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Communications

Directed Metalation/Snieckus Rearrangement of *O*-Benzylic Carbamates

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Summary: Benzylic carbamates undergo 1,2- or 1,4-carbamoyl migration reaction after lithiation with *s*-BuLi or LDA in THF.

The carbamoyl group is a very effective metalation director in aromatic substitution chemistry.[1] Normally, lithiated aryl carbamates are quenched with electrophiles, but if warmed to room temperature in the absence of electrophiles, O–C 1,3-carbamoyl migration (Snieckus rearrangement) occurs (Figure 1).[2] This phenomenon is known for *ortho*-lithiated *O*-aryl carbamates,[2] and for more remote sites as well.[3] Lithium–halogen exchange of an *o*-bromobenzylic carbamate also results in carbamoyl transfer.[4] Hoppe found that *O*-alkyl, *O*-allyl, and *O*-benzylic carbamates are easily deprotonated by *sec*-butyllithium and TMEDA in hexane or ether to form the corresponding carbanions, which behave as excellent nucleophiles (Figure 1).[5] Asymmetric deprotonation of *O*-alkyl carbamates has been achieved by replacing TMEDA with (−)-sparteine, and the method has provided the enantioselective synthesis of 2-hydroxyalkanoic acids,[6] secondary alkanols,[6] alkanediols,[7] and (*S*)-1-methyldodecyl acetate.[8] We report here that lithiated benzylic carbamates, derived by treatment with strong base such as LDA or *sec*-butyllithium in THF, undergo two different carbamoyl migration reactions, 1,4-transfer to the ortho position, or 1,2-transfer to benzylic position (Scheme I). Although other investigators have noticed similar 1,2-transfers as a side reaction,[9] the process appears to be highly useful in its own right.

The results are presented in Table I. *O*-Benzyl carbamates **1**[10] are deprotonated at -78 °C in THF with 1.3 equiv of *sec*-butyllithium or LDA. The solutions are stirred at that temperature for the indicated period of time. The 1,2- or 1,4-carbamoyl migrated products, **2** or **3**, are isolated in good yield. The reactions work well in THF. TMEDA occasionally improves the yields (comparing entry 5 with 6, 13 with 14, and 16 with 17). Methylenedioxy, methoxy, and methoxymethoxy (MOM) are all known *ortho*-directors,[11] yet only methylenedioxy assists the benzylic carbamates in directing the metalation to the ring (cf. entries 1 vs 11, 2 and 3 vs 18, and 8 and 10 vs 19). For either LDA or *sec*-butyllithium, the order of addition (normal or inverse) had no effect (cf. entries 6 or 7 and 8 or 9). In the presence of a methylenedioxy group, branching at the benzylic position results in *ortho*-metalation (entries 1–4). In contrast, benzylic metalation ensues for all branched compounds having a hydrogen, methoxy, or methoxymethoxy group in the meta position.

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(2) Sibi, M. P.; Snieckus, V. *J. Org. Chem.* **1983**, *48*, 1935–1937.

(3) Wang, W.; Snieckus, V. *J. Org. Chem.* **1992**, *57*, 424.

(4) Lamas, C.; Castedo, L.; Dominguez, D. *Tetrahedron Lett.* **1990**, *31*, 6247.

(5) (a) For review, see: Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932–948 and references cited therein. (b) Hoppe, D.; Bronneke, A. *Synthesis* **1982**, 1045–1048.

(6) Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422–1423.

(7) (a) Hintze, F.; Hoppe, D. *Tetrahedron Lett.* **1992**, *33*, 5323–5326. (b) Ahrens, H.; Paetow, M.; Hoppe, D. *Ibid.* **1992**, *33*, 5327–5330.

(8) Hintze, F.; Hoppe, D. *Synthesis* **1992**, 1216–1218.

(9) See ref 5a and: Beak, P.; Carter, L. G. *J. Org. Chem.* **1982**, *46*, 2363.

(10) Prepared from the corresponding alcohols in 84–98% yield. Typical procedure follows: To a 0.1 M solution of alcohol in THF at room temperature was added potassium hydride. The solution was stirred for 20 min and to it was added 1.1 equiv of dialkyl–carbamoyl chloride. The mixture was stirred for 2 h before normal workup.

(11) (a) For review, see ref 1 and: Gschwend, H. W.; Rodriguez, H. R. *Org. React.* **1979**, *26*, 1–475. (b) Townsend, C. A.; Bloom, L. M. *Tetrahedron Lett.* **1981**, *22*, 3923. (c) Townsend, C. A.; Davis, S. G.; Christensen, S. B.; Link, J. C.; Lewis, C. P. *J. Am. Chem. Soc.* **1981**, *103*, 6885. (d) Winkle, M. R.; Ronald, R. C. *J. Org. Chem.* **1982**, *47*, 2101. (e) Corey, E. J.; Das, J. *J. Am. Chem. Soc.* **1982**, *104*, 5551.

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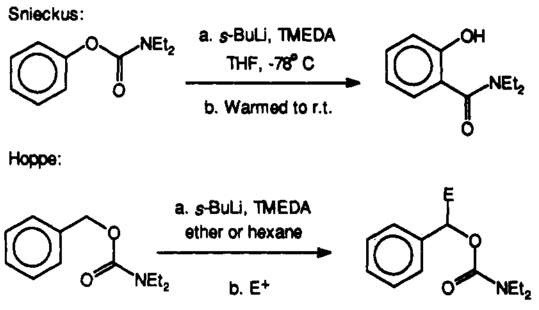


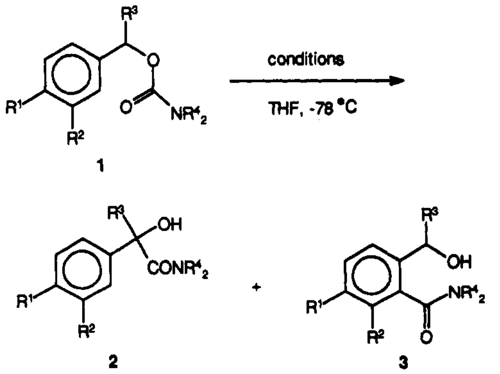
Figure 1.

Table I

entry	substrate	R^1, R^2	R^3	R^4	condns[a]	**2**[b] (%)	**3**[b] (%)
1	**1a**	$-OCH_2O-$	Bu	Et	s-BuLi/2 h		91
2	**1b**	$-OCH_2O-$	Me	Et	LDA/6 h		86
3	**1b**	$-OCH_2O-$	Me	Et	s-BuLi/2 h		75
4	**1c**	$-OCH_2O-$	Me	Me	LDA/6 h		75
5	**1d**	$-OCH_2O-$	H	Et	s-BuLi/TMEDA/2 h	81	
6	**1d**	$-OCH_2O-$	H	Et	s-BuLi/2 h	80	
7	**1d**	$-OCH_2O-$	H	Et	s-BuLi/2 h	72[c]	
8	**1d**	$-OCH_2O-$	H	Et	LDA/6 h	27	61
9	**1d**	$-OCH_2O-$	H	Et	LDA/6 h	22[c]	55[c]
10	**1e**	$-OCH_2O-$	H	Me	LDA/6 h	16	64
11	**1f**	$-OCH_3$, $-OCH_3$	Bu	Et	s-BuLi/overnight	56	
12	**1g**	$-OCH_3$, $-OCH_3$	H	Et	s-BuLi/2 h	80	
13	**1h**	H, H	H	Et	s-BuLi/2 h	81	
14	**1h**	H, H	H	Et	s-BuLi/TMEDA/2 h	85	
15	**1h**	H, H	H	Et	LDA/6 h	86	
16	**1i**	H, H	Me	Et	s-BuLi/2 h	75	
17	**1i**	H, H	Me	Et	s-BuLi/TMEDA/2 h	80	
18	**1j**	H, $-OCH_3$	Me	Et	LDA/6 h	80	
19	**1k**	H, $-OCH_2OCH_3$	H	Et	LDA/6 h	88	

[a] Unless otherwise indicated, the addition order is adding s-BuLi solution into a solution of substrate or adding a solution of substrate into the THF solution of LDA. [b] Isolated and purified product. [c] Inverse addition.

Scheme I



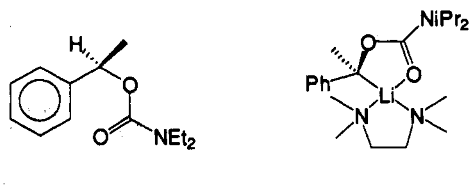
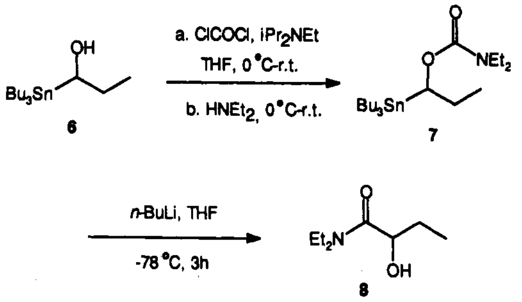


Figure 2.

Scheme II



The factors controlling the site of metalation are not clear. The branching effect in the methylenedioxy compounds (cf. entries 1 and 3 vs 6) suggests that conformational effects may be a factor, but computer modeling has revealed no obvious proximity bias. Treatment of enantiopure carbamate **4**[12] with s-BuLi in the presence or absence of TMEDA in THF affords racemic product **2i** in 80% yield. Treatment of both **1h** and **1i** with s-BuLi and (−)-sparteine in THF or hexane gives racemic **2h** and **2i**, respectively. This means that under the reaction conditions the benzylic carbanion racemizes, in contrast to Hoppe's observation[13] that the intermediary lithium alkanide **5** derived from the corresponding carbamate with s-BuLi/TMEDA is configurationally stable in hexane below −70 °C.

In order to test the possibility of the 1,2-transfer of carbamoyl group in O-alkyl carbamates we prepared compound **7** from alcohol **6**[14] (Scheme II). Tin–lithium exhange (−78 °C) resulted in a 70% yield of hydroxyamide **8**.

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Supplementary Material Available: Procedures and compound characterization (7 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[12] Prepared from commercially available (R)-(+)-sec-phenethyl alcohol in 98% yield.

[13] Hoppe, D.; Carstens, A.; Kramer, T. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1424.

[14] Prepared by the reaction of lithium tributyltin with propionaldehyde in THF. Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481.