REGIOSELECTIVE LITHIATION AND ALKYLATION OF 2-METHOXY-HYDROQUINONE

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Protected 2-methoxyhydroquinone can be lithiated and alkylated regioselectively in 3- or 6-position by proper choice of metalating reagent, solvent and temperature. Di- and trilithiated species can also be produced and react exclusively at the 3-position. Monoprotected and free 2-methoxyhydroquinone are also metalated with excess of lithium reagent in the same ring position. These reactions provide a general access to biologically interesting 3-alkyl-2-methoxy-1,4-benzoquinones.

Keywords: directed ortho-metalation; methoxyhydroquinone; regioselectivy.

Directed ortho-metalation (DoM) has become a widely used method for the synthesis of polysubstituted aromatic compounds[1]. In monosubstituted benzenes no regioselectivity problems can occur, but yields are often low even in the presence of a heteroatom or another efficient directing group. The presence of more than one activating substituent increases the reactivity in the lithiation, but isomer mixtures may be obtained on reaction with electrophiles. Nevertheless, in many cases the regioselectivity can be achieved by proper choice of the directing/protecting groups and of the metalating agent. Our interest in simple alkyl substituted 2-methoxy-1,4-benzoquinones which show interesting allergenic, antimicrobial and antitumour properties[2-4] prompted us to study the lithiation and the alkylation of 2-methoxyhydroquinone.

The tetrahydropyranyl protecting group was chosen because of its easy introduction and cleavage under acidic conditions. The diprotected hydroquinone **1a** was metalated completely by n-butyllithium, in THF, at 0°C, in a few minutes. Quenching with deuterium oxide or n-butyl iodide at room temperature during 15 h indicated reaction in the 3- and 6- positions to **2a** and **3a** in a 48:52 ratio as determined by integration of the aromatic ^{1}H NMR signals of the crude alkylated product (**4a**, **5a**) (Table I). Attack in the 5-position could not be observed by NMR. This unselective product distribution was moved in direction of **2a** by the use of methyllithium. However, change of the solvent to hexane produced complete selectivity in 3-position (Table I). The opposite effect was observed at lower temperature: in THF at -100°C using n-butyllithium, the 6-position was alkylated in 95 %. These experiments show the decisive influence of the solvent and the temperature in DoM reactions. Apparently, the non-polar, non-complexing medium favors the metalation on the site which allows the best complexation of the lithium by substituents and directing groups[5]. On the other hand, at lower temperature and with a good coordinating solvent, the deprotonation occurs under kinetic control at the most accessible position. Most interestingly, no equilibration of the lithiated species was observed during the slow alkylation at room temperature.

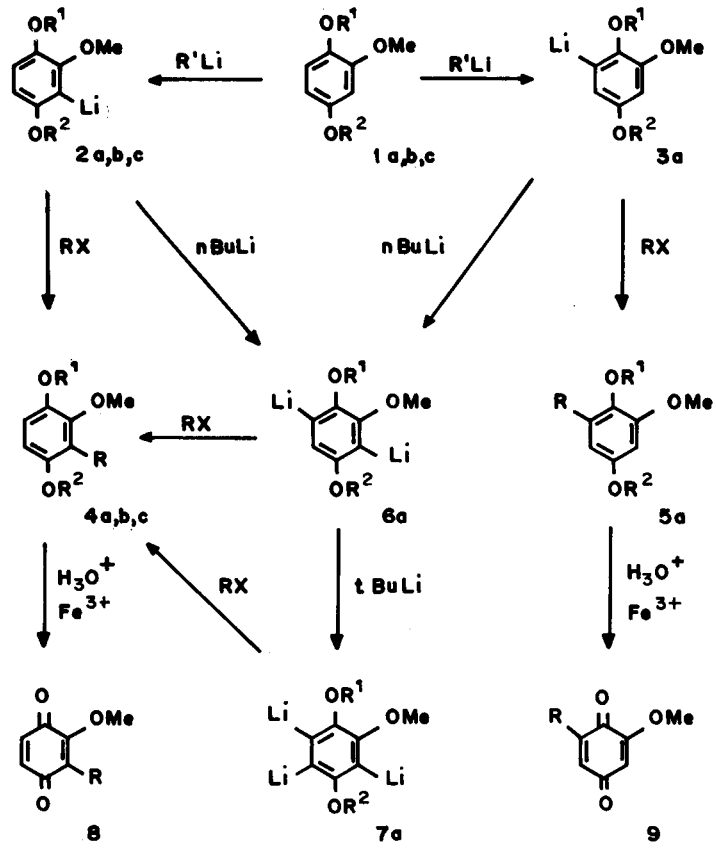
In view of the presence of three activating heteroatoms in the ring, a double metalation seemed possible. Indeed, compound **1a**, with an excess of n-butyllithium, in THF, at 0°C, gave the dilithio-species **6a** as evidenced by quenching with deuterium oxide. The alkylation of **6a** proceeded much faster than in the case of **2a** and **3a** and occurred selectively at the 3-position. An additional equivalent of t-butyllithium produced even the 3,5,6-trilithiated species **7a** which was alkylated also to **4a**, at low temperature. The formation of **7a** was proved by deuterium oxide quenching before and after alkylation. The isolated products showed no remaining aromatic hydrogen. Neither the monolithiated nor the dilithiated species are alkylated under these conditions. Double metalation has already been observed on a symmetric hydroquinone derivative[6], but in this case no selective reactivity could be expected. Only a dilithiated thiophene has been reported to give regioselective reaction with electrophiles[7]. Trilithiated benzenes and their behavior upon alkylation have not been described to date.

Another case of exclusive lithiation and alkylation in 3-position was observed for the monoprotected hydroquinone **1b** producing **4b** when an excess of the lithiating reagent was used (Table I). This successful reaction encouraged us to try the direct ring-metalation of the completely unprotected hydroquinone **1c** with an excess of n-butyllithium and one equivalent of t-butyllithium. Subsequent alkylation followed by oxidative

Table I. Lithiation and alkylation of hydroquinone derivatives **1a-c.**

		Alkylation[a]	
Comp	**Lithiating Conditions**	**4a:5a**	**Yield(%)**
1a	nBuLi, THF, 0°, 10 min.	48:52	
1a	tBuLi, THF, 0°, 10 min.	46:54	
1a	MeLi, Et_2O, 0°, 10 min.[b]	87:13	
1a	nBuLi, hex., 0°, 10 min.	100: 0	88
1a	nBuLi, THF, -78°, 1 h.	10:90	
1a	nBuLi, THF, -100°, 1h.	5:95	90
1a	tBuLi, THF, -100°, 1h.	25:75	
1a	nBuLi[c], THF, 0°, 1h.[d]	95: 5	92
1a	nBuLi[c], tBuLi[e], THF, -78°→-30°, 30 min.[f]	100: 0	83
1b	nBuLi[c], THF, 0°, 1 h.	100: 0	85
1c	nBuLi[c], tBuLi[e], THF, 0°, 1 h.	100: 0	30[g]

a) Standard conditions : 1 equ. nBuI, THF, 30°C, 20 h.
b) Alkylation also in Et_2O.
c) 3 eq. of lithiating agent.
d) Alkylation: 0°C, 2h.
e) 1 eq. of tBuLi.
f) Alkylation: -78°→-30°C, 30 min.
g) Isolated as quinone **8**.



1a-7a: R^1=R^2=THP
1b,4b: R^1=H, R^2=THP
2b: R^1=Li, R^2=THP
1c,4c: R^1=R^2=H
2c: R^1=R^2=Li
4a-c,5a,8,9: R=nBu

Scheme 1

work up produced 3-alkylsubstituted quinone **8**, in 30 % yield. The unsubstituted 2-methoxy-1,4-benzoquinone was also recovered in 42% yield. This partial transformation can probably be explained by the low solubility of the trilithiated species **2c**, in the reaction conditions.

From the preparative point of view, the reactions described above lead after oxidative acidic hydrolysis to the higher homologues of 2-methoxy-3-methyl-1,4-benzoquinone **8** (R = Me). This allergenic constituent of the defensive secretions of many insects has been previously synthesized before by multistep and low yielding procedures which are difficult to extend to higher homologues[8].

EXPERIMENTAL SECTION

^{1}H NMR spectra were obtained on a VARIAN EM 390 instrument at 90 MHz in CCl_4 as solvent. Product ratios were determined by integration of the aromatic hydrogens. The metalation reactions were all carried out under Ar atmosphere using anhydrous solvents distilled over metallic potassium. The metalating agents n-BuLi in hexane, t-BuLi in pentane and MeLi in ether were purchased from Aldrich Chemical Company. 2-Methoxyhydroquinone is available from Fluka A. G.

2-Methoxyhydroquinone di-(2'-tetrahydropyranyl) ether (1a)

To a solution of 2-methoxyhydroquinone (2.80 g, 20 mmol), in 20 ml of anhydrous THF, were added at 0°C 3,4-dihydro-2H-pyran (4.56 ml, 50 mmol) and anhydrous p-toluenesulfonic acid (50 mg). After standing at 5°C for 15 h, 10 ml of 10 % sodium hydroxide were added. The mixture was diluted with 100 ml of water and extracted with cyclohexane (3 x 30 ml). The combined extracts were washed with 10 % NaOH (2 x 20 ml) and then with water. After drying over anhydrous K_2CO_3 the solvent was removed under vacuo and the oily residue purified over a silica gel column (20 g) eluting initially with toluene/cyclohexane 1:1 and passing gradually to pure toluene. Yield 5.126 g (84 %) of colourless oil. ^{1}H NMR (CCl_4) δ: 1.46-2.06 (m, 12 H), 3.86 (s) superimposed to 3.40-4.10 (m, total 7 H), 5.20-6.45 (m, 2 H), 6.48-6.73 (m, 2 H), 7.16 (d, 1 H, J = 9Hz). Anal. calcd. for $C_{17}H_{24}O_5$: C 66.21; H 7.85. Found: C 66.08; H 7.99.

2-Methoxyhydroquinone 4-(2'-tetrahydropyranyl) ether (1b)

The procedure described for **1a** was followed using 20 mmol (1.84 ml) of 3,4-dihydro-2H-pyran. The chromatographic purification was carried out with toluene containing 0-5 % of EtOAc. Yield 1.332 g (30 %) of colourless oil. ^{1}H NMR (CCl_4) δ 1.36-1.98 (m, 6 H), 3.86 (s) superimposed to 3.34-4.00 (m, total 5 H), 5.18 (s) superimposed to 5.13-5.36 (m, total 2 H), 6.40-6.65 (m, 2 H), 6.75 (d, 1 H, J=9Hz). Anal. Calcd. for $C_{12}H_{16}O_4$: C 64.27; H 7.19. Found: C 64.12; H 7.30.

Monolithiation and Alkylation of 1a

To a solution of **1a** (308 mg, 1.0 mmol) in 10 ml of anhydrous solvent (see Table I) the lithium reagent (1.0 mmol) was added at the indicated temperature. After stirring for 30 min, n-butyl iodide (1.0 mmol) was added and the mixture was al-

lowed to warm up to r.t. After 15 h water (100 ml) was added and the mixture was extracted with cyclohexane (3 x 20 ml) The combined extracts were dried over K_2CO_3 and evaporated under reduced pressure. The alkylation products were separated from small quantities of starting material by column chromatography on silica gel (toluene/cyclohexane 1:1). The main fraction containing all the monoalkylated products was examined by ^1H NMR.

Dilithiation and alkylation of ***1a***

To a solution of **1a** (308 mg, 1.0 mmol), in 10 ml of THF, n-BuLi (3.0 mmol) was added at 0°C. After stirring for 1 h at room temperature, the mixture was cooled again to 0°C and n-BuI (1.0 mmol) was added. The mixture was allowed to warm up slowly to r.t. After 15 h, it was hydrolyzed and worked up as described before.

Trilithiation and alkylation of ***1a***

To a solution of **1a** (308 mg, 1.0 mmol), in 10 ml of THF, was added, at -78°C, n-BuLi (3.0 mmol) and t-BuLi (1.0 mmol). The mixture was allowed to warm to -30°C and cooled down again to -78°C and n-BuI (1.0 mmol) was added. When the mixture reached -30°C, water was added and the product was isolated as described before.

3-n-Butyl-2-methoxyhydroquinone di-(2'-tetrahydropyranyl) ether (4a)

Colourless oil. ^1H NMR (CCl_4) δ 0.98 (t, 3 H, J=7.5Hz), 1.18-2.23 (m, 16 H), 2.72 (t, 2H, J=7.5Hz), 4.00 (s) superimposed to 3.53-4.25 (m, total 7 H), 5.30-5.48 (m, 2 H), 6.90 (d, 1 H, J=9Hz), 7.10 (d, 1 H, J=9Hz). Anal. calcd. for $C_{21}H_{32}O_5$: C 69.20; H 8.85. Found: C 69.15; H 9.03.

6-n-Butyl-2-methoxyhydroquinone di-(2'-tetrahydropyranyl) ether (5a)

Colourless oil. ^1H NMR (CCl_4) δ 0.96 (t, 3 H, J=7.5Hz), 1.20-2.22 (m, 16 H), 2.50-2.86 (m, 2H), 3.90 (s) superimposed to 3.42-4.26 (m, total 7 H), 4.95-5.20 (m, 2 H), 6.58 (s, 2 H). Anal. calcd. for $C_{21}H_{32}O_5$: C 69.20; H 8.85. Found: C 69.08; H 8.97.

3-n-Butyl-2-methoxyhydroquinone 4-(2'-tetrahydropyranyl) ether (4b)

To a solution of **1b** (224 mg, 1.0 mmol), in 10 ml of THF, nBuLi (3.0 mmol) was added, at 0°C. After stirring for 1h at r.t., n-BuI (1.0 mmol) was added. After 15 h at r.t. the reaction was hydrolysed, brought to pH 5 with dilute HOAc and extracted with chloroform (3 x 30 ml). The combined extracts were washed with $NaHCO_3$ solution and dried over Na_2SO_4. After evaporation, the residue was purified by column chromatography on silica gel using toluene as eluent. Yield 238 mg (85 %) of **4b** as colourless oil. ^1H NMR (CCl_4) δ: 0.92 (t, 3 H, J = 7.5Hz), 1.15-2.08 (m, 10 H), 2.60 (t, 2 H, J=8.0Hz), 3.80 (s) superimposed to 3.38-4.02 (m, total 5 H), 5.18 (s) superimposed to 5.05-5.33 (m, total 2 H), 6.58 (d, 1 H, J=9.0Hz). Anal. Calcd. $C_{16}H_{24}O_4$: C 68.54; H 8.63. Found: 68.66; H 8.70.

3- and 6-n-Butyl-2-methoxy-1,4-benzoquinones (8 and 9)

The hydroquinone derivatives **4a**, **b** and **5a** (0.5 mmol) were stirred at r.t. in a mixture of 3 N HCl (3 ml) and THF (3 ml) for 10 min. After dilution with water (50 ml) 1 N $FeCl_3$ (3 ml) was added and the mixture was extracted with cyclohexane (3 x 30 ml). The combined extracts were dried over Na_2SO_4 and evaporated. Crude **9** was crystallized from heptane as yellow needles (83 mg, 85 %), m.p. 51-52°C (lit.2: 51-53°C) identical in all respect with a sample obtained by an independent route[2]. The less stable quinone **8** was purified by column chromatography (silica gel, cyclohexane) yielding a yellow oil (48.6 mg, 50 %) which crystallized below 0°C. UV (hexane) $\lambda_{max}(\varepsilon)$ 373 (1320), 257 (10100). IR (neat) ν 1645 cm^{-1}. ^1H NMR (CCL_4) δ 0.96 (t, 3 H, J=7.5Hz), 1.13-2.02 (m, 4 H), 2.40-2.66 (m, 2 H), 4.22 (s, 3 H), 6.76 (d, 1 H, J=9.0Hz), 6.92 (d, 1 H, J=9.0Hz). EIMS m/z 194 (M^+, 44), 179 (7), 152 (100), 123 (42), 109 (36), 95 (26), 65 (11), 54 (16). Anal. Calcd. for $C_{11}H_{14}O_3$: C 68.02; H 7.27. Found: C 67.75; H 7.41.

Lithiation and alkylation of 2-methoxyhydroquinone (1c)

To a solution of **1c** (168.9 mg, 1.2 mmol), in 10 ml of THF, n-BuLi (4.0 mmol) was added, at 0°C, producing a gray precipitate. After stirring for 10 min, t-BuLi (1.0 mmol) and after 1 h n-BuI (1.0 mmol) were added. The mixture was stirred for 2 d at r.t. and then hydrolysed with water and oxidized with 1 N $FeCl_3$ (5 ml). Extraction and chromatographic purification as described before yielded of **8** (30%). 2-Methoxy-1,4-benzoquinone (42%) was also recovered.

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