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CONJUGATE REDUCTION OF QUINONE DERIVATIVES. A ROUTE TO PHENOL KETO–TAUTOMER EQUIVALENTS

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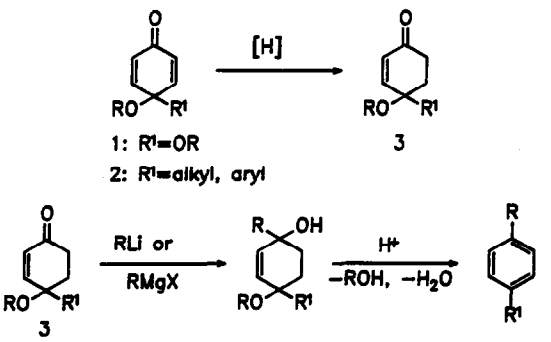
Summary: *1,4-addition of hydride to quinone monoketals 1 and p-quinol ethers 2, mediated by bis-(2,6-di-t-butyl-4-methylphenoxy)-methylaluminum (MAD), affords 4,4-substituted-2-cyclohexen-1-ones 3, which represent keto-tautomer equivalents of phenols.*

Quinone monoketals 1 and *para*-quinol ethers 2 serve as useful synthetic intermediates[1] which are readily available by electrochemical oxidation of substituted phenols and anisoles or by chemical oxidation of phenols.[2] We envisioned quinone derivatives 1 and 2 as possible precursors to keto-tautomer equivalents of substituted phenols via a conjugate reduction process (Scheme 1). The resulting cyclohexenone derivatives 3 would possess a leaving group (-OR) in the 4-position, formally representing a latent double bond via a subsequent elimination process. Reaction of nucleophilic reagents such as RLi or RMgX with 3, followed by acid-catalyzed aromatization would afford substituted aromatic compounds.

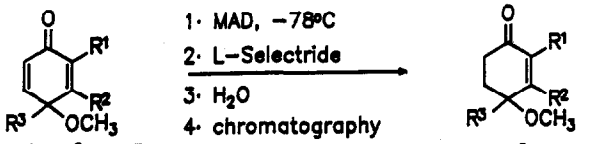


Scheme 1. Phenol Keto-Tautomer Equivalent Strategy

Unfortunately, conventional methods for conjugate reduction using hydride reagents or dissolving metals yield only the corresponding phenols when applied to quinone derivatives 1 or 2.[1] Furthermore, aromatization occurs exclusively from attempted conjugate additions to 1 or 2 using cuprate-type reagents, presumably via electron transfer processes.[1]

Thus, a new approach to conjugate reduction of cyclic enones was investigated,[3a,b] using both a sterically crowded hydride source and the bulky Lewis acid *bis*-(2,6-di-*tert*-butyl-4-methylphenoxy)-methylaluminum (MAD)[4] as a carbonyl-complexing auxiliary. Sterically blocking 1,2-addition of hydride to the carbonyl carbon would force addition to proceed via the 1,4-pathway. This has been observed for the MAD-mediated addition of certain organolithium and organomagnesium compounds to cyclohexenones[5] as well as quinone derivatives 1 and 2.[6]

Table. MAD-Mediated 1,4-Reduction of Quinone Derivatives 1 and 2



1: R^3 = OR
2: R^3 = alkyl, aryl

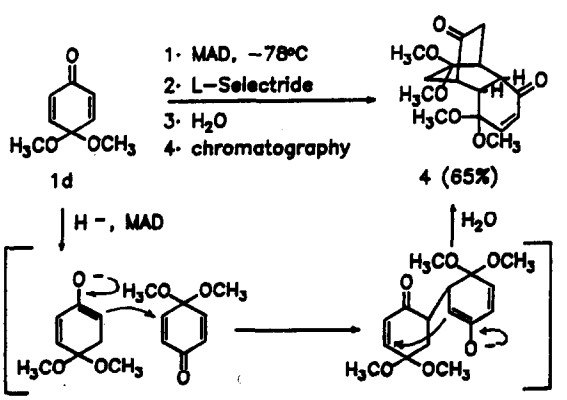
3

entry	dienone 1 or 2	enone 3	yield(%)[a]
1	1a: R^1=H, R^2=OCH_3, R^3=OCH_3	3a	72
2	1b: R^1=H, R^2=CH_3, R^3=OCH_3	3b	60
3	1c: R^1=CH_3, R^2=H, R^3=OCH_3	3c	50
4	1d: R^1=H, R^2=H, R^3=OCH3	3d	0[b]
5	2a: R^1=H, R^2=H, R^3=(p-CH_3O)Ph	3e	80
6	2b: R^1=H, R^2=H, R^3=(p-CH_3)Ph	3f	69
7	2c: R^1=H, R^2=H, R^3=Ph	3g	66
8	2d: R^1=H, R^2=H, R^3=n-butyl	3h	55[b]

[a]isolated yields, based on 1 or 2. [b]dimeric product formed.

Addition of a toluene solution of quinone derivatives 1 or 2 to two equivalents of MAD in toluene was followed by addition of lithium-tri-*sec*-butyl borohydride (L-Selectride)[7] at -78°C until the characteristic dark purple color of the MAD-carbonyl complex dissipated. Standard work up and silica gel chromatography afforded the enone products 3 in fair to good yield.

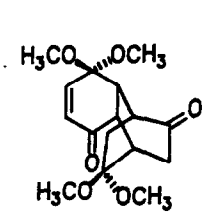
The reduction of unsymmetrically substituted quinone monoketals 1a-c (Table, entries 1-3) showed the expected regiospecificity, affording enone products resulting from addition to the lesser substituted of the two double bonds. For *para*-quinol ethers 2a-d (Table, entries 5-8) reduction gave the corresponding enones with no evidence for competing 1,2-reduction. With the exception of 3e, enone products 3 proved to be reasonably stable and could be stored for several weeks in a freezer in base-washed glassware without aromatization.



Scheme 2. Dimerization of Quinone Monoketal 1d

For unsubstituted quinone monoketal 1d (Table, entry 4), no 1,4-reduction product could be isolated. Instead, a polar, crystalline compound was obtained in 65% yield and subsequently identified by X-ray analysis as dimeric product 4 (Figure 1). Product 4 is presumably formed via initial 1,4-addition of hydride followed by a Michael-Michael addition sequence facilitated in part by the presence of MAD (Scheme 2). This unexpected transformation of 1d occurred exclusively—i.e. no products of type 3 could be detected—even after reversal of the mode of addition of hydride reagent (see representative procedure[8]). That the reduction process was sensitive to steric effects was further emphasized by the formation of only a small amount (5 %) of dimeric product[9] (similar in structure to 4) during reduction of 2d (Table, entry 8). No dimeric products were isolable from reduction of the substituted quinone monoketals 1a-c or from *para*-quinol ethers other than 2d.

The reported directing effect of methoxyl groups in the 4-position on the conjugate addition of organolithium or organomagnesium reagents to quinone derivatives 1 and 2 may not occur here.[6a] The conjugate reduction process reported herein is probably directed primarily by steric effects, since coordination of oxygen with the bulky L-Selectride would be unlikely. The absence of such an effect in similar conjugate reductions has been noted by others.[6b]



4

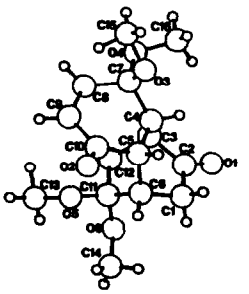
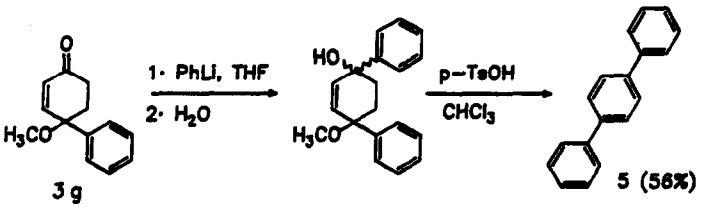


Figure 1. X-Ray Structure of Dimeric Product 4

While we have not extensively studied the chemistry of enones 3, reaction of 3g with phenyllithium followed by treatment of the crude 1,2-adduct with *para*-toluene sulfonic acid in chloroform afforded *para*-terphenyl 5 in 56% yield (Scheme 3). Thus, 3g served as the keto-tautomer equivalent of *para*-phenyl phenol in this reaction sequence, representing a potentially useful new method for the formation of aryl-aryl bonds.



3g

5 (56%)

Scheme 3. Synthesis of *para*-Terphenyl 5

Future work will focus on the synthetic utility of enones 3 in other aryl-carbon bond-forming reactions. Further, the unusual dimerization process observed from reduction of 1d may have implications for the chemistry of kinetic enolates derived from other cyclic enones.

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References and Notes

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3. a) For a recent hydridocuprate reduction method, see: Lipshutz, B.H.; Ung, C.S.; Sengupta, S., *Synlett*, 1989, *1*, 64.
   b) For a recent report of the hydride reduction of a quinone monoketal to its saturated derivative, see: Koenig, T.M.; Daeuble, J.F.; Brestensky, D.M.; Stryker, J.M., *Tetrahedron Lett.*, 1990, 3237.
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6. a) Stern A. J.; Rohde, J. J.; Swenton, J. S., *J. Org. Chem.*, 1989, *54*, 4413.
   b) For the alkoxide directed conjugate reduction of p-quinols, see: Shah, R.D.; Liotta, D.; Cherry, D.A.; Mills, J.E.; Rodgers, J.D.; Maryanoff, C.A., *J. Amer. Chem. Soc.*, 1988, *110*, 3702.
7. In the absence of MAD, only 1,2-reduction occurs. L-Selectride was purchased as a 1.0 M solution in THF, but the THF must be replaced with toluene prior to using the reagent in these reactions.
8. A representative procedure (Table, entry 4) is as follows: to a solution of BHT (2,6-di-t-butyl-4-methyl phenol, 2.8 g, 13 mmol) in toluene (65 mL) under N_2 was added trimethylaluminum (6.5 mmol, 3.25 mL of a 2.0 M solution in toluene) dropwise. After stirring for 15 min, the solution was cooled to -78°C and a solution of 4,4-dimethoxy-2,5-cyclohexadienone 1d (0.5 g, 3.25 mmol) in toluene (1.0 mL) was added. To the resulting purple solution was added L-Selectride (3.25 mmol, 3.25 mL of a 1.0 M toluene solution) over 1 min. The reaction was quenched with sat $NaHCO_3$ (1.0 mL), filtered to remove aluminum salts, dried over $CaSO_4$ and conc in vacuo. The resulting oil was chromatographed on silica gel (6" X 1/2" column, 15:85 EtOAc/hexanes) to yield dimeric product 4 (0.324 g, 65%) as white crystals: mp 98.5-100°C; IR (KBr) cm^{-1} 1732, 1675, 1247, 1114, 1092, 1070, 1032, 1006, 967, 932; ^1H NMR ($CDCl_3$) δ 6.41 (AB_q, J_{AB} = 18 Hz, 2H), 3.20 (s, 3H), 3.13 (s, 3H), 3.03 (s, 3H), 2.95 (s, 3H), 2.89-1.50 (str m, 8H). Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.14. Found: C, 61.73; H, 7.14.
9. The structure of this dimeric product was inferred by comparison with NMR and IR data of 4, but was not rigorously established. IR, NMR and combustion analysis were consistent with a structure analogous to 4.

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