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Synthesis of benzyl chlorides and cycloveratrylene macrocycles using benzylic alcohols under homogeneous catalysis by HCl/dioxane

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Abstract: The synthesis of benzyl chlorides, cyclic derivatives cyclotriveratrylene and cyclotripiperotrylene were carried out in using the HCl/dioxane system as a catalyst. The reaction proceeded with high selectivity and is sensitive to the number of alkyl and methoxy substituent on the aromatic ring.

Keywords: Benzyl alcohols; veratrole alcohol; benzyl chlorides; cyclotripiperotrylene; cyclotriveratrylene.

1. Introduction

Cyclotriveratrylenes (CTVs)[1-4] are cyclic molecular host, which are obtained from condensation of veratrole alcohol. CTVs have been extensively employed in host-guest chemistry as a supramolecular scaffold.[5-9] Some of them possess important physical properties, such as thermotropic mesophases, as well as intrinsic characteristics of liquid crystals.[10] CTVs can be prepared in three different ways: a) by the acid-catalyzed condensation of 1,2-disubstituted benzenes possessing two electron-donating groups with formaldehyde; b) through the condensation of diphenylmethane with 1,2-disubstituted benzenes; and c) most commonly by using dimethoxy-substituted benzyl alcohols under strongly acidic conditions (H_2SO_4/CH_3COOH at 90°C or H_3PO_4 at 80°C).[11-15] It is important to remark that our research group has long studied the behavior of piperonyl alcohol, using the HCl/1,4-dioxane (3:1) system to induce the formation of cyclotripiperotrylene (CPT).[16] In this context and following with our interest in the selective oligomerization of benzyl alcohols,[17,18] now we describe the

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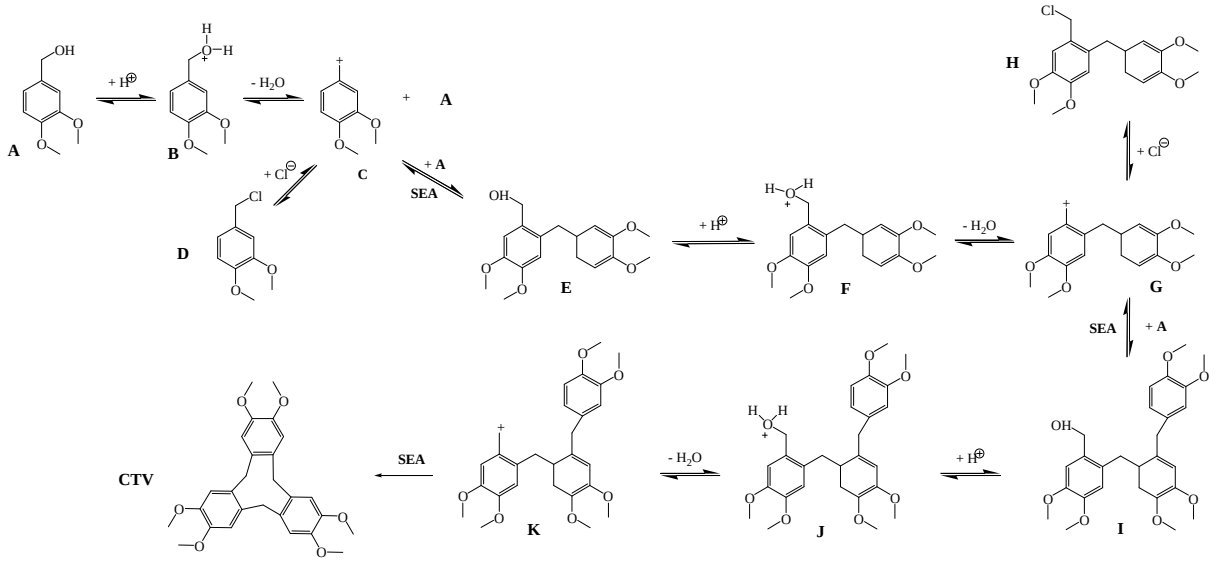
results obtained from a systematic study using mono-di- and trisubstituted benzylic alcohols bearing methyl or methoxy groups on their aromatic rings.

2. Results and discussion

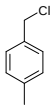
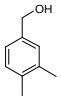
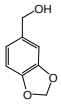
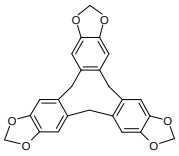
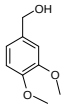
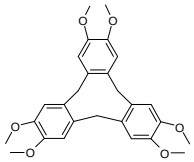
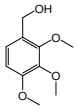
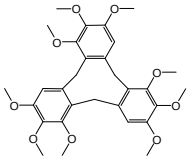
The experiments performed with **1a**-**8a** and HCl/dioxane yielded the results summarized in Table 1. In particular, when compounds **1a**-**4a** were treated with HCl/dioxane (3:1, v/v) at room temperature for 5 h, the corresponding benzyl chlorides **1b**-**4b** were isolated in reasonable yields of 56, 85, 70, and 90% respectively (Table 1, entries 1-4). These results suggest that methyl groups on the phenyl rings promote the substitution of hydroxy by chloride. Furthermore, when the benzyl alcohol was substituted at the *o*- or *m*-position with one methoxy group (**5a** and **6a**), the corresponding chlorides (**5b** and **6b**) were isolated in yields of 60% (Table 1, entries 5 and 6). To our delight, different results were achieved when the benzyl alcohols were substituted with two highly electron-donating methoxy groups on the ring. Thus, when experiments were performed with substituted aromatic derivatives bearing two alkyl groups in the 3- and 4-positions (**7a** and **8a**), the corresponding cyclic trimmers, namely cyclotripiperotrylene **7b** (CPT, 92%) and cyclotriveratrylene **8b** (CTV, 71%) were obtained in reasonable yields (Table 1, entries 7 and 8). It is important to note that, according to the literature, under other acidic conditions the formation of CVT is usually accompanied by some formation of higher cyclic oligomers,[19-21] however in this case the formation of other higher cyclic oligomers was not observed. Finally, 1,2,3,6,7,8,11,12,13-nonamethoxy-10,15-dihydro-5H-trbibenzo[a,d,g] cyclononene 9b(NDTC) was obtained from alcohol **9a** with 55% yield.



Scheme 1. Proposed mechanism for the synthesis of cyclotriveratrylene from veratrole alcohol using the HCl/1,4-dioxane system at room temperature

In the light of the results described above, it is possible to suggest a reasonable mechanism for the formation of cyclotriveratrylene (Scheme 1). In the fast equilibrium reactions, the 3,4-dimethoxybenzylic alcohol **A** is initially protonated to produce **B** and then the carbenium ion **C**. The formation of **C** can be inferred from the isolation of **1b**-**6b**. Thus, in a parallel step, **C** reacts with a chloride ion to yield **D** or reacts with another molecule of **A** through an electrophilic aromatic substitution process to yield **E**. The protonation of **E** generates **F**, subsequent dehydration of which affords a new carbenium ion, **G**. It is important to note that the ion **G** can undergo addition of chloride ion (which is present in excess) to yield **H**, or can react with another molecule of **A** to produce **I**. The trimmer **I** can then produce a new carbenium ion, which is finally involved in the cyclization to produce CTV (Scheme 1).

Table 1. Synthesis of benzyl chlorides and cycloveratrylene macrocycles

Entry	Benzyl alcohol	Product	Yield (%)
1	**1a** 	**1b** 	56
2	**2a** 	**2b** 	85
3	**3a** 	**3b** 	70
4	**4a** 	**4b** 	90
5	**5a** 	**5b** 	60
6	**6a** 	**6b** 	60
7	**7a** 	**7b** 	92
8	**8a** 	**8b** 	71
9	**9a** 	**8b** 	55

3. Conclusion

From these results, it can be inferred that the catalytic reaction of a particular benzyl alcohol in the presence of the HCl/1,4-dioxane system is sensitive to the number of alkyl and methoxy substituent and their position on the aromatic ring. Methyl, dimethyl and methoxy benzyl alcohols furnished their corresponding chlorides using the HCl/dioxane system as a catalyst. However, when benzyl alcohol was substituted with a methylenedioxy, two methoxy or three methoxy groups, a cyclooligomerization process was induced affording the cyclic derivatives cyclotriveratrylene (CTV), cyclotripiperotrylene (CPT) and 1,2,3,6,7,8,11,12,13-nonamethoxy-10,15-dihydro-5H-trbibenzo[a,d,g]cyclononene (NDTC).

4. Experimental

The benzyl alcohols were purchased from Aldrich and were used without further purification. The solvents were also acquired from Aldrich and were purified by standard methods prior to use. Hydrochloric acid (36%) was purchased from J. T. Baker. All 1H and 13C NMR spectra were recorded on a Varian Gemini (300 MHz) spectrometer using $CDCl_3$ as solvent and TMS as an internal reference. Mass spectra were obtained on JEOL JS102 high-resolution mass spectrometer. Thin-layer

chromatographic analyses were performed using Merck silica gel 60 F254 (0.25 mm) pre-coated plates; while products were purified on flash chromatographic columns of silica gel 60 (70-230 mesh).

General procedure for the synthesis of benzyl chlorides 1b-6b and cycloveratrylene macrocycles 7b and 8b using the HCl/dioxane system:

3 mmol of each starting material **1a**-**9a** was vigorously stirred at room temperature for 5 h in the presence of concentrated HCl (30 mL) and 1,4-dioxane (10 mL) as solvent. The reaction mixture was extracted with AcOEt (3x15 mL). Then, the combined organic extract was washed with brine (2x15 mL), dried with Na_2SO_4 and concentrated in vacuo. The resulting residue was purified by column chromatography. Each experiment was repeated three times.

1-(chloromethyl)-2-methylbenzene 1b.[22]**:** Liquid (56% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.1-7.3 (m, 4H, Ar), 4.3 (s, 2H, CH_2Cl), 2.35 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 138.0, 130.1, 128.9, 128.6, 124.9, 43.0, 15.1; HRMS (FAB) calcd. for C_8H_9Cl 140.0339, found 140.0320.

1-(chloromethyl)-3-methylbenzene 2b.[22]**:** Liquid (85% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.07-7.3 (m, 4H, Ar), 4.6 (s, 2H, CH_2Cl), 2.31 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.0, 137.6, 130.5, 130.3, 129.1, 124.7, 52.0, 21.5; HRMS (FAB) calcd. for C_8H_9Cl 140.0339, found 140.0322.

1-(chloromethyl)-4-methylbenzene 3b.[22]**:** Liquid (70% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.8-7.1 (m, 4H, Ar), 4.4 (s, 2H, CH_2Cl), 2.10 (s, 3H, Me); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.2, 134.5, 130.3, 129.1, 51.0, 20.8; HRMS (FAB) calcd. for C_8H_9Cl 140.0339, found 140.0325.

4-(chloromethyl)-1,2-dimethylbenzene 4b.[23]**:** Liquid (90% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (s, 1H, Ar), 7.24 (m, 2H, Ar), 4.65 (s, 2H, CH_2Cl), 2.38 (s, 6H, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.9, 136.8, 134.8, 129.84, 129.79, 126.0, 46.2, 19.6, 19.4; HRMS (FAB) calcd. for $C_9H_{11}Cl$ 154.0549, found 154.0532.

1-(chloromethyl)-3-methoxybenzene 5b.[24]**:** Liquid (60% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.3-6.9 (m, 4, Ar), 4.70 (s, 2 H, CH_2Cl) 3.95 (s, 3H, MeO); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9, 138.8, 130.0, 121.0, 112.7, 114.3, 55.9, 46.7; HRMS (FAB) calcd. for C_8H_9Cl 156.0342, found 156.0338.

1-(chloromethyl)-2-methoxybenzene 6b.[25]**:** Liquid (60% yield); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.3-6.8 (m, 4, Ar), 4.71 (s, 2 H, CH_2Cl) 3.85 (s, 3H, MeO); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.3, 129.8, 129.7, 123.4, 121.3, 114.5, 56.2, 36.5; HRMS (FAB) calcd. for C_8H_9Cl 156.0342, found 156.0334.

Cyclotripiperotrylene 7b. [16]**:** White solid (92%); m.p., descompose over 300 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.0 (s, 6H, Ar-H), 5.89 (d, 3H, O-CH_2-O, *J* = 1.0 Hz), 5.77 (d, 3H, O-CH_2-O, *J* = 1.0 Hz), 4.72 (d, $3H_{ax}$, $ArCH_2Ar$, *J* = 13.7 Hz) 3.45 (d, $3H_{ax}$, $ArCH_2Ar$, *J* = 13.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.3, 132.6, 109.7, 100.8, 36.9; HRMS (FAB) calcd. for $C_{26}H_{26}O_6$ 434.1729, found 434.1718.

Cyclotriveratrylene 8b.[25]***:*** White solid (71%); m.p. 231-232 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.83 (s, 6H, Ar-H), 4.78 (d, $3H_{ax}$, $ArCH_2Ar$, *J* = 13.7 Hz), 3.84 (s, 18H, CH_3O) 3.56 (d, $3H_{ax}$, $ArCH_2Ar$, *J* = 13.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.9 132.0, 113.4, 56.2, 36.7; HRMS (FAB) calcd. for $C_{27}H_{30}O_6$ 450.2042, found 450.2038.

1,2,3,6,7,8,11,12,13-nonamethoxy-10,15-dihydro-5H-trbibenzo[a,d,g]cyclononene 9b.[26]**:** White solid (55%); m.p. 199-202 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.24 (s, 3H, Ar-H), 4.42 (d, $3H_{ax}$, $ArCH_2Ar$, *J* = 13.6 Hz) 4.03 (d, $3H_{ax}$, $ArCH_2Ar$, *J* = 13.6 Hz), 3.97 (s, 9H, CH_3O), 3.80 (s, 9H, CH_3O), 3.77 (s, 9H, CH_3O); ^{13}C NMR (75 MHz, $CDCl_3$): δ 151.5, 151.4, 140.4, 136.2, 125.5, 110.3, 60.6, 60.5, 55.7, 29.9; HRMS (FAB) calcd. for $C_{30}H_{36}O_9$ 540.2359, found 540.2351

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