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Negishi Type Biaryl Cross-Coupling Reactions on Calix[4]arenes

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Introduction

Calix[4]arenes[1,2] have become an important class of compounds in supramolecular chemistry because they are useful in the design and synthesis of artificial receptors for cations,[3] anions,[4] and neutral molecules.[5] Calix[4]arenes possess an *upper rim* defined by the *para*substituents of the phenolic moities and a *lower rim* defined by the phenolic hydroxy groups. Substitution of the phenolic groups produces a cavity that have especially been used for metal ion binding. *p*-*tert*-Butylcalix[4]arene forms molecular complexes in the solid state with benzene,[6] toluene,[7] anisole,[6] and chloroform,[8] where they are imbedded in the lipophilic cavity. In order to encapsulate larger molecules, the size of the cavity has to be increased. This can be achieved by attaching phenyl groups around the periphery of the *upper rim*.

Several groups have synthesized calix[4]arenes substituted with phenyl groups at the upper rim to increase the cavity. Haino *et al.*[9] synthesized an aryl-substituted calix[5]arene by a Suzuki[10] type cross-coupling reaction of an arylboronic acid and bromine-substituted calix[5]arenes in 69% yield. Wong *et al.*[11] synthesized different 5,11,17,23-tetraaryltetraethoxycalix[4]arenes from 5,11,17,23-tetrabromotetraethoxycalix[4]arene and arylboronic acids by a Suzuki type coupling reaction in 15−72% yields. The aryl groups were substituted with CHO (protected as ethylene glycol acetal), CN, and SCH$_3$. Arduini *et al.*[12] synthesized 5,11,17,23-tetraphenylcalix[4]arene by photolysis of the tetraiodo derivative in benzene in 15% yield and 5,11,17,23-tetraphenyl-25,26,27,28-tetrakis(2-ethoxyethoxy)calix[4]arene by a Negishi[13] type cross coupling reaction of phenylzinc chloride and the corresponding tetraiodocalix[4]arene in the presence of Ni(PPh$_3$)$_4$ as catalyst in 95% yield. Recently Arduini *et al.*[14] prepared 5,11,17,23-tetraphenyl-25,26,27,28-biscrown-3-calix[4]arene from the corresponding tetraiodo derivative and phenylzinc chloride in the presence of Ni(PPh$_3$)$_4$ as catalyst in 50% yield.

We are interested in calix[4]arenes as templates for building hosts for small organic molecules. In order to have molecular recognition, it is necessary to attach functionalities/groups in a controlled way at the *upper* or *lower rim*. Furthermore, to monitor a complexation it is necessary to have functionalities that either have redox-active or chromophoric or fluorophoric properties. Attaching aryl groups at the *upper rim* have at least three advantages: (i) it produces larger cavities, (ii) the resulting biaryl−calix[4]arene system has both chromophoric and fluorophoric properties, and (iii) it is possible to control the substitution pattern of the aryl groups.

We have chosen to focus on the Negishi type[15] biaryl cross-coupling reaction to introduce different aryl substituents to further explore this type of extended calix[4]arenes. Thus, two diaryl- and four tetraaryl-substituted tetrapropoxycalix[4]arenes have been prepared in good yields, from the corresponding tetrapropoxycalix[4]arene−dizinc and tetrapropoxycalix[4]arene−tetrazinc chlorides and different aryl iodides. To our knowledge this is the first reported Negishi type biaryl cross-coupling where dizinc or tetrazinc chloride intermediates have been used. Attaching bromoaryl substituents is of value since other functionalities can easily be introduced br Br−Li exchange followed by reaction with electrophiles.

Results and Discussion

Conversion of 5,17-dibromotetrapropoxycalix[4]arene (**1**) or 5,11,17,23-tetrabromotetrapropoxycalix[4]arene (**2**) into the dilithio- or tetralithiotetrapropoxycalix[4]arene[16] followed by reaction with anhydrous zinc chloride in dry THF gave tetrapropoxycalix[4]arene 5,17-dizinc chloride (**3**) or tetrapropoxycalix[4]arene 5,11,17,23-tetrazinc chloride (**4**), respectively. These were reacted with different aryl iodides in dry THF with Pd(PPh$_3$)$_4$ as catalyst for 18 h at ambient temperature, giving 5,17-diaryl-25,26,27,28-tetrapropoxycalix[4]arenes (**5**, **6**) (Scheme 1) and 5,11,17,23-tetraaryltetrapropoxycalix[4]arenes (**7**-**10**) in good yields (Scheme 2). Purification was achieved by flash column chromatography on silica followed by recrystallization. An excess of aryl iodides was used to ensure completion, the excess was easily

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[15] Preliminary results using Suzuki type cross-coupling reaction between **1** or **2** and various substituted arylboronic acids with Pd(0) as catalyst proved less satisfactory. Homo-coupling of the boronic acids produced biaryl biproducts which could not be easily removed by recrystallization or column chromatography.

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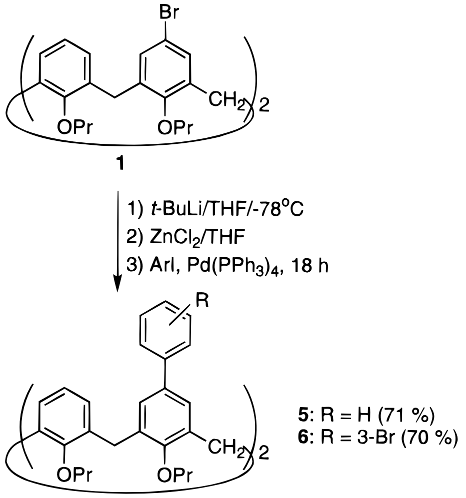
S0022-3263(97)00120-5 CCC: $14.00

Scheme 1



removed by elution with *n*-hexane, and the product was eluted with *n*-hexane/$CHCl_3$ (3:1, v/v). It was not possible to isolate the products from the cross-coupling reaction of **3** or **4** and 4-bromonitrobenzene in a pure state due to the same R_f value in different eluents of 4-bromonitrobenzene and the products. Attempts to purify the crude products by recrystallization also failed probably due to complex formation between the products and 4-bromonitrobenzene. If only a slight excess (2−4%) of 4-bromonitrobenzene was used, the reaction did not go to completion even after prolonged time according to TLC and MALDI-TOF MS.

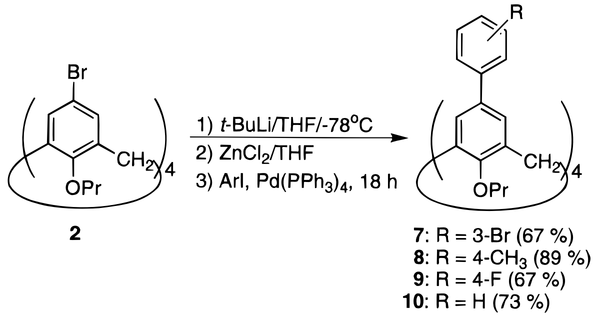
Cross-coupling of **3** or **4** and 3-bromoiodobenzene gave only 5,17-bis(3-bromophenyl)-25,26,27,28-tetrapropoxycalix[4]arene (**6**) in 70% yield and 5,11,17,23-tetrakis(3-bromophenyl)-25,26,27,28-tetrapropoxycalix[4]arene (**7**) in 67% yield, respectively.

Experimental Section

Melting points are uncorrected. The mass spectra are recorded on a MALDI-TOF MS with 2,5-dihydroxybenzoic acid as matrix. ^{1}H NMR and ^{13}C NMR spectra are recorded on an Avance DPX-250 with TMS as internal reference at 300 K. All the NMR spectra were taken in $CDCl_3$. All chemicals were reagent grade and used without further purification, except for THF which was freshly distilled from sodium/benzophenone ketyl. **1** and **2** were synthesized by the method described previously.[16] All reactions were carried out in flame-dried glass apparatus and in an argon atmosphere. The temperatures are internal temperatures. Chromatographic separations were performed on silica gel 60 (SiO_2, 0.040−0.063 mm, 230−240 mesh). TLC was carried out on SiO_2 with *n*-hexane/$CHCl_3$ (2:1, v/v) as eluent.

General Procedure for the biaryl coupling reactions. To a stirred solution of **1** (3.30 g, 4.40 mmol) or **2** (2.00 g, 2.20 mmol) in dry THF (50 mL) at −78 °C was added 1.40 M *t*-BuLi/pentane (15 mL, 20 mmol). The yellow solution was stirred at −78 °C for 1 h, cannulated into a solution of anhydrous $ZnCl_2$ (4.09 g, 30 mmol) in dry THF (20 mL), and stirred for 30 min at 25 °C. The organozinc reagent was cannulated into a solution of aryl iodide (30 mmol) and $Pd(PPh_3)_4$ (50 mg) in dry THF (30 mL) and stirred for 18 h at 25 °C in the dark. The orange mixture was hydrolyzed with 4 M hydrochloric acid (100 mL) and extracted with $CHCl_3$ (2 × 150 mL). The organic phase was washed with brine (100 mL) and 10% Na_2SO_3 (100 mL) and dried (Na_2SO_4) and the solvent removed *in vacuo* to give a brown solid, which was chromatographed on silica gel (100 mL). *n*-Hexane (200 mL) was used as start eluent to remove excess aryl iodide; then the eluent was changed to *n*-hexane/$CHCl_3$ (3:1, v/v).

Scheme 2



5,17-Diphenyl-25,26,27,28-tetrapropoxycalix[4]arene (5) from 1 and Iodobenzene. Recrystallization from $CHCl_3$/MeOH (1:4) gave **5** in 71% yield as white crystals: $R_f \approx 0.52$; mp 261−263 °C; ^{1}H NMR δ 7.40−7.30 (m, 4H), 7.30−7.15 (m, 6H), 7.08 (s, 4H), 6.50−6.40 (m, 6H), 4.51 (d, 4H, $J = 13.2$ Hz), 3.96 (t, 4H, $J = 7.7$ Hz), 3.82 (t, 4H, $J = 7.2$ Hz), 3.22 (d, 4H, $J = 13.2$ Hz), 2.10−1.85 (m, 8H), 1.06 (t, 6H, $J = 7.4$ Hz), 0.97 (t, 6H, $J = 7.4$ Hz); ^{13}C NMR δ 157.3, 155.9, 141.5, 136.4, 135.1, 134.5, 128.8, 128.4, 127.5, 127.1, 126.7, 122.6, 77.3, 77.2, 31.6, 23.8, 23.6, 11.0, 10.6; MS *m/z* 745 (M + H^+), 767 (M + Na^+), 783 (M + K^+). Anal. Calcd for $C_{52}H_{56}O_4$: C, 83.83; H, 7.58. Found: C, 83.56; H, 7.64.

5,17-Bis(3-bromophenyl)-25,26,27,28-tetrapropoxycalix[4]arene (6) from 1 and 3-Bromoiodobenzene. Recrystallization by being dissolved in a minimum of hot CH_2Cl_2 and addition of MeOH until the solution became cloudy gave **6** as white crystals in 70% yield: $R_f \approx 0.68$; mp 249−251 °C; ^{1}H NMR δ 7.37 (s, 2H), 7.26−7.20 (m, 2H), 7.05−6.95 (m, 4H), 6.86 (s, 4H), 6.70−6.55 (m, 6H), 4.50 (d, 4H, $J = 13.3$ Hz), 4.02−3.80 (m, 8H), 3.21 (d, 4H, $J = 13.3$ Hz), 2.05−1.85 (m, 8H), 1.10−0.90 (m, 12H); ^{13}C NMR δ 156.9, 156.3, 143.1, 135.7, 134.6, 133.2, 129.8, 129.5, 129.2, 128.2, 126.8, 125.1, 122.5, 122.2, 76.9, 76.8, 31.1, 23.3, 10.4, 10.3; one signal from β-CH_2 is absent due to accidental isochrony; MS *m/z* 903 (M + H^+), 925 (M + Na^+), 941 (M + K^+). Anal. Calcd for $C_{52}H_{54}Br_2O_4$: C, 69.18; H, 6.03. Found: C, 68.88; H, 6.13.

5,11,17,23-Tetrakis(3-bromophenyl)-25,26,27,28-tetrapropoxycalix[4]arene (7) from 2 and 3-bromoiodobenzene. Recrystallization by being dissolved in a minimum of hot EtOAc, addition of twice the volumn of absolute EtOH, and being left in the refrigerator for 24 h gave **7** as white needles in 67% yield: $R_f \approx 0.58$; mp 226−228 °C; ^{1}H NMR δ 7.28−7.18 (m, 8H), 7.05−6.92 (m, 8H), 6.88 (s, 8H), 4.55 (d, 4H, $J = 13.3$ Hz), 3.93 (t, 8H, $J = 7.5$ Hz), 3.28 (d, 4H, $J = 13.3$ Hz), 2.10−1.85 (m, 8H), 1.05 (t, 12H, $J = 7.4$ Hz); ^{13}C NMR δ 156.6, 143.1, 135.3, 133.8, 129.9, 129.6, 129.3, 127.1, 125.1, 122.6, 77.1, 31.2, 23.3, 10.4; MS *m/z* 1213 (M + H^+), 1235 (M + Na^+), 1251 (M + K^+). Anal. Calcd for $C_{64}H_{60}Br_4O_4$: C, 63.38; H, 4.99. Found: C, 62.97; H, 5.09.

5,11,17,23-Tetrakis(4-methylphenyl)-25,26,27,28-tetrapropoxycalix[4]arene (8) from 2 and 4-Iodotoluene. Recrystallization by being dissolved in a minimum of hot CH_2Cl_2 and addition of MeOH until the solution becomes cloudy gave **8** as white crystals in 89% yield: $R_f \approx 0.67$; mp 268−270 °C; ^{1}H NMR δ 7.06 (d, 8H, $J = 8.0$ Hz), 6.96 (s, 8H), 6.95 (d, 8H, $J = 8.0$ Hz), 4.62 (d, 4H, $J = 13.1$ Hz), 4.00 (t, 8H, $J = 7.5$ Hz), 3.32 (d, 4H, $J = 13.1$ Hz), 2.33 (s, 12H), 2.12−1.95 (m, 8H), 1.10 (t, 12H, $J = 7.4$ Hz); ^{13}C NMR δ 156.6, 139.0, 136.2, 135.8, 135.6, 129.6, 127.5, 127.2, 77.0, 32.0, 24.0, 21.7, 11.1; MS *m/z* 953 (M + H^+), 975 (M + Na^+), 991 (M + K^+). Anal. Calcd for $C_{68}H_{72}O_4$: C, 85.67; H, 7.61. Found: C, 85.75; H, 7.49.

5,11,17,23-Tetrakis(4-fluorophenyl)-25,26,27,28-tetrapropoxycalix[4]arene (9) from 2 and 4-Fluoroiodobenzene. Recrystallization from MeCN gave **9** as white needles in 67% yield: $R_f \approx 0.50$; mp 265−266 °C; ^{1}H NMR δ 7.05−6.95 (m, 8H), 6.90−6.70 (m, 16H), 4.56 (d, 4H, $J = 13.3$ Hz), 3.94 (t, 8H, $J = 7.5$ Hz), 3.26 (d, 4H, $J = 13.3$ Hz), 2.06−1.90 (m, 8H), 1.04 (t, 12H, $J = 7.5$ Hz); ^{13}C NMR δ 161.9 (d, $^{1}J_{C-F} = 245.3$ Hz), 156.2, 137.0 (d, $^{4}J_{C-F} = 3.3$ Hz), 135.2, 134.0, 127.9 (d, $^{3}J_{C-F} = 8.0$ Hz), 126.8, 115.1 (d, $^{2}J_{C-F} = 21.4$ Hz), 77.0, 31.3, 23.3, 10.3;

MS m/z 969 (M + H$^+$), 991 (M + Na$^+$), 1007 (M + K$^+$). Anal. Calcd for $C_{64}H_{60}F_4O_4$: C, 79.31; H, 6.24. Found: C, 79.45; H, 6.18.

5,11,17,23-Tetraphenyl-25,26,27,28-tetrapropoxycalix[4]arene (10) from 2 and Iodobenzene. Recrystallization from MeCN gave **10** as white needles in 73% yield: $R_f \approx$ 0.56; mp 224−226 °C; ^{1}H NMR δ 7.09 (s, broad, 20H), 6.93 (s, 8H), 4.57 (d, 4H, J = 13.1 Hz), 3.95 (t, 8H, J = 7.5 Hz), 3.29 (d, 4H, J = 13.1 Hz), 2.10−1.90 (m, 8H), 1.05 (t, 12H, J = 7.5 Hz); ^{13}C NMR δ 156.1, 141.1, 135.2, 135.0, 128.3, 127.0, 126.6, 126.1, 77.4, 31.3, 23.3, 10.4; MS m/z 897 (M + H$^+$), 919 (M + Na$^+$), 935 (M + K$^+$). Anal. Calcd for $C_{64}H_{64}O_4$: C, 85.68; H, 7.19. Found: C, 85.45; H, 7.33.

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