Nitroimidazoles. XII [1]. A Simple and Efficient Synthesis of 1-Methyl-5-nitroimidazole-2-acetic Acid

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Reaction of 1-methyl-5-nitroimidazole-2-carboxyl chloride (**9**) with diazomethane afforded 2-diazo-1-(1-methyl-5-nitro-2-imidazolyl)ethanone (**10**). Successive rearrangement of compound **10** *via* Arndt-Eastert rearrangement yielded 1-methyl-5-nitroimidazole-2-acetic acid (**1**), which was converted to its corresponding methyl ester **11** with etheral solution of diazomethane.

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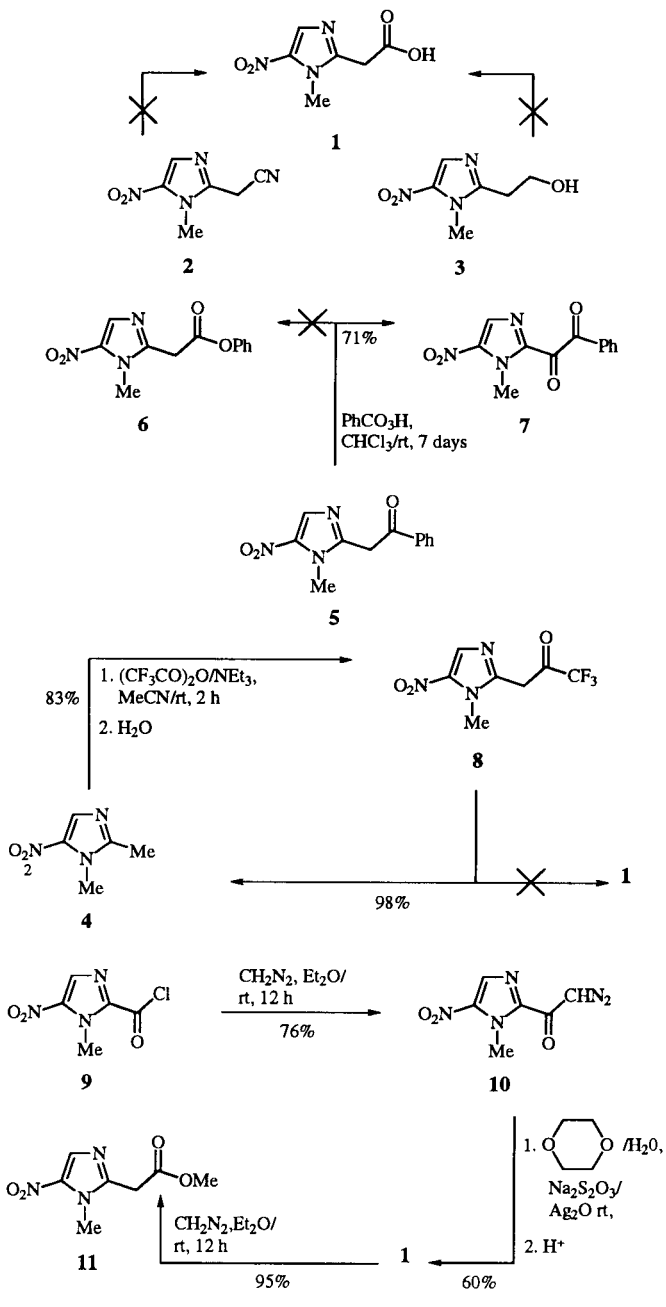
Scheme 1



There have been several reports concerning biological interest for nitroimidazole derivatives [2-4]. For the synthesis of nitroimidazoles as possible effective drugs against tropical diseases [5] we needed 1-methyl-5-nitroimidazole-2-acetic acid (**1**). However, the synthesis of compound **1** has not been reported. In addition, we found that imidazole-2-acetic acids are structurally unstable products and are prone to decarboxylation [6,7]. Therefore, suitable procedure for their Synthesis has not been reported. Herein, we would like to report a simple procedure for the preparation of compound **1**.

Our first approach for preparing **1** *via* hydrolysis of 1-methyl-5-nitroimidazole-2-acetonitrile (**2**) [8] or oxidation of 1-methyl-5-nitroimidazole-2-ethanol (**3**) [9,10] were unsuccessful. Similarly disappointing was the Beayer-Villiger oxidation of 2-(1-methyl-5-nitro-2-imidazolyl)-1-phenylethanone (**5**) [8]. In this reaction alpha-diketone **7** instead of the expected ester **6** was obtained. Another pathway for the preparation of the desired acid is the hydrolysis of 1-methyl-5-nitro-2-imidazolylmethyl triflouromethyl ketone **8**. The latter could be prepared from the reaction of **4** [11] with the triflouroacetic anhydride. However hydrolysis of **8** gave **4** instead of the expected acid **1**.

Finally the acid **1** could be obtained through stepwise Arndt-Eastert rearrangement. The reaction of 1-methyl-5-nitroimidazole-2-carbonyl chloride (**9**) [12] with diazomethane gave 2-diazo-(1-methyl-5-nitro-2-imidazolyl)ethanone (**10**). Rearrangement of **10** in the presence of silver oxide afforded the desired acid **1** . The acid **1** is stable at room temperature for several months. However, it decarboxylated rapidly through heating or attempted crystallization. The acid was converted by diazomethane into its corresponding methyl ester **11** (Scheme 1).

EXPERIMENTAL

Melting points were determined using a Kofler hot stage apparatus and are uncorrected. The ir spectra were obtained using a Perkin-Elmer 781 or Nicolet FT-IR Magna 550 spectrographs.

The ^1H nmr spectra were obtained using Bruker AC-80 or Varian 400 Unity plus spectrometers and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were obtained using a Finnigan TSQ 70 Mass spectrophotometer at 70 ev.

2-(1-Methyl-5-nitro-2-imidazolyl)-1-phenylethanedione (**7**).

To a solution of 2-(1-methyl-5-nitro-2-imidazolyl)-1-phenylethanone (**5**, 2.45 g, 10 mmoles) in chloroform (35 ml) was added a 5% solution of perbenzoic acid in chloroform (27.6 ml, 10 mmoles). After stirring 7 days at room tlemperature, the solvent was evaporated and the residue was crystallized from ether to give 1.84 g (71%) of **7**, mp 170-171°; ir (potassium bromide): ν 1690, 1675 (-CO-CO-), 1545 and 1370 cm^{-1} (NO_2); ^1H nmr (deuteriochloroform): 8.03 (s, 1H, H_4 of imidazole), 7.64 (m, 5H, C_6H_5), 4.49 (s, 3H, NCH_3); ms: m/z (%) 259 (M^+, 18), 106 (22), 105 (100), 77 (85), 51 (15).

Anal. Calcd. for $C_{12}H_9N_3O_4$: C, 55.60; H, 3.50; N, 16.21. Found: C, 55.48; H, 3.63; N, 16.08.

3-(1-Methyl-5-nitro-2-imidazolyl)-1,1,1-trifluoro-2-propanone (**8**).

To a solution of 1,2-dimethyl-5-nitroimidazole (**4**, 1.41 g, 10 mmoles) in acetonitrile (50 ml) were added, trifluoroacetic anhydride (2.9 ml, 20 mmoles) and triethylamine (2.77 ml, 20 mmoles). After 2 hours at room temperature, it was diluted with water (50 ml) and filtered. The yellow powder was recrystallized from ether to give pale yellow crystals of **8**, mp 163-164°; ^1H nmr (deuteriochloroform, 400 MHz): 8.04 (s, 1H, H_4 of imidazole), 5.93 (s, 1H, -CH=C (OH) CF_3), 3.99 (s, 3H, NCH_3); ms: m/z (%) 237 (M^+, 18), 168 (100), 122 (72), 93 (14), 82 (19), 69 (16), 55 (23).

Anal. Calcd. for $C_7H_6F_3N_3O_3$: C, 35.45; H, 2.55; N, 17.72. Found: C, 35.26; H, 2.36; N, 17.56.

Hydrolysis of 3-(1-Methyl-5-nitro-2-imidazolyl)-1,1,1-trifluoro-2-propanone (**8**).

To a solution of **8** (237 mg, 1 mmole) in ethanol (10 ml) was added a 1.12% solution of potassium hydroxide in water (5 ml, 1 mmole). After 30 minutes at room temperature it was acidified with dilute nitric acid, extracted with dichloromethane. The solvent was evaporated under reduced pressure and the residue was crystallized from ether to give 138 mg (98%) of, **4** mp 139-140° (lit [11] mp 140°).

2-Diazo-1-(1-methyl-5-nitro-2-imidazolyl)ethanone (**10**).

To a 2.5% solution of diazomethane in ether (50 ml, 30 mmoles) was added dropwise, a 4.74% solution of 1-methyl-5-nitroimidazole-2-carbonyl chloride in benzene (40 ml, 10 mmoles) at 5-10°. After stirring over night at room temperature, it was dried under reduced pressure and crystallized from acetone-water to give 1.84 g (76%) of **10**, mp 133-134°; ir (chloroform): ν 2116 (-N_2CH), 1536 and 1368 cm^{-1} (NO_2); ^1H nmr (deuteriochloroform, 400 MHz): 7.92 (s, 1H, H_4 of imidazole), 6.53 (s, 1H, -CHN_2) and 4.40 (s, 3H, NCH_3); ms: m/z (%) 195 (M^+, 58), 180 (10), 167 (100), 139 (12), 138 (40), 121 (76), 93 (49), 80 (63), 69 (11), 66 (10), 52 (21), 42 (21).

Anal. Calcd. for $C_6H_5N_5O_3$: C, 36.93; H, 2.58; N, 35.89. Found: C, 36.79; H, 2.63; N, 35.94.

1-Methyl-5-nitroimidazole-2-acetic Acid (**1**).

To a solution of compound **10** (1.95 g, 10 mmoles) in dioxane (50 ml) were added, a 3.2% solution of sodium thiosulfate in water (125 ml, 25 mmoles) and then portionwise, silver oxide (0.2 g). The progress of the reaction was monitored by tlc. When the starting material was finished, the reaction mixture was acidified with dilute nitic acid and extracted with dichloromethane. The solvent was evaporated under reduced pressure to give 1.11 g (60%) of **1**, mp 98-100° dec; ir (chloroform): ν 1690 (C=O), 1559 and 1375 (NO_2), 1250 cm^{-1} (C-O); ms: m/z (%) 185 (M^+, 7), 141 (100), 95 (40), 54 (33), 42 (10).

Methy 1-Methyl-5-nitroimidazole-2-acetate (**11**).

To a 2.5% soltuion of diazomethane in ether (20 ml, 12 mmoles) compound **1** (185 mg, 1 mmole) was added at 5-10°. After stirring over night at room temperature, the solvent was evaporated under reduced pressure and the residue was crystallized from ether to give 190 mg (95%) of **11**, mp 85-86° dec; ir (potassium bromide): ν 1727 (C=O), 1527 and 1375 (NO_2), 1175 cm^{-1} (C-O); ^1H nmr (deuteriochloroform, 80 MHz): δ 7.95 (s, 1H, H_4 of imidazole), 3.94 (s, 3H, NCH_3), 3.91 (s, 2H, -CH_2COO-) and 3.77 (s, 3H, OCH_3).

Anal. Calcd. for $C_7H_9N_3O_4$: C, 42.21; H, 4.55; N, 21.10. Found: C, 42.06; H, 4.68; N, 21.27.

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