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Solvent-free synthesis of pillar[6]arenes

S. Santra,[a] D. S. Kopchuk,[a,b] I. S. Kovalev,[a] G. V. Zyryanov,[a,b] A. Majee,[c] V.N. Charushin[a,b] and O. N. Chupakhin[a,b]

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An efficient solvent-free procedure for the synthesis of pillar[6]arenes has been developed. The procedure involves the solid-state condensation of finely milled 1,4-dialkoxybenzene and paraformaldehyde by grinding in the presence of catalytic amount of H_2SO_4. The use of organic solvents for the extraction of products has also been avoided. Operational simplicity, the compatibility with various 1,4-dialkoxybenzenes, non-chromatographic purification technique, high yields and mild reaction conditions are the notable advantages of this procedure. Large scale reaction demonstrated the practical applicability of this methodology.

Discovered in 2008 by Ogoshi and co-authors pillar[5]arenes[1] and in 2009 by Meier and co-authors pillar[6]arenes[2] are quite young class of aromatic cyclophanes. Due to their rigid penta- or hexagon shape and high-electron rich cavity within 5.5-7.5 Å diameter[1,3] these macrocycles have already found wide applications in supramolecular chemistry as supramolecular hosts and tectons.[4] In material science they act as components in liquid crystals,[5] photoresists,[6] ion-selective membranes,[7] as artificial gas[8] and water[9] channels and receptors for cations,[4] including tropilium[10a] and ferrocenium ones.[10b] Recently some important biological applications of pillar[5]arenes have also been proposed.[11]

Pillar[6]arenes (and higher pillar[*n*]arenes) are often by-products in the synthesis of pillar[5]arenes which involves the Lewis or Brønsted acid-catalyzed cyclocondensation between paraformaldehyde and 1,4-dialkyloxybenzenes **1** in chlorinated solvents.[1-2,12] Normally, synthesis of pillar[5]arenes in the most cases occurs under thermodynamically controlled conditions,[13a] therefore yields of higher pillar[*n*]arenes are very low. Only in one report, Meier and co-authors carried out the synthesis of pillar[6]arenes under kinetically controlled conditions. They have used $FeCl_3$ as catalyst and chloroform as solvent in anhydrous conditions to yield the mixture of pillar[5]- and higher pillar[6]arenes with the preferable formation of larger macrocyclein the ratio, depending on the nature of alkyl substituents and the reaction time.[12c] Other approaches, involving the Brønsted acid-catalyzed self-condensation of bis(alkoxymethyl)-1,4-diethoxybenzene[2,14] or Lewis acid-promoted self-condensation of 2,5-alkoxybenzyl alcohols,[2,13a-b] reported by the Meier's and Huang's research groups to afford only little amount of less stable pillar[6]arenes while pillar[5]arenes were always the major products.

The reaction time was shown to affect the product yield which varies from several minutes[12,15] to several (up to 24) hours.[1,13-14] Among various synthetic pathways, Lewis acid-catalyzed cyclization of readily available 1,4-dialkoxybenzenes with paraformaldehyde in the media of chlorinated solvents is the most common approach for the synthesis of pillar[6]arene derivatives.[12b-c,14a] As the most successful example, Ogoshi and co-authors reported a method for the high-yield synthesis of 1,4-bis(methylcyclohexyl) ether pillar[6]arene in a media of 1-chlorocyclohexane as a template solvent.[16a] Large-scale synthesis involves large volumes of chlorinated solvents and the use of large quantities of Lewis acid (usually 1:1 molar ratio of Lewis acid to aromatic substrate has been used). Only in some reports in the presence of catalytic amount of TFA[12b] or TfOH[14a] pillar[6]arenes were obtained in low yields, and the reaction required up to 24 hours to complete. Thus it is a meaningful effort to develop a very simple and selective synthesis of pillar[6]arenes.

Herein we report the synthesis of pillar[6]arenes (including two novel compounds) achieved under solvent-free conditions by the direct condensation of paraformaldehyde and 1,4-dialkoxybenzene in the presence of catalytic amount of sulphuric acid (Scheme 1).[‡]

The methodology is very simple, high-yielding, energy-efficient and applicable to a variety of 1,4-dialkoxybenzenes as starting materials.

Results and discussion

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[a] Ural Federal University, Chemical Engineering Institute, Yekaterinburg, 620002, Russian Federation. Email: gvzyryanov@gmail.com

[b] I. Ya. Postovskiy Institute of Organic Synthesis, Ural Division of the Russian Academy of Sciences, 22 S. Kovalevskoy Str., Yekaterinburg, 620219, Russian Federation. E-mail: chupakhin@ios.uran.ru

[c] Department of Chemistry, Visva-Bharati (A Central University), Santiniketan-731235, India. E-mail: adinath.majee@visva-bharati.ac.in

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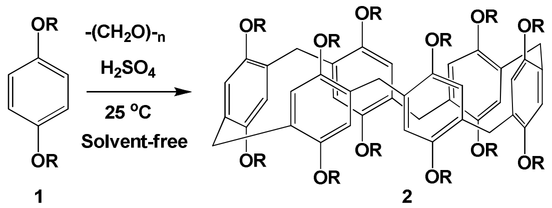
Reaction of 1,4-dialkyloxybenzenes **1** (molar proportion) and paraformaldehyde (molar proportion) has been carried out by simply grinding together in the presence of a catalytic amount (10% molar) of sulphuric acid. The solid phase melts within minutes to yield a sticky solid that hardens further on standing. ^{1}H NMR analysis of this material reveals almost quantitative conversion to crude pillar[6]arene **2.** Crude compound has been isolated by simply washing the ground product with water for effectively removal of the remaining catalyst and paraformaldehyde. Further washing the solid with small amount of ethyl alcohol affords analytically pure pillar[6]arenes **2** in high yields (See ESI for details). This methodology is also applicable on a gram-scale synthesis. We have successfully synthesized the perethylated pillar[6]arene **2a** in 84% yield by the reaction of 1,4-diethoxybenzene (**1a**, 10 mmol) and paraformaldehyde (30 mmol) under the same reaction conditions. To compare the efficiency of our method we have carried out this reaction with mechanical ball milling technique. We have repeated the experiment with mechanical ball milling (PM 100, Retsch GmbH Germany) for synthesizing **2a** using 1.5 g scale. We have got nearly the same results (85% yield).

To the best of our knowledge the synthesis of pillar[6]arenes so far has never been achieved under solvent-free reaction conditions.

In comparison to the time scale for most conventional syntheses of pillar[6]arenes (up to 24 hours),[12-14] our approach by solvent-free reaction conditions reach a substantial degree of conversion within 5-10 minutes. No external heating is required and the grinding method is used to achieve particle size reduction and efficient mixing. An energy expensive high intensity grinding process is also not required as the reaction mixture does not remain dry and powdery but becomes a viscous liquid. Yields are also substantially higher using the solvent-free conditions as it is indicated in Table 1. To our delight, various 1,4-dialkoxybenzenes with ethoxy, propoxy, butoxy, 2-ethylhexyloxy and heptyloxy gave the corresponding pillar[6]arenes with good yields in all cases.



Scheme 1 Solvent-free synthesis of pillar[6]arenes **2a-e**

Table1 Synthesis of Pillar[6]arenes **2a–e.**[a]

Compound	R	Yields (%)[b]	Reported yields (%)[12c]
2a	C_2H_5	84, 85[c]	34
2b	n-C_3H_7	82	35
2c	n-C_4H_9	83	43
2d	2-Ethyl hexyl	80	-
2e	C_7H_{15}	78	-

[a]All reactions were carried out in 5 mmol scale. [b]Yields after work-up. [c] Carried out with mechanical ball milling on 1.5 g scale.

Table 2 shows the optimization of the reaction conditions, depending on the reagents ratio and the amount of catalyst. Although the stoichiometry of the reaction is 1:1, some authors[12a] reported a beneficial effect of using considerable excess of paraformaldehyde. In our case, using the 3-fold excess of paraformaldehydele is the best conditions and afforded 84% yield (entry 6). The reaction is promoted by 98% sulphuric acid and the optimum amount was 10% molar (entry 6). Higher and lower amount of acid resulted in lower yields of pillar[6]arene **2a** (entries 5, 7-8). No reaction has been observed without the catalyst (entry 14). The reaction completes within 5 minutes (the solid melts) and the optimum reaction time was 10 minutes. The prolonged reaction time did not affect the product yield much (entries 9, 10). The possible reason for the preferable formation of pillar[6]arenes is the kinetically controlled reaction conditions, while pillar[5]arenes are thermodynamically controlled products.[13a,15] Under the solvent-free reaction conditions after formation of the kinetically controlled product pillar[6]arenes as precipitation from the reaction mixture interconversions to larger or smaller pillar[*n*]arenes are not possible as these interconversions occur only in the presence of solvent, used as a reaction media or template.[12*b*,16] Thus prevention of interconversion to larger or smaller pillar[*n*]arenes is the main advantage of our solvent-free method. To confirm this hypothesis we took a solid 1:1 mixture of perethylated pillar[5]arene and pillar[6]arene **2a** in the presence of sulphuric acid and the reaction mixture was heated up to 80 °C for 5 h. At the end of reaction no pillar[6]arene or pillar[5]arene observed and only the starting 1,4-diethyloxybenzene **1a** was isolated.

It is worthy to mention that in addition to sulphuric acid some Lewis acids or Brønsted acids (TSA) were tested for the solvent-free pillar[6]arenes synthesis, including the common for pillar[6]arenes synthesis $FeCl_3$[12c] and the common for the pillar[5]arenes and pillar[6]arenes $BF_3{\cdot}OEt_2$.[1,12] In all these experiments the target pillar[6]arene **2a** has in yields not exceeding 28%.

Table 2 Yields for compound **2a**, depending on the time and reagents ratio.[a]

Entry	Amount of PF (equiv.)	Amount of H_2SO_4, mol %	Time (min)	Yields (%)[b]
1	1	5	10	32%
2	1.5	5	10	38%
3	2	5	10	45%
4	2.5	5	10	52%
5	3	5	10	65%
6	**3**	**10**	**10**	**84%**
7	3	15	10	75%
8	3	20	10	58%
9	3	10	20	82%
10	3	10	30	80%
11	1	10	10	45%
12	2	10	10	68%
13	5	10	10	76%
14	3	-	30	-

[a] All reactions are carried out in 5 mmol scale. [b]Yields after washing with water and ethyl alcohol. PF = Paraformaldehyde.

Conclusions

In conclusion, we have demonstrated a simple, solvent-free, energy efficient, clean and high yield pathway for the synthesis of pillar[6]arenes. This method also demonstrates a suitable and cost-effective alternative to commercially available products and solvents for the reaction media. This protocol is also applicable on a gram-scale synthesis. Clean reaction, high yields, ease of product isolation, short reaction time, low catalyst loading and avoidance of toxic solvents are the notable advantages of the present methodology and these features make this procedure to be a green synthetic protocol. We believe that our novel procedure will open up a new practical and convenient route for the synthesis of pillar[6]arenes.

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Notes and references

‡**Representative synthetic procedure of pillar[6]arenes 2:** A mixture of the appropriate 1,4-dialkoxy benzene (5 mmol), paraformaldehyde (0.46 g, 15 mmol) and 98% H_2SO_4 (30 µL, 10 mol%) was ground by means of porcelain mortar and pestle at room temperature. After the continuous grinding for 10 minutes by hand a deep green gummy mass of a crude product was observed. The reaction mixture was then poured into 5 mL of ethanol and 0.5 mL of water. The resulting precipitate was filtered off, washed two-three times with ethyl alcohol and dried in order to get the pure per-alkylated pillar[6]arenes **2** without any other purification by column chromatography or recrystallization.

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Graphical Abstract

Solvent-free synthesis of pillar[6]arenes