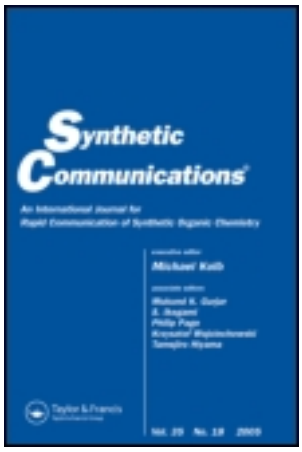

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AN EXPEDITIOUS SYNTHESIS OF 3-NITROPROPIONIC ACID AND ITS ETHYL AND METHYL ESTERS

Paulo C. Silva [a] , Jeronimo S. Costa [a] & Vera L. P. Pereira [b]

[a] Universidade Federal do Rio de Janeiro, Centro de Ciências da Saúde, Núcleo de Pesquisas de Produtos Naturais, Laboratório de Síntese Estereosseletiva de Substâncias Bioativas, Bloco H, Ilha da Cidade Universitária, Rio de Janeiro, RJ, 21941-590, Brazil

[b] Universidade Federal do Rio de Janeiro, Centro de Ciências da Saúde, Núcleo de Pesquisas de Produtos Naturais, Laboratório de Síntese Estereosseletiva de Substâncias Bioativas, Bloco H, Ilha da Cidade Universitária, Rio de Janeiro, RJ, 21941-590, Brazil

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Paulo C. Silva, Jeronimo S. Costa, and Vera L. P. Pereira*

Núcleo de Pesquisas de Produtos Naturais, Laboratório de Síntese Estereosseletiva de Substâncias Bioativas, Universidade Federal do Rio de Janeiro, Centro de Ciências da Saúde, Bloco H, Ilha da Cidade Universitária, 21941-590, Rio de Janeiro, RJ, Brazil

ABSTRACT

The synthesis to 3-nitropropionic acid **1** was easily accomplished, in two steps, from commercially available acrolein in 60% yield. The ethyl and methyl esters of **1** were also obtained.

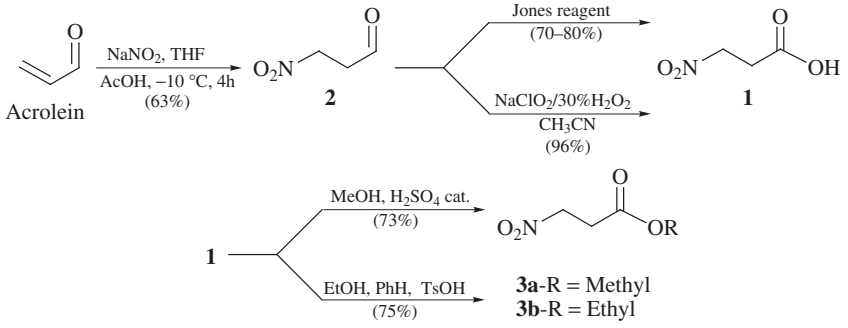
The 3-nitropropionic acid **1**, also known as hiptagenic acid, is a widely distributed plant and fungal neurotoxin. In the vegetal kingdom it is produced by plants of the family *Fabeaceae*, in which it occurs both in the free form and as a component of the glycoside hiptagin (1–3). In fungi it is produced from Pennicillium and Aspergillus genera (4,5). The biosynthesis of **1** seems to occur by quite different routes in fungi and higher plants (6,7). This toxic metabolic presents diverse biological activities. Owing to irreversible inhibitor action of succinate

*Corresponding author. E-mail: Patrocinio@nppn.ufrj.br

dehydrogenase, **1** has been widely used as an animal model for Huntington's disease (8–12). Antihypertensive (13) and carcinogenic (14) properties, among several others, are also observed. Chemically, **1** and its methyl and ethyl esters have been used in the preparation of synthetic products (15–19), natural products (20,21), and in kinetic studies (22).

In an ample program aiming at the synthesis of biological active β-aminoacids by diastereoselective Michael reaction (24,25), we need to prepare multigrams of 3-nitropropionic acid **1** and its methyl and ethyl esters. Although **1** is commercially available (Fluka or Aldrich), the high cost makes the use of this material to direct esterification to the methyl and ethyl esters prohibitive. A detailed inspection of the literature showed us three synthetic routes for obtaining **1** (26–30). Lewkowitsch, in 1879, synthesized **1** for the first time by treatment of β-iodo propionic acid with sodium nitrite (26,27). The yield was not furnished. A second route consists in the slow addition of the expensive and toxic β-propiolactone on aqueous solution of sodium nitrite (28,29). The 3-nitropropionic acid was obtained in 35% yield after successive recrystallizations. Finally, **1** was also produced (30) by nitration in gas phase through complex operating conditions, which led to poor (< 5%) yield. On the other hand, the methyl ester of **1** was produced in 50% yield (31) by treatment of methyl 3-bromopropionate with anhydrous silver nitrite, both expensive reagents, in the absence of solvent to 60°–65°C. However, if the acid **1** is required, for example for biological finalities, hydrolysis will be necessary. Owing to the difficulty of obtaining **1** via the routes described of we have developed an easy and inexpensive route to **1** and its methyl and ethyl esters **3a** and **3b** from commercially available acrolein (see Scheme).

Acrolein was treated with sodium nitrite and acetic acid in THF to furnish 3-nitropropanal **2** in 63% yield according to conditions described in the literature



Scheme.

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(16). Oxidation of **2** to desired 3-nitropropionic acid could be accomplished either by Jones reagent (32) (70–80% yield) or by the use of sodium chlorite and 30% hydrogen peroxide in 96% yield by Dalcanale-Montanary's method (33). The oxidation performed by $NaClO_2$/30% H_2O_2 was found to be more convenient than the first oxidation method, as it presents an easier work-up and low toxicity of the reagents involved, and affordsa higher yield. Esterification to the desired ethyl ester derived **3b** was effected in 75% yield by treatment of **1** with ethanol, catalytic p-toluenesulfonic acid, and benzene in a Dean-Stark apparatus. The corresponding methyl ester was obtained from esterification of **1** using the described procedure (15).

In summary, a simple, rapid, and high-yielding method for preparation of the biologically and synthetically useful 3-nitropropionic acid and its methyl and ethyl esters has been developed that avoids the use of expensive and toxic reagents employed in earlier methods.

EXPERIMENTAL

Acrolein, THF, $NaNO_2$, AcOH, 30% H_2O_2, CrO_3, $NaClO_2$, CH_3CN, MeOH, EtOH, Benzene, TsOH, NaH_2PO_3, Acetone, and H_2SO_4 were commercially available (Aldrich, Merck, or Vetec) and were used as purchased. IR spectra were recorded on a Nicolet Magna-IR-760 spectrometer and only the principal bands are reported. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Gemini-200 Varian spectrometer (200 and 50.4 MHz, respectively) in $CDCl_3$ or CD_3OD with TMS as internal reference. Melting point was determined on a Kofler apparatus and is uncorrected.

3-Nitropropionic Acid 1

Oxidation by $NaClO_2/H_2O_2$

A solution of 8.0 g (70 mmol) of 80% $NaClO_2$ (purchased from the Aldrich Company, technical grade) in 70 mL of water was added dropwise over 2 h to a stirred mixture of 6.6 g (64 mmol) of 3-nitropropanal (16) in 50 mL of acetonitrile and 1.6 g of NaH_2PO_4 in 20 mL of water and 5.0 mL (52 mmol) of 30% H_2O_2, keeping the temperature at 25°C. Oxygen evolved from the solution was monitored until the end of the reaction (about 1 h) with a bubbler connected to the apparatus. Addition of about 0.5 g of Na_2SO_3 and stirring for 10 min destroy the unreacted HOCl and H_2O_2. The reaction mixture is acidified with 10% aqueous HCl, water is added (about 30 mL), and extraction with AcOEt (3 × 50 mL) is accomplished. Solid NaCl is added to the remaining aqueous phase and an additional extraction

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with AcOEt (3 × 50 mL) is effected. The combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure to furnish a light yellow viscous oil. Purification by column chromatography on silica gel (Hexane/AcOEt 1:1) provided **1** as a white solid in high purity; (measured by ^{1}H NMR) yield: 7.3 g (96%). Recrystallization can be effected from $CHCl_3$, mp 65°C; Literature (26–29) 66°C and 65.6°C IR (KBr): ν 3019, 2994, 2935, 1704, 1690, 1558, 1425, 1404, 1377, 1266, 1243, 1212, 956, 874 cm^{-1}.^{1}H NMR(CD_3OD): δ 4.66 (t, 2H), 3.06 (t, 2H); ^{13}C NMR (50.4 Mz, CD_3OD): 174.31(C), 69.24 (CH_2) 30.65 (CH_2).

Oxidation by Jones Reagent

To a mixture, vigorously stirred, of 3-nitropropanal 3.38 g (32.8 mmol) in acetone (90 mL) at −12°C is added dropwise 19.5 mL of Jones reagent (prepared from 10 g CrO_3, 8.6 mL of 96% H_2SO_4, 14 mL of H_2O, and brought up to 40 mL). The reaction mixture is stirred for 2 h and 45 min at 0°C. After this time isopropanol in excess (about 90 mL) is added and the suspension is stirred for about 90 min until the green coloration persists. Neutralization of the reaction mixture with solid $NaHCO_3$ until pH neutral and evaporation of the volatile liquids furnished a green slurry, which was resuspended in Hexane/EtOAc (9:1) and filtered twice through a column of celite. The reunited organic phases were evaporated under reduced pressure and the remaining viscous pale green oil was purified by column chromatography on silica gel (Hexane/EtOAc, 1:1) to give 2.85 g of **1** as a white solid of satisfactory purity by ^{1}H NMR analysis. Recrystallization was effected from $CHCl_3$.

Methyl 3-Nitropropionate 3a

To a solution of 3-nitropropionic acid 7.0 g (58.8 mmol) in anhydrous methanol (100 mL) was added concentrated sulfuric acid (1.5 mL). The reaction mixture was heated at reflux in a Soxhlet apparatus charged with 4Å molecular sieves for a period of 6 h. After this time, methanol was removed under vacuum and the remaining residue diluted with CH_2Cl_2 (80 mL) and washed with water (3 × 40 mL). The combined organic phase was dried in Na_2SO_4 and evaporated under reduced pressure. The remaining oil was distilled in a Kugelhor apparatus, yielding 5.7 g (73%) of **3a** as a light yellow oil, b.p. 85°C/2.5 Torr; (Literature (15,31) 68°C/1Torr and 63°C/0.5Torr). IR (film): ν 3008, 2959, 2926, 1740, 1560, 1380, 1021, 872, 850 cm^{-1}. ^{1}H NMR ($CDCl_3$): 3.00 (t, J = 6.0 Hz), 3.78 (s), 4.64 (t, J = 6 Hz); ^{13}C NMR (50.4 Mz, $CDCl_3$): 169.81(C), 69.34 (CH_3), 51.75 (CH_3), 30.27(CH_2).

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Ethyl 3-Nitropropionate 3b

A mixture of 3-nitropropionic acid (8.92 g 75 mmol), p-toluenesulfonic acid monohydrate (0.25 g 1.31 mmol), ethyl alcohol (15 mL), and benzene (75 mL) under stir was refluxed at 90°C for a period of 6 h in a Dean-Stark apparatus. The resultant solution was cooled to room temperature and the volatile liquids evaporated to furnish a drak yellow viscous oil, which was diluted in 80 mL of dichloromethane and washed with water (30 mL). The organic phase was dried under anhydrous Na_2SO_4, filtered, and concentrated in a rotatory evaporator to give 8.48 g of **1** crude. Distillation in a Kugelhor apparatus yieldes 8.26 g (75%) of **1** as a colorless oil. (b.p 92°C/2.5 Torr) IR (film): ν 2986, 2942, 2878, 1736, 1560, 1381, 1194, 1024, 872, 856 cm^{-1}. ^1H NMR ($CDCl_3$): δ 4.66 (t, J = 6.0 Hz, 2H), 4.11 (q, J = 7.0 Hz, 2H), 2.97 (t, J = 6.0 Hz, 2H), 1.28 (t, J = 7.0 Hz, 2H); ^{13}C NMR (50.4 Mz, $CDCl_3$): 169.28 (C) 69.49 (CH_2), 61.13 (CH_2), 30.72 (CH_2),13.70 (CH_3).

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