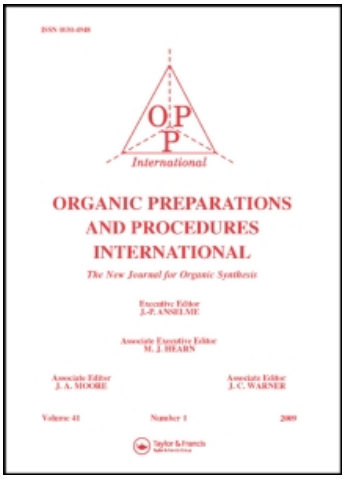

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SYNTHESIS OF HEXASUBSTITUTED NITROBENZENE DERIVATIVES *via* VICARIOUS NUCLEOPHILIC SUBSTITUTION OF HYDROGEN

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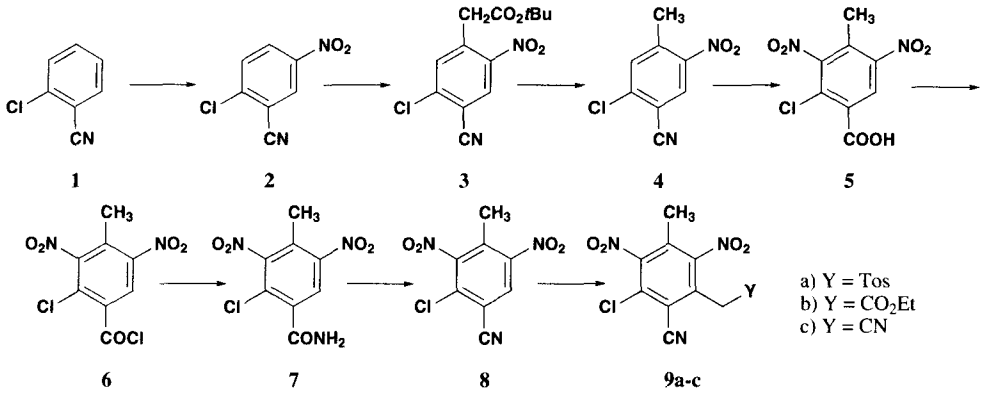
In a synthetic project directed towards natural products, we needed polysubstituted dinitrobenzene derivatives containing versatile substituents in well defined positions as in compound **9**. It appeared to us that such compounds can be most readily prepared using vicarious nucleophilic substitution (VNS) reaction, a process widely used for the introduction of carbon substituents into nitroarenes.[1] The reaction sequence from commercially available *o*-chlorobenzonitrile (**1**) is shown in Scheme 1.



Scheme 1

Nitration of *o*-chlorobenzonitrile carried out according to a published procedure[2] gave the expected 2-chloro-5-nitrobenzonitrile (**2**) which was subjected to the VNS reaction with *tert*-butyl chloroacetate in the presence of *t*-BuOK in DMF. As expected, the substitution proceeded selectively at position 4, most likely because of steric hindrance at position 6, although the yield of **3** was only 56%. The next step - hydrolysis and decarboxylation of **3** to **4** was carried out in a boiling mixture of acetic acid and anhydride as previously described.[3] Recently alkaline conditions were also proposed for this transformation, provided the ethyl ester is used.[4] Nitration of toluene derivative **4** required vigorous conditions such as a nitrating mixture of HNO_3 and H_2SO_4 at 100°. Under such conditions, the nitration proceeded satisfactorily albeit with concurrent hydrolysis of the cyano group to acid **5** in high yield. This result required the additional steps **5** → **8** in Scheme 1.

The overall yield of conversion $ArCO_2H$ → ArCN (**8**) was 86%. Compound **8**, the key intermediate, was subjected to the VNS reaction with chloromethyl *p*-tolyl sulfone, ethyl chloroacetate and

p-chlorophenoxyacetonitrile giving desired products **9a-c**. The conversion to the ester (**9b**) and nitrile (**9c**) proceeded in low yields.

Thus it was shown that the VNS reaction provides a versatile route to polysubstituted nitroarenes.

EXPERIMENTAL SECTION

Melting points are uncorrected. Infrared (IR) spectra were recorded with a Acculab 1 Beckman spectrometer in KBr disks. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Gemini (200 MHz) instrument; chemical shifts are in ppm downfield from TMS as internal standard; coupling constants *J* are given in Hertz. Silica-gel Merck (230-400 mesh ASTM) was used for column chromatography. All reagents were commercially available.Elemental analyses were performed on a Perkin-Elmer 240 elemental analyzer.

***tert*-Butyl-2-nitro-4-cyano-5-chlorophenylacetate (3)**.- To a stirred solution of *t*-BuOK (14 g, 0.125 mol) in dry DMF (180 mL) a solution of 2-chloro-5-nitrobenzonitrile (9.125 g, 0.05 mol) and *tert*-butyl chloroacetate (8.28 g, 0.055 mol) in DMF (30 mL) was added dropwise at -20°. After the addition was complete (45 min), the reaction mixture was stirred for an additional 45 min at 0° and then poured into a solution of conc. hydrochloric acid (15 mL) in water (500 mL). The product was extracted with CH_2Cl_2, the combined extracts were dried with anhydrous $MgSO_4$, and the solvent was evaporated. The product was purifed *via* flash chromatography (hexane/ether - 10/1 eluent). After evaporation of solvents the residue was recrystallized from hexane/methylene chloride to yield 8.3 g, (56%) of white crystals, mp. 111-112°.^{1}H NMR ($CDCl_3$): δ 8.41 (s, 1H), 7.54 (s, 1H), 3.99 (s, 2H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$): δ 167.2, 147.2, 141.5, 136.7, 134.7, 130.5, 113.5, 83.0, 40.9, 27.9; IR: 2239, 1717, 1533, 1338, 1151 cm^{-1}.

Anal. Calcd for $C_{14}H_{13}ClN_2O_4$: C, 52.62; H, 4.42; N, 9.44; Cl, 11.95
Found: C, 52.58; H, 4.32; N, 9.54; Cl, 11.86

2-Chloro-4-methyl-5-nitrobenzonitrile (4).- Compound **3** (14.83 g, 0.05 mol) was heated at reflux in a mixture of acetic acid (100 mL) and acetic anhydride (3 mL) until full conversion of the substrate (TLC control, 4-5 days). Part of the acetic acid was distilled (50-60 mL) and the residue was kept at room temp. for 1 h. The crystalline product was collected, washed with water, dried in air and purified *via* flash chromatography (hexane/methylene chloride - 2/1 eluent). The product was recrystallized from heptane to yield 8.55 g (87%), mp. 93.5-94°, lit.[5] mp. 91.5-92.5°.

2-Chloro-3,5-dinitro-4-methylbenzoic Acid (5).- Compound **4** (7.86 g, 0.04 mol) was dissolved in a mixture of HNO_3 (d = 1.5 g/cm^3, 5 mL) and H_2SO_4 (d = 1.84 g/cm^3, 20 mL) at room temperature. The reaction mixture was stirred and heated slowly to 100° (some foam formation and precipitation of crystals were observed). The reaction was carried out for an additional 30 min at 110°. The mixture was cooled and poured into ice water (400 mL). The precipitate was filtered, washed with water, dissolved in 10% aqueous Na_2CO_3 and boiled with charcoal for 15 min. The charcoal was filtered and the filtrate was acidified with aqueous HCl. The precipitate was collected, washed with water and

recrystallized from aqueous methanol to give 9.28 g (89%) of **5**, mp. 233-234°, lit.[5] mp. 235-237°.

2-Chloro-3.5-dinitro-4-methylbenzoyl Chloride (6).- Compound **5** (10.42 g, 0.04 mol) was refluxed with thionyl chloride (10 mL) and 2 drops of DMF until a clear solution was obtained (30 min). The excess of $SOCl_2$ was distilled at 80°; the residue was kept at room temp. for 1 h. Pentane (10mL) was added; the crystalline product was filtered and washed with pentane to give 10.99 g (98%) of **6**, mp. 107-108° (from heptane/hexane 1/1), lit.[6] mp. 106°.

2-Chloro-3,5-dinitro-4-methylbenzamide (7).- Compound **6** (11,16 g, 0.04 mol) was dissolved in THF (40 mL) and this solution was added slowly to 13% aqueous ammonia (40 mL) at 0°. The reaction mixture was stirred at 0-5° for 15 min and poured into water (400 mL). After 1 h the precipitate was collected, washed with 10% aqueous Na_2CO_3, water and dried in air to give 10.07 g (97%) of **7**, mp. 229-229,5° (from xylene).^{1}H NMR ($CDCl_3$): δ 8.14 (s, 1H), 6.60 (bs, 2H), 2.34 (s, 3H); ^{13}C NMR (acetone d_6): δ 163.3, 150.5, 147.3, 136.1, 126.5, 124.9, 124.5, 12.8; IR: 3362, 3178, 1661, 1541, 1346 cm^{-1}.

Anal. Calcd for $C_8H_6ClN_3O_5$: C, 37.01; H, 2.33; N, 16.19; Cl, 13.66
Found: C, 37.07; H, 2.40; N, 16.19; Cl, 15.59

2-Chloro-3,5-dinitro-4-methylbenzonitrile (8).- A mixture of **7** (8,56 g, 0.033 mol) and PCl_5 (13,76 g, 0.066 mol) was heated on the oil bath at 110° to a complete melt (1.5 h). After cooling, the reaction mixture was dissolved in CH_2Cl_2 (200 mL) and this solution was slowly poured into ice water (600 mL).The organic layer was separated, washed with water and dried with anhydrous $MgSO_4$.The solvent was evaporated and the residue was purified *via* flash chromatography (hexane/methylene chloride 1/1 eluent). Recrystallization from CH_2Cl_2 gave **8** as pale yellow crystals, (7.17 g, 90%), mp. 133-134°. ^{1}H NMR ($CDCl_3$): δ 8.38 (s, 1H), 2.58 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 151.8, 148.3, 132.7, 132.2, 130.1, 114.1, 112.5, 15.3; IR: 2248, 1549, 1532, 1344 cm^{-1}.

Anal. Calcd for $C_8H_4ClN_3O_4$: C, 39.77; H, 1.67; N, 17.40; Cl, 14.67
Found: C, 39.82; H, 1.62; N, 17.37; Cl, 14.64

2-Chloro-3,5-dinitro-4-methyl-6-tosylmethylbenzonitrile (9a).- To a stirred solution of *t*-BuOK (11.2 g, 0.1 mol) in dry THF (50 mL) a mixture of **8** (4.83 g, 0.02 mol) and chloromethyl *p*-tolyl sulfone (4.09, 0.02 mol) in dry THF (15 mL) was added dropwise at -45°. After the addition was completed (30 min) the reaction mixture was stirred at -35° for 30 min and poured into 5% HCl (300 mL). The product was extracted with CH_2Cl_2, the extract was dried with anh. $MgSO_4$ and the solvent was evaporated. The residue was purified *via* column chromatography (hexane/methylene chloride/ethyl acetate - 4/1/1 eluent) giving **9a** (5.32g, 65%), mp.196-198° (hexane/ethyl acetate). ^{1}H NMR (acetone d_6): δ 7.84 (m, 2H), 7.58 (m, 2H), 5.05 (s, 2H), 2.55 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (acetone d_6): δ 151.5, 151.4, 147.3, 136.2, 131.8, 131.6, 131.2 (2C), 129.8, 129.4 (2C), 118.7, 113.0, 58.1, 21.6, 15.1; IR: 2239, 1557, 1545, 1354, 1323, 1165, 1137, 1085 cm^{-1}.

Anal. Calcd for $C_{16}H_{12}ClN_3SO_6$: C, 46.89; H, 2.95; N, 10.25; Cl, 8.65; S, 7.83
Found: C, 47.07; H, 2.78; N, 10.28; Cl, 8.75; S. 7.88

2-Chloro-3,5-dinitro-6-ethylcarboxymethyl-4-methylbenzonitrile (9b).- To a stirred solution of *t*-BuOK (560 mg, 5 mmol) in dry THF (4 mL) a mixture of **8** (241 mg, 1 mmol) and ethyl chloroacetate (123 mg, 1 mmol) in dry THF (1 mL) was added dropwise at -60°. After the addition was completed (5 min) the reaction mixture was allowed to warm to -20° for 45 min and poured into 5% HCl (30 mL). The standard procedure and purification *via* column chromatography (hexane/ methylene chloride/ethyl acetate - 10/2/1 eluent) gave **9b**, (95 mg, 29%), mp. 64-65° (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 4.26 (kw, 2H, *J* = 7.2), 3.93 (s, 2H), 2.36 (s, 3H), 1.31 (t, 3H, *J* = 7.2); IR: 2239, 1734, 1542, 1540, 1357, 1227, 1197 cm^{-1}.

Anal. Calcd for $C_{12}H_{10}ClN_3O_6$: C, 43.98; H, 3.08; N, 12.82; Cl, 10.82
Found: C, 43.81; H, 3.10; N, 12.99; Cl, 10.73

2-Chloro-6-cyanomethyl-3,5-dinitro-4-methylbenzonitrile (9c).- From **8** (241 mg, 1mmol) and *p*-chlorophenoxyacetonitrile (167.5 mg, 1 mmol) according the procedure used for **9b**, **9c** was obtained to yield 84 mg (30%), mp. 151-153° (hexane/ethyl acetate). ^{1}H NMR ($CDCl_3$): δ 4.02 (s, 2H), 2.43 (s, 3H); IR: 2245, 2240, 1549, 1351 cm^{-1}.

Anal. Calcd for $C_{10}H_{15}ClN_4O_4$: C, 42.80; H, 1.80; N, 19.96; Cl, 12.64
Found: C, 42.95; H, 1.86; N, 19.84; Cl, 12.58

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