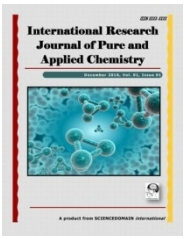

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Improved Procedure for the Synthesis of Calix[4]arenes with Four Amino Groups on the Wide Rim

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Authors' contributions

This work was done in collaboration between all authors. Authors XQS and MOV designed this work, while author HZ carried out all experiments. The experimental results were analyzed by authors HZ and MOV and discussed by all authors. Author MOV wrote the manuscript, while all authors read and approved the final version.

Short Research Article

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ABSTRACT

Calix[4]arenes fixed in the cone conformation and bearing four amino functionalities on the wide rim, are well known and often used starting materials in calixarene chemistry. During our studies in this field we have noticed, that the safe procedures known (which use palladium on carbon as catalyst and hydrazine hydrate as reducing agent in methanol at reflux) not always fit well for the synthesis of all possible even rather simple derivatives of this type and undesired mixtures are usual outcome in these cases. High resolution MS and ^{1}H NMR indicate, that the main impurity (nearly 30%) is a partially reduced calix[4]arene containing three amino- and one nitro groups. We have modified the synthetic procedure by changing the solvent to *iso*-propanol, which allowed to shorten the reaction times and to obtain the desired products in high purity and yields.

Keywords: Aromatic amines; calix[4]arenes; nitro compounds; palladium; reduction.

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1. INTRODUCTION

Calix[4]arenes [1] fixed in the *cone* conformation and bearing four amino groups at the wide rim 1 [2] are used often as the starting materials in the synthesis of many interesting and even useful compounds Fig. 1 such as tetra-ureas [3] (or similar [4]), calixsugars [5], carbamoyl methyl phosphine oxide (CMPO) derivatives [6] and some water soluble calix[4]arenes [2a,b,7]. Calix[4]arene ureas are well known to self-assemble into dimeric molecular capsules [3,8], which can be also used in effective synthesis of mechanically interlocked structures [9]. This self-assembly motif had been also successfully used in assembly of hydrogen bonded polymers [10], dendrimers of defined structures [11], and elucidation of self-sorting phenomena between self- assembled capsules of similar structure [12]. Calixsugars can have plenty of different applications in bio-relevant area including inhibition of lectin binding to cell-surface glycoconjugates [5a]. CMPO derivatives are known for their very high extraction abilities of lanthanides and actinides [6], which potentially can be used in treatment of highly radioactive wastes obtained during exploitation of nuclear reactors. Some of water soluble calix[4]arenes (like guanidinium derivatives shown on Fig. 1) proved to be quite effective in DNA cell transfection [7].

The very first method of the synthesis of calix[4]arene with four amino functions on the wide rim **1** (Scheme 1, large variation of alkyl chains Y) included exhaustive hydrogenation of corresponding tetra-nitro derivatives **2** using iron on active charcoal (obtained in situ) and hydrazine hydrate as reducing agent (Table 1, entry 1) [2a,b]. Interestingly, this method had never been used afterwards, to the best of our knowledge. Instead, another and very often used procedure had been developed, which uses Raney nickel as catalyst and hydrogen as reducing agent [2c], at room temperature (usually, overnight). This is a general procedure for reduction of nitro-compounds, of course. These conditions are known to be very mild ones, which could be applied to many different calix[4]arenes bearing also some sensitive functionalities (like ester groups) on the narrow rim [11]. However, the obvious drawback of this method is the additional safety issues. The first issue is the active Raney nickel, which is flammable in the dry state. That is why one should be always very careful in handling it and especially after the reaction, when the reaction mixture should be filtered. In the last case see sand should be used to prevent the drying out of the catalyst. Then it should be destroyed by treatment with hydrochloric acid. This produces, obviously, additional wastes, that are also not desirable. The second obvious safety issue is the use of gaseous hydrogen, which easily forms explosive mixtures with air and thus is not always welcome in industrial processes in developed countries.

The further development of the reduction conditions includes the use of other reducing reagents like hydrazine hydrate (Table 1, entries 3-5) [2f,g]. This allows already to lower one of the hazards discussed. The usual solvent used in thus modified method is methanol (or ethanol) and times applied, are 2-6 hours. Some other modifications include the change of heterogeneous catalyst from Raney nickel to palladium on carbon (Table 1, entries 6,7) [2h], which also reduces the hazards discussed. Under these hydrogenation conditions the times applied are up to 24 hours (at room temperature). Finally, the most safe method (from the view point of these hazards) includes the use of palladium on carbon as heterogeneous catalyst and hydrazine hydrate (Table 1, entry 8, under reflux, 5 hours). Some other modifications include the use of Adams catalyst (which is also pyrophoric, Table 1, entry 9) or the use of tin dichloride (Table 1, entries 10, 11). The reaction mixtures in the last cases usually are difficult to work-up (due to possible problems with precipitation of tin complexes). In this paper we disclose our studies on the reduction of tetra nitro calix[4]arenes having

alkyl chains of different length on the narrow rim, which show, however, that the desirable conditions (Pd/C and $N_2H_4 \cdot H_2O$, in alcohols) not always give the desired results.

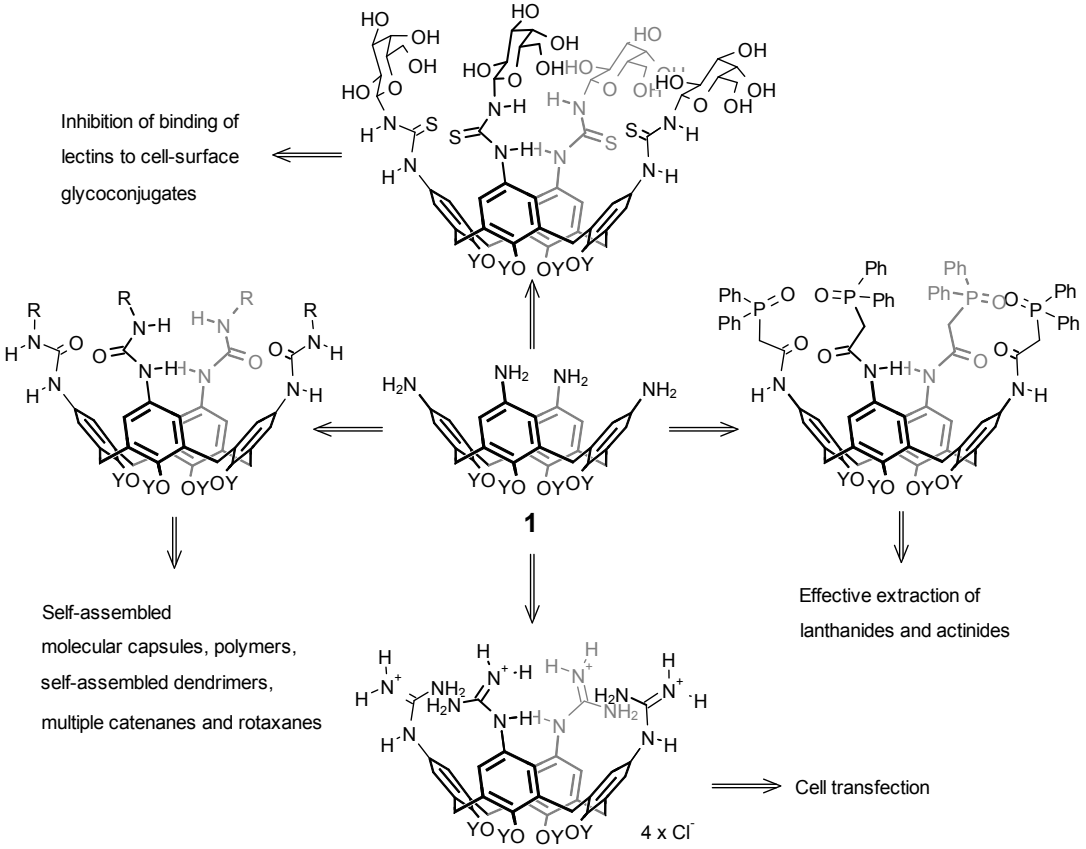
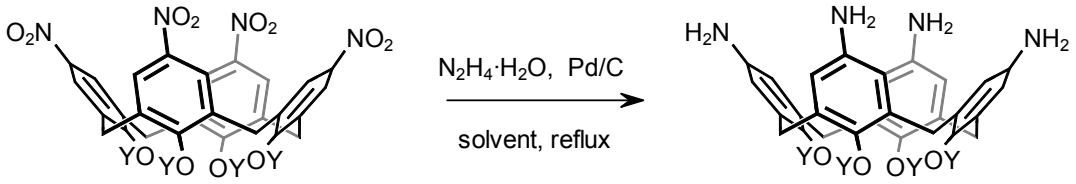


Fig. 1. Derivatives obtained from tetra-amines of calix[4]arenes, and their applications.



2a-d **1a-d**

a Y = C_3H_7 **c** Y = C_5H_{11}

b Y = C_4H_9 **d** Y = $C_{10}H_{21}$

Scheme 1. Synthesis of tetra-amino derivatives of calix[4]arenes 1a-d

Table 1. Summary of the conditions known from the literature, which are used in reduction of tetra-nitro derivatives of the type of 2 (many different alkyl chains Y).

N	(Pre)catalyst	Reducing agent	Solvent	Temperature	Time	Reference
1	$FeCl_3 \cdot 6H_2O$, active charcoal	$N_2H_4 \cdot H_2O$	2-methoxy-ethanol	Reflux	12 h	2a, 2b
2	Raney-Ni	H_2	Toluene or THF	Room temp.	14 h	2c
3	Raney-Ni	$N_2H_4 \cdot H_2O$	MeOH	Reflux	4 h, 2h	2d, 2e
4	Raney-Ni	$N_2H_4 \cdot H_2O$	EtOH	Reflux	6 h	2f
5	Raney-Ni	$N_2H_4 \cdot H_2O$	THF/MeOH	Reflux	2 h	2g
6	Pd/C	H_2 (2 bar)	Ethyl acetate	Room temp.	24 h	2h
7	Pd/C	H_2	EtOH/toluene/ 1M HCl solution	Room temp.	Not specified	2i
8	Pd/C	$N_2H_4 \cdot H_2O$	EtOH	Reflux	5 h	2h
9	PtO_2	H_2	THF	Room temp.	18 h	2k
10	-	$SnCl_2 \cdot 2H_2O$	EtOH	70ºC	48 h	2l
11	-	$SnCl_2 \cdot 2H_2O$	EtOH	Reflux	12 h	2m

2. MATERIALS AND METHODS

The reagents of analytic grade were purchased from Aladdin Chemical Company (China) and were used without further purifications. Compounds 2a-d had been obtained in accordance with the typical methods described in the literature [2c]. ^{1}H NMR spectra were recorded in chloroform-d_1 on a Burker Avance III 300 MHz spectrometer. All reactions were carried out under nitrogen atmosphere.

Typical procedure for synthesis of 1a-d: *Iso*-propyl alcohol (600mL) was poured into the one-neck 1L round-bottom flask containing tetra-nitro compound 2 (9.16mmol), Pd/C (0.75g) and hydrazine hydrate (70mL or 1.44mol). The flask was equipped with condenser ending on the top with a balloon. The reaction mixture was brought to reflux at stirring (as the reaction proceeds, the balloon becomes larger and the system should be opened from time to time for a very short period to let the excess of gases to leave the system). After four hours of reflux, the reaction mixture was cooled to the room temperature, than the solvent was removed at the reduced pressure and the residue was thoroughly dried in vacuum. Dichloromethane (250mL) was added. After swirling for several minutes, the suspension (due to the presence of Pd/C), was filtered through a paper filter, the solution thus obtained, was evaporated and dried yielding the desired compound in 80-95% yield see Table 2. ^{1}H NMR of the products obtained, showed the expected pattern of signals [2].

Table 2. Different conditions applied in our studies for the synthesis of 1a-d.

Product	Solvent	Time	Yield	Purity[a]
1a	methanol	overnight	58%	~70%
1a	*iso*-propanol	4 h	80%	>98%
1b	methanol	overnight	57%	>98%
1b	*iso*-propanol	4 h	83%	>98%
1c	methanol	overnight	65%	>98%
1c	*iso*-propanol	4 h	95%	>98%
1d	methanol	overnight	58%	~86%
1d	*iso*-propanol	4 h	82%	>98%

[a] *Estimated by the integration of signals in ^{1}H NMR spectra*

3. RESULTS AND DISCUSSION

We have applied the modified conditions (Table 1, entry 8, in methanol) to the synthesis of tetra-amino calix[4]arenes 1 fixed in the *cone* conformation, which bear four equal alkyl chains having three, four, five and ten carbons on the narrow rim. In contrast to the reactions on derivatives with butyl and pentyl chains, which went without any problems Table 2, 1b, **c**, the reactions on derivatives with propyl and decyl chains, however, led to the corresponding products only with ~70% and ~86% purity, respectively, to our big surprise Fig. 2. This result was *constantly* reproducible. Increasing the reaction times also did not change much the outcome.

A rough look at ^{1}H NMR spectrum of such mixtures gives a hint, that there is, perhaps, predominantly only one impurity present in each case, since only two additional pairs of doublets for methylene bridge protons Ar-CH_2-Ar are observed (Fig. 2, on example of 1a). If this assumption would be true, this impurity should be of AAAB (or ABAC) substitution type of calix[4]arene skeleton, which should give a) two pairs of doublets for Ar-CH_2-Ar protons and b) two singlets and one pair of *meta*-coupled doublets in the aromatic region, nearly exactly the picture observed in ^{1}H NMR (Fig. 2, two *meta*-coupled doublets are represented

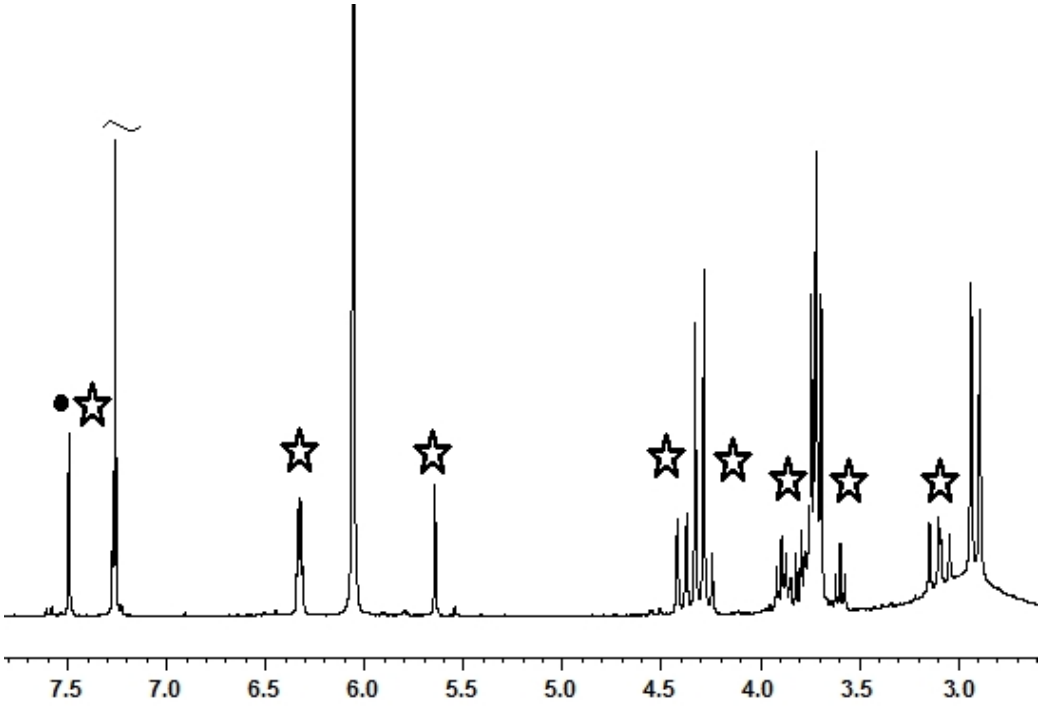


Fig. 2. A part of ^{1}H NMR spectrum (chloroform-d_1, 300 MHz) of product 1a obtained by applying the conditions indicated in Table 2 (methanol, overnight). The signals of main by-product are indicated with a star, another impurity is indicated with a filled black circle, the residual signal of solvent is cutted (indicated with a waved line), while the signals of tetra-amino derivative 1a are *not* indicated.

with a signal of AB-system with close chemical shifts at ~6.35 ppm). To find out the elemental composition, a high resolution MS spectrum was measured for this case. It shows

only one unexpected peak with mass of 683.3813 (the other peaks of mono-charged species of sufficient intensities correspond to **1a**$^+$, [**1a**+H]$^+$, [**1a**+Na]$^+$ and [**1a**+K]$^+$). This mass corresponds well with the formula $C_{40}H_{51}N_4O_6$ (calc. mass 683.3809). This is protonated species of calix[4]arene Fig. 3 having either 1 three amino and one nitro functions on the

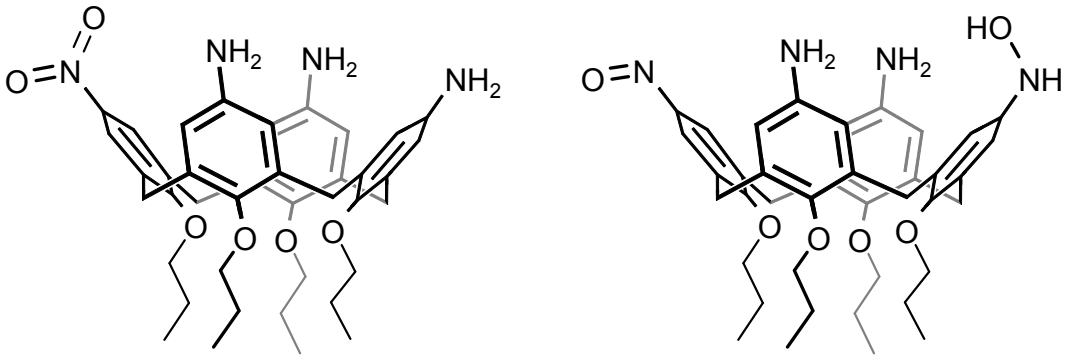


Fig. 3. Possible structures of the main side product observed in the synthesis of 1a.

wide rim (3a), or 2) two amino, one hydroxylamino and one nitroso functions on the wide rim (4a). If these assumptions in the last case should stay in accordance with the ^{1}H NMR spectra, this impurity must have ABAC substitution pattern (4a), in accordance with C_s symmetry (two amino functions on *distal* aromatic units and -NO and -N(OH)H groups on the remaining two ones Fig. 3. In would be very surprising to have such di-amine without having observed the formation of *proximal* regio-isomer, which should have even much more complicated spectrum due to its C_1 symmetry. Thus, taking this fact and the usual chemical liability of nitroso and hydroxylamino functions into account, we suppose to deal rather with tri-amino mono-nitro derivative 3a. This is the first observation in chemistry of calixarenes, which describes a partial reduction of nitro-derivatives of calixarenes, to the best of our knowledge. In searching for new conditions for reductions of 2, we have changed the solvent to *iso*-propanol and kept the reaction mixture under stirring at reflux for four hours only. These conditions appear already quite good ones, which lead to the desired compounds of high purities Fig. 4, Table 2 and in high yields. These facts can be rationalized, most probably, by higher lipophilicity and higher boiling point of *iso*-propanol in comparison to methanol, since the starting materials are not soluble under usual conditions in either of the solvents used. The intermediates (partially reduced calix[4]arenes) should be better soluble in *iso*-propanol than in methanol, thus increasing their concentrations and the rate of the whole process.

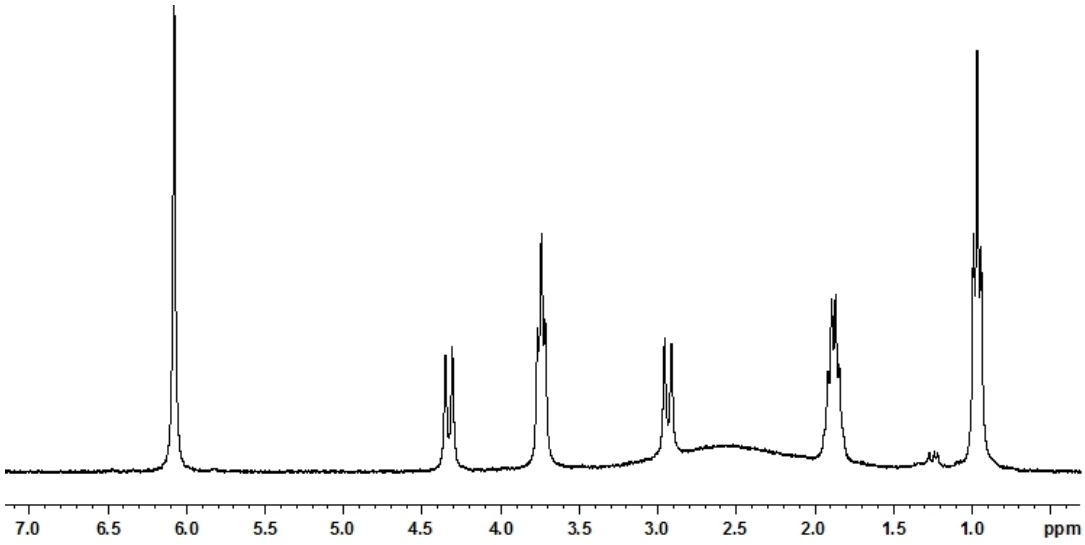


Fig. 4. ^{1}H NMR spectra (chloroform-d_1, 300 MHz) of product 1a obtained by applying new conditions (Table 2, *iso*-propanol, reflux 4h).

4. CONCLUSION

The reduction conditions including Pd/C as heterogeneous catalyst, hydrazine hydrate as reducing agent and methanol as solvent are typical most safe conditions used in exhaustive reduction of calix[4]arenes with four nitro groups on the wide rim. They work well, however, in 50% of cases only. The main impurity identified by high resolution MS and ^{1}H NMR, is the tri-amino mono-nitro derivative (formed up to nearly 30%). This is the first report on *partial* hydrogenation reaction of nitro compounds in calixarene chemistry. The use of *iso*-propanol instead of methanol, leads already to the reliable method giving the desired tetra-amino derivatives in high yields (80-95%) and high purities (>98%).

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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