Oxidations with Silver Carbonate/Celite. V.[1] Oxidations of Phenols and Related Compounds[2]

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Silver carbonate on Celite in neutral media effects selective oxidative coupling of hindered phenols giving the corresponding dipheno- and stilbenequinones in high yields. Bis phenols obtained by reduction of these quinones were also oxidized by silver carbonate. When coupling was not possible due to steric factors, the stable phenoxy radicals were isolated quantitatively. Hydroquinones and pyrocatechols gave the corresponding *p*- and *o*-quinones in excellent yields. Oxidation of *p*-hydroxydiphenylamine and *o*-aminophenol gave the corresponding monoanil and phenoxazone, respectively.

Phenol coupling is an important synthetic tool and an essential step in the biosynthesis of many alkaloids and other natural products.[3] The reagents most extensively employed to effect this coupling (ferricyanide, ferric chloride, metal oxides, *e.g.*, MnO_2, PbO_2, HgO, Ag_2O, etc.) often suffer from poor selectivity and usually give a mixture of quinones, dimers, and polymers, the product distribution varying widely with the nature of the reagent. Moreover, the alkaline or acidic media required for these oxidations limit their applicability when sensitive functional groups are present.

The recently reported oxidizing agents, vanadium tetrachloride[4] and vanadium oxychloride, are useful in the preparation of some diphenols and diamino phenols. The oxychloride has been used advantageously in the intramolecular oxidative coupling[5] of 1,3-bis(hydroxyphenyl)propane; however when applied to hindered phenols either they did not react or gave comparatively poor yields.

Manganic tris(acetylacetonate) (MTA),[6] another new reagent which acts in homogeneous solution, has been found to bring about coupling of phenols to diphenols in fair yields, and the reaction can be controlled to give diphenols rather than quinones, but neither the experimental details nor its scope has yet been published.

Isoamyl nitrite[7] oxidizes 2,6-disubstituted phenols to the diphenoquinones in 50–60% yield, but the yields are lowered when the substituents are bulky or deactivating. Furthermore, there is the complication of the possible oximination by the reagent.

An interesting modification of PbO_2 oxidation carried out in polar solvents[8] gives diphenoquinones or *p*-benzoquinones almost exclusively.

MnO_2–silica gel[9] has been employed for the biogenetic type oxidative coupling of reticuline to salutaridine in 4% yield. Despite the somewhat higher yield obtained with this reagent, it still falls short of being a useful synthetic tool.

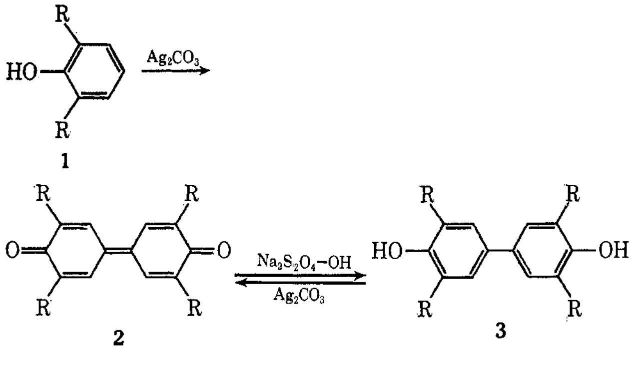
Some cobalt complexes of the salcomine type[10] have been reported to catalyze the autoxidation of phenols.

In spite of the obvious advantages, the anodic oxidation of phenols[11] has not been studied extensively since the early work by Fichter. None of the few recent examples[12,13] effects carbon–carbon coupling as the main feature.

We report here on the oxidation of phenols by silver carbonate/Celite a highly specific and selective oxidizing agent, the usefulness of which in the oxidation of a variety of aliphatic and alicyclic hydroxy compounds has already been demonstrated.[1] Oxidation of phenols by this reagent is superior to the existing reagents in the ease of operation and the homogenity and facile recovery of the products. The reaction is conducted in an inert organic solvent under mild conditions. Whenever coupling is observed, it is exclusively carbon–carbon.

Results

Selective Oxidative Coupling.—Oxidation of 2,6-dimethyl-, 2,6-diisopropyl-, and 2,6-di-*tert*-butylphenol give the corresponding diphenoquinones **2a–c** resulting



a, R = CH_3
b, R = $CH(CH_3)_2$
c, R = $C(CH_3)_3$

from para–para C–C coupling and subsequent oxidation of the dimers **3a–c**. The redox potential of the reagent ($Ag^+ + e^- \rightarrow Ag \sim 0.80$ V) is high enough to oxidize the dimers to extended quinones. The di-

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[1] (a) Part I: M. Fétizon and M. Golfier, *C. R. H. Acad. Sci.*, **267**, 900 (1968). (b) Part II: V. Balogh, M. Fétizon, and M. Golfier, *Angew. Chem.*, **81**, 423 (1969); *ibid.*, *Int. Ed. Engl.*, **8**, 444 (1969). (c) Part III: M. Fétizon, M. Golfier, and J-M. Louis, *Chem. Commun.*, 1102 (1969). (d) Part IV: M. Fétizon, M. Golfier, and J-M. Louis, *ibid.*, 1118 (1969).

[2] For a preliminary communication on this subject, see ref 1b.

[3] W. I. Taylor and A. R. Battersby, "Oxidative Coupling of Phenols," Marcel Dekker, New York, N. Y., 1967, and papers cited therein.

[4] W. L. Carrick, G. L. Karapinka, and G. T. Kwiatkowski, *J. Org. Chem.*, **34**, 2388 (1969).

[5] M. A. Schwartz, R. A. Holton, and S. W. Scott, *J. Amer. Chem. Soc.*, **91**, 2800 (1969).

[6] M. J. S. Dewar and T. Nakaya, *ibid.*, **90**, 7134 (1968).

[7] R. A. Jerussi, *J. Org. Chem.*, **35**, 2105 (1970).

[8] C. R. H. I. de Jonge, H. M. van Dort, and L. Vollbracht, *Tetrahedron Lett.*, **22**, 1881 (1970).

[9] B. Frank, Z. Dunkelmann, and H. J. Lubs, *Angew. Chem.*, *Int. Ed. Engl.*, **6**, 1075 (1967).

[10] L. H. Vogt, Jr., J. G. Wirth, and H. L. Finkbeiner, *J. Org. Chem.*, **34**, 273 (1969).

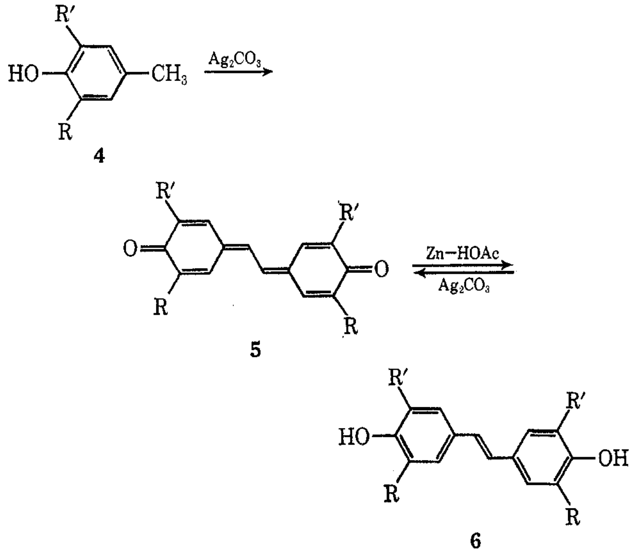
[11] A. I. Scott, *Quart. Rev.*, *Chem. Soc.*, **19**, 1 (1965).

[12] F. W. Steuber and K. Dimroth, *Chem. Ber.*, **99**, 258 (1966).

[13] A. B. Suttie, *Tetrahedron Lett.*, **21**, 953 (1969), and papers cited therein.

phenoquinones **2a–c** were reduced by sodium hydrosulfite in weakly alkaline solutions. These diphenols could be readily reoxidized to the parent quinones by silver carbonate.

Oxidation of hindered phenols bearing a methyl group at the para position (**4a–c**) gives the corresponding stilbenequinones **5a–c** in high yields; dimerization probably occurs *via* the intermediate benzyl radicals. On reduction with zinc and acetic acid these quinones give the corresponding 4,4′-dihydroxystilbenes **6a–c** which are reconverted to the stilbenequinones by oxidation with silver carbonate (Tables I and II).



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a, R = R′ = CH$_3$
b, R = R′ = C(CH$_3$)$_3$
c, R = CH$_3$; R′ = C(CH$_3$)$_3$

TABLE I

Phenol	Mol of Ag$_2$CO$_3$	Reaction time, hr	Product, % yield	Mp, °C Found	Mp, °C Lit.
1a	4.4	0.5	**2a**, 98	217–218	215[a]
1b	5.0	1.5	**2b**, 100	200–201	199–203[b]
1c	4.4	2.0	**2c**, 99	248	245–247[c]
3a	4.2	0.5	**2a**, 98	218–219	
3b	4.3	1.5	**2b**, 97	198–200	
3c	4.1	2.0	**2c**, 95	247	
4a	4.4	2.0	**5a**, 93	227–228	220–230[d]
4b	4.2	1.0	**5b**, 90	313–314	316[e]
4c	4.5	2.0	**5c**, 97	225	225[f]
6a	32.0	0.5	**5a**, 83	228–229	
6b	32.0	1.0	**5b**, 90	312–314	
6c	37.0	2.0	**5c**, 83	249–250	
7	6.1	2.0	**8**, 100	~80 dec	~80 dec[g]
10	14.3	3.0	**11**, 98	154–155	157.5[h]

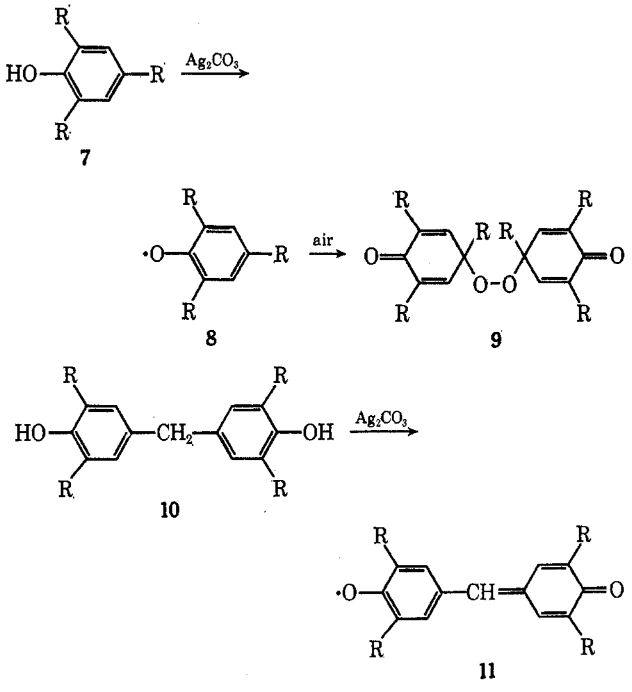
[a] R. G. R. Bacon and A. R. Izzat, *J. Chem. Soc. C*, 791 (1966). [b] W. B. Wheatley and C. T. Holdrege, *J. Org. Chem.*, **23**, 568 (1958). [c] H. Hart and F. A. Cassis, Jr., *J. Amer. Chem. Soc.*, **73**, 3179 (1951). [d] K. Fries and E. Brandes, *Justus Liebigs Ann. Chem.*, **542**, 48 (1939). [e] R. H. Bauer and G. M. Coppinger, *Tetrahedron*, **19**, 1201 (1963). [f] J. R. Dunn and W. A. Waters, *J. Chem. Soc.*, 2993 (1953). [g] C. D. Cook, D. A. Kuhn, and P. Fianu, *J. Amer. Chem. Soc.*, **78**, 2002 (1956). [h] M. S. Kharasch and B. S. Joshi, *J. Org. Chem.*, **22**, 1435 (1957).

TABLE II

Quinone	Product, % yield	Mp, °C Found	Mp, °C Lit.
2a	**3a**, 85	228–229	226[a]
2b	**3b**, 89	118–119	115–117[b]
2c	**3c**, 95	184–185	185[c]
5a	**6a**, 81	237–240	239–240[d]
5b	**6b**, 80	244–246	240–241[e]
5c	**6c**, 89	167–168	171[f]

[a] See footnote *a* in Table I. [b] *Chem. Abstr.*, **63**, 5561*f* (1965); Neth. Appl. 6,410,238 (Mar 4, 1965). [c] M. S. Kharasch and B. S. Joshi, *J. Org. Chem.*, **22**, 1439 (1957). [d] See footnote *d* in Table I. [e] C. D. Cook, *J. Org. Chem.*, **18**, 261 (1953). [f] *Chem. Abstr.*, **49**, 3263*a* (1955); British Patent 699,180 (Nov 4, 1953).

Stable Free Phenoxy Radicals.—The formation of a stable free phenoxy radical by one-electron oxidation of a phenol becomes possible when all C–C coupling positions are protected by bulky groups. Thus oxidation of 2,4,6-tri-*tert*-butylphenol and 4,4′-dihydroxy-3,5,3′,5′-tetra-*tert*-butyldiphenylmethane in benzene solutions under argon atmosphere gives the free radicals **8** and **11** quantitatively. In the presence of air **8** gives the peroxide **9**. In contrast, **11** in benzene solution is quite stable toward molecular oxygen; however in methanol it decomposes to 2,6-di-*tert*-butyl-*p*-hydroxybenzaldehyde, 3,5,3′,5′-tetra-*tert*-butyldiphenoquinone, and a trace of an unidentified red oil.



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R = C(CH$_3$)$_3$

***o*-Quinones.**—Oxidation of catechols **12a–d** by silver carbonate affords highly pure *o*-quinones **13a–d** in essentially quantitative yields (Table III). Oxidations of this type using other reagents[14] in the few cases where yields were specified reportedly ranged from 12 to 81%.

***p*-Quinones.**—A large number of known oxidizing agents are able to transform hydroquinones to quinones in high yields.[15] Silver carbonate/Celite also converts hydroquinones to quinones quantitatively and is a

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[14] See, for some of the examples, Table III, footnotes *a–d*.

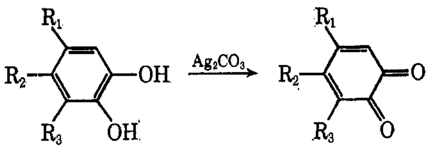
[15] See Table III, footnote *a*.

TABLE III

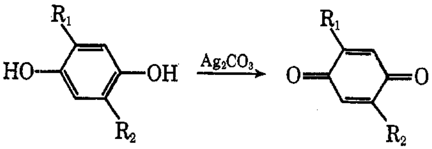
Phenol	Mol of Ag_2CO_3	Reaction time, hr	Product, % yield	Mp, °C Found	Mp, °C Lit.
12a	5.0	2.00	**13a**, 98	60–70	60–70[a]
12b	5.0	3.00	**13b**, 100	76–80	75–84[b]
12c	5.0	3.00	**13c**, 98	66–67	68[c]
12d	5.0	3.00	**13d**, 99	114–115	113–114[d]
14a	2.0	1.00	**15a**, 97	116	116[e]
14b	2.0	1.00	**15b**, 98	65.5–66.5	68–69[f]
14c	2.0	1.00	**15c**, 100	139–141	145[g]
14d	2.5	1.00	**15d**, 98	44–45	46–47[h]
14e	5.0	2.00	**15e**, 98	152	152–153[i]
14f	5.0	2.00	**15f**, 99	290	290[a]
16	2.5	1.25	**17**, 100	123.5–124.5	124–125[j]
18	2.0	0.16	**19**, 97	102–103	100–101[k]
20	4.0	0.25	**21**, 33	255–256	249[l]

[a] Z. E. Jolles in "Chemistry of Carbon Compounds," Vol. IIIB, Elsevier, New York, N. Y., 1956, p 704, *et seg.* [b] J. Cason, *Org. React.*, **4**, 314 (1948). [c] *Chem. Abstr.*, **52**, 432*i* (1958); U. S. Patent 2,782,210 (Feb 10, 1957). [d] *Chem. Abstr.*, **57**, 8504*g* (1962); German Patent 1,126,852 (April 5, 1962). [g] F. Kehrman and E. Hoehn, *Helv. Chim. Acta*, **8**, 221 (1925). [e] P. T. T. Sah, *Recl. Trav. Chim. Pays-Bas*, **59**, 454 (1940). [f] L. I. Smith and W. B. Irwin, *J. Amer. Chem. Soc.*, **63**, 1036 (1941). [h] L. F. Fieser, *J. Amer. Chem. Soc.*, **70**, 3165 (1948). [i] S. G. Cohen, *ibid.*, **69**, 1057 (1947). [j] L. F. Fieser in "Organic Syntheses," Collect. Vol. I, 2nd ed, Wiley, New York, N. Y., 1941, p 383. [k] R. Willstätter and C. W. Moore, *Chem. Ber.*, **40**, 2665 (1907). [l] A. M. Osman and I. Bassioni, *J. Amer. Chem. Soc.*, **82**, 1607 (1960).

particularly useful reagent to prepare acid- or base-sensitive quinones. Thus to prepare **15c** from the hydroquinone **14c**, oxidation by 2 equiv of silver carbonate in methylene chloride is by far the best available method. Oxidation of 1,4-dihydroxynaphthalene (**16**) gives 1,4-naphthaquinone (**17**). (*Cf.* Table III.)

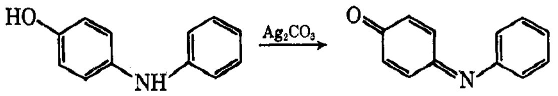


12a, $R_1 = R_2 = R_3 = H$ **13**
b, $R_1 = R_3 = H; R_2 = CH_3$
c, $R_1 = R_3 = H; R_2 = C(CH_3)_3$
d, $R_2 = H; R_1 = R_3 = C(CH_3)_3$

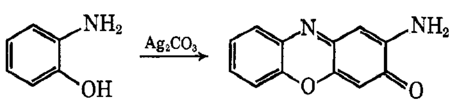


14a, $R_1 = R_2 = H$ **15**
b, $R_1 = H; R_2 = CH_3$
c, $R_1 = H; R_2 = OCH_3$
d, $R_1 = CH_3; R_2 = C(CH_3)_3$
e, $R_1 = R_2 = C(CH_3)_3$
f, tetrachlorohydroquinone

Oxidation of Aminophenols.—Silver carbonate oxidation of *p*-hydroxydiphenylamine (**18**) gives the quinone monoanil **19** in quantitative yield. *o*-Aminophenol gives the dimeric phenoxazone **21** (Table III), a product which has been obtained using other oxidants.[11]



18 **19**



20 **21**

Experimental Section

A. **Preparation of the Reagent.**—The Celite support is purified by washing it successively with methanol containing 10% concentrated HCl and then with distilled water until neutral; it is finally dried at 120°.

Purified Celite (30 g) is added to a mechanically stirred solution of 34 g (200 mmol) of silver nitrate in 200 ml of distilled water. A solution of 30 g (105 mmol) of $Na_2CO_3 \cdot 10H_2O$ (or 21 g, 210 mmol of $KHCO_3$) in 300 ml of distilled water is then added slowly to the resulting homogeneous suspension. When the addition is complete, stirring is continued for a further 10 min. The yellow-green precipitate which is formed is then filtered off and finally dried in a rotary evaporator over a period of several hours. The silver carbonate/Celite reagent contains about 1 mmol of Ag_2CO_3, 0.57 g.

B. **Oxidations. General Procedure.**—Before use, the reagent is freed from the residual water azeotropically by distillation with benzene. The compound to be oxidized is then added and refluxed in benzene (*ca.* 200 ml for 0.5–2.0 g of compound). At the end of the reaction, determined by tlc monitoring, the solid phase is filtered off and the solvent evaporated. The product is usually highly pure and recrystallization is unnecessary. Reaction times and molar ratios are given in Tables I and III.

Free radicals 8 and 11 forming reactions are conducted under argon atmosphere.

Pyrocatechol and its derivatives **12b–d** are oxidized at 0° and room temperature, respectively, under constant stirring.

Hydroquinones 14a–c and *o*-aminophenol (**20**) are oxidized in boiling methylene chloride. The oxidation of **18** is carried out in the same solvent but at room temperature.

C. **Reductions. General Procedures. 3,3′,5,5′-Tetramethyl-4,4′-dihydroxybiphenyl (3a).**—To a suspension of 0.65 g of the diphenoquinone **2a** in 35 ml of ether a solution of 6.5 g of sodium hydrosulfite in 70 ml of aqueous NaOH (1 *N*) is added. After shaking the mixture for about 30 min the colorless aqueous layer is acidified by concentrated HCl. Filtration gives 0.57 g of a white precipitate which is dried *in vacuo:* mp 228–229°; nmr (D_3CCOCD_3) δ 7.17 (s, 4), 3.12 (s, 2), 2.30 (s, 12).

Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.3; H, 7.5; O, 13.2. Found: C, 79.4; H, 7.5; O, 13.4.

3,3′,5,5′-Tetramethyl-4,4′-dihydroxystilbene (6a).—A solution of 0.05 g of the stilbenequinone **5a** in 100 ml of acetic acid is shaken with 4 g of zinc dust for about 1 hr. The colorless mixture is filtered and the filtrate neutralized by sodium bicarbonate. Extraction by ether and evaporation of the solvent gives 0.04 g of yellow crystals: mp 237–240°; nmr (D_3CCOCD_3) δ 7.12 (s, 3.8), 6.87 (s, 1.9), 3.00 (s, 2.1), 2.24 (s, 12.1).

Anal. Calcd for $C_{18}H_{20}O_2$: C, 80.6; H, 7.5; O, 11.9. Found: C, 80.4; H, 7.5; 0, 12.0.

Oxidation and reduction products were identified by their melting points[16] and elemental analyses.[17] The spectral measurements are all in agreement with the reported structures.

Registry No.—**3a**, 2417-04-1; **6a**, 25347-59-5, silver carbonate, 534-16-7.

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[16] Melting points were determined on a Kofler hot stage and are uncorrected.

[17] Satisfactory combustion analytical data have been obtained on the following compounds—diphenoquinones **2a–c**, stilbenequinones **5a–c**, dihydroxybiphenyls **3a–c**, 4,4′-dihydroxystilbenes **6a–c**, peroxide **9**, radical **11**, *o*-quinones **12a–d**, *p*-quinones **15b–e**, quinone monoanil **19**, and phenoxazone **21**: Ed.