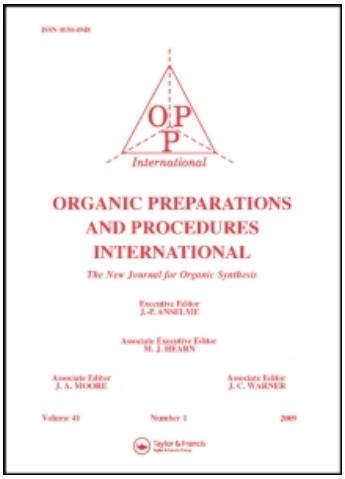

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AN EFFICIENT SYNTHESIS OF 3, 5-*bis*(2-CYANOISOPROPYL)TOLUENE

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AN EFFICIENT SYNTHESIS OF 3,5-*bis*(2-CYANOISOPROPYL)TOLUENE

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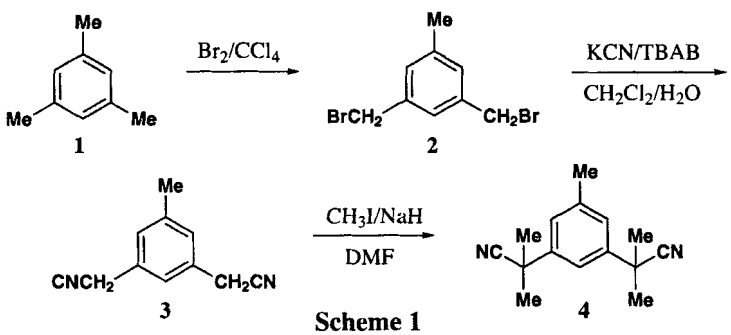
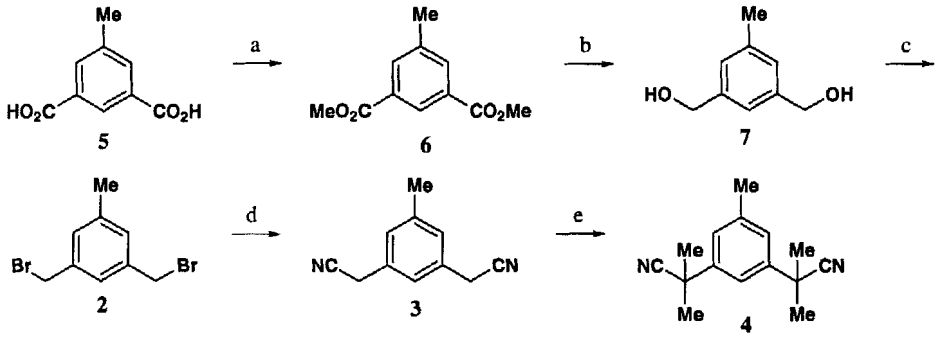
3,5-*bis*(2-Cyanoisopropyl)toluene (**4**) is a key intermediate for the preparation of *anastrozole*, an anti-tumor drug for the treatment of breast cancer. So far, the only synthetic route to **4** involves three steps from mesitylene (*Scheme 1*).[1,2] However, this patented approach suffers from low yield, environmentally unfriendly chemicals (CCl_4 and benzoyl peroxide) and high cost (expensive iodomethane).



Scheme 1

As a part of our exploration of a facile synthesis of *anastrozole*, we have developed an efficient preparation of 3,5-*bis*(2-cyanoisopropyl)toluene (**4**) from commercially available 5-methylisophthalic acid (**5**) (*Scheme 2*).



a) H_2SO_4, CH_3OH, reflux, 90%; b) KBH_4, LiCl, THF, 75%; c) PBr_3, CH_2Cl_2, 90%; d) KCN, TBAB, CH_2Cl_2, H_2O 78%; e) NaH, DMF, methyl *p*-toluenesulfonate, 86%

Scheme 2

Reduction of **6**, obtained from compound **5** *via* esterification in methanol, gave diol **7** in 75% yield.[3] Treatment of **7** with PBr_3 afforded **2** in 90% yield.[4, 5] Reaction of **2** with KCN proceded smoothly to give compound **3** in 78% yield. The final step was modified slightly, using methyl *p*-toluenesulfonate instead of expensive iodomethane as the methylating reagent. After crystallization from ethanol, 3,5-*bis*(2-cyanoisopropyl)toluene (**4**) was obtained in 86% yield, in better than 99% purity.

In conclusion, we have developed an efficient synthesis of 3,5-*bis*(2-cyanoisopropyl)toluene (**4**) in 41% overall yield. The advantages of this procedure include mild conditions, simple work-up procedures and avoidance of toxic solvent and expensive reagent.

EXPERIMENTAL SECTION

Melting points were determined on a Büchi 510 melting point apparatus. ^1H NMR spectra were recorded on a Bruker DRX-500 (500 MHz). ^{13}C NMR spectra were obtained on a JNM-EX100 (400 MHz). Mass spectra (MS) were determined on a Finnigan MAT-95 mass spectrometer.

Methyl 5-Methyl-1,3-benzenedicarboxylate (6).- A solution of 5-methylisophthalic acid (**5**) (180 g, 1.0 mol), sulfuric acid (8 mL) in methanol (400 mL) was refluxed for 16 h. The mixture was then evaporated to remove methanol. The residue was poured into 5% aqueous Na_2CO_3 (300 mL) to precipitate a white solid, that was collected, washed with water, dried with Na_2SO_4, and evaporated to give compound **6** (186 g, 90% yield), mp. 96-98°C. ^1H NMR (500 MHz, $CDCl_3$): δ 2.45 (s, 3H), 3.99 (s, 6H), 8.04 (s, 2H), 8.48 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 52.3, 127.9, 130.5, 134.4, 138.6, 166.4. MS (EI): m/z = 208.

Anal. Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.36; H, 5.73

3,5-*bis*(Hydroxymethyl)toluene (7).- A mixture of **6** (20.8 g, 0.10 mol), KBH_4 (37.1 g, 0.70 mol), LiCl (29.7 g, 0.70 mol) in THF (100 mL) was heated to reflux for 6 h, then cooled to room temperature and quenched with saturated NH_4Cl solution (40 mL). After stirring for 1 h, the mixture was filtered to remove insoluble solids. Then, the filtrate was extracted with ethyl

acetate, washed with brine, dried with $MgSO_4$, and concentrated to give **7** as a white solid (11.4 g, 75% yield), mp. 41-43°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.27 (s, 3H), 4.35 (s, 2H), 4.41 (s, 4H), 6.93 (s, 2H), 7.00 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 64.4, 122.5, 126.7, 137.9, 140.9. MS (EI): m/z = 152.

Anal. Calcd. for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 70.76; H, 7.94.

3,5-*bis*(Bromomethyl)toluene (2).- To a solution of compound **7** (11.46 g, 75 mmol) in CH_2Cl_2 (65 mL) at 0°C, was added PBr_3 dropwise over a period of 30 min. Then the mixture was stirred for 4 h at room temperature and poured into ice water (100 mL). The solution was extracted with CH_2Cl_2, washed with brine, dried with Na_2SO_4, and evaporated to dryness to give solid **3** (18.6 g, 89% yield), mp. 64-66°C, (*lit.*[2] mp. 66°C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.34 (s, 3H), 4.44 (s, 4H), 7.14 (s, 2H), 7.26 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.1, 32.9, 126.7, 129.8, 138.2, 139.2. MS (EI): m/z = 278. HPLC: 99.7%.

3,5-*bis*(2-Cyanoisopropyl)toluene (4).- To a mixture of NaH (6.32 g, 160 mmol) in DMF (30 mL) under a nitrogen atmosphere at 0°C was added a solution of compound **4** (6 g, 35 mmol) and methyl *p*-toluenesulfonate (26.4 g, 140 mmol) in DMF (30 mL). Then, the mixture was stirred for 30 min, poured into ice water (100 mL) to precipitate a white solid, which was collected, washed with water and dried to give crude **4**. Crystallization from ethanol gave pure solid **4** (6.8 g, 86% yield), mp. 126-127°C, (*lit.*[1] mp. 126-127°C), purity > 99% (HPLC analysis). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.73 (s, 12H), 2.40 (s, 3H), 7.26 (s, 2H), 7.32 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.5, 28.9, 29.0, 37.13, 118.6, 124.2, 125.4, 139.5, 142.1. MS (EI): m/z = 226.

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