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Selective catalytic carbanionic ethylation of methylphenols: influence of catalyst and substitution pattern

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Abstract—Addition of ethylene to the carbanions formed by the metallation of the lithium salts of di- and trimethylphenols by the strongly basic system, *n*-BuLi-LiK($OCH_2CH_2NMe_2$)$_2$ provides a useful synthetic route to a range of alkylphenols. The ease of alkylation of the methyl groups decreases in the order *ortho*>*meta*>*para* while the inclusion of Mg(OCH_2CH_2OEt)$_2$ in the catalyst restricts alkylation to the methyl groups *ortho* to the hydroxy group. Dialkylation occurs only at the *ortho*-methyl groups and only if the adjacent *meta*-position is unsubstituted. The potential of these products for the synthesis of sterically hindered ligands is outlined.

1. Introduction

Bulky aromatic molecules are of interest in view of the possibility they offer for the stabilisation of low oxidation states and unsaturated compounds, as well as for the construction of sterically demanding ligands, which in recent years have played an important role in coordination chemistry and homogeneous catalysis.[1] Metal complexes with bulky phenoxide and anilide substituents, and imine ligands derived from bulky aniline or salicylaldehyde derivatives feature prominently in these areas.[2] These molecules also have potential applications in other areas of chemistry, not only because of their bulk but by virtue of the highly enhanced lipophilicity which they are able to confer. We have reported a method for the facile preparation of a series of bulky aromatic hydrocarbons containing 1-ethylpropyl substituents,[3] and we are now studying the synthesis and properties of their functionalised derivatives.[4,5] Here we describe a particularly simple preparation of some sterically hindered phenols.

2. Results and discussion

The preparative route used is similar to that previously reported for hydrocarbons although there are some significant differences in reactivity and this is reflected in the range of products obtained. Phenols containing *ortho*-methyl groups, after initially having been converted to their lithium salts, are readily metallated in methylcyclohexane by the strongly basic reagent derived from *n*-butyllithium and the mixed alkoxide, lithium–potassium bis(2-dimethylaminoethanolate),[6] and subsequent reaction with ethylene gives rise to the products summarised in Table 1. In the presence of Mg(OCH_2CH_2OEt)$_2$, the metallated products readily add one or two molecules of ethylene at the *ortho*-benzylic position to give the corresponding *o*-propyl or *o*-1-ethylpropyl derivatives (compounds **1**–**4**, **7**, **9** and **11**). Addition of two molecules of ethylene to the *ortho*-methyl groups occurs (compounds **1**–**4** and **9**) unless this group is flanked by another methyl group as well as by the OH group (Eqs. 1 and 2). In the latter cases, spectroscopic analysis of the products indicated that monoethylation at the hindered *ortho*-position occurs (compounds **9** and **11**) and this resembles the similar behaviour that was observed for the hydrocarbon series for the addition of ethylene to methyl groups flanked on both sides by other methyl groups.[3] Steric factors would seem to be the reason for this, the phenolates possibly existing as

Keywords: Bulky aromatic; Organolithium; Phenol; Superbase; Metallation; Carbometalation; Schiff base; Catalysis; Lipophilic.
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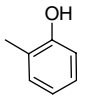
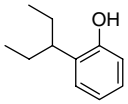
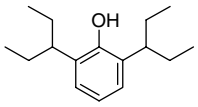
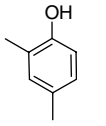
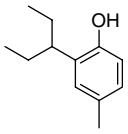
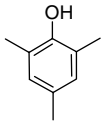
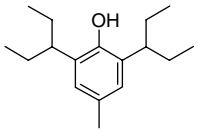
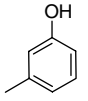
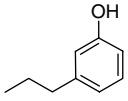
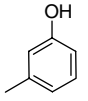
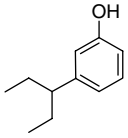
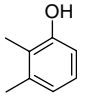
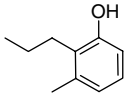
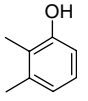
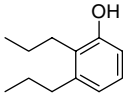
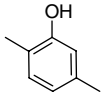
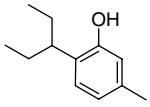
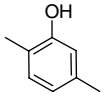
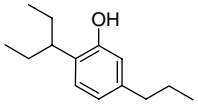
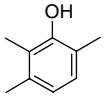
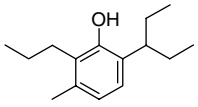
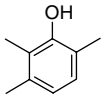
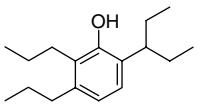
Table 1. Major products from reactions of metallated phenols with ethylene

	Additive[a]	Major product		Yield (%)[c]
	Yes		**1**[b]	65
	Yes		**2**	70
	Yes		**3**[b]	72
	Yes		**4**	65
	Yes		**5**[b]	50
	No		**6**[b]	35[d]
	Yes		**7**[b]	79
	No		**8**[b]	61
	Yes		**9**	48
	No		**10**	55
	Yes		**11**	62[e]
	No		**12**	63[e]

[a] Indicates whether or not $Mg(OCH_2CH_2OEt)_2$ is added to the reaction mixture.

[b] The following compounds have been previously reported (CAS RN in parentheses): **1** (80751-97-9),[7] **3** (96558-48-4),[8] **5** (621-27-2),[9] **6** (97218-43-4),[10] **7** (66142-79-8),[11] **8** (863418-21-7).[12]

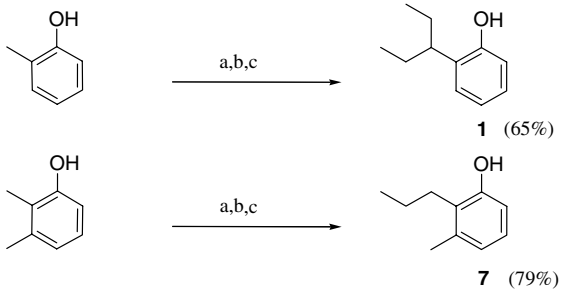
[c] Yield of isolated product unless noted otherwise.

[d] **5** also produced (44% yield).

[e] Yields calculated from GC analysis of product mixtures obtained after vacuum distillation.

oligomeric rather than monomeric species or as mixed aryl-/alkoxide aggregates with the other components of the reaction mixture.

Addition to methyl groups in *meta* or *para* positions occurs only to a minor extent, if at all, when this reaction is carried out in the presence of $Mg(OCH_2CH_2OEt)_2$ (compounds **5**, **7**, **9** and **11**). GC/MS analysis of the products from prolonged reaction times at elevated temperatures indicated only the probable presence of some monoethylation of *meta*-methyl groups.

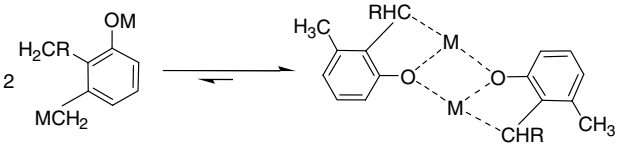


1 (65%) (1)

7 (79%) (2)

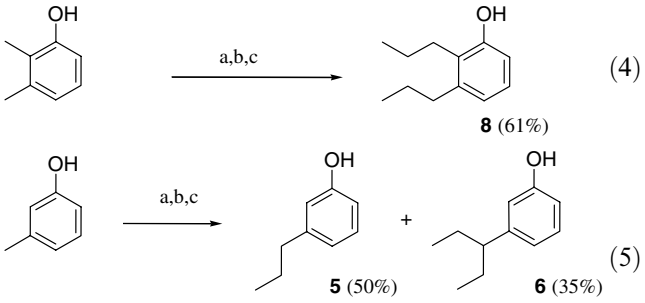
a) 1 eq. *n*-BuLi; b) 10 mol% *n*-BuLi / $LiK(OCH_2CH_2NMe_2)_2$, 2.5 mol% $Mg(OCH_2CH_2OEt)_2$, 10 atm C_2H_4, 80 °C, 24 h; c) H^+/H_2O

The metallation of benzylic protons in a position *para* to an electron donating group has been studied by others. For example, while the *para*-methyl group of *N*,*N*-4-trimethylaniline can be metallated using *n*-BuLi/KOBu-*t* in THF at −75 °C,[13] metallation with TMEDA-activated butyllithium in hexane at room temperature occurs exclusively at the ring position *ortho* to the amino group.[14] Our system, which not only contains a tertiary amino group but also uses an inert hydrocarbon solvent, more closely resembles the latter system and this is consistent with the lack of reaction that we observe at the *para*-position. This lack of reactivity has been ascribed to a strong interaction of the metallating reagent with the heteroatom, which directs its reactivity almost exclusively to the *ortho*-position.[13,15] The reduced reactivity at the *meta*-position is probably due to similar factors while electronic factors may also be responsible for the observed differentiation in reactivity between the *para* and *meta* positions. However, when there are no methyl groups *ortho* to the hydroxy group, as in the case of *m*-cresol, it proved possible to monoethylate to some extent to give compound **5**, albeit using somewhat more severe conditions. A reasonable explanation for this would be that, using the base system comprised of *n*-butyllithium, lithium–potassium bis(2-dimethylaminoethanolate) and $Mg(OCH_2CH_2OEt)_2$, a carbanion derived by metallation at the *meta*-benzylic position is rapidly protonated by *ortho*-benzylic protons to give a species which can give a favourable aggregate structure such as that speculated in Eq. 3,[16] and that only when these protons are not available can ethylation at this position occur to any significant extent.



(3)

If the reactions described above are carried out in the absence of $Mg(OCH_2CH_2OEt)_2$, whereas the reactivity of *ortho*-methyl groups is similar, monoethylation of methyl groups in the *meta*-position becomes more facile and significant, and by increasing the reaction time the corresponding monoethylated product can be obtained as the major one (Eq. 4). Only very minor quantities were detected by GC and GC–MS of the products of even further ethylation except where *ortho*-methyl groups were absent, in which case a significant amount of the diethylated product, **6**, was obtained as well (Eq. 5). Methyl groups in the *para*-position, however, just as in the reaction in the presence of $Mg(OCH_2CH_2OEt)_2$, were not ethylated.



a) 1 eq. *n*-BuLi; b) 10 mol% *n*-BuLi / $LiK(OCH_2CH_2NMe_2)_2$, 10-15 atm.C_2H_4, 80 °C, 48 h; c) H^+/H_2O

The reactions and products are summarised in Eqs. 1–5 and Table 1. Most of the products could readily be obtained in a pure state either by recrystallisation or by vacuum distillation. For 2,3,6-trimethylphenol, however, the products were generally a mixture of the main product, **11** or **12**, indicated in Table 1 together with partially alkylated products and other uncharacterised materials. Completely pure products could not be obtained even after very careful vacuum distillation and the yields given are based on GC analysis of the distillate. Nevertheless, it proved possible to extract NMR data for these products which are fully consistent with the structures given.

Products of addition of ethylene to the ring were not observed in any of these reactions. Phenol itself with the same reagents was also examined. At 90 °C and 20 atm pressure virtually no reaction occurred, although there was a trace of product observed by GC–MS with *m*/*z* 150 and with a fragmentation pattern consistent with a formulation such as (1-methylpropyl)phenol which could have been formed by initial ethylation of the ring followed by a second ethylation at the new benzylic site. The reaction was accompanied by large amounts of insoluble, presumably polymeric material whose nature has not yet been determined.

In summary, we have developed routes to a range of alkylated phenols, the nature of the products depending on the ring substitution of the starting materials used and on the reaction conditions employed. The 1-ethylpropyl group is estimated from experimental observations and computational studies to have a steric effect similar to that of the *tert*-butyl group[17] and many of the alkylphenols reported here could have potential as starting materials for bulky ligands. For example, we have shown that **1** may be converted readily to the corresponding salicylaldehyde and thence to a variety of Schiff bases[18] some of which are being investigated by us as ligands in transition metal homogeneous catalysis. Simple estimates of CLogP values using ChemDraw® also indicate that phenols possessing the 1-ethylpropyl substituent are rather more lipophilic than the corresponding *tert*-butyl derivatives. For example, CLogP for **1** and **2** are 3.76 and 6.05, respectively, while for 2-*tert*-butylphenol and 2,6-bis(*tert*-butyl)phenol the values are 3.20 and 4.93. The lipophilicity of certain of these products, coupled with the steric crowding they present, has recently been exploited by us for the preparation of a series of stilbenoids with promising anti-oxidant properties. This work is the subject of a patent application[19] and will be subsequently published in detail elsewhere.

3. Experimental

Metallation reactions were carried out under an argon atmosphere using Schlenk techniques. Parr Instrument stirred pressure reactors of 300 and 600 ml capacity were used for the reactions with ethylene. Solutions of $LiK(OCH_2CH_2NMe_2)_2$ in MCH were prepared as described previously.[6] All new compounds gave satisfactory elemental analyses unless otherwise stated. Spectroscopic data are given for all new compounds as well as those previously reported compounds where such data was unavailable (i.e., all except **5** and **8**).

3.1. Typical procedures

3.1.1. *A*: 2-(1-Ethylpropyl)phenol 1. *n*-BuLi (60 ml, 110 mmol; 1.85 M in methylcyclohexane) was added slowly to 2-methylphenol (0.47 mol) in methylcyclohexane (110 ml) at 25 °C. After the exothermic reaction mixture had cooled to room temperature, $LiK(OCH_2CH_2NMe_2)_2$ (80 ml, 0.65 M in methylcyclohexane) was added and the resulting yellow mixture was stirred at rt for 30 min before being transferred to a stirred pressure reactor containing $Mg(OCH_2CH_2OEt)_2$ (2.5 g, 12 mmol). After stirring for 30 min, the reactor was filled with ethylene to 10 atm and stirred with heating at 80 °C. After 24 h,[20] the mixture was hydrolysed with H_2SO_4 (20%) and the product extracted into hexane. The organic extract was dried over anhydrous Na_2SO_4. Subsequent filtration and removal of the solvent gave the crude product, which was purified by recrystallisation from hexane. Yield 65% mp 63–64 °C (lit.[13] 64 °C). ^1H NMR ($CDCl_3$, 300 MHz): δ 0.85 (6H, t, J 7.3, CH_3), 1.7 (4H, m, CH_2), 2.81 (1H, m, CH), 4.76 (1H, s, OH), 6.78 (1H, d, J 7.9, ArH), 6.95 (1H, t, J 7.3, ArH), 7.09 (1H, m, ArH), 7.15 (1H, t, J 7.3, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.1, 29.1, 41.5, 115.4, 121.0, 126.6, 127.9, 131.4, 153.8; MS (EI) *m*/*z* (relative intensity %): (EI) 164 (M^+, 26%), 135 (48), 107 (100), 91 (10), 77 (10).

A similar procedure was used for the following:

3.1.2. 2,6-Bis(1-ethylpropyl)phenol 2. Bp 78–80 °C/0.1 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.90 (12H, t, J 7.3, CH_3), 1.70 (4H, m, CH_2), 1.81 (4H, m, CH_2), 2.79 (2H, m, CH), 4.80 (1H, s, OH), 7.01 (3H, m, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.2, 28.5, 42.0, 120.6, 124.6, 130.6, 152.3; MS (EI) m/z (relative intensity %): 234 (M^+, 20%), 205 (100), 177 (55), 147 (7), 128 (5), 107 (6).

3.1.3. 2-(1-Ethylpropyl)-4-methylphenol 3. Mp 70–71 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.83 (6H, t, J 7.5, $CH(CH_2\mathit{Me})_2$), 1.80–1.52 (4H, m, $CH(C\mathit{H}_2Me)_2$), 2.28 (3H, s, Me), 2.80–2.65 (1H, m, $C\mathit{H}Et_2$), 4.54 (1H, s, OH), 6.67 (1H, d, J 8.0, ArH), 6.87 (1H, dd, J 8.0 and 2.0, ArH), 6.90 (1H, d, J 2.0, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.1, 20.7, 28.1, 41.6, 115.0, 126.8, 128.3, 129.8, 130.9, 151.4; m/z (EI) 178 (M^+, 29%), 149 (70), 133 (5), 121 (100), 91 (13).

3.1.4. 2,6-Bis(1-ethylpropyl)-4-methylphenol 4. Bp 80–81 °C/0.1 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.83 (12H, t, J 7.5, $CH(CH_2\mathit{Me})_2$), 1.82–1.50 (8H, m, $CH(C\mathit{H}_2Me)_2$), 2.27 (3H, s, Me), 2.65–2.60 (2H, m, $C\mathit{H}Et_2$), 4.50 (1H, s, OH), 6.73 (2H, s, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.1, 21.0, 28.5, 41.9, 125.1, 129.1, 130.4, 149.8; m/z (EI) 248 (M^+, 19%), 220 (16), 219 (100), 192 (6), 191 (52), 161 (10), 149 (14), 147 (5), 121 (17), 105 (6), 91 (6).

3.1.5. 3-Propylphenol 5. Bp 88–90 °C/2 mbar (lit.[9] bp 93–95 °C/2.3 mmHg). Spectroscopic data were in agreement with those reported.[15]

3.1.6. 3-Methyl-2-propylphenol 7. Bp 90–93 °C/2 mbar (lit.[11] mp 29–32 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.08 (3H, t, J 7.3, CH_3), 1.64 (2H, m, CH_2), 2.38 (3H, s, $ArCH_3$), 2.60–2.63 (2H, dd, J 7.9, 8.0, CH_2), 4.7 (1H, br s, OH), 6.67 (1H, d, J 7.7, ArH), 6.83 (1H, d, J 7.7, ArH), 7.01 (1H, t, J 7.7, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 14.5, 19.6, 22.4, 28.5, 113.0, 122.9, 126.3, 127.5, 138.0, 153.6; MS (EI) m/z (relative intensity %): 150 (M^+, 36%), 121 (100), 93 (7), 91 (22), 77 (17).

3.1.7. 2-(1-Ethylpropyl)-5-methylphenol 9. Bp 78–80 °C/0.3 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.84 (6H, t, J 7.3, $CH_2C\mathit{H}_3$), 1.6–1.7 (4H, m, CH_2), 2.30 (3H, s, $ArCH_3$), 2.74 (1H, m, CH), 4.6 (1H, br s, OH), 6.60 (1H, s, ArH), 6.76 (1H, d, J 7.3, ArH), 7.01 (1H, d, J 7.3, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.1, 21.0, 28.1, 41.2, 116.1, 121.7, 127.7, 128.2, 136.4, 153.6; MS (EI) m/z (relative intensity %): 178 (M^+, 36%), 149 (95), 121 (100), 91 (13), 77 (9).

3.1.8. 6-(1-Ethylpropyl)-3-methyl-2-propylphenol 11. The product co-distilled in the range 83–86 °C/0.5 mbar with **12** and was not obtained analytically pure. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.90 (6H, t, J 7.3, $CH(CH_2C\mathit{H}_3)_2$), 1.06 (3H, t, J 7.3, $CH_2CH_2C\mathit{H}_3$), 1.6 (4H, m, CH_2), 1.7 (2H, m, CH_2), 2.32 (3H, s, $ArCH_3$), 2.6 (3H, m, CH+CH_2), 4.72 (1H, s, OH), 6.77 (1H, d, J 7.3, ArH), 6.88 (1H, d, J 7.3, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.1, 14.4, 19.4, 22.4, 28.1, 28.9, 41.7, 121.4, 124.4, 126.2, 127.9, 138.9, 151.9; MS (EI) m/z (relative intensity %): 220 (M^+, 19%), 191 (100), 163 (39), 149 (9), 121 (12), 105 (4), 91 (7).

3.1.9. *B*: 3-(1-Ethylpropyl)phenol 6. The procedure described above was followed except that no $Mg(OCH_2CH_2OEt)_2$ was added and the reaction time was extended to 40 h.[20] Compound **7** was formed in 44% yield. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.80 (6H, t, J 7.3, CH_3), 1.6 (4H, m, CH_2), 2.28 (1H, m, CH), 5.4 (1H, br s, OH), 6.7 (3H, m, ArH), 7.2 (1H, m, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.2, 29.2, 49.6, 112.9, 114.7, 120.7, 129.4, 148.1, 155.2; MS (EI) m/z (relative intensity %): 164 (M^+, 39%), 136 (71), 107 (100), 91 (10), 77 (13).

The following were prepared in a similar fashion:

3.1.10. 2,3-Dipropylphenol 8. Bp 95–98 °C/1 mbar. Spectroscopic data were in agreement with those reported.[12]

3.1.11. 2-(1-Ethylpropyl)-5-propylphenol 10. Bp 85–88 °C/0.3 mbar. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.81 (6H, t, J 7.3, $CH(CH_2C\mathit{H}_3)_2$), 0.94 (3H, t, J 7.3, $CH_2CH_2C\mathit{H}_3$), 1.5–1.7 (6H, m, CH_2), 2.51 (2H, t, J 7.3, CH_2), 2.70 (1H, m, CH), 4.64 (1H, s, OH), 6.59 (1H, s, ArH), 6.74 (1H, d, J 7.3, ArH), 7.00 (1H, d, J 7.3, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.1, 13.9, 24.3, 28.1, 37.5, 41.3, 115.3, 121.1, 127.5, 128.3, 141.3, 153.5; MS (EI) m/z (relative intensity %): 206 (M^+, 26%), 177 (100), 149 (55), 133 (7), 107 (15).

3.1.12. 6-(1-Ethylpropyl)-2,3-dipropylphenol 12. The product co-distilled in the range 83–86 °C/0.5 mbar with **11** and was not obtained analytically pure. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.90 (6H, t, J 7.3, $CH(CH_2C\mathit{H}_3)_2$), 1.07 (3H, t, J 7.3, $CH_2CH_2C\mathit{H}_3$), 1.10 (3H, t, J 7.3, $CH_2CH_2C\mathit{H}_3$), 1.7 (4H, m, CH_2), 1.8 (4H, m, CH_2), 2.7 (5H, m, CH+2 × CH_2), 4.77 (1H, s, OH), 6.82 (1H, d, J 7.3, ArH), 6.95 (1H, d, J 7.3, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 12.2, 14.4, 23.3, 24.5, 28.3, 28.7, 35.1, 41.9, 121.4, 124.4, 126.2, 127.9, 138.9, 151.9; MS (EI) m/z (relative intensity %): 248 (M^+, 15%), 219 (100), 191 (38), 161 (10), 149 (8), 121 (9).

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20. For best results, the optimum reaction time was determined by sampling the reaction mixture. A small amount was taken and extracted into hexane using the workup procedure given and then analysed by GC.