The Synthesis of α-Hydroxycarboxylic Acids by Aeration of Lithiated Carboxylic Acids in Tetrahydrofuran Solution

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A novel route to α-acyloxy carboxylic acids has recently been described by Taylor, Altland, and McGillivray[1] and references to prior synthetic routes to α-hydroxy and α-bromo acids are listed therein. Additionally, α-hydroxy acids have been prepared by a Favorski process.[2]

We earlier reported[3] that the reaction of the di-lithiated 2-phenylbutanoic acid with benzophenone gave only the 2-hydroxy-2-phenylbutanoic acid and we have found that this result was caused by the oxygen contaminant in the nitrogen passed through the reaction system during the reaction. Pfeffer[4] in his work with metalated long-chain fatty acids using tetrahydrofuran/hexane/hexamethylphosphortriamide solutions has indicated the possibility of reaction with oxygen.

The aeration in tetrahydrofuran solution of di-lithiated carboxylic acids prepared by the reaction of the carboxylic acid with lithium diisopropylamide[5] is in several instances a very simple and effective route to the α-hydroxy acids. Air is bubbled into the tetrahydrofuran solution of the lithiated acid at room temperature. Formation of a precipitate occurs almost immediatly. At the end of the aeration, the mixture is decomposed with water and ether. The separated aqueous phase is acidified and the acidic product isolated by extraction or by filtration. Aeration times were usually 14–18 hr. Over-oxidation occurred noticeably only in the case of (4-methoxyphenyl)-acetic acid. In each attempt, the product was a mixture of 4-methoxymandelic acid and 4-methoxybenzoic acid and was separated by crystallization from isopropyl ether/cyclohexane. Longer periods of aeration (overnight) gave almost solely 4-methoxybenzoic acid and it was found necessary to shorten the aeration time to 5–6 hours.

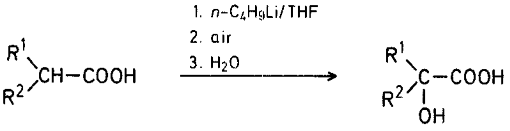
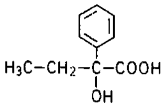
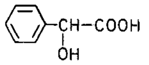
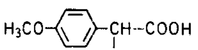
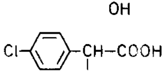
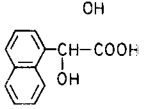
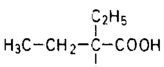
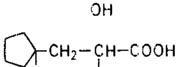
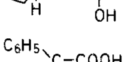
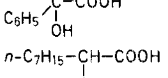


Table 1. Preparation of α-Hydroxycarboxylic Acids

α-Hydroxycarboxylic Acid[a]	Yield[c] %	m.p. (Lit. m.p.)[b]
	67	131–133° [d] (132.5°)
	66	118–120° [e] (118–119°)
	48	98–102° [f] (108°)
	72	118–120° [f] (119–122°)
	32	92°, 125° [g] (98–99°) (91°) (125°)
 $H_3C{-}CH_2{-}C(C_2H_5)(OH){-}COOH$	49	78–79° [d] (80°)
	51	66–68° [d,h]
 $(C_6H_5)_2C(OH){-}COOH$	90	148–150° [e] (150°)
 $n{-}C_7H_{15}{-}CH(OH){-}COOH$	51	67–69° [d] (70°)

[a] The starting acids were used as commercially available.

[b] Identification was made by comparison with literature melting points from standard handbooks and by I.R. and N.M.R. analysis.

[c] Yields are as isolated material from
[d] heptane, [e] isopropyl ether, [f] isopropyl ether and cyclohexane, [g] water.

[h] New compound.

$C_8H_{14}O_3$	calc.	C 60.75	H 8.92
	found	60.87	9.11

Preparation of α-Hydroxycarboxylic Acids; General Procedure: Redistilled diisopropylamine (2 molar equiv) and tetrahydrofuran (dried over calcium hydride and run through basic alumina just prior to use) are introduced into a nitrogen-swept flask and cooled to 0–5°. Butyllithium in heptane solution (2.1 molar equiv) is introduced in a fine stream. The mixture is then stirred for 15–30 min. at 0–5°. A solution of 1 molar equiv of the carboxylic acid in dry tetrahydrofuran is dropped in with continued cooling and stirring. Stirring is continued for 30 min. at 0–5° and then at 40–50° for 1–1.5 hr. The reaction is then cooled to room temperature and air bubbled into the solution for ~18 hr (i.e. overnight). Water (~2 vols) is added and the mixture extracted with ether. The separated aqueous layer is cooled and made acid with conc. hydrochloric acid. The product is extracted with ether, the extract washed with water, and dried with magnesium sulfate. The crude product is obtained by evaporation of the solvent.

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[1] E.C. Taylor, H.W. Altland, G. McGillivray, Tetrahedron Lett. **1970**, 5285.
[2] J.G. Aston et al., Org. Synth., Coll. Vol III, 538 (1955).
[3] G.W. Moersch, A.R. Burkett, J. Org. Chem. **36**, 1149 (1971).
[4] P.E. Pfeffer, L.S. Silbert, J. Org. Chem. **35**, 262 (1970).
[5] P.L. Creger, J. Amer. Chem. Soc. **89**, 2500 (1967); **92**, 1396, 1397 (1970).