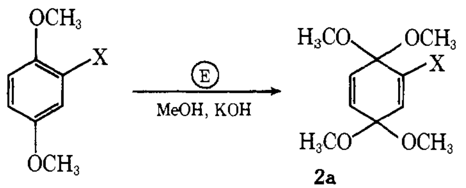
Communications to the Editor

Latent Quinone Carbanions via Anodic Oxidation of 2-Bromo-1,4-dimethoxybenzene. An "Umpolung" Reagent for Quinones[1]

Sir:

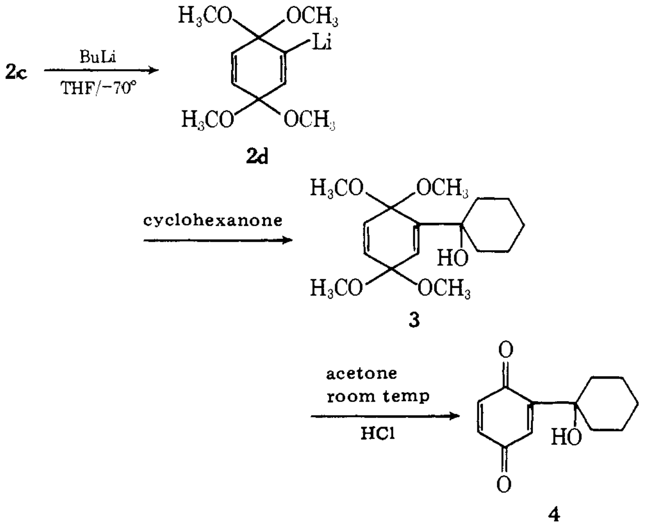
In spite of the wide occurrence of the quinone fragment in a variety of natural products, methods for the direct functionalization of this highly reactive moiety are limited.[2,3] In connection with synthetic studies toward a regioselective construction of anthracycline antibiotic ring systems, we have developed a versatile reverse-polarity reagent (umpolung) for quinones. Thus, anodic oxidation of 2-bromo-1,4-dimethoxybenzene (**1c**) affords the bromoquinone ketal **2c** which readily metalates at −70° in tetrahydrofuran. Reaction of this organolithium reagent with carbonyl compounds yields functionalized quinone ketals which may be hydrolyzed to their respective quinones.

While the anodic oxidation of *p*-dimethoxybenzene (**1a**) to the quinone ketal, **2a**, was reported more than 12 years ago,[4,5] the utilization of this reaction in organic synthesis has been quite limited.[6] We have found that both 2-chloro- (**1b**), and 2-bromo-1,4-dimethoxybenzene (**1c**) undergo anodic oxidation in 1% methanolic potassium hydroxide at a platinum anode to afford **2b** (83%) and **2c** (75%), respectively.[7] VPC analysis indicated only minor amounts of product arising from reductive cleavage of the halogen, and the pure compounds were readily obtained on a 30–40-g scale by recrystallization.[8] While the chloro derivative **2b** did not readily undergo metalation under a variety of conditions, the bromo derivative **2c** was smoothly metalated upon treatment with 1 equiv of butyllithium at −70° to afford **2d**. Quenching of this solution with deuterium oxide afforded the parent ketal (86%) with >95% monodeuterium incorporation (NMR analysis). The reaction of this preformed anion with cyclohexanone at −70° followed by quenching the reaction mixture with water afforded **3** in 81% yield by recrystallization.[9] Hydrolysis of **3** with acetone/1 N HCl (1:1) at room temperature for 4 h gave the corresponding quinone **4** in 80% isolated yield. Similarly, reaction of **2d** with benzophenone, benzaldehyde, and benzil afforded **5**, **6**, and **7** in yields of 72, 64, and 60%, respectively, after chromatography on activity III neutral alumina (ether-hexane eluent). The success of the reaction of the lithium derivative with ketones may be dependent upon the competition between addition and enolization. Thus cycloheptanone afforded only a 40% yield of adduct under these conditions whereas cyclopentanone gave primarily the debrominated quinone ketal, **2a**.



1a, X = H
b, X = Cl
c, X = Br

2a
b, mp 60-61°
c, mp 63-64°



2d

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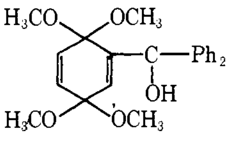
4



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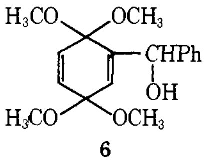

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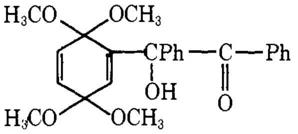

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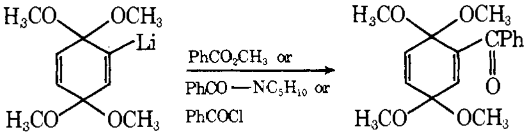
We had originally supposed that addition of **2d** to various acid derivatives would be severely complicated by products of double addition as is observed with usual organolithiums, but such was not the case. Reaction of **2d** with methyl benzoate, benzoylpiperidine, and benzoyl chloride afforded **8** in isolated yields of 78, 68, and 67%, respectively, the remaining **2d** being largely accounted for as recovered **2a**. Only in the case of benzoyl chloride was inverse addition necessary to minimize the formation of the alcohol side product. Of especial interest in connection with projected synthetic studies was the utility of this reagent in the monofunctionalization of diacid deriva-



2d **8**

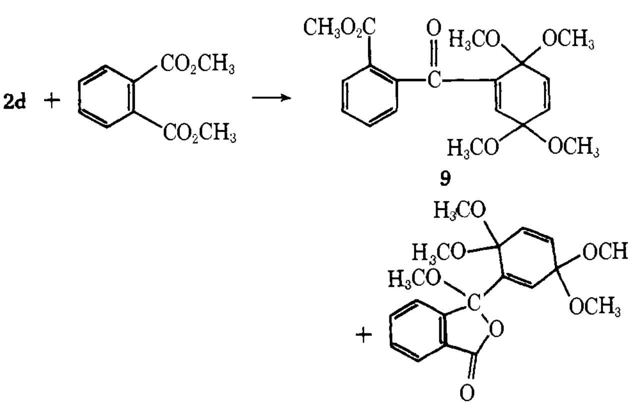


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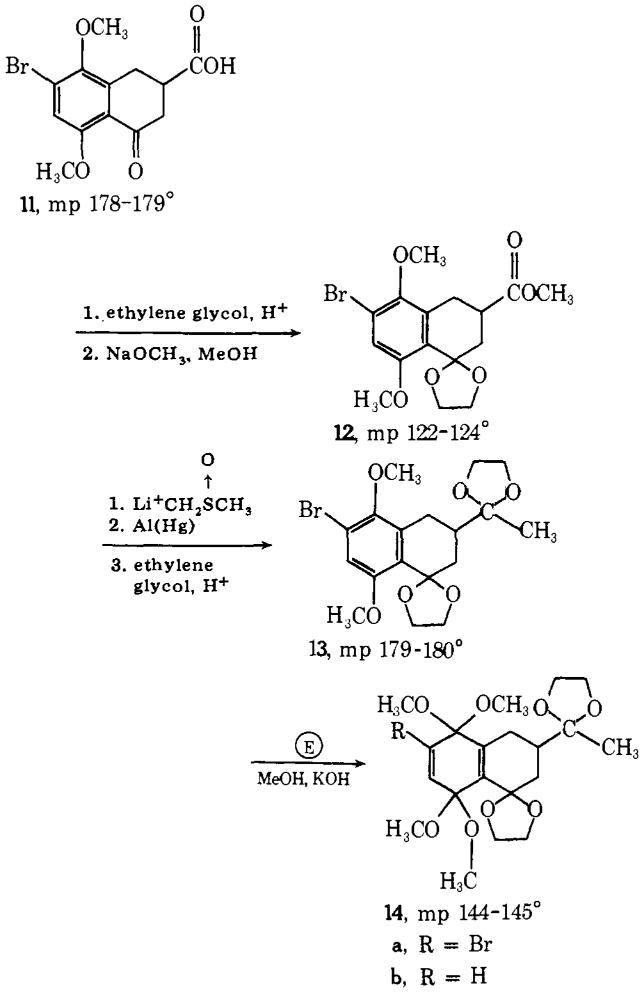
Table I. Reaction of 1-Lithio-3,3,6,6-tetramethoxy-1,4-cyclohexadiene (**2d**) with Carbonyl Compounds[a]

2c (mmol)	Carbonyl compound (mmol)	Adduct Yield[d] (%)	Adduct Mp (°C)	Quinone Yield[d] (%)	Quinone Mp (°C)
3.0	Cyclohexanone (3.0)	81	82-83	80	64-65
1.5	Cycloheptanone (1.5)	40	72-73	83	54-55
1.5	Cyclopentanone (1.5)		[b]		
3.0	Benzaldehyde (3.0)	68	50-51	88	59-61
1.5	Benzophenone (1.5)	72	94-95	74	151-153
1.5	Benzil (1.5)	60	96-97	88	137-139
4.5	Methyl benzoate (4.5)	78	66-67		[c]
3.0	Benzoylpiperidine (3.0)	68	66-67		[c]
3.0	Benzoyl chloride (4.5)[e]	67	66-67		[c]

[a] All new compounds gave acceptable combustion analyses (±0.3%) and showed NMR and ir spectra in agreement with the assigned structures. [b] No adduct has been obtained as yet. [c] Hydrolysis of these systems to the quinone was not performed. [d] Isolated yields of crystalline compounds. [e] Inverse addition was employed in this reaction. Normal addition in this instance gave rise to appreciable quantities of a bis addition product.

tives. Reaction of **2d** with 1 equiv of dimethyl phthalate afforded a 70% isolated yield of ca. 2:1 mixture of **9** and **10**.[10] The reagent thus shows promise for monofunctionalization of phthalate derivatives. Work at improving this procedure and exploring the regioselectivity of the addition is in progress.

The generality of this synthetic method rests with the elucidation of structural features compatible with the anodic oxidation since considerable literature precedent is available on the lability of various groups to butyllithium at low temperature. To establish the potential of this method in more highly substituted systems, the anodic oxidation of **13** has been investigated. This bicyclic compound is readily available in quantity from **11**, itself prepared via a synthetic route analogous to that of Wong.[11] Indeed, anodic oxidation of **13** at −3° afforded **14a** in 80% isolated yield,[12] thus emphatically demonstrating the applicability of this reaction to complex systems of synthetic interest. We will report in our full manuscript the scope of the anodic oxidation of other functionalized systems.



11, mp 178-179°

12, mp 122-124°

13, mp 179-180°

14, mp 144-145°

a, R = Br

b, R = H

The sequence of anodic oxidation followed by metalation serves as a versatile synthon for quinone carbanions of obvious synthetic potential. Careful monohydrolysis serves as a route to quinone hemiketals which should complement the use of the trimethylsilyl cyanide[13] procedure to such systems. We are currently exploring the effect of gegenion in modifying and extending the reactivity of these and other quinone ketals. Application of this reaction in natural products synthesis is in progress and will be reported at a later date.[14,15]

References and Notes

(1) D. Seebach, *Angew Chem.*, **81**, 690 (1969).

(2) (a) L. S. Hegedus, E. L. Waterman, and J. Catlin, *J. Am. Chem. Soc.*, **94**, 7155 (1972); (b) K. Sato, S. Inoue, and K. Saito, *J. Chem. Soc., Perkin Trans. 1*, 2289 (1973); (c) L. S. Hegedus and E. L. Waterman, *J. Am. Chem. Soc.*, **96**, 6789 (1974); (d) A. A. Matnishyan, G. V. Fomin, E. V. Prut, B. I. Liogon'kii, and A. A. Berlin, *Zh. Fiz. Khim.*, **45**, 1308 (1971); (e) *Chem. Abstr.*, **75**, 48087 (1971).

(3) For a pertinent discussion of the synthetic routes to functionalized quinone systems, see C. D. Snyder and H. Rapoport, *J. Am. Chem. Soc.*, **96**, 8046 (1974), and references cited therein.

(4) B. Belleau and N. L. Weinberg, *J. Am. Chem. Soc.*, **85**, 2525 (1963).

(5) For a recent discussion of anodic oxidation, see S. Ross, M. Finkelstein, and E. F. Rudd, "Anodic Oxidation", Academic Press, New York, N.Y., 1975.

(6) (a) G. L. Buchanan, R. A. Raphael, and R. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 373 (1973); (b) A. Nilsson, A. Ronlan, and V. Parker, *Tetrahedron Lett.*, 1107 (1975); (c) P. Margaretha and P. Tissot, *Helv. Chim. Acta*, **58**, 933 (1975); (d) W. Bornatsch and E. Vogel, *Angew. Chem. Int. Ed. Engl.*, **14**, 420 (1975).

(7) Anodic oxidations were performed in a magnetically stirred, ice-cooled methanolic potassium hydroxide or sodium methoxide solution of the compound. The Pt sheet (8 × 8 mm) cathode was placed in the center of a circular Pt gauze (33 mm diameter × 28 mm high) anode and current supplied by an Electro Products Lab, Inc., Electro Model EC-2 power supply. Reactions were performed at the maximum voltage setting (30 V). The current density at the anode was estimated to be 1 amp/35 cm^2.

(8) Electrolysis of 12.85 g (0.059 mol) of **1c** in 0.3% methanolic potassium hydroxide for 15 h followed by concentration in vacuo gave a light yellow semisolid. This material was dissolved in ca. 200 ml of petroleum ether and filtered, and the organic phase washed with water and saturated brine solution. After calcium sulfate drying, concentration of the solution yielded a light yellow solid which was recrystallized from petroleum ether to yield 12.4 g (75%) of **2c**.

(9) For all these additions it is critical that the reaction temperature be monitored below −65° to maximize yield.

(10) Compound **9** was obtained as a viscous oil homogeneous by TLC while the pseudoester **10** was a white crystalline solid, mp 106–108°. Both compounds showed spectroscopic properties fully in accord with the assigned structures.

(11) C. M. Wong, R. Schwenk, D. Popien, and T. Ho, *Can. J. Chem.*, **51**, 466 (1973). We wish to thank Professor Wong for experimental details concerning the preparation of the unbrominated series of compounds.

(12) The temperature of the reaction appears important in minimizing the debromination product. Thus, anodic oxidation of **13** at >−3° afforded a 91:9 mixture of **14a** and **14b**.

(13) D. A. Evans, J. M. Hoffman, and L. K. Truesdale, *J. Am. Chem. Soc.*, **95**, 5822 (1973).

(14) All new compounds gave acceptable C, H, and Br combustion analyses (±0.3%).

(15) We wish to thank Professors L. B. Anderson and R. L. McCreery for several discussions. This project was supported by Grant No. 5 PO1 CA16058-02 awarded by the National Cancer Institute, The American Cancer Society, and the Graduate School Small Grants Program.

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