Selective synthesis of "paco" or "alt" isomers of acetoxylcalixarenes catalysed by $Bi(OTf)_3$

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The "paco" or "alt" isomers of acetoxylcalixarenes were selectively prepared in the presence of catalytic amount (2 mol%) of $Bi(OTf)_3$,. Calix[4]arenes selectively gave two different isomers under specified conditions with a good selectivity, but, calix[6]arenes and calix[8]arenes only gave the "alt" isomers with a high selectivity.

Keywords: stereoselective synthesis, acyloxyl-calixarenes, $Bi(OTf)_3$

Calixarenes and their derivatives are known for their specific structures.[1–3] There are many types of calix[*n*]arenes (*n* = 4, 6, 8, *etc.*). However, calix[4]arenes are the best known and have four major isomers including cone, partial cone ("paco"), 1,2-alternate ("1,2-alt"), and 1,3-alternate ("1,3-alt") (Fig. 1)[1].

Esterification of the hydroxyl groups of calixarenes was normally catalysed by acid, such as sulfuric acid,[4,5] p-TSA[6] and $AlCl_3$,[7,8] but the results were not satisfactory giving poor yields and a low selectivity, and the ratio of two isomers is *ca* 1:1.

We now report a novel and convenient method for the esterification of calixarenes catalysed by metal triflates to obtain stereoselective products in good yields. In previous research,[9–12] metal triflates have been demonstrated to be excellent catalysts in many organic reactions. Recently, metal triflates have attracted much attention due to their low toxicity, high efficiency and stability[13]. To the best of our knowledge, there are no reports of the selective preparation of calix[4]arene isomers, using catalytic amount of metal triflates.

Firstly, acetylation of *p-tert*-butyl-calix[4]arene **1a** was chosen as the model reaction to optimise the reaction conditions, including catalysts, solvents, reaction temperature and time. The result was summarised in Table 1. Most metal triflates showed a better activity than the traditional catalysts such as H_2SO_4 and *p*-TSA. It was also found that $Bi(OTf)_3$ was the best (Table 1, Entries 1-6). Further study has shown that a larger amount (20 mol%) of the $Bi(OTf)_3$ had no significant influence on the reaction yield (Table 1, Entry 6 and 8), while higher temperature produced unwanted black solid (Table 1,

Table 1 Screening conditions[a]

Entry	Cat./mol %	Solvents	Temp./°C	Time/h	Yield[b]/%
1	$La(OTf)_3$(2)	Ac_2O	140	2	45
2	$Zn(OTf)_2$(2)	Ac_2O	140	2	50
3	$Yb(OTf)_3$(2)	Ac_2O	140	1	66
4	$Yb(OTf)_3$(2)	Ac_2O	75	1	70
5	$Bi(OTf)_3$(2)	Ac_2O	140	1	65
6	$Bi(OTf)_3$(2)	Ac_2O	50	1	80
7	$Bi(OTf)_3$(2)	Ac_2O	r.t.	1	75
8	$Bi(OTf)_3$(20)	Ac_2O	50	1	83
9	H_2SO_4(10)	Ac_2O	140	2	56[4,5]
10	*p*-TSA(10)	Ac_2O	140	20	54[6]
11	$Bi(OTf)_3$(2)	$CHCl_3$	50	1	60
12	$Bi(OTf)_3$(2)	CH_2Cl_2	40	1	78
13	$Bi(OTf)_3$(2)	Toluene	50	1	65
14	$Bi(OTf)_3$(2)	$(CH_2)_2Cl_2$	50	1	20
15	$Bi(OTf)_3$(2)	CH_3CN	50	1	60

[a] All reactions were run with 1.0 mmol **1a** under different reaction conditions.
[b] Isolated yields of product **2a** plus **3a** based on **1a**.

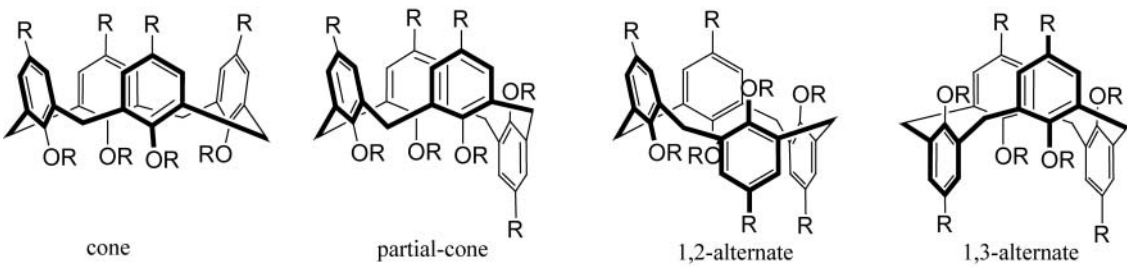
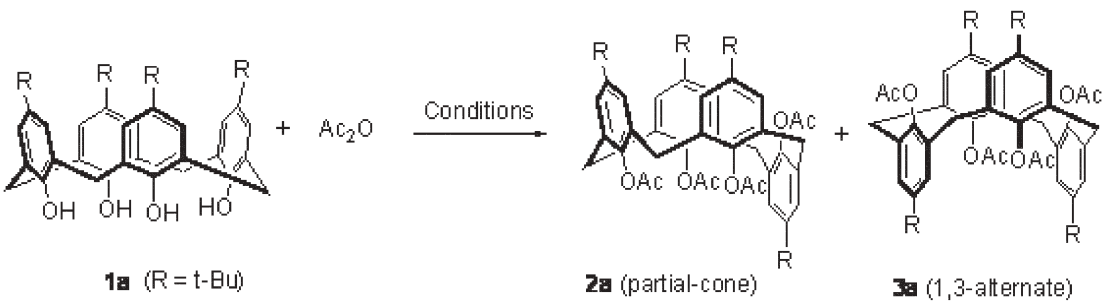


Fig. 1 Isomers of calix[4]arene derivatives.



Scheme 1

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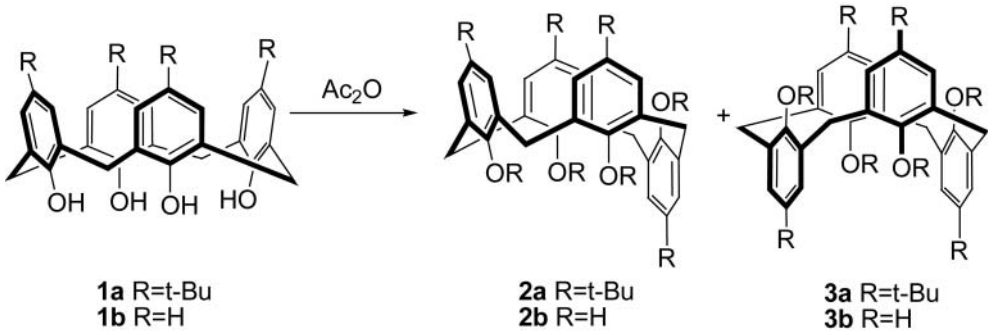


Scheme 2

Entry 5). Furthermore, in the presence of 2 mol% $Bi(OTf)_3$, 78% and 80% yields of acetylated products (**2a** plus **3a**) were obtained in CH_2Cl_2 or excess Ac_2O respectively. If the reaction was carried out in other solvents, the yields were not satisfactory.

It should be noted that the catalysts and solvents affected the conformation of the acetylated product (Scheme 2). When H_2SO_4 or *p*-TSA was used as catalyst, the products were a mixture of the two isomers, partial-cone (**2a**) and 1,3-alternate (**3a**), and the ratio of these two isomers is about 1:1 by TLC. Interestingly, if the reaction was carried out at 50 °C for 1 h using Ac_2O as solvent in the presence of $Bi(OTf)_3$, the main product was **2a**. Unexpectedly, the proportion of product **2a** gradually decreased when the reaction time was prolonged to 2 h. On the contrary, **3a** was the unique product if $CHCl_3$ was used as solvent at refluxing for 1h in the presence of $Bi(OTf)_3$. Hence, the isomer that was formed could be controlled by using different conditions (Scheme 2). Under other reaction conditions, the products that were obtained were mixtures of tetraacetates with low selectivity.

With these data in hand, tetrahydroxycalix[4]arene **1b** was chosen to investigate the stereoselectivity of this novel method. The product are tetra-acetates that exist in the 1,3-alternate and partial cone conformation (Table 2). It is shown that the distribution among these conformers is dependent on a variety of factors including temperature and solvent. It can be concluded that under the strong acidic condition (Table 2, entries 1 and 4) leads to the partial cone conformation, while neutral conditions at higher temperature favour the 1,3-alternate conformation (Table 2, entries 3 and 6).

Table 2 Effect of temperature and solvents on the conformation distribution in the acetylation of calix[4]arene

Entry	R	Solvents	Temp. /°C	Yield /%	
				2	**3**
1	*t*-Bu	Ac_2O	50	72	**8**
2	*t*-Bu	CH_2Cl_2	Reflux	33	45
3	*t*-Bu	$CHCl_3$	Reflux	Trace	65
4	H	Ac_2O	50	64	16
5	H	CH_2Cl_2	Reflux	42	40
6	H	$CHCl_3$	Reflux	Trace	70

The two isomers of partial-cone and 1,3-alternate were revealed by TLC, since their R_f value was different. The ^{1}H NMR spectrum for each isomer is distinctive. It contains a singlet resonance for the $ArCH_2Ar$ methylene hydrogens of the 1,3-alternate isomer (Fig. 1), and several doublets for the methylene hydrogens of the partial cone isomer. The ^{1}H NMR spectra of each product was identified from authentic samples in the literature.

We also tried to synthesise other O-acetyl calix[*n*]arenes (*n* = 6, 8) using $Bi(OTf)_3$ as catalyst (Table 3). This showed that the method could be used for different calix[*n*]arenes with high yield. The traditional method to synthesise these product **3c–f** used CH_2Cl_2 as a solvent and excess $AlCl_3$ and acetyl chloride under reflux for 1–2 h to afford the products. The yield was about 30–50%. The ^{1}H NMR spectrum of **3c** and **3d** revealed their 1,3,5-alternate conformation whilst **3e** and **3f** were 1,3,5,7-alternate conformations (Fig. 2) which were the same as the literature.[7,14]

In summary, the present procedure describes an efficient selective synthesis of acetoxy-calix[*n*]arenes isomers catalysed by $Bi(OTf)_3$. We believe that this procedure would provide a better and more practical alternative to the existing procedures for the preparation of derivatives of calix[*n*]arenes.

Experimental

p-tert-Butyl-calix[*n*]arene and de-*tert*-butyl-calix[*n*]arenes were prepared according to the literature.[3,8] $M(OTf)_n$ was prepared from M_2O_n and triflic acid. Melting points were measured on a Büchi B-540 capillary melting point apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 400 MHz or Bruker Avance III (500 MHz) instrument using $CDCl_3$ as the solvent, and chemical shifts were expressed in parts per million (ppm) using TMS as an internal standard. Mass spectra were measured with a Trace Finnigan DSQ. All spectroscpic data for the products were identical to authentic samples.

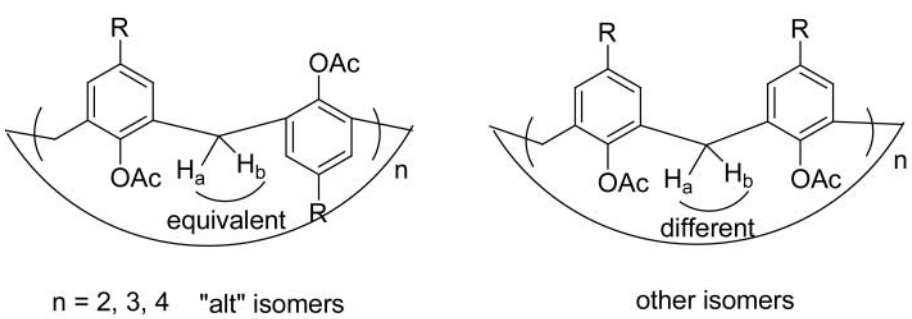
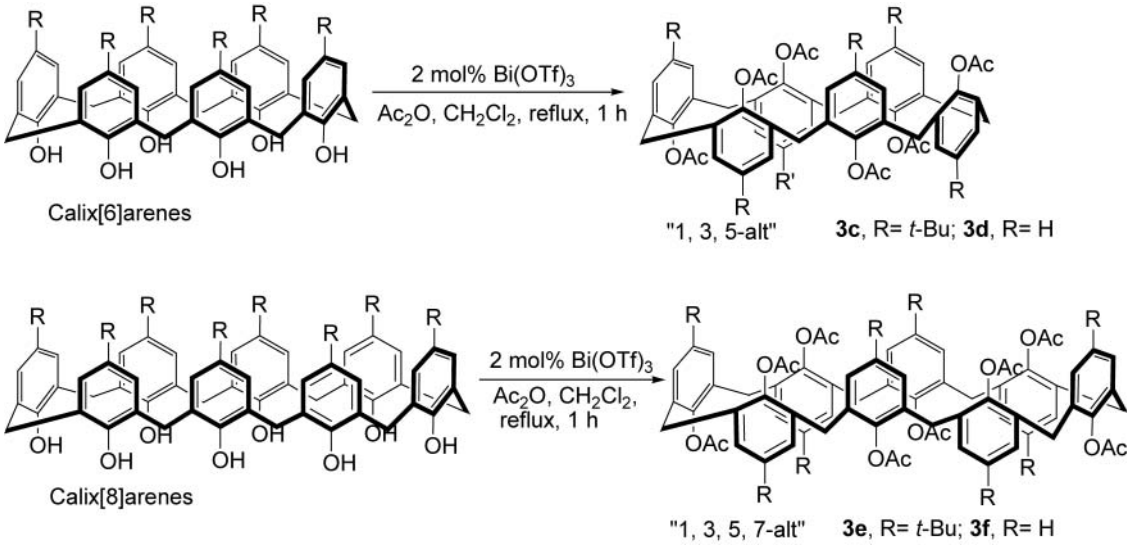


Fig. 2 H NMR difference of protons on methene.



Scheme 3

Table 3 The preparation of O-acetoxy-calix[*n*]arene

Entry	R	*n*	Solvent	Product	Yield [a]/%
1	*t*-Bu	6	CH_2Cl_2	**3c**	84
2	H	6	CH_2Cl_2	**3d**	71
3	*t*-Bu	8	CH_2Cl_2	**3e**	82
4	H	8	CH_2Cl_2	**3f**	72

[a] Isolated yield based on **1c–f**.

25,26,27,28-Tetraacetoxy-5,11,17,23-tetra-tert-butylcalix[4]arene (**2a**): A 0.5 g (0.8 mmol) sample of **1a** was dissolved in Ac_2O (6 mL), treated with $Bi(OTf)_3$ 0.011 g (0.016 mmol) and heated at 50 °C for 1 h. The solvent was evaporated under reduced pressure, the remainder washed with methanol, filtered and dried to give a white solid. This was separated by silica gel column chromatography to give 0.45 g (72%) the paco-conformer **2a**. white solid; m.p. 324.5–326.1 °C (lit.[6] m.p. 320 °C); ^{1}H NMR($CDCl_3$) δ 1.09 (s, 18H), 1.36 (s, 9H), 1.40 (s, 9H), 1.90 (s, 3H), 1.99 (s, 3H), 2.32 (s, 6H), 3.24 (d, 2H, *J* = 13.6 Hz), 3.51 (d, 2H, *J* = 13.6 Hz), 3.56 (d, 2H, *J* = 15.2 Hz), 3.63 (d, 2H, *J* = 15.2 Hz), 6.83 (s, 4H), 7.23(s, 4H); ^{13}C NMR ($CDCl_3$) δ 21.5, 22.2, 22.6, 31.4, 31.6, 32.0, 34.3, 34.7, 34.8, 38.3, 125.7, 125.9, 127.0, 127.4, 131.3, 132.1, 133.4, 134.2, 144.3, 144.9, 147.3, 147.5; MS (ESI): *m/z* = 816.7 (M^+)

25,26,27,28-Tetraacetoxy-5,11,17,23-tetra-tert-butylcalix[4]arene (**3a**): A mixture of 0.5 g (0.8 mmol)**1a** was treated with Ac_2O 0.65 g (6.4 mmol)and 8 mL $CHCl_3$ and $Bi(OTf)_3$ 0.011g (0.016 mmol). It was heated under reflux for 1 h, cooled to room temperature and poured into 50 mL water. The organic layer was dried with anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the product was recrystallised from MeOH–$CHCl_3$ to give 0.4 g (65%) the 1,3-alt conformer **3a** as a white solid; m.p. 382.6–384.0 °C (lit.[6] m.p. > 300 °C); ^{1}H NMR ($CDCl_3$) δ 1.29 (s, 36H), 1.48 (s, 12H), 3.74 (s, 8H), 7.04 (s, 8H); ^{13}C NMR ($CDCl_3$) δ 20.3, 31.2, 34.0, 37.8, 125.5, 132.0, 145.6, 147.1, 167.7; MS (ESI): *m/z* =816.7 (M^+)

25,26,27,28-Tetraacetoxy-calix[4]arene (**2b**): A 0.34 g (0.8 mmol) sample of **1b** was dissolved in Ac_2O (6 mL), treated with $Bi(OTf)_3$ 0.011 g (0.016 mmol) and heated at 50 °C for 1 h. The solvent was evaporated and the remainder was washed with methanol, filtered and dried to give a white solid, which was separated by silica gel column chromatography to get 0.30 g (64%) paco-conformer **2b** as colourless plates; m.p. > 400 °C (lit.[6] m.p. 402–403 °C); ^{1}H NMR ($CDCl_3$) δ 1.79 (s, 3H), 2.07 (s, 3H), 2.37 (s, 6H), 3.29 (d, 2H, *J* =13.6 Hz), 3.57 (d, 2H, *J* =13.6 Hz), 3.65 (d, 2H, *J* =14.8 Hz), 3.70 (d, 2H, *J* = 14.8 Hz), 6.74–6.93 (m, 6H), 7.16–7.24 (m, 2H), 7.26–7.29 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 21.0, 21.4, 21.5, 30.7, 37.3, 124.7, 125.3, 126.1, 129.0, 129.4, 129.5, 130.1, 131.4, 132.5, 134.0, 134.8, 145.9, 147.6, 149.2, 168.3, 168.8, 170.2; MS (ESI): *m/z* =591.7 (M^+)

25,26,27,28-Tetraacetoxy-calix[4]arene (**3b**): A mixture of 0.34 g (0.8 mmol) **1b** was treated with Ac_2O 0.65 g (6.4 mmol) and 8 mL $CHCl_3$ and $Bi(OTf)_3$ 0.011 g (0.016 mmol) and heated under reflux for 1 h. It was cooled to room temperature, poured into 50 mL water, and the organic layer was dried with anhydrous sodium sulfate. The solvent was evaporated under reduced pressure and the product was recrystallised from MeOH–$CHCl_3$ to give 0.33 g (70%) 1,3-alt conformer **3b**. colourless needle. m.p. > 400 °C (lit.[6] m.p. 405–406 °C); ^{1}H NMR($CDCl_3$) δ 1.55 (s, 12H), 3.76 (s, 8H), 7.07 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 20.3, 37.5, 125.4, 129.0, 133.1, 148.2, 167.9; MS (ESI): *m/z* = 591.7 (M^+)

37,38,39,40,41,42-hexaacetoxy-5,11,17,23,29,35-hexa-tert-butylcalix[6]arene (**3c**): A sample of 0.97 g (1 mmol) **1c** was treated with Ac_2O 1.22 g (12 mmol) and 20 mL CH_2Cl_2 and $Bi(OTf)_3$ 0.013 g (0.02 mmol), and heated under reflux for 1h. The mixture was cooled to room temperature, poured into ice water, and the organic layer was dried with anhydrous sodium sulfate. The solvent was evaporated and the product recrystallised from MeOH–$CHCl_3$ to give **3c** 1.02 g (84%) as a white solid; m.p. 334.3–335.3 °C (lit[7] > 280 °C); ^{1}H NMR($CDCl_3$) δ 1.17 (s, 54H), 1.89 (s, 18H), 3.62 (s, 12H), 6.95 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 20.2, 31.2, 34.3, 126.0, 131.2, 145.1, 148.3, 168.6; MS (ESI): *m/z* = 1224 (M^+)

37,38,39,40,41,42-hexaacetoxy-calix[6]arene (**3d**): A 0.63 g (1 mmol) sample **1d** was treated with Ac_2O 1.22g (12 mmol) and 20 mL CH_2Cl_2 and $Bi(OTf)_3$ 0.013 g (0.02 mmol) and heated under reflux for 2 h. It was cooled to room temperature and poured into ice water. The organic layer was dried with anhydrous sodium sulfate and the solvent was evaporated. Recrystallisation of the product from MeOH–$CHCl_3$ gave 0.63 g (71%) **3d** as a white solid; m.p. 335.0–335.6 °C (lit.[8] 335–336 °C); ^{1}H NMR ($CDCl_3$) δ 1.90 (s, 18H), 3.67 (s, 12H), 6.92–7.25 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 20.5, 31.6, 126.4, 129.3, 132.4, 147.7, 169.0; MS (ESI): *m/z* =888.2 (M^+)

49,50,51,52,53,54,55,56-octaacetoxy-5,11,17,23,29,35,41,47-octa-tert-butylcalix[8]aren (**3e**): A 1.29 g (1 mmol) sample **1e** was treated with Ac_2O 1.62 g (16 mmol) and 20 mL CH_2Cl_2 and $Bi(OTf)_3$ 0.013 g (0.02 mmol), and heated under reflux for 1 h. It was cooled to room temperature, poured into ice water and the organic layer was dried over anhydrous sodium sulfate. The solvent was evaporated. Recrystallisation from MeOH–$CHCl_3$ gave 1.24 g (82%) **3e** as a white solid; m.p. 353.8–354.6 °C (lit.[7] > 280 °C); ^{1}H NMR($CDCl_3$) δ 1.17 (s, 72H), 1.89 (s, 24H), 3.63 (s, 16H), 6.95 (s, 16H); ^{13}C NMR ($CDCl_3$) δ 20.2, 31.2, 34.3, 126.1, 131.2, 145.1, 148.3, 168.6; MS (ESI): *m/z* = 1632.5 (M^+)

49,50,51,52,53,54,55,56-octaacetoxy-calix[8]arene (**3f**): A 0.84 g (1 mmol) sample **1f** was treated with Ac_2O 1.62 g (16 mmol) and 20 mL CH_2Cl_2 and $Bi(OTf)_3$ 0.013 g (0.02 mmol) and heated under reflux for 2 h. It was cooled to room temperature, poured into ice water and the organic layer was dried with anhydrous sodium sulfate. The solvent was evaporated. Recrystallisation from MeOH–$CHCl_3$ gave 1.17 g (72%) **3f** as a white solid; m.p. 327–328 °C (lit[8]. m.p. 327–330 °C) ^{1}H NMR($CDCl_3$) δ 1.99 (s, 24H), 3.66 (s, 16H), 6.92–7.04 (m, 24H). ^{13}C NMR ($CDCl_3$) δ 20.5, 31.6, 126.4, 129.3, 132.4, 147.7, 169.0; MS (ESI): *m/z* = 1184.4 (M^+)

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