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A GENERAL APPROACH TO QUINONE IMINE KETALS. INTERESTING INTERMEDIATES FOR PREPARATION OF 5-OXYGENATED INDOLES AND QUINONE IMINES

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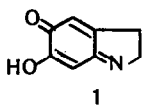
Abstract: *A general route for the preparation of quinone imine ketals is reported.*

Quinone imines and quinone diimines have been of long-standing interest in chemistry,[1-3] and the former moieties have been proposed or established as intermediates (see **1** and **2**) in a number of biological processes,[1-3] most notably the metabolism of a number of biochemically important cathecholamines[4-7] and most recently in the biological oxidation of N-methylellipticinium acetate.[8] Quinone imines[9] are usually quite unstable under conditions used for their generation. This has prevented their isolation and a more detailed study of their chemistry, spectroscopy, and biology under well-defined conditions. We report herein a general route for the preparation of isolable, protected derivatives of these compounds--quinone imine ketals. Additionally, this chemistry serves as a convenient route to 5-oxygenated indole and 6-oxygenated quinoline derivatives.



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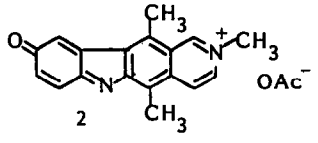

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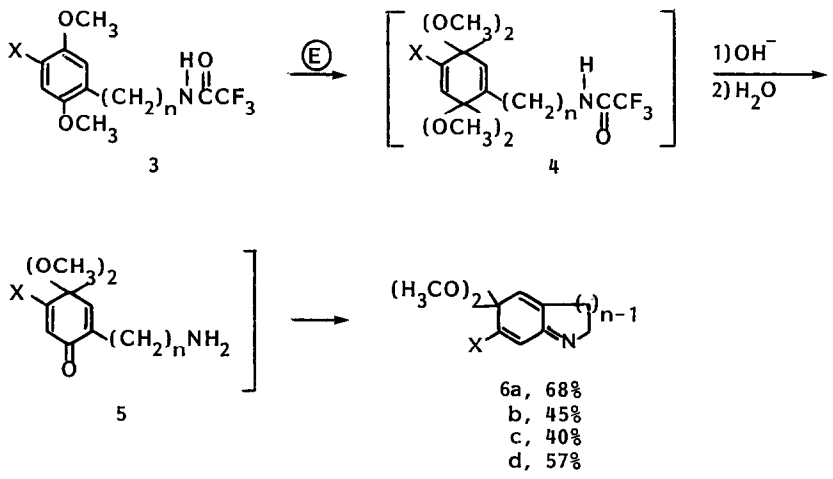
One synthetic approach to quinone imines is to prepare these compounds in protected form and generate the highly reactive quinone imine via a mild deblocking procedure. Thus, an initial question was the stability of simple quinone imine ketals. A direct approach for preparing these compounds and thus establishing their stability is the intramolecular condensation reaction of quinone monoketals such as **5a**. With the readily available aromatic derivative as the starting material, this route would require the selective oxidation of the aromatic ring in the presence of the amino group and a regioselective hydrolysis of the resulting bisketal.

Anodic oxidation of the corresponding trifluoracetamide was examined since the trifluoroacetamide would not only block oxidation at the amino group but also allow deprotection to the amine by hydrolysis under mild basic conditions. Monitoring the electrochemical oxidation[10] of **3a** by UV spectroscopy showed disappearance of the maximum at 290 nm concurrent with the formation of two isobestic points at 267 and 247 nm. Concentration of the solvent in vacuo followed by addition of water and stirring at room temperature for two



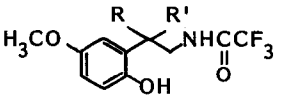
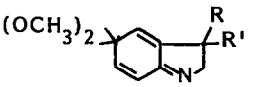
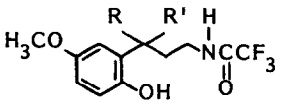
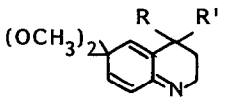
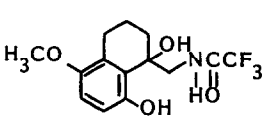
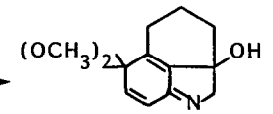
a, X = OCH_3, n = 1; b, X = OCH_3, n = 2; c, X = Br, n = 1; d, X = Br, n = 2

hours deblocked the amino group and afforded **5a** as a thick oil which was stirred in water (pH 6.5-7) for 16 h. Standard workup and chromatography on Florisil afforded the quinone imine ketal **6a** as a white solid, mp 72-75 °C. In a similar manner, anodic oxidation, deblocking, hydrolysis, and condensation furnished the quinone imines **6b-d** in the overall yields shown. The compounds are stable under nitrogen in base-washed glassware but are quantitatively transformed to the respective indoles with a trace of acid.

While the above approach gives acceptable yields considering four chemical steps are involved, it is severely limited by requiring a group which directs hydrolysis to the ketal function adjacent to the side chain containing the amino group. For the above systems, the methoxyl and bromo substituent direct the hydrolysis in this manner,[11] but all attempts to prepare the unsubstituted compounds via this strategy afforded difficult-to-separate mixtures. For preparation of the unsubstituted compounds, anodic oxidations of the respective phenols were studied (see Table). Electrochemical oxidation of the phenols[12,13] followed by base hydrolysis afforded the quinone imine ketals in excellent overall yields (Table). This second approach gives much better overall yields and overcomes the requirement of regioselective bisketal hydrolysis. Since derivatives of o-hydroxybenzaldehydes are readily available, this comprises a general route to quinone imine ketals. Furthermore, derivatives such as **8c** and **10b** are quite stable and can be stored for weeks in base-washed apparatus at 0 °C, making them more convenient for examining the chemistry of the quinone imines.

The quinone imine ketals can be converted to their respective heterocyclic ring systems by standard chemical operations: reaction of **6a,c** with p-toluenesulfonic acid in benzene afforded the respective indoles in excellent yield; reaction of **6b** with DDQ in refluxing benzene gave 6,7-dimethoxyquinoline (70%), and heating **6d** in a mixture of toluene/isopropyl alcohol afforded the expected tetrahydroisoquinoline (70%).[14] There are numerous routes to indoles[15] and quinolines starting with anilines and nitrobenzene derivatives, and the ease of preparation of the benzenoid precursor is often a major consideration in the method selected for a particular compound. Our approach to such ring systems complements these more classical procedures. Furthermore, functionalization of these quinone imine ketals

Table. Quinone Imines from Phenol Derivatives

Compound	Imine
	
7a, R = R' = H	8a, 82%
b, R = OH, R' = H	b, 91%
c, R = OH, R' = CH_3	c, 81%
	
9a, R = OH, R'= H	10a, 91%
b, R = OH, R' = CH_3	b, 89%
	
11	12, 89%

followed by aromatization could afford highly functionalized indole and quinoline derivatives.

In summary, a general route to a new class of protected quinone imine derivatives has been developed. This chemistry serves as a convenient route to oxygenated indole and quinoline ring systems and presents an approach for generation of quinone imine derivatives by deblocking appropriate mixed ketal derivatives of quinone imines.[16]

Acknowledgments. *We thank the National Science Foundation and the Donors of the Petroleum Research Fund for support of this research.*

References and Notes

(1) For a review of the older literature, see: S. Patai, "The Chemistry of the Carbon-Nitrogen Double Bond," Interscience Publishers: New York, 1970, pp. 633-729.

(2) K.C. Brown and J.F. Corbett, J. Chem. Soc., Perkin II, 886 (1981) and earlier papers in the series.

(3) T. Nogami, T. Hishida, M. Yamada, H. Mikawa, and Y. Shirota, Bull Chem. Soc Japan 48, 3709 (1975).

(4a) M. d'Ischia, A. Palumbo, G. Prota Tetrahedron Lett. 26, 2801 (1985); (b) A. Napolitano, M. Grazia, G. Prota Ibid 2805 (1985).

(5) S.P. Harmalker and D.T. Sawyer, J. Org. Chem. 49, 3579 (1984) and references cited therein.

(6a) T.E. Young and W.T. Beidler, J. Org. Chem. 49, 4833 (1984); (b) T.E. Young and B.W. Babbitt, Ibid. 48, 562 (1983) and references cited therein.

(7a) E.M. Boyd and G.M. Bereczky, Brit. J. Pharmacol. 26, 606 (1966); (b) W.Z. Potter, D.C. Davis, J.R. Mitchell, D.J. Jollow, J.R. Gillette, and B.B. Brodie, J. Pharmacol. Exp. Ther. 187, 203 (1973); (c) M.W. Gemborys, G.H. Mudge, and G.W. Gribble, J. Med. Chem. 23, 304 (1980); (d) I.C. Calder, J.S. Hart, K. Healey, and K.N. Ham, Ibid. 24, 988 (1981).

(8a) J-B. LePecq, Nguyen-Dat-Xuong, C. Gosse, and C. Paoletti, Proc. Natl. Acad Sci. 71, 5078 (1974); (b) G. Meunier, B. Meunier, C. Auclair, J. Bernadou, and C. Paoletti, Tetrahedron Lett. 24, 365 (1983); (c) G. Pratviel, J. Bernadou, and B. Meunier, J. Chem. Soc., Chem. Commun., 60 (1985); (d) V.K. Kansal, S. Funakoshi, P. Mangeney, P. Potier, B. Gillet, E. Guittet, and J.Y. Lallemand, Tetrahedron Lett. 25, 2351 (1984); (e) J. Bernadou, B. Meunier, G. Meunier, C. Auclair, C. Paoletti, Proc. Natl. Acad. Sci. 81, 1297 (1984); (f) V.K. Dansal, R. Sundaramoorth, B.C. Das, P. Potier et al. Tetrahedron Lett. 26, 4933 (1985).

(9) For leading references to the phenylsulfonyl derivatives of quinone imines and diamines see: R. Adams and J.H. Looker, J. Amer. Chem. Soc. 73, 1145 (1951); R. Adams and L. Whitaker, Ibid. 78, 658 (1956).

(10) These studies were conducted in an H-type divided cell at 10-15 °C using a platinum gauze electrode and a platinum plate cathode at a controlled potential of 1.0-1.3 V vs. a platinium wire. It was subsequently found that the reactions of **3a** and **3b** could be much more conveniently performed in a single cell apparatus at constant current with no effect on yield.

(11) See C-P. Chen and J.S. Swenton, J. Org. Chem. 50, 4569 (1985) and references cited therein.

(12) A. Nilsson, A. Ronlan, Tetrahedron Lett., 1107 (1975); C-P. Chen, J.S. Swenton, J. Chem. Soc., Chem. Commun., 1291 (1985).

(13) A representative procedure is as follows. A solution of **7c** (1.04 g, 3.6 mmol) in 1% $LiClO_4/CH_3OH$ (130 mL) was electrolyzed in a single cell using a cyclindrical platinium gauze electrode (3.5 cm diameter via 5 cm. high) as anode and a platinum sheet cathode at 0 °C. Passage of 0.08 amp for 3.5 h (ca. 70% current efficiency) resulted in consumption of starting material. Concentration in vacuo and extractive workup yielded a yellow oil which was dissolved in THF/5% aqueous KOH (100 mL:5 mL) and stirred for 5 h at room temperature. Concentration in vacuo at room temperature followed by extractive workup (CH_2Cl_2) gave a nearly colorless oil (0.63 g, 81%). This showed spectra identical with material further purified by chromatography on a neutral alumina column and is acceptable for further chemical reactions.

(14) Isopropyl alcohol apparently serves as the reducing agent in this reaction.

(15a) L.A. Paquette, "Principles of Modern Heterocyclic Chemistry"; Benjamin/Cumming: London, 1968; (b) P.G. Gassman, T.J. Van Bergen, D.P. Gilbert, B.W. Cue, J. Am. Chem. Soc. 96, 5495 (1974); (c) The Nenitzescu route also complements the other classical routes to indoles but suffers from regiochemical problems. (c) G.A. Allen, "Organic Reactions"; Vol. 20, 1973, p. 337.

(16) All compounds reported showed IR and ^1H NMR (80 MHz) consistent with the assigned structures and gave combustion analyses or exact mass measurements within acceptable limits. The preparation of the starting materials was accomplished via adaption of known procedures and will be reported in detail in our full manuscript. The mp of solid samples are as follows: **3a**, 95-97 °C; **3b**, 61-63 °C; **3c**, 129-130 °C; **3d**, 114-115 °C; **6a**, 72-74 °C; **6b**, 95-97 °C; **6d**, 52-53 °C; **7b**, 115-117 °C; **12**, 129-131 °C. The remaining compounds are liquids.

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