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Selective *Ipso*-Nitration of *tert*-Butyl Calix[4]arene Ether Derivatives under Mild and Heterogeneous Conditions

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Nitration of *p*-*tert*-butyl calix[n]arene propyl ethers under variety of reaction conditions has been examined. *Ipso*-Nitration of tri and tetra propoxy tetra-*p*-*tert*-butyl calix[4]arene with silica supported sulfuric acid and nitric acid give best yields of *p*-nitro calixarenes in simple work up conditions. The obtained nitrated products are key intermediates for construction of molecular receptors based on calixarenes.

Key Words: *Ipso*-nitration, Calix[4]arene, Heterogeneous condition.

INTRODUCTION

Calix[4]arenes are emerging as a new class of synthetic hosts that have attracted interest in several areas of bioorganic and bio mimetic chemistry, calix[4]arene is a structurally well defined macro cyclic molecule that is readily available in large quantities and easily modified by chemical reactions[1]. These molecules have attracted considerable interest as building blocks for constructing selective host molecules[2]. Upper rim functionalized caliarenes can be obtained in a multi-step procedure from suitably substituted precursors[3]. Mono and Di-nitrated calix[4]arenes are especially useful for this purpose. Nitration of calix[4]arenes has been attempted by a number of researchers using direct and indirect methods[4-8]. The reported methods are limited by low yields, multiplicity of steps or over oxidation of starting calixarenes by the nitrating mixture[9]. The heterogeneous reagent systems have many advantages such as simple experimental procedures, mild reaction condition and minimization of chemical wastes as compared to their liquid phase counterparts[10]. The silica sulfuric acid in a superior proton source to many of the reported acidic solid supports or acidic resins such as polystyrene sulfonic acid and nafion-H[11], for running reaction under heterogeneous condition. We have used this inorganic acid resin (silica sulfuric acid and silica nitric acid) for the

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incite generation of HNO_2 when used in conjunction with and without $NaNO_3$, we reported the selective substitution of one or two nitro groups by direct replacement of *tert*-butyl groups *via* an *ipso*-aromatic nitration[12]. In the present study, we obtained nitro derivatives of calixarene in high yield *via* nitration-oxidation reaction with silica sulfuric acid and silica nitric acid at room temperature. These compounds afford important starting materials for the construction of molecular receptors based on calixarenes.

EXPERIMENTAL

Melting points are taken on a Büchi SMP-20 apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Brüker AM-400 MHz in $CDCl_3$ with Me_4Si as an internal standard. Elemental analyses were carried out on Carlo-Erba analyzer model 1104. IR spectra were recorded on a Brüker IF S-25 spectrophotometer. The calix[4]arene **1** and **2** were prepared according to the published procedure.

Preparation of compound (3): A mixture of (**1**) (1 g, 0.774 mmol), $NaNO_3$ (10.9 g, 0.928 mmol) and SiO_2-OSO_3H (1 g) in CH_2Cl_2 (12 mL) was stirred at room temperature for 3 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered and residue was dried over anhydrous magnesium sulphate. The solvent was removed by distillation using a water bath. The crude product thus obtained was crystallized in mixture of dichloromethane and methanol to yield **3** in 87%. m.p., 182-184ºC. IR ν_{max} (KBr, cm^{-1}) 3456, 1592, 1472, 1334, 1201, 1006; δH (400 MHz, $CDCl_3$) 0.83 [18H, s, $C(CH_3)_3$)], 0.95 [3H, t, CH_3], 1.10 [6H, t, CH_3], 1.35 [9H, s, $C(CH_3)_3$], 1.93 [4H, m ,CH_2], 2.2 [2H, m, CH_2], 3.19 and 4.34 [4H, d of d, J = 12.6 Hz, $ArCH_2Ar$], 3.75 [2H, t, OCH_2], 3.81 [4H, t, OCH_2], 3.39 and 4.31 [4H, d of d, J = 13.9 Hz, $ArCH_2Ar$], 6.45 [2H, d, J = 2.3 Hz, ArH], 6.60 [2H, d, J = 2.3 Hz, ArH], 7.16 [2H, s, ArH], 7.22 [1H, s, OH], 8.06 [2H, s, ArH]; δC (100 MHz) 9.56, 10.70, 22.55, 23.37, 31.10, 31.36, 31.47, 31.68, 33.74, 34.15, 58.46, 76.15, 78.01, 124.31, 125.68, 125.70, 129.80, 132.65, 135.76, 139.34, 145.82, 151.75, 153.78, 159.98; m/z (FD) 764 (m, 100%). Anal. (%) Calcd. for $C_{49}H_{65}NO_6$: C, 77.06; H, 8.52; N, 1.84. Found C, 76.80, H, 8.70; N, 2.00.

Preparation of compound (4): A mixture of (**2**) (1 g, 0.82 mmol), $NaNO_3$ (11.6 g, 0.984 mmol) and SiO_2-OSO_3H in CH_2Cl_2 (15 mL) was stirred at room temperature for 3 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered and residue was dried over anhydrous magnesium sulphate. The solvent was removed by distillation using a water bath. The crud product thus obtained was crystallized in mixture of dichloromethane and methanol to yield **3** in 65%. m.p., 191-194ºC. IR ν_{max} (KBr, cm^{-1}) 2962, 1523, 1482, 1342, 1208; δH (400 MHz,

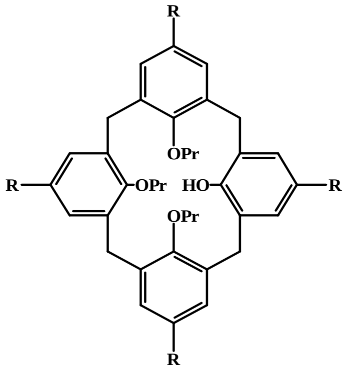
$CDCl_3$) 0.63 [9H, s, $C(CH_3)_3$)], 0.93 [6H, t, CH_3] , 1.9 [3H, t, CH_3], 1.24 [3H, t, CH_3], 1.37 [18H, s, $C(CH_3)_3$)], 1.89 [4H, m, CH_2], 2.03 [2H, m, CH_2], 3.13, 4.39 [4H, d of d, J = 13.5 Hz, $ArCH_2Ar$], 3.15, 4.47 [4H, d of d, J = 12.9 Hz, $ArCH_2Ar$], 3.67 [2H, t, OCH_2], 3.72 [2H, t, OCH_2], 3.89, 4.08 [4H, m, OCH_2], 6.21 [2H, s, ArH], 7.12 [2H, d, J = 2.13 Hz, ArH], 7.15 [2H, d, J = 2.4Hz, ArH], 7.26 [2H, s, ArH].

Preparation of compound (5) and (6): A mixture of **1** (1g, 0.774 mmol), and SiO_2-HNO_3 (1 g) in CH_2CL_2 (15 mL) was stirred magnetically at room temperature. The reaction was complete after 5 h and the reaction mixture was than filtered. The residue was washings with CH_2Cl_2. Anhydrous Na_2SO_4 (0.5 g) was added to the combined filtrate and washings. After 15 min the mixture was filtered. The solvent was removed by distillation using a water bath. **5** is obtained as a white crystals in 70% separated yield (crystallized from a mixture of **5** and **6**) m.p., 214-217ºC; (**6**) was purified by column chromatography of the mother liquors (silica gel, *n*-heptane, ethyl acetate, 1:9); yield 30% mp, 225-228ºC.

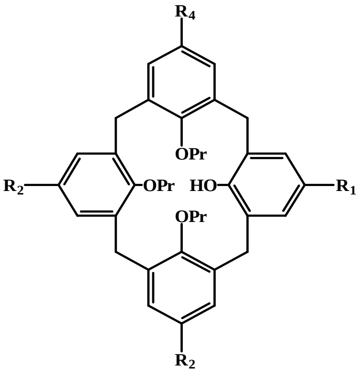
Spectral data for **5**: IR ν_{max} (KBr, cm^{-1}) 3510, 1598, 1513, 1343 and 1014. δH (400 MHz; $CDCl_3$) 0.86 [18H, s, $C(CH_3)_3$], 0.97 [3H, t, CH_3], 1.11 [6H, t, CH_3], 1.94 [4H, m, CH_2], 2.22 [2H, m, CH_2], 3.35 and 4.42 [4H, d of d, J = 12.9 Hz, $ArCH_2Ar$], 3.78 [4H, t, OCH_2], 3.96 [2H, t, OCH_2], 3.43, 4.29 [4H, d of d, J = 13.8 Hz, $ArCH_2Ar$], 6.56 [4H, s, ArH], 7.37 [1H, s, OH], 8.07 [2H, s, ArH], 8.10 [2H, s, ArH]; δC (100MHz) 9.48, 10.66, 22.44, 23.40, 33.01, 31.13, 3143, 33.87, 76.67, 78.15, 124.12, 124.46, 125.28, 125.46, 129.43, 130.30, 130.98, 138.06, 140.10, 143.05, 146.64, 151.83, 159.70, 164.05; m/z(FD) 753 (m, 100%). Anal. (%) Calcd. for $C_{45}H_{56}N_2O_8$: C, 71.79 ; H, 7.50; N, 3.72. Found C, 71.50, H, 7.50; N, 3.10.

Spectral data for **6**: IR ν_{max} (KBr, cm^{-1}) 3508, 1592, 1521, 1341 and 1005; δH (400 MHz; $CDCl_3$) 0.74 [9H, s, $C(CH_3)_3$], 0.92 [3H, t, CH_3], 1.12 [3H, t, CH_3], 1.13 [3H, t, CH_3], 1.40 [9H, s, $C(CH_3)_3$], 1.90 [2H, m, CH_2], 2.08 [2H, m, CH_2], 2.23 [2H, m, CH_2], 3.21 and 4.40 [2H, d of d, J = 13.1 Hz, $ArCH_2Ar$], 3.25 and 4.30 [2H, d of d, J = 13.0 Hz, $ArCH_2Ar$], 3.42 and 4.46 [2H, d of d, J = 13.7 Hz, $ArCH_2Ar$], 3.51 and 4.20 [2H, d of d, J = 14.5 Hz, $ArCH_2Ar$], 3.77 [6H, m, OCH_2], 6.17 [1H, s, OH], 6.45 [1H, d, J = 2.1 Hz, ArH], 6.51 [1H, d, J = 2.1 Hz, ArH], 7.21 [1H, d, J = 2.3 Hz, ArH], 7.22 [1H, d, J = 2.6 Hz, ArH], 7.24 [1H, d, J=2.2 Hz, ArH], 7.25 [1H, d, J = 2.6 Hz, ArH], 8.14 [1H, d, J = 2.5 Hz, ArH]; δC (100 MHz) 9.43, 10.69, 10.71, 22.52, 23.34, 23.46, 30.63, 30.80, 31.05, 31.08, 31.63, 34.01, 34.30, 76.45, 77.63, 78.24, 122.31, 123.51, 124.30, 124.66, 124.77, 125.88, 126.72, 126.77, 128.64, 128.77, 129.94, 133.56, 133.78, 134.80, 135.08, 136.00, 139.93, 142.81, 146.78, 147.54, 150.68, 153.79, 159.31, 161.73; m/z(FD) 753 (m, 100%). Anal. (%) Calcd. for $C_{45}H_{56}N_2O_8$: C, 71.79, H, 7.50, N, 3.72. Found C, 71.60, H, 7.50, N, 3.10.

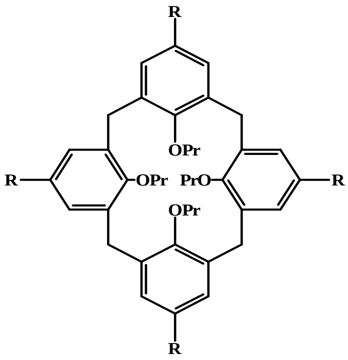
RESULTS AND DISCUSSION



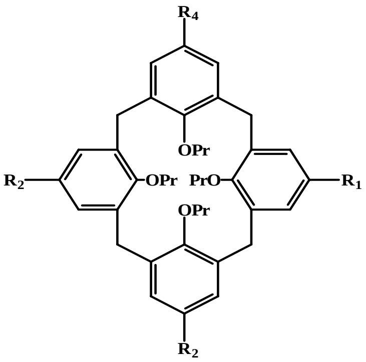
1: R = *tert*-butyl



3: $R_1 = NO_2$, $R_2 = R_3 = R_4 =$ *tert*-butyl
5: $R_1 = NO_2$, $R_3 = NO_2$, $R_2 = R_4 =$ *tert*-butyl
6: $R_1 = NO_2$, $R_2 = NO_2$, $R_3 = R_4 =$ *tert*-butyl



2: R = *tert*-butyl



4: $R_1 = NO_2$, $R_2 = R_3 = R_4 =$ *tert*-butyl

The cone conformation of tri-propoxy calix[4]arene (**1**) and tetra propoxy calix[4]arene (**2**) reacted with 1.2 equimolar of sodium nitrate supported on silica sulfuric acid in dichloromethane at room temperature and afforded the 23-mono nitro calix[4]arene (**3**) and (**4**), respectively in high yield. The present method offers both milder reaction condition and an improved yield in comparison with other similar methods[13]. The structure of compounds **3** and **4** were characterized with ^{1}H NMR, ^{13}C NMR, FT-IR, Mass spectrum and CHN analysis. The synthesized *p*-nitro calix[4]arene propyl ethers showed strong absorption at 1345-1340 and 1518 cm^{-1}. These absorptions can be assigned to NO_2 groups in the product. In ^{1}H NMR spectra, both **3** and **4** showed methylene bridge protons as two set of 2d at δ 3.19, 4.31 and 3.39, 4.34 for **3** and 3.21, 4.29 and 3.23, 4.16 for **4** indicating that they exist in the cone conformation. This was based on comparison of the NMR data with that available in the literature conclusion[14].

In the other experiment treatment of **1** with sodium nitrate on silica nitric acid and dichloromethane at room temperature under similar conditions after 3 h afforded the di-nitro compounds of **5** and **6** in 1:1 ratio according to the ^{1}H NMR spectrum. **5** and **6** were separated by column chromatography and identified with ^{1}H NMR, ^{13}C NMR, FT-IR, Mass spectrum and CHN analysis. The spectrum of **5** exhibits two set of 2d for the bridge methylene protons, indicating a central plane of symmetry. The spectrum of **6** exhibits four set of 2d signals indicating an asymmetric molecule. The inherently calixarene **6** can be used as a starting material to build up chiral hosts based on calixarene to mimic the enzyme function.

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