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Solvent-free Mannich-type reaction as a strategy for synthesizing novel heterocalixarenes

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Abstract—Novel calix[2]imidazolidin[2]arenes were synthesized by solvent-free Mannich-type reaction, in quantitative yields, from 1,3-bis(2′-hydroxy-benzyl)imidazolidines and 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD).

1. Introduction

Twenty-five years have passed since the first synthesis of calix[*n*]arenes by Zinke et al.;[1] studying these cyclic compounds was re-introduced and developed by Gutsche and co-workers[2,3] as they have hydrophilic cavities having great chemical interest due to the possibility of their forming host–guest complexes.[4–6] The chemical study of heterocalixarenes (calixarenes possessing phenol units alternated with heterocycles) is more recent and, depending on the nature of the heterocyclic unit, encompass numerous new opportunities for interactions with electron-rich and electron-deficient systems.[7–10]

A previous paper[11] reported that macrocyclic aminal 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD) **1** reacted with phenols to produce 1,3-bis(2′-hydroxy-benzyl)imidazolidine **2** Mannich bases having yields ranging from 20% to 30% and resinous mixtures from which it was impossible to isolate characterizable products.

Several syntheses were assayed based on our research group's knowledge regarding 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD) **1** reactivity to phenols and considering that 1,3-bis(2′-hydroxy-benzyl)imidazolidines **2** have phenol rings with *ortho*-activated positions for introducing a new 1,3-bis-methylene-imidazolidine unit, aiming at obtaining calixarene compounds due to their interest both as complexation hosts for ions and molecules and as frameworks for elaborating more complex structures.

All attempts failed when reactions were done in solution and both starting materials TATD **1** and 1,3-bis[2′-hydroxy-benzyl]imidazolidines **2** were recovered. The lack of TATD **1** reactivity to 1,3-bis(2′-hydroxy-benzyl)imidazolidines **2** using this method led us to explore new procedures and other reaction conditions. Some modern variants on the Mannich reaction have been developed to avoid substrate limitations and environmental problems, that is, using catalyst in combination with a surfactant in aqueous medium.[12] Herein, we wish to disclose our results regarding solvent-free Mannich-type reactions using a series of 1,3-bis(2′-hydroxy-4′ or 5′-substituted-benzyl)imidazolidines **2a–d**, synthesized according to the described methodology, reacting with TATD **1** to quantitatively produce calix[2]imidazolidin[2]arenes **3a–d** (Scheme 1).

It was first proved that TATD **1** did not undergo any chemical alteration when submitted to high temperatures, even to those above its melting point. A sample of TATD (100 mg) was thus heated to its melting point (204 °C) and, once melted, the temperature was then raised to 230–235 °C; this temperature was maintained for 1 h. It was left until it solidified and then analyzed. No changes in physical aspect, solubility or melting point were observed. GC–MS showed a single peak having a retention time equal to that of initial TATD in the chromatogram; mass spectra M^+ and diagnostic peaks were identical to those of TATD.

The reactions between **1** and **2a–d** were performed in solvent-free conditions. Once **1** and **2a–d** were mixed

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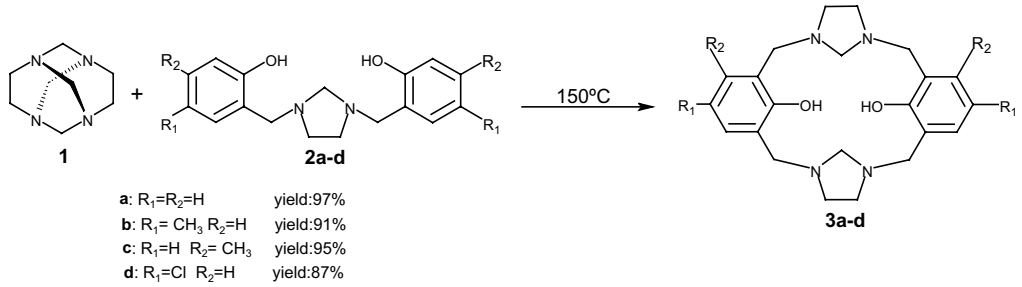


Scheme 1.

in 1:1 molar ratio, the mixture was heated using a 10 °C/min gradient until reaching 150 °C. The liquid state was reached in all cases at phenol's melting point. The mixture was heated until a semisolid material was obtained; the heat source was taken away and, once cold, the product was easily isolated by dispersing the crude reaction mixture in a small volume of ethanol. Additional experiments were carried out where temperature was varied from 130 to 160 °C. The yields obtained were similar in all cases, but at temperatures close to 130 °C longer reaction times were needed. By-products formation was observed when temperatures greater than 160 °C were used. This Mannich-type reaction happened at 145–150 °C according to these results, indicating that the effect of electron behavior and the nature of the substituents in the aromatic ring did not play a vital role in such transformation.

Calix[2]imidazolidin[2]arenes **3a**–**d** structures were assigned by ^{1}H NMR spectra in solution and by force field energy minimization studies. ^{1}H NMR spectra for compounds **3a**–**d** exhibited ph-CH_2–N and ph-H units as multiplets generated by coupling to four bonds as shown by the COSY experiment. The ^{1}H NMR spectrum for **3b** N–CH_2–N units appeared as two multiplets originated by coupling to four bonds with ethylene and benzylic hydrogens as established by the COSY experiment. The N–CH_2–CH_2–N units generated three multiplets ca. 3.0 ppm in a 1:2:1 ratio, demonstrating the presence of two different imidazolidine rings. One of these rings presented a more complex A_2X_2 system due to coupling to four bonds. The multiplets which were observed in ^{1}H NMR spectra for **3c** were as expected when heterocalixarene is asymmetric. In this case, **3c** could present several conformational isomers due to the position of the substituent in the aromatic ring. On the other hand, ^{1}H NMR spectrum for **3d**, N–CH_2–N and N–CH_2–CH_2–N units appeared as singlet-broad signals.

Variable temperature ^{1}H NMR experiments for **3d** in $CDCl_3$ (Fig. 1) showed that this calixarene could present conformational isomerism. The spectrum registered at 50 °C thus exhibited the signals observed at 25 °C accompanied by a new set of signals lesser intensity, similar to those observed in the ^{1}H NMR spectrum for **3b**, indicating the presence of a new conformer. Ethylene hydrogens originate two triplets symmetrically displaced to both sides of the initial singlet (Fig. 1A) had $\delta = 2.74$ and 3.15 ppm. Aminalic hydrogens appeared as two singlets displaced to both sides of the initial singlet (had

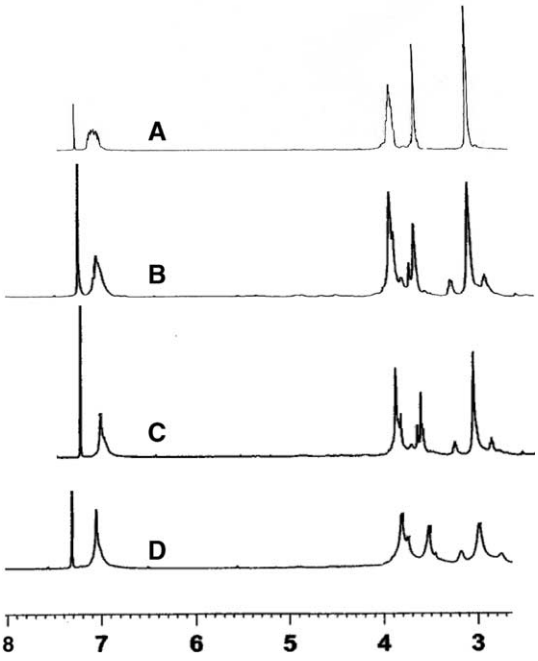
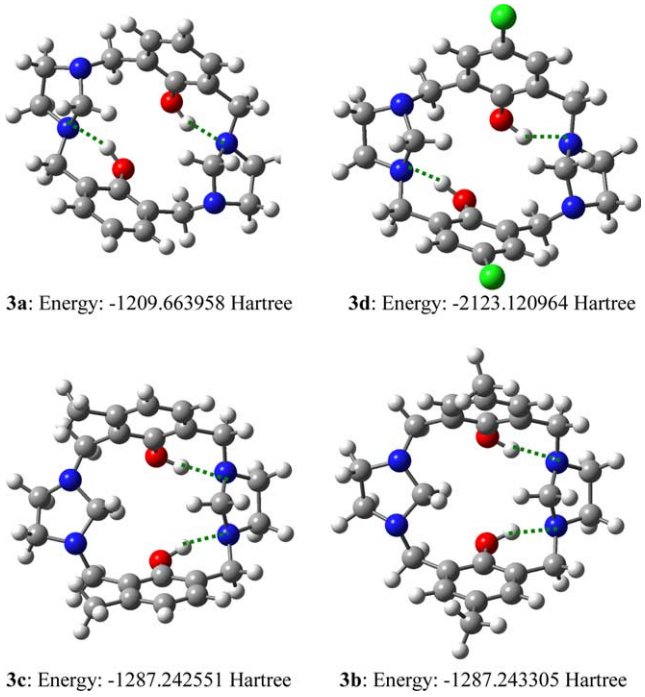


Figure 1. Variable temperature ^{1}H NMR spectra of 5-chlorocalix[2]imidazolidin[2]arene **3d** in $CDCl_3$. A: 25 °C, initial. B: 50 °C. C: 0 °C. D: −50 °C.

3.49 and 3.56 ppm; Fig. 1B) and benzylic hydrogens were observed as a singlet at 3.72 ppm. Less defined signals were observed in ^{1}H NMR spectra on lowering the temperature (Fig. 1C and D) and not conformational interchange to **3d** was observed.

The formation of the **3d** conformer was probably due to rupture and reorganization of intra-molecular hydrogen bond between phenolic hydroxyls and nitrogens from the imidazolidine rings, characteristics of an aminomethylphenol.[13]

Computational calculations using Gaussian 98 software,[14] 3-21G basis set, showed that the most stable conformation for calix[2]imidazolidin[2]arenes **3a**–**d** was that for the cone with horizontal imidazolidine rings orientated inwards (Scheme 2). The calculations led to it being inferred that spectroscopic differences had been originated by conformers having different intra-molecular hydrogen bond orientation between a phenolic hydroxyl and a nitrogen from an imidazolidine ring. OH–N bond in **3a**,**d** were over nitrogens from different imidaz-



Scheme 2.

olidine rings making the molecule more symmetrical and, in turn, allowing shorter distances between oxygens (**3a**: 3.04916 Å; **3d**: 3.14239 Å); **3b**,**c** presented OH—N bond over the same imidazolidine ring reducing the molecule's symmetry and the distance between oxygens (**3b**: 3.90922 Å; **3c**: 3.92370 Å). This conformational behavior explains differences in ^{1}H NMR spectra, showing the presence of two conformers for **3d** following heating to 50 °C and the non-inter-conversion between them at low temperatures, allowing it to be established that the size of the cone's cavity depends on the intra-molecular hydrogen bond's orientation in the ring.

On the other hand, we recently reported a general tetrahydrosalen synthesis procedure using 1,3-bis(2′-hydroxy-benzyl)imidazolidines **2** hydrolysis.[15] These tetrahydrosalen **4a**–**d** also reacted with 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane (TATD) **1** in solvent-free conditions and produced calix[2]imidazolidin[2]arenes **3a**–**d** (Scheme 3), having high yields close to those obtained from respective 1,3-bis(2′-hydroxy-benzyl)-imidazolidine.

In conclusion, our protocol thus provides an expedient approach to calix[2]imidazolidin[2]arenes derived from 1,3-bis(2′-hydroxy-benzyl)imidazolidines, easily obtained from a variety of phenols and 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane. This method also has several advantages such as its easy preparation, easy handling, stability, easy recovery, readily available starting materials, high yields, operational simplicity, and eco-friendly nature.

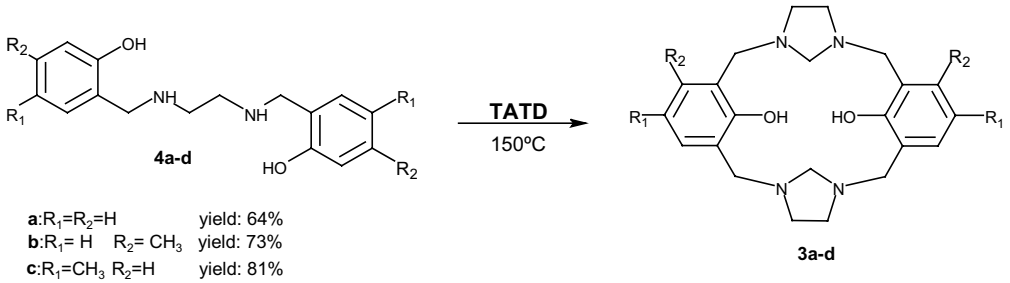
2. Experimental

2.1. Typical procedure for calix[2]imidazolidin[2]arene formation

A TATD (1.0 g) and 1,3-bis(2′-hydroxy-benzyl)imidazolidine **2** (6.0 mmol) mixture was heated to 150 °C with shaking until reaching melting point and heated until solidification (3–20 min). The reaction mixture was left to cool until reaching room temperature and then pulverized in a mortar. The obtained dust was suspended in ethanol; the insoluble solid was separated by filtration, washed with water (3 × 5 mL) and then with ethanol (3 × 5 mL).

2.1.1. Spectroscopic data for compounds 3. 1^{2},5^{2}-Dihydroxy-1(1,3),5(1,3)-dibenzene-3(1,3),7(1,3)-di-imidazolidincyclooctaphane or calix[2]imidazolidin[2]arene **3a**. (97%) mp 220 °C with decomposition; Anal. Calcd for $C_{22}H_{28}N_4O_2$: C, 69.45; H, 7.42; N, 14.73. Found: C, 68.167; H, 6.801; N, 14.199.

1^{5},5^{5}-Dimethyl-1^{2},5^{2}-dihydroxy-1(1,3),5(1,3)-dibenzene-3(1,3),7(1,3)-di-imidazolidincyclooctaphane or 5-methyl-calix[2]imidazolidin[2]arene **3b**. (95%) mp 102 °C; ^{1}H NMR (CD_3OD) δ: 2.20 (m, 6H, CH_3), 2.75 (m, 2H, N–CH_2–CH_2–N), 2.90 (m, 4H, N–CH_2–CH_2–N), 3.05 (m, 2H, N–CH_2–CH_2–N), 3.47 (m, 2H, N–CH_2–N), 3.53 (m, 2H, N–CH_2–N), 3.72 (m, 8H, ph-CH_2–N), 6.90 (m, 4H, ph-*H*); ^{13}C NMR δ: 20.47 (CH_3), 45.16, 45.24, 52.22, 52.37 (N–C–C–N), 69.91 and 73.88 (N–C–N), 55.86 and 54.63 (ph-*C*–N), 154.66 and 154.72 (C1), 130.5 and 130.46 (C3, C5), 123.96



a:R$_1$=R$_2$=H yield: 64%
b:R$_1$= H R$_2$= CH$_3$ yield: 73%
c:R$_1$=CH$_3$ R$_2$=H yield: 81%
d:R$_1$=CH$_3$ R$_2$=H yield: 89%

Scheme 3.

(C2, C6), 129.05 and 130.05 (C4); Anal. Calcd for $C_{24}H_{32}N_4O_2$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.467; H, 8.122; N, 13.709; MS (MALDI-TOF) *m*/*z* 407.3.

1^4,5^4-Dimethyl-1^2,5^2-dihydroxy-1(1,3),5(1,3)-dibenzene-3(1,3),7(1,3)-di-imidazolidincyclooctaphane or 4-methyl-calix[2]imidazolidin[2]arene **3c**. (91%) mp 230 °C with decomposition; ^{1}H NMR (CD_3OD) δ: 2.25 (m, 6H, CH_3), 2.76 (m, 4H, N–CH_2–CH_2–N), 2.95 (m, 4H, N–CH_2–CH_2–N), 3.51 (m, 2H, N–CH_2–N), 3.56 (m, 2H, N–CH_2–N), 3.78 (m, 4H, ph-CH_2–N), 3.84 (m, 4H, ph-CH_2–N), 6.61 (m, 2H, ph-*H*), 6.93 (m, 2H, ph-*H*); Anal. Calcd for $C_{24}H_{32}N_4O_2$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.493; H, 8.031; N, 13.718; MS (MALDI-TOF) *m*/*z* 407.2.

1^5,5^5-Dichloro-1^2,5^2-dihydroxy-1(1,3),5(1,3)-dibenzene-3(1,3),7(1,3)-di-imidazolidincyclooctaphane or 5-chloro-calix[2]imidazolidin[2]arene **3d**. (87%) mp 177–179 °C; ^{1}H NMR ($CDCl_3$) δ: 2.94 (s, 8H, N–CH_2–CH_2–N), 3.53 (s, 4H, N–CH_2–N), 3.79 (s, 8H, ph-CH_2–N), 7.08 (m, 4H, ph-*H*). ^{13}C NMR δ: 51.60; 51.81, 51.96 (N–C–C–N), 75.06 and 75.37 (N–C–N), 53.96 and 58.04 (ph-*C*–N), 156.52 and 154.06 (C1), 127.94 (C3, C5), 125.46 and 125.08 (C2, C6), 123.68 (C4l); Anal. Calcd for $C_{22}H_{26}Cl_2N_4O_2$: C, 58.80; H, 5.83; N, 12.47. Found: C, 58.931; H, 5.779; N, 12.478; MS (MALDI-TOF) *m*/*z* 449.3.

2.2. Typical procedure for calix[2]imidazolidin[2]arene formation from tetrahydrosalens

A TATD (1.0 g) and the respective tetrahydrosalen **4a**–**d** (6.0 mmol) mixture was heated with shaking 150 °C to melting and heat was maintained until solidification (3–20 min). The reaction mixture was left to reach room temperature and then pulverized in a mortar. The obtained dust was suspended in ethanol; the insoluble solid was separated by filtration, washed with water (3×5 mL) and then with ethanol (3×5 mL).

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