COMMUNICATION

New approach to *p*-hydroxybenzylation of arenes *via* a quinomethane generated *in situ* from a Mannich base

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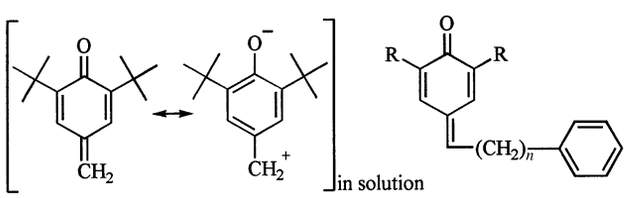
***p*-Hydroxybenzylation of arenes can be performed efficiently using a Mannich base and $(MeO)_2SO_2$ at reflux in the presence of $ZnCl_2$.**

Benzoquinomethanes are interesting compounds that have been proposed as intermediates in various chemical reactions[1] and biosyntheses.[2] Of special interest is 2,6-di-*tert*-butyl-*p*-quinomethane which has not been isolated but has been characterized by ^{1}H NMR spectroscopy in dilute solution.[3] Even though considerable effort has been devoted to studying the reactions of 2,6-di-*tert*-butyl-*p*-quinomethane, the utility of this transient intermediate is limited because of its instability and method of generation. A few methodologies have so far been developed to generate 2,6-di-*tert*-butyl-*p*-quinomethane *in situ*; (i) oxidation of 2,6-di-*tert*-butyl-*p*-cresol (BHT) with Ag_2O[1d,3,4a] or PbO_2,[4] (ii) treatment of 2,6-di-*tert*-butyl-4-hydroxybenzyl bromide with triethylamine,[3,5] (iii) thermal decomposition of (4-hydroxy-3,5-di-*tert*-butylbenzyl)trimethylammonium iodide generated from the Mannich base and MeI[6] and (iv) treatment of 4-(benzotriazol-1-ylmethyl)-2,6-di-*tert*-butylphenol with base.[1e]

Quinomethanes are not only homologues of vinyl ketones, resonance structure **A**, they can also react as benzylic cation intermediates, resonance structure **B** (Scheme 1). The methylidene group of *p*-quinomethanes has been employed in Diels–Alder reactions.[1c,6c,7] In addition, the electrophilic character of the exocyclic alkylidene carbon has been widely exploited in reactions with nucleophiles,[8] such as phosphites,[8b] phosphines,[8c] amines[8d] or phenoxides.[1e] On the other hand, *p*-quinomethanes with substituents on the terminal methylene, structure **C**, are isolable and stable.[3b,9] Thus, Lewis acid-catalysed intramolecular electrophilic substitution reactions of aryl ring-substituted *p*-quinomethanes **C** have been well studied by Angle and co-workers.[1d,9] However, there has been little application of 2,6-di-*tert*-butylquinomethane in electrophilic aromatic substitution reactions, despite its electrophilic character.[1b,1e]



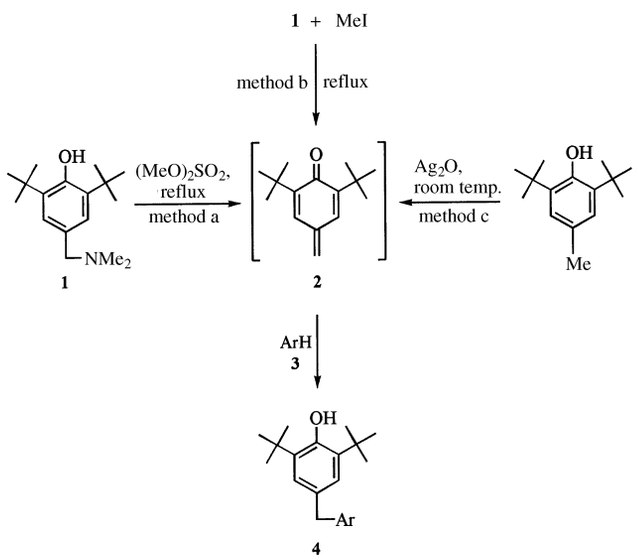
A **B** **C** (isolable)

Scheme 1

We report here that the Mannich base–$(MeO)_2SO_2$ system provides a novel and efficient route to the *p*-hydroxybenzylation of arenes *via in situ* generated quinomethanes in the presence of $ZnCl_2$ by intermolecular electrophilic substitution.

Results and discussion

The thermal decomposition of readily available Mannich base **1** and $(MeO)_2SO_2$ in chlorobenzene (method a, Scheme 2)



Scheme 2

afforded 2,6-di-*tert*-butylquinomethane. Surprisingly, the GC–MS (EI) analysis of the quinomethane showed a molecular ion peak (*m*/*z* 218) of $C_{15}H_{22}O$, and characteristic peaks at *m*/*z* 203 and 161 indicating that the methyl and *tert*-butyl groups, respectively, were fragmenting from the quinomethane. Thus, the ion peak at *m*/*z* 218 in the EI mass spectrum might represent a 2,6-di-*tert*-butylquinomethane. We also found that the formation of the quinomethane could be easily monitored by GLC (equipped with an HP-1 capillary column) analysis, showing no sign of decomposition upon flame ionization detection. A most remarkable feature was the observation of this transient quinomethane with ease by GLC analysis. After the formation of quinomethane was completed, 1 equiv. of anisole and 3 equiv. of $ZnCl_2$ were added. The mixture was further refluxed for 5 h to yield *p*-hydroxybenzylated product **4** in 94% yield with 89 : 11 *para*/*ortho* regioselectivity.

In the case of method b employing the Mannich base and MeI,[6] we also monitored the formation of quinomethane at the same retention time on GLC analysis and recorded the same mass spectrum. After the Mannich base had been transformed into 2,6-di-*tert*-butylquinomethane, anisole and $ZnCl_2$ were added under the same conditions as for method a. Surprisingly, only 5% of *p*-hydroxybenzylated product **4** was formed; instead the dimer[1b] was formed in 65% yield. In the case of method a, it was observed by GLC analysis that no dimerization of 2,6-di-

Table 1 *p*-Hydroxybenzylation of anisole

Entry	Method[a]	Lewis acid (equiv.)	Solvent[b]	*t*/h	GC Yield of **4** (%)
1	a	$ZnCl_2$ (3)	Chlorobenzene	5	94 (89 : 11)[c]
2	b	$ZnCl_2$ (3)	Chlorobenzene	10	5
3	c	$ZnCl_2$ (3)	Chlorobenzene	10	7
4	a	—	Chlorobenzene	11	63 (87 : 13)[c]
5	a	$AlCl_3$ (3)	Chlorobenzene	10	trace (65)[d]
6	a	$TiCl_4$ (3)	Chlorobenzene	10	trace
7	a	$ZnCl_2$ (3)	THF	10	0

[a] Method a: Mannich base (1.4 equiv.), $(MeO)_2SO_2$ (1.4 equiv.). Method b: Mannich base (1.4 equiv.), MeI (1.6 equiv.). Method c: BHT (1.4 equiv.), Ag_2O (2.0 equiv.). [b] Anhydrous solvent. [c] *para*/*ortho* ratio. [d] De-*tert*-butyl product was obtained.

Table 2 Electrophilic substitution reaction of arenes with *p*-hydroxyquinomethane[a]

Entry	Arene	*t*/h	Product	Yield[b] (%)
1	Anisole **3a**	5	**4a**	94 (89 : 11)[c]
2	*p*-Cresol **3b**	11	**4b**	88
3	2,6-Di-*tert*-butylphenol **3c**	15	**4c**	69
4	*p*-Methylanisole **3d**	16	**4d**	51
5	*N*,*N*-Dimethylaniline **3e**	10	**4e**	78 (88 : 12)[c]
6	*N*,*N*-Dimethyl-*p*-toludine **3f**	10	**4f**	71
7	*p*-Xylene **3g**	9	**4g**	59
8	Toluene **3h**	20	**4h**	70 (84 : 16)[c]

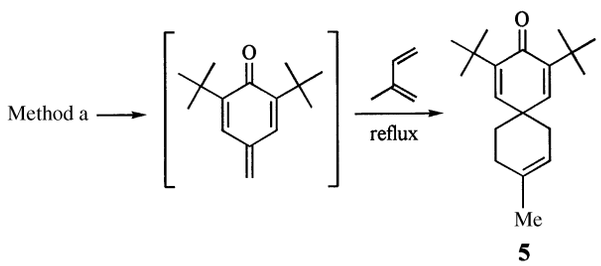
[a] Reactions were performed by using arene (1.0 mmol), 1.4 equiv. of Mannich base, 1.4 equiv. of $(MeO)_2SO_2$ and 3 equiv. of $ZnCl_2$ in 10 ml of chlorobenzene at reflux. [b] Isolated yield based upon arene. [c] *para*/*ortho* ratio.

tert-butylquinomethane occurred before all the Mannich base and $(MeO)_2SO_2$ were decomposed to quinomethane. However, 2,6-di-*tert*-butylquinomethane generated from method b slowly dimerized as soon as it formed in solution. In an effort to prove the possible difference in chemical environments, we examined the intermolecular electrophilic substitution reaction of 2,6-di-*tert*-butylquinomethane generated *via* method c; oxidation of BHT with Ag_2O.[1d,3,4d] Even though the formation of quinomethane was observed by GLC and in the EI mass spectrum, *p*-hydroxybenzylation of anisole gave only 7% of product **4** under the conditions employed in method a. The dimerization of quinomethane was the major reaction pathway.[1b] In fact, the use of $(MeO)_2SO_2$ in the thermal decomposition of a Mannich base to generate quinomethane has never been reported. Only the Mannich base–MeI system (method b) has been employed.[6]

In general, most reactions with quinomethane generated *in situ* have been in chloroform, hexane or toluene as the solvent.[1,3] In our case, the majority of the reactions were carried out in chlorobenzene (Table 1). A variety of other solvents and reaction conditions were tried, but yields of **4** in methods a, b and c did not improve. Using chlorobenzene as a solvent, $ZnCl_2$ was the most effective Lewis acid for the electrophilic substitution reaction of 2,6-di-*tert*-butylquinomethane. In the absence of $ZnCl_2$, the rate and yield were decreased. Attempts to increase the product yields in methods b and c by use of excess $ZnCl_2$ yielded complex mixtures. In a similar manner, when $ZnCl_2$ was replaced with $TiCl_4$ or $AlCl_3$ in methods a, b or c, all attempts to make the *p*-hydroxybenzylated products were unsuccessful.

We extended the intermolecular electrophilic substitution of quinomethane to a variety of arenes (Table 2). In all cases, *p*-hydroxybenzylated products were obtained in high yields. In general, the reaction was highly regioselective (>84%) in giving the *para*-substituted products with a monosubstituted benzene and the regioselectivity was independent of the substituent. In addition, arenes with less powerful activating groups, such as toluene, also afforded **4** in moderate yield. It was found that in both experimental protocols, the complete preformation of quinomethane and the simultaneous addition of all reagents led to similar results. Thus for the synthesis of the *p*-hydroxybenzylated product, it is not necessary to preform the benzoquinomethane. However, in the case of methods b or c, the simultaneous addition of all reagents to obtain the *p*-hydroxybenzylated product was unsuccessful.

The application of homologues of conjugated ketones in benzoquinomethane in Diels–Alder reactions is of considerable interest. Herein, we also report a significant improvement in the cycloaddition reactions with quinomethane generated from the Mannich base–$(MeO)_2SO_2$ system. After the formation of the 2,6-di-*tert*-butylquinomethane dienophile (by method a), a slight excess of isoprene was introduced into the flask (equipped with an ice-cooled condenser) to give spiro ketone **5** in yields as high as 92% (Scheme 3). Although high



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Scheme 3

yields were possible from the cycloaddition reactions of quinomethane generated from method b, a pressure bottle had to be used in the literature preparation.[1c,6c,7] Thus, the Mannich base–$(MeO)_2SO_2$ system affords an efficient dienophile as well as a simple experimental protocol at atmospheric pressure.

In summary, we have developed an efficient method for performing the *p*-hydroxybenzylation of arenes which proceeds by way of the benzoquinomethane intermediate generated *in situ* from a Mannich base and $(MeO)_2SO_2$ in the presence of $ZnCl_2$. On the other hand, the desired *p*-hydroxybenzylation product **4** is not readily formed in methods b and c where competing side-reactions leading to dimerization occur to a significant degree.

Experimental

General method for the *p*-hydroxybenzylation of arenes

To a mixture of a Mannich base[10] (0.369 g, 1.4 mmol), $ZnCl_2$ (0.409 g, 3 mmol) and dimethyl sulfate (0.103 ml, 1.4 mmol) in chlorobenzene (10 ml) was added an arene (1.0 mmol). The resulting mixture was refluxed for the time given in Table 2. Water (20 ml) and CH_2Cl_2 (20 ml) were added. The organic layer was washed with water and dried with $MgSO_4$. The solvent was removed *in vacuo* and the residue chromatographed with hexane–ethyl acetate (9 : 1) to give the product.

2,6-Di-*tert*-butyl-4-[(4-methoxyphenyl)methyl]phenol 4a (*para* product). Mp 136–137 °C; ^{1}H NMR ($CDCl_3$): δ 1.33 (s, 18 H), 3.70 (s, 3 H), 3.73 (s, 2 H), 4.97 (s, 1 H), 6.75 (d, *J* 8.5 Hz, 2 H), 6.90 (s, 2 H), 7.04 (d, *J* 8.5,† 2 H); ^{13}C NMR ($CDCl_3$): δ 30.6, 34.6, 41.2, 55.5, 114.0, 125.6, 130.0, 132.3, 134.2, 136.1, 152.2, 158.1; MS (EI) *m*/*z* 326 (M^+) (HRMS: calc. for $C_{22}H_{30}O_2$, 326.2246. Found, 326.2237).

2,6-Di-*tert*-butyl-4-[(2-hydroxy-5-methylphenyl)methyl]-phenol 4b.[1e] Oil; ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 18 H), 2.18 (s, 3 H), 3.80 (s, 2 H), 4.59 (s, 1 H), 5.02 (s, 1 H), 6.65 (m, 1 H), 6.85 (m, 2 H), 6.98 (s, 2 H); ^{13}C NMR ($CDCl_3$): δ 19.5, 29.3, 33.3,

† *J* Values are given in Hz.

35.5, 114.6, 124.1, 126.0, 127.0, 128.9, 130.4, 135.2, 150.7, 151.4; MS (EI) *m*/*z* 326 (M^+) (HRMS: calc. for $C_{22}H_{30}O_2$, 326.2246. Found, 326.2246).

2,6-Di-*tert*-butyl-4-[(4-hydroxy-3,5-di-*tert*-butylphenyl)-methyl]phenol 4c. Mp 152.5–153.7 °C; ^{1}H NMR ($CDCl_3$): δ 1.34 (s, 36 H), 3.76 (s, 2 H), 4.96 (s, 2 H), 6.95 (s, 4 H); ^{13}C NMR ($CDCl_3$): δ 29.3, 33.3, 40.3, 124.3, 130.9, 134.6, 150.8; MS (EI) *m*/*z* 424 (M^+) (HRMS: calc. for $C_{29}H_{44}O_2$, 424.3341. Found, 424.3344).

2,6-Di-*tert*-butyl-4-[(2-methoxy-5-methylphenyl)methyl]-phenol 4d. Oil; ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 18 H), 2.14 (s, 3 H), 3.71 (s, 3 H), 3.76 (s, 2 H), 4.90 (s, 1 H), 6.66 (m, 1 H), 6.81 (s, 1 H), 6.86 (m, 1 H), 6.97 (s, 2 H); ^{13}C NMR ($CDCl_3$): δ 19.4, 29.4, 33.2, 34.6, 54.6, 109.3, 124.4, 126.3, 128.6, 129.2, 130.6, 131.0, 134.7, 150.8, 154.3; MS (EI) *m*/*z* 340 (M^+) (HRMS: calc. for $C_{23}H_{32}O_2$, 340.2403. Found, 340.2400).

2,6-Di-*tert*-butyl-4-[(4-dimethylaminophenyl)methyl]phenol 4e (*para* product). Oil; ^{1}H NMR ($CDCl_3$): δ 1.41 (s, 18 H), 2.90 (s, 6 H), 3.81 (s, 2 H), 4.97 (s, 1 H), 6.66 (d, *J* 12.9, 2 H), 6.99 (s, 2 H), 7.07 (d, *J* 8.5, 2 H); ^{13}C NMR ($CDCl_3$): δ 30.7, 34.7, 41.2, 41.4, 113.5, 125.7, 129.8, 130.6, 132.8, 136.1, 149.4, 152.3; MS (EI) *m*/*z* 339 (M^+) (HRMS: calc. for $C_{23}H_{33}NO$, 339.2563. Found, 339.2569).

2,6-Di-*tert*-butyl-4-[(2-dimethylaminophenyl)methyl]phenol 4e (*ortho* product). Mp 149.8–152.6 °C; ^{1}H NMR ($CDCl_3$): δ 1.39 (s, 18 H), 2.67 (s, 6 H), 3.99 (s, 2 H), 5.02 (s, 1 H), 6.94–7.35 (m, 6 H); ^{13}C NMR ($CDCl_3$): δ 12.6, 30.8, 34.7, 37.0, 119.8, 123.8, 126.0, 127.0, 131.0, 132.4, 136.0, 137.3, 152.2, 153.1; MS (EI) *m*/*z* 339 (M^+) (HRMS: calc. for $C_{23}H_{33}NO$, 339.2563. Found, 339.2560).

2,6-Di-*tert*-butyl-4-[(2-dimethylamino-5-methylphenyl)-methyl]phenol 4f. Oil; ^{1}H NMR ($CDCl_3$); δ 1.33 (s, 18 H), 2.15 (s, 3 H), 2.59 (s, 6 H), 3.88 (s, 2 H), 4.94 (s, 1 H), 6.84 (s, 1 H), 6.89 (dd, *J* 1.9, 8.2, 1 H), 6.93 (s, 2 H), 6.96 (d, *J* 2.2, 1 H); ^{13}C NMR ($CDCl_3$): δ 13.1, 19.8, 29.3, 33.3, 35.4, 44.5, 118.5, 124.6, 126.2, 130.2, 131.1, 131.9, 134.4, 135.8, 149.2, 150.7; MS (EI) *m*/*z* 353 (M^+) (HRMS: calc. for $C_{24}H_{37}NO$, 353.2720. Found, 353.2726).

2,6-Di-*tert*-butyl-4-[(2,5-dimethylphenyl)methyl]phenol 4g. Mp 74.1–75.8 °C; ^{1}H NMR ($CDCl_3$): δ 1.32 (s, 18 H), 2.13 (d, *J* 4.6, 3 H), 2.18 (d, *J* 3.9, 3 H), 3.77 (s, 2 H), 4.95 (s, 1 H), 6.83–6.85 (m, 4 H), 6.96 (d, *J* 7.4, 1 H); ^{13}C NMR ($CDCl_3$): δ 18.3, 20.0, 29.3, 33.3, 38.1, 124.3, 125.7, 129.0, 129.4, 129.9, 132.2, 134.2, 134.7, 138.5, 150.9; MS (EI) *m*/*z* 324 (M^+) (HRMS: calc. for $C_{23}H_{32}O$, 324.2453. Found, 324.2448).

2,6-Di-*tert*-butyl-4-(methylphenylmethyl)phenol 4h. Mixture of *ortho*/*para* products, as an oil; ^{1}H NMR ($CDCl_3$): δ 1.39 (s, 18 H of *ortho*), 1.40 (s, 18 H of *para*), 2.29 (s, 3 H of *ortho*), 2.31 (s, 3 H of *para*), 3.82 (s, 2 H of *para*), 3.89 (s, 2 H of *ortho*), 5.01 (s, 1 H of *para*), 5.28 (s, 1 H of *ortho*), 6.93–7.16 (m, 6 H of *ortho*/*para*); ^{13}C NMR ($CDCl_3$): δ 21.0, 30.4, 34.3, 39.2, 41.5, 125.4, 126.1, 128.7, 129.0, 130.1, 131.9, 135.2, 135.9, 138.8, 151.9; MS (EI) *m*/*z* 310 (M^+) (HRMS: calc. for $C_{22}H_{30}O$, 310.2297. Found, 310.2307).

Diels–Alder reaction of Mannich base–dimethyl sulfate with isoprene

To a mixture of a Mannich base (0.369 g, 1.4 mmol) and $ZnCl_2$ (0.409 g, 3 mmol) in chlorobenzene (10 ml) in a reaction flask equipped with an ice-cooled condenser was added dimethyl sulfate (0.101 ml, 1.4 mmol). Isoprene (1 ml) was introduced and the resulting mixture was refluxed for 3 h. After cooling, water and CH_2Cl_2 were added. The organic layer was washed with water and dried with $MgSO_4$. The solvent was removed *in vacuo* and the residue chromatographed to give the product, 2,4-di-*tert*-butyl-9-methyl-spiro[5.5]undeca-1,4,8-trien-3-one **5**: mp 73–75 °C (lit.,[7] 73–74 °C); ^{1}H NMR ($CDCl_3$): δ 1.18 (s, 18 H), 1.53 (t, 2 H), 1.67 (s, 3 H), 1.84–2.18 (br m, 4 H), 5.45 (s, 1 H), 6.69 (s, 2 H).

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10 (4-Hydroxy-3,5-di-*tert*-butylbenzyl)dimethylamine **1** was prepared from 2,6-di-*tert*-butylphenol, formaldehyde and dimethylamine according to a published procedure: M. Tramontini and L. Angiolini, *Mannich Base*, CRC Press, Boca Raton, 1994, pp. 2–76.

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