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Molecular iodine: An efficient and environment-friendly catalyst for the synthesis of calix[4]resorcinarenes

Iode moléculaire : un catalyseur efficace et écologique pour la synthèse de calix[4]résorcinarènes

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ABSTRACT

Iodine catalyzes the cyclocondensation of various aldehydes with resorcinol to give tetrameric cyclic products, resorcinarenes. Through the reaction of resorcinol with aromatic aldehydes, the product is obtained as a mixture of two isomers, the all-*cis* isomer (rccc) and the *cis-trans-trans* isomer (rctt), whereas a single diastereomer, the all-*cis*, is formed with aliphatic aldehydes. Besides excellent isolated yields, the use of iodine makes this procedure simple, convenient, cost-effective and practical.

RÉSUMÉ

L'iode catalyse la cyclo-condensation de divers aldéhydes avec le résorcinol afin de préparer des produits cycliques tétramériques appelés résorcinarènes. Les produits obtenus avec des aldéhydes aromatiques présentent deux isomères (RCCC et RCTT), tandis qu'un seul diastéréoisomère (RCCC) est formé avec les aldéhydes aliphatiques. Ainsi, cette nouvelle procédure faisant intervenir l'iode comme catalyseur constitue une nouvelle méthode simple et rentable pour l'obtention de calix[4]resorcinarènes.

1. Introduction

Calix[4]resorcinarenes (resorcinarenes) are widespread cyclic tetrameric host compounds for ions, sugars and organic molecules; as a consequence they are used as starting materials for a variety of cavitands or other macrocyclic host molecules[1]. They have also been applied as stationary phases in HPLC [2] and chiral capillary gas chromatography for the separation of positional isomers of substituted benzenes [3]. Furthermore, they can exhibit a liquid-crystalline behavior through the appropriate choice of the R groups on the resorcinarene [4]. Fig. 1 represents the general procedure for the formation of calix[4]resorcinarenes by cyclocondensation of resorcinol and aldehydes.

The most common synthetic method still involves mineral acid catalysis of this condensation in hot alcohol solution [5], in which the use of large quantities of concentrated HCl leads to excessive waste streams that are

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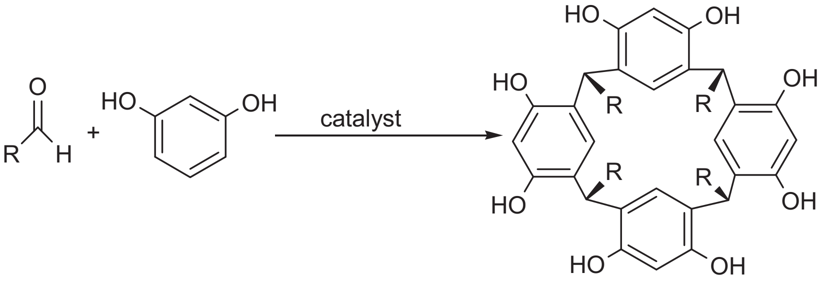


Fig. 1. Synthesis of calix[4]resorcinarenes by cyclocondensation of resorcinol and aldehydes.

environmentally unfriendly and expensive to deal with. A solvent-free synthesis method of calix[4]resorcinarenes using *p*-TsOH as the catalyst has also been reported [6]. This convincing green approach was unsuccessful because the longer the alkyl chain of the aldehyde, the lower the reaction yield. Classical Lewis acids like $BF_3.OEt_2$, $AlCl_3$ and $SnCl_4$ have been used only for the synthesis of aromatic aldehyde-derived resorcinarenes [7]. Unfortunately, this method has several disadvantages such as the use of large quantities of these Lewis acids to obtain good yields of the product and the sensitivity of these catalysts to water, which results in acidic and metal oxide by-products upon aqueous work-up. More recently, triflate-based catalysts such as ytterbium(III) triflate [8] and bismuth(III) triflate [9] have been introduced for this condensation. Expensive preparation and corrosive starting material to prepare triflate salt could be one of the disadvantages of this method. The use of lanthanide sulfonate [10] and the microwave-assisted synthesis of resorcinarene in the presence of HCl and tungstophosphoric acid (TPA) has also been reported [11]. Therefore, the development of new synthetic methods would be of special interest.

Molecular iodine as a mild Lewis acid has received considerable attention as an inexpensive, non-toxic, readily available and environmentally friendly catalyst in organic and pharmaceutical syntheses [12]. It is also highly tolerant to air as well as to moisture. Recent studies indicate that iodine can be effectively used as a catalyst for acetylation [13], protections and deprotections, oxidations, three-component synthesis of protected homoallylic amines [14], direct oxidative conversion of alkyl halides into nitriles, synthesis of bis(indolyl) methanes [15], alkylation of active methylene compounds [16], and synthesis of amidophenol [17]. We now report the utility of iodine as an efficient catalyst for the condensation of aldehydes and resorcinol to give the corresponding resorcinarenes in excellent yields.

2. Results and discussion

Initially the reaction between pentanal and resorcinol was used as a model reaction. To optimize the catalyst's loading, amounts of 0, 5, 10, and 20 mol% of iodine were tested, respectively. The results are summarized in Table 1. A 20 mol% loading of iodine was sufficient to obtain the best yield of resorcinarene **1a** (Table 1, entry 4). To optimize the reaction temperature, the synthesis of compound **1a** was carried out in ethanol at room temperature, 30, 50, and 78 °C, respectively (Table 2). We found that below the reflux temperature of ethanol, no reaction occurred. Therefore, the desired reaction temperature should be 78 °C (Table 2, entry 4).

Table 1
The effect of different amounts of iodine for the synthesis of **1a** ($R = C_4H_9$).

Isolated yield [%]	Iodine [mmol%]	Entry
–	0	1
73	5	2
80	10	3
95	20	4

Conditions: pentanal (1 mmol) and resorcinol (1 mmol) in presence of different catalytic amounts of catalyst at 80 °C in ethanol for 2 h.

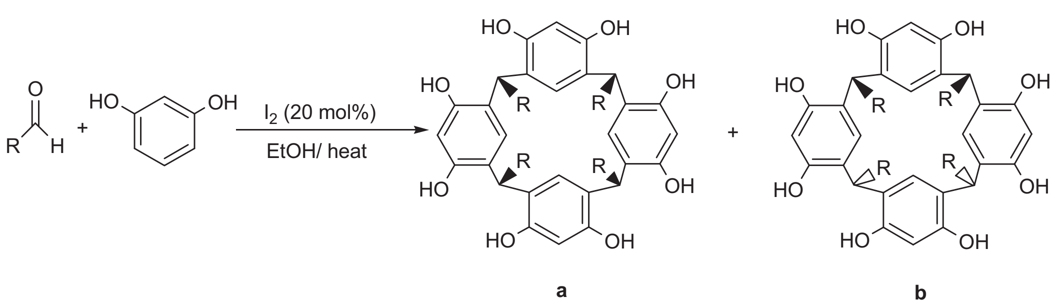
We carefully analyzed the ^{1}H NMR spectra of **1**, **2**, **3** (aliphatic) and **4**, **5**, **6** (aromatic). The condensation reaction of resorcinol with aromatic aldehydes in the presence of iodine formed a mixture of diastereomers (Fig. 2). With benzaldehyde, the product was obtained as a mixture of diastereomers, all-*cis* (rccc, C_{4v}) isomer (**a**) and the *cis-trans-trans* (rctt, C_{2v}) isomer (**b**). The ^{1}H NMR spectrum of benzaldehyde-derived resorcinarene showed one singlet at $\delta = 5.37$ for the bridge benzylic protons (4 H) and two singlets at $\delta = 5.55$ and 6.11 for the intra-annular aromatic protons H_{in} (each 2 H), indicating that the C_{2v} isomer had been produced. An equivalent single resonance for the four ortho protons of resorcinol rings at $\delta = 6.12$ and the four meta protons at $\delta = 6.33$ were consistent with those previously reported for the C_{4v} isomer. Other aromatic aldehydes such as 4-hydroxybenzaldehyde and 4-methoxybenzaldehyde were also tested.

In both cases, the corresponding resorcinarenes were a mixture of C_{4v} and C_{2v} isomers as well. For the ^{1}H NMR

Table 2
Optimization of temperature for the synthesis of **1a** ($R = C_4H_9$).

Isolated yield [%]	Temp. [°C]	Entry
–	r.t.	1
–	30	2
–	50	3
95	78	4

Conditions: pentanal (1 mmol) and resorcinol (1 mmol) in the presence of a catalytic amount of catalyst (20 mol%) in ethanol for 2 h.



1 R = C_4H_9, t = 120 min, Yield = 95%, (1a:1b = 1:0)
2 R = C_8H_{17}, t = 95 min, Yield = 86%, (2a:2b = 1:0)
3 R = C_9H_{19}, t = 130 min, Yield = 85%, (3a:3b = 1:0)
4 R = Ph, t = 73 min, Yield = 98%, (4a:4b = 3:1)
5 R = 4-OH-Ph, t = 68 min, Yield = 97%, (5a:5b = 1:1)
6 R = 4-CH_3O-Ph, t = 70 min, Yield = 97%, (6a:6b =2:1)

Fig. 2. Condensation reaction of resorcinol with aromatic aldehydes in the presence of iodine, affording a mixture of diastereomers.

spectrum of resorcinarene **5**, one singlet at $\delta = 5.42$ and two singlets at $\delta = 5.92$ and 6.09 indicated the presence of the rctt isomer, while a single resonance for the four ortho protons of resorcinol rings at $\delta = 6.08$ and the four meta protons at $\delta = 6.31$ proved the existence of the rccc configuration. The thermodynamically favored all-*cis* isomer (via single resonances at $\delta = 6.11$ and 6.30) besides the *cis-trans-trans* isomer (based on singlet resonances at $\delta = 5.45$, 5.55 and 6.11) were clearly identified in the ^1H NMR spectrum of resorcinarene **6**. The ratio of diastereomers after completion of the reaction (as judged by the disappearance of the starting materials by TLC) was obtained by integration of the signals of the benzylic hydrogens of the rccc isomer to the signals of the benzylic hydrogens of the rctt isomer. For the resorcinarenes derived from aliphatic substrates, the tetrameric nature of the products was only that of the all-*cis* (rccc) isomer.

Finally, a comparison was made between the synthesis of resorcinarene **4** and other reported procedures. The results summarized in Table 3 indicate that the present procedure is better than all the earlier reported protocols in terms of availability and cost of the catalyst.

Table 3
Comparison between various methods and this work for the synthesis of **4a**[a].

Entry	Catalyst	Time	Yield(%)	cccc:cttc[b]	Reference
1	HCl	11days	83	32:1	[5c]
2	$[Yb(H_2O)_9](OTf)_3$	48 h		1.4:1	[8]
3	PTSA	60 min		1:2[c]	[6]
4	$BiCl_3$	75 min	66	1:1.2	[9]
5	$Yb(TOS)_3$	24 h	93	1:1.2	[10]
6	I_2	75 min		3:1	This work

[a] Reaction conditions: benzaldehyde (1 mmol), resorcinol (1 mmol), ethanol, catalyst.
[b] Diastereomeric ratio from ^1H NMR.
[c] Solvent-free conditions.

3. Conclusion

In summary, we have developed an alternative and simple method for the preparation of calix[4]resorcinarenes in the presence of iodine as a catalyst. The advantages of this method include reasonable reaction time, the use of very cheap and easy available catalyst, excellent yields, and simple workup. The reactions could also be carried out in air, since iodine is not moisture sensitive. Consequently, this method has wide scope for further applications.

4. Experimental

4.1. General remarks

All the chemicals were purchased from Merck Chemicals and used without further purification. The melting points were taken in open capillary tubes with an Electrothermal 9100 Apparatus. FT–IR (KBr) spectra were recorded on an ABB FT-IR FTLA 2000 spectrometer. ^1H NMR spectra were run on a Bruker DRX-300 (300 MHz) AVANCE instrument using TMS as an internal standard and DMSO-d_6 as a solvent. The chemical shifts (δ) are reported in ppm relative to TMS as an internal standard and J values are given in Hz. ^{13}C spectra were recorded at 75 MHz. Mass spectra were recorded using a Hewlett Packard 5973 mass spectrometer.

4.2. Typical procedure for the synthesis of resorcinarenes

Iodine (20 mol%) was added to a solution of resorcinol (1 mmol) and of an aldehyde (1 mmol) in 2 mL of absolute ethanol. The solution was stirred at 78 °C. After a given period of time, the solution was cooled and poured into 10 mL of an ice-cold saturated sodium thiosulfate aqueous solution. The resulting precipitate was collected by filtration and washed with water. The precipate was dried at 90 °C and identified.

4.2.1. *Spectroscopic data of 2,4,8,20-tetrabutylpentacyclo[19.3.1.1.1.1]octacosa 1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol (**1a**)*

^{1}H NMR (DMSO-d_6) δ (ppm): 0.79 (t, 12H, J = 7.33 Hz, CH_3), 1.08 (m, 8H, CH_2CH$_3$), 1.28 (quin, 8H, J = 6.84 Hz, CH_2CH$_2$CH$_3$), 2.01 (q, 8H, J = 6.73, ArCHCH_2), 4.19 (t, 4H, J = 7.69 Hz, methine) 6.13 (s, 4H, ArH, ortho to OH), 7.14 (s, 4H, ArH, meta to OH), 8.85 (s, 8H, 8OH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 14.1, 22.2, 30.1, 32.9, 33.6, 75.5, 102.3, 123.1, 125.0, 151.6. EI–MS, m/z = 712 (M$^+$).

4.2.2. *Spectroscopic data of 2,4,8,20-tetraoctylpentacyclo[19.3.1.1.1.1]octacosa 1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol (**2a**)*

^{1}H NMR (DMSO-d_6) δ (ppm): 0.81 (t, 12H, J = 7.33 Hz, CH_3), 1.20 (br, 48H, (CH_2)$_6$CH$_3$), 1.96 (br, 8H, J = 6.84 Hz, CHCH$_2$), 4.23 (t, 4H, J = 7.69 Hz, methine) 6.14 (s, 4H, ArH, ortho to OH), 7.08 (s, 4H, ArH, meta to OH), 8.85 (s, 8H, 8OH). ^{13}C NMR (DMSO-d_6): δ (ppm) = 14.0, 22.6, 29.2.2, 22.4, 27.6, 31.6, 31.9, 34.1, 75.5, 102.7, 123.2, 124.8, 151.8. EI–MS, m/z = 938 (M$^+$).

4.2.3. *Spectroscopic data of 2,4,8,20-tetranonylpentacyclo[19.3.1.1.1.1]octacosa 1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol (**3a**)*

^{1}H NMR (DMSO-d_6) δ (ppm): 0.812 (t, 12H, J = 7.33 Hz, CH_3), 1.20 (br, 56H, (CH_2)$_7$CH$_3$), 1.96 (br, 8H, J = 6.84 Hz, CHCH$_2$), 4.21 (t, 8H, J = 7.69 Hz, methine) 6.15 (s, 4H, ArH, ortho to OH), 7.06 (s, 4H, ArH, meta to OH), 8.87 (s, 8H, 8OH). ^{13}C NMR (DMSO-d_6): δ (ppm) =13.9, 14.1, 20.7, 22.1, 27.8, 28.7, 29.1, 29.2, 31.4, 59.8, 102.3, 122.8, 123.7, 151.7. EI–MS, m/z = 993 (M$^+$).

4.2.4. *Spectroscopic data of 2,4,8,20-tetraphenylpentacyclo[19.3.1.1.1.1]octacosa 1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene-4,6,10,12,16,18,22,24-octol (**4a**/**4b**)*

^{1}H NMR (DMSO-d_6) δ (ppm): 5.53(s, 4H, ArCH (C_{2v})), 5.55 (s, 2H, ArH (C_{2v}) ortho to OH), 5.62(s, 4H, ArCH (C_{4v})), 6.11 (s, 2H, ArH (C_{2v}) ortho to OH) 6.12 (s, 4H, ArH (C_{4v}), ortho to OH), 6.33 (s, 4H, ArH (C_{4v}), meta to OH), 6.34 (s, 4H, ArH (C_{2v}), meta to OH), 6.58–6.60 (m, 8H, ArH (C_{2v})), 6.72–6.74 (d, 8H, ArH (C_{4v})), 6.83 (d, 12 H,, ArH (C_{2v})), 6.93 (d, 12 H,, ArH (C_{4v})), 8.44 (s, 4 OH, ArOH (C_{2v})), 8.55 (s, 4OH (C_{2v}) 8OH (C_{4v}), ArOH)

4.2.5. *Spectroscopy data 2,4,8,20-tetra4-hydroxy phenylpentacyclo[19.3.1.1.1.1] octacosa1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene 4,6,10,12,16,18,22,24-octol (**5a**/**5b**)*

^{1}H NMR (DMSO-d_6) δ (ppm): 5.42 (s, 4H, ArCH (C_{2v})), 5.52 (s, 4H, ArCH (C_{4v})), 5.92 (s, 2H, ArH (C_{2v}) ortho to OH), 6.08 (s, 4H, ArH (C_{4v}), ortho to OH), 6.02 (s, 2H, ArH (C_{2v}) ortho to OH), 6.27 (s, 2H, ArH (C_{2v}), meta to OH), 6.31 (s, 4H, ArH (C_{4v}), meta to OH), 6.33 (s, 2H, ArH (C_{2v}) meta to OH), 6.41–6.43 (d, 8H, J = 4.71 Hz, ArH (C_{4v})), 8.35 (s, 4OH, ArOH (C_{2v}), 8.39 (s, 4OH, ArOH (C_{2v})), 8.43 (s, 4OH, ArOH (C_{4v})), 8.66 (s, 4 OH, ArOH (C_{2v}), 8.83 s, 4OH, ArOH (C_{4v})).

4.2.6. *Spectroscopic data of 2,4,8,20-tetra4-methoxy phenylpentacyclo[19.3.1.1.1.1] octacosa1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene 4,6,10,12,16,18,22,24-octol (**6a**/**6b**)*

3.63 (s, 12 H CH_3 (C_{2v})), 3.70 (s, 12 H CH_3 (C_{4v})), 5.45 (s, 4H, ArCH (C_{2v})), 5.55 (s, 2H, ArCH (C_{2v}) ortho to OH), 5.58 (s, 4H, ArCH (C_{4v})), 6.11 (s, 4H, ArH (C_{4v}), ortho to OH and 2H, ArH (C_{2v}), ortho to OH), 6.28 (s, 2H, ArH (C_{2v}) meta to OH), 6.30 (s, 2H, ArH (C_{2v}), meta to OH and 4H, ArH (C_{4v})), 6.43–6.45 (d, 8H, J = 4.71 Hz, ArH (C_{4v})), 6.49–6.51 (d, 8H, J = 4.8 Hz, ArH (C_{2v})), 6.53–6.55 (d, 8H, J = 4.8 Hz, ArH (C_{2v})), 6.59–6.61 (d, 8H, J = 4.71 Hz, ArH (C_{4v})), 8.41 (s, 4 OH, ArOH (C_{2v}), 8.50 (s, 4 OH, ArOH (C_{2v}).

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