Efficient Carbamate Synthesis via a Three-Component Coupling of an Amine, CO_2, and Alkyl Halides in the Presence of Cs_2CO_3 and Tetrabutylammonium Iodide

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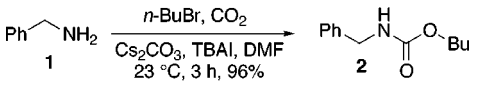
The carbamation of amines has frequently been utilized in the synthesis of organic carbamates,[1] which hold unique applications in the field of pharmaceuticals[2] and agriculture.[3] Organic carbamates have also played an important role in the area of synthetic organic chemistry primarily as key intermediates or as novel protecting groups.[4] However, the scope of existing methodologies[5] for carbamate formation are limited by the need for specialized reagents, and operational complexity due to the use of either toxic or cumbersome reagents such as phosgene. Because of the toxicity of these materials, we have undertaken a significant effort for the development of more efficient and safer protocols. Recently, we reported a cesium base-promoted carbonylation method, which successfully allows for the efficient coupling of various alcohols with halides in the presence of cesium carbonate, tetrabutylammonium iodide (TBAI), and carbon dioxide.[6] Analogous to this route, we applied this carbonate technology to the synthesis of carbamates, envisioning high yields under mild reaction conditions. Although there have been several examples with regards to carbamate formation utilizing carbon dioxide alkylation, these precedented conditions lack in practicality mainly because they require severe reaction conditions.[7] Furthermore, *N*-alkylation reactions, resulting in the formation of tertiary amines,[5b] usually accompany these carbamations.

Under our developed conditions, carbamations were smooth and convenient to generate the desired carbamates efficiently. For instance, carbamate **2** was found to exclusively form in high yield through the three-component coupling of amine **1**, CO_2, and 1-bromobutane by applying a similar procedure to our carbonylation protocol.[6a] In this conversion, the reaction mixture was saturated with CO_2 by bubbling the gas continuously in the presence of Cs_2CO_3 at room temperature while *N*,*N*-dimethylformamide proved to be the solvent of choice. Interestingly, tetrabutylammonium iodide (TBAI) was found to be a crucial additive in averting direct *N*-alkylations and overalkylation of the produced carbamate.[8] Thus, this procedure is highly chemoselective, convenient, and efficient, which overcomes the common problems encountered utilizing similar methods (vide supra).

Scheme 1



As shown in Table 1, numerous substrates were examined and found to be suitable to the newly developed techniques. Various amines with primary alkyl chains were efficiently united with benzyl chloride in high yields (entries 1−4). As depicted in entry 5, cyclooctylamine **7**, a relatively bulky amine, underwent consolidation easily to provide the desired carbamate in good yield while secondary amine **8** (i.e., 4-benzylpiperazine, entry 6) required longer reaction time. Likewise, treatment of an unreactive bromide such as **10** with numerous primary amines afforded the desired carbamates in less than 8 h (entries 7−11). Interestingly, tryptamine **14** was found to carbonylate at the primary amine selectively, leaving the secondary amine intact.

Using the conditions described above, we next investigated carbamate formation using aromatic and other heterocyclic amines. As summarized in Table 2, aromatic amines underwent facile carbamation in high yields using two different reactive electrophiles (entries 1 and 2). As expected, the secondary aromatic amine, *N*-ethylaniline **17**, reacted slowly to afford the carbamate in 78% yield after a 22 h time period (entry 3). Heterocyclic amines including 2- and 3-aminopyridines were noticed to react in a similar fashion with bromide **10** (entries 4 and 5). Subsequently, with the introduction of an electron-withdrawing substituent on the aromatic ring (i.e., carbonyl or nitro group), the amine was rendered less nucleophilic; hence, the reactions were sluggish and

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(1) For a comprehensive review on organic carbamates, see Adams, P.; Baron, F. A. *Chem. Rev.* **1965**, *65*, 567.

(2) Barthelemy, J. *Lyon Pharm.* **1986**, *37* (6), 297.

(3) (a) Tai-The, W.; Huang, J.; Arrington, N. D.; Dill, G. M. *J. Agric. Food Chem.* **1987**, *35*, 817. (b) Kato, T.; Suzuki, K.; Takahashi, J.; Kamoshita, K. *J. Pesticide Sci.* **1984**, *9*, 489. (c) Picardi, P. *La Chimica e l'Industria* **1986**, *68*, 108. (d) Rivetti, F.; Romano, U.; Sasselli, M. U.S. Patent 4514339, ECS 1985.

(4) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; J. W. Wiley and Sons: New York, 1999; pp 503−550 and references therein.

(5) For traditional synthetic methods for carbamate formation, see (a) Babad, H.; Zeiler, A. G. *Chem Rev.* **1973**, *73*, 75. (b) Butcher, K. J. *Synlett* **1994**, 825. (c) Sasaki, Y.; Dixneuf, P. *J. Org. Chem.* **1987**, *52*, 314. (d) Ohta, A.; Inagawa, Y.; Mitsugi, C. *J. Heterocycl. Chem.* **1985**, *22*, 1643. (e) Parra, V. G.; Sanchez, F.; Torres, T. *Synthesis* **1985**, 282. (f) Tartar, A.; Gesquiere, J. C. *J. Org. Chem.* **1979**, *44*, 5000. (g) Sasaki, Y.; Dixneuf, P. H. *J. Org. Chem.* **1987**, *52*, 314. (h) Raucher, S.; Jones, D. S. *Synth. Commun.* **1985**, *15*, 1025.

(6) For our cesium-promoted carbonate formation, see (a) Kim, S.-I.; Chu, F.; Dueno, E. E.; Jung, K. W. *J. Org. Chem.* **1999**, *64*, 4578. (b) Chu, F.; Dueno, E. E.; Jung, K. W. *Tetrahedron Lett.* **1999**, *40*, 1847. For our cesium-promoted carbonate and carbamate synthesis on solid phase, see (c) Salvatore, R. N.; Flanders, V. L.; Ha, D.; Jung, K. W. *Org. Lett.* **2000**, *2*, 2797.

(7) (a) Yamazaki, N.; Iguchi, T.; Higashi, F. *Tetrahedron*, **1975**, *31*, 3031. (b) Yoshida, Y.; Inoue, S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 3146. (c) Casadei, M. A.; Moracci, F. M.; Zappia, G. *J. Org. Chem.* **1997**, *62*, 6754. (d) Aresta, M.; Quaranta, E. *Tetrahedron* **1992**, *48*, 1515. (e) McGhee, W.; Riley, D.; Christ, K.; Pan, Y.; Parnas, B. *J. Org. Chem.* **1995**, *60*, 2820.

(8) In a similar fashion, tetrabutylammonium bromide (TBABr) and various other onium salts have been utilized in supercritical carbon dioxide for the selective formation of urethanes. See: Yoshida, M.; Hara, N.; Okuyama, S. *Chem. Commun.* **2000**, 151.

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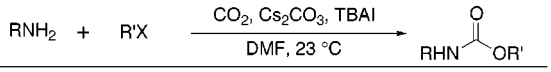
Table 1. Carbamate Formation Using Aliphatic Amines, Halides, and CO_2 in the Presence of Cs_2CO_3 and TBAI



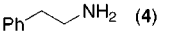
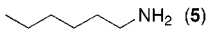
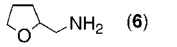
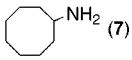
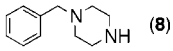
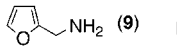
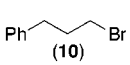
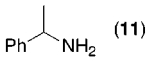
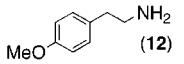
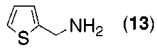
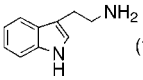
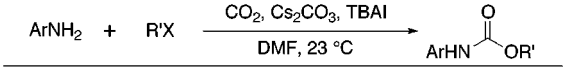
entry	amine (RNH_2)	halide (R'X)	time	yield
1	**1**	BnCl (**3**)	5 h	96%
2	 (**4**)	**3**	6 h	88%
3	 (**5**)	**3**	10 h	93%
4	 (**6**)	**3**	6 h	93%
5	 (**7**)	**3**	6 h	78%
6	 (**8**)	**3**	12 h	85%
7	 (**9**)	 (**10**)	6 h	82%
8	 (**11**)	**10**	7 h	93%
9	 (**12**)	**10**	6 h	85%
10	 (**13**)	**10**	5 h	90%
11	 (**14**)	**10**	8 h	89%

Table 2. Carbamate Formation Using Aromatic and Heterocyclic Amines



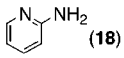
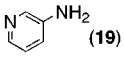
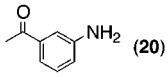
entry	amine ($ArNH_2$)	halide (R'X)	time	yield
1	Aniline (**15**)	**3**	5 h	98%
2	*p*-Toluidine (**16**)	**10**	4 h	96%
3	*N*-Ethylaniline (**17**)	**10**	22 h	78%
4	 (**18**)	**10**	7 h	80%
5	 (**19**)	**10**	4 h	87%
6	 (**20**)	**3**	14 h	47%
7	*p*-Nitroaniline (**21**)	**10**	19 h	50%
8	*m*-Nitroaniline (**22**)	**10**	12 h	73%

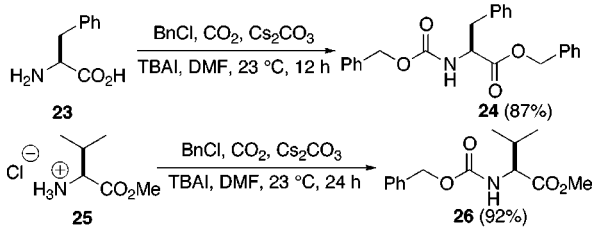
Table 3. Carbamate Formation Using Aromatic Amines Containing Electron-Withdrawing Groups with BnCl

entry	amine ($ArNH_2$)	temp, °C	time	yield, %
1	20	23	5 d	81
2	20	70	24 h	70
3	21	23	5 d	87
4	21	70	24 h	60
5	22	23	5 d	96
6	22	70	24 h	65

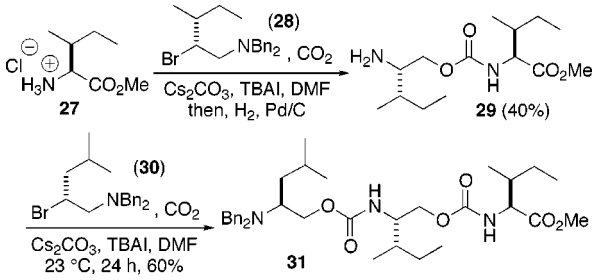
unreacted starting material was recovered along with the carbamate (entries 6−8).

In a continuing study, we endeavored to optimize the conditions for the aromatic amines containing electron-withdrawing groups (Table 3). At higher temperatures (70 °C), similar trends to the previous reactions (entries 6−8, Table 2) were noted. After 24 h, although yields improved slightly, a complicated mixture of other side products were accompanied with the carbamate (entries 2, 4, and 6).[9] Therefore, allowing the reaction to proceed at room temperature for longer duration (e.g., 5 days), the starting amine was found to be consumed. These optimal conditions gave rise to the exclusive formation of the desired products in excellent yields (entries 1, 3, and 5) without any concomitant formation of side products.

Scheme 2



Scheme 3



Keeping peptidomimetic synthesis in mind, we directed our attention toward carbamate formation using amino acids and their derivatives. As depicted in Scheme 2, amino acids and esters were smoothly converted to the corresponding carbamates in excellent yields. For example, when phenylalanine **23** was subjected to the standard conditions, carbamation was accompanied along with the anticipated esterification. Also, valine ester **25** reacted efficiently to afford **26** in high yield without any degree of saponification.

Since the carbamation of amino acids and their derivatives proved to be successful, the preparation of higher order peptidomimetics such as trimer **31** was facile and expeditious by applying our carbamation techniques as outlined in Scheme 3. After amino bromide **28** was prepared through our bromination techniques,[10] it was coupled with isoleucine methyl ester **27** and followed by removal of dibenzyl moieties to afford the peptidomimetic dimer **29**, where the secondary bromide was rearranged to the desired primary form via the corresponding aziridinium salt during the alkylations.[10] Subsequently, dimer **29** was conjugated with bromide **30** to synthesize trimer **31** cleanly. Using our developed protocol, racemizations were not detected during any alkylations of these chiral substrates while complications stemming from hydrolysis were not observed to a noticeable extent.[11]

In summary, a three-component coupling was performed using amines, carbon dioxide, and halides, leading to the efficient synthesis of carbamates, in the presence of cesium carbonate and TBAI. Various aliphatic and

(9) Various side products were detected by thin-layer chromatography, but their structural elucidation was not carried out due to their complicating patterns.

(10) Nagle, A. S.; Salvatore, R. N.; Chong, B. D.; Jung, K. W. *Tetrahedron Lett.* **2000**, *41*, 3011.

(11) ^{1}H NMR, ^{13}C NMR, and 2D NMR analyses indicate the product as a single isomer.

aromatic amines containing electron-donating and electron-withdrawing groups were compatible while reactive, unreactive, and secondary halides were examined to demonstrate substrate versatility. These convenient and safe procedures were superior when compared to known methods since these methodologies avert common side reactions such as the *N*-alkylation of the amine and overalkylation of the carbamate. Furthermore, our technologies offer mild reaction conditions such as ambient temperatures and short reaction times. Thus, chiral substrates encompassing amino acids and amino acid derivatives were resistant to racemization, and labile functionalities including ester were tolerant. These techniques are strongly believed to offer a general synthetic method for various carbamates, offering a wide variety of applications. Efficient synthesis of peptidomimetics and preparation of combinatorial libraries will be reported in due course.

Experimental Section

Representative Experimental Procedure. To benzylamine **1** (200 mg, 1.9 mmol) in anhydrous *N*,*N*-dimethylformamide (10 mL) were added cesium carbonate (1.8 g, 6.0 mmol, 3 equiv) and tetrabutylammonium iodide (2.1 g, 6.0 mmol, 3 equiv). Carbon dioxide gas (flow rate ≈ 25−30 mL/min) was bubbled into the reaction mixture for 1 h, and then 1-bromobutane (770 mg, 0.6 mL, 6.0 mmol, 3 equiv) was added into the suspension. The reaction proceeded at an ambient temperature with CO_2 gas bubbling for 3 h, during which time the starting material (benzylamine) was consumed. The reaction mixture was then poured into water (30 mL) and extracted with EtOAc (3 × 30 mL). The organic layer was washed with water (2 × 30 mL) and brine (30 mL) and dried over anhydrous sodium sulfate. Evaporation of solvent followed by flash column chromatography (hexanes−EtOAc, 9:1 v/v) afforded the carbamate **2** (480 mg, 96%) as an oil. Data for **2**: ^{1}H NMR (360 MHz, $CDCl_3$) δ 0.85 (t, 3 H, J = 7.23 Hz) 1.32 (m, 2 H), 1.52 (m, 2 H), 4.02 (t, 2 H, J = 6.26 Hz), 4.28 (d, 2 H, J = 4.71 Hz), 4.93 (bs, N*H*), 7.17−7.27 (m, 5 H). ^{13}C NMR (90 MHz, $CDCl_3$) δ 13.72, 19.03, 31.04, 44.99, 64.88, 127.40, 127.47,128.61, 138.59, 156.77. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.31; H, 8.21; N, 6.76.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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