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A facile, moisture-insensitive method for synthesis of pillar[5]arenes—the solvent templation by halogen bonds

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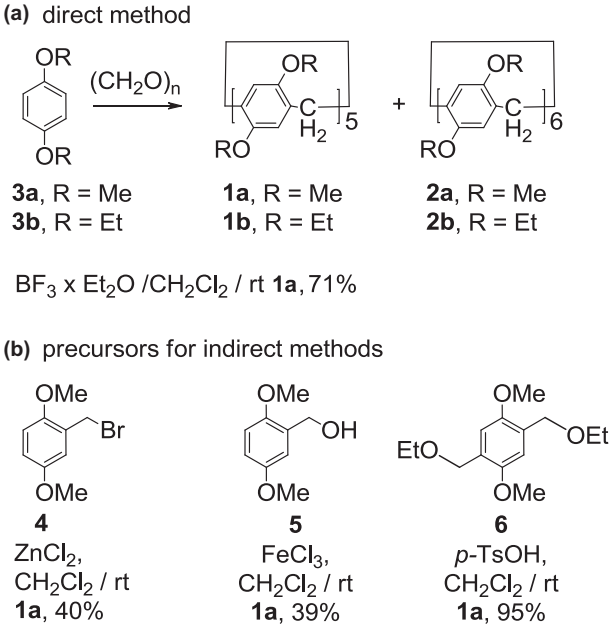
ABSTRACT

A new, very efficient, and selective preparation method of peralkylated pillar[5]arenes is presented. By replacing typical Lewis acids with trifluoroacetic acid (TFA) we were able to eliminate the need of anhydrous conditions without a loss of effectiveness. The method is highly practical: a) it is moisture-insensitive, b) starting from simple and cheap reagents and reactants, and c) allows for chromatography-free isolation of the products. The results indicate that the interactions with solvent molecules can modulate stability of the products and influence the reaction outcome. Dichloromethane (DCM) and dichloroethane (DCE) are complexed within the cyclopentamer cavity with association constants of 120 M^{-1} and 600 M^{-1}, respectively ($CDCl_3$). The interactions involve a combination of hydrogen–pi and halogen–pi bonds.

1. Introduction

Pillar[*n*]arenes are an emerging class of macrocyclic compounds consisting of 1,4-*O*-disubstituted hydroquinone subunits linked by methylene bridges at 2- and 5-positions.[1–3] They can be considered analogs of calixarenes, however, their shape is different. Pillar[5]arenes (e.g., permethylated **1a**, Scheme 1) and pillar[6]arenes (e.g., **2b**), the two known family members, are highly symmetrical tubular-shaped macrocycles. They complement the family of other known tubular building blocks, for example, cucurbiturils or bambusurils. Pillarenes can be easily synthesized from simple starting materials and modified at ethereal positions, that make them promising candidates as new macrocyclic hosts. It is not surprising that, since their first synthesis in 2008 by Ogoshi and Nakamoto,[4] the interest in their applications is growing impressively fast. During this short period of time many groups reported numerous applications including sensing,[5–8] construction of rotaxanes,[9–11] supramolecular polymers,[12–15] switches[16–18] or artificial channels.[19] Therefore, there is a great interest in elaboration of highly practical, and, most importantly, selective, preparation methods of pillar[*n*]arenes. Here we describe a new, highly practical method of selective preparation of pillar[5]arenes in high yield. We also analyze the factors that influence reaction selectivity, including the possible solvent-templation effects.



Scheme 1. Literature methods for synthesis of symmetrical pillar[5]arenes (Ref. 20–22).

The currently known procedures for synthesis of pillar[5]arene **1a** are quite efficient, but they have some minor disadvantages: they either require anhydrous conditions and/or synthesis of precursors.

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They can be divided into two classes: a) direct methods involving condensation of 1,4-dialkoxybenzenes **3** and paraformaldehyde and, b) indirect methods involving more elaborate precursors (Scheme 1). Among the direct methods, the most efficient one is reported by Nakamoto and Ogoshi.[20] It utilizes $BF_3 \cdot Et_2O$ as a catalyst in anhydrous CH_2Cl_2 and allows for formation of permethylated pillar[5]arene **1a** in 71% yield. Application of other Lewis acids gave worse results. The indirect methods involve synthesis of precursors, e.g., 2,5-dialkoxybenzyl bromides **4**, 2,5-dialkoxybenzyl alcohols **5** or 2,5-bis(alkoxymethyl)-1,4-dialkoxybenzenes.[21,22] After the subsequent coupling using various Lewis acids or *p*-toluenesulfonic acid precursors **4**–**6** give cyclic product **1a** in high yields. The indirect methods, although interesting from the methodological point of view, in synthetic practice can not compete with direct methods. The increase of yield does not compensate the effort required for precursors' preparation. In all the reactions the cyclopentamer is the major product. It has been explained by the proper bond angles that make the structure conformationally stress-free (pentagon angle 108° has similar value to the optimal C–C–C bond angle of 109.5°). Preparation of other family members is more difficult, as they are always obtained as a mixture with a considerable amount of pillar[5]arenes. Reasonable yields are possible only when the alkyl substituents of the starting dialkoxybenzene derivatives are bulky.[21,23,24]

2. Results/discussion

2.1. Synthesis

In our search for a facile and reliable method of pillar[*n*]arene synthesis we have applied trifloroacetic acid (TFA) in the reaction between 1,4-dimethoxybenzene **3a** and paraformaldehyde in 1,2-dichloroethane (DCE). TFA is a highly potent acid in organic solvents. Due to its interesting properties, such as low toxicity, solubility in water, and organic solvents, TFA is considered to be a special catalyst for promotion of numerous organic reactions. It is commonly used in some reactions of activated aromatics with aldehydes, for example, pyrrole to produce cyclic calix[4]pyrroles.[25] However, its application in the synthesis of polyphenolic macrocycles is limited.[26,27] In our case, application of TFA in the direct condensation between 1,4-dimethoxybenzene and paraformaldehyde lead to the efficient formation of pillar[5]arene **1a**.

These first results encouraged us to optimize the reaction conditions (Table 1). Firstly, it is important to note, that we used commercially available solvents and TFA, without additional drying. Additional experiments involving intentional addition of water (at 0.05 M concentration, entry 7) showed negligible influence of wet conditions on the reaction yield. Therefore, we claim that our procedure is moisture-insensitive. Application of non-dried solvents to other known procedures involving Lewis acids leads to formation of mainly polymeric products (tests in our laboratory). At 1% (vol/vol) TFA concentration, reaction required 24 h to complete (entry 1), however at higher catalyst concentration 2 h were sufficient to get a high yield of **1a** (entry 6). We have found that the outcome of the reaction is highly dependent on the substrate concentrations. At higher concentrations the yields of cyclopentamer are lower (entries 1, 3, and 4). Although the stoichiometry of the reaction is 1:1, some authors reported a beneficial effect of using considerable excess of paraformaldehyde.[20] In our case, using an excess of paraformaldehyde led to much lower yield with subsequent formation of large amounts of impurities (entry 2). Application of other chlorinated solvents like $CHCl_3$ and CH_2Cl_2 gave **1a** in considerably lower yields (entries 8 and 9). The reaction is not promoted by AcOH, and HCl (entries 10, 11). Application of *p*-TsOH in this direct cyclization leads to formation of **1a**, however, in much lower yield (entry 12). The procedure is universal and allows also for the formation of other peralkylated pillar[5]arenes, e.g., **1b** (entry 13). In conclusion, the best practical method for synthesis of pillar[5]arenes is 0.1 M concentration of both reactants, 5% (vol/vol) concentration of TFA in refluxing DCE (2 h) giving **1a** in 81% yield.

In the current approach we replaced Lewis acids with a Bronsted acid. The only previously reported procedure that involves a Bronsted acid as a catalyst is a cyclization of 2,5-bis(alkoxymethyl)-1,4-dialkoxybenzenes **6** using *p*-TsOH.[22] This *indirect method* gave excellent yield of **1a**, however, *p*-TsOH when applied in a *direct cyclization* gave worse results than TFA (Table 1, entry 11). The same group also tried TFA as a catalyst and did not get any product.[24] As compared with Cao's method we used higher acid concentrations and higher temperature that allowed us to obtain **1a** in high yield. This result suggested that reaction is thermodynamically controlled and therefore requires harsher conditions to equilibrate. Indeed a scrambling experiment involving **1a** and **1b** showed that under the current conditions the reaction is reversible. Since the cyclopentamer is believed to be most thermodynamically stable, it is preferentially formed. However, the reaction is highly solvent-dependent that suggests that the equilibrium can be additionally modulated by external interactions (specific or nonspecific).

Table 1
Synthesis of peralkylated pillarenes

Entry	Solvent	**3**/$(CH_2O)_n$ [M]	Catalyst vol %	Time	Product	Yield %[a]
1	DCE	0.1/0.1	TFA, 1%	24 h	**1a**	69
2	DCE	0.1/0.5	TFA, 1%	24 h	**1a**	28
3	DCE	0.2/0.2	TFA, 1%	24 h	**1a**	28
4	DCE	0.5/0.5	TFA, 1%	24 h	**1a**	17
5	DCE	0.1/0.1	TFA, 5%	24 h	**1a**	73
6	DCE	0.1/0.1	TFA, 5%	2 h	**1a**	81
7	DCE	0.1/0.1	TFA, 5%+0.05 M H_2O	2 h	**1a**	77
8	CH_2Cl_2	0.1/0.1	TFA, 5%	2 h	**1a**	26
9	$CHCl_3$	0.1/0.1	TFA, 5%	2 h	**1a**	15
	TCE[b]	0.1/0.1	TFA, 5%	2 h	**1a**	7
10	DCE	0.1/0.1	AcOH, 5%	2 h	**1a**	0
11	DCE	0.1/0.1	HCl	2 h	**1a**	0
12	DCE	0.1/0.1	*p*-TsOH, 5 equiv	2 h	**1a**	38
13	DCE	0.1/0.1	TFA, 5%	2 h	**1b**	59

[a] Yields are for chromatographically isolated products.
[b] TCE 1,1,2,2-tetrachloroethane.

2.2. Complexation

The crucial dependence of the reaction outcome on the solvent suggests participation of solvent molecules in the reaction equilibrium. We have analyzed the available crystal structures of pillar[5]arenes with chlorinated solvents and found that DCM can be considered a good template for a cyclopentamer formation. At the proper orientation, it has a very good size complementarity and a possibility of forming numerous favorable non-covalent interactions (Fig. 1a). They involve concurrent formation of two CH···π hydrogen bonds and one Cl·π halogen bond, as is manifested in the crystal structure of pillar[5]arene ⊃ $(DCM)_2$.[6] We have found that these interactions are also present in solution. In $CDCl_3$, the DCM signal is upfield shifted in the presence of **1a** in agreement with complexation inside the aromatic cavity. Complexation of DCM by **1a** is fast on the NMR timescale (298 K, 400 MHz). Titration experiment gave an association constant K_a(DCM)=120 M^{-1} and the complexation induced chemical shift for DCM of −0.24 ppm (Supplementary data). For **1b**, bearing larger substituents, complexation is slow on the NMR timescale and two sets of signals are obtained (for complexed and free species, Fig. 2). Considering the chemical similarity of the solvent ($CDCl_3$) and the guest (DCM) such selectivity is striking and can only be explained