J Incl Phenom Macrocycl Chem (2009) 63:379–382
DOI 10.1007/s10847-008-9520-7

Microwave assisted synthesis of Thiacalix[*n*]arenes

Mitesh H. Patel · Pranav S. Shrivastav

Received: 4 October 2008 / Accepted: 14 November 2008 / Published online: 29 November 2008

Abstract As a part of our ongoing investigations to unfold the chemistry of thiacalixarenes, this communication presents microwave assisted synthesis of thiacalix[*n*]arene macrocycles. This methodology entails combination of conventional heating and microwave irradiation to synthesize the entire series of thiacalix[*n*]arene analogs ($n = 4, 5, 6, 7$ and 8) with optimal yields and reaction time. LC-MS was used to monitor the progress/outcome of such reactions.

Keywords Microwave · Thiacalixarenes · LC-MS · TC7A · Oligomers

Introduction

Thiacalixarenes, the sulfur reminiscent of classical (methylene bridged) calixarenes have invoked large interest recently, partly due to their considerably different properties as compared to their calixarene analogs and greater complexing abilities [1, 2]. As has been pointed out in our recent publications [3, 4], though there has been significant amount of work carried out for their derivatization, little efforts have been directed to explore their basic chemistry, in particular, regarding mechanism and alternative pathways for synthesis.

Dedicated to our dear colleague late Kejal P. Jayswal on the 2nd anniversary of his departure.

M. H. Patel · P. S. Shrivastav (✉)
Chemistry Department, School of Sciences, Gujarat University, Ahmedabad 380009, India
e-mail: pranav_shrivastav@yahoo.com

M. H. Patel
e-mail: mitesh9@gmail.com

In one of our earlier reports, we had investigated the standard thiacalixarene synthesis protocol [5] with diverse variation of reaction parameters (solvent, temperature, catalyst, template, substituted phenols, reaction time, heating rate, etc.) and summarized our observations as a reaction mechanism [4]. In the same article, we reported our failure for direct synthesis of TC*n*A macrocycles through microwave assisted technique, and envisaged the possibility that the microwave assisted heating may help during the cyclization step. Herein we report the successful manifestation of thiacalixarene macrocycles using traditional-microwave combined approach.

Results and discussions

Initially, all attempts to synthesize TC*n*A macrocycles using microwave assisted heating were unsuccessful, yielding phenol-dimer (mono-sulfide) as the only product [4]. Our interpretation of these results was—"microwave heating assists in sulfurization process, yet limits polymerization (or oligomerization), which in turn is essential for calix-formation." The point taken was, that, if the reaction can be carried out up to halfway (acyclic tetramer), the cyclization can be achieved via microwave synthesis with very high efficiency.

Also, in above mentioned study of the reaction mechanism of thiacalixarene synthesis, we were able to determine the quantitative component distribution of individual products (through LC-MS analysis). Thus, it was rendered possible to stop the reaction when the abundance of any particular intermediate (acyclic tetramer in this case) would be highest. In practice, we started the reaction with conventional heating and followed the established temperature

profile until the mole fraction of the acyclic tetramer reached its maximum. The heating was stopped and the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was then exposed to microwave irradiation, and as anticipated, within short time, the reaction was complete with very good yields of TC4A accompanied by TC5A, TC6A, TC8A and even TC7A, as identified by LC-MS analysis (Fig. 1).

Encouraged by positive results, we applied the microwave assisted synthetic technique to cyclize previously prepared acyclic sulfur-bridged oligophenols in hope of preparing higher macrocycles. The acyclic oligomers were prepared by previously reported procedure [6, 7] and subjected to microwave irradiation (as standard stoichiometric reaction mixtures). Noteworthy success was achieved in such experiments, especially, the illusive heptamer (TC7A) was achieved in isolable amount, enough for characterization (characterization of TC7A: IR (KBr) ν (cm^{-1}) 3364 (O–H), 2956 (C–H), 1444 (C–C), 693 (C–S), ^{1}H NMR(400 MHz, $CDCl_3$, 25 °C, TMS): δ8.62 (s, 7H; Ar–OH), 7.56 (s, 14H; Ar–H), 1.21 (s, 63H; *t*-Bu); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ31.3, 34.2 (*t*-Bu), 120.4, 134.7, 144.4, 154.9 (Ar); ESI MS: Calcd. 1260, Found: 1260; Elemental analysis for $C_{70}H_{84}O_7S_7$: Calcd: C 66.63, H 6.71; Found: C 66.56, H 6.79).

Table 1 lists results of synthetic exercises performed employing the above cited approach. Experiments were conducted following two procedures (described as method A and method B in the experimental section). Important outcomes may be listed as (1) prominent increase in yields for TC4A (2) synthetically useful yields of higher TC*n*As in almost all cases, namely, TC5A (7%), TC6A (12%), TC8A (13%) and most importantly, TC7A (12%). With some more vigorous efforts, the procedures can be refined to obtain even higher yields of these cyclic oligomers. Eventually, this is the first report on the synthesis and characterization of thiacalix [7]arene or TC7A.

The success of microwave irradiation in the cyclization step reveals some interesting facts that deserve a brief mention here. First and foremost, it confers to the assertion that thiacalixarenes are thermodynamically (and not kinetically) stable products. That is, the products achieved at the end of any thiacalixarene synthesis exercise depends upon the temperature and period of heating, not the kinetic stability of the intermediates/products. Unlike kinetically stable products (e.g., calixresorcinarenes), in case of thiacalixarenes, prolonged heating causes the products to degrade into lower homologs. In present case, the cyclization is accomplished in a brief period (ca. 10 min), and hence, the cyclized products do not get enough time and/or heating to undergo degradation, as compared to traditional approach. This is the main reason why higher TC*n*As are achieved in such good yields in present case. Essentially, what microwave heating does is, it freezes the reaction by cyclizing all the intermediate poly-phenolsulfide chains (capable of cyclizing). It is not surprising then, that, if we manage to produce long poly-phenolsulfide chains (perhaps in situ), and by some mechanism (via templation by large guests or templates) facilitate their pre-organization in a state favorable for cyclization, much larger TC*n*A derivatives can also be prepared via microwave irradiation. However, this is impossible in traditional heating approach, because (a) the chain degrades before cyclization is accomplished or (b) the cyclized product itself degrades into thermodynamically more stable products.

Table 1 % Yields of various TC*n*As from microwave assisted reaction methods A and B in presence of different base/template

Base/template	TC4A		TC5A		TC6A		TC7A		TC8A	
	A	B	A	B	A	B	A	B	A	B
NaOH	84	80	1	3	3	3	4	6	2	2
KOH	23	18	3	7	2	2	8	7	2	3
CsOH	11	5	3	6	8	12	7	12	10	13

Experimental

All the reagents used were of AR grade, procured from Sigma-Aldrich. The reagents were used without further purification. The solvents were dried appropriately wherever required. Microwave assisted synthesis were carried out on Biotage Advancer from Biotage AB, Sweden, having operating temperature range from 60 to 250 °C; power and pressure range from 0 to 1,200 W and 1–20 bar,

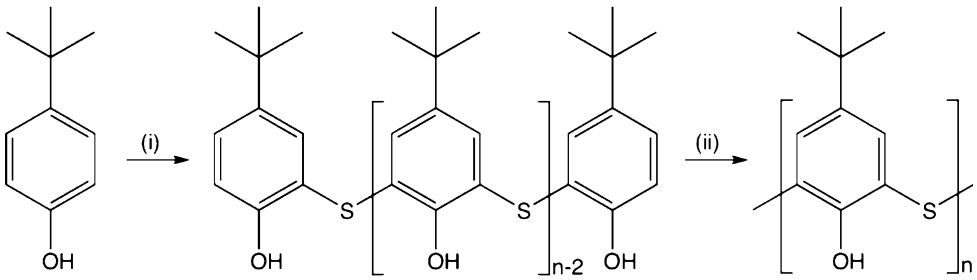

Fig. 1 Schematic representation of synthetic route for thiacalix[*n*]arenes ($n = 4$–8). Reaction conditions: S_8, NaOH, *p-tert*-butylphenol in Ph_2O with (i) traditional heating up to 230 °C (ii) microwave irradiation

respectively. During the entire study, the power (o/p) and pressure settings were kept constant, 600 W and 10 bar, respectively.

Melting points were taken in a single capillary tube using Toshniwal melting point apparatus and are uncorrected. Elemental analysis was carried out on Heraeus Carlo Erba 1108 elemental analyzer. ^{1}H NMR spectra were recorded on Bruker DPX-400 AVANCE in DMSO-d6 with tetramethylsilane as internal standard. Liquid chromatography was conducted on Perkin Elmer 200 Series Liquid Chromatograph with Thermo Electron Betasil C-18 reversed phase column (3 μm particle size, 100 mm long and 3.0 mm internal diameter) maintained at 45 °C, mobile phase composition was methanol: 0.01% acetic acid (90:10 v/v). Mass measurements were done on Thermo Finnigan TQS Quantum Discovery Mass Spectrometer using electrospray ionization. Solid phase extraction (SPE) was performed on Oasis HLB cartridges procured from Waters Corporation, Milford, Massachusetts, USA.

Method A: optimized procedure for microwave assisted synthesis of TC*n*As (from *p-tert*-butylphenol)

A mixture of *p-tert*-butylphenol (6.5 g, 0.05 mol), elemental sulfur S_8 (1.4 g, 0.05 mol), and NaOH (0.9 g, 0.02 mol) in super-dry diphenylether (50 mL) was stirred for 15 min, heated gradually to 160 °C over a period of 1 h and kept at this temperature for further 3 h. Subsequently, the temperature of the reaction mixture was brought down to 80 °C and additional sulfur (1.4 g, 0.05 mol) was added carefully. The temperature was raised to 230 °C over a period of 3 h. The reaction was continuously monitored by online LC-MS analysis of reaction mixture. The resulting dark brown reaction mixture was cooled to ambient temperature and subjected to microwave irradiation for 10 cycles, each comprising 30 s irradiation followed by 30 s rest (during which sampling was accomplished).

Method B: optimized procedure for microwave assisted synthesis of TC*n*As (from *p-tert*-butylphenol-sulfur oligomers)

A solution of *p-tert*-butylphenol (30 g, 0.2 mol), CaO (2.8 g, 0.05 mol), and sulfur S_8 (9.6 g, 0.3 mol) in the mixed solvent consisting of diphenylether and ethylene glycol was stirred at high temperatures (60–200 °C) for 6 h. After completion of reaction, precipitation with acetic acid afforded the oligomer poly-*p-tert*-butylphenolsulfide (16.2 g, ca. 50% yield) as off-white powder. The oligomer was dispersed in diphenyl ether along with NaOH (2 g, 0.05 mol) and S_8 (2 g, 0.06 mol). Further, the reaction mixture was stirred vigorously for 10 min and subjected to microwave irradiation for 10 cycles, each comprising 30 s irradiation followed by 30 s rest.

To monitor the buildup of cyclic oligomers (TC*n*As) with proportionate decrease in their acyclic counterparts, LC-MS analysis was carried out. 1 mL of reaction mixture was sampled after every 30 s, loaded on solid phase extraction cartridge and washed with acetonitrile (1 mL × 3) to selectively retain TC*n*As. The products were then eluted with methanol (1 mL × 5) and 50 μL of the eluate was injected for quantitative analysis of products. The identity of the products (TC*n*As) was confirmed by M.P., ^{1}H NMR, Elemental analysis and MS. (A more detailed description of the LC-MS assisted reaction monitoring approach has been provided in the electronic supplementary information of reference 3, and hence not repeated here.)

Conclusion

A new approach, namely, traditional-microwave combined synthesis, for preparation of thiacalixarenes has been developed and successfully manifested for synthesis of various TC*n*As. This could well be the entry point for thiacalixarene chemistry to the fascinating field of microwave assisted synthesis. Also, the much awaited member of thiacalixarene family, TC7A has been synthesized and characterized, as well as yield of other cyclo-oligomers have been improved. The whole exercise has been accomplished by LC-MS analysis, and is very good example of reaction monitoring with such sensitive analytical technique, providing the experimentalist a close scrutiny of the progress of the reaction.

Acknowledgments One of the authors (Mitesh Patel) wishes to acknowledge the financial assistance provided by the University Grant Commission (UGC, New Delhi, India) through a senior research fellowship (SRF).

References

1. For recent reviews on thiacalixarenes see: Morohashi, N., Narumi, F., Iki, N., Hattori, T., Miyano, S.: Thiacalixarenes. Chem. Rev. **106**, 5291–5306 (2006). doi:10.1021/cr050565j
2. For recent reviews on thiacalixarenes see: Lhotak, P.: Chemistry of thiacalixarenes. Eur. J. Org. Chem. 1675–1692 (2004). doi:10.1002/ejoc.200300492
3. Patel, M.H., Patel, V.B., Shrivastav, P.S.: Design, synthesis, characterization, and preliminary complexation studies of chromogenic vanadophiles: 1, 3-alternatethiacalix[4]arene tetrahydroxamic acids. Tetrahedron. **64**, 2057–2062 (2008). doi:10.1016/j.tet.2007.12.048
4. Patel, M.H., Patel, V.B., Shrivastav, P.S.: Genesis of thiacalixarenes: a one-pot highly efficient synthesis of TC4A. Tetrahedron Lett. **49**, 3087–3091 (2008). doi:10.1016/j.tetlet.2008.03.052

5. Kumagai, H., Hasegawa, M., Miyanari, S., Sugawa, Y., Sato, Y., Hori, T., Ueda, S., Kamiyama, H., Miyano, S.: Facile synthesis of p-tert-butylthiacalix[4]arene by the reaction of p-tert-butylphenol with elemental sulfur in the presence of a base. Tetrahedron Lett. **38**, 3971–3972 (1997). doi:10.1016/S0040-4039(97)00792-2
6. Kondo, Y., Endo, K., Iki, N., Miyano, S., Hamada, F.: Synthesis and crystal structure of p-tert-butylthiacalix[8]arene: a new member of thiacalixarenes. J. Incl. Phenom. Macrocycl. Chem. **52**, 45–49 (2005). doi:10.1007/s10847-004-2384-6
7. Kondo, Y., Hamada, F.: Improvement method for synthesis of p-tert-butylthiacalix[n]arenes: effect of using base catalyst with carboxylic acid. J. Incl. Phenom. Macrocycl. Chem. **58**, 123–126 (2007). doi:10.1007/s10847-006-9133-y