Nitroimidazoles. IX [1]. Synthesis of 2-Acetyl-1-methyl-5-nitroimidazole

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Manganese dioxide oxidation of 2-hydroxymethyl-1-methyl-5-nitroimidazole (**6**) gave 1-methyl-5-nitroimidazole-2-carboxaldehyde (**7**) in high yield. Reaction of diazomethane with **7** afforded the title compound **1** in low yield. Treatment of ethyl acid malonate with two equivalents of isopropylmagnesium bromide in THF and subsequent addition to 1-methyl-5-nitroimidazole-2-carbonylimidazolide (**12**) yielded ethyl (1-methyl-5-nitroimidazole-2-carbonyl)acetate (**10**) in 70% yield. Hydrolysis and decarboxylation of compound **10** gave the desired compound **1** in 97% yield.

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There have been several reports concerning biological interest for nitroimidazole derivatives [2-7]. For the synthesis of nitroimidazoles as possible effective drugs against tropical diseases [8] we needed 2-acetyl-1-methyl-5-nitroimidazole (**1**). However, the synthesis of compound **1** has not yet been reported.

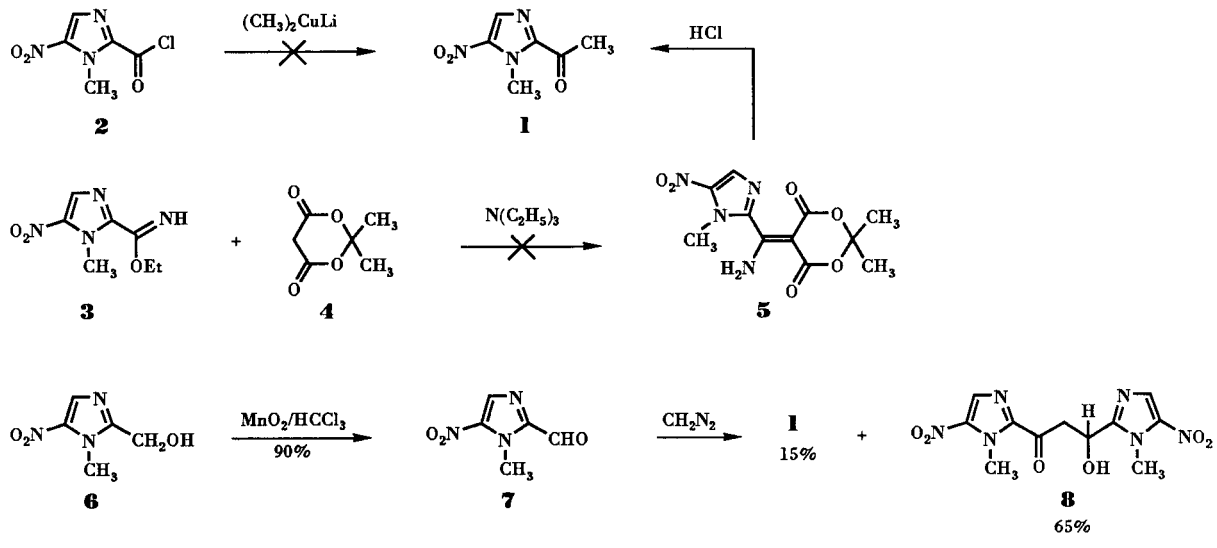
Herein we report a practical, high yield procedure for the preparation of compound **1**.

Ketones having a nitro group could be prepared from the reaction of dimethyl copperlithium with an acid chloride [9]. However the reaction of dimethyl copperlithium with 1-methyl-5-nitroimidazole-2-carbonyl chloride (**2**) [10] did not give the desired compound **1**. Another method for the preparation of ketones is the reaction of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione) (**4**) with imidates and subsequent acid hydrolysis of the intermediate β-enaminodiester [11]. However the reaction of Meldrum's acid with ethyl 5-nitro-1-methylimidazole-2-carboximidate (**3**) [12] did not give the β-enaminodiester **5** (Scheme 1).

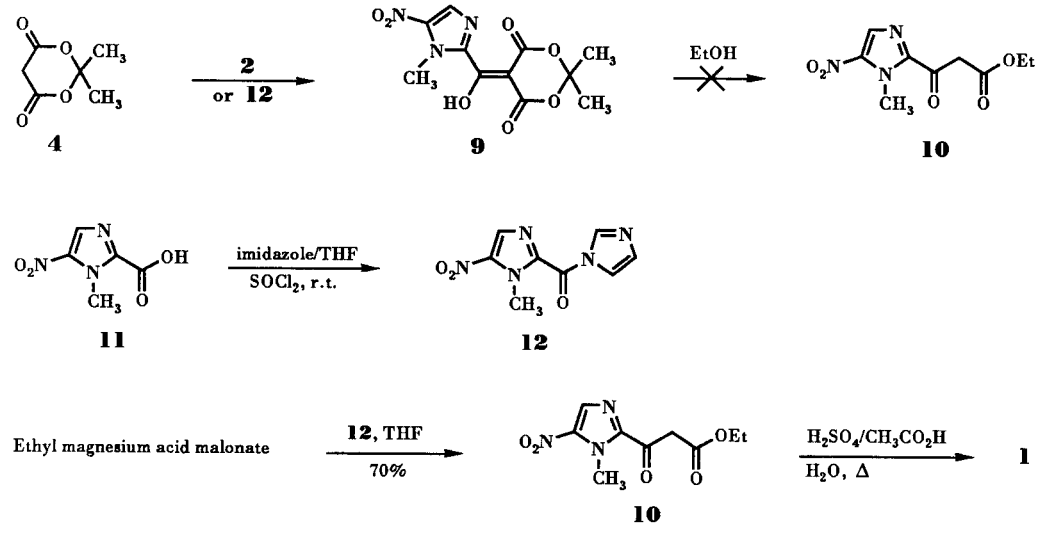
Another procedure for the preparation of methyl ketones is the reaction of diazomethane with an aldehyde [13]. Manganese dioxide oxidation of 2-hydroxymethyl-1-methyl-5-nitroimidazole (**6**) [14] gave 1-methyl-5-nitroimidazole-2-carboxaldehyde (**7**) [15] in high yield. Reaction of diazomethane with **7** afforded in addition to the desired compound **1** in low yield, a dimer **8** as a major product. The structure of the dimer was established by elemental analysis, ir, nmr and mass spectral data.

The other method for the preparation of ketones having a nitro group is the hydrolysis of β-ketoesters [16]. Condensation of methyl acetate with methyl 1-methyl-5-nitroimidazole-2-carboxylate [17] or methyl acetoacetate with the latter in the presence of a base [18] or ethyl acetoacetate and sodium [19] with compound **2** did not give the β-ketoester. In addition, the reaction of Meldrum's acid **4** with imidates and subsequent reaction of the intermediate β-enaminodiester **5** with sodium ethoxide [11] or the reaction of Meldrum's acid with carboxylic acid chloride **2** or imidazolide **12** and the subsequent reaction of the enol form **9** with ethanol [20] did not afford the β-ketoester.

Scheme 1



Scheme 2



Finally, ethyl (1-methyl-5-nitroimidazole-2-carbonyl)-acetate (**10**) could be prepared by a modification of a procedure for the preparation of a β-ketoester [21]. Treatment of ethyl acid malonate with two equivalents of isopropylmagnesium bromide in tetrahydrofuran gave the magnesium chelate. The addition of the latter to imidazolide **12** in THF afforded the desired β-ketoester **10** in 70% yield. Hydrolysis and decarboxylation of compound **10** with sulfuric acid-acetic acid-water mixture yielded the desired keton **1** in 97% yield (Scheme 2).

EXPERIMENTAL

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. The ir spectra were obtained using a Perkin-Elmer Model 267 spectrograph (potassium bromide disks). The ^{1}H nmr spectra were recorded on a Varian T-60A spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. The mass spectra were run on a Varian Model MAT MS-311 spectrometer at 70 ev.

1-Methyl-5-nitroimidazole-2-carboxaldehyde (**7**).

To a stirred solution of 2-hydroxymethyl-1-methyl-5-nitroimidazole (**6**, 15.7 g, 0.1 mole) in chloroform (1 l) was added manganese dioxide (100 g). The stirring was continued for 2 hours and filtered. The filtrate was evaporated and the residue was crystallized from acetone to give 13.45 g (90%) of compound **7**, mp 97-98° [15]; ir (potassium bromide): ν 3118, 1705 (C=O), 1530, 1350 cm^{-1} (NO_2); ^{1}H nmr (deuteriochloroform): 4.40 (s, 3H, CH_3), 8.10 (s, 1H, H_4) and 9.90 ppm (s, 1H, HCO).

Anal. Calcd. for $C_5H_5N_3O_3$: C, 38.71; H, 3.25; N, 27.09. Found: C, 38.55; H, 3.15; N, 27.21.

Reaction of Diazomethane with 1-Methyl-5-nitroimidazole-2-carboxaldehyde (**7**).

To a stirred solution of compound **7** (1.55 g, 0.01 mole) in ether (50 ml) was added diazomethane (0.42 g, 0.01 mole) in ether (30 ml) dropwise. After the addition was complete, the stirring was continued for 1 hour. The precipitate was filtered and crystallized from acetone to give 1.05 g (65%) of compound **8**, mp 158-160°; ir (potassium bromide): ν 3240 (OH), 3115, 1695 (C=O), 1535, 1520 cm^{-1} (NO_2); ^{1}H nmr (deuteriochloroform): 3.90 (q, 2H, CH_2), 4.55 (s, 3H, NCH_3), 4.30 (s, 3H, NCH_3), 5.0 (bs, 1H, OH, exchangeable with deuterium oxide), 7.80 (s, 1H, H_4), and 8.03 ppm (s, 1H, H_4); ms: m/z (%, relative intensity) 324 (M^+, 21), 307 (23), 306 (30), 260 (22), 219 (31), 191 (14), 180 (11), 171 (22), 170 (100), 169 (47), 156 (47), 154 (60), 152 (32), 139 (61), 128 (35), 125 (38), 110 (25), 97 (17), 81 (39), 80 (27), 68 (11), 66 (10), 54 (29), 44 (69), 43 (23).

Anal. Calcd. for $C_{11}H_{12}N_6O_6$: C, 40.74; H, 3.73; N, 25.92. Found: C, 40.55; H, 3.55; N, 25.75.

The filtrate was evaporated and the residue separated by preparative tlc on silica gel using chloroform/methanol (9.5:0.5) as the eluent to give 0.25 g (15%) of **1**, mp 108-109°; ir (potassium bromide): ν 3100, 1680 (C=O), 1525, 1340 cm^{-1} (NO_2); ^{1}H nmr (deuteriochloroform): 2.73 (s, 3H, $COCH_3$), 4.33 (s, 3H, NCH_3), 8.0 ppm (s, 1H, H_4); ms: m/z (%, relative intensity) 169 (M^+, 80), 154 (34), 139 (85), 108 (11), 97 (20), 81 (63), 80 (43), 68 (12), 54 (25), 43 (46).

Ethyl (1-Methyl-5-nitroimidazole-2-carbonyl)acetate (**10**).

Thionyl chloride (595 mg, 5 mmoles) was added to a stirred solution of imidazole (1.36 g, 0.02 mole) in tetrahydrofuran (17 ml). After 15 minutes the suspension was filtered and washed with THF (3 ml). To the stirred filtrate was added the acid **11** (0.855 g, 5 mmoles). The mixture was stirred for 15 minutes. To the stirred suspension was added ethyl magnesium acid malonate [which was prepared from magnesium (0.23 g, 0.01 mole), isopropyl bromide (1.23 g, 0.01 mole) and ethyl acid malonate (0.66 g, 5 mmoles) in tetrahydrofuran (25 ml)]. The mixture was stirred at room temperature for 3 hours. The mixture was added to 4% hydrochloric acid (20 ml) and extracted with ether (3 x 50 ml). The organic layer was washed with sodium bicarbonate solution, water, dried (sodium sulfate) and filtered. The ether was evaporated and the residue was crystallized from ethanol to give 0.84 g (70%) of **10**, mp 64-65°; ^{1}H nmr (deuteriochloroform): 1.28

(t, 3H, CH_3), 4.16 (s, 2H, CH_2), 4.14 (q, 2H, CH_2), 4.40 (s, 3H, CH_3N) and 8.03 ppm (s, 1H, H_4 imidazole); ms: m/z (%, relative intensity) 241 (M^+, 94), 196 (97), 169 (59), 165 (51), 154 (100), 139 (51), 127 (62), 119 (24), 97 (31), 85 (39), 71 (54), 57 (88), 43 (73).

Anal. Calcd. for $C_9H_{11}N_3O_5$: C, 44.82; H, 4.60; N, 17.42. Found: C, 44.95; H, 4.47; N, 17.53.

2-Acetyl-1-methyl-5-nitroimidazole (**1**).

A stirred mixture of compound **10** (2.41 g, 0.01 mole) in sulfuric acid/acetic acid/water (1:3:5) was heated at 95-100° for 2 hours. After cooling water (20 ml) was added and extracted with chloroform (50 ml). The organic layer was washed with water, dried (sodium sulfate) and filtered. The solvent was evaporated and the residue was crystallized from petroleum ether to give 1.64 g (97%) of compound **1**, mp 108-109°.

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