Generation of the Lithium α-Benzyloxy- and α,α-Diphenoxy-α-lithioacetate Synthons and Their Alkylation

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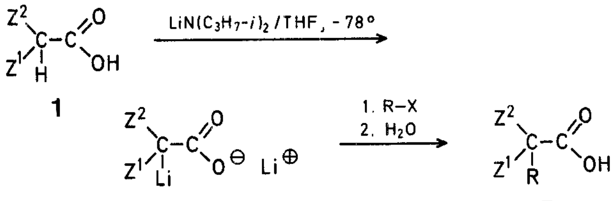
Recently, we reported[1] on the generation and synthetic utilization of the versatile lithium α-lithio-α-phenoxycarboxylate **2** synthon, conveniently prepared from the corresponding carboxylic acids by direct α-lithiation with lithium diisopropylamide (LDA).



2 $Z^1 = C_6H_5{-}O{-}$, $Z^2 = H$
3 $Z^1 = C_6H_5{-}CH_2{-}O{-}$, $Z^2 = H$
4 $Z^1 = Z^2 = C_6H_5{-}O{-}$

We extend this synthetic methodology to the preparation of the hitherto unknown lithium α-benzyloxy- (**3**) and α,α-diphenoxy-α-lithiocarboxylate (**4**) synthons and demonstrate their synthetic utility by means of their alkylation with reactive alkyl halides to give the acids **5**. Similar work has been reported on lithium α-alkoxy-α-lithiocarboxylates of the type **3** by others[2]; but the generation of the lithium α,α-diphenoxy-α-lithiocarboxylate (**4**) and its alkylation is unprecedented.

As described previously[1] for **2**, the lithium α-lithiocarboxylates **3** and **4** were generated from the benzyloxy- and diphenoxyacetic acids, respectively, by treatment with LDA in tetrahydrofuran at −78°. The conversion was better than 95% as confirmed by ^{1}H-N.M.R. spectra of the α-deuterated (D_2O) carboxylates. In the case of the diphenoxy derivative **4**, hexamethylphosphoric triamide (HMPT) had to be used to prevent its precipitation.

When the clear, yellow lithium α-lithiocarboxylate solutions were allowed to warm up beyond −60°, they quickly decomposed into intractable materials. Consequently, the subsequent reaction of these synthons with alkyl halide electrophiles had to be performed at −78°. In the case of benzyl bromide, addition of catalytic amounts of sodium iodide (for the *in situ* generation of benzyl iodide) improved the yields significantly. The methylation and benzylation leading to the corresponding α-benzyloxy and α,α-diphenoxy acids **5a, b** are summarized in the Table. The α,α-diphenoxy acids **5c, d** could not be directly characterized since these labile materials liberated phenol by auto-catalyzed acidolysis on attempted purification. Therefore, the crude α,α-diphenoxy acids **5c, d** were converted immediately to their methyl esters with diazomethane and characterized as such. Typical procedures are described for the benzylation of **3** and **4**.

2-Benzyloxy-3-phenylpropanoic Acid (5b):

To a stirred solution of lithium diisopropylamide (50 mmol) in anhydrous tetrahydrofuran (50 ml), freshly prepared by addition of stoichiometric amounts of diisopropylamine and butyllithium, is added slowly at −78° the α-benzyloxyacetic acid (25 mmol) in anhydrous tetrahydrofuran (5 ml). The clear, yellow solution is stirred at −78° for an additional 15 min and then benzyl bromide (42.75 g, 250 mmol) is added all at once. After stirring at −78° for 120 min, the mixture is allowed to warm up slowly to room temperature, poured onto an equal volume of crushed ice, transferred to a separatory funnel, and extracted with ether (2 × 50 ml) to remove neutral components. The clear aqueous solution is acidified with conc. hydrochloric acid to pH ~ 3, and extracted with ether (5 × 50 ml). The combined ether extracts are washed once with water, dried with magnesium sulfate, roto-evaporated (~ 30°/25 torr) to remove solvent, and fractionally distilled affording the pure acid **5b** after recrystallization from hexane/benzene; yield: 4.5 g (72%); m.p. 60–62°.

2,2-Diphenoxy-3-phenylpropanoic Acid (5d):

To a stirred solution of lithium diisopropylamide (50 mmol) in anhydrous tetrahydrofuran (50 ml) (freshly prepared by addition of stoichiometric amounts of diisopropylamine and butyllithium),

Table. α-Benzyloxy- and α,α-Diphenoxycarboxylic Acids (**5**)

5	Z^1	Z^2	R	Yield [%]	m.p. or b.p.	Molecular formula	I.R. (CCl_4) ν_{max} [cm^{-1}]	^{1}H-N.M.R. (CCl_4) δ [ppm]
a	$C_6H_5{-}CH_2{-}O{-}$	H	CH_3	80	b.p. 115–120°/ 0.15 torr[a]	$C_{10}H_{12}O_3$ (180.2)	3400–2400 (OH); 1715 (C=O)	11.1 (s, OH); 7.2 (m, 5 H_{arom}); 4.4 (AB, 2H, CH_2—O, J = 3 Hz); 3.9 (q, 1H, CH, J = 1.5 Hz); 1.4 (d, 3H, CH_3, J = 1.5 Hz)
b	$C_6H_5{-}CH_2{-}O{-}$	H	$-CH_2C_6H_5$	72	m.p. 60/62° (hexane/ benzene)[b]	$C_{16}H_{16}O_3$ (256.3)	3400–2400 (OH); 1715 (C=O)	11.1 (s, OH); 6.8–7.3 (m, 10 H_{arom}); 4.4 (AB, 2H, CH_2O, J = 3 Hz); 3.9 (m, 1, CH); 3.0 (d, 2, CH_2, J = 1.5 Hz)
c	$C_6H_5{-}O{-}$	$C_6H_5{-}O{-}$	CH_3	60	[b.p. 90–95°/ 0.01 torr][b, c]	$C_{16}H_{16}O_4$ (272.3)[c]	[1760 (C=O)][c]	[6.8–7.3 (m, 10 H_{arom}); 1.6 (s, 3H, CH_3); 3.6 (s, 3H, OCH_3)][c]
d	$C_6H_5{-}O{-}$	$C_6H_5{-}O{-}$	$-CH_2C_6H_5$	65	[b.p. 120–130°/ 0.01 torr][b, c]	$C_{22}H_{20}O_4$ (328.4)[c]	[1755 (C=O)][c]	[6.7–7.2 (m, 15 H_{arom}); 3.4 (s, 2H, CH_2); 3.3 (s, 3H, OCH_3)][c]

[a] Ref.[3], b.p. 118–120°/0.15 torr.

[b] The microanalyses showed the following maximum deviation from the calculated values: C, ±0.40; H, ±0.20. The mass spectra (70 eV) showed the appropriate M^+ or $M^+ - H_2O$ ions.

[c] Characterized as methyl ester (oil) which was purified by molecular distillation; b.p. represent minimum bath temperature required for distillation.

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a solution of diphenoxyacetic acid (6.1 g, 25 mmol) in anhydrous tetrahydrofuran (5 ml) + HMPT (5 ml) is added slowly at $-78°$. The clear, yellow solution is stirred at $-78°$ for 15 min and then transferred dropwise by means of a steel capillary syphon (15 G), by employing a slight nitrogen pressure, into a stirred solution of benzyl bromide (42.75 g, 250 mmol) in anhydrous tetrahydrofuran (50 ml) containing sodium iodide (0.5 g) kept at $-78°$. After complete addition, the reaction mixture is stirred for 120 min, warmed up slowly to 0–5°, poured onto an equal volume of crushed ice, transferred to a separatory funnel, and extracted with ether (2 × 20 ml) to remove neutral components. The cold, clear, aqueous solution is acidified with 10% hydrochloric acid to pH ~ 3 while keeping the temperature below 10°, and extracted with ether (5 × 20 ml). The combined ether extracts are washed once with saturated sodium hydrogen sulfite solution (to remove iodine), dried with magnesium sulfate, and roto-evaporated (~ 30°/25 torr) to give the crude acid **5d**. This sensitive substance was isolated in the form of its methyl ester by immediate esterification with diazomethane. The physical constants and spectral data are given in the Table.

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