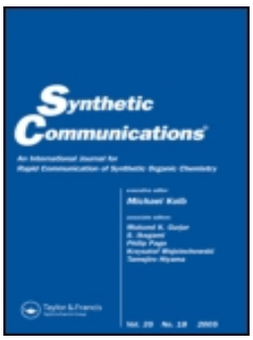

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Synthesis of 25,26,27-*tris*(Ethoxycarbonylmethoxy)-28-(substituted Oxy-carbonylmethoxy) Calix-4-arene: First Example of Calix-imidazole/ Benzimidazole Analog

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ABSTRACT

Synthesis of calix-imidazole/benzimidazole analog i.e., 25,26,27-*tris*-(ethoxycarbonylmethoxy)-28-({2′-phenylcarbamoyl} benzimidazolyloxycarbonylmethoxy) calix-4-arene. 6_a, 25,26,27-*tris*- (ethoxycarbonylmethoxy)-28-({2″-phenylcarbamoyl} 4′,5′-dihydroimidazolyloxy-carbonylmethoxy) calix-4-arene. 6_b and 25,26,27-*tris*-

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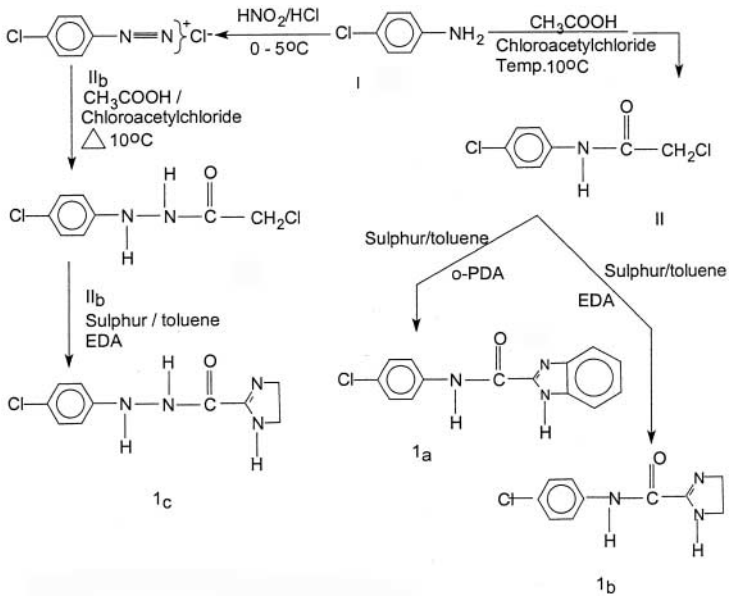
(ethoxycarbony-methoxy) calix-4-arene 6_c have been described. Structure elucidation explains the interaction of substituted imidazole/benzimidazole ($1_{a–c}$) with calix-4-arene system. Purity of all the synthesized products was ascertained on the basis of their column chromatographic resolution on silica gel using chloroform–ethylacetate (7:3, v/v) as eluent and recrystallization from a mixture of chloroform–methanol (1:1, v/v).

INTRODUCTION

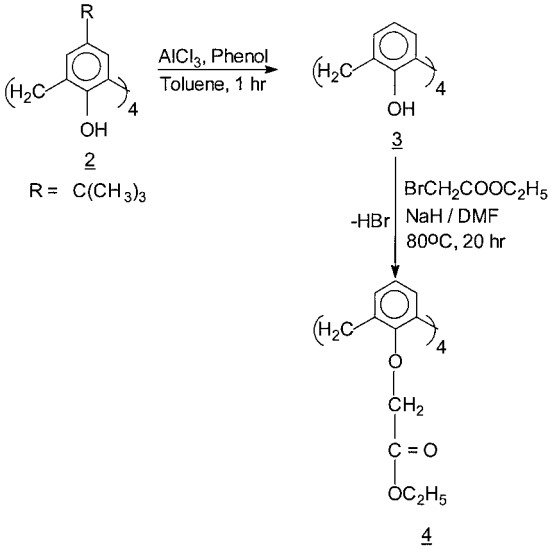
Calixarenes are a class of versatile molecular hosts with growing applications in the field of supramolecular chemistry.[1,2] They are recently rediscovered phenolic macrocyclic compounds which have immense potential for obtaining molecular receptor[1–5] that are not only important for recognition of small ions and organic molecules,[6–13] but are also useful for the design of new drug delivery systems, chromogenic indicators and chemical sensors.[14–15] It has been observed that calix(n)arene can form complexes in the solid state as well as in the solution phase.[16–19] The aggregation of calix(n)arene to yield molecular voids and micelle like structures in solution has not been investigated in detail though some water soluble calixarene sulphonates have been examined earlier by conductometry.[20] Investigations into the aggregation of calix(n)arenes in non-aqueous solutions have been reported.[21–22]

In this communication we report herein the synthesis of the calix-imidazole/benzimidazole analog, 25,26,27-*tris*(ethoxycarbonylmethoxy)-28-(substituted oxycarbonylmethoxy) calix-4-arene. $6_{a–c}$

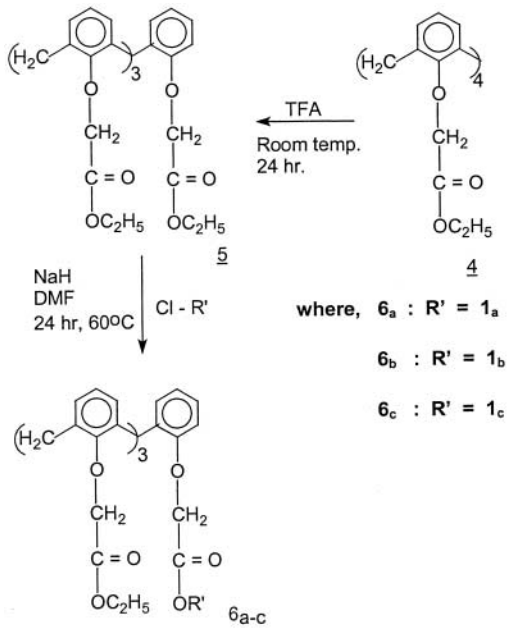
Substituted imidazole/benzimidazole compound $1_{a–c}$ have been synthesized by adding *o*-phenylenediamine/ethylenediamine in the presence of sulphur to their respective chloroacetyl derivatives[23] (Sch. 1). 5,11,17,23-tetra-butyl-25,26,27,28-tetrahydroxycalix-4-arene(2) was synthesized by the condensation of formaldehyde with *p*-(*t*-butyl)phenol in the presence of sodium hydroxide by the Gutsche's method.[1] This (2) was then workup[24] to form 25,26,27-*tris*(ethoxycarbonyl-methoxy)-28-(carboxy-methoxy) calix-4-arene (5) (Sch. 2). Compound (5) was condensed with substituted imidazole/benzimidazole $1_{a–c}$ in the presence of NaH/THF to give the desired calix-imidazole/benzimidazole $6_{a–c}$.



Scheme 1.



Scheme 2.



Scheme 3.

EXPERIMENTAL SECTION

General Reaction Procedure

2-(4′-Chlorophenylcarbamoyl) benzimidazole (1_a): Chloroacetylchloride (5.6 mL, 0.05 mol) was added to a stirred solution of *p*-chloroaniline (I) (0.05 mol) in glacial acetic acid (40.0 mL) at 10°C. The temperature slowly rose to 28–30°C. This was stirred for 25–30 min. A 60% solution of sodium acetate (50.0 mL) was then added and the mixture stirred for 20 min. The precipitate formed was filtered, washed with water and dried at 80°C and recrystallized from a mixture of dimethylformamide and ethanol 3:7 (v/v), in order to obtain *N*-chloroacetylated derivative (II). Now, *o*-phenylenediamine (2.6 g, 0.02 mol) was added portionwise to a mixture of II (4.28 g, 0.02 mol) in toluene (60.0 mL) and sulphur (1.28 g, 0.03 mol) at 100°C during 2 h. The reaction mixture was then heated at 100°C under stirring for 4 h and filtered hot. The insoluble solid was discarded. The filtrate was concentrated to 1/5th volume and cooled to

0°C. A gummy precipitate was formed. This was decanted and recrystallized from methanol to give a crystalline precipitate of 1_a.

1_a: M.p. 230°C, yield 72% (Found: C, 61.62; H, 3.60; N, 15.40. Calc. for $C_{14}H_{10}N_3OCl$: C, 61.87; H, 3.68; N, 15.46); IR (nujol) cm^{-1}: 1600 (aromatic), 1770 (C=O), 3313 (−NH); NMR ($CDCl_3$) δ: 2.5 (4H, CH_2 proton), 4.0 (2H, ArNHR proton).

2-(4′-Chlorophenylcarbamoyl)-4,5-dihydroimidazole: Chloroacetylchloride (5.6 mL, 0.05 mol) was added to a stirred solution of *p*-chloroaniline (I) (0.05 mol) in glacial acetic acid (40.0 mL) at 10°C. The temperature slowly rose to 28–30°C. This was stirred for 25–30 min. A 60% solution of sodium acetate (50.0 mL) was then added and the mixture stirred for 20 min. The precipitate formed was filtered, washed with water and dried for 20 min. The precipitate formed was filtered, washed with water and dried at 80°C and recrystallized from a mixture of dimethylformamide and ethanol 3:7 (v/v), in order to obtained *N*-chloroacetylated derivative (II).

Now, ethylenediamine (0.02 mol) was added portionwise to a mixture of II (4.28 g, 0.02 mol) in toluene (60.0 mL) and sulphur (1.28 g, 0.03 mol) at 100°C during 2 h. The reaction mixture was then heated at 100°C under stirring for 4 h and filtered hot. The insoluble solid was discarded. The filtrate was concentrated to 1/5th volume and cooled to 0°C. A gummy precipitate was formed. This was decanted and recrystallized from methanol to give a crystalline precipitate of 1_b: m.p. 228°C, yield 73% (Found: C, 54.11; H, 3.57; N, 18.91. Calc. for $C_{12}H_8N_3OCl$: C, 54.17; H, 3.61; N, 18.96); IR (nujol) cm^{-1}: 1600 (aromatic), 17.68 (–C=O), 3312 (–NH), NMR ($CDCl_3$) δ: 2.4 (4H, CH_2 proton), 3.9 (2H, ArNHR proton).

2-(4′-Chlorophenylaminocarbamoyl)-4,5-dihydroimidazole: Scheme 1: Chloroacetylchloride (5.6 mL, 0.05 mol) was added to a stirred solution of *p*-chlorophenylhydrazine[25] (II_b) (0.05 mol) in glacial acetic acid (40.0 mL) at 10°C. The temperature slowly rose to 28–30°C. This was stirred for 25–30 min. A 60% solution of sodium acetate (50.0 mL) was filtered, washed with water and dried at 80°C and recrystallized from a mixture of dimethylformamide and ethanol 3:7 (v/v) in order to obtained *N*-chloroacetylated derivative (II_b).

Now, ethylenediamine (0.02 mol) was added protionwise to a mixture of II_b (0.02 mol) in toluene (60.0 mL) and sulphur (1.28 g, 0.03 mol) at 100°C during 2 h. The reaction mixture was then heated at 100°C under stirring for 4 h and filtered hot. The insoluble solid was discarded. The filtrate was concentrated to 1/5th volume and cooled to 0°C. A gummy precipitate was formed. This was decanted and recrystallized from

methanol to give a crystalline precipitate of 1_c: m.p. 237°C, yield 77% (Found: C, 54.37; H, 4.10; N, 25.40. Calc. for $C_{10}H_9N_4OCl$: C, 54.42; H, 4.08; N, 25.39); IR (nujol) cm^{-1}: 1590 (atomatic), 1765 (–C=O), 3312 (–NH); NMR ($CDCl_3$) δ: 2.4 (4H, CH_2 proton), 3.9 (2H, ArNHR proton).

25,26,27-*tris*(Ethoxycarbonylmethoxy)-28-({2′-phenylcarbamoyl}benzimidazolyloxy carbonylmethoxy) calix-4-arene (6_a): Scheme 3: To a mixture of 2-(4′-chlorophenylcarbamoyl) benzimidazole (1_a) (1.02 mmol) and sodium hydride (0.126 g, 1.0 mmol) in dry tetrahydrofuran (20.0 mL), 5 (0.81 g, 1.13 mmol) was added and stirred for 24 h. Removal of solvent under reduced pressure gave a residue which was dissolved in chloroform dried (sodium sulphate) and evaporated to yield 6_a. It was purified by column chromatography over silica gel 200 g using chloroform–ethylacetate (1:1) as eluent and recrystallized (chloroform–methanol) to give white needles 6_a: m.p. 228°C, yield 42% (Found: C, 68.61; H, 5.25; N, 4.30. Calc. for $C_{55}H_{51}N_3O_{13}$: C, 68.67; H, 5.30; N, 4.37); IR (Nujol) cm^{-1}: 1715 (–C=O); ^{1}H NMR ($CDCl_3$) δ: 7.25–6.60 (m, 15H, ArH), 6.02 (S, 1H, H–C=C).

25,26,27-*tris*(Ethoxycarbonylmethoxy)-28-({2′-phenylcarbamoyl}-4′,5′-dihydraimidazolyloxycarbonylmethoxy) calix-4-arene (6_b): Scheme 3: To a mixture of 2-(4′-chlorophenylcarbamoyl)-4,5-dihydroimidazole (1_a) (1.02 mmol) and sodium hydride (0.126 g, 1.0 mmol) in dry tetrahydrofuran (20.0 mL) 5 (0.81 g, 1.13 mmol) was added and stirred for 24 h. Removal of solvent under reduced pressure gave a residue which was dissolved in chloroform dried (sodium sulphate) and evaporated to yield 6_b. It was purified by column chromatography over silica gel 200 g using chloroform–ethylacetate (1:1) as eluent and recrystallized (chloroform–methanol) to give white needles 6_b: m.p. 226°C, yield 45% (Found: C, 67.12; H, 5.28; N, 4.56. Calc. for $C_{51}H_{49}N_3O_{13}$: C, 67.17; H, 5.37; N, 4.61); IR (nujol) cm^{-1}: 1710 (–C=O); ^{1}H NMR ($CDCl_3$) δ: 7.35–6.80 (m, 12H, ArH), 6.0 (S, IH, H–C=C).

25,26,27-*tris*(Ethoxycarbonylmethoxy)-28-({2′-phenylaminocarbamoyl}-4′,5′-dihydraimidazolyloxycarbonylmethoxy) calix-4-arene (6_c): Scheme 3: To a mixture of 2-(4′-chlorophenylaminocarbamoyl)-4,5-dihydroimidazole (1_c) (1.02 mmol) and sodium hydride (0.126 g, 1.0 mmol) in dry tetrahydrofuran (20.0 mL), 5 (0.81 g, 1.13 mmol) was added and stirred for 24 h. Removal of solvent under reduced pressure gave a residue which was dissolved in chloroform dried (sodium sulphate) and evaporated to yield 6_c. It was purified by column chromatography over silica gel 200 g using chloroform–ethylacetate (1:1) as eluent and recrystallized (chloroform–methanol) to give white needless 6_c: m.p. 227°C, yield 44%

(Found: C, 67.21; H, 5.42; N, 6.18. Calc. for $C_{51}H_{50}N_4O_{13}$: C, 67.25; H, 5.49; N, 6.15); IR (nujol) cm^{-1}: 1712 (–C=O); ^1H NMR ($CDCl_3$) δ: 7.33–6.90 (m, 12H, ArH), 6.0 (S, 1H, H–C=C).

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