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Environmentally Benign Syntheses of Calixarene Derivatives

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Environmentally Benign Syntheses of Calixarene Derivatives

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Abstract: New hydroxamic acid derivatives of calixarene have been synthesized by conventional and microwave method.

Keywords: Calixarene; hydroxamic acid; microwave

The calixarenes are a class of cyclooligomers formed via a phenol–formaldehyde condensation.[1] Their rigid conformation enables calixarenes to act as host molecules as a result of their preformed cavities. By functionally modifying the upper and/or lower rims, it is possible to synthesize their various derivatives with applications such as enzyme mimetics,[2] ion-sensitive electrodes or sensors,[3] selective membrames,[4] nonlinear optics,[5] high-performance liquid chromatography (HPLC) stationary phase,[6] and anion[7] and cation[8] extractant.

The elimination of volatile organic solvents in organic syntheses is the most important need in green chemistry. Microwave-irradiated organic reactions make syntheses simpler, save energy, and prevent solvent wastes, hazards, and toxicity. Keeping this in mind, in the present investigation the microwave-assisted syntheses of tetranitrocalix[4]arene (TNC4A) **(3)**, hexacarboxycalix[6]arene (HCC6A) **(5)**, pyridinium bearing calix[4]-arenehydroxamic acid (PC4AHA) **(9)**,coumarin-calix[4]arenehydroxamic acid (CC4AHA) **(12)**, and tetracarboxycalix[6]crownhydroxamic acid (TCC6CHA) **(16)** are reported.

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Compounds **3** and **5** (Fig. 1) were synthesized by the acid-catalyzed condensation of formaldehyde with *p*-nitrophenol and *p*-hydroxy benzoic acid respectively.[9,10] Compound **3** was partially reduced with hydrazine hydrate in the presence of Raney Ni (W-2) at 0–10 °C for 1 h to obtain corresponding hydroxylamine **(6)**, which was condensed with isonicotinoyl chloride **(8)** and coumarin-3-carbonyl chloride **(11)** in the presence of an aqueous suspension of sodium bicarbonate at 0–10 °C to yield PC4AHA **(9)** and CC4AHA **(12)** (Fig. 1), respectively. The products were purified by crystallization from chloroform.

Compound **5** was refluxed with 1,4-dibromo butane in the presence of K_2CO_3 using acetonitrile as a solvent at 80 °C for 24 h to yield compound **13**. This was further reacted with diethylene triamine in the presence of K_2CO_3 to obtain compound **14**. Compound **14** was refluxed with thionyl chloride in the presence of dimethylformamide for 4 h and condensed with N-phenylhydroxylamine in the presence of an aqueous suspension of sodium bicarbonate at 0–10 °C to get TCC6CHA **(16)** (Fig. 2).

The microwave-assisted synthetic procedures were developed for calixarene derivatives to give better yield, purity, and time savings. They are also solvent free and prevent waste.

The composition and the structure of synthesized calixarene derivatives have been confirmed by elemental analysis (for C,H,N), FT-IR, ^{1}H NMR, and ^{13}C NMR spectroscopy.

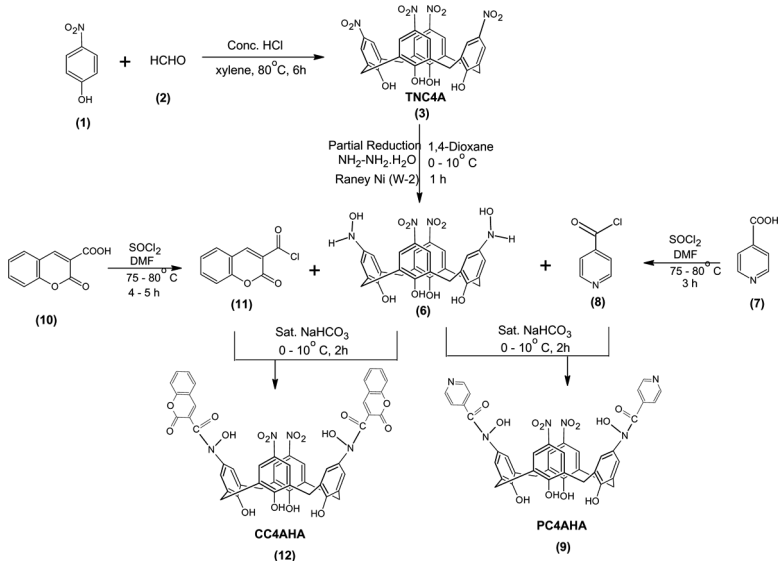

Figure 1. Synthetic route for compounds **9** and **12**.

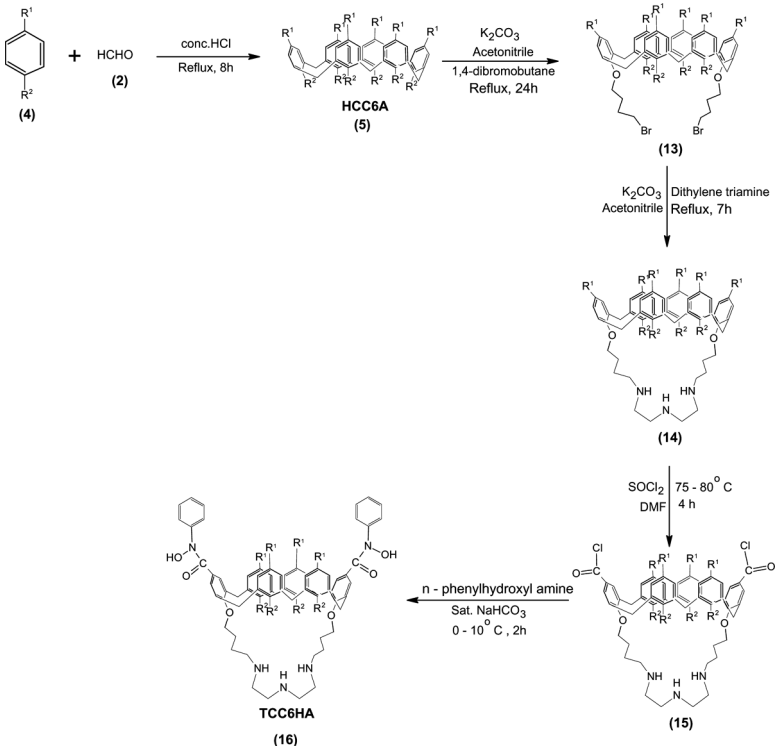

Figure 2. Synthetic route for compounds **16** ($R^1 = COOH$, $R^2 = OH$).

The Fourier transform infrared spectrometer (FT-IR) (KBr) spectrum of compounds **3**, **5**, **9**, **12**, and **16** displayed three sharp bands at 3185, 1635, and 920 cm^{-1}, confirming the υ_{OH}, $\upsilon_{C=O}$, and υ_{N-O} of the hydroxamic acid functional group. The band at 3185 cm^{-1} is due to O–H stretching vibration. It is known that O–H stretching vibration bands occur at around 3600 cm^{-1}; hydrogen bonding shifts these bands to lower frequencies. In hydroxamic acids, the –OH group is placed very close to the polar carbonyl C=O group. The band at 1635 cm^{-1} is assigned to the C=O of the hydroxamic acid group. A sharp band at 920 cm^{-1} is attributed to N–O stretching vibrations. Compounds **3**, **9**, and **12** displayed a sharp band at 1350 cm^{-1} for $-NO_2$ stretching vibrations.

The structures of compounds **3**, **5**, **9**, **12**, and **16** were established by elemental analysis and ^1H NMR and ^{13}C NMR spectra. These compounds display singlets around 7.82, 7.70, 7.60, 7.51, 7.45, and 6.82 for aromatic protons. A pair of doublets appears at δ 4.50 and 3.90 for $ArCH_2Ar$ protons in the ^1H NMR. Prominent signals appeared at

δ 9.00, 9.20, and 9.90 for aromatic hydroxyl protons and at δ 10.27, 10.28, and 10.70 for the hydroxamic group. In compounds **3**, **9**, and **12**, a prominent downfield shift in the position of the hydroxyl signal suggested that nitro groups were present at positions *para* to the hydroxyl groups. A singlet appears at δ 10.32 for each carboxyl hydrogen present in compounds **5** and **16**. Notice that this peak is not sharp; it was broadened by hydrogen bonding and exchange. Two singlets appear at 8.01 and 3.40 for NH and CH_2CH_2OAr respectively.

The ^{13}C NMR (dimethyl sulfoxide (DMSO)) spectrum of compounds **3**, **5**, **9**, **12**, and **16** displayed singlets at δ 116–125 and 128–137 for aromatic protons and one singlet near δ 167 and 166 for ketone groups. In addition, compounds **5** and **16** displayed a singlet at 166.86 for the carboxylic acid group and doublets at δ 35.12 and 34.63 for bridged methane groups. Compound **16** displayed one triplet at δ 51.48 for crown moiety.

The results obtained from elemental analysis of compounds **3**, **5**, **9**, **12**, and **16** confirm the presence of hydroxamic acid groups.

In conclusion, we have synthesized novel hydroxamic derivatives of calixarenes by conventional and microwave methods.

EXPERIMENTAL

Melting points are uncorrected and were obtained using a melting-point apparatus (Electroquip). IR spectra were recorded on Jasco FT/IR 6100 spectrometer. ^1H NNR and ^{13}C NMR were recorded on a DRX 300 spectrophotometer operating at 300 MHz in $CDCl_3$ with TMS as an internal standard. Microwave synthesis was carried out using a Kenstar OM 20 DGQ domestic microwave oven.

Synthesis of Compound (3)

Conventional Method

Compound **3** was synthesized by a previously reported method.[9]

Microwave Method

A mixture of *p*-nitrophenol (1 g, 0.0073 M), 37% formaldehyde (0.6 ml, 0.0073 M), and conc. hydrochloric acid (1 ml) was placed into the Kenstar domestic microwave at 20% power output for 180 s to obtain a white solid, which was washed with hot water and with hot alcohol to get compound **3**.

Data

TNC4A: yield 93%, mp 140–142 °C, IR (KBr): υ = 3185, 1635, 1350, 920 cm^{-1}. ^1H NMR (DMSO): $\delta = 9.20$ (s, 4H, ArOH), 4.50 (d, 4H, $ArCH_2Ar$), 3.90 (d, 4H, $ArCH_2Ar$), 7.82 (s, 8H, ArH). ^{13}C NMR (DMSO): $\delta = 35.12$ (d, Ar-CH_2-Ar), 119.05–132.10 (s, ArC).

Synthesis of Compound (5)

Conventional Method

Compound **5** was synthesized by a previously reported method.[10]

Microwave Method

A mixture of *p*-hydroxybenzoic acid (1 g, 0.0072 M), 37% formaldehyde (4 ml, 0.0015 M), and conc. hydrochloric acid (2.5 ml) was placed into the Kenstar domestic microwave at 40% power output for 120 s to obtain a white solid, which was washed with hot distilled water to remove acidic impurities and recrystallized from acetone–petroleum ether (60–80 °C) to get compound **5**.

Data

HCC6A: yield 95%, mp 110–111 °C, IR (KBr): υ = 3185, 1635, 920 cm^{-1}. ^1H NMR (DMSO): $\delta = 9.90$ (s, 6H, ArOH), 4.44 (d, 6H, $ArCH_2Ar$), 3.85 (d, 6H, $ArCH_2Ar$), 7.45 (s, 12H, ArH), 10.32 (s, 6H, COOH). ^{13}C NMR (DMSO): $\delta = 34.63$ (d, Ar-CH_2-Ar), 120.20–125.52 (s, ArC), 127.26–134.94 (s, ArC), 166.86 (s, COOH). Anal. calcd. for $C_{48}H_{36}O_{18}$: C, 64.0%; H, 4.03%. Found: C, 63.91%; H, 4.10%.

Synthesis of Compound (6)

Conventional Method

Nitrocalix[4]arene (10 g, 0.015 M), hydrazine hydrate (10 ml, 0.205 M), and Raney-Ni (W-2) (2–2.5 g) in 1,4-dioxane were stirred at 0–10 °C for 1 h to get compound **6**, which was filtered immediately and used in situ for the preparation of hydroxamic acid derivatives.

Microwave Method

Nitrocalix[4]arene (1 g, 0.0015 M), hydrazine hydrate (1 ml, 0.0205 M), and Raney-Ni (W-2) (0.2–0.3 g) were placed into the Kenstar domestic microwave at 0% power output for 120 s to get compound **6**.

Synthesis of Compound (9)

Conventional Method

Thionyl chloride (15 ml) was slowly added to a stirred mixture of isonicotinic acid **7** (10 g, 0.0813 M) and dimethylformamide (1 ml). The mixture was stirred at 75–80 °C for 3 h. The isonicotinoylchloride hydrochloride **8** was precipitated as a white powder by adding 50 ml of dried petroleum ether.

Acid chloride **8** (2.3 g, 0.0016 M) was condensed with compound **6** (3.60 g, 0.0064 M) in the presence of an aqueous suspension of sodium bicarbonate (2 g) at 0–10 °C for 2 h to get compound **9**.

Microwave Method

A mixture of isonicotinic acid **(7)** (1 g, 0.0081 M), dimethylformamide (0.1 ml), and thionyl chloride (1.5 ml) was placed into the Kenstar domestic microwave at 40% power output for 120 s. The isonicotinoylchloride hydrochloride was precipitated as a white powder by adding 50 ml of dried petroleum ether.

The acid chloride **8** (1.5 g, 0.0011 M) was condensed with compound **6** (1 g, 0.0015 M) in the presence of an aqueous suspension of sodium bicarbonate (2 g) in the oven at 0% power output for 120 s to get compound **9**.

Data

PC4AHA: yield 91%, mp 186–188 °C, IR (KBr): $\upsilon = 3185, 1635, 1350, 920\,cm^{-1}$. ^{1}H NMR (DMSO): $\delta = 10.27$ (s, 2H, NOH), 9.20 (s, 4H, ArOH), 4.50 (d, 4H, $J = 12.9$ Hz, $ArCH_2Ar$), 3.90 (d, 4H, $J = 12.9$ Hz, $ArCH_2Ar$), 7.70 (s, 4H, ArH), 7.82 (s, 4H, ArH), 6.82–7.45 (s, 8H, ArH). ^{13}C NMR (DMSO): $\delta = 35.12$ (d, Ar-CH_2-Ar), 119.05–126.62 (s, ArC), 128.21–137.48 (s, ArC), 167.12 (s, C=O). Anal. calcd. for $C_{40}H_{30}N_6O_{12}$: C, 61.07%; H, 3.84%; N, 10.68%. Found: C, 61.48%; H, 3.55%; N, 10.72%.

Synthesis of Compound (12)

Conventional Method

Thionyl chloride (10 ml) was slowly added to a stirred mixture of coumarin-3-carboxylic acid[11] (3 g, 0.015 M) and dimethylformamide (0.8 ml). The mixture was stirred at 75–80 °C for 4–5 h. The coumarin-3-carbonylchloride was precipitated as a white powder by adding 40 ml of dried petroleum ether. The acid chloride was condensed with freshly prepared compound **6** (3.60 g, 0.0064 M) in the presence of an aqueous suspension of sodium bicarbonate (2 g) at 0–10 °C for 2 h to obtain compound **12**.

Microwave Method

A mixture of coumarin-3-carboxylic acid[11] (1 g, 0.05 M), dimethylformamide (0.3 ml), and thionyl chloride (3.35 ml) was placed into the Kenstar domestic microwave at 40% power output for 120 s. The coumarin-3-carboylchloride was precipitated as a white powder by adding 40 ml of dried petroleum ether.

The acid chloride was condensed with compound **6** (1 g, 0.0015 M) in the presence of an aqueous suspension of sodium bicarbonate (2 g) in the oven at 0% power output for 120 s to get compound **12**.

Data

CC4AHA: yield 93%, mp 239–241 °C, IR (KBr): $\upsilon = 3185, 1635, 1350, 920\,cm^{-1}$. ^1H NMR (DMSO): $\delta = 10.70$ (s, 2H, NOH), 9.00 (s, 4H, ArOH), 4.26 (d, 4H, $J = 12.9$ Hz, $ArCH_2Ar$), 3.82 (d, 4H, $J = 12.9$ Hz, $ArCH_2Ar$), 7.70 (s, 4H, ArH), 7.82 (s, 4H, ArH), 6.82–7.40 (s, 10H, ArH). ^{13}C NMR (DMSO): $\delta = 35.12$ (d, Ar-CH_2-Ar), 116.05–120.62 (s, ArC), 127.18–134.80 (s, ArC), 166.07 (s, C=O). Anal. calcd. for $C_{48}H_{32}N_4O_{16}$: C, 62.61%; H, 3.50%; N, 6.08%. Found: C, 62.75%; H, 3.45%; N, 6.01%.

Synthesis of Compound (16)

Conventional Method

Anhydrous K_2CO_3 (0.7 g, 0.005 M) to a suspension of compound **5** (5 g, 0.005 M) and 1,4-dibromopropane (2.7 g, 0.0125 M) in acetonitrile

(100 ml), was added and the reaction mixture was stirred under reflux for 24 h. After the solvent was removed under reduced pressure, the residue was then purified by crystallization form chloroform to get compound **13**.

Anhydrous K_2CO_3 (0.5 g, 0.00358 M) and diethylene triamine (2.0 g, 0.002 M) were added to a solution of compound **13** (2 g, 0.00179 M) in acetonitrile (25 ml). The mixture was refluxed about 7 h. The solvent was removed by rotary evaporator. Then CH_2Cl_2 (10 ml) was added. The organic layer was then washed with distilled water (2×5 ml), and organic phase was evaporated under reduced pressure to dryness. Residue was purified by crystallization from chloroform to get compound **14**.

Compound **14** was refluxed with thionyl chloride in the presence of dimethylformamide for 4 h, and excess thionyl chloride was removed under reduced pressure to get compound **15**, which was added to a mixture of N-phenyl hydroxyl amine and sodium bicarbonate in 1,4-dioxane at 0–10 °C within 1 h. Reaction mixture was further stirred for 1 h more, then filtered. Solid was washed with water and purified by crystallization from chloroform to get compound **16**.

Microwave Method

A mixture of compound **5** (1 g, 0.001 M), 1,4-dibromobutane (0.6 g, 0.0025 M), and anhydrous K_2CO_3 (0.15 g, 0.001 M) was placed into the Kenstar domestic microwave at 20% power output for 240 s to get compound **13**.

A mixture of **13** (0.5 g, 0.0005 M), anhydrous K_2CO_3 (0.13 g, 0.00090 M), and diethylene triamine (0.5 g, 0.0005 M) was placed into the Kenstar domestic microwave at 20% power output for 180 s to get compound **14**.

Compound **14** (2 g, 0.0017 M), dimethylformamide (0.3 ml), and thionyl chloride (2.5 ml) was placed into the Kenstar domestic microwave at 40% power output for 120 s to get compound **15**, which was condensed with N-phenyl hydroxyl amine in the presence of sodium bicarbonate (2 g) in the microwave oven at 0% output for 120 s to get compound **16**.

Data

TCC6HA: yield 66%, mp 219–222 °C, IR (KBr): $\upsilon = 3185, 1635, 1350, 920\,cm^{-1}$. ^1H NMR (DMSO): $\delta = 10.28$ (s, 2H, NOH), 9.90 (s, 4H, ArOH), 4.44 (d, 6H, $J = 13.5$ Hz, $ArCH_2Ar$), 3.85 (d, 6H, $J = 13.5$ Hz, $ArCH_2Ar$), 7.45 (s, 8H, ArH), 7.51 (s, 4H, ArH), 7.60 (s, 4H, ArH), 7.17 (s, 6H, ArH), 10.32 (s, 4H, COOH), 8.01 (br s, 3H, NH),

3.40 (s, 4H, CH_2CH_2OAr). ^{13}C NMR (DMSO): $\delta = 34.63$ (d, Ar-CH_2-Ar), 120.20–125.52 (s, ArC), 127.26–134.94 (s, ArC), 166.86 (s, COOH), 167.73 (s, C=O). Anal. calcd. for $C_{72}H_{71}O_5N_{18}$: C, 66.81%; H, 5.53%; N, 5.41%. Found: C, 66.75%; H, 5.60%; N, 5.57%.

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