

Reduction of Some Esters of Pyrazole-3,4-dicarboxylic Acid

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3,4-Bishydroxymethylpyrazole was prepared by reduction of diethyl pyrazole-3,4-dicarboxylate and of *SS*-diethyl pyrazole-3,4-dicarbothioate. A reduction of dimethyl pyrazole-3,4-dicarboxylate to methyl 4-formylpyrazole-3-carboxylate is also described.

IN connection with another study, we had need of 3,4-bishydroxymethylpyrazole (I). We describe here several preparations and a novel reduction of dimethyl pyrazole-3,4-dicarboxylate.

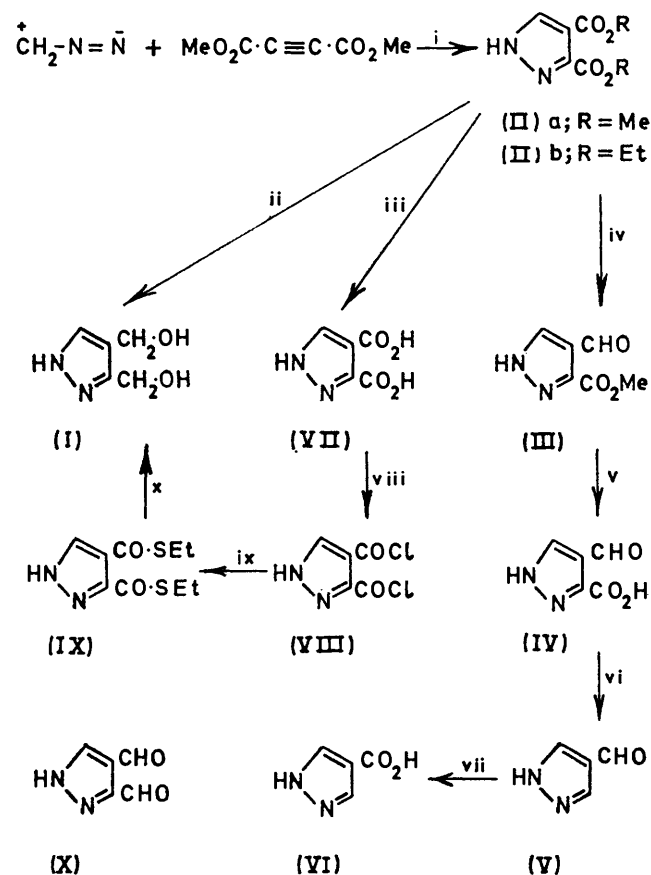
A 1,3-dipolar cyclo-addition of diazomethane to dimethyl acetylenedicarboxylate (see Scheme) at low temperature gave dimethyl pyrazole-3,4-dicarboxylate (IIa). This was a more convenient preparation than the cyclization of ethyl ethoxymethyleneoxalacetate with hydrazine hydrate¹ which we had initially employed for obtaining the diethyl ester (IIb).

Treatment of di-isobutylaluminium hydride (DIBAL-H) with the diethyl ester (IIb) in toluene between -75 and -65° gave the diol (I) in 36–43% yield. Since DIBAL-H is very pyrophoric, the dimethyl ester (IIa) was treated with a 10% molar excess of sodium or lithium aluminium hydride (LAH) in tetrahydrofuran (THF) at low temperature. Instead of the diol (I), the previously unknown methyl 4-formylpyrazole-3-carboxylate (III) was obtained. The best yields of compound (III) (41–60%) were obtained in the temperature range from -73 to -70° . Attempts to produce pyrazole-3,4-dicarbaldehyde² (X) from the diester (IIa) consistently led to the formation of the formyl ester (III) or decomposition products at higher temperatures. We were unable to reduce further either the aldehyde group (at -78 to -70°) or the carboxylate group (at -65 to -50°) of (III): either (III) was recovered unchanged or decomposition resulted.

The structure of (III) was determined by elemental, i.r., and mass spectral evidence. The compound was distinguished from the isomeric 3-formylpyrazole by hydrolysis to the formylpyrazole-carboxylic acid (IV), which subsequently was decarboxylated with copper in quinoline. Comparison of the product with the known pyrazole-3-carbaldehyde³ indicated that it was the 4-carbaldehyde (V). This was verified by oxidation with moist silver oxide to pyrazole-4-carboxylic acid⁴ (VI).

Since thioesters are reduced more readily than ordinary esters with LAH,⁵ we applied this reagent to *SS*-diethyl pyrazole-3,4-dicarbothioate (IX). The thioester was prepared from the ester (IIa), which, after hydrolysis to pyrazole-3,4-dicarboxylic acid (VII), was heated under reflux with thionyl chloride (or heated with

phosphorous pentachloride) to afford the acid chloride (VIII). Treatment of (VIII) with ethanethiol in pyridine gave the thioate (IX). The reduction of (IX)



Reagents: i, ether, 10° ; ii, DIBAL-H, from -65 to -75° ; iii, 6*N*-HCl; iv, NaAlH_4 or LiAlH_4 -THF, from -73 to -70° ; v, H_3O^+ ; vi, Cu-quinoline; vii, Ag_2O ; viii, SOCl_2 or PCl_5 ; ix, EtSH-pyridine; x, Raney Ni or LiAlH_4 .

with LAH in THF at -75° produced only low yields of the diol (I). However, the use of Raney nickel of varying activities^{6,7} led to the diol (I) in yields of 36–50%. The best yields were obtained with a modified W-2 catalyst.⁸

We subjected the acid chloride (VIII) to treatment with lithium tri-*t*-butoxyaluminium hydride under con-

¹ R. G. Jones and C. W. Whitehead, *J. Org. Chem.*, 1955, **20**, 1342.

² K. Henkel and F. Weygand, *Ber.*, 1943, **76**, 812.

³ R. Huttel, *Ber.*, 1941, **74B**, 1681.

⁴ R. Huttel and M. E. Schon, *Annalen*, 1959, **625**, 55.

⁵ M. L. Wolfram and J. V. Karabinos, *J. Amer. Chem. Soc.*, 1944, **66**, 909.

⁶ H. Adkins and J. Pavlic, *J. Amer. Chem. Soc.*, 1947, **69**, 3039.

⁷ R. Mazingo, H. Adkins, and L. Richard, *Org. Synth.*, 1941, **21**, 15.

⁸ R. Mazingo, D. Wolf, S. Harris, and K. Folkers, *J. Amer. Chem. Soc.*, 1943, **65**, 1015.

ditions described by Brown and his co-workers⁹ for the reduction of terephthaloyl and isophthaloyl chlorides to the corresponding dialdehydes. However, this procedure did not afford pyrazole-3,4-dicarbaldehyde² (X) but only the hydrolysis product, the acid (VII).

EXPERIMENTAL

I.r. spectra were measured on a Beckmann IR-8 spectrophotometer for KBr discs unless otherwise specified. Mass spectra were recorded with a CEC 21-103C spectrometer. Microanalyses were performed by Alfred Bernhardt, 5257 Elbach, West Germany, or Schwarzkopf Microanalytical Laboratory, Woodside, New York.

Lithium aluminium hydride, sodium aluminium hydride, Raney nickel alloy, and lithium tri-*t*-butoxyaluminium hydride were purchased from Ventron Corporation. Diisobutylaluminium hydride was obtained from Texas Alkyls.

Dimethyl Pyrazole-3,4-dicarboxylate (IIa).—To a stirred solution of diazomethane (10 g, 0.24 mol) in ether (500 ml) cooled to 0°, dimethyl acetylenedicarboxylate (35.8 g) was added dropwise during 0.5 h below 10°. The precipitate was filtered off, washed with ether, and vacuum dried to give white crystals (30.8 g), m.p. 140–141° (from benzene) (lit.,¹⁰ 141°) (Found: C, 45.3; H, 4.55; N, 15.2. Calc. for C₇H₈N₂O₄: C, 45.65; H, 4.35; N, 15.2%).

Methyl 4-Formylpyrazole-3-carboxylate (III).—To a stirred solution of the dicarboxylate (IIa) (3.7 g) in tetrahydrofuran (200 ml) at –73 to –70°, lithium aluminium hydride (0.91 g) was added in small portions (0.5 h). Stirring was continued at –72 to –68° for 0.5 h. Addition of 2*N*-hydrochloric acid (25 ml) decomposed the complex and the pH of the solution was then adjusted to 8 with 2*N*-sodium hydrogencarbonate. The aqueous layer was extracted with chloroform-ethanol (3 × 50 ml; 1.5:1 v/v). The dried (MgSO₄) extracts were added to the dried tetrahydrofuran layer and evaporated to leave the formylpyrazole (III) as white crystals (1.5 g), m.p. 200–201° [from pyridine-water (1:1 v/v)] (Found: C, 46.9; H, 4.2; N, 18.0. C₆H₆N₂O₃ requires C, 46.75; H, 4.0; N, 18.1%), ν_{\max} 3150 (NH), 2780 (Me), 1710 (CHO), 1670 (CO₂Me), and 1370 cm⁻¹ (Me), *m/e* 154 (*M*⁺), 139 (*M* – 15), 123 (*M* – 31), and 95 (*M* – 59).

4-Formylpyrazole-3-carboxylic Acid (IV).—The formylpyrazole (III) (0.9 g), suspended in 6*N*-hydrochloric acid (50 ml), was heated under reflux for ^{at –75°} and decomposed when cooled, and the precipitate was filtered off. After ^{the water was removed} (1.5:1 v/v) washing with water, the product was air-dried to afford the acid (IV) (0.5 g), m.p. 268–270° (decomp.), ν_{\max} 3210 (OH), 3150 (NH), 1710 (CHO), 1680 (CO₂H), and 1430 (C–OH) cm⁻¹.

Pyrazole-4-carbaldehyde (V).—A mixture of copper dust (0.05 g), dry quinoline (1.5 ml), and the formylpyrazole (IV) (0.5 g) was heated at 185° for 2 h. The mixture was poured into a slurry of crushed ice (5 g) and hydrochloric acid (1 ml), then filtered and evaporated. The resultant oil was dissolved in absolute ethanol (10 ml) and treated with ether until the solution became turbid and then cooled to 0° to give crystals of the aldehyde (V) (0.10 g), m.p. 82–83°, ν_{\max} 3150 (NH), 1710 (CHO), and 1580 (C=C) cm⁻¹.

Pyrazole-4-carboxylic Acid (VI).—A suspension of silver oxide (0.46 g), *n*-sodium hydroxide (4 ml), and the pyrazole-carbaldehyde (V) (0.1 g) was stirred for 10 min at 0° and filtered. The filtrate, acidified to pH 5 with hydrochloric

acid, was evaporated at reduced pressure to give the acid (VI) as a white powder, m.p. 273–275° (lit.,⁴ 275–276°), ν_{\max} 3210 (OH), 3150 (NH), 1680 (CO₂H), and 1430 (C–OH) cm⁻¹.

Pyrazole-3,4-dicarboxylic Acid (VII).—The ester (IIa) (18.4 g) in 6*N*-hydrochloric acid (380 ml) was heated under reflux for 4 h and cooled. The gelatinous precipitate was filtered off and dried *in vacuo* (85–90°), affording the dicarboxylic acid (VII) (14.6 g), m.p. 260–261° (decomp.) [lit.,¹¹ 260° (decomp.)].

Pyrazole-3,4-dicarbonyl Chloride (VIII).—A mixture of the dicarboxylic acid (VII) (0.6 g) and thionyl chloride (12 ml) was heated under reflux for 10 h. Removal of the excess of thionyl chloride gave the acid chloride (VIII) as an off-white powder, m.p. 310–315°. Its *dicarboxamide derivative* formed tan crystals, m.p. 325–326° (decomp.) [lit.,¹¹ 327° (decomp.)].

SS-Diethyl Pyrazole-3,4-dicarbothioate (IX).—Ethanethiol (7.2 g) and pyridine (3.4 g) were added to the acid chloride (VIII) (5.5 g) in dry benzene (50 ml) whereupon a large volume of gas was evolved. When evolution ceased, the flask was stoppered and stored at room temperature (48 h). The yellow solution was diluted with water (200 ml) and extracted with ether (4 × 50 ml). The combined extracts were washed successively with (2 × 50 ml) dilute sodium carbonate, dilute hydrochloric acid, and then water. Evaporation of the dried (MgSO₄) extract gave the dicarbothioate (IX) as a yellow, chromatographically pure (silica gel, benzene) oil which decomposed on attempted distillation, ν_{\max} 3100 (NH), 3050, 2980 (C–S), 1750 (C=O), and 1480 cm⁻¹ (C–S).

3,4-Bishydroxymethylpyrazole 4 h, 1(a) From the dicarbothioate (IX) with W-2 modified Raney nickel. A solution of the dicarbothioate (IX) (1.1 g) in 80% ethanol was treated with W-2 modified⁸ Raney nickel catalyst (15 g), heated under reflux for 2 h, then filtered, and the filtrate was evaporated to a gum. This gave the *diol* (I) as white crystals (0.32 g), m.p. 45–46° (from pyridine-water, 1:1 v/v).

(b) *From the dicarbothioate (IX) with lithium aluminium hydride.* A solution of (IX) (1.1 g) in tetrahydrofuran (50 ml) was treated with lithium aluminium hydride (0.1 g) in small portions with stirring at –75°. After 3 h, the mixture was warmed to 10° and decomposed with 15% methanol, and the aqueous layer was separated and extracted with chloroform-ethanol (1.5:1 v/v; 3 × 50 ml). These extracts, combined with the tetrahydrofuran layer were dried (MgSO₄) and evaporated to an off-white solid (0.24 g), m.p. 45–46° (from pyridine-water).

(c) *From the pyrazole-dicarboxylate (IIa) with diisobutylaluminium hydride.* Under a nitrogen atmosphere, a solution of (IIa) (3.18 g) in toluene (125 ml) at –78° was treated dropwise (1 h) with diisobutylaluminium hydride (4.3 g) in toluene (45 ml). After stirring at –75 to –65° for 1 h, 15% methanol (150 ml) was added and the aluminium hydroxide was filtered off. The toluene layer was separated, dried (MgSO₄), and evaporated *in vacuo* to afford the *diol* (I) (1 g), m.p. 45–46° (from pyridine-water) (Found: C, 46.95; H, 6.3; N, 22.0. C₅H₈N₂O₂ requires C, 46.9; H, 6.25; N, 21.9%), ν_{\max} 3320 (OH) and 3210 (NH) cm⁻¹.

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⁹ H. C. Brown and R. F. McFarlin, *J. Amer. Chem. Soc.*, 1956, **78**, 252; 1958, **80**, 5372; H. C. Brown and B. C. Subba Rao, *ibid.*, p. 5377.

¹⁰ H. V. Peckmann and E. Steal, *Ber.*, 1899, **32**, 2292.

¹¹ E. A. Falco and G. H. Hitchings, *J. Amer. Chem. Soc.*, 1956, **78**, 3143.