during our exaustive literature search where a procedure was described for lactam formation of α,ω-amino acids [$H_2N(CH_2)_nCO_2H$, n equals to 3, 4, or 5] using 2 equiv of triethylaluminium. There was no description on the scope and limitation of this transformation beyond these three intramolecular examples of unfunctionalized and unsubstituted α,ω-amino acids, i.e., intermolecular amidation, functional-group compatibility, steric and electronic factors were not examined. Furthermore, no rationale of the reaction was offered. See: Yamamoto, Y.; Furuta, T. *Chem. Lett.* **1989**, *5*, 797.

(4) Comerford, J. W.; Clark, J. H.; Macquarrie, D. J.; Breeden, S. W. *Chem. Commun.* **2009**, 2562.

(5) **Typical Procedures**
Into a 8 mL 15 × 75 mm tube was added amine (1.0 mmol) and a solution/suspension of 1.0 mmol acid in toluene (1.0 mL). To this mixture was then added 2 M Me_3Al/toluene solution (Aldrich, 0.50 mL). The resulting mixture, usually a clear solution, was then shaken at 90 °C for 1 h. The reaction mixture was then diluted with CH_2Cl_2 (50 mL), and the resulting organic solution was washed with 20% NH_4OH (50 mL). The organic layer was then concentrated to give pure product usually in greater high purity (>90%). The less pure products were purified further via crystallization in a mixture of hexane and EtOAc or flash column chromatography.

(6) Yield based on LC-MS evaporative light scattering detection (ELSD) using a gradient H_2O–MeCN–TFA mobile phase on a 5 micron reverse phase C8 analytical column (4.6 × 50 mm).

(7) Product confirmed by ^1H NMR, LC-MS, HPLC- and HRMS.
Biphenyl-4-carboxylic Acid Cyclohexylmethylamide
^1H NMR (300 MHz, CD_3OD): δ = 7.87 (d, *J* = 8.0 Hz, 2 H), 7.69 (d, *J* = 8.8 Hz, 2 H), 7.64 (d, *J* = 7.2 Hz, 2 H), 7.44 (t, *J* = 7.2 Hz, 2 H),7.35 (t, *J* = 7.6 Hz, 1 H), 3.22 (d, *J* = 6.8 Hz, 2 H), 1.77 (t, *J* = 15.2 Hz, 4 H), 1.65 (m, 2 H), 1.25 (m, 3 H), 0.99 (m, 2 H). ^{13}C NMR (500 MHz, CD_3OD): δ = 168.00, 144.33, 140.11, 133.41, 128.81, 127.84, 127.65, 126.91, 126.81, 46.12, 38.11, 30.91, 26.42, 25.86. MS: *m/z* = 294.2 [M + H]. HRMS: *m/z* calcd: 294.1858 [M + H]; found: 294.1866.

(8) (a) Tang, P. *Org. Synth.* **2004**, *81*, 262. (b) Ishihara, K.; Ohara, S.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4196. (c) Maki, T.; Ishihara, K.; Yamamoto, H. *Tetrahedron* **2007**, *63*, 8645. (d) For catalytic amidation effected by boronic acid at milder conditions, see: Al-Zoubi, R. M.; Marion, O.; Hall, D. G. *Angew. Chem. Int. Ed.* **2008**, *47*, 2876. (e) Arnold, K.; Davies, B.; Herault, D.; Whiting, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 2673.