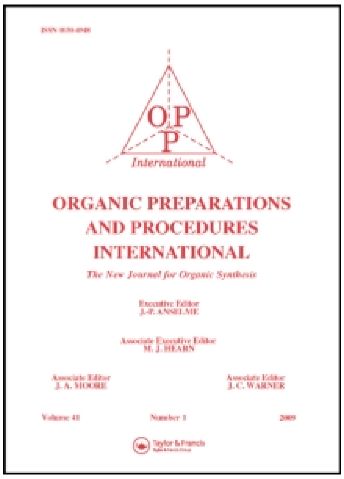

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AN IMPROVED SYNTHESIS OF 1-(4-NITROBENZYL)-1.2-ETHYLENEDIAMINE, PRECURSOR OF THE CORRESPONDING ETHYLENEDIAMINETETRAACETIC ACID

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OPPI BRIEFS

AN IMPROVED SYNTHESIS OF 1-(4-NITROBENZYL)-1,2-ETHYLENEDIAMINE, PRECURSOR OF THE CORRESPONDING ETHYLENEDIAMINETETRAACETIC ACID

Submitted by
(11/10/88)

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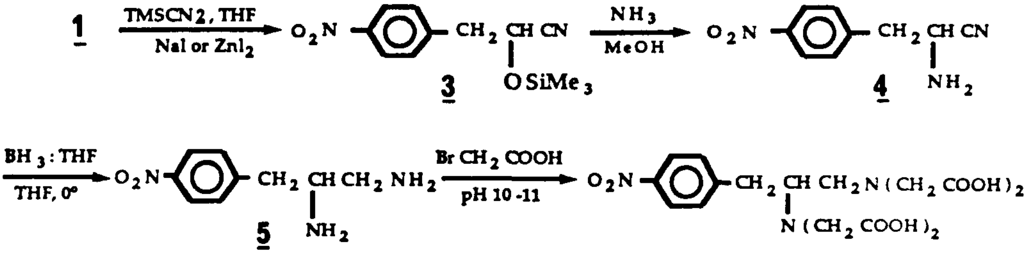
Radioactive cations such as $^{67}Ga^{3+}$, and $^{111}In^{3+}$ and $^{99m}Tc^{4+}$ are widely used in nuclear medicine[1] for the diagnosis of various diseases. Furthermore, the extensive use of monoclonal antibodies in cancer detection and chemotherapy has increased the demand for methods of labelling those biospecific macromolecules with metallic radionuclides. Yeh, Brechbiel and De Riemer[2] have previously reported a six-step preparation of 1-(4-nitrobenzyl)-1,2-ethylenediaminetetraacetic acid from phenylalanine with an overall yield of only 8%. We now report a simpler method for the synthesis of this very useful bifunctional chelating agent involving a three-step procedure starting from 4-nitrophenylacetaldehyde which gives a better overall yield (23%).

Mai[4] has reported the one-pot formation of α-aminonitriles 4 in very good yield (> 83%)



by addition of trimethylsilyl cyanide 2 to aromatic aldehydes or substituted phenylacetaldehydes (1), in the presence of a catalytic amount of zinc iodide followed by the subsequent amination of the α-cyanotrimethylsilyl ether intermediate 3 with ammonia in dry methanol; it must be pointed out that the same reaction conducted on 4-nitrobenzaldehyde led to an intractable mixture of compounds.

An advantageous approach to the synthesis of compound 6 could involve the reduction of α-aminonitrile 4. With this perspective, 4-nitrophenylacetaldehyde (1) was converted in high yield (> 90%) to 2-amino-3-(4-nitrophenyl)propionitrile (4) by using a somewhat similar procedure, sodium iodide being used instead of zinc iodide as catalyst. The nature and yield of the reaction were not affected. Compound 4 was then converted to the diamine 5 with the borane-tetrahydrofuran complex as reported by Brown.[5] Finally, 1-(4-nitrobenzyl)-1,2-ethylenediamine (5) was alkylated according to Yeh[2b] or Brechbiel[2c] by using bromoacetic acid to give the desired 6 in 30 to 35% yield.

EXPERIMENTAL SECTION

4-Nitrophenylacetaldehyde and trimethylsilyl cyanide were prepared according to reported procedures.[3,6] Tetrahydrofuran was purified from sodium-benzophenone ketyl immediately before use. Methanol was refluxed over magnesium-iodine, distilled and saturated at 0° with dry ammonia just prior to use. Infrared spectra were taken on a Unicam SP 1200 instrument; ^{1}H NMR spectra were taken on a Varian EM 390 or XL-200 spectrometer using TMS as the internal standard. Elemental analyses were performed at the Department of Chemistry at the University of Alberta.

2-Amino-3-(4-nitrophenyl)propionitrile (4).- To a well-stirred suspension of 1.65 g (10 mmoles) of 4-nitrophenylacetaldehyde and 15 mg of dry sodium iodide in anhydrous tetrahydrofuran was slowly added 1.24 g (12.5 mmoles) of freshly distilled trimethylsilyl cyanide.The reaction mixture was sonicated for 20 min. at room temperature and 15 ml of a saturated solution of methanolic ammonia was added in one portion. The temperature was raised to 50° and the reaction mixture stirred for 2 hrs. After cooling, the solvent was evaporated under vacuum and the residue taken up in ether (50 ml); the solution was washed with water (2 x 15 ml), dried over anhydrous sodium sulfate, filtered and concentrated to a brownish oil which solidified under vacuum. Purification by column chromatography on silica gel (60-200 mesh) and elution with a mixture of hexanes and ethyl acetate (3:2) provided 1.7 g (90%) of a yellow solid, mp. 70-72°. IR (KBr): 3500, 3400, 2200, 1520, 1340 cm^{-1}; ^{1}H NMR (CDCl$_3$): δ 8.2-7.3 (dd, 4H), 4.7 (t, 1H), 3.8 (br s, exchangeable with D_2O, 2H), 3.15 (d, 2H).

Anal. Calcd. for $C_9H_9N_3O_2$: C, 56.74; H, 4.72; N, 21.87. Found: C, 56.68; H, 4.51; N, 21.66

1-(4-Nitrobenzyl)-1,2-ethylenediamine Dihydrochloride (5).- To a cooled (ice bath) and stirred solution of 191 mg (1 mmole) of 2-amino-3-(4-nitrophenyl) propionitrile in 10 ml of anhydrous tetrahydrofuran was added dropwise 6 ml (6 mmoles) of the BH_3: THF complex (1.0 M) and after 30 min., the mixture was allowed to warm to room temperature and gently refluxed overnight. Excess hydride was carefully destroyed by adding a minimal amount of anhydrous methanol at 0°. The mixture was brought to room temperature after which the solvent was evaporated. The residue was taken up in 10 ml of dry ethanol, saturated with gaseous HCl and heated to reflux for 2 hrs. The reaction mixture was evaporated and the residue crystallized from a mixture of ethanol and ether to provide 192 mg (72%) of a white to slightly brownish solid which decomposed on heating. IR (KBr): 3350, 2927, 2590, 1532, 1352 cm^{-1}; ^{1}H NMR (D_2O, pH 11.5): δ 8.1 (d, 2H), 7.4 (d, 2H), 3.1 (m, 1H), 2.9 (dd, 1H), 2.75 (dd, 1H), 2.7 (dd, 1H), 2.6 (dd, 1H). The IR and NMR spectra were concordant to those previously reported.[2b,c]

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SYNTHESIS OF 2-HEXYLNAPHTHALENE

Submitted by (06/15/88)

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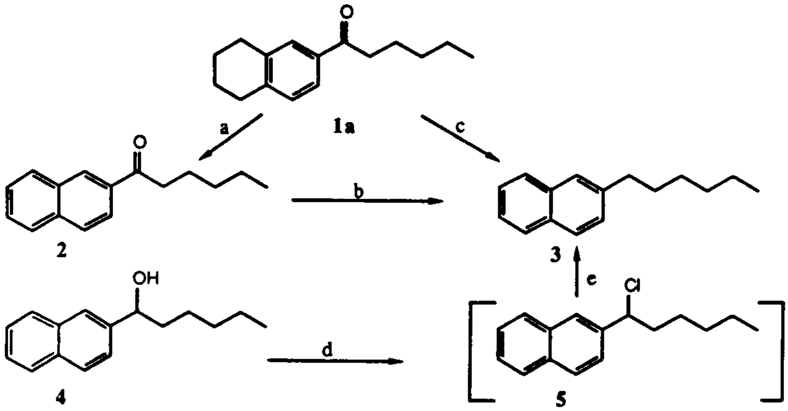
The reaction sequence (1a→2→3) was used to prepare 3 as a high-purity, model hydrocarbon for precise thermodynamic studies of fossil fuel constituents by the National



a) Pd/C, p-cymene, Δ. b) NH_2NH_2, OH^-, DEG, Δ. c) Pd/C, Δ. d) Conc. HCl, toluene. e) H_2, Pd/C, C_2H_5OH.