Tetrahedron Letters No. 20, pp 1679 - 1682, 1977. Pergamon Press. Printed in Great Britain.

ANODIC OXIDATION AS A SYNTHETIC EXPEDIENT TO NAPHTHOQUINONE MONO- AND BISKETALS

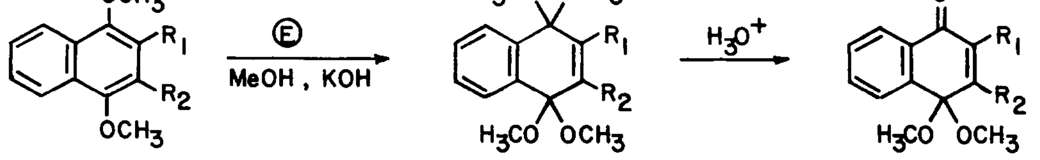
Michael J. Manning, Daniel R. Henton, and John S. Swenton

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

(Received in USA 21 January 1977; received in UK for publication 5 April 1977)

While the anodic oxidation of 1,4-dimethoxybenzene itself has been extensively investigated,[1] little information is available on the generality of the reaction in substituted 1,4-dialkoxybenzenes[2] and naphthalenes. Our need for an economical, general route to quinone bis- and monoketals prompted us to investigate the preparative anodic oxidation of substituted 1,4-dimethoxyaromatics. We report here that the anodic oxidations of 1,4-dimethoxynaphthalene derivatives produce in excellent yields the respective bisketals and that a sequence of anodic oxidation-hydrolysis or anodic oxidation-functionalization-hydrolysis presents a general, high-yield, regioselective route to functionalized quinone monoketals. In view of the widespread importance of the quinone moiety in natural products and the dearth of procedures for the preparation of quinone bis- and monoketals,[3] we anticipate much use for these electrochemically derived reagents.

The single cell, constant current, anodic oxidation of 1,4-dimethoxynaphthalenes 1a and 1b afforded excellent yields of the bisketals 2a and 2b. Unfortunately, for the brominated compounds 1c and 1d, this procedure resulted in substantial amounts of debromination[4] However, the use of a divided cell completely suppressed this side reaction, resulting in excellent yields of 2c and 2d. The ready availability of these brominated derivatives should



1

a, $R_1=R_2=H$ c, $R_1=H, R_2=Br$

b, $R_1=H, R_2=CH_3$ d, $R_1=CH_3, R_2=Br$

2 e, $R_1=CH_3, R_2=SCH_3$ 3

f, $R_1=H$, $R_2=SCH_3$

markedly extend the scope of the chemistry presented here.[2] Thus metallation of 2d with butyllithium and reaction with dimethyl disulfide afforded 2e in 95% yield. A similar sequence applied to 2c afforded after chromatography and hydrolysis the quinone monoketal 3f (vide infra).

Table. Naphthoquinone Bisketals and Monoketals

Bisketal (%, mp)[a, b]	Hydrolysis Conditions	Regioselectivity of Hydrolysis	Monoketal (%, mp)[b]
2a (74, 42.0- 43.5°)	1:3 2% HOAc/THF 5-6 h at RT	----	3a (81, oil)
2b (75, 65.5- 66.5°)	1:2 2% HOAc/acetone 1.5 h at 0°	>95%[d]	3b (90, 64.0- 65.0°)
2c (84, 65.0- 67.0°)	1:1 1.0 N HCl/THF 1.5 h at RT	>95%[d]	3c (85, 52.0- 53.0°)
2d (85, 147.0-149.0°)	1:1 1.0 N HCl/THF 1 h at RT	>95%[d]	3d (94, 102.0-103.0°)
2e (95, 100.0-101.0°)	1:1 0.1 N HCl/acetone 0.5 h at RT	ca 9:1	3e (58, 38.0- 40.0°)
2f[c]	1:1 2% HOAc/acetone 10 min at 0°	>95%[d]	3f[e] (56, 85.0- 86.0°)

[a] Electrolyses were performed on a 1-4 g scale using the apparatus previously described.[2] Compounds 1c and 1d were electrolyzed in an H-cell with the two compartments separated by a fritted disc. The products were isolated by standard workup[2] and recrystallization.

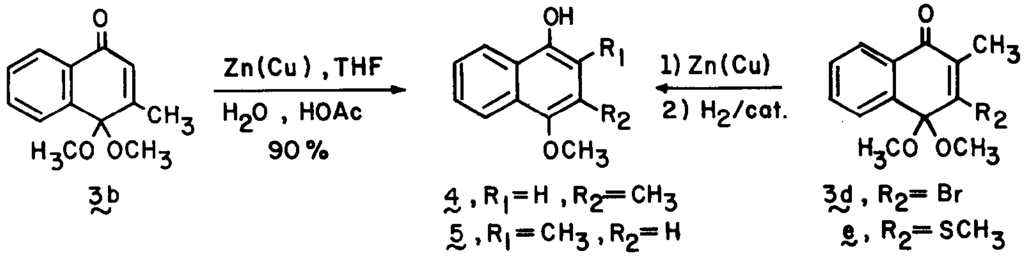
[b] Yields, except for 3a, are for recrystallized product. Ketal 3a was chromatographed on silica gel and was unstable to storage, forming a blue material.

[c] No attempt was made to isolate the bisketal due to its ease of hydrolysis.

[d] The alternate hydrolysis product was not detected in these cases by either NMR spectroscopy or the subsequent transformations of the product.

[e] The yield for 3f is calculated on the basis of starting 2c.

In addition to the utility of the bisketals in the synthesis of functionalized naphthoquinones, their regioselective monohydrolysis also produces high yields of synthetically valuable naphthoquinone monoketals. Thus acid hydrolysis of 2a-d at room temperature (Table) afforded after workup good yields of a single naphthoquinone monoketal. Since spectroscopic evidence did not allow definitive structure assignment, chemical proof of structure was performed. Reduction of 3b with zinc-copper couple gave in 90% yield the known 4.[5] Similarly, reduction of 3d with zinc-copper couple followed by hydrogenolysis of the bromine, or alternatively, reduction of 3d with Raney nickel and hydrogen, gave the known 5.[5] The orientation of substituents in 3b and 3d is then rigorously established. This



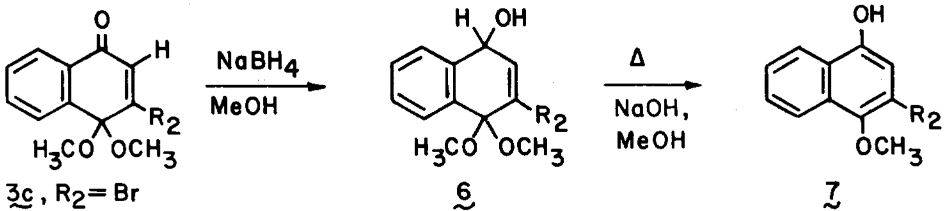
3b

4, $R_1=H$, $R_2=CH_3$
5, $R_1=CH_3$, $R_2=H$

3d, $R_2=Br$
e, $R_2=SCH_3$

approach also proved applicable to 3e since reduction followed by desulfurization afforded 5. Only in the hydrolysis of 2e was evidence of the alternate monoketal obtained. Thus treatment of the crude hydrolysis mixture from 2e as above afforded a 5:4 mixture (ca. 9:1, NMR analysis).[6]

The above reaction sequence was not useful in establishing the structures of 3c and 3f since the respective naphthols are not known. However, reduction of these compounds with sodium borohydride afforded the alcohols 6c and 6f as isolable, but labile, compounds.[7,8] The NMR spectra of the compounds showed the vinyl and tertiary protons (after equilibrating with D_2O) as doublets (J = 4 Hz). This coupling constant is only consistent with the β-substituted enone systems 3c and 3f. Heating 6c or 6f in methanolic sodium hydroxide yields the naphthalene derivatives 7c and 7f.



3c, $R_2=Br$
f, $R_2=SCH_3$

6

7

These preparations of naphthoquinone bis- and monoketals are characterized by simple equipment,[2] inexpensive reagents, high yields, and ease of isolation. Furthermore, these preparations of naphthoquinone monoketals offer advantages over the trimethylsiloxycyanide blocking procedure[3a] in that the methoxyketal is much more stable towards nucleophilic attack than the cyano group, introduces no new asymmetric center, and does not require the expensive silver fluoride for deblocking.

Acknowledgment

We wish to thank the Camille and Henry Dreyfus Fund and Petroleum Research Fund for partial support of this work.

References

1. (a) B. Belleau and N. L. Weinberg, J. Amer. Chem. Soc. 85, 2525 (1963); (b) S. Andreades and E. W. Zahnow, ibid. 91, 4181 (1969); (c) B. Belleau and N. L. Weinberg, Tetrahedron 29, 279 (1973); (d) G. L. Buchanan, R.A. Raphael, and R. Taylor J. Chem. Soc. Perkin Trans 1, 373 (1973); (e) A. Nilsson, A. Ronlan and V. Parker, Tetrahedron Lett., 1107 (1975); (f) P. Margaretha and P. Tissot, Helv. Chim. Acta. 58, 933 (1975); (g) N. L. Weinberg, D.H. Marr, and C.N. Wu, J. Amer. Chem. Soc. 97, 1499 (1975) and references cited therein.

2. M. J. Manning, P. W. Raynolds, and J. S. Swenton, ibid. 98, 5008 (1976).

3. (a) D.A. Evans, J. M. Hoffman, and L. K. Truesdale, ibid. 95, 5822 (1973); (b) Recently, the production of quinone monoketals by thallium(III) nitrate oxidation of 4-alkoxyphenols has been extensively studied. Where these latter compounds are available, this serves as a general procedure for benzoquinone monoketals. A. McKillip, D.H. Perry, M. Edwards, S. Antus, L. Farkas, M. Nogradi, and E. C. Taylor, J. Org. Chem. 41, 282 (1976) and references cited therein.

4. This electrochemical debromination was not unexpected. For a discussion of the debromination of 1-bromonaphthalene and a recent example of electrochemical debromination, see: (a) A. J. Fry, Synthetic Organic Electrochemistry (New York: Harper and Row, 1972), Chapter 5; (b) J.R. Falck, L. L. Miller, and F.R. Stermitz, Tetrahedron 30, 931 (1974).

5. C. D. Snyder and H. Rapoport, J. Amer. Chem. Soc. 96, 8046 (1974).

6. While the NMR spectra of 4 and 5 are quite similar, in 1:1 $CDCl_3$:acetone-d_6 the vinyl and methoxy signals are base line separated to allow analysis.

7. Compound 6c was obtained as a crystalline solid (89%) (pet ether-CH_2Cl_2) mp 152-3° (decomp), while 6f was obtained in 80% yield as a clear oil.

8. Physical properties and yields via zinc-copper couple reduction of 3c and 3f were: 7c, mp 145.5-146.0°, 77%; 7f, mp 131.5-132.5°, 92%. All new compounds afforded acceptable exact mass measurements or combustion analyses.