Pergamon

Tetrahedron Letters 42 (2001) 1799–1801

TETRAHEDRON LETTERS

Efficient and selective *N*-alkylation of carbamates in the presence of Cs_2CO_3 and TBAI

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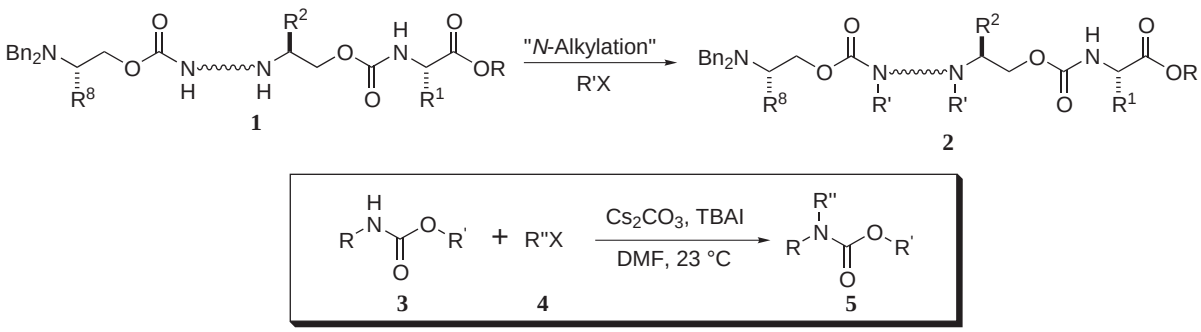
Received 12 December 2000; accepted 3 January 2001

Abstract—Mild and selective *N*-alkylation of carbamates was carried out in the presence of cesium carbonate, tetrabutylammonium iodide (TBAI), and a halide. This protocol was highly selective and efficient, offering aliphatic and aromatic *N*-alkyl carbamates exclusively in high yields. © 2001 Published by Elsevier Science Ltd.

The carbamate moiety is an important structural element in numerous biologically active compounds[1] and has played a crucial role in the area of synthetic organic chemistry primarily as a novel protecting group.[2] Therefore, functionalization of organic carbamates offers great potential in the generation of large combinatorial libraries for rapid screening[3] and drug design.[4] During our efforts towards efficient syntheses of carbamate peptidomimetic analog **2**, we found that direct *N*-alkylation methods of carbamate **1** proved problematic since they employ harsh reaction conditions, such as the use of a strong base which commonly causes hydrolysis or epimerization.[2] Furthermore, other alkylation methods use toxic[5] or expensive exotic reagents[6] to carry out the desired transformation. Thus, these methods lack in generality, prompting us to embark on a selective *N*-alkylation protocol suited for carbamates under mild reaction conditions, which circumvent these shortcomings.

Recently, we reported a cesium base mediated chemoselective procedure for the mono-*N*-alkylation of a primary amine[7] as well as a synthetic methodology for carbamate formation using a three component coupling of an amine, CO_2, and an alkyl halide in the presence of a cesium base.[8] In a continuing study, as illustrated in Scheme 1, subsequent alkylations of carbamates progressed smoothly using cesium carbonate and tetrabutylammonium iodide (TBAI) at ambient temperatures, to give the corresponding *N*-alkylated products exclusively using *N*,*N*-dimethylformamide as the solvent.

As delineated in Table 1, the newly developed techniques[9] were applicable with various mixed alkyl carbamates. Benzyl carbamates **6** and **7** reacted quickly with benzyl chloride offering *N*,*N*-dibenzyl carbamates in high yields. Aliphatic phenethylamine carbamates **8** and **9** proved facile, whereas the TIPS carbamate **10**, a



Scheme 1.

* Corresponding author.

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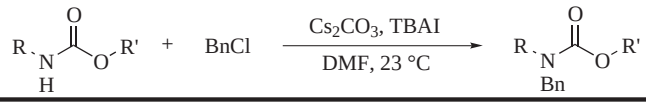
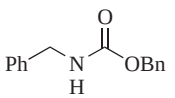
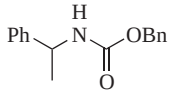
PII: S0040-4039(01)00019-3

Table 1.

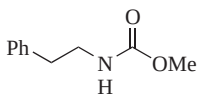




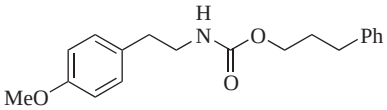
(**6**, 5 h, 96%)



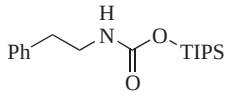
(**7**, 5 h, 92%)



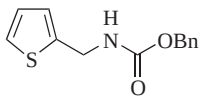
(**8**, 8 h, 91%)



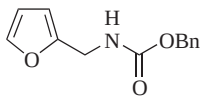
(**9**, 3 h, 90%)



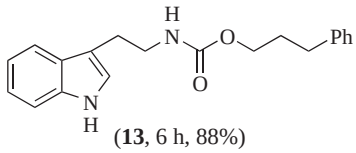
(**10**, 12 h, 75%)



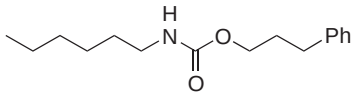
(**11**, 7 h, 91%)



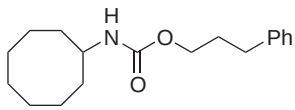
(**12**, 6 h, 93%)



(**13**, 6 h, 88%)

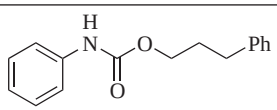
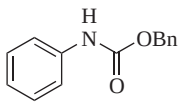
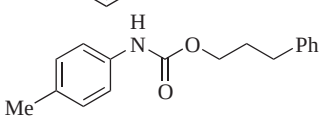
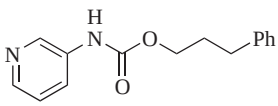
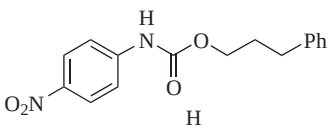
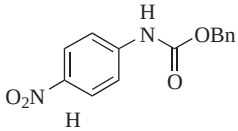
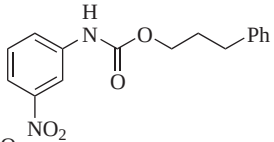
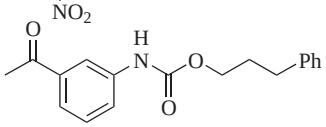


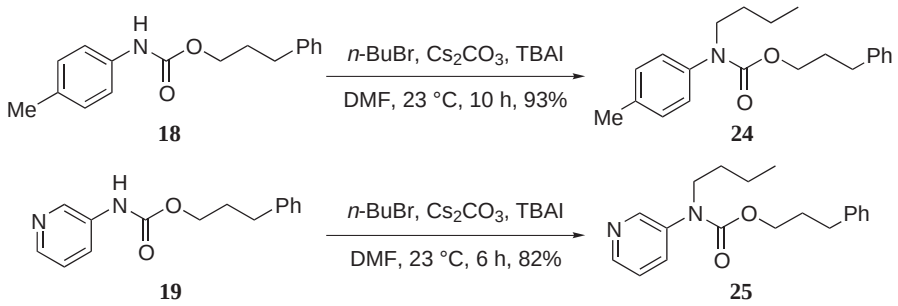
(**14**)



(**15**)

Table 2.

entry	aromatic carbamate		time	yield
1		**(16)**	5 h	98%
2		**(17)**	5 h	96%
3		**(18)**	6 h	93%
4		**(19)**	6 h	88%
5		**(20)**	6 h	93%
6		**(21)**	6 h	90%
7		**(22)**	6 h	93%
8		**(23)**	6 h	96%



Scheme 2.

novel protecting group,[10] also demonstrated to be pragmatic. Various heterocyclic amines (**11**–**13**) were subjected to similar conditions to produce the desired alkylation products. However, much to our surprise and disappointment, lipophilic carbamate **14** and sterically hindered cyclooctyl carbamate **15** were resistant to alkylations under the developed conditions, and the unreacted starting materials were recovered.

Next, our attention was directed towards *N*-alkylation of aromatic carbamates. As exemplified in Table 2, carbamates of aniline moieties reacted efficiently, giving similar results to the aliphatic showcases (entries 1–3). In addition, pyridine containing carbamates reacted smoothly to offer the corresponding products in high yields (e.g. entry 4). Comparatively, regardless of the introduction of an electron withdrawing substituent, which would render the carbamate less basic, nitrocarbamates (entries 5–7) or acetophenone carbamate **23** reacted expeditiously, affording the desired dialkyl carbamates respectively in outstanding yields. In all the attempted examples, our conditions were highly chemoselective and efficient, and no side products were detected whatsoever.

To demonstrate prospects of mildness and substrate versatility, *N*-alkylations were also successful using an unreactive halide such as 1-bromobutane. As illustrated in Scheme 2, carbamates **18** and **19** underwent facile alkylations, implying this technology is compatible with various alkyl bromides.

In conclusion, an efficient synthetic method was developed to prepare fully substituted carbamates. The newly found alkylation conditions were mild and high yielding to offer a general method with substrate versatility. Furthermore, applications of this protocol to the synthesis of carbamate peptidomimetics will be reported in due course.

Acknowledgements

We gratefully acknowledge financial supports from the H. Lee Moffitt Cancer Center & Research Institute and the American Cancer Society (Institutional Research Grant #032).

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8. (a) 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: (b) Salvatore, R. N.; Flanders, V. L.; Ha, D.; Jung, K. W. *Org. Lett*. **2000**, *2*, 2797.
9. Representative experimental procedure: Under a nitrogen atmosphere, carbamate **16** (0.11 g, 0.43 mmol) was dissolved in anhydrous DMF (5 mL), then Cs_2CO_3 (0.42 g, 1.29 mmol, 3 equiv.) and TBAI (0.48 g, 1.29 mmol, 3 equiv.) were added to the solution. After stirring for 30 minutes at ambient temperature, BnCl (0.17 g, 1.29 mmol, 3 equiv.) was added into the suspension. The reaction mixture was stirred for 5 hours, 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. Column chromatography (5:1 hexanes:EtOAc) gave the desired carbamate (0.15 g, 98%) as an oil. **^{1}H NMR** (360 MHz, $CDCl_3$) δ 1.83 (t, 2 H, J=6.7 Hz), 2.48 (t, 2 H, J=7.1 Hz), 4.10 (t, 2 H, J= 5.8 Hz), 4.82 (s, 2 H), 7.00–7.27 (m, 15 H). **^{13}C NMR** (90 MHz, $CDCl_3$) δ 30.51, 31.94, 54.14, 64.93, 125.82, 126.42, 126.83, 127.21, 127.68, 128.31, 128.38, 128.76, 137.98, 141.22, 142.11, 155.73. **IR** (thin film) 3389, 3085, 3062, 3028, 2952, 2858, 1948, 1876, 1803, 1702, 1597, 1496, 1404, 1275, 1223 cm^{-1}.
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