Pergamon

Tetrahedron Letters 42 (2001) 6023–6025

TETRAHEDRON LETTERS

An efficient one-pot synthesis of *N*-alkyl carbamates from primary amines using Cs_2CO_3

Ralph Nicholas Salvatore, Jeremy A. Ledger and Kyung Woon Jung*

Department of Chemistry, University of South Florida, 4202 E. Fowler Avenue, Tampa, FL 33620-5250, USA

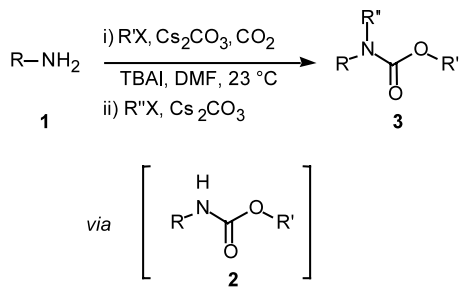
Received 22 June 2001; accepted 5 July 2001

Abstract—A facile one-pot synthesis of *N*-alkyl carbamates is described. A primary amine, CO_2, and an alkyl halide underwent a three-component coupling using cesium carbonate and tetrabutylammonium iodide (TBAI) giving rise to the resultant carbamate. In the presence of Cs_2CO_3, subsequent *N*-alkylation of the in situ generated carbamate with a different alkyl halide afforded various aliphatic *N*-alkyl carbamates, respectively.

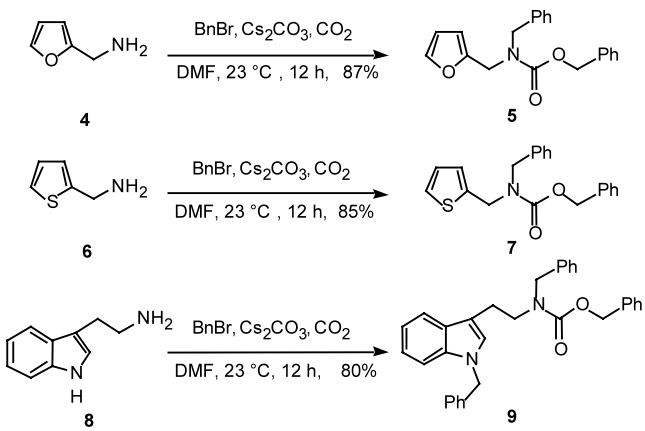
Organic carbamates are valuable synthetic intermediates,[1] which are ubiquitously found in a variety of biologically active compounds.[2] Functionalization of the carbamate moiety offers an attractive method for the generation of derivatives, which may constitute interesting medicinal and biological properties.[3] During the course of our peptidomimetic synthesis, we envisaged that such a scaffold could serve as a crucial template in the construction of carbamate libraries which may be useful in search of potential drug candidates.[4] However, the generation of functionalized carbamates is often hampered by harsh reaction conditions,[5] use of toxic[6] or exotic reagents,[7] and requires multiple steps. Recently, we have disclosed an efficient and safe method for the carbamation of amines[8] as well as a mild procedure for *N*-alkylation of carbamates using cesium bases in both transformations.[9] In the context of this ongoing research, we report herein a useful application of these methodologies for a direct one-pot synthesis of *N*-alkyl carbamates beginning from primary amines. Combination of these two technologies would offer a general synthetic method, which would clearly augment existing techniques.

Owing to the above mentioned protocols, carbamate **2** was generated via a three-component coupling of primary amine **1**, CO_2, and an alkyl halide in the presence of cesium carbonate and tetrabutylammonium iodide (TBAI) in anhydrous *N*,*N*-dimethylformamide (DMF) (Scheme 1). Upon conversion of the starting amine **1** to carbamate **2** (monitored by TLC), an additional 3 equiv. of Cs_2CO_3 were added to the mixture, and stirred for 30 min. Direct *N*-alkylation using a different alkyl halide gave rise to the desired *N*-alkyl carbamate **3** and isolation of the intermediate **2** proved unnecessary offering shortened synthetic sequences.[10]

As delineated in Scheme 2, our initial approach towards a one-pot carbamation followed by *N*-alkylation proce-



Scheme 1.



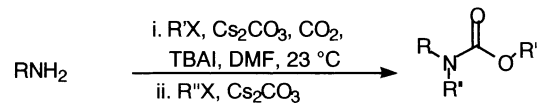
Scheme 2.

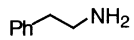
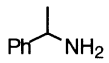
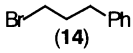
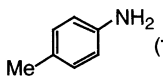
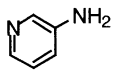
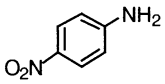
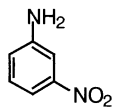
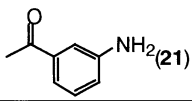
Keywords: carbamate; *N*-alkylation; cesium carbonate.

* Corresponding author.

0040-4039/01/$ - see front matter
PII: S0040-4039(01)01198-4

Table 1.



entry	amine		R'X	R''X	time	yield[a]
1		(10)	MeI (11)	BnBr (12)	20 h	87%
2		(13)	 (14)	12	22 h	75%
3	4		14	12	20 h	61%
4	6		14	12	20 h	75%
5	Aniline	(15)	14	12	24 h	72%
6		(16)	14	12	24 h	60%
7			14	*n*-BuBr (17)	24 h	68%
8		(18)	14	12	30 h	56%
9		(19)	14	12	6 d	92%
10		(20)	14	11	6 d	52%
11		(21)	14	 (22)	6 d	62%

[a] Isolated yields of *N*-alkyl carbamates. The carbamates were not consumed completely during the reaction, accounting for additional mass balance.

dure began employing the use of an active halide. Heterocyclic amines **4** and **6** reacted similarly using excess benzyl bromide, generating the corresponding *N*-alkyl carbamates **5** and **7**, respectively, in high yields after 12 h. Tryptamine **8** proved facile as well, generating substituted carbamate **9** in 80% yield.

On the basis of these results, we next directed our attention towards a one-pot synthesis of mixed *N*-alkyl carbamates utilizing a sequential addition approach with different halides during each alkylation step. As illustrated in Table 1, *N*-alkyl carbamates of aliphatic amines were compatible with both active and unreactive halides (entries 1–4). In addition, aromatic amines were sufficiently converted to the corresponding products after 24 h (entries 5–8). Comparatively, amines containing electron withdrawing substituents, including nitro (entries 9 and 10) or carbonyl (entry 11), reacted slowly after 6 days to afford the desired fully substituted carbamates. In all represented examples, our conditions were highly chemoselective, and no side products other than the intermediate carbamate were detected.[11]

In conclusion, we have developed a simple and efficient one-pot synthesis of various *N*-alkyl carbamates starting with primary amines using cesium carbonate. This reaction is compatible with a diverse range of amines and alkyl halides providing a general method to prepare functionalized carbamates in moderate to high yields. This in situ sequence addresses a four-component coupling of an amine, CO_2, and two electrophiles, which seems to be suitable for generation of combinatorial libraries.

Acknowledgements

We gratefully acknowledge financial supports from the National Institutes of Health (RO1 GM62767) and the American Cancer Society (Institutional Research Grant #032).

References

1. For a comprehensive review of organic carbamates as synthetic intermediates, see: Adams, P.; Baron, F. A. *Chem Rev.* **1965**, *65*, 567.

2. (a) Vauthey, I.; Valot, F.; Gozzi, C.; Fache, F.; Lemaire, M. *Tetrahedron Lett*. **2000**, *41*, 6347; (b) Barthelemy, J. *Lyon. Pharm*. **1986**, *37*, 297.
3. (a) Folkmann, M.; Lund, F. J. *Synthesis* **1990**, 1159; (b) Gogate, U. S.; Repta, A. J.; Alexander, J. *Int. J. Pharm*. **1987**, *40*, 235.
4. (a) Warrass, R.; Weismuller, K.-H.; Jung, G. *Tetrahedron Lett*. **1998**, *39*, 2715; (b) Li, Z.; Bitha, P.; Lang, Jr., S. A.; Lin, Y. *Bio. Med. Chem Lett*. **1997**, *7*, 2909; (c) Bundgaard, H. *Drugs Future* **1991**, *16*, 443.
5. (a) Dorwald, F. Z. *Organic Synthesis on Solid Phase, Supports, Linkers, Reactions*; Wiley-VCH: Weinheim, 2000; pp. 338–340; (b) Sunami, S.; Sagara, T.; Ohkubo, M.; Morishima, H. *Tetrahedron Lett*. **1998**, *39*, 2715; (c) Buchstaller, H. P. *Tetrahedron Lett*. **1998**, *54*, 3465; (d) Salvino, J. M.; Mervic, M.; Mason, H. J.; Kiesow, T.; Teager, D.; Airey, J.; Labaudiniere, R. *J. Org. Chem*. **1999**, *64*, 6.
6. (a) Rafik, C.; Abboud, J. L. M.; Guiheneuf, G. *J. Org. Chem*. **1983**, *24*, 4761; (b) Radeglia, R.; Andersch, J.; Schroth, W. *Z. Naturforsch. B*. **1989**, *44*, 181.
7. (a) Sheludyakov, V. D. *J. Chem. USSR* **1972**, *42*, 357; (b) Moertl, M.; Knausz, D.; Kolos, Z. S.; Szakacs, L.; Csakvari, B. *J. Organomet. Chem*. **1994**, 183.
8. Salvatore, R. N.; Shin, S. I.; Nagle, A. S.; Jung, K. W. *J. Org. Chem*. **2001**, *66*, 1035. For our solid phase carbamation protocol, see: Salvatore, R. N.; Flanders, V. L.; Ha, D.; Jung, K. W. *Org. Lett*. **2000**, *2*, 2797. Recently, this methodology has also been highlighted in the cover story of *C&EN* **2001**, *79*, 56.
9. Salvatore, R. N.; Shin, S. I.; Flanders, V. L.; Jung, K. W. *Tetrahedron Lett*. **2001**, *42*, 1799.
10. Representative experimental procedure: Under a nitrogen atmosphere, *p*-nitroaniline **19** (0.28 g, 2 mmol) was dissolved in anhydrous DMF (10 mL), then Cs_2CO_3 (1.95 g, 6 mmol, 3 equiv.) and TBAI (2.21 g, 6 mmol, 3 equiv.) were added to the solution. Carbon dioxide (flow rate ~25–30 mL/min) was bubbled into the suspension for 1 h, and then 1-bromo-3-phenylpropane (0.51 mL, 6 mmol, 3 equiv.) was added to the mixture. The reaction proceeded at ambient temperature with CO_2 gas bubbling for 5 days, during which time the starting material (*p*-nitroaniline) was consumed. Carbon dioxide bubbling was then stopped, additional Cs_2CO_3 (1.95 g, 6 mmol, 3 equiv.) was added, and DMF (5 mL). After 30 min of stirring, benzyl bromide (0.71 mL, 6 mmol, 3 equiv.) was added, and the reaction was allowed to proceed for 12 h at room temperature. The solution was poured into water and extracted with EtOAc (3×30 mL). The combined organic layers were washed with water (2×30 mL), brine (30 mL), and dried over anhydrous sodium sulfate. After filtration and solvent removal in vacuo, purification by column chromatography (20:1 hexanes:EtOAc) afforded the *N*-benzyl nitrocarbamate (0.72 g, 92%) as an orange oil. **^{1}H NMR** (250 MHz, $CDCl_3$): δ 1.97 (m, 2H), 2.59 (t, 2H, $J=7.3$ Hz), 4.25 (t, 2H, $J=6.4$ Hz), 5.01 (s, 2H), 7.09–7.11 (d, 2H, $J=6.7$ Hz), 7.20–7.45 (m, 10H), 8.16–8.19 (d, 2H, $J=9.1$ Hz). **^{13}C NMR** (70 MHz, $CDCl_3$) δ 30.35, 32.06, 53.55, 65.93, 124.32, 125.69, 126.07, 126.94, 127.70, 128.37, 128.47, 128.86, 137.12, 140.97, 144.82, 148.15, 154.93.
11. No other side products other than the produced carbamates were detected at any given time during the reaction. These products were isolated and accounted for the additional mass balance. However, if the starting amine was not fully converted to the carbamate, a mixture of products usually resulted using different halides.