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INTRAMOLECULAR RADICAL COUPLING OF A PHENOLIC ENOLATE : OXIDATIVE FRAGMENTATION OF THE SPIRODIKETONE INTERMEDIATE

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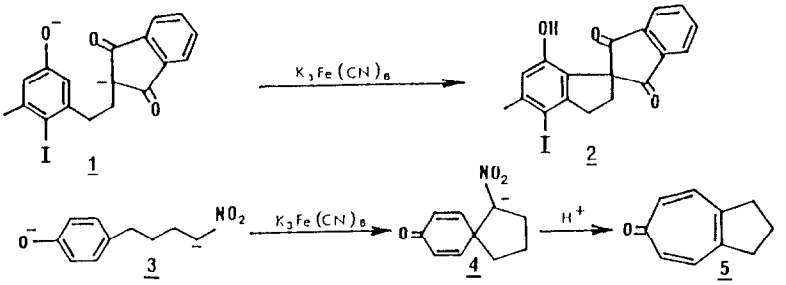
Abstract - Ferricyanide oxidation of the dianion of the phenolic β-diketone 6b in basic conditions effects intramolecular radical coupling to form the spirocyclic diketone 7 which leads to the hydroxy tetralone 8 via an oxidative fragmentation process.

Whereas the oxidative coupling of phenols through phenoxy radical intermediates is a well established biosynthetic and synthetic pathway,[1] the intramolecular coupling of phenolic enolates by the action of one-electron oxidants is extremely rare. One such example is oxidative cyclization of the phenolic indandione 1, leading to the spiro(4,4)nonanedione 2 model for the spirocyclic core of the antitumor antibiotic fredericamycin A.[2] More recently, the oxidative cyclization of the phenolic nitronate 3 to yield the tropone 5 by way of the spirocyclic intermediate 4 has been described.[3]

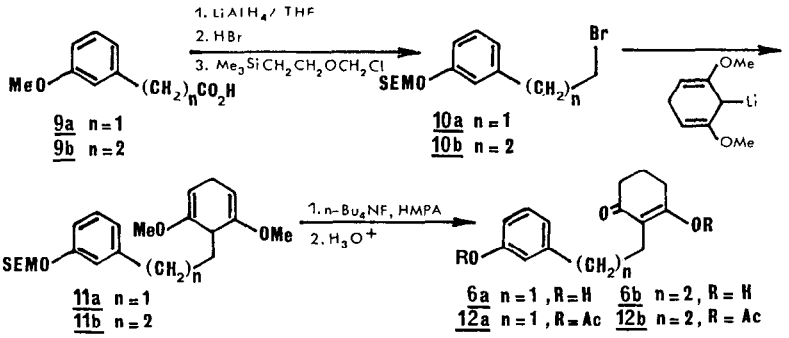


1 2 3 4 5

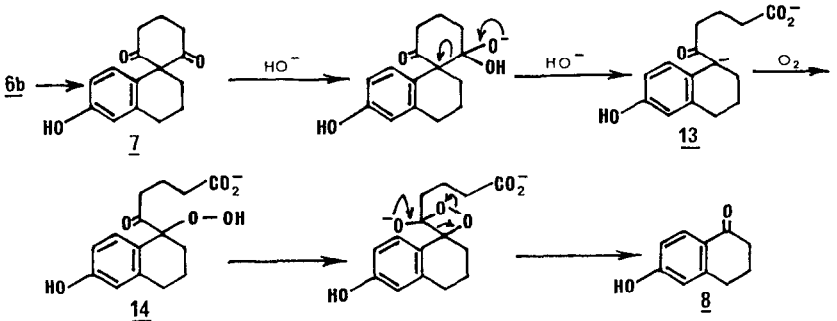
In a study of the scope of this potentially important radical cyclization method we have examined the chemistry of certain phenolic 1,3-cyclohexanediones. We now report an unexpected fragmentation sequence (6b → 8) during our study of the ferricyanide oxidation of such a system.

The m-methoxyphenyl acids 9a and 9b were transformed by the procedures of Moreau and Rouessac[4] into the corresponding SEM bromides 10a and 10b respectively. Since direct C-alkylations of 1,3-cyclohexanedione enolates by the bromides 10 were unsuccessful, an alternative cyclohexanedione synthon equivalent was employed. The lithium derivative of 1,5-dimethoxy-1,4-cyclohexadiene was alkylated by the bromides 10a and 10b according to the precedent of Piers and Grierson[5] to yield the intermediates 11a and 11b, which on deprotection (HMPA, 3 eq n-Bu_4NF, 40°C, 2 h) followed by careful acid hydrolysis (acetone, 1 M HCl, argon, RT, 1.5 h) gave respectively the sensitive, enolic 1,3-cyclohexanediones 6a and 6b in overall yields of 23 % and 51 % from 10. The structures of 6a and 6b were confirmed by IR, NMR, mass spectra,[6] and conversion to the stable diacetates[7] 12a and 12b (Ac_2O - Pyr, argon, RT, 1h).

Reaction of 6b in 0.5 M Na_2CO_3 with 6 molar equiv. of 0.5 M $K_3Fe(CN)_6$ for 3 h at 0°C, then 14 h at 25°C followed by acidification with citric acid gave on extraction and separation with preparative silica gel TLC (AcOEt/hexane 75/25), a single crystalline product 8 in 25-30 % yield[8].



Formation of the tetralone 8 requires an initial oxidative cyclization of 6b to the spirodiketone 7. It is likely that in the basic medium this will undergo a retro-Claisen scission of the nonenolizable 1,3-diketone unit to yield the enolate 13, which ultimately react with oxygen to give the hydroperoxide 14. Subsequent intramolecular fragmentation[9] as shown below would then yield the observed tetralone.



When similar conditions were applied to the lower homologue 6a, we were unable to isolate any identifiable product. The use of varying pH or of other oxidants (e.g., NaOH, 0,1N/$K_3Fe(CN)_6$ or $VOCl_3$/ether) upon either 6a or 6b likewise failed to give an isolable product.

The above results indirectly extend the role of phenolic enolate oxidative cyclization to a phenolic β-diketone, but they also show an evident limitation for these systems.

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6. 6a oil : IR ($CHCl_3$, ν) : 3400 broad, 1715, 1690, 1600 ; ^{1}H NMR 200 MHz (CD_3OD, δ) : 1,9 (m,2H), 2,37 (m, 4H), 2,52 (s, 4H), 6,53 (d, 1H), 6,68 (m, 2H), 7,01 (t, 1H) ; MS (EI) : 232 ($M^{+\cdot}$).
6b oil : IR ($CHCl_3$, ν) : 3340 broad, 1710, 1695, 1615 ; ^{1}H NMR 200 MHz (CD_3OD, δ) : 1,58 (m,2H), 1,9 (m,2H); 2,33 (m,4H), 2,5 (m, 4H), 6,63 (m, 3H), 7,08 (m, 1H) ; MS (EI) : 246 ($M^{+\cdot}$).
7. 12a oil : IR ($CHCl_3$, ν) : 1750 broad, 1640 ; ^{1}H NMR 80 MHz (CD_3OD, δ) : 2 (m, 2H), 2,16 (s, 3H), 2,25 (s, 3H), 2,5 (m, 4H) ; MS (EI) : 316 ($M^{+\cdot}$), m/e : 274, 232.
12b oil : IR ($CHCl_3$, ν) : 1750 broad, 1650 ; ^{1}H NMR 80 MHz (CD_3OD, δ) : 1,75 (m, 4H), 2,07 (s, 3H), 2,27 (s, 3H), 2,3 (m, 2H), 2,5 (m,6H), 7,12 (m, 4H) ; MS (EI) : 330 ($M^{+\cdot}$), m/e : 287, 268, 245, 227.
8. Treatment of compound 8 with CH_2N_2 in ether, gave the corresponding 6-methoxy derivative which proved to be identical with an authentic sample (m.p., ^{1}HNMR, IR).
9. For a related reaction see the oxidation and cleavage of 20-keto steroids by way of 17-hydroperoxides, Siddall, J. ; Baddeley, G. ; Edwards, J., Chem. Ind. (London), 1966, 25. The dioxetane cleavage mechanism is that suggested by E.P. Oliveto in "Organic Reactions in Steroid Chemistry", Vol. II, Ed. Fried, J. ; Edwards, J.A. (Van Nostrard Reinhold, New York, 1972), pp. 156-157.

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