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# CARBAMATE DIANIONS: GENERATION AND ALKYLATION OF α-OXO CARBANIONS

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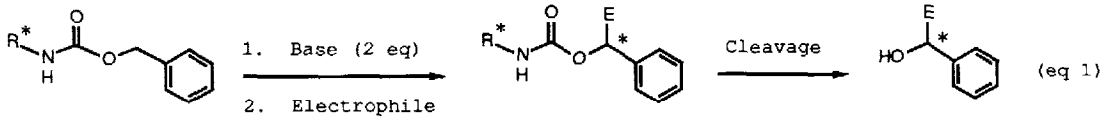
**Summary:** Dianions from simple N-$^t$butyl benzylic-type carbamates are readily formed with alkyllithium bases and undergo alkylation with a variety of electrophiles. Both secondary and tertiary α-oxo carbanions are easily accessible. DIBAL cleavage of the carbamate provides a high yield, general synthesis of alkylated benzylic alcohols.

The ability to generate and homologate α-hetero carbanions continues to receive widespread attention in research and application. In addition to classic examples of carbanionic centers adjacent to phosphorus, sulfur, and silicon, recent advances in α-amino carbanion chemistry,[1] particularly in the area of asymmetric synthesis,[2] serve to demonstrate the vitality of endeavors in this expanding field. Increasing numbers of reports concerning α-oxo carbanions are appearing, with particular emphasis upon the preparation of hydroxymethyl anion equivalents[3] and α-alkoxy carbanions.[4] Such species are commonly prepared from α-alkoxy stannanes by tin/lithium exchange, although direct lithiation by proton abstraction has been described in specialized systems.[5] Indeed, Beak has demonstrated that hindered aromatic esters of primary alcohols are subject to metallation/alkylation, thus providing an α-lithio alcohol synthetic equivalent.[6] In conjunction with our efforts directed toward the asymmetric synthesis of alcohols utilizing carbamate dianions (eq 1), we have completed an initial study in simple achiral systems using N-$^t$butyl benzylcarbamate **1** (eq 2). Our rationale in using $^t$butylamine (1° amine)

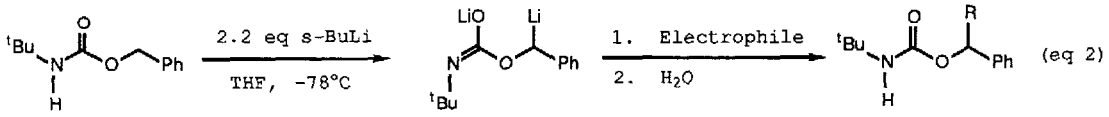



in the preparation of our model carbamate was guided by the fact that many nitrogen-containing chiral auxiliaries viewed as candidates in our asymmetric process are readily available by reduction of primary α-amino acids.

Benzylcarbamate **1** was conveniently prepared in 92% with $^t$butylamine and benzyl chloroformate in $CH_2Cl_2$. Upon addition of 2.2 equivalents of sec-BuLi to **1** (THF,-78°C), a deep red-colored solution was produced, characteristic of dianion formation. Dianion **2** underwent alkylation with a variety of

electrophiles in excellent yields, the results of which are depicted in Table 1.[7] Alkyl chlorides and tosylates failed to alkylate **2**, even at higher temperatures (-50°C) or with the addition of TMEDA. In addition, similar experiments with unactivated carbamates (e.g. N-$^t$butyl ethylcarbamate) have been unsuccessful to date in the metallation step.

**Table 1. Mono Alkylation of N-$^t$Butyl-benzylcarbamate 1.**



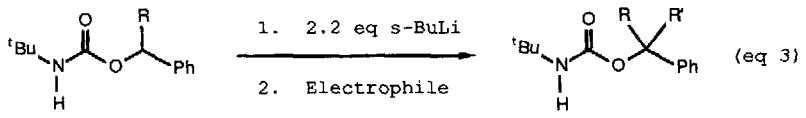

**1** **2** **3**

| Entry | Electrophile [a] | R | % Yield [b] |
|---|---|---|---|
| a. | MeI | - Me | 91 |
| b. | $PhCH_2Br$ | - $CH_2Ph$ | 82 |
| c. | $CH_2=CHCH_2Br$ | - $CH_2CH=CH_2$ | 86 |
| d. | $CH_2=C(CH_2Cl)_2$ | - $CH_2C(CH_2Cl)=CH_2$ | 89 |
| e. | $ClCH_2CH=CHCH_2Cl$ | - $CH_2CH=CHCH_2Cl$ | 81 |
| f. | $Br(CH_2)_3Cl$ | - $(CH_2)_3Cl$ | 86 |
| g. | $Br(CH_2)_4Cl$ | - $(CH_2)_4Cl$ | 82 |
| h. | $Me_3SiCl$ | - $SiMe_3$ | 85 |
| i. | PhCHO | - CH(OH)Ph | 88[c] |
| j. | $ICH_2C(CH_3)_2CHO$ | - $CH(OH)C(CH_3)_2CH_2I$ | 87[c] |
| k. | $CH_3CHBrCH_2CH_2Br$ | - $CH_2CH_2CHBrCH_3$ | 82[c] |

a. Dried and distilled prior to use except for MeI. b. Purified yields following silica gel chromatography. c. Approximately 1:1 mixture of diastereomers.

Having ascertained the feasibility of this approach in providing monoalkylated benzylcarbamates, we sought to extend this method as applied to dialkylated carbamates. Initially there was a question as to whether we would be able to generate tertiary α-oxo carbanions, however this proved not to be a problem in most cases studied. Dianion formation occurred readily at -78°C upon treatment, for example, of **3a** with 2.2 equivalents of sec-BuLi. Following addition of the electrophile, good yields of dialkylated material were obtained. It is of interest to note that carbamate **3h** (R=$SiMe_3$) could not be metallated/alkylated under a variety of conditions, with complete recovery of starting material. Table 2 lists representative results obtained in the dialkylation experiments.

**Table 2. Second Alkylation of Carbamate Tertiary αOxo Carbanions.**



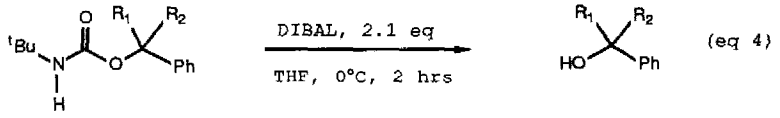

3 4

| Entry | R | Electrophile [a] | R' | % Yield [b] |
|---|---|---|---|---|
| a. | - Me | MeI | - Me | 80 |
| b. | - Me | $Me_3SiCl$ | - $SiMe_3$ | 79 |
| c. | - $CH_2Ph$ | MeI | - Me | 82 |
| d. | - $CH_2CH=CH_2$ | MeI | - Me | 69 |
| e. | - Me | $Br(CH_2)_3Cl$ | - $CH_2(CH_2)_2Cl$ | 77 |

a. Dried and distilled prior to use except for MeI. b. Purified yields following silica gel chromatography.

In order to achieve one of our initial goals in the study of carbamate dianions, we required an efficient method for cleavage of the carbamate functionality. Hydrolytic cleavage was investigated extensively under numerous

**Table 3. Generation of Alcohols by Carbamate Reductive Cleavage.**




3, 4 5

| Entry | Carbamate | $R_1$ | $R_2$ | % Yield [a] |
|---|---|---|---|---|
| a. | 3c | - H | - $CH_2CH=CH_2$ | 91 |
| b. | 3d | - H | - $CH_2C(CH_2Cl)=CH_2$ | 90 |
| c. | 3e | - H | - $CH_2CH=CHCH_2Cl$ | 84 |
| d. | 3f | - H | - $(CH_2)_3Cl$ | 89 |
| e. | 3g | - H | - $(CH_2)_4Cl$ | 89 |
| f. | 3h | - H | - $SiMe_3$ | 81 |
| g. | 3j | - H | - $CH(OH)C(CH_3)_2CH_2I$ | 64 |
| h. | 3k | - H | - $CH_2CH_2CHBrCH_3$ | 88 |
| i. | 4e | - Me | - $(CH_2)_3Cl$ | 73 |

a. Purified yields following silica gel chromatography.

conditions, however long reaction times and poor yields necessitated finding a more expedient procedure. DIBAL (2.1 eq) in THF (0°C) has proven to be most effective, giving excellent yields of alcohols (**5**) within 2 hours as shown in Table 3. Noteworthy is that DIBAL in $CH_2Cl_2$ failed to cleave the carbamates.

In summary, our interest in α-oxo carbanion chemistry has led to the development of a general, high yield synthesis of secondary and tertiary benzylic alcohols. Further studies addressing the synthesis of various heterocycles and the asymmetric synthesis of alcohols are in progress.

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7. All new compounds exhibited spectral characteristics ($^1$H- and $^{13}$C-NMR, IR, MS) and microanalytical data (C,H,N or HRMS) consistent with their assigned structures. A representative alkylation procedure is as follows: A flame-dried 100mL round bottom flask under an argon atmosphere charged with benzylcarbamate **1** (1.02g, 4.82mmol) in dry tetrahydrofuran (40mL) was cooled to -78°C and treated with a 1.16 M solution of sec-BuLi (9.10mL, 10.16mmol) dropwise over 10 min with continuous stirring. After 1 hr, benzyl bromide (0.91g, 5.31mmol) was added neat dropwise to the red-colored solution, and stirring was continued at -78°C for an additional 1 hr. The reaction was quenched by the addition of 5mL of saturated aqueous $NH_4Cl$ and 5mL water, and the product extracted into ethyl acetate (3 x 25mL). The extract was washed with 5mL water followed by 5mL brine, and was dried over anhydrous $Na_2SO_4$. Following filtration and concentration *in vacuo*, the residue was chromatographed on silica gel (10% EtOAc in hexane) giving 1.17g (82%) of carbamate **3b** as white fluffy crystals. Recrystallized from hexane: mp 58-59°C. IR (solid film) 3314, 1699, 1603, 1534, 1274, 1090, 756, 698 $cm^{-1}$. $^1$H-NMR ($CDCl_3$, 270 MHz) δ 7.3-7.0 (m, 10H), 5.84 (m, 1H), 4.66 (s, 1H, NH), 3.10 (ABX, 2H, $\Delta\nu_{AB}$= 41.2 Hz, $J_{AB}$=13.7, $J_{AX}$=6.8, $J_{BX}$=6.8 Hz), 1.23 (s, 9H). $^{13}$C-NMR ($CDCl_3$, 67.8 MHz) δ 154.0, 140.6, 137.1, 129.5, 128.1, 128.0, 127.6, 126.4, 126.3, 76.1, 50.2, 43.2, 28.9. Anal. Calcd. for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71. Found: C, 76.86; H, 8.00; N, 4.70.

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