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Role of polar solvents for the synthesis of pillar[6]arenes

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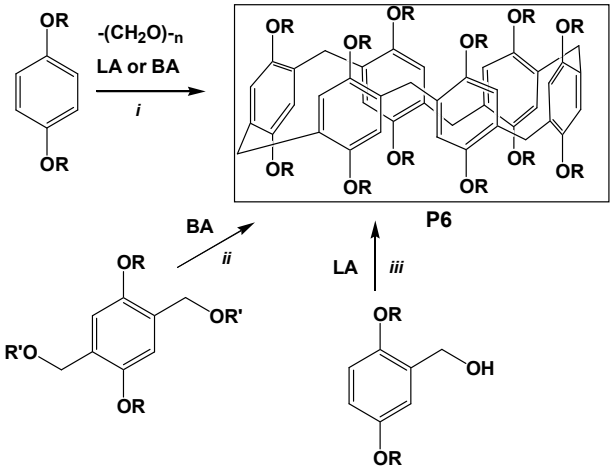
An efficient procedure for the synthesis of pillar[6]arenes has been developed. The procedure involves the condensation of 1,4-dialkoxybenzenes and paraformaldehyde in the presence of catalytic amount of H2SO4 or BF3•OEt2 in a polar solvents media (acetonitrile, ethyl alcohol, acetone etc.). In all the cases the interaction afforded pillar[6]arenes in high yields.

Pillar[n]arenes (n = 5[1] or 6[2]) are called "a fascinating cyclophanes with a bright future".[3] Indeed, these macromolecules are quite prospective molecular cavity containers due to their rigid penta- or hexagon shape and high-electron rich cavity of 5.5-7.5 Å diameter.[1,4] Pillararenes have wide applications in supramolecular chemistry as supramolecular hosts and tectons,[4] in analytical chemistry as sensor molecules,[5] for instance, the colorimetric detection of metal cations,[6] fluorescent[7] or electrochemical[8] detection of nitrogen-based cations, as well as anions sensing[9] and some neutral molecules binding/encapsulation.[10] In material science pillararenes have been used as components in liquid crystals,[11] photoresists,[12] ion-selective membranes,[13] as artificial gas[14] and water[15] channels. Some important biological applications of pillar[5]arenes have also been reported.[16]

Pillar[6]arenes (and higher pillar[n]arenes) are commonly isolated as by-products in the synthesis of pillar[5]arenes, which involves the Lewis or Brønsted acid-catalyzed cyclocondensation between paraformaldehyde and 1,4-dialkyloxybenzenes in chlorinated solvents (Scheme 1, way i).[1] In fact, the formation of pillar[5]arenes in the most cases occurs under thermodynamic control, therefore yields of higher pillar[n]arenes, the kinetic products, are normally low.[17a-b] Only in one report Cao, Meier and co-authors carried out the synthesis of pillar[6]arenes under the kinetically controlled conditions by using $FeCl_3$ in anhydrous chloroform to yield the mixture of pillar[5]- and pillar[6]arenes with the preferable formation of larger macrocycle in the ratios, depending on the nature of alkyl substituents and the reaction time.[17c] Other approaches, including the Brønsted acid-catalyzed self-condensation of bis(alkoxymethyl)-1,4-dialkoxybenzene[2,17d] (way ii) or Lewis acid-promoted self-condensation 2,5-alkoxybenzyl alcohols (way iii),[2,17e-f] reported by the Meier's and Huang's research groups afforded only the minor amounts of less stable pillar[6]arenes. Recently, Ogoshi and co-authors observed the formation of some pillar[6]arenes in high yields using 1-chlorocyclohexane as reaction media and as a template.[19a] Very recently, the Zhang group developed a method for the synthesis of pillar[6]arene with 53% yield by condensation of 1,4-dialkoxybenzene and paraformaldehyde with the choline chloride (ChCl)/ferric chloride ($FeCl_3$) deep eutectic solvent in CH_2Cl_2 at room temperature.[20]



Scheme 1. Common approaches to the synthesis of pillar[6]arenes.

All these methodologies reported so far for synthesis of pillar[6]arenes furnished very poor yields and use of chlorinated solvent is another drawback. So, high-yield

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synthesis in non-chlorinated and/or polar solvents is demanding for current working practice.

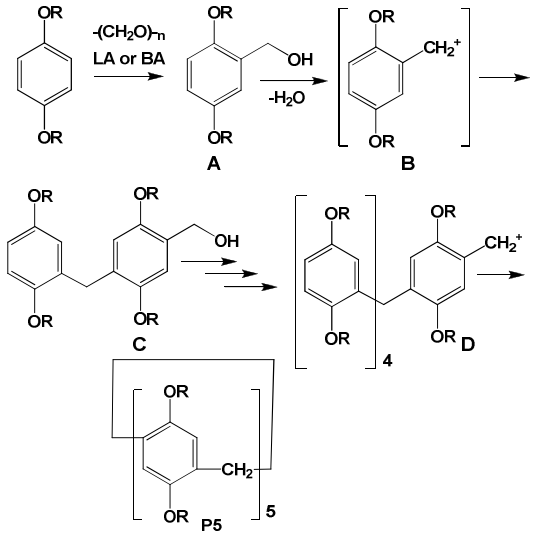
In continuation of our research in organic methodologies we have reported very recently a very clean synthesis of pillar[6]arenes[18] in absence of solvent. To investigate the role of solvent we have examined the synthesis of pillar[6]arenes (including one novel compound) in acetonitrile and other common polar solvents in the presence of catalytic amount of sulphuric acid or $BF_3 \bullet OEt_2$.

Results and discussion

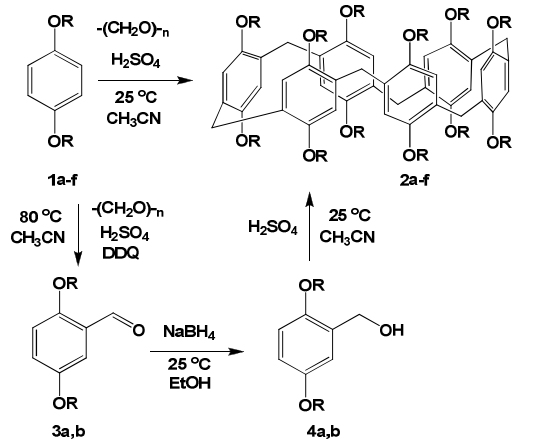
According to Ogoshi and co-authors[19a] the role of the non-polar chlorinated solvent in a synthesis of pillar[n]arenes is in the template effect, promoting the formation of the desired pillar[n]arene (mostly n = 5), depending on the geometric size of the solvent. Thus, in the classical Ogoshi's procedure[1] and its following modifications[21] linear dichloroalkanes occupy the cavity of pillar[5]arene to promote the preferable formation of more stable pillar[5]arenes over pillar[6]arenes during the thermodynamically controlled cyclisation reaction. In the absence of linear dichloroalkanes, for instance in chloroform,[17b-c] under the kinetic control the reaction led to the mixture of pillar[n]arenes with the preferable formation of pillar[6]arenes and larger macrocycles which are kinetic products, and upon standing their following interconversion to pillar[5]arenes and/or linear oligomers occurs. If the solvent for the reaction media has a proper size to template the pillar[6]arene; this macrocycle was the only product due to its "internal locking" by the template solvent. For instance, Ogoshi and co-authors isolated pillar[6]arenes as major products using 1-chlorocyclohexane as a solvent.[19a] The preferable formation of pillar[5]arenes in solvents other than 1-chlorocyclohexane is based on mechanistic aspects of this reaction as a Friedel-Crafts alkylation.

Thus, according to the literature,[22] on the first step the acid-catalyzed hydroxyl methylation reaction of 1,4-dialkoxy benzene with paraformaldehyde (or in some cases formaldehyde[22a] or 1,3,5-trioxane[23]) afforded the benzyl alcohol **A** (Scheme 2). Elimination of water molecule from the benzyl alcohol **A** converts it to a benzylic cation **B**. The benzylic cation under acidic conditions underwent further reaction with another molecule of benzyl alcohol to give a dimeric benzylic cation **C**, and finally other oligomeric cations **D**. At the final step, the oligomeric cation **D** stabilized through the cyclization to the most stable pillar[n]arene, i.e. pillar[5]arene **P5**.

On the other hand Neumann and co-authors[24] described a high yield method for the preparation of aromatic aldehydes *via* the oxidative hydroxymethylation reaction of various arenes by paraformaldehyde in acetonitrile catalyzed by H_2SO_4 in the presence of oxidant (DDQ). In this reaction the *in situ* formed benzyl alcohol quantitatively converts into the corresponding aldehyde. Surprisingly, the authors only mentioned the possibility for the formation of higher linear diarylmethanes as by-products under the hydroxymethylation conditions if no oxidant would present.



Scheme 2. The proposed mechanism for the formation of pillar[n]arenes.



Scheme 3. Synthesis of pillar[6]arenes **2a-f** in polar solvents media

Table 1. Yields of products **2a-f**[a]

Product	R	Yield [%][b]	Product	R	Yield [%][b]
2a	Et	71	**2d**	Hept	61
2b	*n*-Pr	70	**2e**	Bn	0[c]
2c	Bu	66	**2f**	$CH_2CO_2CMe_3$	42

[a] All reactions were carried out on 2 mmol scale; [b] Isolated yields; [c] No cyclic oligomers observed.

Keeping in mind that pillar[n]arenes have been efficiently obtained by the Friedel–Crafts alkylation reaction in chlorinated solvents, we became interested in developing of other synthetic procedures to pillar[n]arenes, for instance based on the modified Neumann's procedure, i.e. in oxidant-free conditions.

The outcome of the reaction was quite unexpected. Effectively, no linear oligomeric compounds or pillar[5]arene could be isolated and the pillar[6]arene **2a** was the major cyclized product. As shown in Scheme 3, treatment of 1,4-

diethoxybenzene (**1a**) with H_2SO_4 in acetonitrile at room temperature gave pillar[6]arene **2a**. Meanwhile, other 1,4-dialkoxybenzenes (except R = Bn) under this conditions afforded pillar[6]arenes **2b-d** in good yields (Table 1). Moreover, this present methodology is also applicable for synthesizing ester substituted pillar[6]arene (**2f**) with moderate yield.

The yields of pillar[6]arenes **2** are improved significantly over those previously reported for the synthesis of pillar[6]arenes (36-53%, except the recent Ogoshi's report). The optimization of the reaction conditions is shown in Table 2. The optimum ratio of 1,4-diethoxybenzene:paraformaldehyde:H_2SO_4 is 1:2:0.3 (30% molar) (entry 3). The increasing of the amount of paraformaldehyde did not improve the yield of **2a** significantly. The variation of the amount of H_2SO_4 (entries 6-8) resulted in the decreasing of the yield of **2a**. Probably, use of large amount of H_2SO_4 results the formation of insoluble long chain polymer. The reaction is completed normally within 5 minutes, and the prolonging of the reaction time decreased the yield of the target product (entries 9-10).

Table 2. Optimization of the reaction conditions in the presence of H_2SO_4.[a]

Entry	Amount of PF used (equiv.)	Amount of H_2SO_4	Time [min][b]	Yields of **2a** [%][c]
1	1	30 mol%	5	53
2	1.5	30 mol%	5	61
3	**2**	**30 mol%**	**5**	**71**
4	2.5	30 mol%	5	69
5	3	30 mol%	5	68
6	2	50 mol%	5	51
7	2	10 mol%	5	31
8	2	20 mol%	5	55
9	2	30 mol%	10	68
10	2	30 mol%	15	62

[a] All reactions were carried out on 2 mmol scale in 2 mL of acetonitrile. [b] Time was counted after addition of the catalyst. [c] Yields after washing with ethyl alcohol. PF = Paraformaldehyde.

Surprisingly, similar results were observed in acetonitrile in the presence of the Lewis acid, i.e. BF_3•OEt_2, which is the most common for the pillar[5]arene synthesis: the pillar[6]arene **2a** was isolated in up to 67% yield (see Table 1, ESI).

Similarly to the previously reported procedures the reaction proceeds *via* the *in situ* formation of benzyl alcohols. To prove that we synthesized benzyl alcohols **4a**, **4b** and their following condensation in acetonitrile in the presence of H_2SO_4 afforded pillar[6]arenes **2a**, **2b** in high yields (see Scheme 1, ESI).

To investigate further the influence of the nature and the polarity of solvents on the selective formation of pillar[6]arene, we examined several other solvents and results are presented in Table 3. According to the experimental data in the media of most polar solvents with a high dipole moment (entries 1-7) the pillar[6]arene **2a** was obtained in 55-72% yields depending on catalyst. The decreasing of the dipole moment of solvents resulted in the lower yields of **2a** (see Fig. 1, ESI). Some common solvents with low polarity such as ethyl cyanoacetate, nitromethane, chloroacetonitrile, acetone and ethyl alcohol also served as good solvents to produce pillar[6]arene **2a** (entries 4-8).

Finally, when we reproduced the classical Ogoshi's procedure[1,21b] in a media of neat 1,2-dichloroethane, neat acetonitrile or in a 1:1 mixture of both solvents the resulting pillar[6]arene **2a** was isolated in 0%, 67%, and 63% yields respectively. Similar results observed in the presence of H_2SO_4 (see Table 2, ESI).

Table 3. Synthesis of **2a** in different solvents[a-b]

Entry	Solvent	Dipole moment,[c] D	Yield [%]
1	Benzonitrile	4.51	72(63)[d]
2	Nitrobenzene	4.28	71 (70)[d]
3	Acetonitrile	3.92	71(67)[d]
4	Ethyl cyanoacetate	3.80	67(60)[d]
5	Nitromethane	3.56	61
6	Chloroacetonitrile	3.00	58
7	Acetone	2.88	55
8	Ethyl alcohol	1.69	43(52)[d]
9	Benzyl cyanide	N/A	0[e]
10	Dichloroacetonitrile	2.33[f]	N/A
11	Trichloroacetonitrile	1.38[f]	0[g]
12	1,2-Dichloroethane	1.80	Traces
13	Chloroform	1.15	34[j](15)[h]
14	Dichloromethane	1.14	Traces

[a]All reactions were carried out on 2 mmol scale in different solvents. [b] Based on ^{1}H NMR data after workup. [c] Dipole moment values are published elsewhere. [d] BF_3•OEt_2 used as a catalyst. [e] The 1,4-diethoxybenzene did not dissolve properly. [f] Dipole moment values were calculated using DFT (B3LYP 6-311G) calculations. [g] The addition of H_2SO_4 caused the polymerisation of the reaction mixture. [j] From ref. [17c]. [h] From ref. [17b].

The possible role of polar solvents in this reaction is both the stabilization and the "external blocking" of *in situ* formed oligomeric cation (Figure 1, top) and the following "external blocking"/templating of the cyclic cation (Figure 1, middle) and the target hexamer (Figure 1, bottom).[22,25]

The larger the dipole moment of solvent the stronger the oligomeric cation/dipole interactions, causing the more efficient charge distribution in a solute cation and the better stabilization of the cation due to the solvent effects,[26] the higher its conversion into pillar[6]arene **2a**. In some cases at the certain point the precipitation and further isolation of pillar[6]arene **2a** from the reaction media may occur. All of these factors prevent further the interconversion of pillar[6]arenes into pillar[5]arenes, larger pillararenes or linear oligomers/polymers, which was possible during the preparation of pillararenes under the Friedel-Crafts conditions in chlorinated non-polar solvents due to the "dynamic character of covalent bond formation".[22a]

This polar-solvent protocol is also applicable on a gram-scale synthesis. Upon ten times increasing of the amount of reagents in the presence H_2SO_4 or BF_3•OEt_2 in acetonitrile solution the yield of **2a** was 69% and 64% respectively (see Scheme 2, ESI).

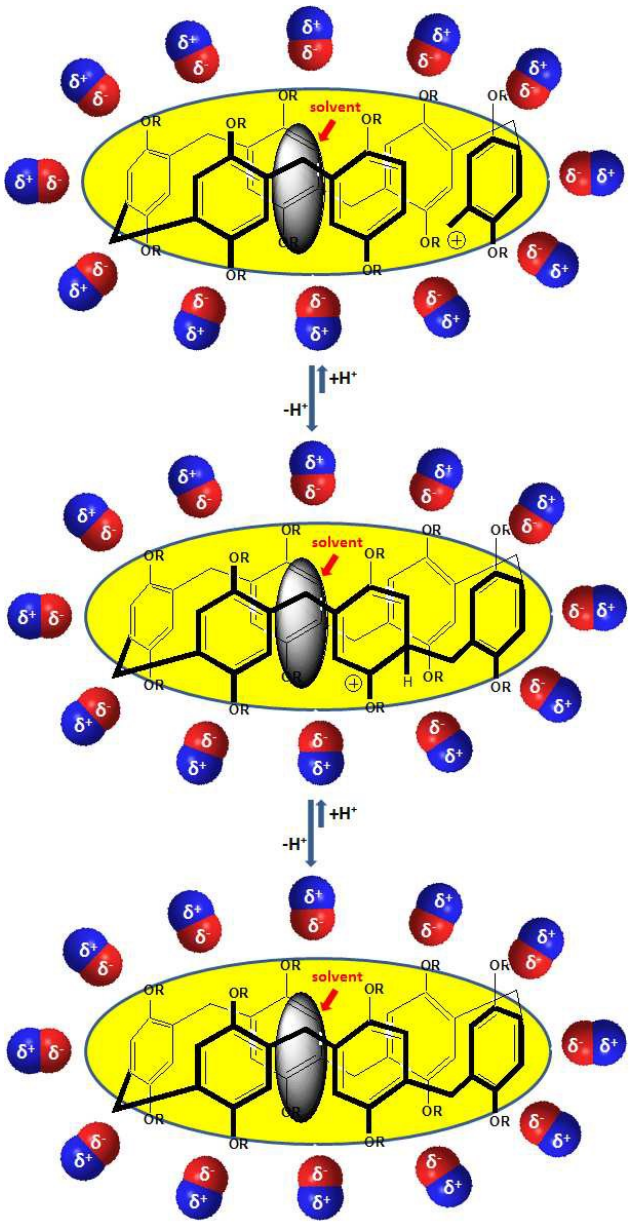


Figure 1. The possible role of polar solvent in the synthesis of pillar[6]arenes.

Conclusions

In conclusion, we have demonstrated that H_2SO_4 in acetonitrile and other polar solvents media can serve as a robust and efficient catalytic system for the preparation of pillar[6]arenes. Due to the simplicity and practicability of both starting materials and the catalytic system, our findings would be expected to bring new insights in the research field of pillar[n]arene-based supramolecular chemistry and material science. The reaction was found to afford mainly pillar[6]arenes in a media of other common polar solvents and/or common Lewis acids.

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Notes and references

‡**Representative synthetic procedure of pillar[6]arenes 2:** To a solution of the appropriate 1,4-dialkoxy benzene (2 mmol) in 2 mL of acetonitrile, paraformaldehyde (124 mg, 4 mmol) was added. The reaction mixture was stirred for 5 minutes. Then conc. H_2SO_4 (32 µL, 30 mol%) was added to that reaction mixture and stirred at room temperature for 5 minutes. After that 5 mL of ethanol was poured into the reaction mixture. The resulting precipitate was filtered off, washed with ethanol, dried and, depending on the type of pillar[6]arene purified by column chromatography to result in analytically pure per-alkylated pillar[6]arenes. Experimental details are provided in the Supporting Information.

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Role of polar solvents for the synthesis of pillar[6]arenes

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