Chapter - II

Environmentally benign syntheses of calixarene derivatives
ABSTRACT

New hydroxamic acid derivatives of calixarene has been synthesized by conventional and microwave method. Calixarene hydroxamic acids were synthesized by reacting corresponding hydroxyl amine with acid chlorides at low temperature in an aqueous suspension of sodium bicarbonate. The comparison of conventional and microwave-assisted synthesis methods have been discussed. These hydroxamic acids were characterized by elemental analysis, FT-IR, $^1$H NMR & $^{13}$C NMR.
INTRODUCTION

Calixarenes were developed later than crown ether and cyclodextrins but have still been extensively researched /1-2/. Macrocycles of calix[n]arenes are constructed by linking a number of phenol residues via methylene moieties. Like crown ethers, the name “calixarene” reflects the structures of these molecules, since a calix is a chalice. Different conformations of calixarene are described in chapter 1. As part of the continuing investigation of calixarene ligands, one of my research objectives is to synthesize a group of highly lipophilic calixarene hydroxamic acid derivatives.

A promising series of reagents, hydroxamic acids, is the versatile chelating agent and extensively studied for separation, preconcentration and recovery of several metal ions. Introduction of coumarin, pyridine and aza crown along with hydroxamic acid can enhance the complexing ability, extraction efficiency and stability of calixarene based ligand with the metal ions /11-17/.

Coumarin, pyridine and aza crown derivatives have been reported for analytical applications /18-26/. With this in view a new series of calixarene hydroxamic acids containing the coumarin, pyridine and aza crown moiety are synthesized for better chromogenic reagent.
The use of microwaves in organic synthesis has increased dramatically in the last few years, receiving widespread acceptance and becoming an indispensable tool /3/. Microwave radiation is converted into heat with high efficiency, so that "superheating" becomes possible at ambient pressure. Enormous accelerations in reaction time can be achieved, if superheating is performed in closed vessels under high pressure; a reaction that takes several hours under conventional conditions can be completed over the course of minutes. Microwave technology has become a powerful tool in organic synthesis, since by employing this technique it is generally possible to prepare organic compounds very fast, with high purity and better yields compared to other more conventional methods /4-6/. Here, conventional as well as microwave assisted methods have been developed for the synthesis of new calixarene hydroxamic acid derivatives.

**EXPERIMENTAL**

**Apparatus**

Melting points were determined in capillaries and are uncorrected. KENSTAR 20 OM DGQ domestic oven has been used for the microwave-irradiated synthesis. IR spectra were recorded on JASCO FT/IR 6100 spectrophotometer. $^1$H and $^{13}$C NMR spectra were recorded on DRX 300.
Chemicals

All the chemicals used were of A.R. grade of Fluka, BDH or E. Merck unless otherwise specified. The solvents were purified as described elsewhere /10/.

SYNTHESIS


Synthesis of compound (3)

Conventional method

Compound 3 was synthesized by previously reported method /7/.

Microwave method

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

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. Filtered immediately and used in-situ for the preparation of hydroxamic acid derivatives.

**Microwave Method**

Nitrocalix[4]arene (1g, 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 sec to get compound 6.

**Synthesis of compound (9)**

**Conventional method**

Thionyl chloride (15 ml) slowly added to a stirred mixture of isonicotinic acid 7 (10g, 0.0813M) and dimethylformamide (1 ml). Mixture was stirred at 75-80°C for 3 hours. The isonicotinoylchloride hydrochloride 8 was precipitated as white powder by adding 50 ml of dried petroleum ether. The acid chloride 8 (2.3g, 0.0016M) was condensed with compound 6 (3.60g, 0.0064M) in the presence of an aqueous suspension of sodium bicarbonate (2g) at 0-10°C for 2 h to get compound 9.

**Microwave method**

A mixture of isonicotinic acid (7) (1g, 0.0081M), dimethylformamide (0.1ml) and thionyl chloride (1.5ml) placed into the Kenstar domestic microwave at 40% power out put for 120 sec. The isonicotinoylchloride hydrochloride was precipitated as white powder by adding 50 ml of dried petroleum ether.
The acid chloride 8 (1.5g, 0.0011M) was condensed with compound 6 (1g, 0.0015M) in the presence of an aqueous suspension of sodium bicarbonate (2g) in the oven at 0% power output for 120 sec. to get compound 9.

**Figure 1.** Synthetic route for compound 9 and 12.
Synthesis of compound (12)

Conventional method:

Thionyl chloride (10 ml) slowly added to a stirred mixture of coumarin-3-carboxylic acid /9/ (3g, 0.015M) and dimethylformamide (0.8 ml). Mixture was stirred at 75-80°C for 4-5 hours. The coumarin-3-carbonylchloride was precipitated as white powder by adding 40 ml of dried petroleum ether. The acid chloride was condensed with freshly prepared compound 6 (3.60g, 0.0064M) in the presence of an aqueous suspension of sodium bicarbonate (2g) at 0-10°C for 2 h to obtain compound 12.

Microwave method:

A mixture of coumarin-3-carboxylic acid /9/ (1g, 0.05M), dimethylformamide (0.3 ml) and thionyl chloride (3.35ml) was placed into the Kenstar domestic microwave at 40% power output for 120 sec. The coumarin-3-carboylchloride was precipitated as white powder by adding 40 ml of dried petroleum ether.

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


Synthesis of compound (5)
Conventional method:

Compound 5 was synthesized by previously reported method /8/.

Microwave method:

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

**Synthesis of compound (16)**

Conventional method:

To a suspension of compound 5 (5g, 0.005 M) and 1,4-dibromopropane (2.7g, 0.0125 M) in acetonitrile (100 ml) was added anhydrous K$_2$CO$_3$ (0.7g, 0.005 M) 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.

To a solution of compound 13 (2g, 0.00179 M) in acetonitrile (25 ml) were added anhydrous K$_2$CO$_3$ (0.5g, 0.00358 M) and diethylene triamine (2.0g, 0.002M). The mixture was refluxed about 7 h. The solvent was removed by
rotary evaporator. Then CH₂Cl₂ (10 ml) was added. Organic layer was then washed with distilled water (2 X 5 ml), organic

phase was evaporated under reduced pressure to dryness. Residue purified by crystallization from chloroform to get compound 14.

**Figure 2.** Synthetic route for compound 16 (R¹=COOH, R²=OH).
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 (1g, 0.001M), 1,4-dibromobutane (0.6g, 0.0025M) in and anhydrous K₂CO₃ (0.15g, 0.001M) was placed into the Kenstar domestic microwave at 20% power output for 240 sec to get compound 13.

A mixture of 13 (0.5g, 0.0005M), anhydrous K₂CO₃ (0.13g, 0.00090M) and diethylene triamine (0.5g, 0.0005M) was placed into the Kenstar domestic microwave at 20% power output for 180 sec to get compound 14.

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

RESULTS AND DISCUSSION


Compound (3) and (5) (Figure 1) were synthesized by the acid catalyzed condensation of formaldehyde with p-nitrophenol and p-hydroxy benzoic acid respectively /7,8/. 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) 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) (Figure 1), respectively. The products were purified by crystallization from chloroform.
Compound (5) was refluxed with 1,4-dibromo butane in the presence of K₂CO₃ using acetonitrile as a solvent at 80°C for 24 h to yield compound (13). Then further reacted with diethylene triamine in the presence of K₂CO₃ 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) (Figure 2).

The FT-IR (KBr) spectrum of compounds 3, 5, 9, 12 and 16 displayed three sharp bands at 3185, 1635, and 920 cm⁻¹ confirms the υOH, υC=O and υN=O of the hydroxamic acid functional group. The band at 3600-3200 due to the O-H of phenolic calixarene. The band at 3185 cm⁻¹ is due to O–H stretching vibration. It is known that O–H stretching vibrations 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 for 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 –NO₂ stretching vibrations.

The structures of compounds 3, 5, 9, 12 and 16 were established by elemental analysis, ¹H NMR and ¹³C NMR spectra. These compounds display singlet 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 ArCH₂Ar protons in the ¹H NMR. Prominent signals appeared at δ 9.00, 9.20 and 9.90 for aromatic hydroxyl protons and δ 10.27, 10.28 and 10.70 for hydroxamic group. In compound 3, 9 and 12 a prominent downfield shift in the position of hydroxyl signal suggested that nitro groups were present at positions para to the hydroxyl groups.

A singlet appears at δ 10.32 is for each carboxyl hydrogen present in compound 5 and 16. Notice that this peak is not sharp; it has broadened by hydrogen bonding and exchange. Two singlets appear at 8.01 and 3.40 for NH and CH₂CH₂OAr respectively.

The ¹³C NMR (DMSO) spectrum of compounds 3, 5, 9, 12 and 16 displayed singlet at δ 116-125 and 128-137 for aromatic protons and one singlet near δ 167 and 166 for ketone groups. In addition compound 5 and 16 displayed singlet at 166.86 for carboxylic acid group and doublet 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 compound 3, 5, 9, 12 and 16 confirm the presence of hydroxamic acid groups.
<table>
<thead>
<tr>
<th>Compounds</th>
<th>Conventional method</th>
<th>Microwave method</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Melting Point (ºC)</td>
<td>Yield (%)</td>
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<tr>
<td>TNC4A</td>
<td>140-142</td>
<td>70</td>
</tr>
<tr>
<td>HCC6A</td>
<td>110-111</td>
<td>80</td>
</tr>
<tr>
<td>PC4AHA</td>
<td>239-241</td>
<td>58</td>
</tr>
<tr>
<td>CC4AHA</td>
<td>186-188</td>
<td>61</td>
</tr>
<tr>
<td>TC6CHA</td>
<td>219-222</td>
<td>66</td>
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</table>
Table 2  Physico-chemical properties of calix[4]arene hydroxamic acids

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Molecular Formula</th>
<th>Molecular Weight</th>
<th>Melting Point (°C)</th>
<th>Elemental Analysis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>PC4AHA</td>
<td>C_{40}H_{30}N_{6}O_{12}</td>
<td>786</td>
<td>186-188</td>
<td>61.07 (61.48)</td>
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<tr>
<td>CC4AHA</td>
<td>C_{48}H_{32}N_{4}O_{16}</td>
<td>920</td>
<td>239-241</td>
<td>62.61 (62.75)</td>
</tr>
<tr>
<td>TCC6CHA</td>
<td>C_{72}H_{71}N_{18}O_{5}</td>
<td>1267</td>
<td>219-222</td>
<td>66.81 (66.75)</td>
</tr>
</tbody>
</table>

The experimental values are given in parenthesis.
**TNC4A**

mp 140-142° C, IR (KBr): \( \nu = 3185, 1635, 1350, 920 \) cm\(^{-1} \). \(^1\)H NMR (DMSO): \( \delta = 9.20 \) (s, 4H, ArOH), 4.50 (d, 4H, ArCH\(_2\)Ar), 3.90 (d, 4H, ArCH\(_2\)Ar), 7.82 (s, 8H, ArH). \(^{13}\)CNMR (DMSO): \( \delta = 35.12 \) (d, Ar-CH\(_2\)-Ar), 119.05-132.10 (s, ArC).

**HCC6A**

mp 110-111° C IR (KBr): \( \nu = 3185, 1635, 920 \) cm\(^{-1} \). \(^1\)H NMR (DMSO): \( \delta = 9.90 \) (s, 6H, ArOH), 4.44 (d, 6H, ArCH\(_2\)Ar), 3.85 (d, 6H, ArCH\(_2\)Ar), 7.45 (s, 12H, ArH), 10.32 (s, 6H, COOH). \(^{13}\)CNMR (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%.

**PC4AHA**

mp 186-188° C, IR (KBr): \( \nu = 3185, 1635, 1350, 920 \) 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\(_2\)Ar), 3.90 (d, 4H, J=12.9 Hz, ArCH\(_2\)Ar), 7.70 (s, 4H, ArH), 7.82 (s, 4H, ArH), 6.82-7.45 (s, 8H, ArH) \(^{13}\)CNMR (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\(_6\)O\(_{12}\): C, 61.07%; H, 3.84%; N, 10.68%. Found: C, 61.48%; H, 3.55%; N, 10.72%.

**CC4AHA**

mp 239-241° C, IR (KBr): \( \nu = 3185, 1635, 1350, 920 \) cm\(^{-1} \). \(^1\)H NMR (DMSO): \( \delta = 10.70 \) (s, 2H, NOH), 9.00 (s, 4H, ArOH), 4.26 (d, 4H, J=12.9 Hz, ArCH\(_2\)Ar), 3.82
(d, 4H, J=12.9 Hz, ArCH₂Ar), 7.70 (s, 4H, ArH), 7.82 (s, 4H, ArH), 6.82-7.40 (s, 10H, ArH) $^{13}$CNMR (DMSO):

$\delta = 35.12$ (d, Ar-CH₂-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$_4$O$_{16}$: C, 62.61%; H, 3.50%; N, 6.08%. Found: C, 62.75%; H, 3.45%; N, 6.01%

TCC6HA

mp 219-222° C, IR (KBr): $\nu = 3185, 1635, 1350, 920$ cm$^{-1}$. $^1$H NMR (DMSO): $\delta = 10.28$ (s, 2H, NOH), 9.90 (s, 4H, ArOH), 4.44 (d, 6H, J=13.5 Hz, ArCH₂Ar), 3.85 (d, 6H, J=13.5 Hz, ArCH₂Ar), 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, CH₂CH₂OAr), $^{13}$CNMR (DMSO): $\delta = 34.63$ (d, Ar-CH₂-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$_5$N$_{18}$: C, 66.81%; H, 5.53%; N, 5.41%. Found: C, 66.75%; H, 5.60%; N, 5.57%.

**CONCLUSION**

The microwave assisted synthetic procedures is developed for calixarene derivatives which gives better yield, purity and time saving. It is also solvent free and preventing the waste.
REFERENCES


