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Microwave-assisted synthesis of calix[4]resorcinarenes

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Abstract—Microwave-assisted synthesis of calix[4]resorcinarenes by cyclocondensation of various aldehydes and resorcinol catalysed by 12-tungstophosphoric acid type Keggin ($H_3PW_{12}O_{40}\cdot 13H_2O$) or concentrated HCl is described. Excellent isolated yields (up to 90%) were attained within short reaction times (typically, 3–5 min) when the reaction was performed under microwaves irradiation.

1. Introduction

Interest in the chemistry of calixarenes has increased in recent years. Of particular significance has been the preparation of a range of calix[4]resorcinarene derivatives in high yields.[1] Self-assembled monolayers of resorcinarene derivatives on gold surfaces provide an important starting point for fabricating and operating nanoscale devices for advanced information technologies. Resorcinarene derivatives have also been used as stationary phase in achiral capillary gas chromatography for the separation of positional isomers of substituted benzenes.[2]

Recently, Robert et al.[1] and Cave et al.[1] obtained the *C*-methylcalix[4]resorcinarene and five arylcalix[4]resorcinarenes by simply grinding together resorcinol and aldehydes in the presence of catalytic quantities of *p*-toluenesulfonic acid. The final product partition was carried out either at room temperature (for aromatic aldehydes) or at −78 °C (for acetaldehyde). These 'green' approaches to synthetize resorcinarenes were convincing and efficient but it seems that their application to both aromatic and aliphatic aldehydes was not claimed by the authors. The use of aliphatic aldehydes as starting material in these approaches was unsuccessful since the longer the alkyl chain of aldehydes, the lower the reaction yield. For this purpose, we searched for a simple and rapid synthesis pathway that applies most of the green chemistry principles and that is efficient for both aromatic and aliphatic aldehydes.

Tungstophosphoric acid (TPA), an effective catalyst in the series of Keggin-structure HPAs, is believed to have extensive prospects of application in synthesis chemistry, analysis chemistry, biology, medicine, catalysis and materials science. Especially, its utility and versatility in catalysis and various medical applications would thereby be increased. Their significantly higher Brønsted acidity, compared with the acidity of traditional mineral acid catalysts, is of great importance for catalysis because HPA-based catalysts have higher activity than known traditional catalysts. Using HPA-based catalysts, it is frequently possible to obtain higher selectivity and successfully solve ecological problems.[3]

In recent decades microwave technology has taken an undeniable place in chemical laboratory practise as a very effective and non-polluting method for activating reactions. Examples of this technology in organic synthesis and to organo-metallic chemistry are numerous. The greater successes achieved have been to perform reactions very efficiently in closed vessels or in the reduction or absence of organic solvents. The uses of microwaves provide fast volumetric heating of the chemicals thus enhancing reaction rates and dramatically shortening preparation times.[4]

Herein, we report the first synthesis of calix[4]resorcinarenes using aldehydes and resorcinol catalysed by 12-tungstophosphoric acid type Keggin ($H_3PW_{12}O_{40}\cdot 13H_2O$)

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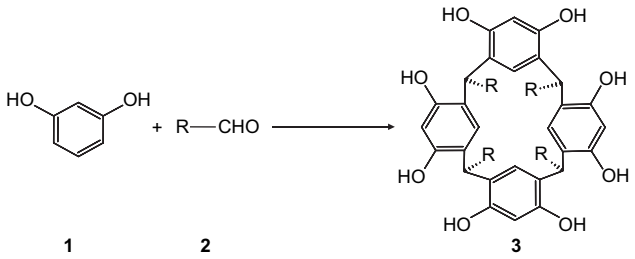
or concentrated HCl under microwave irradiations. The reaction takes place in excellent yield (>90%) with short reaction times (<3–5 min) and does not require harsh conditions. The reaction allows the presence of some functional groups thanks to the rather mild acidic conditions.

2. Results and discussion

Scheme 1 represents the general procedure for the formation of calix[4]resorcinarenes **3** by acid-catalysed cyclocondensation of resorcinol **1** and aldehydes **2**. Selected reaction data obtained from model compounds **2a–i** were illustrated in Table 1 according to different experimental procedures. The process involves microwave irradiation (modified domestic microwave oven) of a mixture containing the resorcinol **1** and aldehydes **2** with a catalytic amount of TPA (procedure D) for 5 min or HCl (procedure B) for 3 min. The corresponding thermal reaction takes 5 h with TPA catalyst (procedure C) and 10 h with concentrated HCl (procedure A).

Products (**3a–i**) were dried at 70 °C under vacuum. Microanalyses, ^{1}H and ^{13}C NMR spectra confirmed their good purity. We carefully analyzed ^{1}H NMR spectra of **3a**, **3i** (aromatic) and **3c**, **3d**, **3f**, **3g** (aliphatic). All of them exhibited an equivalent single resonance for the four *ortho* protons of resorcinol rings. It was also the case for the four *meta* protons. These NMR data were consistent with those previously reported for the C_{4v} isomer.[1] Thus, using our procedure, we obtained the **3a–i** products with high yield, purity and stereoselectivity. This synthesis route can fruitfully used to expand possibilities of molecular recognition in solution of resorcinarenes.[1]



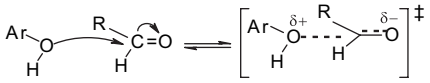
Scheme 1. Synthesis of calix[4]resorcinarenes by cyclocondensation of resorcinol and aldehydes.

Table 1. Microwave-assisted cyclocondensation of resorcinol **1** and aldehydes **2a–i**

Product	R–	Procedures	Conditions			Yield (%)	Mp (°C)
			Power (W)	Time (min)	*T* (°C)		
3a	*p*-But-*O*-C_6H_4	A	—	600	80	86	>300
		B	100	3	80	96	
		C	—	300	80	78	
		D	300	5	108	91	
3b	CH_3	A	—	600	80	60	>300
		B	100	3	80	88	
		C	—	300	80	67	
		D	300	5	108	89	
3c	$CH_3(CH_2)_3$	A	—	600	80	69	>300
		B	100	3	80	82	
		C	—	300	80	91	
		D	300	5	108	88	
3d	$CH_3(CH_2)_4$	A	—	600	80	87	>300
		B	100	3	80	95	
		C	—	300	80	88	
		D	300	5	108	91	
3e	$CH_3(CH_2)_6$	A	—	600	80	79	>300
		B	100	3	80	93	
		C	—	300	80	84	
		D	300	5	108	91	
3f	$CH_3(CH_2)_7$	A	—	600	80	82	280
		B	100	3	80	96	
		C	—	300	80	91	
		D	300	5	108	90	
3g	$CH_3(CH_2)_8$	A	—	600	80	84	295
		B	100	3	80	93	
		C	—	300	80	87	
		D	300	5	108	89	
3h	$CH_3(CH_2)_{10}$	A	—	600	80	85	285
		B	100	3	80	93	
		C	—	300	80	—	
		D	300	5	108	90	
3i	C_6H_5	A	—	600	80	88	300
		B	100	3	80	94	
		C	—	300	80	78	
		D	300	5	108	95	

Analysis of selected reaction data (see Table 1) obtained from model compounds **2a–i** shows the following outstanding facts:

(a) Comparison between conventional heating and microwave irradiation (same temperature, same reagents) revealed a strong specific effect of microwaves because, under conventional heating, the reaction occurred in a very limited extension. After 30 min, thermal reaction did not allow to produce any calix[4]resorcinarenes using 2-ethoxyethanol as solvent with procedures B or C. A possible explanation for the favourable effect of microwaves is that they enhance dipole–dipole interaction in the transition state (Scheme 2).



Scheme 2. Dipolar transition state.

However, a crucial role for the acid during the dehydratation step cannot be excluded since we obtained very low yields in all reactions carried without acid.

(b) Calix[4]resorcinarenes **3** have been synthesised after 5–10 h by conventional heating with fairly moderate yields between 60 and 90%. Under microwave irradiation, excellent yields (between 80 and 99%) were obtained after 3–5 min.
(c) The power range was set to 100 W for HCl catalyst and 300 W for TPA catalyst, since an excessive power could cause the degradation of the product.
(d) When microwave irradiation is applied, less solvent is necessary for conducting cyclocondensation acid-catalysed by HCl or TPA. One of the goals of the 'green chemistry' is to avoid or to reduce the use of solvents in organic chemistry.
(e) In general, the cyclocondensation worked well with alkyl or aryl aldehydes with or without functional groups.

Microwaves are used as a useful tool for preparative organic synthesis: reactions can be carried with less solvent under monitored temperature. There is a fundamental difference between microwave irradiation and conventional heating; conventional heating is an inward heat transfer (from the heating device, e.g., the walls of the reactor for jacketed tanks, to the medium); in microwave irradiation, thermal energy is generated in situ due to the interaction of polar molecules or ionic species with the electric field. Physical acceleration (higher temperature) or chemical activation (enhancement in dipole moment) could be happened using microwaves, which reduce reaction times and enhance yields in comparison with conventional reflux reaction conditions.

3. Conclusion

An extremely simple method for the preparation of calix[4]-resorcinarenes **3** by acid-catalysed cyclocondensation of aldehydes **2** and resorcinol **1** has been perfected using microwave technology. The reaction can be carried out in environmentally friendly conditions: less solvent, less added acid and less reaction time, which means less energy consumed for heating. This 'green' procedure for cycloaddition reaction may set the basis for its application assisted by microwaves in a near future.

4. Experimental

Procedure A: to a solution of resorcinol **1** (10 mmol) and aldehydes **2** (10 mmol) was added a solution of ethyl alcohol (25 mL, 95%) and concentrated HCl (7 mL). This mixture was heated by conventional heated jacket for 10 h. The reaction mixture was cooled in an ice bath and the solid material formed was filtered off and washed by water to eliminate acid trace. The filtrate was dried at 70 °C and analysed by ^{1}H and ^{13}C NMR spectra recorded in $CDCl_3$ or acetone-d_6 solutions, on a VARIAN spectrometer operating at 300 MHz. Melting points were determined on a Stuart scientific SPM3 apparatus fitted with a microscope. Procedure B: to a solution of resorcinol **1** (10 mmol) and aldehydes **2** (10 mmol) was added a solution of 2-ethoxyethanol (2 mL) and concentrated HCl (2 mL). This mixture was heated by microwaves for 3 min with a fixed power of 100 W. Procedure C: to a solution of resorcinol **1** (10 mmol) and aldehydes **2** (10 mmol) was added a solution of ethyl alcohol (12 mL, 95%) and TPA (0.31 g, 1% molar). This mixture was heated by conventional heated jacket for 5 h. Procedure D: to a solution of resorcinol **1** (10 mmol) and aldehydes **2** (10 mmol) was added a solution of 2-ethoxyethanol (2 mL) and TPA (0.31 g; 1% molar). This mixture was heated by microwaves for 5 min with affixed power of 300 W.

^{1}H and ^{13}C NMR spectroscopic data example of calix[4]-resorcinarene (300 MHz): 2,8,14,20-tetra(*p*-butoxyphenyl)-pentacyclo[19,3,1,1,1]octacosa-1(25),3,5,7,(28),9,11,13(27) 15,17,19(26),21,23, dodecanene-4,6,10,12,16,22,24-octol (**3a**); ^{1}H NMR (acetone-d_6) δ_H (ppm): 0.98 (12H, t, J=6.72 Hz,CH_3), 1.50 (8H, m, CH_2), 1.75 (8H, m, CH_2), 4.00 (8H, t, J=7.8 Hz, OCH_2), 5.75 (4H, s, CH), 6.30 (4H, s, ArH *meta* of OH), 6.34 (4H, s, ArH *ortho* OH), 6.69 (8H, m, ArH *meta* of *O*-alkyl), 6.78 (8H, m, ArH *ortho* of *O*-alkyl), 7.51 (8H, s, ArOH); ^{13}C NMR (acetone-d_6) δ_C (ppm): 14.26, 20.00, 32.38, 42.00, 67.87, 102.00, 114.00, 122.26, 130.39, 132.06, 137.30, 153.70, 157.42.

The multimode microwave reactor (a modified microwave oven candy mga20m) has a single magnetron (2450 MHz) with a maximum delivered power of 800 W. It was directly graduated in W (from 100 to 800 W). Experiments were carried out in a Pyrex reactor fitted with a condenser. During experiments, time, temperature and power were monitored. Temperature was monitored with the aid of an external infrared IR thermometer (Flashpoint FZ400).

Resorcinol, aldehydes, ethyl alcohol, 2-ethoxyethanol and HCl, were purchased from Aldrich and TPA synthesized by authors following literature procedures.[5]

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