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A FACILE SYNTHESIS OF 4-HYDROXYINDOLE VIA ELECTROCHEMICAL OXIDATIVE C-C COUPLING

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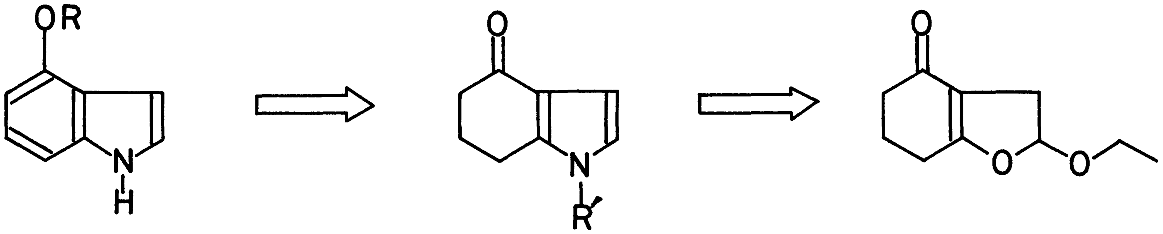
4-Hydroxyindole (1a), a useful intermediate for Pindolol (1b), has been prepared *via* electrooxidative coupling of 1,3-cyclohexadione with ethyl vinyl ether followed by ammonolysis and dehydrogenation.

Synthesis of 4-hydroxyindole (1a), a useful intermediate for Pindolol(1b)[1] (an arrhythmic agent), has been received much attention. Since usual reactions of indole give 5-substituted products rather than 4-substituted ones, either construction of pyrrole ring from 2-alkyl-3-nitrophenol derivatives[2] or aromatization of 4,5,6,7-tetrahydro-4-oxoindole (2) has been employed.
However, the latter approach involves inefficient condensation of 1,3-cyclohexadione with aminoacetoaldehyde diethylacetal[3] and oxoiminoglyoxal.[4] Thus, Stetter selected the transformation of 5a into a pyrrole derivative in which the 3-carboxy group is necessary for activating the furan ring in ammonolysis.[5] In this communication we describe a straightforward synthetic route of 1a involving an electrochemical one-step preparation of 3, which would be much more reactive toward amine than 5 because of its nonaromaticity.

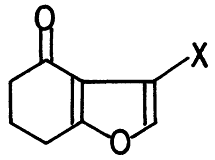


1a R = H

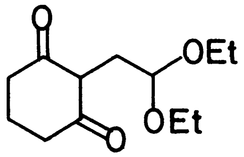
b R = $CH_2CH(OH)CH_2NHCH(CH_3)_2$

2

3



5a $X = CO_2H$, 5b $X = H$



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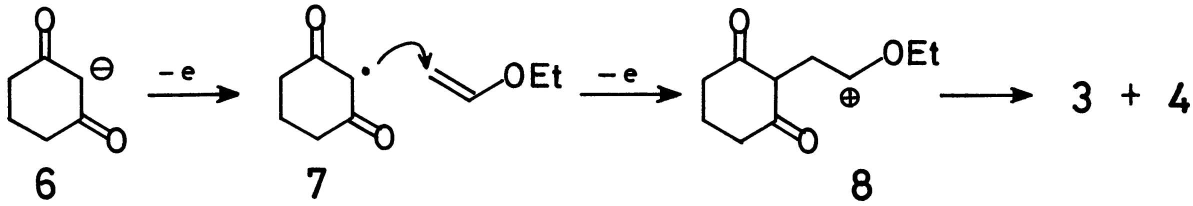
A solution of 1,3-cyclohexadione (5 mmol), sodium ethoxide (2.5 mmol), ethyl vinyl ether (100 mmol) in 40 ml of anhydrous EtOH was electrolyzed at room temperature using Pt foils (4x3 cm^2) under constant current (14 mA/cm^2) for 80 min (1.5 F/mol). The usual workup gave 3 and 4 (3:4 = 51:49) in 65% yield (83% based on recovered 6). The compound 3 was a major product after a long reaction time, since 4 was gradually converted into 3 in the reaction condition. Sodium or potassium hydroxide in EtOH was effective to the conversion, but triethyl amine was useless.

A tentative reaction mechanism is shown in the following scheme. The carbanion 6 can be electrochemically oxidized at a low electrode potential generating the corresponding radical 7,[6] which adds to the electron rich C=C of ethyl vinyl ether[7] followed by one-electron oxidation to give 8. The carbonium ion 8 undergoes either an intramolecular (8 → 3) or an intermolecular (8 → 4) nucleophilic reaction.



Both 3 and 4 can be transformed into 2 more efficiently by the action of $(NH_4)_2CO_3$ in MeOH than that of dry NH_3 in MeOH.[5a] Thus, a solution of 3 and 4 (3:4 = 88:12) (0.53 mmol) and $(NH_4)_2CO_3$ (0.58 mmol) in MeOH (1 ml) was heated in a glass tube at 150 °C for 40 h, affording 2 (R'= H) in 80% yield. Likewise, reactions of 3 and 4 with propyl, butyl, and benzyl amines gave 2 [R' = Pr(60%), Bu (62%), and Bz(56%)], respectively. Finally, 2 (R' = H) was dehydrogenated by Pd/C in refluxing p-cymene affording 1a in 69% yield (73% based on recovered 2).[8]

References and Notes

1) K. Saemeli, Helv. Physiol. Acta, 25, 221 (1967).
2) A. Stoll, F. Troxler, J. Peyer, and A. Hoffmann, Helv. Chim. Acta, 38, 1463 (1955).
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4) K. Schoen, Tokkyo Koho, 44-9904 (1969).
5) (a) H. Stetter and R. Lauterbach, Ann. Chem., 655, 20 (1962); (b) H. Stetter and E. Siehnhold, Chem. Ber., 88, 271 (1955).
6) (a) H. G. Thomas, M. Streukens, and R. Peek, Tetrahedron Lett., 45 (1978); (b) T. Chiba, M. Okimoto, H. Nagai, and Y. Takata, J. Org. Chem., 44, 3519 (1979).
7) The controlled potential electrolysis of both methyl malonate and methyl acetoacetate in the presence of ethyl vinyl ether afforded the correponding C-C coupling products in 36-37% yields. H. Schäfer and A. Alazrak, Angew. Chem. internat. Edit., 7, 474 (1968).
8) 3: PMR ($CDCl_3$) δ 5.74 (dd, 1, J=7.1, 3.7 Hz, CHO), 3.87-4.15 (m, 2, CH_2O), 1.90-3.10 (m, 8, CH_2), 1.26 (t, J=7.1 Hz, CH_3); IR, 1640 (C=O) cm^{-1}; MS, m/e 182 (M^+), 98 (base peak).

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