Microwave-Assisted Synthesis of *p*-Alkylcalix[n]arene Catalyzed by KOH

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Abstract: The paper researched the synthesis of *p*-methylcalix[6]arene and *p*-tertbutylcalix[8]arene catalyzed by KOH in moderate yields under microwave irradiation. The effects of different factors on this condensation reaction have been discussed. Compared with classical method, this method had some merits such as easy obtaining the raw materials, short reaction route, simple and convenient aftertreatment, being beneficial to environmental protection.

Key words: microwave irradiation; formaldehyde; calix[n]arene

Introduction

Calixarene macrocycles are the subject for increasing interest in the field of supramolecular chemistry or host-guest chemistry as basic skeleton for the synthesis of host compounds for ions or neutral molecules¹. Although the complexation properties of calixarenes have not been examined as extensively as those of cyclodextrins, calixarenes^{2,3} have been used in the recovery of cesium and uranium, ion selective electrodes and field effect transistors. Other applications, such as phase transfer agents, hydrolysis catalysts and separation of organic molecules have also been reported. In 1944, Zinke and Ziegler found the reaction of para-substituted phenols and formaldehyde under base condition gave compounds with cyclic tetrameric structure⁴. Later it was found para-alkylsubstituted phenol only gave calix[6]arene and calix[8]arene with low yield (10%)⁵. The most interesting is calix[7]arene can be obtained with the 22% yield if *p*-cresol and formaldehyde are mixed together⁶. In this paper, we will report the first synthesis of *p*-methylcalix[6]arene and *p*-tertbutylcalix[8]arene under microwave irradiation catalyzed by KOH. Though microwave irradiation has been applied to accelerate some condensation reactions⁷⁻¹⁰, the synthesis of calix[n]arene has not been reported. This paper is about our preliminary findings obtained by comparison of the results of the classical methods and the novel methods. We wish to report a fast and efficient procedure to synthesize calix[n]arene under microwave irradiation. The results show microwave irradiation can enhance this condensation reaction. The synthesis route is as shown in **Scheme 1**.

Scheme 1

Experimental

Melting points were uncorrected and were measured with micro-melting point apparatus. IR spectra (KBr) were obtained on a Perkin-Elmer 983G spectrometer. ¹H NMR spectra were determined on a Bruker AC-400 spectrometer using C₅D₅N as solvent and tetramethylsilane (TMS) as internal reference. Mass spectra were determined on a VG7070E spectrometer (ESI). Microwave irradiation was carried out with commercial microwave oven (650W, 2450MHz). The products were characterized by ¹H NMR spectra and comparison of their melting point with literature values. Element analysis data was obtained by Yanaco CHN CORDER MT-3. All other chemicals used were of commercial grade without further purification.

General procedure for the synthesis of *p*-methylcalix[6]arene.

A mixture of 36% formaldehyde 3ml (56.23mmol), *p*-methylphenol 2ml (18.85mmol) and KOH 0.170g (3.03mmol), in a cone bottle was introduced into the microwave oven and irradiated for 2-8min (output power at 100%). The solution changed from yellow clearly to glued thickly. The progress of the reaction was monitored by TLC. Then, dimethylbenzene 10ml, which was heated up near boiling, was added to the reaction mixture quickly. The solution was transferred to a rockered-bottle and refluxed 40 min continually. After cooling, the solution was filtrated to give a white solid. The crude products were washed by dimethylbenzene and were treated with the mixture of hydrochloric acid and chloroform. The target compound was obtained in 0~81.7% yields. m.p. 361-362°C; Anal. Calcd for C₄₈H₄₈O₆: C, 80.00; H, 6.71. Found: C, 80.02; H, 6.70; ESI-MS: 719[M⁺]; ¹H-NMR(C₅D₅N, 400MHz) δ: 1.27(S, 3, CH₃), 7.19(S, 2, ArH), 9.6 (S, 1, OH), 4.16 (BR, 2, CH₂); IR(KBr, cm⁻¹): 3250, 1480, 860, 800.

General procedure for the synthesis of *p*-tertbutylcalix[8]arene.

A mixture of 36% formaldehyde 1.1ml (20.00mmol), *p*-tertbutylphenol 75.0mg (5.00mmol) and KOH 28.8mg (1.60mmol), in a cone bottle was introduced into the microwave oven and irradiated for 4-8min (output power at 100%). The solution changed from yellow clearly to yellow thickly. The progress of the reaction was monitored by TLC. Then, dimethylbenzene 10ml, which was heated up near boiling, was added to the reaction mixture quickly. The solution was transferred to a rockered-bottle and refluxed 3 hours continually. After cooling, the solution was filtrated to give a white solid. The crude products were washed by dimethylbenzene and were treated with the mixture of hydrochloric acid and chloroform. The target compound was obtained in 0~88.8% yields. The ¹H-NMR spectra in CDCl₃ solutions show the characteristic pattern containing a single sharp resonance at δ1.25 for the tert-butyl protons, a somewhat broadened singlet at δ4.16 for the methylene protons, a broad at δ7.33 for the aromatic protons and a resonance varying from sharp to broad at δ9 for the hydroxyl protons. m.p. 371-375°C; Anal. Calcd for C₈₈H₁₁₂O₈: C, 81.44; H, 8.70. Found: C, 81.45; H, 8.69; ESI-MS: 1297[M⁺]; ¹H-NMR(C₅D₅N, 400MHz) δ: 7.33(S, 2, ArH), 1.25(s, 9, C(CH₃)₃), 3.52 (d, J=12.8Hz, 1, CH₂), 4.37(d, J=12.8Hz, 1, CH₂). IR (KBr, cm⁻¹): 3230, 1480, 860, 800.

Results and Discussion

Synthesis of p-methylcalix[6]arene

The paper discussed the effects of different factors on the condensation of formaldehyde and *p*-methylphenol. This condensation reaction has been investigated at various mole ratio of *p*-methylphenol and formaldehyde when the power of microwave irradiation and the reaction time were kept unchanged. The results were showed in **Table 1**. The yields were increased with the mole ratio of reactant **1** and **2** up to 1:1.5 and then leveled off. When the other reaction conditions were invariable, the effect of different microwave power on the reaction was shown in **Table 2**. This may be due to the fact that the more molecules absorb microwave energy in short time the better the results are as microwave irradiation intensity increases.

Table 1 Change the mole ratio of *p*-methylphenol and formaldehyde under microwave irradiation

Entry	Mole ratio ^a	Power (%)	Time (min)	Yield (%)
1	4:1	100	6	0
2	3:1	100	6	31.1
3	2:1	100	6	53.0
4	1:1	100	6	65.1
5	1:1.5	100	6	81.7
6	1:2.5	100	6	73.3
7	1:3	100	6	53.3
8	1:4	100	6	20.8

^a The mole ratio is *p*-methylphenol and formaldehyde.

Table 2 Change the power of microwave irradiation

Entry	Mole ratio ^a	Power (%)	Time (min)	Yield (%)
1	1:1.5	100	6	81.7
2	1:1.5	70	6	65.0
3	1:1.5	50	6	59.2
4	1:1.5	30	6	0

Table 3 Change the reaction time of the condensation reaction

Entry	Mole ratio ^a	Power (%)	Time (min)	Yield (%)
1	1:1.5	100	2	0
2	1:1.5	100	3	12.5
3	1:1.5	100	4	49.2
4	1:1.5	100	5	69.1
5	1:1.5	100	6	81.7
6	1:1.5	100	7	65.0
7	1:1.5	100	8	38.3

When the other reaction conditions were invariable, the effect of different reaction time on the condensation reaction was shown in **Table 3**. As summarized in **Table 3**, the yields were increased with the longer reaction time before 6min, after it the yields were reduced because of the increase of side reaction. In order to prevent from producing the emergence of boiling phenomenon, the reflux devices were installed while reacting in the microwave oven.

Synthesis of p-tertbutylcalix[8]arene

Similar to the synthesis of *p*-methylcalix[6]arene, the effects of the different reaction factors had been discussed in the microwave-assisted reaction. The results were showed in from Table 4 to Table 7. In conclusion, change the mole ratio of *tert*butylphenol and formaldehyde, the ratio of KOH, the reaction time and the power of microwave irradiation had the similar influences comparing to the synthesis of

p-methylcalix[6]arene. These results showed microwave can speed up the synthesis of calix[n]arene, and had more merits than custom reported¹¹.

Table 4 Change the mole ratio of tertbutylphenol and formaldehyde under microwave irradiation

Entry	Mole ratio ^b	Power (%)	Time (min)	Yield (%)
1	1:2:0.34	100	6	11.8
2	1:3:0.34	100	6	62.5
3	1:4:0.34	100	6	88.8
4	1:5:0.34	100	6	70.4
5	1:6:0.34	100	6	53.8
6	1:7:0.34	100	6	22.0

^b The mole ratio is tertbutylphenol, formaldehyde and KOH.

Table 5 Change the mole ratio of KOH under microwave irradiation

Entry	Mole ratio ^b	Power (%)	Time (min)	Yield (%)
1	1:4:0.30	100	6	55.7
2	1:4:0.32	100	6	64.5
3	1:4:0.34	100	6	88.8
4	1:4:0.35	100	6	78.7
5	1:4:0.37	100	6	61.2
6	1:4:0.38	100	6	51.5

Table 6 Change the reaction time under microwave irradiation

Entry	Mole ratio ^b	Power (%)	Time (min)	Yield (%)
1	1:4:0.35	100	4	38.9
2	1:4:0.35	100	5	60.4
3	1:4:0.35	100	6	88.8
4	1:4:0.35	100	7	71.0
5	1:4:0.35	100	8	67.1

Table 7 Change the power of microwave irradiation

Entry	Mole ratio ^b	Power (%)	Time (min)	Yield (%)
1	1:4:0.35	100	6	88.8
2	1:4:0.35	70	6	65.2
3	1:4:0.35	50	6	49.3
4	1:4:0.35	30	6	0

Conclusions

It was concluded that the best synthetical conditions of the p-methylcalyx[6]arene were the mole ratio of p-methylphenol and formaldehyde is 1:1.5, the power of microwave irradiation was 100%(2450MHz), reaction time was 6 min, and the yield of calyx[6]arene was up to 81.7%. And the best synthetical conditions of the p-tertbutylcalix[8]arene were the mole ratio of p-tertbutylphenol and formaldehyde is 1:4, the power of microwave irradiation was 100%(2450MHz), reaction time was 6 min, and the yield of calyx[6]arene was up to 88.8% (It is better than the 63% yields reported by the document¹²). In conclusion, the rapid and efficient methods for the preparation of calyx[n]arene had been provided, which had the characteristic such as its operational simplicity, moderate yields, short reaction time and low cost. In addition, pollution could be further reduced and at the same time argon gas was avoided using in the procedure of reaction.

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