Pergamon

Tetrahedron Letters, Vol. 35, No. 38, pp. 7073-7076, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01460-4

Metal-template *Ortho*-Regioselective Mono- and Bis-de-*tert*-Butylation of Poly-*tert*-Butylated Phenols

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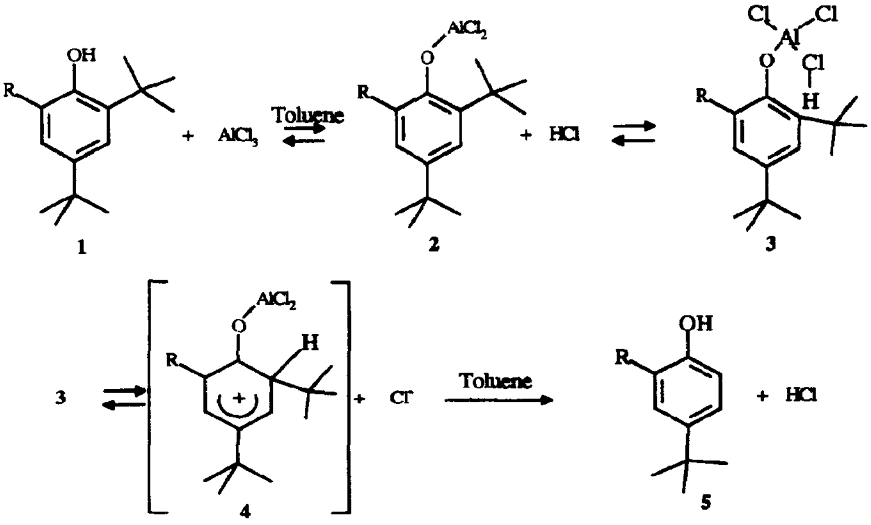
Abstract: A metal-template *ortho*-regioselective mono- and bis-de-*tert*-butylation of poly-*tert*-butylated phenol-formaldehyde oligomers is reported.

As part of our program aimed at studying new macrocyclic ligands for ions and neutral molecules, we recently required an efficient convergent synthesis of calixarenes bearing different functional groups on the methylene bridges[1].

A combination of bromine atom and *tert*-butyl group was commonly utilized to protect the *ortho* and *para* positions of phenol rings in the preparation of definite phenol-formaldehyde oligomers, which constitute fundamental building blocks for the convergent calixarene synthesis[2].

Evidently, the possibility of utilizing *tert*-butyl as the sole protective group in the rational synthesis of these oligomers represents a great improvement of the entire process.

Scheme 1



We report here the results of our studies indicating that the controlled *ortho*-regioselective mono- and bis-de-*tert*-butylation of poly-*tert*-butylated phenolic compounds can be accomplished *via* a "metal-template process"[3].

Our working hypothesis was that a dichloroaluminium phenolate **2**, obtained by reaction of the phenolic substrate **1** with $AlCl_3$ in dry toluene[4], could give rise to a selective metal-template *ortho*-protonation (**4**) thus favouring the transalkylation process (**4**→**5**).

First, 2,4-di-*tert*-butyl phenol (**1a**: R=H), selected as the model substrate, was treated with $AlCl_3$ (molar ratio 1:1) in dry toluene at 25 °C for 1 hour. In agreement with the sequence shown in the Scheme **1**, *p*-*tert*-butyl phenol **5a** was recovered in 85% yield accompanied by trace of phenol (5% yield). These results suggest that the "metal-template effect" contributes significantly to the *ortho*-regioselective mono-de-*tert*-butylation of substrates such as **1**.

Scheme 2

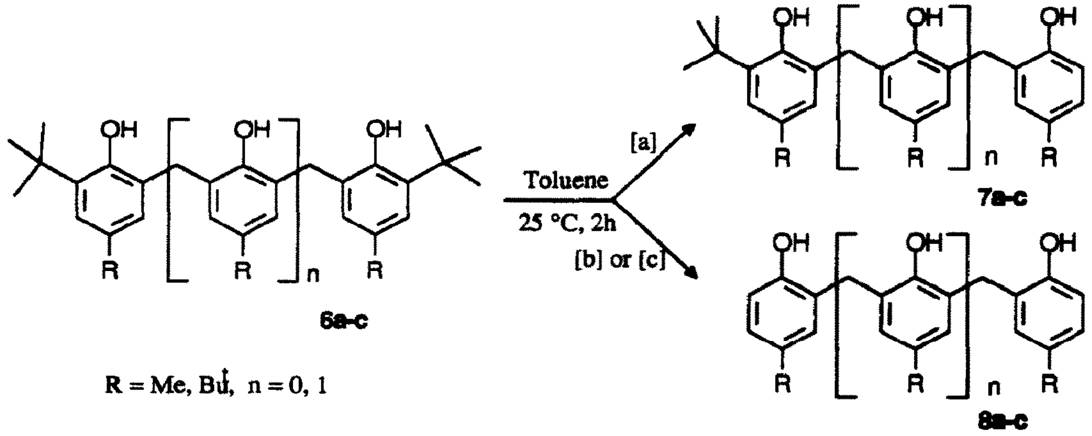


Table 1: De*tert*-butylation of **6a**, **b**, **c** with $AlCl_3$ in dry toluene.

Entry	Substrate	Procedure	Product yields (%) and selectivities (%)
1	**6a** (R=Me; n=0)[6]	[a]	**7a** (60), (86)
2	**6a** (R=Me; n=0)	[b]	**8a** (82), (89)
3	**6b** (R=Me; n=1)	[a]	**7b** (83), (93)
4	**6b** (R=Me; n=1)	[b]	**8b** (79), (89)
5	**6c** (R=Bu^t; n=0)	[a]	**7c** (70), (88)*
6	**6c** (R=Bu^t; n=0)	[c]	**8c** (72), (94)*

*Larger scale reaction was better performed at 0 °C for 15 minutes in order to avoid transbenzylation.

Next, the transalkylation of the more interesting telomers **6a, b, c** was similarly attempted. After a number of trials with different ratios **6a** : $AlCl_3$, we have found that the selective mono- and bis-de-*tert*-butylation of **6a** was conveniently performed by employing 1 or 2 equivalents of $AlCl_3$ (experimental conditions [a] and [b] respectively) (Scheme 2).

Compounds **7a** and **7b** or **8a** and **8b** were obtained in 60-80% yields and good selectivities (~ 90%) by reacting **6a, b** with $AlCl_3$ (molar ratio 1 :1 or 1 : 2) in dry toluene for 2 hours at 25 °C (Table 1, entries 1-4).

The extension of the operative conditions [a] to the tetra-*tert*-butylated substrate **6c** resulted in the production of **7c** (70% yield, 88% selectivity). On the contrary, by treatment of **6c** with two equivalents of $AlCl_3$ a mixture of phenolic derivatives including transbenzylated compounds was obtained. In this particular case we decided to utilize the $AlCl_3 \cdot CH_3NO_2$ complex which was previously described to be active in the selective transalkylation of poly-*tert*-butylated arenes, but not in the isomerization of diphenylmethanes (*via* [c])[5].

Thus, compound **6c** was treated with $AlCl_3$ and CH_3NO_2 (molar ratio 1 : 2 : 10) in dry toluene for 2 hours. Product **8c** was then recovered in 72% yield.

Experimental Procedures and data

General Procedure [a]. Solid $AlCl_3$ (1.33 g, 0.01 mol) was added to a solution of the phenolic substrate(0.01 mol) in dry toluene (100 mL) under nitrogen. The solution was stirred at room temperature for 2 hrs, then 10% aq. HCl solution (100 mL) was added. The mixture was extracted with diethyl ether (2×100 mL) and dried (Na_2SO_4). Products were purified by chromatography on silica gel plates (eluent hexane-ethyl acetate 10%).

General Procedure [b]. The reaction is conducted as described in *via* [a] by using a different molar ratio phenolic substrate : $AlCl_3$ (1:2).

General Procedure [c]. The reaction is conducted as described in *via* [a] by using the complex $AlCl_3 \cdot CH_3NO_2$ instead of the sole $AlCl_3$. The complex is prepared by mixing $AlCl_3$ (0.01 mol) and CH_3NO_2 (3 mL, 0.05 mol) in dry toluene.

2,2'-dihydroxy-3-*tert*-butyl-5,5'-dimethyldiphenylmethane (7a). Yield 1.70g (60%), white solid; m.p. 110-112 °C; ^1H NMR ($CDCl_3$, 300 MHz): d 1.38 (s, 9H, $(CH_3)_3C$), 2.24 (s, 3H, CH_3), 2.25 (s, 3H, CH_3), 3.84 (s, 2H, CH_2), 5.7 (br s, 1H, OH), 6.5 (br s, 1H, OH), 6.63 (d, J=8.1 Hz, 1H, H-3'), 6.87 (dd, J=8.1 and 2.0 Hz, 1H, H-4'), 6.95 (s, 2H, H-4 and H-6), 7.07 (d, J=2.0 Hz, 1H, H-6'); MS (C.I.): m/z=285 (M^++1, 23%), 284 (M^+, 100), 229 (50), 177 (91); IR (KBr): 3215 cm^{-1}(OH); Found: H 8.34, C 80.35%; calcd for $C_{19}H_{24}O_2$: H 8.51, C 80.24%.

2,2'-dihydroxy-5,5'-dimethyldiphenylmethane (8a). Yield 1.87g (82%), white solid; m.p. 125-126 °C (m.p.$^{lit.7}$ 125-126 °C).

2,2'-dihydroxy-3-*tert*-butyl-3'-(2''-hydroxy-3''-*tert*-butyl-5''-methylbenzyl)-5,5'-dimethyldiphenylmethane (6b). Prepared from 2-*tert*-butyl-4-methylphenol and 2,6-dihydroxymethyl-4-methylphenol, following the general procedure previously described[6] (Yield 78%). White solid; m.p. 140 °C; ^1H NMR ($CDCl_3$, 300 MHz): d 1.38 (s, 18H, $(CH_3)_3C$), 2.23 (s, 9H, CH_3), 3.82 (s, 4H, CH_2), 6.5 (br s, 2H, OH), 6.91 (d, J=2.0 Hz, 2H, H-4 and H-4" or H-6 and H-6"), 6.94 (d, J=2.0 Hz, 2H, H-6 and H-6" or H-4 and H-4"), 6.95

(s, 2H, H-4' and H-6'); MS (C.I.): m/z=461 (M^++1, 24%), 460 (M^+, 100), 297 (77); IR (KBr): 3030 cm^{-1} (OH); Found: H 8.64, C 81.02; calcd for $C_{31}H_{40}O_3$: H 8.75, C 80.83%.

2,2'-dihydroxy-3-*tert*-butyl-3'-(2"-hydroxy-5"-methylbenzyl)-5,5'-dimethyldiphenylmethane (7b). Yield 3.35g (83%), white solid; m.p. 170-172 °C; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): d 1.37 (s, 9H, $(CH_3)_3C$), 2.19 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 2.23 (s, 3H, CH_3), 3.80 (s, 2H, CH_2), 3.81 (s, 2H, CH_2), 6.62 (d, J=8.1 Hz, 1H, H-3"), 6.82 (dd, J=8.1 and 2.1 Hz, 1H, H-4"), 6.9-7.0 (m, 4H, H-4, H-6, H-4' and H-6'), 7.03 (d, J=2.1 Hz, 1H, H-6"), 7.1 (br s, 1H, OH), 7.3 (br s, 1H, OH), 8.2 (br s, 1H, OH); MS (C.I.): m/z=405 (M^++1, 25%), 404 (M^+, 72), 241 (100); IR (KBr): 3164 cm^{-1}(OH); Found: H 8.07, C 80.32%; calcd for $C_{27}H_{32}O_3$: H 7.97, C 80.16%.

2,2'-dihydroxy-3-(2"-hydroxy-5"-methylbenzyl)-5,5'-dimethyldiphenylmethane (8b). Yield 2.75g (79%), white solid; m.p. 212-214 °C (m.p.$^{lit.7}$ 213-214 °C).

2,2'-dihydroxy-3,3',5,5'-tetra-*tert*-butyldiphenylmethane (6c). Prepared from 2,4-di-*tert*-butylphenol and formaldehyde, following the procedure previously described[6] (Yield 85%). White solid; m.p. 147 °C; ^1H NMR ($CDCl_3$, 100 MHz): d 1.28 (s, 18H, $(CH_3)_3C$), 1.40 (s, 18H, $(CH_3)_3C$), 3.93 (s, 2H, CH_2), 5.90 (s, 2H, OH), 7.16 (s, 4H, H-4, H-6, H-4' and H-6'); MS (C.I.): m/z=424 (M^+, 100%), 409 (33), 214 (61); IR (KBr): 3509 cm^{-1} (OH); Found: H 10.55, C 81.98%; calcd for $C_{29}H_{44}O_2$: H 10.44, C 82.02%.

2,2'-dihydroxy-3,5,5'-tri-*tert*-butyldiphenylmethane (7c). Yield 2.58g (70%), white solid; m.p. 47-49 °C; ^1H NMR ($CDCl_3$, 300 MHz, 25 °C): d 1.26 (s, 9H, $(CH_3)_3C$), 1.29 (s, 9H, $(CH_3)_3C$), 1.40 (s, 9H, $(CH_3)_3C$), 6.5 (br s, 1H, OH), 6.60 (d, J=8.4 Hz, 1H, H-3'), 6.9 (br s, 1H, OH), 7.03 (dd, J=8.4 and 2.1 Hz, 1H, H-4'), 7.18 (s, 2H, H-4 and H-6), 7.31 (d, J=2.1 Hz, 1H, H-6'); MS (C.I.): m/z=368 (M^+, 100%), 353 (37), 219 (39); IR (KBr): 3279 cm^{-1} (OH); Found: H 9.79, C 81.61%; calcd for $C_{25}H_{36}O_2$: H 9.85, C 81.47%.

2,2'-dihydroxy-5,5'-di-*tert*-butyldiphenylmethane (8c). Yield 2.25g (72%), white solid; m.p. 155-157 °C (m.p.$^{lit.8}$ 157-158°C).

Acknowledgements

This work was supported by the Consiglio Nazionale delle Ricerche (C.N.R., Roma), Progetto Finalizzato Chimica Fine e Secondaria II and by the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (M.U.R.S.T.).

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(*Received in UK* 13 *June* 1994; *revised* 21 *July* 1994; *accepted* 29 *July* 1994)