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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 (CCl₄ and benzoyl peroxide) and high cost (expensive iodomethane).

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) H₂SO₄, CH₃OH, reflux, 90%; b) KBH₄, LiCl, THF, 75%; c) PBr₃, CH₂Cl₂, 90%;

d) KCN, TBAB, CH₂Cl₂, H₂O 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 PBr₃ 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). ¹³C 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 Na₂CO₃ (300 mL) to precipitate a white solid, that was collected, washed with water, dried with Na₂SO₄, and evaporated to give compound 6 (186 g, 90% yield), mp. 96-98°C. ¹H NMR (500 MHz, CDCl₃): δ 2.45 (s, 3H), 3.99 (s, 6H), 8.04 (s, 2H), 8.48 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 21.1, 52.3, 127.9, 130.5, 134.4, 138.6, 166.4. MS (EI): m/z = 208.

Anal. Calcd. for C₁₁H₁₂O₄: 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), KBH₄ (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 NH₄Cl solution (40 mL). After stirring for 1 h, the mixture was filtered to remove insoluble solids. Then, the filtrate was extracted with ethyl

Volume 40, No. 5 (2008) OPPI BRIEFS

acetate, washed with brine, dried with MgSO₄, and concentrated to give 7 as a white solid (11.4 g, 75% yield), mp. 41-43°C. ¹H NMR (500 MHz, CDCl₃): δ 2.27 (s, 3H), 4.35 (s, 2H), 4.41 (s, 4H), 6.93 (s, 2H), 7.00 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): δ 21.1, 64.4, 122.5, 126.7, 137.9, 140.9. MS (EI): m/z = 152.

Anal. Calcd. for C₀H₁₂O₂: 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). ¹H NMR (500 MHz, CDCl₃): δ 2.34 (s, 3H), 4.44 (s, 4H), 7.14 (s, 2H), 7.26 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): 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*. mp. 126-127°C), purity > 99% (HPLC analysis). ¹H NMR (500 MHz, CDCl₃): δ 1.73 (s, 12H), 2.40 (s, 3H), 7.26 (s, 2H), 7.32 (s, 1H). ¹³C NMR (100 MHz, CDCl₃): 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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