

A Simple Route to α -Aminoketones and Related Derivatives by Dianion Acylation Reactions; an Improved Preparation of δ -Aminolevulinic Acid

By DAVID A. EVANS* and PHILIP J. SIDEBOTTOM

(Department of Chemistry, The University, Southampton SO9 5NH)

Summary Acylation of the dianion (**1**) derived from ethyl hippurate (**2**) using anhydrides, followed by acid hydrolysis, provides a general route to α -aminoketones; a short and convenient preparation of the porphyrin precursor δ -aminolevulinic acid (as the hydrochloride) by the foregoing procedure is described.

THE Dakin-West reaction¹ between α -amino-acids and carboxylic anhydrides, proceeding through 5(4*H*)-oxazolones and acylamidoketones as intermediates, provides a major route to the preparation of α -aminoketones. However, this procedure is frequently found to be unsatisfactory for compounds of the type $\text{NH}_2\text{CH}_2\text{COR}$ owing to low or irreproducible yields and to difficulties in purifying products.² Furthermore, the free bases are prone to rapid oxidative dimerisation to 2,5-dialkylpyrazines. We report here a more satisfactory preparation of such α -aminoketones by acylation of the lithio-dianion (**1**), followed by acid-catalysed hydrolysis.

The reaction of ethyl hippurate (**2**) with lithium diisopropylamide has been reported to proceed to (**1**) in *ca.* 80% yield, as indicated by deuteration studies assayed by n.m.r. spectroscopy, and the synthetic utility of (**1**) in alkylation reactions has been described.³ In our studies, we attempted to acylate (**1**) with acetyl chloride in tetrahydrofuran (THF).[†] However, the desired ethyl 2-acetyl-2-benzamidoacetate (**3c**) was produced in only 15% yield, whereas *NN*-di-isopropylacetamide (**4**) was obtained as the major product (64% based upon acetyl chloride).[‡] However, the selectivity of the reaction towards the desired product was increased by the use of acid anhydrides. Thus, the reaction of (**1**) with succinic anhydride (**5**) in THF, followed by quenching with ice and work-up as reported earlier,³ produced (**3a**) which was recrystallized from water (59%, m.p. 114–116 °C).[§] Reaction with glutaric anhydride (**6**) produced (**3b**) in 47% yield, the reaction mixture being quenched with ice cold aqueous ammonium chloride solution and worked up as above with final purification being effected by benzene-water partition. Reaction

[†] In our work, the generation of the dianion (**1**) was carried out essentially by the method described in ref. 3. In our hands, the assay of dianion formation by D_2O quenching followed by examination of the resulting deuteriated ethyl hippurate by n.m.r. spectroscopy was found to be unreliable owing to the inherent inaccuracy of the comparison of integration values. However, recrystallization of the deuteriated ethyl hippurate followed by mass spectrometric determination provided a consistent method which indicated at best only 60% dianion formation.

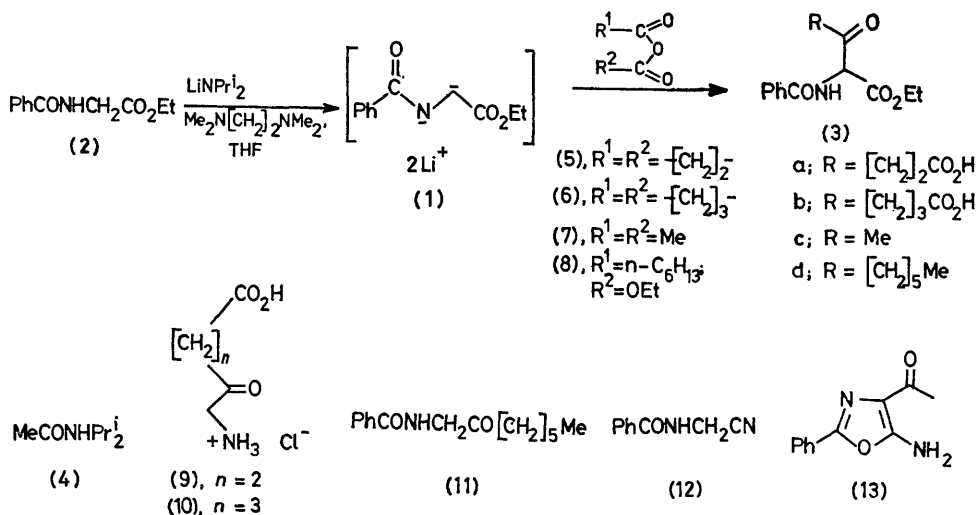
[‡] This complication has also been observed in analogous cases, *e.g.*, see A. P. Krapcho, D. S. Kashdan, E. G. E. Jahngen Jr., and A. J. Lovey, *J. Org. Chem.*, 1977, **42**, 1189.

[§] All new compounds were fully characterised by a combination of microanalytical data and spectroscopic analysis.

with acetic anhydride (7) and the mixed anhydride, ethyl heptanoyl carbonate (8), gave respectively (3c) (40%, semicarbazone m.p. 173—176 °C, lit.³ 172—173 °C) and (3d) (semicarbazone m.p. 100—103 °C), both obtained pure by column chromatography on silica gel. In all cases, the extent of dianion formation was found to be the major

logues in 40% overall yield competes most favourably with the best method previously reported.⁴

Under less vigorous conditions of hydrolysis, selective removal of the ester function was achieved to afford α -benzamidoketones. Thus, (11) was produced in 85% yield by stirring (3d) and 6 N aqueous HCl for 40 h at 80 °C.



limiting factor with respect to product yield. Although the avoidance of strongly alkaline conditions during the work-up by quenching with saturated aqueous ammonium chloride solution did not consistently improve the yield, it was found in several runs that a cleaner product was given.

Attempts to hydrolyse the acylated product (3c) under aqueous alkaline conditions led only to hippuric acid, presumably *via* a reverse Claisen reaction. However, conversion into pure α -aminoketone hydrochlorides was accomplished smoothly in *ca.* 70% yield by refluxing with 6 N aqueous HCl for 12 h, [*e.g.*, (3a) to δ -aminolevulinic acid hydrochloride (9), 68%; (3b) \rightarrow (10), 71%]. This convenient two-step route to δ -aminolevulinic acid and ana-

An attempt further to increase the versatility of dianion acylation reactions by using 2-benzamidoacetonitrile (12) was only partially successful. Dianion formation in the usual manner followed by treatment with acetic anhydride resulted in a cyclised acetylated product, 4-acetyl-5-amino-2-phenyloxazole (13) as the major product. Similar cyclisations have been reported elsewhere.⁵

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¹ H. D. Dakin and R. West, *J. Biol. Chem.*, 1928, **78**, 91; numerous papers have been published on details of the mechanism of this reaction, see for example G. Hofle, A. Prox, and W. Steglich, *Chem. Ber.*, 1972, **105**, 1718, and references quoted therein.

² J. Attenburrow, D. F. Elliot, and G. F. Penney, *J. Chem. Soc.*, 1948, 310.

³ A. P. Krapcho and E. A. Dundulis, *Tetrahedron Letters*, 1976, 2205.

⁴ A. Neuberger and J. J. Scott, *J. Chem. Soc.*, 1954, 1820.

⁵ 'The Chemistry of Penicillins,' eds. J. W. Cornforth and H. T. Clarke, Princeton University Press, Princeton, 1949, p. 702.