Carbon Dioxide. A Reagent for the Protection of Nucleophilic Centers and the Simultaneous Activation for Electrophilic Attack. Part 4.[1] The α-Substitution of (i) Benzyl Alcohol and (ii) Benzylamine

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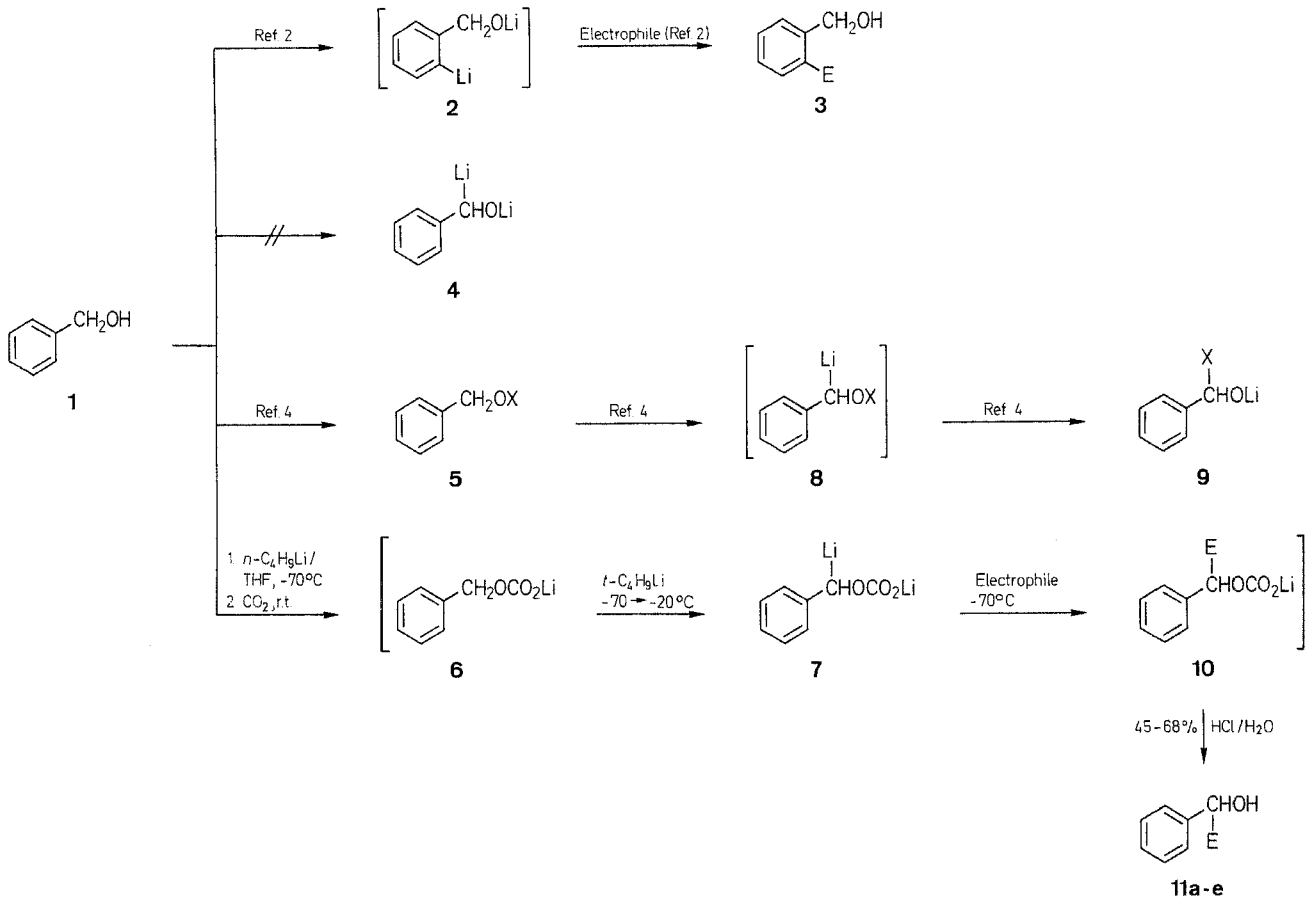
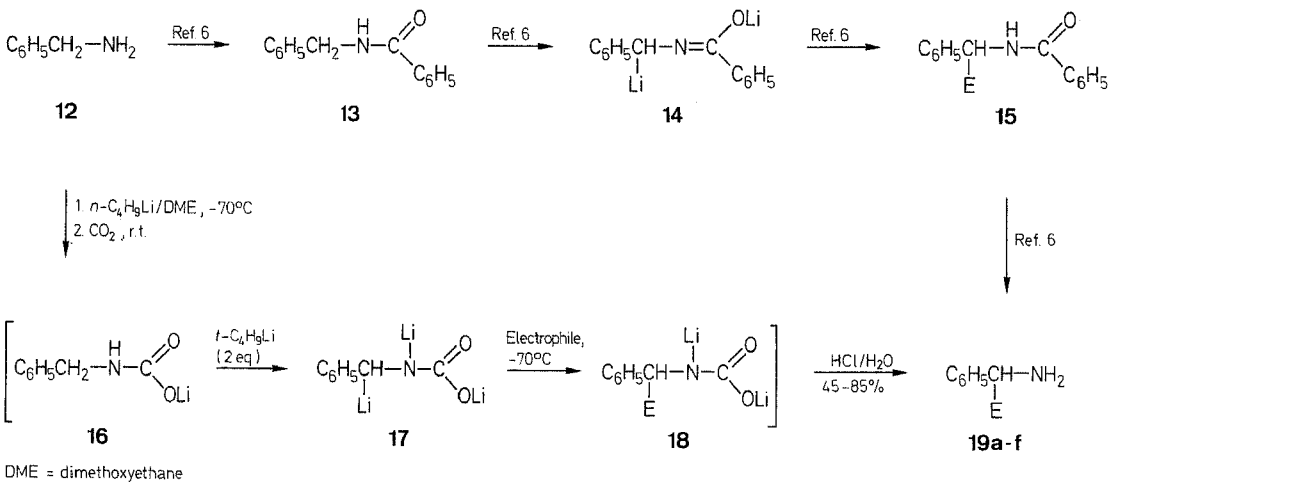
Benzyl alcohol is converted into a variety of α-substituted derivatives by a one-pot sequence involving lithiation of an intermediate hemicarbonate ester. Benzylamine is similarly converted by a one-pot sequence to α-substituted benzylamines: here an intermediate carbamate salt is involved.

Meyer and Seebach[2] have shown that benzyl alcohols **1** are doubly deprotonated by excess *n*-butyllithium in *N,N,N',N'*-tetramethylethylenediamine (TMEDA) pentane to give lithium *ortho*-lithio alkoxides **2**, which react with electrophiles to afford a variety of *ortho*-substituted products **3**. Thus, the direct approach to the α-lithiated species **4** is not available, although the corresponding synthon $^-CH_2O^-$ derived from methanol has been reported.[3] If a benzyl alcohol derivative **5** is used, the product is usually that **(9)** of the Wittig rearrangement[4] of carbanion **8**, although α-functionalization by an external electrophile can sometimes occur to a small extent.[5] We now report the successful application of our method[1] of carbon dioxide protection-activation to the one-pot preparation of α-substituted benzyl alcohols **(11)** *via* the sequence **1** → **6** → **7** → **10** → **11**.

α-Substitution of benzylamine has previously been achieved *via* three step sequences of protection, substitution and deprotection. Thus, Tischler and Tischler[6] used *N*-benzylbenzamide in this way in the sequence **12** → **13** → **14** → **15** → **19**. The use of isocyanides[4] is also well known, and other groups have been utilized,[7] but without exception, all these previous methods require three operations. We now report the successful application of our method[1] of carbon dioxide protection-activation to achieve a convenient one-pot preparation of α-substituted benzylamines **19** *via* the sequence **12** → **16** → **17** → **18** → **19**.





DME = dimethoxyethane

The reaction procedures are as follows. Benzyl alcohol was lithiated with *n*-butyllithium/tetrahydrofuran and benzylamine was lithiated with *n*-butyllithium/dimethoxyethane, as appropriate, at −70 °C under argon, and in each case carbon dioxide was then passed into the reaction mixture at 25 °C. The resulting lithium carboxylate salt was treated with t-butyllithium (two equivalents were used for experiments with benzylamine). The desired electrophile was added to the resulting dianion (benzyl alcohol) or trianion (benzylamine) solution at −70 °C. The reaction product was decarboxylated with hydrochloric acid to give the crude product, which was purified by column chromatography or recrystallization.

Results are shown in Tables 1 and 2 and demonstrate that a variety of electrophiles react with the dianion **7** to give the products **11**, and with the trianion **17** to give products **19**, in fair to good yields. In this way an alkyl, acyl, carbamoyl, or hydroxyalkyl group or a deuterium atom has been introduced into the α-position of benzyl alcohol or of benzylamine.

1,1,2-Triphenylethanediol (11b); Typical Procedure:
Benzyl alcohol (1.08 g, 0.01 mol) in tetrahydrofuran (30 ml) in a Schlenk type reactor under argon is cooled to −70 °C and *n*-butyllithium (2.5 M *n*-hexane solution, 4.0 ml) is slowly added drop-

Table 1. α-Substituted Benzyl Alcohols Prepared from Benzyl Alcohol

11	α-Substit.	Electrophile	Yield[a] (%)	m.p. (°C) found	m.p. (°C) reported	NMR ($CDCl_3$/TMS)[b] δ (ppm)
a	CO_2H	CO_2	65	119–120	115–117[8]	5.27 (s, 1H, CH); 7.2–7.8 (m, 7H, C_6H_5, OH, CO_2H)
b	$C(OH)(C_6H_5)_2$	$(C_6H_5)_2CO$	47	165–167	168[a]	2.5 (br s, 1H, OH); 3.2 (br s, 1H, OH); 5.7 (s, 1H, CH); 7.1–7.9 (m, $15H_{arom}$)[c]
c	C_6H_5CO	$C_6H_5CO_2C_2H_5$	51	135–137	132–135[10]	4.5 (br s, 1H, OH); 6.02 (s, 1H, CH); 7.3–7.7 (m, $8H_{arom}$); 7.85–8.15 (m, $2H_{arom}$)
d	CH_3	CH_3I	45[d]	–	–	1.4 (d, 3H, $J = 6$ Hz); 4.72 (q, 1H, $J = 6$ Hz, $CHCH_3$); 7.18 (s, $5H_{arom}$)
e	D	D_2O	68[d]	–	–	3.28 (s, 1H, OH); 4.77 (s, 1H, CHDOH); 7.47 (s, $5H_{arom}$)

[a] Isolated yield after purification.
[b] Recorded on a Varian EM 360L spectrometer.
[c] ^{13}C-NMR ($CDCl_3$): δ = 76.6 (CH), 79.7 (C–CH), 126.5, 126.3, 127.4, 127.2, 128.7, 141.9, 146.0, 146.6 ppm (C_{arom}).
[d] ^{1}H-NMR yield.

Table 2. α-Substituted Benzylamines Prepared from Benzylamine

19	α-Substit. E	Electrophile	Yield[a] (%)	m.p. (°C) or b.p. (°C)/torr found	m.p. (°C) or b.p. (°C)/torr reported	^{1}H-NMR ($CDCl_3$/TMS) δ (ppm)
a	CO_2H	CO_2	61	275–279[b]	256[b,11]	5.43 (br s, 1H, CH); 7.60 (s, $5H_{arom}$); 7.75 (s, 2H, NH_2)[c]
b	CH_3	CH_3I	67	185–188/760	182–185/760[12]	1.40 (d, 3H, CH_3); 1.52 (s, 2H, NH_2); 4.05 (q, 1H, $CHCH_3$); 7.42 (s, $5H_{arom}$)
c	C_6H_5CO	$C_6H_5CO_2C_2H_5$	54	105–107	109[13]	4.63 (d, 2H, NH_2); 6.54–7.92 (m, 11H, CH, H_{arom})
d	C_6H_5NHCO	C_6H_5NCO	45	112–114	117.5–118.5[14]	4.42 (d, 2H, NH_2); 6.25 (s, 1H, CH); 6.9–7.65 (m, $10H_{arom}$); 8.35 (br s, 1H, CONH)
e	D	D_2O	85[d]	–	–	1.95 (d, 2H, NH_2); 4.60 (s, 1H, $CHDNH_2$); 7.32 (s, $5H_{arom}$)
f	t-C_4H_9NHCO	t-C_4H_9NCO	57	114–115	–[e]	1.25 (s, 9H, $C(CH_3)_3$); 4.15 (d, 2H, NH_2); 5.00 (s, 1H, $CHNH_2$); 5.40 (s, 1H, CONH); 7.13 (s, $5H_{arom}$)

[a] Isolated yield after purification.
[b] With sublimation.
[c] Solvent: CF_3CO_2H.
[d] ^{1}H-NMR yield.
[e] New compound: $C_{12}H_{18}N_2O$ (206.3) calc. C 69.87 H 8.80 N 13.58; found 69.93 9.18 13.44

wise. The resulting solution is kept at −70 °C for a few minutes, and then allowed to rise to 25 °C. Carbon dioxide gas is passed into the reaction mixture for several minutes.

The solvent is removed under reduced pressure, leaving a pale yellow residue of lithium benzyl carbonate. The atmosphere is replaced by argon, tetrahydrofuran (50 ml) added, the solution cooled to ca. −70 °C, and t-butyllithium (1.7 M n-pentane solution, 6 ml) is added slowly. The cooling bath is replaced by an ice bath, and the solution is kept at −20 °C for 1 h. The reaction mixture is again cooled to −70 °C, and benzophenone (1.82 g, 0.01 mol) in tetrahydrofuran (3 ml) is added. The reaction mixture is allowed to regain 20 °C and stirred overnight. 2 Normal aqueous hydrochloric acid (10 ml) is added at 0 °C. The acidic solution is neutralized by sodium hydrogen carbonate, and extracted with chloroform (3 × 20 ml). The organic extract is dried with sodium sulfate, filtered, and the solvent evaporated to give crude product, which is recrystallized from hexane/ether to give **11b**; yield: 1.36 g (47%).

Phenylglycine Anilide (19d); Typical Procedure:
Benzylamine (1.07 g, 0.01 mol) in dimethoxyethane (40 ml) under argon is cooled to −70 °C and n-butyllithium (2.5 molar n-hexane solution, 4.0 ml) is added dropwise. The solution temperature is allowed to rise to 25 °C. Carbon dioxide gas is added. The solvent is removed under reduced pressure, leaving a pale residue of lithium carbamate. The atmosphere is replaced again by argon, and dimethoxyethane (70 ml) followed by t-butyllithium (1.7 molar n-pentane solution, 12 ml) is added slowly at −70 °C. The cooling bath is replaced by an ice-salt bath, and the resulting solution is kept at −20 °C for 1 h and then cooled to −70 °C again. Phenyl isocyanate (1.19 g, 0.01 mol) in tetrahydrofuran (3 ml) is added at −70 °C. The reaction mixture is allowed to regain 25 °C over 3 hours. 2 Normal aqueous hydrochloric acid (10 ml) is added at 0 °C. After neutralization with sodium hydrogen carbonate, the solution is extracted with chloroform (3 × 20 ml). The organic extract is dried with sodium sulfate, filtered, and the solvent is evaporated to give the crude product, which is recrystallized from chloroform/hexane to give **19d**; yield: 0.95 g (45%).

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