Scope of the Direct Trimerization to C_3-Symmetric Cyclotribenzylene Derivatives

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Abstract:

The scope of the trimerization reaction of 3-substituted benzyl alcohols was explored. Several C_3-symmetric cyclotribenzylene derivatives were obtained in preparative useful yields in one step and applied to the short synthesis (one or two steps) of two CTB derivatives, so far only accessible in six or seven linear steps.

Keywords: cyclotribenzylene, cyclotrimerisation, cyclotriveratrylene,

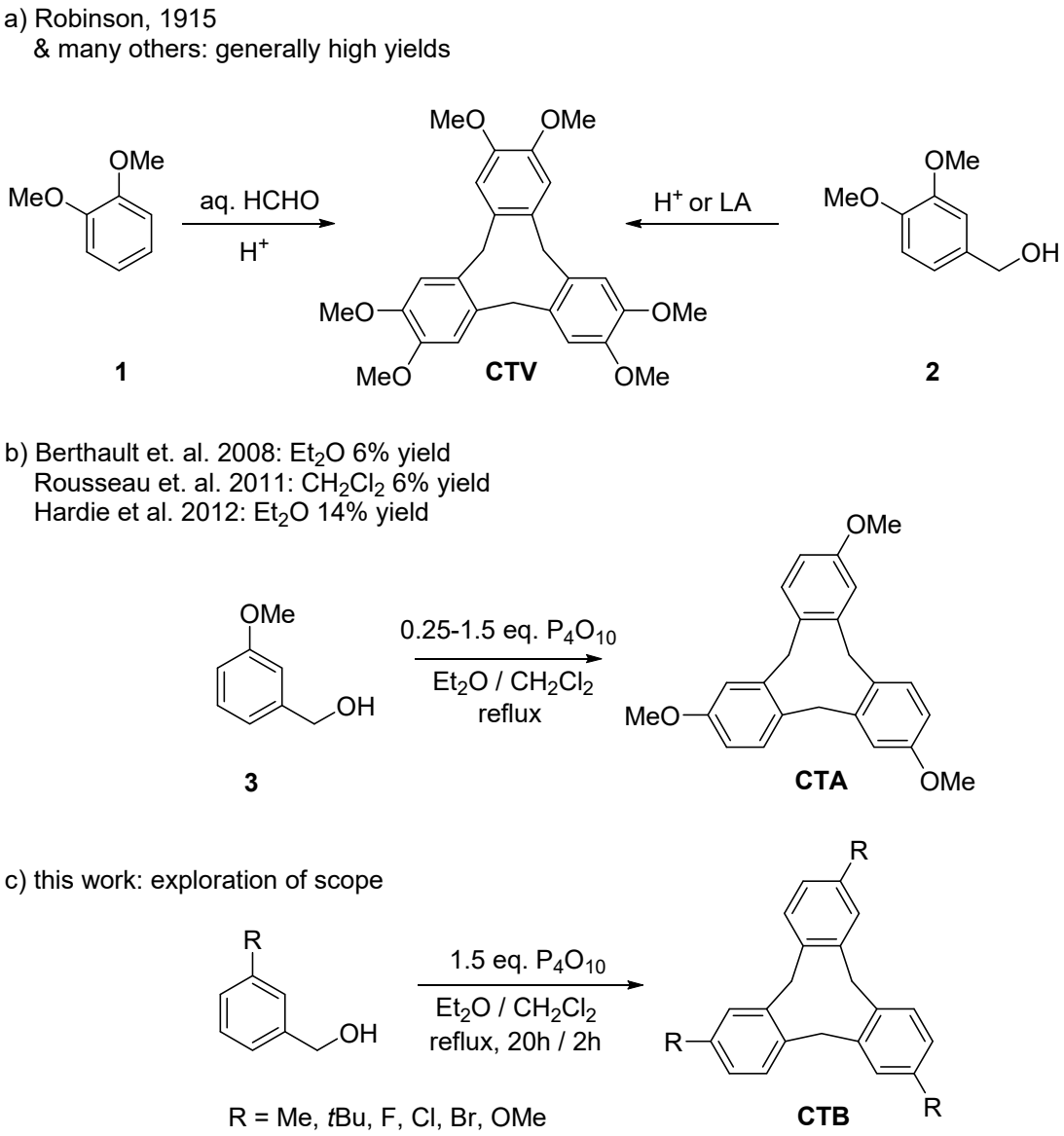
Introduction

Macrocyclic, shape persistent molecules constitute a cornerstone in supramolecular chemistry (1-5). They function as host structures themselves, or after suitable derivatization, for a variety of applications, ranging from molecular recognition/sensing, to catalysis, or even medicinal applications (6-13).

Cyclotribenzylenes (CTB, Scheme 1c) represent one family of such macrocycles. These molecules contain a nine-membered ring with three ortho-disubstituted and methylene bridged benzene units. The most easily accessible compound of this class is cyclotriveratrylene (CTV, Scheme 1a), first synthesized but wrongly assigned in 1915

(14). This hexasubstituted derivative can be obtained in high yields starting from veratrole **1** and formaldehyde or veratryl alcohol **2** in combination with either Lewis- or Brønsted acids in a one-step trimerization (Scheme 1a) (15-19).

However, access to trisubstituted CTBs is less facile. Due to our interest for catalytic applications of self-assembled molecular capsules (20), we became interested in C_3-symmetric trisubstituted CTBs. The direct synthesis of the methoxy-substituted cyclotrianisylene (CTA, Scheme 1b) caught our attention. Three procedures for the cyclization of **3** are known (21-23), and all rely on the use of phosphorus(V) oxide (P_4O_{10}) as reagent. Although the yields are quite moderate (6-14%), these procedures allow the shortest access to valuable trimethoxy-substituted C_3-symmetric cyclotribenzylenes. We decided to explore the scope of these procedures that so far, to our knowledge, has not been reported. Such a one-step route would provide a direct excess to valuable trisubstituted C_3-symmetric cyclotribenzylenes that are, if reported at all, only accessible via long synthetic sequences.



Scheme 1. Overview about synthetic approaches to selected cyclotribenzylenes. a) First reported access to Cyclotriveratrylene (CTV); b) previously reported conditions to access the CTB-derivative cyclotrianisylene (CTA); c) exploration of the scope, reported in this work.

Results and Discussion

Exploration of the scope

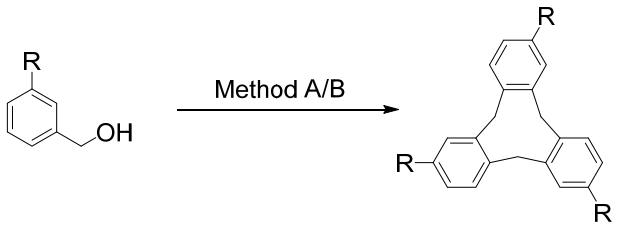
In our hands, the following two reaction conditions gave the highest yields. Method A involves 1.5 eq. of P_4O_{10}, addition via syringe pump over 5h and reflux for 20h in diethyl

ether (0.4 M). For method B, dichloromethane is utilized as solvent and the reaction time is reduced to 2h under otherwise identical conditions. These conditions are slight modifications of the reported procedures for the synthesis of CTA (21-23) and produce comparable yields of CTA (Table 1, entry 8). We next explored the conversion of other activating substituents as we expected them to be most promising for the electrophilic aromatic substitution reaction. Indeed, 3-methylbenzyl alcohol produced CTB-Me **4** in useful 8% yield (Method A, 2%, Method B, entry 1). Even higher yields (15%, Method A) were obtained with 3-*tert*-butylbenzyl alcohol as substrate (entry 2). Removal of the activating group (R = H), led to decomposition and only traces of the CTB **6** were detected (entry 3). As side products, open oligomeric species as well as the cyclic dimer were observed. More interestingly, halogenated benzyl alcohols were suitable substrates for the trimerization reaction. The fluoro- and the chloro-CTBs **7** and **8** were obtained in 5% and 4% yields, respectively (Method B, entries 4-5). Even better yields were obtained for the synthetically more useful CTB-Br **9** (8%, Method B, entry 6). The attempted isolation of the iodo-derivative **10** failed, due to its instability towards light and column chromatography conditions. Unfortunately, isolation via different precipitation procedures also did not lead to success. Nevertheless, the isolated bromo-derivate **9** should be a synthetically equivalent building block. Since CTB-Br **9** was also used on a preparative scale (see below), this reaction was scaled up (4 g scale), yielding 4% of the product. Subsequently, also the unprotected phenol (R = OH) and aniline (R = NH2) were tested. Unsurprisingly, no product was observed. Interestingly, also the protected aniline derivatives (acetamide and phtalimide) failed to deliver product; only starting material was recovered.

A general trend is observable: for activated benzyl alcohols, method A usually gives higher yields, for halogenated benzyl alcohols, method B seems to be the method of

choice.

Table 1: Scope of the cyclotrimerisation.



Entry	Substrate	Product	Yield Method A[a]	Yield Method B[b]
1	(R = Me)	**4**	8%	2%
2	(R = tBu)	**5**	15%	2%
3	(R = H)	**6a**	<1%	---
4	(R = F)	**7**	4%	5%
5	(R = Cl)	**8**	2%	4%
6	(R = Br)	**9**	5%	8% (4%)[c]
7	(R = I)	**10**	<1%	<1%
8	(R = OMe)	**11**	9%	4%
9	(R = OH)	**12**	---	---
10	(R = NH2)	**13**	---	---
11	(R = NHAc)	**14**	---	---
12	(R = NHPhtal)	**15**	---	---

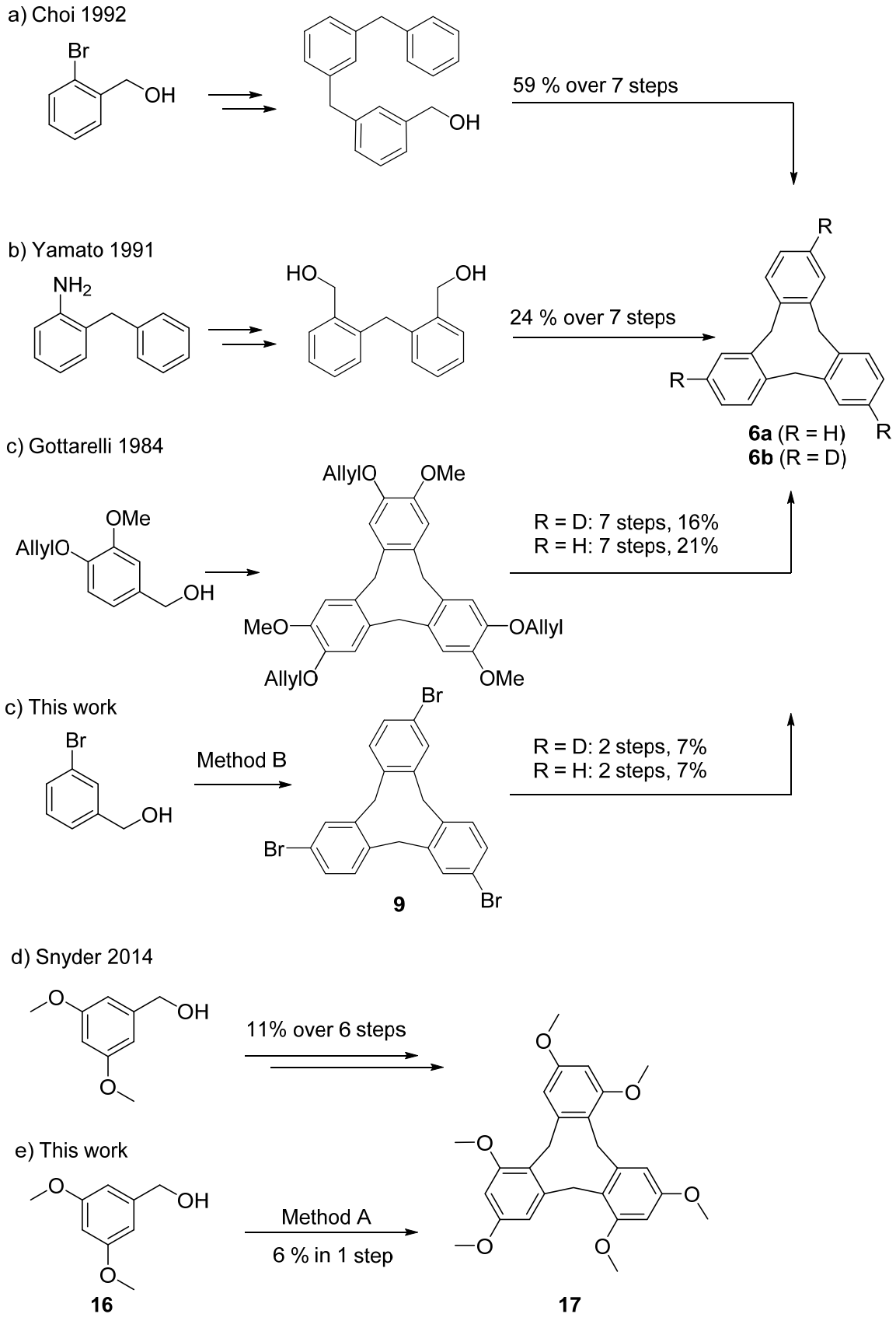
[a] addition of alcohol over 5 h, 1.5 eq. P_4O_{10}, 0.4M , Et_2O, reflux, 20 h, [b] addition of alcohol via syringe over 5 min, 1.5 eq. P_4O_{10}, 0.4M, CH_2Cl_2, reflux, 2 h, [c] yield on preparative scale (4 g starting material).

Application to the short synthesis of known CTB-derivatives

After the scope of the reaction was established, we decided to apply this methodology to the synthesis of CTB-derivatives that are only accessible via long synthetic routes (six to seven linear steps) so far. As a first target we identified the unsubstituted CTB **6a** (R=H). Although three independent routes are available, all require seven steps (Scheme 2a-c) (24-26).

In one case access to the deutero-derivative **6b** (R = D) was also achieved in seven steps

(25). Since the direct trimerization to produce **6a** was unsuccessful (Table 1, entry 3), we decided to use CTB-Br **9**, which was defunctionalized via *n*-butyllithium and subsequently quenched with methanol or methanol-d4 to produce the target **6a** and **6b** in 86% and 83% yield, respectively. This two step route produced **6a/b** in 7% yield over two steps from commercially available 3-bromobenzyl alcohol. Although the yield reported for the two literature routes is higher, the brevity of the developed synthetic route makes it attractive since less effort and time is required to access the material. In contrast to the alternative sequences, CTB can be obtained in one single day since the steps involve rather short reaction times. The second application involved the synthesis of the C_3-symmetric hexamethoxy substituted CTB **17**, originally synthesized in 14% yield over six steps (27). Interestingly, the authors reported that a direct cyclization of **16** failed. Although no specific conditions were reported, the reference to CTV syntheses indicated that Brønsted-acidic conditions were explored. We found that method B directly delivered the desired trimer **17** in 6% yield in one single step, highlighting the synthetic potential of the two reaction conditions explored in this work.



Scheme 2: Application of the method to the synthesis of CTBs 6a/b and 17 and

comparison with previous synthetic routes. a-c) Literature routes to 6a/b. d) This work: Access to 6a/b in two steps. e) Literature synthesis of 17. f) This work: Access to 18 in one step.

Conclusion

It was demonstrated that a variety of meta-substituted benzyl alcohols can be directly converted to C_3-symmetric trisubstituted CTBs. This one-step synthesis allows fast access to valuable bowl-shaped molecules and, therefore, facilitates their use as molecular scaffolds. The advantages of these protocols was demonstrated by the short syntheses of two literature-known CTB derivatives, which previously required six to seven synthetic steps.

Acknowledgement

Disclosure statement

No potential conflict of interest was reported by the authors.

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