ORGANIC LETTERS

2012
Vol. 14, No. 1
214–217

$AlMe_3$-Promoted Formation of Amides from Acids and Amines

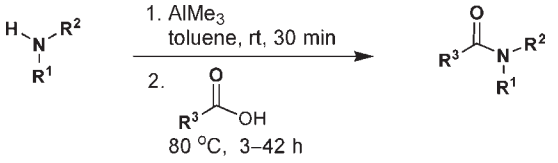
Jianqing Li,*,† Krishnananthan Subramaniam,† Daniel Smith,† Jennifer X. Qiao,‡ Jie Jack Li,† Jingfang Qian-Cutrone,§ John F. Kadow,§ Gregory D. Vite,† and Bang-Chi Chen†

Bristol-Myers Squibb Company, Research and Development, P.O. Box 4000, Princeton, New Jersey 08543-4000, United States, 311 Pennington-Rocky Hill Road, Pennington, New Jersey 08534, United States, and 5 Research Parkway, Wallingford, Connecticut 06492, United States

**Jianqing.li@bms.com*

Received November 7, 2011

ABSTRACT

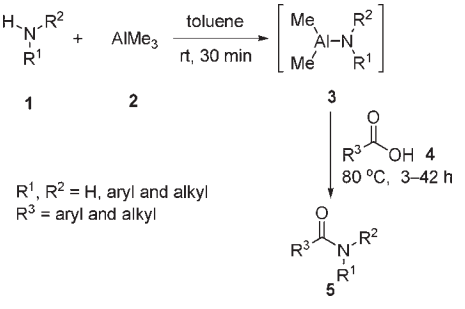


In the presence of $AlMe_3$, amines can be directly coupled with acids through dimethylaluminum amide intermediates to form the corresponding amides. A wide range of amines and acids including less nucleophilic amines, bulky amines, unprotected secondary amino acids, and acids with poor solubility were coupled smoothly to give the desired products in 55−98% yields.

Amide formation from acids and amines is one of the most fundamental reactions in organic synthesis. It plays a key role in peptide synthesis and medicinal chemistry. The general strategy for amide bond formation is the activation of carboxylic acids as acyl halides, acylimidazoles, acylazide, anhydrides, and active esters followed by aminolysis. Although numerous activating reagents have been developed to facilitate amide formation, they all have advantages and limitations due to the structural diversity of the substrates.[1] The development of new coupling reagents and conditions is still needed, especially for less nucleophilic amines, bulky amines, unprotected amino acids, and acids with poor solubility.

Since Weinreb and co-workers reported $AlMe_3$ promoted amide synthesis from esters and amines in 1977,[2] the $AlMe_3$-mediated amide and lactam formation from esters has found many applications in organic synthesis.[3,4] Using aluminum amides, carbamates can be directly converted to ureas.[5] To the best of our knowledge, the direct synthesis of amides from acids and amines using $AlMe_3$ as a coupling reagent has not been reported.[6] Herein, we wish to report a highly efficient $AlMe_3$-promoted coupling reaction between acids and amines to give amides (Scheme 1).

Scheme 1. $AlMe_3$-Promoted Formation of Amides **5** from Amines **1** and Acids **4**



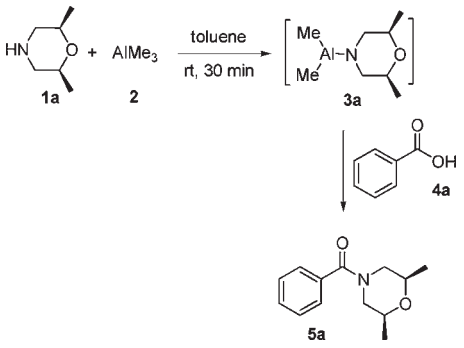
† Bristol-Myers Squibb Company, Princeton, New Jersey.
‡ Bristol-Myers Squibb Company, Pennington, New Jersey.
§ Bristol-Myers Squibb Company, Wallingford, Connecticut.

(1) Montalbetti, C. A. G. N.; Falque, V. *Tetrahedron* **2005**, *61*, 10827 and references therein.
(2) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *48*, 4171.
(3) Bracher, F. *J. Prakt. Chem.* **1999**, *341*, 88.
(4) Ooi, T.; Maruoka, K. *Sci. Synth.* **2004**, *7*, 230.
(5) Lee, S.-H.; Matsushita, H.; Clapham, B.; Janda, K. D. *Tetrahedron* **2004**, *60*, 3439.
(6) After the original presentation of this work at the 240th ACS National Meeting August 22−26, 2010, another transformation was reported: Chung, W.; Uccello, D. P.; Choi, H.; Montgomery, J. I.; Chen, J. *Synlett* **2011**, *14*, 2072−2074

10.1021/ol203007s
Published on Web 12/07/2011

In one of our research projects, we attempted to use $AlMe_3$ to selectively transform an ester group to an amide while keeping an acid function intact in the same molecule. Surprisingly, a substantial amount of diamide formation was observed. This discovery prompted us to investigate the direct coupling of acids with amines to give amides. In a model study (Table 1), (2*R*,6*S*)-2,6-dimethyl-morpholine (**1a**) (2 equiv) was treated with 2 equiv of $AlMe_3$ in toluene at rt under N_2 for 30 min, followed by addition of 1 equiv of benzoic acid (**4a**). The reaction mixture was stirred at rt for 18 h. LCMS indicated ~60% conversion (Table 1, entry 1). The reaction mixture was further heated at 80 °C for 18 h. However, the conversion was not increased. When 3 equiv of $AlMe_3$ and 3 equiv of the amine **1a** were used and the reaction was run at rt for 2 days, 80% conversion was observed (Table 1, entry 2). Quickly, we found that the reaction completed after 3 equiv of the amine **1a** was treated with 3 equiv of $AlMe_3$ for 30 min at rt followed by the reaction with 1 equiv of the acid **4a** at 80 °C for 16 h (Table 1, entry 3).

Table 1. Reaction Condition Screen for the $AlMe_3$-Promoted Direct Coupling of Benzoic Acid (**4a**) with (2*R*,6*S*)-2,6-Dimethylmorpholine (**1a**)



entry	equiv of amine and $AlMe_3$	temp	time (h)	conversion (%)
1	2	rt	18	60
2	3	rt	48	80
3	3	80 °C	16	100

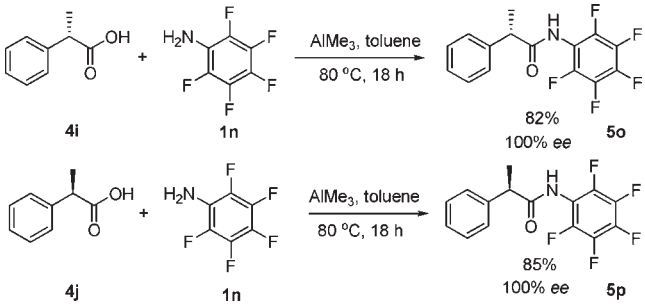
With the above conditions in hand, we examined a range of acids and amines. As shown in Table 2, aromatic, heteroaromatic, and aliphatic acids **4a**–**h** all can be tranferred to the corresponding amides **5a**–**n** in good to excellent yields. As reported previously, 5-bromoorotic acid (**4h**) coupled to an acid chloride (an amide precursor) proved to be problematic due to the insolubility of the acid in a variety of solvents appropriate for chlorination.[7] Under our current conditions using toluene as the solvent, the amides **5m** and **5n** (Table 2, entry 13 and 14) were obtained easily by quenching the reaction mixture with MeOH and 1 N HCl followed by filtration.

(7) Decicco, C. P.; Nelson, D. J. *Tetrahedron Lett*. **1993**, *34*, 8213.

Furthermore, primary and secondary aromatic and aliphatic amines **1a**–**m** were also transferred to the corresponding amides. Even highly hindered 8-methyl-1,2,3,4-tetrahydroquinoline (**1e**) coupled with benzoic acid (**4a**) gave amide **5e** in 68% isolated yield (Table 2, entry 5). In contrast, this bulky amine **1e** was reported to couple with an acid using EDAP/HOBt/Hunig's base to give an amide in 39% yield.[8] The weak amine such as 2-fluoro-5-aminopyridine **1k** required the acid component to be activated to acyl halide in order to form the corresponding amide in good yield.[9] However, assisted by $AlMe_3$, **1k** coupled with 1-benzylpyrrolidine-2-carboxylic acid (**4g**) to afford the amide **5l** in 68% yield (Table 2, entry 12).

Encouraged by the above results, we were interested in applying the method to the synthesis of *N*-(perfluorophenyl)aliphatic amides which are useful substrates for Pd(II)-catalyzed olefination of sp^3 C–H bonds. Because of the strong electron-withdrawing nature of the perfluorophenyl ring, this kind of amide formation required acid chloride formation followed by aminolysis under basic conditions at high temperature.[10] It is also interesting to see if racemization could occur when a chiral acid is employed under our $AlMe_3$ conditions. Scheme 2 showed that $AlMe_3$ promoted the coupling of pentafluoroaniline (**1n**) with (*S*)- and (*R*)-2-phenylpropanoic acids (**4i** and **4j**), yielding the corresponding (*S*)- and (*R*)-*N*-(perfluorophenyl)-2-phenylpropanamides (**5o** and **5p**) in excellent yields, remarkably, with no racemization.

Scheme 2. $AlMe_3$-Promoted Coupling of (*S*)- and (*R*)-2-Phenylpropanoic acid (**4i** and **4j**) with Pentafluoroaniline (**1n**)



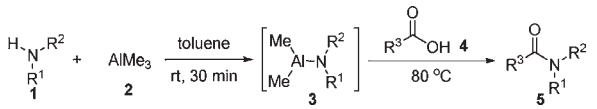
Based on the above results from Table 2 and Scheme 2, we proposed the reaction mechanism illustrated in Scheme 3. Dimethylaluminun amide **3** generated from the reaction of amine **1** with $AlMe_3$ reacted with acids **4** to form

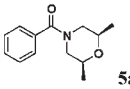
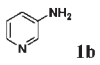
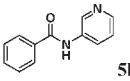
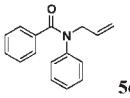
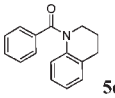
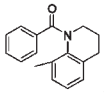
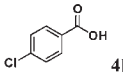
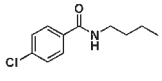
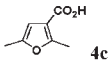
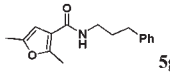
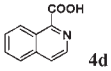
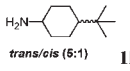
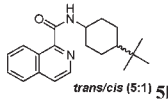
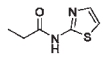
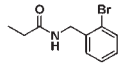
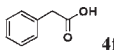
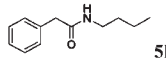
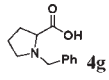
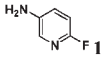
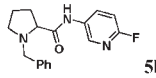
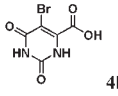
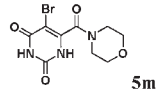
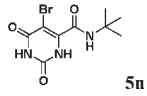
(8) Chong, J. A.; Fanger, C.; Larsen, G. R.; Lumma, W. C.; Moran, M. M.; Ripka, A.; Underwood, D. J.; Weigele, M.; Zhen, X. U.S. Pat. Appl. Publ., 2007213321, 13 Sep 2007.

(9) Wittman, M. D.; Carboni, J. M.; Yang, Z.; Lee, F. Y.; Antman, M.; Attar, R.; Balimane, P.; Chang, C.; Chen, C.; Discenza, L.; Frennesson, D.; Gottardis, M. M.; Greer, A.; Hurlburt, W.; Johnson, W.; Langley, D. R.; Li, A.; Li, J.; Liu, P.; Mastalerz, H.; Mathur, A.; Menard, K.; Patel, K.; Sack, J.; Sang, X.; Saulnier, M.; Smith, D.; Stefanski, K.; Trainor, G.; Velaparthi, U.; Zhang, G.; Zimmermann, K.; Vyas, D. M. *J. Med. Chem*. **2009**, *52*, 7360.

(10) Wasa, M.; Engle, K. M.; Yu, J.-Q. *J. Am. Chem. Soc*. **2010**, *132*, 3680.

Table 2. $AlMe_3$-Promoted Formation of Amides **5a**–**n** from Acids and Amines

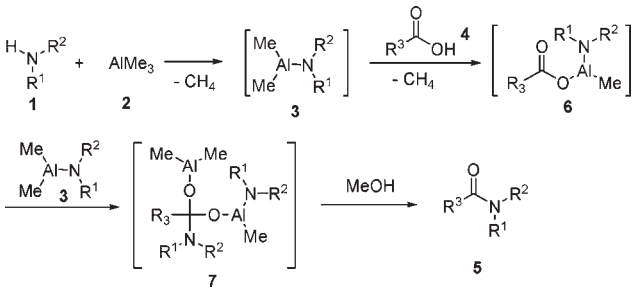


entry	acid	amine	product *amide*	time (h)	isolated yield (%)
1	 **4a**	 **1a**	 **5a**	16	95
2	**4a**	 **1b**	 **5b**	18	86
3	**4a**	 **1c**	 **5c**	18	98
4	**4a**	 **1d**	 **5d**	20	91
5	**4a**	 **1e**	 **5e**	42	68
6	 **4b**	 **1f**	 **5f**	20	61
7	 **4c**	 **1g**	 **5g**	24	92
8	 **4d**	 *trans/cis* (5:1) **1h**	 *trans/cis* (5:1) **5h**	24	98
9	 **4e**	 **1i**	 **5i**	18	90
10	**4c**	 **1j**	 **5j**	18	74
11	 **4f**	 **1f**	 **5k**	18	73
12	 **4g**	 **1k**	 **5l**	18	68
13	 **4h**	 **1l**	 **5m**	20	55
14	**4h**	 **1m**	 **5n**	18	94

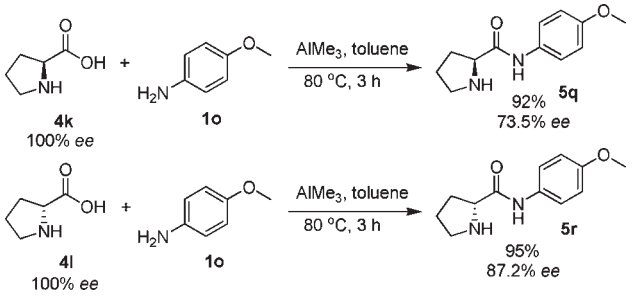
intermediate **6**. The formation of **3** and **6** was evidenced by the observation of gas evolution (presumably methane). Intermediate **6** was then reacted with another equivalent of **3** to give the tetrahedral intemediate **7**, which upon treatment with MeOH afforded amide **5**.

According to the reaction pathway of Scheme 3, we envisioned that if the Al–N bond of **3** were relatively stable, unprotected amino acid could couple with acids without cross-coupling. Indeed, we found unprotected L- and D-prolines (**4k** and **4l**) reacted with the aluminun anisidine (**1o**) complex to give the products **5q** and **5r** in excellent yields (Scheme 4). No cross-coupling products were observed. However, 6.4% to 13.2% racemization occurred. The coupling of primary amino acids such as 2-phenylglycine with anisidine (**1o**) became complicated since cross-coupling products appeared to be predominated based on LCMS. Most likely, in the proline case, the secondary amino group from proline was much slower to

Scheme 3. Proposed Mechanism



Scheme 4. Direct Coupling of Unprotected L- and D-Prolines (**4k** and **4l**) with Anisidine (**1o**)



replace the anisidine group in complex **3** due to steric hindrence. These results also confirmed that complex **3** is labile.[11] Nevertheless, the results from Scheme 4 could be potentially useful.

In summary, we have developed a highly efficient $AlMe_3$-promoted amide formation from acids and amines. The advantages of this method include the following: a wide range of acids and amines were coupled in good to excellent yields; weak nucleophilic and bulky amines can be transferred to the corresponding amide in high yields; and unprotected secondary amino acids can be converted to primary amides. The limitations of this method include functional groups such as esters, nitro, and cyano groups are not tolerated under these conditions and 3 equiv of amines and $AlMe_3$ are required.

Note Added after ASAP Publication. This paper was published ASAP on December 7, 2011. A new reference 6 was added and it reposted December 15, 2011.

Supporting Information Available. Experimental procedures, characterization data, and NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(11) Sidler, D. R.; Lovelace, T. C.; McNamara, J. M.; Reider, P. J. *J. Org. Chem.* **1994**, *59*, 1231.