One-Pot Synthesis of Tweezer-Like Calix[4]**resorcinarene Decorated with Pendant Heterocyclic Moieties: An Efficient and Recyclable Heterogeneous PTC for the Preparation of Azidohydrins in Water**

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Abstract Direct incorporation of ionic liquid onto the upper rim of calix[4]resorcinarene led to the formation of tweezer-like calix[4]resorcinarene via one-pot strategy. The formation of this cationic supramolecular structure was confirmed by ¹H NMR, ¹³C NMR, CHNS, TGA and DTA techniques. The hydrophobic central cavity and hydrophilic cationic arms render it a suitable heterogeneous phase transfer catalyst for the preparation of valuable azidohydrins in water. The recovered catalyst could be used for several times without any significant loss of activity.

Keywords Dicationic calix[4]resorcinarene · Tweezerlike · Heterogeneous phase transfer catalyst · Azidohydrins · Eco-benign strategy

1 Introduction

Nowadays, heterogeneous phase-transfer catalysis (PTC) appears to be a prime synthetic tool, being appreciated not only in various fields of organic chemistry but also among widespread industrial applications. In this context, the utilization of supramolecular PTC has become an area of tremendous importance and a significant amount of research has been carried out in this direction [1–4].

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A. Mouradzadegun (⊠) · S. Elahi · F. Abadast Department of Chemistry, Faculty of Science, Shahid Chamran University, Ahvaz, Iran e-mail: arash m@scu.ac.ir Resorcinarene, commonly referred to as one of the pillars in supramolecular chemistry, is well-known tetrameric macrocyclic octols that possess a bowl-shaped molecular cavity formed by four resorcinol units. The possibility of modifying this structure either via substitutions on the aromatic ring, the phenol hydroxyl groups, or the lower rim increases its potential for forming multifunctional compounds. Acylation and alkylation of hydroxyl group in upper rim were usually used for the synthesis of neutral, positively and negatively charged supramolecular structures [5].

The cationic heterocyclic moiety is one of the valuable headgroups that can be used in the synthesis of cationic supramolecular structures. In recent years, the positively charged imidazolium groups have been incorporated onto various molecular frameworks such as calixarene, cavitand based on resorcinarene and in lower rim of calix[4]resorcinarene. However, functionalization of these molecular frameworks has several drawbacks such as stepwise procedures, long reaction times, require tedious HPLC and large amounts of toxic organic solvents or reverse phase separations [6–8]. Moreover, numbers of these supramolecular imidazolium salts are expensive, non-recyclable and susceptible to moisture, which render them unsuitable for using in some of the reaction conditions. Hence, the exploration of newer and greener method for the synthesis of such structures with improved properties is still desirable in synthetic organic chemistry.

One-pot synthesis is a strategy to improve the chemical reaction efficiency whereby a reactant is sequentially subjected to reactions in just one reactor. To our best knowledge, there is no report on the functionalization of calix[4]resorcinarene via one-pot method.

Considering the above-mentioned points and in light of our success in the development of simple and environmentally friendly experimental procedure for the synthesis of significant compounds [9–12], in this work we propose, for the first time, functionalization of calix[4]resorcinarene via one-pot strategy for the synthesis of novel tweezer-like dicationic calix[4]resorcinarene containing two pendant imidazolium salt that might act as heterogeneous PTC.

2 Experimental

2.1 General

Chemicals were purchased from Fluka, Merck and Aldrich chemical companies and used without further purification. Products were characterized by physical data, IR, ¹H and ¹³C NMR. IR spectra were obtained on a Bomen MB:102 FT-IR spectrophotometer. ¹H and ¹³C NMR spectra were recorded on a Brucker spectrometer at 400 and 100 MHz, respectively, in CDCl₃ or DMSO. Elemental analysis was performed at Thermo Finnigan Flash EA 1112 CHNS-Analyzer and thermal stability of the catalyst was investigated by NETZSCH STA 409 PC/PG.

2.2 Synthesis of Tweezer-Like Dicationic Calix[4]resorcinarene (2)

The mixture of 12 mmol (3-chloropropyl)trimethoxysilane and 12 mmol of 1-methylimidazole (freshly distilled) was refluxed at 95 °C for 24 h under nitrogen atmosphere. The reaction mixture was cooled down and 1-methyl-3-(trimethylsilylpropyl) imidazolium chloride ([pmim]Cl) (slightly yellow viscous oil) was obtained with 98 % yield [13]. Then, 0.5 g (1 mmol) of calix[4]resorcinarene in 10 mL of toluene was added to 1.5 g (6 mmol) of [pmim]Cl. After heating the slurry at 90 °C for 24 h the solid was isolated by filtration. Owing to the solubility of unreacted calix[4]resorcinarene in ethanol and ([pmim]Cl) in water, the resulting solid was washed several times with ethanol and distilled water to remove unreacted materials. Then, the solid was dried under high vacuum to give violet powder with 89 % yield.

2.3 Synthesis of Azidohydrin Derivatives in the Presence of Novel Phase Transfer Catalyst (2)

NaN₃ (2 mmol) was added to a mixture of epoxide (1 mmol) and dicationic calix[4]resorcinarene (0.03 g) in water (1.5 mL). The suspension was magnetically stirred at 70 °C for the lengths of time shown in Table 1. After completion of the reaction as judged by TLC (using *n*-hexane/ethyl acetate (4:2) as eluent), the catalyst was

removed by filtration. The products were obtained upon extraction with ethyl acetate (3×5 mL). The extract was dried over CaCl₂, and then solvent was evaporated under high vacuum to give the azidohydrins.

The recovered catalyst was washed with water, ethanol and ethyl acetate, respectively. Then was dried under vacuum and reused for the next reaction.

3 Results and Discussions

Initially, [pmim]Cl was prepared according to literature procedure, starting from 3-chloro trimethoxysilane and methyl imidazole [13] (Scheme 1). Then, calix[4]resorcinarene (1) was added to the same pot to form functionalized calix[4]resorcinarene containing ionic liquid (IL) arms. To remove unreacted calix[4]resorcinarene and ([pmim]Cl), the resulting solid was washed several times with ethanol and distilled water. The formation of functionalized calix[4]resorcinarene was confirmed by ¹H NMR and ¹³C NMR spectra (see Supplementary Data).

Along with the usual calix[4]resorcinarene peaks, ¹H NMR spectrum of the product displayed the characteristic peaks of the imidazolium protons, indicating successful incorporation of the IL onto calix[4]resorcinarene. Inspection of the integral ratio of calix[4]resorcinarene and imidazolium peaks clearly show that two imidazolium salts built onto calix[4]resorcinarene skeleton which could be exist at 1,2- or 1,3-position. Since an increase in the amount of IL did not improve the number of cationic groups, it can be concluded that the steric effect play a critical role in the position of the cationic groups. This finding further supports this assumption that the cationic groups are at 1,3-position (Scheme 1) (the detailed characterization study is available in Supplementary Materials).

It is worth noting that, the broadened signals in ¹H NMR of **2** testify to the existing equilibrium between the crown, chair and diamond conformers of **2**, which is completely adapted with the previously reported data for functionalized calix[4]resorcinarene [14–17] (more details are available in Supplementary Materials).

To shed more light on the purity of product, elemental analysis was performed (Calcd for $C_{46}H_{58}N_4 O_{12} Si_2Cl_2$: C, 56.02; H, 5.92; N, 5.68 %. Found: C, 55.99; H, 5.94; N, 5.71). This result gave us confidence that, the product to be pure enough and calix[4]resorcinarene bearing two IL arms have been successfully prepared. This coincides well with the integrals of each proton in the ¹H NMR spectrum of this compound.

Thermal stability of compound (2) was investigated by thermal gravimetric analysis (Fig. 1) at a heating rate of 10 °C per min under nitrogen atmosphere. Compound (2)shows three distinct steps of weight loss in the combined



Scheme 1 Synthesis of novel tweezer-like dicationic calix[4]resorcinarene



	$R \xrightarrow{O} + NaN_3 \xrightarrow{Cat. 0.03 \text{ g}}_{water / 70°C} R \xrightarrow{OH} N_3 + \frac{N_3}{R} \xrightarrow{OH} OH$					
Entry	Substrate	Product	Time (min)	Yield (%)		
1	0	ОН	10	89		
2		OH N3	25	91		
3	PhOH ₂ C	OH PhOH ₂ C	50	73		
4	\sim	OH N ₃	15	87		
5	\sim	OH N ₃	75	78		
6	o	_	360	0		

OH

Table 1 Reaction of various epoxides with sodium azide in the presence of the representative catalyst in water

TGA/DTG curves. The initial slight weight loss occurs before 150 °C, which can be attributed to the evaporation of hydrated water or residual solvent. The compound (2) then displayed a stage decomposition caused by the loss of the IL arms at about 350 °C followed by degradation of the calix[4]resorcinarene backbone. Therefore, compound (2) demonstrated high thermal stability, with decomposition starting at around 350 °C.

The thermally stability of this compound allows heat demanding chemical transformations along its backbone and side chains without leaching of the active species in the reaction media. Moreover, tweezer-like calix[4]resorcinarene is effectively insoluble in water, thereby providing an excellent heterogeneous catalyst for conducting chemical transformations in water.

In light of the aforementioned points and considering this assumption that the cavity of this novel dicationic calix[4]resorcinarene can act as a host for wide variety of compounds, we became interested to evaluate the ability of this novel water-sustainable supramolecular imidazolium salts as PTC in nucleophilic substitution reaction in water.

Importance of azidohydrins as precursors in the synthesis of vicinal amino alcohols, carbohydrates, nucleosides, lactames and oxazolines [18–20], encouraged us to survey the reaction of epoxides with sodium azide for the synthesis of these valuable compounds in water.

To develop suitable reaction conditions, 2,3-epoxypropyl methacrylate was chosen as a model compound and parameters including temperature, molar ratio of the reagent/substrate and amount of catalyst were examined in detail. After some experiments, it was found that the use of 2 equivalent of NaN₃ per epoxide in the presence of the catalyst 2 (0.03 g) at 70 °C were the best conditions.

The success of the first set of experiments using dicationic calix[4]resorcinarene as PTC promoted us to increase the scope and generality of the present reaction to other epoxides (entries 1-5, Table 1).

The reactions of all epoxides with sodium azide were found to be highly regioselective and only one isomer (I) was obtained (entries 1-5, Table 1). It is noteworthy that no evidence for the formation of diol as by-product was observed. Hence, all products were obtained in pure form without further purification. The structure of products were established unambiguously from spectroscopic (IR, ¹H NMR, ¹³C NMR) data and by direct comparison with authentic samples [10, 21].

The formation of these products (entries 1-5, Table 1) by this methodology are of considerable interest since this is the first attempt to the synthesis of these privileged compounds in the presence of cationic supramolecular structure as an efficient heterogeneous PTC.

 Table 2
 Comparison of

 azidolysis of model compound
 with different catalysts in water

Entry	Catalyst	Catalyst (g)	Reagent/ substrate (mmol)	Temp	Time (h)	Yield (%)
1	(2)	0.03	2	70	0.25	91
2	3D-Network porous polymer based on calix[4]resorcinarenes [10]	0.1	3	80	1.40	84
3	Dowex-PEG ₃₀₀ [21]	0.1	1.2	Reflux	1.5	90
4	SiO ₂ -PEG [22]	0.1	3	Reflux	2	90
5	Poly[<i>N</i> -(2-aminoethyl)acrylamido]-trimethyl ammonium iodide [23]	0.2	5	RT	12	95



Fig. 2 Proposed catalytic mechanism

The promoting effect of catalyst was definitely confirmed by the reaction of model compound with sodium azide, without adding catalyst or in the presence of the initial calix[4]resorcinarene under optimized reaction conditions. TLC analysis of the reaction mixture did not show completion of the reaction after 8 h [10].

In order to show the merit of this novel catalyst, Table 2 compares our results obtained from the model reaction in the presence of 2 with the same results reported in literature. To our delight, heterogeneous catalyst 2 exhibited significantly higher catalytic activity in terms of the reaction time and amount of catalyst (entry 1, Table 2).

The catalytic activity of water-sustainable supramolecular imidazolium salts (2) could be attributed to the synergetic effect of its hydrophobic cavity and hydrophilic arms. In water, the hydrophobic cavity of 2 could act as microvessel and accommodate nonpolar epoxide derivatives based on hydrophobic interaction. Meanwhile, the hydrogen bonding of the epoxide oxygen to the outer OH of the catalyst could promote the formation of this inclusion complex. The hydrogen bonding could also activate the epoxide and accelerate the nucleophilic substitution reaction. Moreover, the hydrophilic exterior imidazolium moieties could form a complex with nucleophile in the aqueous phase via well-known ion exchange reaction, which increases the nucleophilicity of the azide anion owing to the weak interaction between azide anion and the imidazolium moieties onto compound 2 (Fig. 2).

To exhibit a more clear understanding of the reaction mechanism and the promoting effect of the inclusion complex on the catalytic efficiency, the reaction of bulky epoxide 12-oxa-bicyclo[9.1.0]dodecane with sodium azide under optimized reaction conditions was investigated. Interestingly, no evidence for the formation of corresponding azidohydrin was observed, even after prolonged reaction time (entry 6, Table 1). It could be concluded that in this case probably inclusion complex has not been formed. In this way the promoting effect of inclusion complex was confirmed.

As illustrated in Table 2, catalyst 2 show a much higher catalytic activity than polymeric calix[4]resorcinarene (entries 1, 2, Table 2). This result further supports this assumption that besides the hydrophobic cavity of 2, cationic arms play a crucial role in its catalytic activity and contribute to the rapid progress of the nucleophilic reaction.

Under these results, we expect that this cationic catalyst (2) will be a suitable alternative to the existing catalysts.

4 Conclusions

In the present study we disclose a new and fascinating approach for the synthesis of supramolecular imidazolium salts based on calix[4]resorcinarene skeleton. A survey of the literatures indicate that, this is the first report on the one-pot synthesis of this cationic calix[4]resorcinarene via silylation of hydroxyl groups on the upper rim of calix[4]resorcinarene without the use of acidic or basic catalyst. The reaction procedure is convenient, involving simple experimental procedure and product isolation, thus dispense with expensive chromatographic purification steps. Hence, the procedure opens a novel entry to the convenient synthesis of a number of functionalized resorcinarene. Following the synthetic strategy, the application of this novel three dimensional imidazolium salt as PTC for the preparation of azidohydrins was investigated. The catalytic activity of this valuable compound could be attributed to the synergetic effect of methylimidazolium cation and cavity of skeleton. Further studies on the other applications of novel tweezer-like dicationic calix[4]resorcinarene which concluded from its structure, are currently under way in our laboratory.

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