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Organic Preparations and Procedures International: The New Journal for Organic Synthesis

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/uopp20

A CONCISE SYNTHESIS OF SYMMETRIC 1,3,5-C_3-TRISUBSTITUTED BENZENES

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Published online: 09 Feb 2009.

To cite this article: M. W. Majchrzak , J. N. Zobel , D. J. Obradovich & G. A. Peterson (1997) A CONCISE SYNTHESIS OF SYMMETRIC 1,3,5-C_3-TRISUBSTITUTED BENZENES, Organic Preparations and Procedures International: The New Journal for Organic Synthesis, 29:3, 361-364, DOI: 10.1080/00304949709355214

To link to this article: http://dx.doi.org/10.1080/00304949709355214

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A CONCISE SYNTHESIS OF SYMMETRIC 1,3,5-C_3-TRISUBSTITUTED BENZENES

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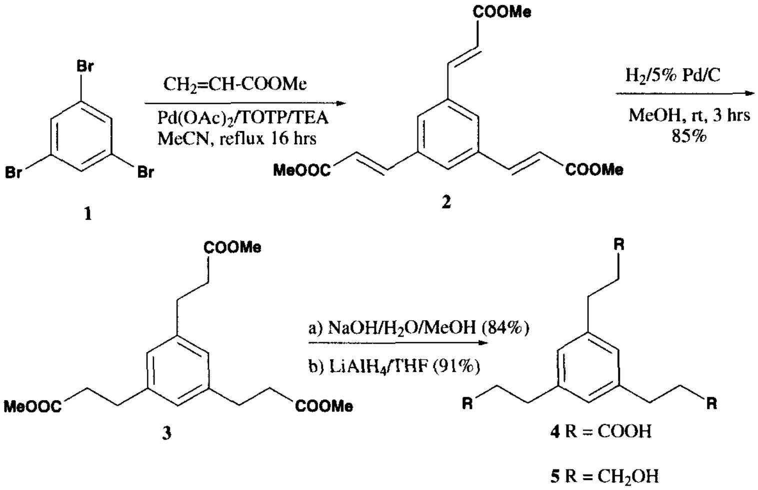
1,3,5-Trisubstituted benzenes represent an important class of compounds because of their unique symmetry, and their importance in the syntheses of cascade macromolecules.[1,2] They also have shown interesting pharmacological properties, such as anticoagulant and antiplatelet effects.[3] Their preparation has been based either upon 1,3,5-triacetylbenzene[3] or benzene-1,3,5-tricarboxylic acid,[4,5] but unfortunately, the syntheses of the three-carbon chain congeners required the application of laborious chain elongation procedures.[3-5]

In the course of our studies on the industrial applications of Pd-mediated cross couplings, we have found that 1,3,5-tribromobenzene reacts smoothly with methyl acrylate in the presence of palladium acetate, tri-(*o*-tolyl)phosphine and triethylamine in refluxing acetonitrile (Heck reaction[6]), to give methyl 1,3,5-benzenetriacrylate (**2**), which represents a versatile starting material for the syntheses of various 1,3,5-trisubstituted benzenes containing three-carbon chains, as shown in the scheme below.



EXPERIMENTAL SECTION

Mps were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were obtained using a Mattson FT-IR spectrometer. ^{1}H NMR spectra were recorded on a Brucker 250 MHz spectrometer using TMS as an internal standard. GC analyses were performed on Hewlett-Packard 5890 Series II Gas Chromatograph equipped with a fused silica capillary column, (Alltech Heliflex AT-1 impregnated with 100% dimethylpolysiloxane, 15 m) and FID detector. TLC analyses were performed on precoated HPTLC-HLF UV 254 glass plates purchased from Analtech using the indicated solvent systems. Components were visualized under UV light. Microanalyses were performed by the Galbraith Laboratories, Knoxville, TN 37950, USA. All reagents were purchased from Aldrich Chemical Company, Inc. and were used without further purification. Glass fiber filter pads (Whatman Glass Microfiber Filters, GF/A Grade) were also purchased from Aldrich.

1,3,5-*tris*(2-Carbomethoxyethenyl)benzene (2).- To a solution of 1,3,5-tribromobenzene (100 g, 0.32 mol) in MeCN (300 mL), were added Pd(OAc)$_2$ (1.42 g, 6.3 mmol), tri-(*o*-tolyl)phosphine (3.8 g, 12.6 mmol) and Et$_3$N (250 mL). The mixture was stirred under an inert gas atmosphere and methyl acrylate (60 g, 0.69 mol) was added in a steady stream under reflux. The mixture changed to a dark brown coloration, and a grayish precipitate formed. After 2 hrs at reflux, GC analysis showed a 50% conversion. The mixture was treated further with methyl acrylate (27.5 g, 0.32 mol), Pd(OAc)$_2$ (0.71 g, 3.3 mmol) and tri-(*o*-tolyl)phosphine (1.9 g, 6.3 mmol). Reflux was continued until GC analysis showed complete disappearance, (ca. 3 hrs) of the starting 1,3,5-tribromobenzene, (peak at 3.7

minutes). The concentration of the product in the mixture (peak at 10.9 min.) was at 77% at the end of the reaction. The mixture was then cooled to 25° and after the addition of water (200 mL), was stirred for ten min. and filtered. The grayish solid was washed with water and then hexane (2 x 100 mL). The crude product was dissolved in boiling dioxane (1.0 L), treated with charcoal, filtered though a glass fiber filter and cooled in an ice bath. The sand colored precipitate was collected, washed with CH_2Cl_2 and hexane, (50 mL, each), and dried *in vacuo* at 40° to give 50 g (48%) of white crystals. The original filtrate was concentrated *in vacuo*, and the solid residue was dissolved in CH_2Cl_2 (2.0 L), washed with water, 10% HCl and water (2 x 200 mL), respectively. The organic layer was treated with charcoal, dried ($MgSO_4$), filtered and evaporated *in vacuo*. The residue was recrystallized twice from 300 mL of dioxane, to give an additional 16.6 g of the same material. The combined yield of colorless product, mp. 210-211°, was 66.6 g (63%); TLC (SiO_2, CH_2Cl_2): R_f - 0.47; ^{1}H NMR ($CDCl_3$): δ 7.67 (d, J = 17.5 Hz, 3, CH), 7.63 (s, 3, Ar), 6.49 (d, J = 17.5 Hz, 3, CHCO), 3.63 (s, 9, Me). IR (KBr): 1714, 1678, 1446, 1285 cm^{-1}.

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found : C, 65.55; H, 5.66

1,3,5-*tris*(2-Carbomethoxyethyl)benzene (3).- Into a solution of **2** (20.0 g, 0.06 mol) in THF (600 mL) in a 2 L Parr bottle, 5% Pd/C (3 g) was added. The bottle was placed into the Parr shaker. The reaction mixture was purged with argon and hydrogen (3x to 30 psi, each), and finally the system was charged with hydrogen to 50 psi. The hydrogenation was carried out at 40-50° and continued until the hydrogen absorption stopped (ca. 1 hr). The system was purged twice with argon (to 30 psi), and the catalyst was filtered through a glass fiber filter (***Caution, the spent catalyst is pyrophoric***). The filtrate was concentrated *in vacuo* to give a clear colorless oil, (17.3 g; 85%), which was distilled *in vacuo*, bp. 175-180°/0.3 mm Hg. TLC (SiO_2, CH_2Cl_2): R_f - 0.40; ^{1}H NMR ($CDCl_3$): δ 6.85 (s, 3, Ar), 3.64 (s, 9, OMe), 2.86 and 2.57 (t, J = 7.5 Hz, 6, CH_2); IR (KBr):1750, 1607, 1464 cm^{-1}. Lit. ^{1}H NMR ($CDCl_3$): δ 6.90 (s, 3, Ar), 3.61 (s, 9, OMe), 2.38-31.0 (m, $H^{\alpha,\beta}$).[4]

1,3,5-*tris*(2-Carboxyethyl)benzene (4) was prepared by the saponification of **3** in 80% yield, mp. 94-96°, lit.[5] mp. 94-95° (benzene) and lit.[4] mp. 134-135° (water);

^{1}H NMR ($CDCl_3$): δ 12.11 (s, 3, OH), 6.89 (s, 3, Ar), 2.74 and 2.49 (t, J = 7.5 Hz, 6, CH_2); IR (KBr): 3400-2300, 1710, 1446 cm^{-1}.

1,3,5-*tris*(3-Hydroxypropyl)benzene (5) was prepared by the reduction of **3** with three equivalents of $LiAlH_4$ in THF in 91% yield; bp. 230-235°/0.1 mm Hg; upon standing at 0°, the oil crystallized, mp. 49-51°, lit.[4] mp. 43-45°; ^{1}H NMR (DMSO-d_6): δ 6.79 (s, 3, Ar), 4.38 (t, J = 5.0 Hz, 3, OH), 3.38 (dd, J = 5.0 and 12.5 Hz, 6, CH_2O), 2.52 (t, J = 7.5 Hz, 6, CH_2Ar), 1.67 (p, J = 7.5 Hz, 6, CH_2); IR (KBr): 3250, 2929, 1050 cm^{-1}.

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