Hydroxyquinone Annelation

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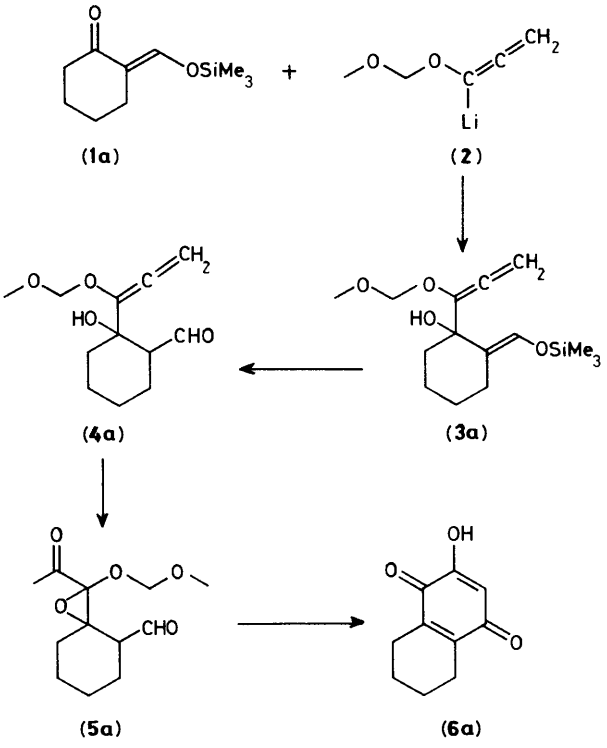
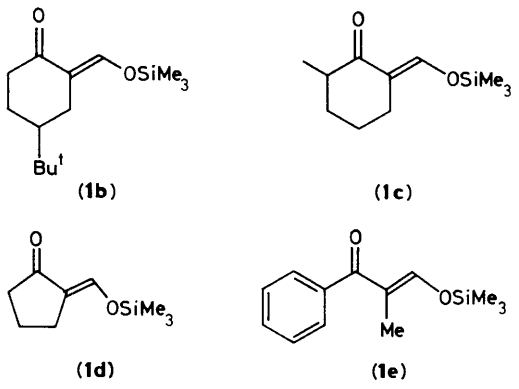
The epoxidation reaction of alkoxyallene (**4a**) produced epoxy ketoaldehyde (**5a**) through an intermediate oxyallyl zwitterion; an intramolecular aldol reaction, followed by air oxidation produced hydroxyquinone (**6**).

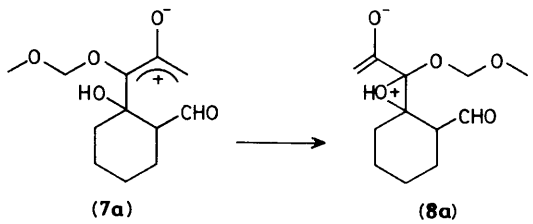
Hydroxyquinones and aminoquinones are common structural elements of natural products, including a number of antibiotics and anticancer compounds of current interest.[1] Regioselective methods for hydroxyquinone synthesis from non-aromatic precursors provide a flexible strategy for the total synthesis of these important compounds. Early work from our laboratories has resulted in effective methods for converting α-unsubstituted ketones to phenols,[2] catechol monoethers,[3] pyridines,[4] biphenyls,[5] terphenyls,[6] naphthalenes,[7] and methyl phenyls.[8] In order to extend our methodology to hydroxyquinone annelation, a highly unsaturated three carbon nucleophile was chosen for the reaction with a vinylogous silyl ester (**1**)[8] (Scheme 1). The lithio anion (**2**) derived from (methoxy)methoxyallene[9] was an attractive choice for the three carbon fragment. This highly reactive nucleophile was prepared very conveniently by isomerizing methoxymethyl prop-2-ynyl ether with potassium t-butoxide according to Brandsma's conditions.[9] The allene was stable to storage at −10 °C for several weeks in the presence of small amounts of calcium carbonate. The quantitative generation of anion (**2**) took place in ether/tetrahydrofuran (1/1) at −78 °C upon treatment with 1.1 equiv. of n-butyl-lithium. Addition of (**2**) to vinylogous trimethylsilyl ester (**1**) produced the tertiary alcohol (**3**) in high yield. The intermediates (**3**) had been prepared previously for a cyclopentenone synthesis.[9a] Indeed, exposure of (**3**) or the aldehyde (**4**) (the latter being a product of tetra-n-butylammonium fluoride induced desilylation), to protic or Lewis acids caused rapid cyclization to a five-membered ring.

Oxidation of the allene was the next task prior to cyclization. The epoxidation of (**4**) in a two-phase reaction mixture of aqueous sodium hydrogen carbonate and an ether solution of *m*-chloroperoxybenzoic acid led to (**5**). The formation of (**5**) presumably occurred through the intermediacy of an oxyallylzwitterion[10] (**7**) which was trapped intramolecularly by the oxygen atom of the tertiary alcohol to



Scheme 1





Scheme 2

Table 1.[a,b] Synthesis of ring fused hydroxybenzoquinones *via* an annelation reaction involving an unusual zwitterionic rearrangement.

Starting material	Intermediates (% yield)		Product[c] (% yield), m.p., *t*/°C
(**1a**)	(**3a**), (65)	(**5a**), (56)	(**14a**), (55), 187
(**1b**)	(**3b**), (56)	(**5b**), (67)	(**14b**), (61), 143
(**1c**)	(**3c**), (70)	(**5c**), (66)	(**14c**), (46), 136
(**1d**)	(**3d**), (48)	(**5d**), (64)	(**14d**), (61), 167

[a] All compounds produced satisfactory ^{1}H n.m.r., i.r., and mass spectra; supplementary spectral data for (**14a—d**) were available for the referees. [b] Percentages refer to overall yields of materials which were purified by flash column chromatography on silica gel.

form (**8**) (Scheme 2). Proton transfer reactions produced (**5**) which was formed as a diastereoisomeric mixture. Fortunately, the stereochemistry of (**5**) did not affect the subsequent cyclization reaction.

The base-catalysed cyclization of (**5**) was most effectively accomplished by treatment with 1 M potassium hydroxide in methanol at 25 °C. After neutralization of the base with dilute hydrochloric acid and extraction into dichloromethane, hydroxybenzoquinone (**6**) was isolated in good yield. The conversion of (**5**) to (**6**) is most easily rationalized by the mechanism shown in Scheme 3. Enolization of the aldehyde resulted in the rapid cleavage of the epoxide ring and in the formation of the diketone (**10**). The reversible enolization of (**10**) was followed by aldol ring closure *via* the enolate (**11**). Under the reaction conditions the alkoxide (**12**) can be expected to undergo rapid and irreversible base catalysed enolization to produce the hydroxy-aromatic compound (**13**). Oxidation of the electron rich aromatic ring by adventitious oxygen led to formation of hydroxyquinone (**6**). The ease with which this oxidative step took place made it difficult to isolate the trihydroxybenzene intermediate (**13**). Careful degassing of all solvents and conducting the cyclization reaction with a constant stream of argon bubbling through the solution failed to suppress the oxidation completely. The triacetate of (**13**) was isolated by treating (**6**) with sodium borohydride followed by an excess of acetic anhydride.

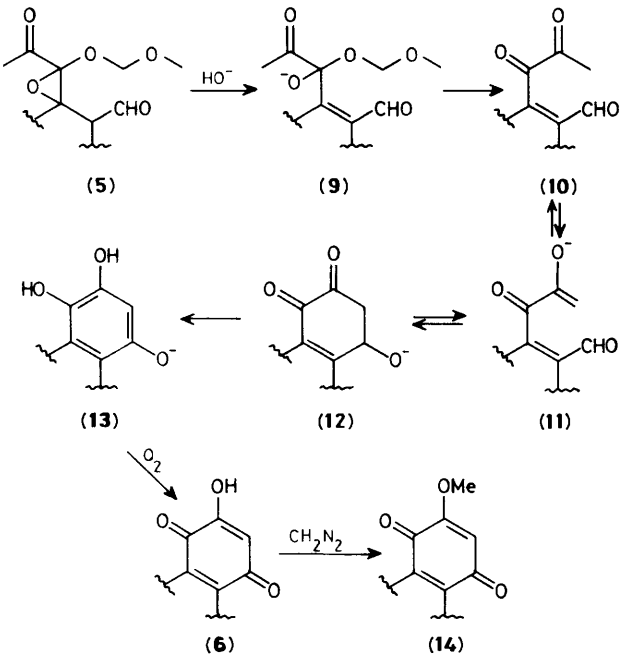
The hydroxyquinone products were not stable to storage. They were immediately converted to the corresponding methyl ethers (**14**)† by treatment with diazomethane in ether. This method was applied to the hydroxymethylene ketones shown in Table 1. Good results were obtained with five- and six-membered rings. Alkyl substitution α to the carbonyl group of the vinylogous silyl ester was tolerated, *i.e.* (**1c**). The method failed for the acyclic case (**1e**). The aldol reaction of (**5e**) produced a complicated mixture of products none of

† *Selected spectral data* for (**14a**): m.p. 187 °C, recrystallized from ethyl acetate/hexanes; t.l.c. R_f = 0.41 (25% ethyl acetate/hexanes); ^{1}H n.m.r. (300 MHz, $CDCl_3$) 5.83 (s, 1 H), 3.77 (s, 3 H), 2.41 (m, 4 H), 1.67 (m, 4 H) p.p.m.; i.r. (CH_2Cl_2) 2940, 1720, 1600, 1440, 1220 cm^{-1}; *m/z* 192 (M^+), 177, 163, 77, 69 (100%), 53; calcd. for $C_{11}H_{12}O_3$ 192.0787, found 192.0786.

(**14b**): m.p. 143 °C; t.l.c. R_f = 0.45 (25% ethyl acetate/hexanes); ^{1}H n.m.r. (300 MHz, $CDCl_3$) 5.84 (s, 1 H), 3.78 (s, 3 H), 2.8—2.6 (m, 2 H), 2.4—1.9 (m, 3 H) 1.3—1.0 (m, 2 H), 0.91 (s, 9 H) p.p.m.; i.r. (CH_2Cl_2) 2950, 1690, 1460, 1220 cm^{-1}; *m/z* 248 (M^+), 233, 213, 194, 137, 79, 69, 57 (100%); calcd. for $C_{15}H_{20}O_3$ 248.1413, found 248.1423.

(**14c**): m.p. 136 °C; t.l.c. R_f = 0.28 (20% ethyl acetate/hexanes); ^{1}H n.m.r. (300 MHz, $CDCl_3$) 5.82 (s, 1 H), 3.76 (s, 3 H), 2.94 (m, 1H), 2.62–2.50 (m, 1 H), 2.30—2.15 (m, 1 H, 1.8—1.6 (m, 4 H), 1.10 (d, *J* = 7 Hz, 3 H) p.p.m.; i.r. (CH_2Cl_2) 2950, 1720, 1605, 1420, 1225 cm^{-1}; *m/z* 206 (M^+), 191, 93, 77, 69, 55, 43 (100%); calcd. for $C_{12}H_{14}O_3$ 206.0943, found 206.0943.

(**14d**): m.p. 167 °C; t.l.c. R_f = 0.44 (25% ethyl acetate/hexanes); ^{1}H n.m.r. (300 MHz, $CDCl_3$) 5.79 (s, 1 H), 3.79 (s, 3 H), 2.78 (t, *J* = 8 Hz, 4 H), 2.04 (quintet, *J* = 8 Hz, 2 H) p.p.m.: i.r. (CH_2Cl_2) 2950, 1725, 1600, 1420, 1225 cm^{-1}; *m/z* 178 (M^+), 163, 148, 109, 91, 77, 67, 45 (100%); calcd. for $C_{10}H_{10}O_3$ 178.0630, found 178.0631.



Scheme 3

which was the desired hydroxyquinone. The success of the reaction in the case of (**1a**)—(**1d**) is likely to be a consequence of the enforced proximity of the ketone enolate and aldehyde groups (*cf.* **11**) due to the presence of the ring. The failure in the acyclic case suggests that this method will complement the elegant quinone synthesis reported by Liebeskind,[11] Wulff,[12] and others.[13] Both of these methods proceed from acetylenic precursors and are therefore unsuitable for the preparation of hydroxyquinones fused to small rings, since the cyclic acetylenes are unavailable.

An unusual zwitterionic rearrangement has been exploited to develop a synthesis of ring fused hydroxybenzoquinones. This annelation reaction is without precedent and promises to be useful for the preparation of diverse natural products.

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