ORGANIC LETTERS

2010
Vol. 12, No. 6
1340−1343

Parallel Synthesis of Ureas and Carbamates from Amines and CO_2 under Mild Conditions

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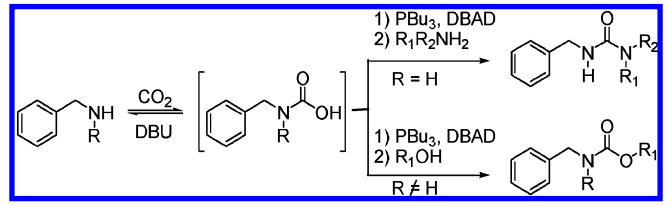
Received February 1, 2010

ABSTRACT



A mild and efficient library synthesis technique has been developed for the synthesis of ureas and carbamates from carbamic acids derived from the DBU-catalyzed reaction of amines and gaseous carbon dioxide. Carbamic acids derived from primary amines reacted with Mitsunobu reagents to generate isocyanates in situ which were condensed with primary and secondary amines to afford the desired ureas. Similarly, carbamic acids from secondary amines reacted with alcohols activated with Mitsunobu reagents to form carbamates.

The structure−activity relationships (SAR) of urea and carbamate-containing bioactive compounds are often explored in the development of pharmaceutically active agents.[1] Typically, efficient synthesis of the urea functional group is achieved through the condensation of an amine with an isocyanate[2] or the coupling of amines with phosgene or a phosgene equivalent.[3] Given the limited number of commercially available isocyanates and the toxicities related to the use of phosgene, an alternative environmentally benign and high-throughput synthesis technique for the construction of ureas is desirable.

The chemistry of carbamic acids derived from the reaction of amines with carbon dioxide gas has been established[4] and utilized for the synthesis of isocyanates,[5] carbamates,[6] and ureas.[7] However, while the potential versatility of this chemistry is clear, the scope of amenable building blocks has not been defined sufficiently to predict a successful parallel synthesis approach. Here, we have optimized and expanded the scope and efficiency of this reaction to be amenable to library synthesis. This method allows for the rapid SAR development of compounds containing ureas or carbamates.

Initially, we investigated the parallel synthesis of unsymmetrical disubstituted ureas. Using a Bohdan MiniBlock

(1) (a) Dinsmore, C. J.; Hartman, G. D. WO 9727752 A1. (b) Decieco, C. S.; Seng, J. L.; Kennedy, K. E.; Covington, M. B.; Welch, P. K.; Arner, E. C.; Magolda, R. L.; Nelson, D. J. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 2331.

(2) (a) Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. *Tetrahedron Lett.* **1996**, *37*, 7193. (b) Burgess, K. D.; Linthicum, S.; Shin, H. *Angew. Chem., Int. Ed.* **1995**, *34*, 907.

(3) (a) Huang, K. T.; Sun, C. M. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 271. (b) Raju, B.; Kassir, J. M.; Kogan, T. P. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3043. (c) Paio, A.; Crespo, R. F.; Seneci, P.; Ciraco, M. *J. Comb. Chem.* **2001**, *3*, 354. (d) Scialdone, M. A.; Shuey, S. W.; Soper, P.; Hamuro, Y.; Burns, D. M. *J. Org. Chem.* **1998**, *63*, 4802.

(4) Hampe, E. M.; Rudkevich, D. M. *Tetrahedron* **2003**, *59*, 9619.

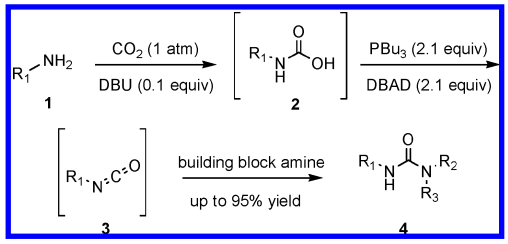
(5) (a) Horvath, M. J.; Saylik, D.; Elmes, P. S.; Jackson, W. R.; Lovel, C. G.; Moody, K. *Tetrahedron Lett.* **1999**, *40*, 363. (b) Waldmann, T. E.; McGhee, W. D. *J. Chem. Soc., Chem. Commun.* **1994**, 957.

(6) Using alkyl halides as electrophiles: (a) McGhee, W.; Riley, D.; Christ, K.; Pan, Y.; Parnas, B. *J. Org. Chem.* **1995**, *60*, 2820. (b) Hooker, J. M.; Reibel, A. T.; Hill, S. M.; Schueller, M. J.; Fowler, J. S. *Angew. Chem., Int. Ed.* **2009**, *48*, 3482. Using Mitsunobu's reagents at elevated temperature: Chaturvedi, D.; Mishra, N.; Mishra, V. *Montash. Chem.* **2007**, *138*, 57.

(7) (a) Yamazaki, N.; Higashi, F.; Iguchi, T. *Tetrahedron Lett.* **1974**, *15*, 1194. (b) Cooper, C. F.; Falcone, S. J. *Synth. Commun.* **1995**, *25*, 2467. (c) Tai, C. C.; Huck, M. J.; McKoon, E. P.; Woo, T.; Jessop, P. G. *J. Org. Chem.* **2002**, *67*, 9070.

10.1021/ol100259j
Published on Web 02/22/2010

Scheme 1. Proposed Mechanism for the Synthesis of Ureas



synthesizer fitted with an inert gas manifold,[8] up to 24 primary amines (**1**, Scheme 1) were treated with CO_2 gas to form the resulting carbamic acids (**2**) in situ. The carbamic acids were then dehydrated under Mitsunobu[9] conditions to yield the intermediate isocyanates (**3**),[5] which were condensed with the corresponding building block amines to form the desired ureas (**4**).

Using benzylamine (**5**) as a model substrate, the scope of this reaction was explored (Table 1). The reaction proved to be efficient in generating ureas from a diverse set of building block amines. Secondary amines such as tetrahydroisoquinoline, morpholine, and benzylmethylamine (entries 1, 6, and 7) all coupled in >80% yield.

Alkylamines such as *p*-methylbenzylamine (entry 2) proceeded in almost quantitative yield, while coupling with the two other methyl regioisomers was achieved in good yield (entries 3 and 4). The sterically hindered *tert*-butylamine (entry 8) added to the isocyanate in 29% yield, and similar results were observed with 2-chlorobenzylamine (entry 12).

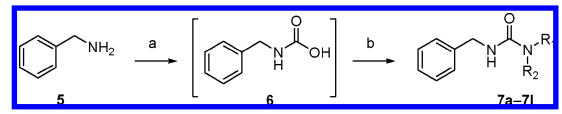
Aromatic amines, such as aniline, coupled into the isocyanate in good yield (entry 9), while the less nucleophilic 3-aminopyridine resulted in lower conversion (entry 10). The aminomethyl pyridine (entry 11) was still very efficient in this transformation.

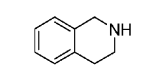
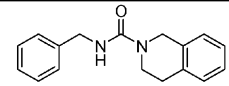
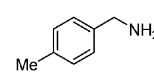
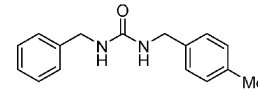
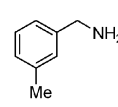
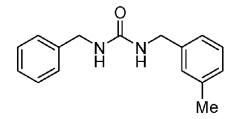
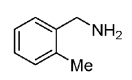
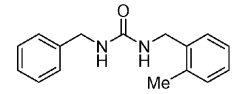
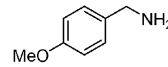
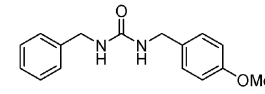
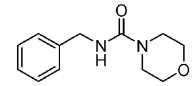
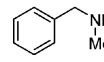
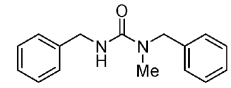
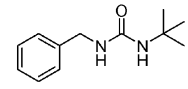
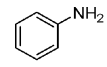
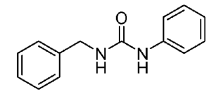
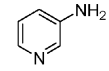
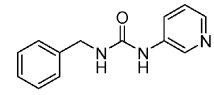
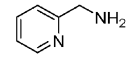
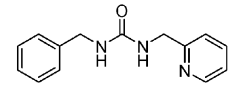
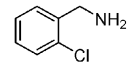
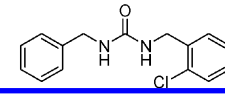
Consistent with the proposed reaction mechanism, carbamic acids derived from secondary amines can not react further to form the isocyanate intermediate and did not undergo the desired transformation. For this reason, tri- and tetrasubstituted ureas derived from secondary amine carbamic acids could not be prepared under these reaction conditions.[10]

Treating aromatic amines, such as aniline, with CO_2−DBU and then PBu_3/DBAD generated phenyl isocyanate which reacted with secondary amines to form trisubstituted ureas (Table 2). Almost quantitative yield was observed with methylbenzylamine (entry 3), while excellent yields were noted with morpholine and tetrahydroisoquinoline (entries 1 and 2).

The synthesis of disubstituted ureas from aniline and alkylamines generally proceeded in lower isolated yield, and often the symmetrical dialkylamine urea was observed as an undesired byproduct. For example, a lower yield was obtained for 1-benzyl-3-phenylurea (cf. **7i** in Tables 1 and 3) when aniline was treated with CO_2 and attempts were made to couple benzylamine (Table 3, entry 1) as compared to the inverse order of addition (Table 1, entry 9). Conducting the experiment at a lower temperature (0 °C) slowed the formation of the undesired homocoupled urea. However, even at a lower temperature, treating aniline with CO_2 and then other substituted benzylamines followed by Mitsunobu

Table 1. Synthesis of Ureas from Benzylamine[a]



entry	coupling partner	product		yield (%)
1			**7a**	94
2			**7b**	95
3			**7c**	63
4			**7d**	81
5			**7e**	84
6			**7f**	78
7			**7g**	88
8			**7h**	29
9			**7i**	68
10			**7j**	28
11			**7k**	81
12			**7l**	30

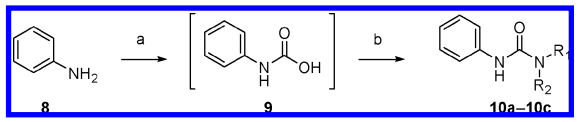
[a] Reaction conditions: (a) benzylamine (1 equiv), DBU (0.1 equiv), MeCN, CO_2 (1 atm) 45 min; (b) building block amine (1.5 equiv) followed by PBu_3 (2.1 equiv) and DBAD (2.1 equiv) premixed in MeCN, 60 min under N_2 (1 atm).

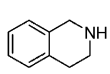
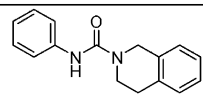
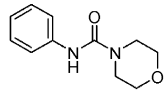
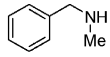
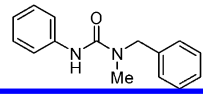
(8) See the Supporting Information for an image of the Bohdan MiniBlock.

(9) For a recent review of the Mitsunobu reaction, see: Swamy, K. C. K.; Kumar, N. N. B.; Balaraman, E.; Kumar, K. V. P. *Chem. Rev.* **2009**, *109*, 2551.

(10) Contrary to a recent communication (Chaturvedi, D.; Mishra, N.; Mishra, V. *Monatsh. Chem.* **2008**, *139*, 267.) where symmetrical tetrasubstituted ureas were reported. When the conditions reported in this report are utilized, neither symmetrical or unsymmetrical tetrasubstitiuted ureas are observed. See the Supporting Information for details.

Table 2. Synthesis of Trisubstituted Ureas from Aniline[a]



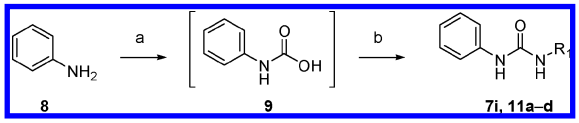
entry	coupling partner	product		yield (%)
1			**10a**	92
2			**10b**	89
3			**10c**	99

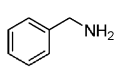
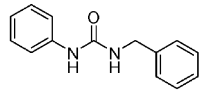
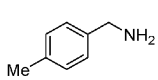
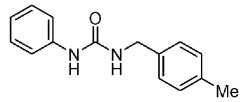
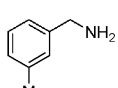
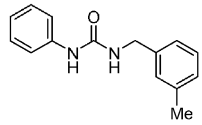
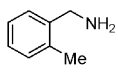
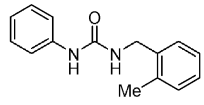
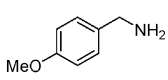
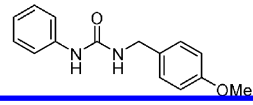
[a] Reaction conditions: (a) aniline (1 equiv), DBU (0.1 equiv), MeCN, CO_2 (1 atm) 45 min; (b) building block amine (1.5 equiv) followed by PBu_3 (2.1 equiv) and DBAD (2.1 equiv) premixed in MeCN, 60 min under N_2 (1 atm).

reagents often led to lower isolated yields of the desired ureas (Table 3, **11a**−**d**).

A competing reaction mechanism appears to be operating when an aromatic amine reacts with CO_2 and then couples

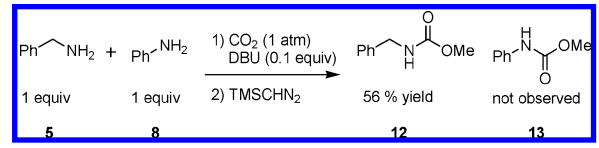
Table 3. Synthesis of Disubstituted Ureas from Aniline[a]



entry	coupling partner	product		yield (%)
1			**7i**	46
2			**11a**	18
3			**11b**	40
4			**11c**	25
5			**11d**	29

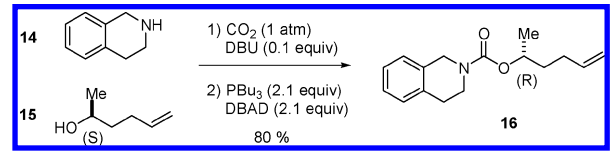
[a] Reaction conditions: (a) aniline (1 equiv), DBU (0.1 equiv), CO_2 (1 atm), 0 °C, 45 min; (b) building block amine (1.5 equiv) followed by PBu_3 (2.1 equiv) and DBAD (2.1 equiv) premixed in MeCN, 60 min under N_2 (1 atm).

Scheme 2. Carbamic Acid Trapping Experiment



with primary alkylamines. The proposed mechanism that proceeds through the generation of the aryl isocyanate is assumed to account for some of the observed product in this reaction. However, under these conditions the alkylamine also forms a carbamic acid and subsequent isocyanate.[11] Scheme 2 shows a competition experiment between aniline and benzylamine. In this example, the benzylamine preferentially formed the corresponding carbamic acid which was trapped as the methyl carbamate (**12**) upon treatment with TMS-diazomethane, while competing formation of the methyl phenylcarbamate (**13**) was not observed.

Scheme 3. Inversion of Stereochemistry in Carbamate Formation



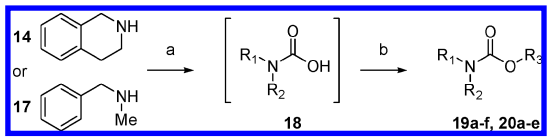
The extension of this chemistry to carbamate library synthesis was next explored. In principle, a primary amine could proceed through the carbamic acid−isocyanate reaction manifold already described (**1**−**3**, Scheme 1) and subsequently combine with an alcohol to produce a carbamate product. While this is precedented by an intramolecular reaction variant to produce cyclic carbamates,[12] the desired intermolecular coupling was not successful under the established reaction conditions.[13] However, carbamic acids generated from secondary amines did react with alcohols under Mitsunobu conditions to generate the corresponding carbamates. This reaction did not proceed through the isocyanate intermediate, as described above, but rather through an S_N2 displacement of the activated alcohol. The evidence to support this hypothesis is that inversion of stereochemistry was observed upon conversion of a chiral secondary alcohol to the corresponding carbamate (Scheme 3). In the reaction between the carbamic acid derived from tetrahydroisoquinoline (**14**) and (*S*)-5-hexen-2-ol (**15**), the carbamate (**16**) was

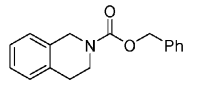
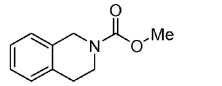
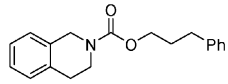
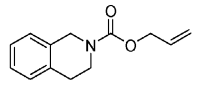
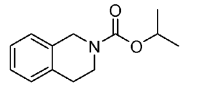
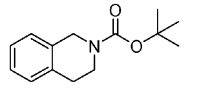
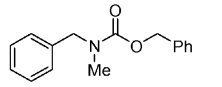
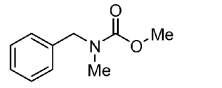
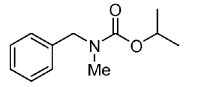
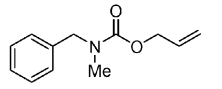
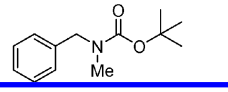
(11) Based upon the observed formation of the bis-alkylamine urea. This product is formed from the alkylamine condensing with the isocyanate generated from the alkylamine carbamic acid.

(12) (a) Dinsmore, C. J.; Mercer, S. P. *Org. Lett.* **2004**, *6*, 2885. (b) Kodaka, M.; Tomohiro, T.; Okuno, H. *J. Chem. Soc., Chem. Commun.* **1993**, 81.

(13) Reacting benzylamine and benzyl alcohol under these reaction conditions produced the bis-benzyl urea rather than the carbamate. See the Supporting Information for details.

Table 4. Carbamates from Secondary Carbamic Acids[a]



entry	amine	alcohol	product		yield (%)
1	**14**	Ph–OH		**19a**	96
2	**14**	H_3C–OH		**19b**	67
3	**14**	Ph–OH		**19c**	58
4	**14**	OH		**19d**	50
5	**14**	OH		**19e**	46
6	**14**	OH		**19f**	0[c]
7	**17**	Ph–OH		**20a**	71
8	**17**	H_3C–OH		**20b**	54
9	**17**	OH		**20c**	62
10	**17**	OH		**20d**	50
11	**17**	OH		**20e**	0[c]

[a] Reaction conditions: (a) secondary amine (1 equiv), building block alcohol (1.5 equiv) DBU (0.1 equiv), MeCN, CO_2 (1 atm), 45 min; (b) PBu_3 (2.1 equiv) and DBAD (2.1 equiv) premixed in MeCN, 60 min under N_2 (1 atm); (c) Reaction run at 100 °C.

formed and the stereogenic center was determined to be (*R*)-configured[14] (i.e., inverted). With this promising result, we sought to define the scope of the reaction and to demonstrate its application to library sythesis techniques.

Secondary amines generally performed well in this transformation, generating common carbamate protecting groups in moderate to excellent yield (amines **14** and **17** are illustrative, see Table 4). The Cbz group was installed in 96% and 71% yield (entries 1 and 7), while the Alloc group was formed in approximately 50% yield for both amines (entries 4 and 10). Other primary and secondary alcohols were tolerated by this process (entries 2, 3, 5, 8, and 9) while no reaction was observed with the sterically hindered *tert*-butyl alcohol (entries 6 and 11) even at elevated temperatures.

In summary, we have identified reaction conditions and reactant substrate scope for successfully and predictably coupling amines, CO_2 and alcohols to produce ureas and carbamates, thereby outlining a useful technique for the parallel construction of compound libraries. Unsymmetrical di- and trisubstituted ureas are constructed through an intermediate isocyanate, formed by the dehydration of a primary amine carbamic acid. Secondary amine carbamic acids react through an S_N2 mechanism with activated alcohols to generate a variety of carbamates. We expect that the efficiency of this process will enable more rapid expansion of useful SAR analysis in drug discovery.

Acknowledgment. This work was completed as part of the Co-Op Education Program with Northeastern University, Boston, MA (S.M.S). We thank our Merck colleagues Sam Kattar for helpful discussions regarding parallel synthesis techniques and Dr. Charles W. Ross III for high-resolution mass determination. Bruce Adams and Bridget Becker, also from Merck, are acknowledged for assistance with NMR structure determinations.

Supporting Information Available: Experimental procedures; characterization data of compounds; copies of ^1H and ^{13}C NMR spectra and HRMS for **7a**−**l**, **10a**−**c**, **11a**−**d**, **19a**−**e**, and **20a**−**d**; experimental details to support the proposed reaction mechanisms. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Stereochemistry was assigned on the basis of comparison to a reference compound synthesized by CDI coupling of (*R*)-5-hexen-2-ol and tetrahydroisoquinoline. See the Supporting Information for details.