Pyrrolizin-3-one

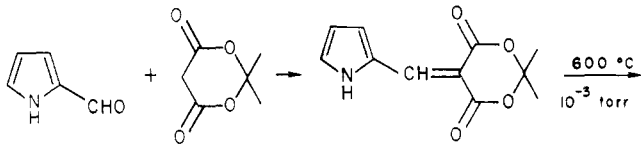
Hamish McNab

Department of Chemistry, University of Edinburgh, Edinburgh EH9 3JJ, Scotland

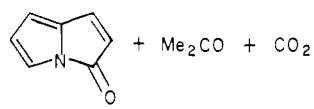
Received February 4, 1981

Some years ago, Flitsch and Neumann prepared pyrrolizin-3-one (**3**), in 14% overall yield, by condensation of malonic acid with pyrrole-2-carboxaldehyde and subsequent cyclization in acetic anhydride.[1] However, due to its sensitivity and its relatively high volatility, it proved difficult to isolate and purify the product, and so it has found little subsequent application in synthesis. This note describes a simple and efficient preparation of **3** which depends on the generation of the lactam function by gas-phase pyrolysis of a derivative of 2,2-dimethyl-1,3-dioxane-4,6-dione[2] (Meldrum's acid, **1**). Such reactions have been observed in solution by Danishevsky[3] and by Lesher;[4] gas-phase pyrolysis of Meldrum's acid derivatives has been extensively studied by Brown and co-workers.[5] For the present example, these short-contact-time gas-phase conditions were chosen because they are particularly suitable for the preparation of sensitive compounds. In addition, the workup problem of separating the product from an excess of inert, involatile solvent is avoided in this way.

Reaction of pyrrole-2-carboxaldehyde with Meldrum's acid at room temperature overnight gives the condensation product **2**[6] as yellow crystals (84%). Flash vacuum pyrolysis of **2** at 500 °C generates an acetone solution of pyrrolizin-3-one (**3**) together with some unreacted starting material. The conversion is complete at 600 °C, however, and the pure heterocycle is obtained directly by distillation of the pyrolysate (88%).



1 **2**



3

Pyrrolizin-3-one (**3**) is a deep red mobile liquid. It is stable indefinitely at −30 °C but rapidly becomes dark on exposure to the air at room temperature.

Experimental Section

2,2-Dimethyl-5-(pyrrol-2-ylidine)-1,3-dioxane-4,6-dione (2).[6] A solution of pyrrole-2-carboxaldehyde (4.3 g, 50 mmol) and 2,2-dimethyl-1,3-dioxane-4,6-dione (**1**; 7.2 g, 50 mmol) in benzene (130 mL) was treated with acetic acid (1 mL) and piperidine (1 mL) and set aside overnight. The yellow crystals which had formed were filtered, washed thoroughly with the filtrate, and dried in vacuo over phosphoric anhydride to give **2** (9.29 g, 84%) in sufficient purity for the next stage of the sequence: mp 178–180 °C (from ethanol)(lit.[6] mp 182 °C); ^{1}H NMR ($CDCl_3$) δ 8.25 (s, 1 H), 7.43 (m, 1 H), 7.10 (m, 1 H), 6.52 (m, 1 H), 1.75 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 164.04 (q), 143.12, 131.89, 130.09, 114.23, 104.03 (q), 100.12 (q), 35.85 (q) 27.00.

Pyrrolizin-3-one (3).[1] Freshly prepared **2** (4.42 g, 20 mmol) was sublimed at 120–140 °C (10^{-3} torr) over a period of 4 h into a horizontal 30 × 2.5 cm silica tube held at 600 °C. The products were condensed in a liquid nitrogen trap at the exit point of the furnace. At the end of the pyrolysis, the trap was rinsed out with some acetone which was subsequently evaporated at the water pump. Bulb-to-bulb distillation of the residue at 130 °C (16 torr) [lit.[1] bp 35–40 °C (0.05 torr)] gave pure pyrrolizin-3-one (**3**): 2.10 g (88%); ^{1}H NMR ($CDCl_3$) δ 7.04 (d, 1 H, J = 6 Hz), 6.85 (t, 1 H, J = 2 Hz), 5.95 (d, 2 H, J = 2 Hz), 5.63 (d, 1 H, J = 6 Hz); ^{13}C NMR ($CDCl_3$) δ 165.45 (q), 138.06, 136.75 (q), 121.82, 118.68, 115.25, 111.42; mass spectrum, m/e 119 (M^+, 100%), 91 (59), 64 (41), 63 (22). Anal. Calcd for C_7H_5NO: C, 70.59; H, 4.20; N, 11.76. Found: C, 70.68; H, 4.28; N, 11.74.

Registry No. **1**, 2033-24-1; **2**, 23111-03-7; **3**, 34610-37-2; pyrrole-2-carboxaldehyde, 1003-29-8.

(1) Flitsch, W.; Neumann, U. *Chem. Ber.* **1971**, *104*, 2170.
(2) McNab, H. *Chem. Soc. Rev.* **1978**, *7*, 345.
(3) Danishevsky, S.; Singh, R. K. *J. Am. Chem. Soc.* **1975**, *97*, 3239.
(4) Lesher, G. Y. U.S. Patent 3 907 798, 1976; *Chem. Abstr.* **1976**, *84*, 44130.
(5) Armstrong, R. J.; Brown, R. F. C.; Eastwood, F. W.; Romyn, M. E. *Aust. J. Chem.* **1979**, *32*, 1767 and earlier papers in the series.
(6) Schuster, P.; Polansky, O. E.; Wessely, F. *Monatsh. Chem.* **1964**, *95*, 53.

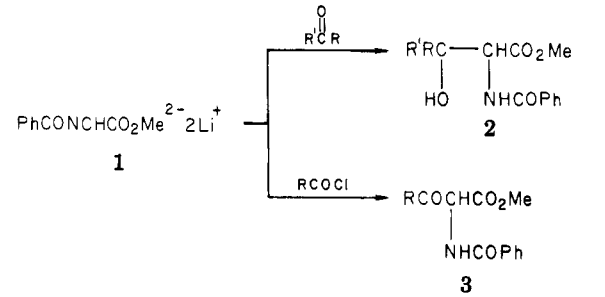
Hydroxyalkylation and Acylation Reactions of Methyl Hippurate

Kenn E. Harding,* Louis N. Moreno, and V. Mark Nace

Department of Chemistry, Texas A&M University, College Station, Texas 77843

Received October 10, 1980

Our interest in the use of α-amino-β-hydroxy and α-amino-β-keto esters as synthetic intermediates for heterocyclic amino acids related to furanomycin and steptolutine led us to examine the reactions of the lithio dianion of methyl hippurate (**1**) with carbonyl compounds (**1** → **2**, hydroxyalkylation) and with acid chlorides (**1** → **3**, acylation).[1] We have found that hydroxyalkylation proceeds readily in high yield[2] and that, contrary to an earlier report,[3] the acylation reaction (**1** → **3**) can be effected in good yield with most acyl halides.



1 **2** **3**

Lithio dianion **1** is readily prepared by treatment of methyl hippurate at −78 °C with lithium diisopropylamide (LDA) in THF containing TMEDA as reported by Krapcho.[4] In our studies, we also investigated the use of hindered amide bases other than LDA, including lithium tetramethylpiperidide (LTMP) and lithium hexamethyl-

(1) Some of the results reported here were presented at the 179th National Meeting of the American Chemical Society, Houston, TX, Mar 24–28, 1980, Abstract ORGN 17, and the 35th Southwest Regional Meeting of the American Chemical Society, Austin, TX, Dec 5–7, 1979, Paper 193.
(2) Following our initial studies in this area, the hydroxyalkylation of the dianion of *N*-(carbobenzoxy)glycine ethyl ester was reported. Shanzer, A.; Somekh, L.; Butina, D. *J. Org. Chem.* **1979**, *44*, 3967.
(3) Evans, D. A.; Sidebottom, P. J. *J. Chem. Soc., Chem. Commun.* **1978**, 753.
(4) Krapcho, A. P.; Dundulis, E. A. *Tetrahedron Lett.* **1976**, 2205. We found no evidence that dianion formation was limiting the yields of our reactions as was reported to be the case by Evans and Sidebottom[3] in their studies with the dianion of ethyl hippurate.

0022-3263/81/1946-2809$01.25/0