A Convenient Synthesis of *p*-Quinol Benzoates

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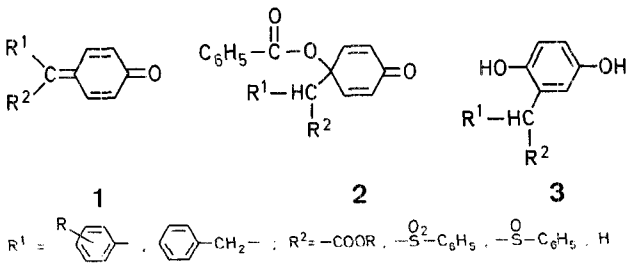
In order to facilitate the synthesis of quinone methides of the type **1** (R^2 = electron withdrawing group), a general method for the preparation of the required intermediates, the *p*-quinol benzoates **2** was needed.



1 **2** **3**

R^1 = , ; R^2 = −COOR , $-\overset{O_2}{S}-C_6H_5$, $-\overset{O}{S}-C_6H_5$, H

Certain *p*-quinol benzoates have been synthesised by the reaction of phenols with benzoyl peroxide[1], but this method is only applicable to the oxidation of 2,4,6-trisubstituted phe-

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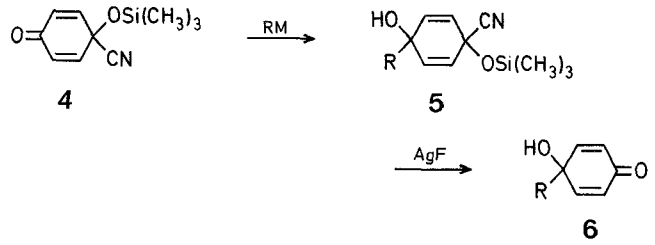
nols. In this paper we report a convenient synthesis of *p*-quinol benzoates of type **2**, which seems capable of being applied to the preparation of most *p*-quinol benzoates.

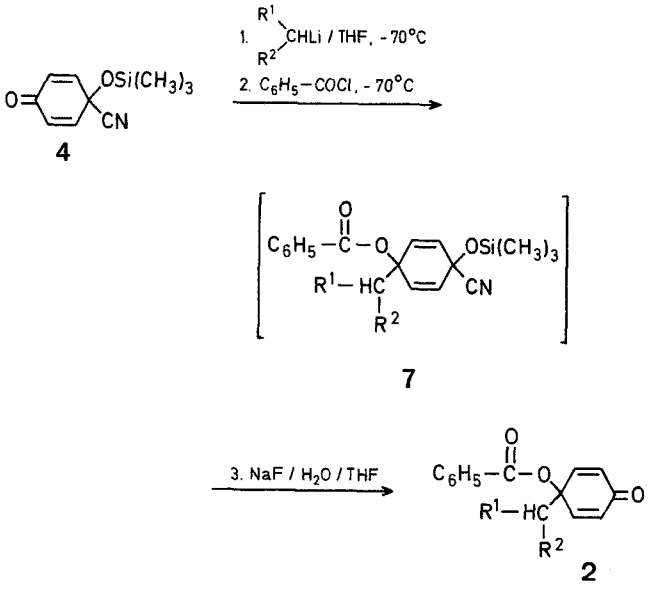
Recent reports described the preparation of the protected quinone **4**[2] and its reactions with alkyllithium[3] and both aryl-[3] and alkylmagnesium bromides[4] to give the protected quinols **5**. Deprotection of compounds **5** using silver fluoride gave the *p*-quinols **6** or their rearrangement products in excellent yield.



4 **5** **6**

An obvious approach to the synthesis of the *p*-quinol benzoates **2** ($R^1 = C_6H_5$) would be to utilise the reaction of **4** with various benzylmetallic compounds to give the *p*-quinols **6** ($R = C_6H_5—CH_2—$ etc.) followed by a subsequent benzoylation step. However, when the model reaction of benzylmagnesium bromide with the mono-protected quinone **4** was investigated only a 25% yield of the *p*-quinol **6** ($R = C_6H_5—CH_2—$) was obtained. Furthermore, the *p*-quinol was unstable and underwent the dienone-phenol rearrangement to give the hydroquinone **3** ($R^1 = C_6H_5$, $R^2 = H$). Appreciable rearrangement occurred on standing overnight at 0 °C and an instant, *p*-toluenesulphonic acid-catalysed rearrangement took place in toluene solution at room temperature. Similar rearrangements occurred when the reactions of the masked quinone **4** with the lithio derivatives of ethyl phenylacetate and methyl *o*-methoxyphenylacetate were studied, only the hydroquinone derivatives **3** ($R^1 = C_6H_5$, $R^2 = COOC_2H_5$) and **3** ($R^1 = 2\text{-}H_3CO—C_6H_4—$, $R^2 = COOCH_3$) were isolated after deprotection with sodium fluoride.

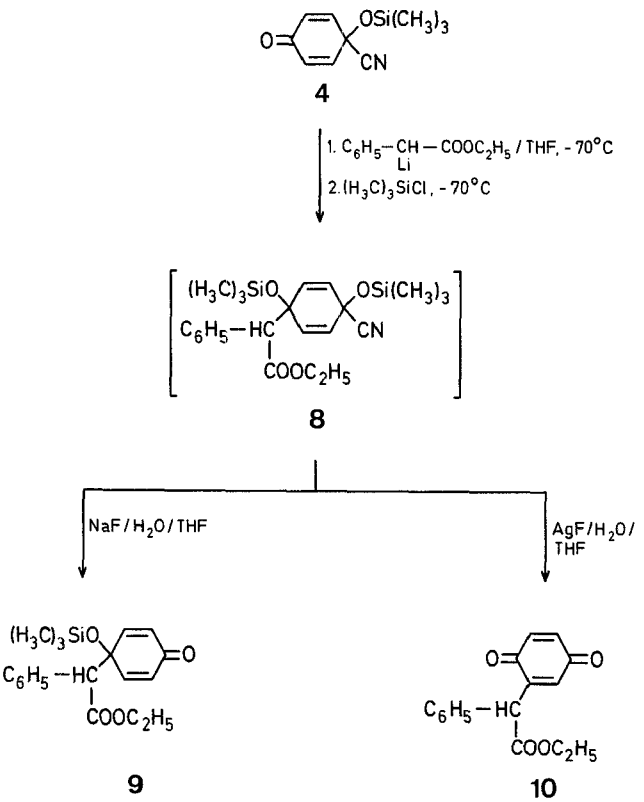
The ease with which the 4-benzyl-4-hydroxycyclohexadienones **6** ($R = C_6H_5—CH_2—$ etc.) underwent the dienone-phenol rearrangement precluded their isolation as intermediates in the projected *p*-quinol benzoate synthesis. In order to circumvent this problem, the masked quinone **4** was reacted with the various benzyllithium derivatives at −70 °C and the resulting anion trapped, still at −70 °C, with benzoyl chloride to give the protected quinol benzoate **7**. Deprotection of **7** (not isolated) with sodium fluoride furnished the required benzoates **2** in good yield (Table).



4 **7** **2**

In the case of example **2c**, the two diastereoisomers could be readily separated using flash chromatography. The *p*-quinol benzoates **2a–e**, unlike the *p*-quinols, were stable at room temperature, showing no tendency to undergo the dienone-phenol rearrangement. Extensions of this *p*-quinol benzoate synthesis involving the reactions of the lithio derivative of 2-phenylethyl phenyl sulphone and 2-phenylethylmagnesium bromide with **4** gave the required benzoates **2f** and **2g**. These results suggest that a wide range of *p*-quinol benzoates can be synthesised using this procedure.

The anions generated from the masked quinone **4** and the various organometallic derivatives used could be trapped by other electrophiles. For example, the anion formed by treatment of **4** with the lithio derivative of ethyl phenylacetate readily reacted with trimethylsilyl chloride to give the protected quinol **8**. Deprotection of **8** (without isolation) using sodium fluoride gave the *p*-quinol derivative **9** whereas deprotection with silver fluoride furnished the quinone **10**. The formation of **10** resulted from the removal of both trimethylsilyl groups, followed by a rearrangement of the *p*-quinol and finally oxidation of the hydroquinone to give **10**.

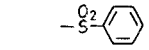
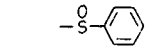
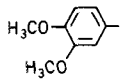
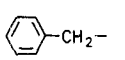
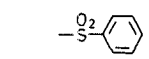
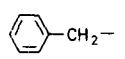


4 **8** **9** **10**

All experiments described in the following were performed under argon.

4-Benzyl-4-hydroxy-2,5-cyclohexadienone (6, $R = C_6H_5—CH_2—$): Cyanotrimethylsilane (2.75 ml, 22 mmol) is added over a period of 5 min to a stirred solution of *p*-benzoquinone (2.16 g, 20 mmol) and the potassium cyanide/18-crown-6 catalyst[5] (0.04 g) in dry tetrahydrofuran (40 ml) at 5 °C. After the addition, the mixture is stirred at room temperature for 30 min. This solution of the protected quinone **4** is added using a syringe to a solution, cooled to −70 °C, of the Grignard reagent prepared from benzyl chloride (2.64 ml, 23 mmol) and magnesium (0.53 g, 22.4 mmol) in dry ether (30 ml). After the addition, the

Table. Quinol Benzoates (**2**)

2	R^1	R^2	Yield [%]	m.p. [°C] (solvent)	Molecular formula[a]	^{1}H-N.M.R. ($CDCl_3$/TMS) δ [ppm]
a		$-COOC_2H_5$	64	122–123° (toluene/hexane)	$C_{23}H_{20}O_5$ (376.2)	7.95 (dd, $2H_{arom}$); 7.25 (m, $8H_{arom}+1C$=CH); 6.85 (dd, 1CH=C); 6.2 (m, 2CH—CO); 4.25 (s, CH); 4.15 (dq, CH_2); 1.2 (t, CH_3)
b			63	149–150° (toluene/hexane)	$C_{26}H_{20}O_5S$ (444.3)	8.3 (m, $2H_{arom}$); 7.7 (dd, CH=C); 7.35 (m, $13H_{arom}$); 6.85 (dd, CH=C); 6.2 (m, 2CH—CO); 4.5 (s, CH)
c			30	150°[b] (ethanol)	$C_{26}H_{20}O_4S$ (428.3)	8.3 (dd, $2H_{arom}$); 7.3 (m, 2C=CH+$13H_{arom}$); 6.3 (d, 2CH—CO); 3.8 (s, CH)
			20	166–167°[c] (ethanol)	$C_{26}H_{20}O_4S$ (428.3)	8.25 (dd, $2H_{arom}$); 8.05 (dd, 1C=CH); 7.4 (m, $13H_{arom}$); 6.3 (m, 1CH=C+2CH—CO); 3.85 (s, CH)
d		$-COOCH_3$	55	128–129° (toluene/hexane)	$C_{23}H_{20}O_6$ (392.2)	8.0 (dd, $2H_{arom}$); 7.2 (m, $7H_{arom}+2C$=CH); 6.25 (dd, CH—CO); 6.0 (dd, CH—CO); 5.05 (s, CH); 3.8 (s, OCH_3); 3.7 (s, $COOCH_3$)
e		$-COOCH_3$	53	139–141° (toluene/hexane)	$C_{24}H_{22}O_7$ (422.2)	8.0 (dd, $2H_{arom}$); 7.1 (m, 2C=C+$6H_{arom}$); 6.3 (dd, CH—CO); 6.2 (dd, CH—CO); 4.2 (s, CH); 3.8 (s, $2OCH_3$); 3.7 (s, $COOCH_3$)
f			75	153–154° (ethyl acetate/hexane)	$C_{27}H_{22}O_5S$ (458.3)	7.3 (m, $15H_{arom}+2C$=CH); 6.4 (dd, CH—CO); 6.25 (dd, CH—CO); 4.5 (t, CH); 3.3 (dd, CH_2); 2.8 (dd, CH_2)
g		H	25	122–124° (hexane)	$C_{21}H_{18}O_3$ (318.2)	8.05 (dd, $2H_{arom}$); 7.4 (m, $6H_{arom}$); 7.0 (d, C=CH); 6.4 (d, CH—CO); 2.8 (m, CH_2); 2.3 (m, CH_2)

[a] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.3, H, ±0.3; S, ±0.3.
[b] Isomer A, less polar isomer.
[c] Isomer B, more polar isomer.

mixture is stirred at −70°C for 15 min and the reaction then quenched with a solution of ammonium chloride (1.18 g, ~22 mmol) in water (4 ml). The mixture is allowed to reach ambient temperature and is then poured into ether (80 ml). The ether solution is dried with magnesium sulphate and evaporated. The resultant oil is stirred for 4 h with sodium fluoride (0.85 g, >20 mmol) using tetrahydrofuran/water (10/1; 60 ml) as solvent. The mixture is partitioned between ether and water and the ether layer is separated. The ether solution is washed with first 10% aqueous sodium carbonate, then with water, and is dried with magnesium sulphate and evaporated. The crude oil is flash-chromatographed on Merck silica 60 using toluene/ethyl acetate (20/3) as solvent to give, in order of elution:

Benzyl-p-benzoquinone; yield: 0.26 (6%); m.p. 42°C (Ref.[6], m.p. 44°C).

2-Benzylhydroquinone; yield: 0.35 g (9%); m.p. 106°C (Ref.[6], m.p. 104°C).

Quinol **6** (R = C_6H_5—CH_2—): The solvent is removed at room temperature to avoid rearrangement; yield: 0.92 g (24%).

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 7.25 (m, $5H_{arom}$); 6.8 (d, 2C=CH); 6.1 (d, 2CH—CO); 2.95 ppm (s, CH_2).

Methyl α-(2,5-Dihydroxyphenyl)-α-(2-methoxyphenyl)-acetate (3, R^1 = 2-H_3CO—C_6H_4—, R^2 = $COOCH_3$):

A 1.55 molar solution (6.45 ml, 10 mmol) of butyllithium in hexane is added over 5 min to a stirred solution of diisopropylamine (1.41 ml, 10 mmol) in dry tetrahydrofuran (20 ml) at 0°C. The solution is stirred at 0°C for a further 15 min and then cooled to −70°C. Methyl 2-methoxyphenylacetate (1.8 g, 10 mmol) in dry tetrahydrofuran (5 ml) is added over 5 min and after this addition the mixture is stirred for a further 15 min at −70°C before being cooled to −90°C. A solution of the protected quinone **4** [prepared as described in the preceding example from benzoquinone (1.08 g, 10 mmol) and cyanotrimethylsilane (1.4 ml, 10 mmol) in dry tetrahydrofuran (15 ml)] is added to the anion solution at −90°C and after the addition the mixture is maintained at −70°C for 30 min. Acetic acid (0.57 ml, 10 mmol) is added and the mixture allowed to return to room temperature. The mixture is poured into ether, filtered and evaporated to give the protected quinol as a brown oil. It is deprotected by stirring with sodium fluoride (0.45 g, >10 mmol) in tetrahydrofuran/water (10/1; 40 ml) at room temperature for 5 h. The resultant solution is partitioned between ether and water to give, after evaporation, the crude product as a brown oil which is purified by flash chromatography on Merck silica 60 using chloroform/methanol (20/1) as solvent; yield: 1.1 g (40%); m.p. 170–172°C (toluene/ethyl acetate).

$C_{16}H_{16}O_5$	calc.	C 66.7	H 5.6
(288.3)	found	66.9	5.6

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 6.9 (m, $7H_{arom}$); 5.5 (s, CH); 3.8 (s, OCH_3); 3.7 ppm (s, $COOCH_3$).

Ethyl α-(2,5-Dihydroxyphenyl)-α-phenylacetate (3, $R^1 = C_6H_5$, $R^2 = COOC_2H_5$):

The reaction is carried out in an identical way to the preceding example except ethyl phenylacetate (1.59 ml, 10 mmol) is used in place of methyl 2-methoxyphenylacetate. The crude product is purified by flash chromatography on Merck silica 60 using toluene/ethyl acetate (4/1) as solvent; yield: 1.0 g (37%); m.p. 127–128°C (benzene/hexane).

$C_{16}H_{16}O_4$	calc.	C 70.6	H 5.9
(272.3)	found	70.8	6.1

^{1}H-N.M.R. ($CDCl_3$/TMS): δ = 7.5 (m, $6H_{arom}$); 6.7 (m, $2H_{arom}$); 5.2 (s, CH); 4.2 (q, OCH_2); 1.25 ppm (t, CH_3).

Quinol Benzoates (2); General Procedure:

A solution of lithium diisopropylamide is prepared by adding a 1.55 molar solution (6.45 ml, 10 mmol) of butyllithium in hexane to a solution of diisopropylamine (1.41 ml, 10 mmol) in dry tetrahydrofuran (15 ml) at 0°C. This solution is cooled to −70°C and a solution of the carbanion precursor (R^1—CH_2—R^2; 10 mmol) in dry tetrahydrofuran (5 ml) is added with stirring over 5 min. [In the case of **2g**, the organometallic compound is generated from 2-phenylethyl bromide (1.85 g) and magnesium (0.25 g) in dry tetrahydrofuran (20 ml).] After the addition, the mixture is stirred at −70°C for a further 30 min and then cooled to −90°C. A solution of the protected quinone **4** [prepared as in the first procedure from *p*-benzoquinone (1.08 g, 10 mmol) and cyanotrimethylsilane (1.4 ml, 10 mmol) in dry tetrahydrofuran (15 ml)] is added to the solution of the anion. After this addition, the reaction temperature is maintained at −70°C for 30 min before quenching the anion by the addition of benzoyl chloride (1.16 ml, 10 mmol). The

mixture is kept at −70 °C for a further 30 min before allowing the temperature to rise to ambient temperature. The mixture is drowned out into dry ether (100 ml). Filtration and evaporation gives the crude protected *p*-quinol benzoate **7**, which is deprotected by stirring at room temperature for 5 h with sodium fluoride (0.45 g, > 10 mmol) in tetrahydrofuran/water (10/1; 50 ml). The mixture is shaken with ether + water, the organic phase dried with magnesium sulphate, and evaporated to give the crude benzoate, which is purified by flash chromatography on Merck silica 60. Toluene/ethyl acetate (10/1) is used to chromatograph **2b, c, e**, toluene/ethyl acetate (20/1) for **2a, d, g**, and toluene/ethyl acetate (4/1) for **2f**.

4-(α-Ethoxycarbonylbenzyl)-4-trimethylsiloxy-2,5-cyclohexadienone (9):

The reaction is carried out in an identical manner to the general procedure for the synthesis of the *p*-quinol benzoates except that the anion generated from **4** and ethyl phenylacetate (1.59 ml, 10 mmol) is trapped by trimethylsilyl chloride (1.3 ml, 10 mmol) instead of benzoyl chloride. After deprotecting using sodium fluoride, the crude product is triturated with ether to give **9**; yield: 2.2 g (65%); m.p. 107–108 °C (toluene/hexane).

$C_{19}H_{24}O_4Si$	calc.	C 66.3	H 7.0
(334.5)	found	66.2	7.1

^{1}H-N.M.R. ($CDCl_3$/TMS): $\delta = 7.4$ (dd, C=CH); 7.2 (m, $5H_{arom}$); 6.7 (dd, C=CH); 6.05 (2 dd, CH—CO); 4.1 (dq, CH_3); 3.95 (s, CH); 1.25 (t, CH_3); 0.05 ppm [s, $Si(CH_3)_3$].

2-(α-Ethoxycarbonylbenzyl)-*p*-benzoquinone (10):

The procedure in the previous example is followed except that in the deprotection step the crude masked quinol is stirred for 48 h with silver fluoride (3.1 g, >24 mmol) instead of sodium fluoride. The product is purified by flash chromatography on Merck silica 60 using hexane/ethyl acetate (4/1) as solvent; yield: 1.05 g (39%); m.p. 89–90 °C (hexane).

$C_{16}H_{14}O_4$	calc.	C 71.1	H 5.2
(270.3)	found	71.1	5.4

^{1}H-N.M.R. ($CDCl_3$/TMS): $\delta = 7.35$ (m, $5H_{arom}$); 6.75 (s, 2CH—CO); 6.35 (s, CH—CO); 4.95 (s, CH); 4.2 (q, CH_2); 1.2 ppm (t, CH_3).

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