Chinese Chemical Letters Vol. 15, No. 9, pp 1019-1021, 2004 1019
http://www.imm.ac.cn/journal/ccl.html

Synthesis of Calix[4]resorcinarene Amide Derivatives

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Abstract: Three different synthetic routes were developed to introduce carbamoyloxy functional groups at the upper periphery of two calix[4]resorcinarenes. By treating activated esters **2a-b** with excess corresponding amine such as 3-(dimethylamino)propylamine **3**, α-phenethylamine **4** and triethylenetetramine **5**, six amide derivatives **6a~8b** were obtained in high yield (Route 1). The pyridine-linked amide derivatives **9a-b** were prepared by using acid chloride intermediate (Route 2). The amide derivatives **10a-b** were obtained in moderate yields by direct alkylation of phenolic hydroxyl groups of **1a-b** with N,N-dipropylchloroacetoamide in the presence of K_2CO_3/KI in acetone (Route 3).

Keywords: Calix[4]resorcinarene, amide, supramolecular chemistry.

The molecular design of receptor molecules that can precisely recognize and specifically bind guest molecules has been the focus of recent attention[1]. The versatile organizing properties of calixarenes platform were also tested with the introduction of the ester or amide residues, which showed recognition properties for alkaline, and alkaline earth cations[2]. Remarkable progress has been achieved in this decade on calix[n]arene-based receptors[3-9], while calix[4]resorcinarene based receptors bearing amides were less concerned[10]. Considering, that introduction of amide at the periphery of calix[4] resorcinarenes may improve their potential complexing abilities, we synthesized a series of novel calix[4]resorcinarenes through three synthetic routes.

The first route is direct amidation of calix[4]resorcinarene ester (route 1 in **Scheme 1**). **1a-b** were reacted with ethyl bromoacetate to give eight or twelve ethoxycarbonyl methoxy substituted derivatives **2a-b** (**2a**, 58.1%; **2b**, 56.5%). It should be noticed that the p-hydroxyl groups at outer phenyl substituent of 1b was also alkylated at this condition. As shown in **Table 1**, refluxing corresponding esters with excess primary amines such as 3-(dimethylamino)propylamine **3**, α-phenethylamine **4** and triethylenetetramine **5** for 6 h gave six amide products **6a~8b**. These six amides are octopus type compounds with long soft carbamoyloxy groups chains, **6a-b** also has additional terminal tertiary amine groups and 8a-b have additional terminal primary amine groups, which can be easily converted to other useful functional groups.

The preparation of amide derivatives **9a-b** was represented the second route, in which 2-aminopyridine can be introduced into calix[4]resorcinarene in three steps *in situ*. The

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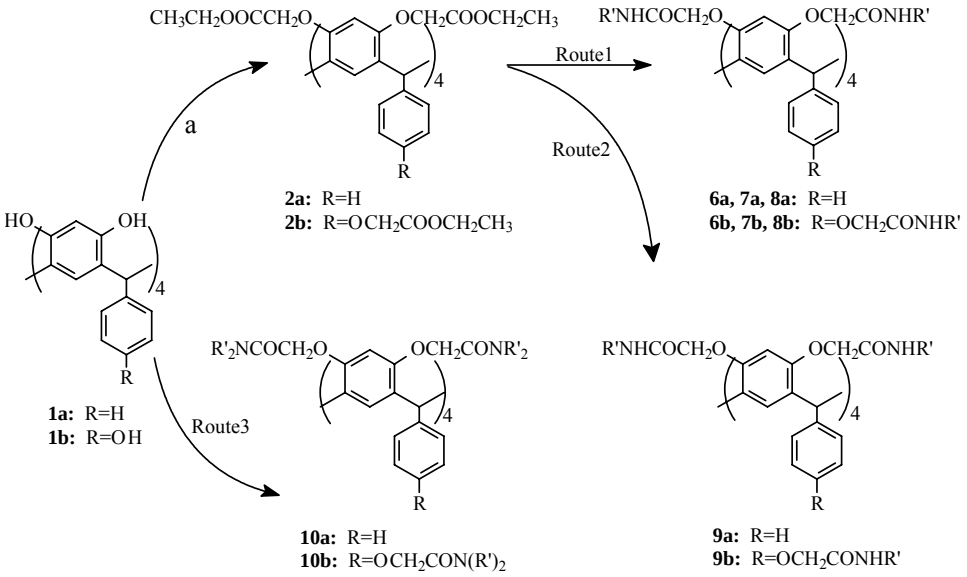
Scheme 1



Reagents and conditions: (a) $BrCH_2COOCH_2CH_3$, K_2CO_3, acetone, reflux, 2d (Route 1) $NH_2(CH_2)_3N(CH_3)_2$ **3**, $C_6H_5CH(NH_2)CH_3$ **4** or $NH_2CH_2CH_2NHCH_2CH_2NHCH_2CH_2NH_2$ **5**, reflux, 6h (Route2) 10%KOH(aq.), reflux, 6h; $SOCl_2$, CCl_4, reflux, 2h; 2-aminopyridine, Et_3N, THF, rt, 1d (Route3) $ClCH_2CON(CH_2CH_2CH_3)_2$, K_2CO_3, KI, acetone, reflux, 2d

obtained ester **2a-b** was first hydrolyzed to acid in 10% potassium hydroxide solution, which was transformed into acid chloride by reaction with $SOCl_2$, which in turn to react with 2-aminopyridine in tetrahydrofunan in the presence of pyridine to give the desired amide **9a-b** in total of 76.5 or 72.1% yields. Because of bearing multiple pyridine-linked amide groups **9a-b** can be used as complementary chelating ligands for molecular recognition.

The third route is a normal direct alkylation approach. The phenolic hydroxyl groups of calix[4]resorcinarenes **1a-b** were directly alkylated with N,N-dipropyl chloroacetoamide. The alkylation reaction was finished by using of K_2CO_3/KI in refluxing acetone for 2 days to give amides **10a-b** in moderate yield (**10a**: 62.0%, **10b**: 65.8%).

The structure of all amide products was characterized with ^1H NMR and IR spectroscopy. In their IR the C=O stretching frequency usually exhibit at 1647 cm^{-1}. In ^1H NMR spectroscopy besides other character peak of each group, the $-OCH_2CO-$ group usually has single peaks at about 4.30-4.50 ppm.

In summary, a series of novel calix[4]resorcinarene amide derivatives which are potentially useful host molecules were synthesized in moderate to high yields by using three different routes. The further research on their properties as complexing reagents and as building blocks for high generation of dendrimers is on the way. Preliminary extraction studies of compound **6** with alkaline, alkaline earth and other transition metal ions were investigated by UV-Vis spectroscopy. An obvious red shift of the peak position was

observed in the absorption spectrum of compound **6** when soft metal ions, such as Cd^{2+}, Ag^{+}, Pb^{2+} and Hg^{2+}, were added in the neutral media. In addition, free amino groups in compound **8** were reacted with salicylaldehyde to form corresponding Schiff base derivatives, which gives a great chance to synthesize dendrimeric metal complexes.

Table 1 Amide derivatives **3a~7b** produced *via* **Scheme 1**

Entry	R	R′	Yield (%)
6a	H	$(CH_2)_3N(CH_3)_2$	96.9
6b	$OCH_2CONH(CH_2)_3N(CH_3)_2$	$(CH_2)_3N(CH_3)_2$	98.2
7a	H	$CH(CH_3)C_6H_5$	96.5
7b	$OCH_2CONHCH(CH_3)C_6H_5$	$CH(CH_3)C_6H_5$	94.3
8a	H	$CH_2(CH_2NHCH_2)_2CH_2NH_2$	86.3
8b	$OCH_2NHCH_2(CH_2NHCH_2)_2CH_2NH_2$	$CH_2(CH_2NHCH_2)_2CH_2NH_2$	89.4
9a	H	C_5H_4N	76.5
9b	$OCH_2CONHC_5H_4N$	C_5H_4N	72.1
10a	H	$CH_2CH_2CH_3$	62.0
10b	$OCH_2CON(CH_2CH_2CH_3)_2$	$CH_2CH_2CH_3$	65.8

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Received 18 July, 2003