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# Investigation of O-Methylation of *p-tert*-Butylcalix[6]arene using Methyl *p*-Tosylate

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**Abstract :** O-methylation of *p-tert*-butylcalix[6]arene with methyl *p*-tosylate in acetonitrile under limiting conditions of base and electrophile has been investigated, which led to isolation of all twelve O-methylated derivatives from the reaction mixture. Previously unreported direct single step syntheses of (1,2,4-tri)-, (1,2,3,4-tetra)- and (1,2,3,5-tetra)-O-methylated derivatives from *p-tert*-butylcalix[6]arene have been achieved in this study and are reported here for the first time.

**Keywords :** *p-tert*-butylcalix[6]arene, O-methylation, methyl *p*-tosylate, $Cs_2CO_3$.

## Introduction

Calixarenes are widely utilized as scaffolds for host-guest type receptors[1,2]. In order to utilize calixarenes as useful receptors, their regioselective derivatization is a crucial requirement since number and position of the ligating group influences their recognition behaviour[3,4]. Though well defined protocols are available for calix[4]arene system to get all possible O-alkylation products[5-8], relatively lesser volume of literature is available for the selective O-alkylation reaction of calix[6]arenes. This is because larger number of hydroxyls, bigger π-basic cavity and greater conformational flexibility in case of calix[6]arenes as compared to calix[4]arenes, makes regioselective alkylation of calix[6]arenes a fairly challenging task.

Though reports entailing O-methylation of *p-tert*-butylcalix[6]arene (**1**) are available in the literature, but in most of the cases syntheses of tri-(1,3,5)/hexa-O-methyl ethers of **1** are discussed. Only limited data is available on the synthesis of other O-methylated products of **1**[9-12]. Also, to the best of our knowledge syntheses of (1,2,4)-tri-, (1,2,3,4)-tetra- and (1,2,3,5)-tetra-O-methylated derivatives of **1** from its direct O-methylation in a single step have not yet been reported in the literature. Multistep reactions involving alkylation/dealkylation or protection/deprotection are required for formation of (1,2,4)-tri-, (1,2,3,4)-tetra- and (1,2,3,5)-tetra-O-methylated derivatives of **1**, which are low yielding and cumbersome because in each case, purification of the desired compound from a complex reaction mixture is required[10,12]. For example, (1,2,4)-tri-O-methylated derivative of **1** was synthesized by Shinkai and co-workers in three steps from **1** in overall yield of 6 % requiring overall reaction time of 48 h, which involved protection with a *m*-xylenyl group, followed by exhaustive methylation and then deprotection of xylenyl units with $Me_3SiBr$[12]. In another report, (1,2,3,4)-tetra-O-methyl ether of **1** was synthesized in three steps by Neri and co-workers[10]. Thus, there is still a need to develop protocols for O-methylation of **1**.



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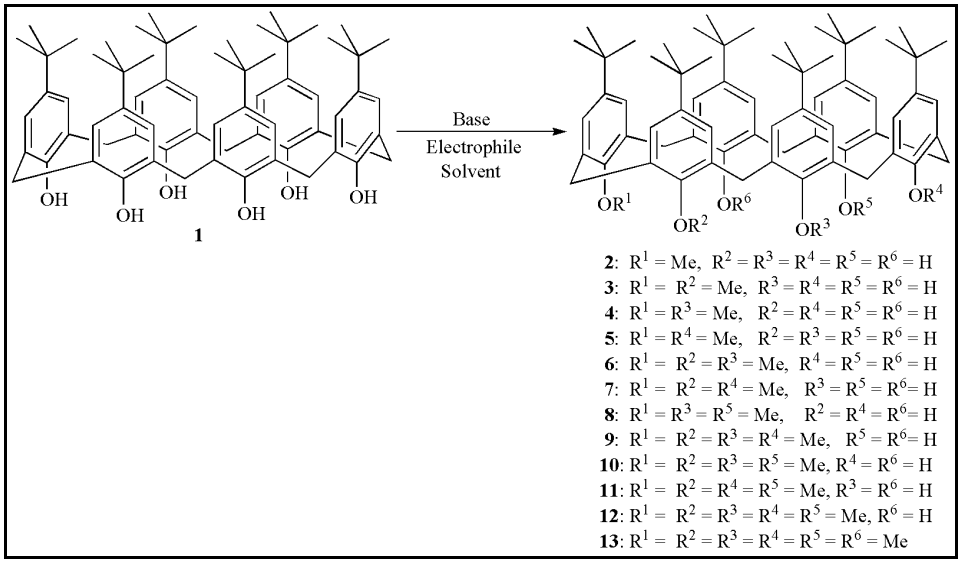
Since past two decades, I have been involved in exploiting calixarene based hosts for various targets like cesium[13,14] and fullerenes[15-17], and developing synthetic protocols for selective functionalization of calixarenes[18,19].

In order to realize full potential of calix[6]arenes as receptors, syntheses of its higher alkylated derivatives are needed. Therefore, the present study to investigate O-methylation of **1** using methyl *p*-tosylate is undertaken (Scheme 1).




**Scheme 1: O-methylation of *p-tert*-butylcalix[6]arene 1**

## Experimental

All the reagents and the chemicals (Fluka and Aldrich) were of analytical grade and used as received if not mentioned otherwise. Compound **1** was dried under vacuum at 100 °C for 6 h before use. Anhydrous $K_2CO_3$, $KHCO_3$ and $Cs_2CO_3$ were obtained by heating analytical grade materials on flame and then stored in a dessicator. Acetonitrile and acetone were dried and distilled over $P_2O_5$. All the reactions were carried out in flame dried glass apparatus kept under an argon atmosphere. Melting points were taken on Fisher-Johns melting point apparatus and are uncorrected. $^1$H NMR spectra were recorded with a Bruker AC 200 spectrometer at ambient temperature.

### General procedure for methylation of 1:

A mixture of **1** (487 mg, 0.5 mmol) and base in the solvent (50 mL) was refluxed for 2 h. The mixture was cooled to room temperature and the alkylating agent was added, and the mixture refluxed for 20 h. The solvent was removed in vacuo and water was added to the residue. The mixture was acidified with 1 N HCl and extracted with $CHCl_3$. The organic layer was washed with water, brine and dried ($Na_2SO_4$) and then concentrated to dryness. The residue was then subjected to column chromatography followed in some instances by preparative thin layer chromatography over silica gel ($CH_2Cl_2$/Hex) to afford O-methylated compounds **2-13**.

### Spectral data of compounds

***5,11,17,23,29,35-Hexa-tert-butyl-37-methoxy-38,39,40,41,42-pentahydroxycalix[6]arene (2)*[9]:** White solid. mp: >300 °C (lit.[9] mp: >320 °C). $^1$H NMR (200 MHz, $CDCl_3$): δ 1.16 (s, 9H), 1.23 (s, 9H), 1.26 (s, 18H), 1.29 (s, 18H), 3.74 (s, 4H), 3.91-3.94 (m, 8H), 4.01 (s, 3H), 7.00 (s, 2H), 7.10-7.13 (m, 10H), 8.78 (s, 2H), 9.47 (br s, 1H), 9.73 (s, 2H).

***5,11,17,23,29,35-Hexa-tert-butyl-37,38-dimethoxy-39,40,41,42-tetrahydroxycalix[6]arene (3)*[12]:** White solid. mp: 269-271 °C (lit.[12] mp: 270-272 °C). $^1$H NMR (200 MHz, $CDCl_3$): δ 1.13 (s, 18H), 1.24 (s, 18H), 1.26 (s, 18H), 3.73-3.80 (m, 12H), 3.90 (s, 4H), 4.09 (s, 2H), 6.93 (s, 2H), 6.99-7.10 (m, 10H), 8.17 (br s, 2H), 8.63 (br s, 2H).

***5,11,17,23,29,35-Hexa-tert-butyl-37,39-dimethoxy-38,40,41,42-tetrahydroxycalix[6]arene (4)*[12]:** White solid. mp: 252-254 °C (lit.[12] mp: 253-255 °C). $^1$H NMR: δ 1.08 (s, 18H), 1.24 (s, 9H), 1.27 (s, 27H), 3.77 (m, 10H), 3.89-3.92 (m, 8H), 6.90-6.94 (m, 4H), 7.04-7.09 (m, 9H), 7.99 (s, 2H), 8.70 (s, 1H).

***5,11,17,23,29,35-Hexa-tert-butyl-37,40-dimethoxy-38,39,41,42-tetrahydroxycalix[6]arene (5)*[12]:** White solid. mp: >300 °C (lit.[12] mp: >340 °C). $^1$H NMR: δ 1.15 (s, 18H), 1.21 (s, 36H), 3.69 (s, 6H), 3.87 (m, 12H), 6.96-7.01 (m, 8H), 7.10 (m, 4H), 8.21 (s, 4H).

***5,11,17,23,29,35-Hexa-tert-butyl-37,38,39-trimethoxy-40,41,42-trihydroxycalix[6]arene (6)*[12]:** White solid. mp: >300 °C (lit.[12] mp: 300-302 °C). $^1$H NMR: δ 1.10 (s, 18H), 1.18 (s, 18H), 1.24 (s, 9H), 1.28 (s, 9H), 3.01 (s, 3H), 3.78 (s, 4H), 3.84-3.87 (m, 10H), 4.05 (s, 4H), 6.95-6.98 (m, 6H), 7.06-7.12 (m, 6H), 7.65 (s, 1H), 8.26 (s, 2H).

***5,11,17,23,29,35-Hexa-tert-butyl-37,38,40-trimethoxy-39,41,42-trihydroxycalix[6]arene (7)*[12]:** White solid. mp: 275-277 °C (lit.[12] mp: 274-276 °C). $^1$H NMR: δ 0.89 (s, 9H), 1.09 (s, 18H), 1.15 (s, 18H), 1.25 (s, 9H), 3.14 (s, 3H), 3.30 (s, 3H), 3.34 (s, 3H), 3.88-3.98 (m, 12H), 6.70-7.18 (m, 13H), 7.68 (s, 1H), 9.01 (s, 1H).

***5,11,17,23,29,35-Hexa-tert-butyl-37,39,41-trimethoxy-38,40,42-trihydroxycalix[6]arene (8)*[12]:** White solid. mp: 272-274 °C (lit.[12] mp: 272-274 °C). $^1$H NMR: δ 1.04 (s, 27H), 1.23 (s, 27H), 3.50 (s, 9H), 3.92 (s, 12H), 6.82 (s, 3H), 6.93 (s, 6H), 7.04 (s, 6H).

***5,11,17,23,29,35-Hexa-tert-butyl-37,38,39,40-tetramethoxy-41,42-dihydroxycalix[6]arene (9)*[12]:** White solid. mp: 121-123 °C (lit.[12] mp: 122-124 °C). $^1$H NMR: δ 1.05 (s, 18H), 1.15 (s, 18H), 1.26 (s, 18H), 3.16 (s, 6H), 3.62 (s, 2H), 3.70 (s, 6H), 3.80 (s, 4H), 4.03 (s, 6H), 6.86 (m, 2H), 6.95 (m, 2H), 7.02-7.06 (m, 8H), 7.54 (s, 2H).

***5,11,17,23,29,35-Hexa-tert-butyl-37,38,39,41-tetramethoxy-40,42-dihydroxycalix[6]arene (10)*[12]:** White solid. mp: 230-232 °C (lit.[12] mp: 229-231 °C). $^1$H NMR: δ 0.91 (s, 18H), 1.09 (s, 18H), 1.22 (s, 9H), 1.35 (s, 9H), 2.22 (s, 3H), 2.59 (s, 3H), 3.87(m, 8H), 3.98-4.03 (m, 10H), 6.65-6.73 (m, 4H), 6.98-7.08 (m, 6H), 7.22 (s, 2H), 7.65 (s, 2H).

***5,11,17,23,29,35-Hexa-tert-butyl-37,38,40,41-tetramethoxy-39,42-dihydroxycalix[6]arene (11)*[12]:** White solid. mp: 278-280 °C (lit.[12] mp: 275-277 °C). $^1$H NMR: δ 0.96 (s, 18H), 1.20 (s, 36H), 3.15 (s, 12H), 3.89 (s, 8H), 3.99 (s, 4H), 6.72 (s, 4H), 7.04-7.09 (m, 8H), 8.03 (s, 2H).

***5,11,17,23,29,35-Hexa-tert-butyl-37,38,39,40,41-pentamethoxy-42-hydroxycalix[6]arene (12)*[12]:** White solid. mp: 256-258 °C (lit.[12] mp: 254-256 °C). $^1$H NMR: δ 0.92 (s, 9H), 1.14 (s, 9H), 1.18 (s, 18H), 1.20 (s, 18H), 3.07 (s, 12H), 3.52 (s, 3H), 3.83 (s, 4H), 3.95-3.97 (m, 8H), 6.82-6.90 (m, 4H), 7.03-7.11 (m, 8H), 7.36 (s, 1H).

***5,11,17,23,29,35-Hexa-tert-butyl-37,38,39,40,41,42-hexamethoxycalix[6]arene (13)*[12]:** White solid. mp: >300 °C (lit.[12] mp: 315-317 °C). $^1$H NMR: δ 1.14 (s, 54H), 2.98 (s, 18H), 3.95 (m, 12H), 7.01 (s, 12H).

## Results and Discussion

Identity of the base, electrophile and solvent play a crucial role in determining the regioselectivity in O-alkylation reactions of calixarenes. In fact, during selective alkylation of *p-tert*-butylcalix[8]arene by Neri and coworkers, it was observed that changing the electrophile led to altogether different regioselectivity[20]. Since mostly MeI as the electrophile has been explored for O-methylation of **1** in the literature, thus we envisaged that utilizing methyl tosylate as an alternative electrophile for this reaction, might affect its product profile. Therefore, in the present work, O-methylation of **1** using methyl *p*-tosylate in acetonitrile was investigated by using different stoichiometric ratios of bases ($KHCO_3$, $K_2CO_3$ and $Cs_2CO_3$) under the limiting conditions of base and electrophile (Scheme 1), and the results are presented in Table 1.

**Table 1: Product composition for O-methylation of *p-tert*-butylcalix[6]arene (1) at the lower rim.**[a]

| Entry | Base (equiv.) | Electrophile (equiv.) | Product (% yield) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** | **13** |
| 1 | $K_2CO_3$ (1.2) | MeOTs (1.4) | b | 14 | b | b | - | - | 10 | 17 | - | b | b | - | - |
| 2 | $KHCO_3$ (1.2) | MeOTs (1.2) | 15 | 38 | - | b | - | - | b | 10 | - | - | - | - | - |
| 3 | $Cs_2CO_3$ (1.2) | MeOTs (1.9) | b | 12 | 26 | 20 | 10 | - | b | 6 | - | b | b | - | - |
| 4 | $K_2CO_3$ (2.1) | MeOTs (2.1) | - | 6 | 31 | b | - | 11 | b | 12 | - | b | 6 | - | - |
| 5 | $K_2CO_3$ (2.2) + $KHCO_3$ (1.1) | MeOTs (3.3) | - | - | - | - | - | 19 | - | 15 | - | 19 | 14 | 12 | b |
| 6 | $KHCO_3$ (3.3) | MeOTs (3.3) | 8 | 11 | 14 | b | - | - | - | 18 | - | 17 | 7 | - | - |
| 7 | $K_2CO_3$ (3.1) | MeOTs (3.1) | - | - | - | - | - | b | - | 15 | - | 42 | 8 | b | b |
| 8 | $K_2CO_3$ (3.1) | MeOTs (3.2) | - | - | 25 | 6 | - | 6 | - | 18 | - | b | b | - | - |
| 9 | $Cs_2CO_3$ (3.3) | MeOTs (4.1) | - | - | - | - | - | 29 | - | - | 16 | - | - | - | 25 |
| 10 | $K_2CO_3$ (4.1) | MeOTs (4.1) | - | - | - | - | - | - | - | 10 | - | 40 | 13 | 8 | b |
| 11 | $K_2CO_3$ (3.1) | MeI (9) | - | 41 | 9 | 11 | - | - | - | b | - | - | b | - | - |
| 12 | $K_2CO_3$ (3.1) | MeI (15) | - | - | - | - | - | - | - | 27 | - | 18 | 24 | - | - |

[a] All reactions are in $CH_3CN$ except entries 8 and 12 where solvent is acetone. All reactions are refluxed for 22 h except entry 12 which is refluxed for 5 days.

[b] Traces detected in TLC and in $^1H$ NMR data of the product mixture, and yields found to be <5% on isolation.

All the compounds synthesized were characterized by their respective spectral data which matches well with the reported data. Under the appropriate reaction conditions, we have been able to isolate all the twelve possible O-methylated derivatives of **1** in variable yields. The advantage of this study is further shown by syntheses of compounds **7**, **9** and **10** directly in one step from **1** for the very first time.

Using 3.1 equiv. of $K_2CO_3$ in $CH_3CN$ yielded **10** (42 %yield) as the major product but by changing the solvent to acetone, **3** and **8** were isolated as the major products in 25 and 18 % yields, respectively (Table 1, Entries 7 and 8). It shows that solvent is also playing a role in the alkylation reaction.

Utilizing 3-4 equiv. of $K_2CO_3$ with MeOTs-$CH_3CN$ combination invariably resulted in isolation of **10** as the major product (40-42%yield) (Table 1, Entries 7 and 10). Interestingly, changing the electrophile from MeOTs to MeI, product distribution for alkylation of **1** got changed; with MeOTs **10** was obtained as the major product in 42 %yield whereas by using MeI as the electrophile, **2** was obtained as the major product in 41 %yield (Table 1, Entries 7 and 11) where 3.1 equiv. of $K_2CO_3$ has been utilized in both the cases. It clearly outlines the difference between the electrophiles MeOTs and MeI for the O-methylation reaction with **1**.

More interesting was the O-methylation of **1** in the presence of $Cs_2CO_3$ which presented a different scenario. When $Cs_2CO_3$ was used as a base (1.2 equiv.) **3** and **4** were obtained in 26 and 20 %yields respectively

along with minor amounts of **2** (12% yield), **5** (10 %yield) and **8** (6% yield) (Table 1, Entry 3). Using 3.3 equiv. of $Cs_2CO_3$ afforded **6**, **9** and **13** in 29 %, 16 % and 25 %yields respectively (Table 1, Entry 9). With $Cs_2CO_3$ as the base, proximally substituted products (**3**, **4**, **6** and **9**) have been isolated in appreciable yields (>15 % yield) whereas using $KHCO_3$ or $K_2CO_3$ as the base led to formation of other substituted products too (**7**, **8**, **10** and **11**); and nowhere formation of **5** and **9** was observed with $KHCO_3$ or $K_2CO_3$. These results indicate that metal cation present in the base is also playing a crucial role in product formation. Similar formation of less stable oxyanions has been observed by Neri and co-workers during the alkylation of *p-tert*-butylcalix[8]arene in the presence of weak bases and could be related either to the temporary conformational preferences of the intermediates or to the conformational mobility of the calixarene[20,21].

## Conclusion

In conclusion, O-methylation of *p-tert*-butylcalix[6]arene with methyl *p*-tosylate under the limiting conditions of base and alkylating agent, has led to isolation of all of its twelve derivatives from the reaction mixture; **2** (41 %), **3** (31 %), **4** (20 %), **6** (29 %), **8** (27 %), **10** (42 %), **11** (24 %) and **13** (25 %) in modest yields and other derivatives were obtained in lower yields (10-16 % yields) where in some cases, yields and/or reaction times are better than the existing reports. It is noteworthy that this work is the first report in the literature where single step syntheses of compounds **7**, **9** and **10** are realized from direct O-methylation of **1**.

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