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AN ANNELATION ROUTE TO QUINONES

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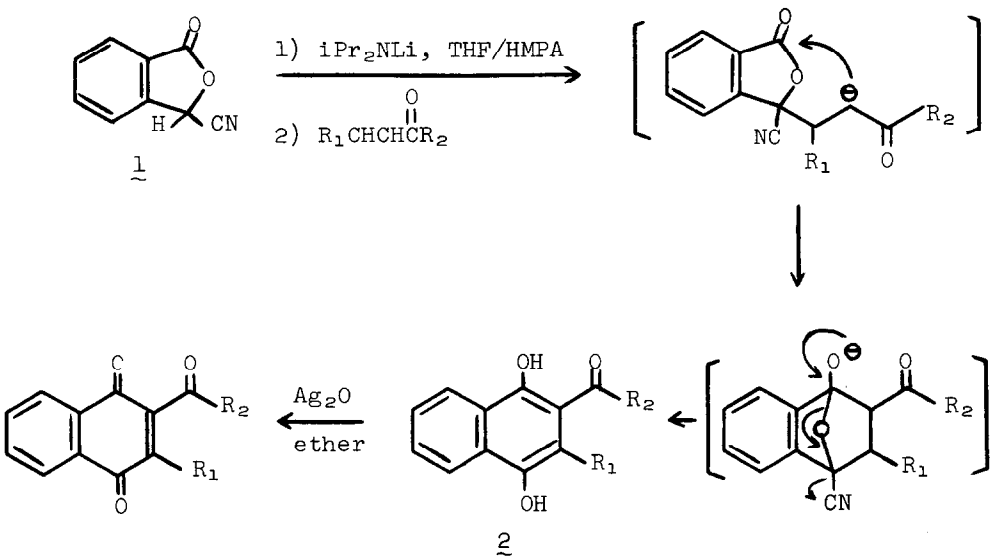
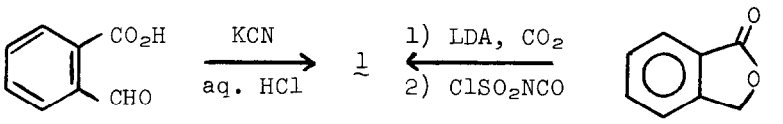
The quinone moiety is an integral feature of many biologically significant natural products.[1] As a result, many synthetic methods for the preparation of quinones have been developed. Most procedures which involve the oxidation of phenols or substituted benzenes are incompatible with the presence of readily oxidizable functionality such as alkenes and alcohols.[2] We wish to report a novel hydroquinone synthesis which proceeds under mild conditions. The basic strategy is outlined below.

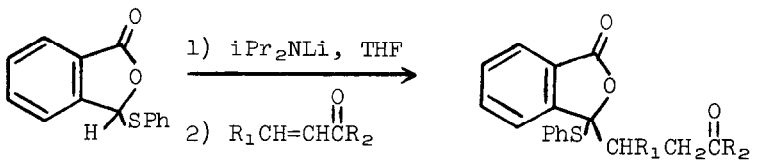


1 2

Phthalide 1 can be readily prepared from o-carboxy-benzaldehyde and HCN by the method of Robinson[3] or by carboxylation of commercially available phthalide and conversion of the phthalide carboxylic acid to a nitrile.[4] Interestingly, the direct preparation of 1 from 3-chlorophthalide under a variety of reaction conditions (KCN, acetone, DMSO or HMPA; benzene, 18-crown-6; copper cyanide in refluxing benzene) was unsuccessful.

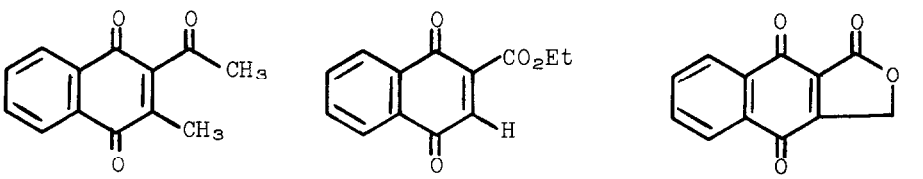


The cyano moiety is crucial for a successful reaction. The use of 3-thiophenyl phthalide (3) affords only Michael adduct 4 in good yield.[5]



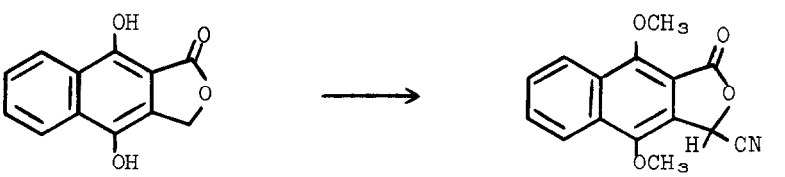
3 4

The use of compounds such as 3-methoxy phthalide and 3-chlorophthalide afforded complex product mixtures. Quinones 5, 6 and 7 can be prepared from 1 in overall isolated yields of 85, 60 and 50% respectively.



5 6 7

The structures of 5 and 6 were confirmed by comparison (IR, NMR, TLC) with authentic samples.[6,7] Interestingly, the hydroquinone precursor to 7[8] can be converted into 8 which can undergo another annelation sequence.[9]



8

In a typical experiment, a solution of 3 mmol of 3-cyano phthalide in 3 mL of THF was added over two min to 3.3 mmol of lithiumdiisopropylamide in four mL THF and 1 mL HMPA at -78° C. After the solution was stirred at -78° for 10 min, 3 mmol of the Michael acceptor in 3 mL THF was added over 1 min. The solution

was allowed to warm slowly to 0° C, quenched with acetic acid and diluted with ether and water. The organic layer was dried and concentrated in vacuo. The crude product was chromatographed on silica gel to yield pure hydroquinone.

The regiospecific preparation of 7-substituted phthalides is currently underway.[10] We are studying the application of this method to the synthesis of kalafungin and the anthracyclines.

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References and Notes

1. F. Arcamone, S. Penco and A. Vigevani, Cancer Chemotherapy Reports, Part 3, 6(2), 123 (1975).
P. F. Wiley, R. B. Kelly, E. L. Caron, V. H. Wiley, J. H. Johnson, F. A. Mackellar and S. A. Mizsak, J. Amer. Chem. Soc., 99, 542 (1977).
T. K. Devon and A. I. Scott, Handbook of Naturally Occurring Compounds, 1, (Academic Press, 1975), 309-375.
Kalafungin: H. Hoeksema and W. C. Krueger, J. Antibiotics, 29, 704 (1976).
L. E. Johnson and A. Dietz, Appl. Microbiol., 16, 1815 (1968).
J. St. Pyrek, O. Achmatowica, Jr., and A. Zamojski, Tetrahedron, 33, 673 (1977).
Quinocycline-A: A. Tulinsky, J. Amer. Chem. Soc., 86, 5368 (1964).
Versicolorin A: T. Hamasaki, Y. Hatsuda, N. Terashima and M. Renbutsu, Agr. Biol. Chem. (Tokyo), 31, 11 (1967).
2. For excellent reviews see Rodd's Chemistry of Carbon Compounds, 3B (Elsevier, 1974), second edition, S. Coffey, ed.
S. Patai (ed.), The Chemistry of Quinonoid Compounds, Part 1, (Wiley Interscience, 1974), 111-162.
C. A. Buehler and D. E. Pearson, Survey of Organic Synthesis, (Wiley Interscience, 1970), 724-743.
A. W. Johnson, Science Progress, 45, 86-85, 511-518 (1957).
These reviews indicate the difficulties encountered in the oxidation of phenols and alkyl benzenes. Note that Fremy's salt can not be used to prepare compounds 5, 6 or 7.
3. W. H. Perkin, Jr., J. N. Ray and R. Robinson, J. Chem. Soc., 127, 740 (1925).
4. Phthalide can be efficiently carboxylated by deprotonation with lithium diisopropylamide (.5M THF, -78° C), followed by inverse addition via double edged needle to a THF solution saturated with CO_2 at 0° C. This procedure affords a reproducible yield of 45%. Conversion of the phthalide carboxylic acid to a nitrile can be effected with either chlorosulfonyl isocyanate[11] or the procedure described in Reference 9. The above procedure affords 1 in an overall yield of 30%.

5. G. A. Kraus and H. Sugimoto, Synthetic Communications, 515 (1977).
6. G. Read and V. M. Ruiz, J. Chem. Soc. (Perkin I), 235 (1973).
7. For hydroquinone preparation see R. B. Desai and S. Sethna, J. Ind. Chem. Soc., 28, 213 (1951). The oxidation procedure was identical to that in Reference 6. Spectral data for quinone 6: NMR ($CDCl_3$): 1.3δ (t, 3H, J = 7 Hz), 4.37δ (q, 2H, J = 7 Hz), 7.20δ (s, 1H), 7.65-8.2δ (m, 4H); IR (nujol mull) 1600, 1675, 1740 cm^{-1}. m.p. 153-155° C.
8. Spectral data for hydroquinone 7: NMR (DMSO) 5.45δ (s, 2H), 7.45-8.4δ (m, 4H). IR (nujol mull) 3480 (spike), 3400 br, 1710 cm^{-1}. m.p. 235-240d. Quinone: NMR (DMSO) 5.6δ (s, 2H), 7.5-8.4δ (m, 4H). IR (nujol mull) 1675, 1740, 1770.
9. This can be efficiently accomplished by methylation (K_2CO_3, Me_2SO_4, refluxing acetone), carboxylation (LDA, -78° C, CO_2) and conversion to the nitrile (chlorosulfonyl isocyanate or $SOCl_2$ (neat), NH_3 in CH_2Cl_2 and dehydration with TSCl/pyridine). The latter sequence is performed without purification of intermediates.
10. While this paper was in review, a similar approach has appeared: F. M. Hanser and R. P. Rhee, J. Org. Chem., 43, 178 (1978).
11. H. Vorbrüggen, Tet. Lett., 1631 (1968).