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INTRAMOLECULAR RADICAL CYCLIZATION OF PHENOLIC NITRONATES: FACILE SYNTHESIS OF ANNELATED TROPONE AND TROPOLONE DERIVATIVES

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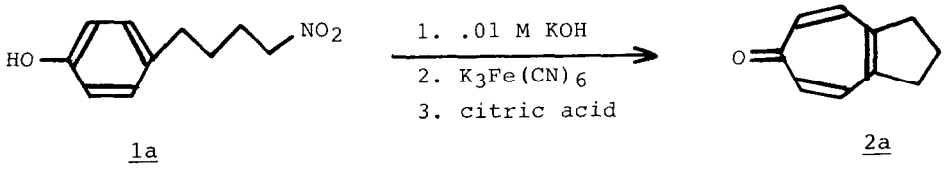
Summary: Treatment of the phenolic nitroalkanes 1 in dilute base with $K_3Fe(CN)_6$ results in the formation of spirocyclic nitro dienones 3 which undergo facile rearrangement to annelated tropone or tropolone derivatives.

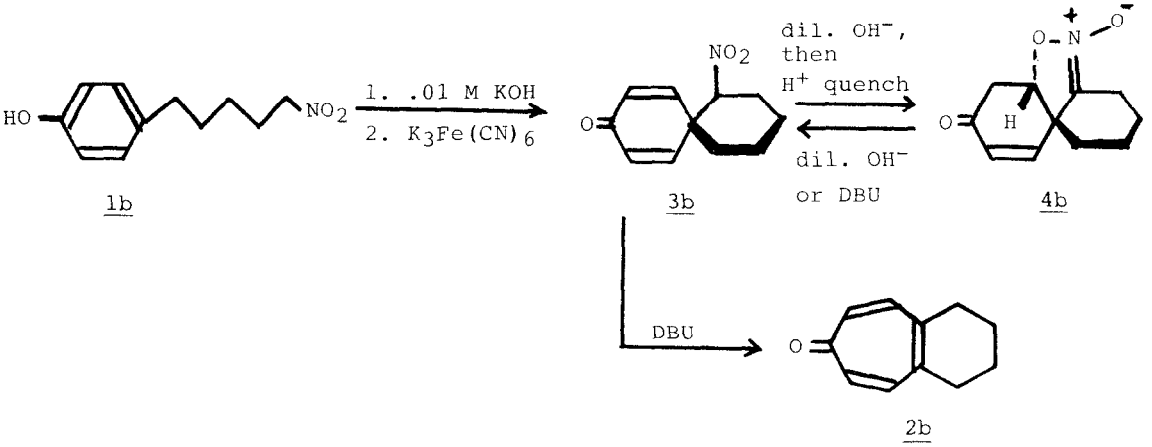
The intramolecular radical coupling of a phenol ring to a stabilized enolate is a potentially powerful method for the formation of carbon-carbon bonds, yet one that has been scarcely examined.[1] We now report the unprecedented intramolecular oxidative coupling of a phenolate to a nitronate anion in a transformation which has led to a novel synthesis of annelated tropone and tropolone derivatives.

Reaction of the phenolic nitroalkane **1a**[2] in .01 M aqueous KOH at 0°C with 4 eqts. of $K_3Fe(CN)_6$, followed after 20 minutes by quenching with excess citric acid, led on $CHCl_3$ extraction to an 80% yield of a neutral crystalline $C_{10}H_{10}O$ product, mp 105-106°C [IR($CHCl_3$): 1640, 1552, 1512, 1430, 1260 cm^{-1}; UV(MeOH): λ_{max} 324, 232 nm, log ε 4.26, 4.01; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.17(2H,d,J=12), δ 6.95(2H,d,J=12), δ 2.98(4H,t), δ 2.03(2H,quintet)]. The above properties, especially the ^{1}H-NMR data, pointed uniquely to symmetrical structure **2a**. This tropone had been prepared in 1966 by a multistep sequence,[3] and its mp, IR, UV, ^{13}C-NMR and ^{1}H-NMR were in accord with our own observations.



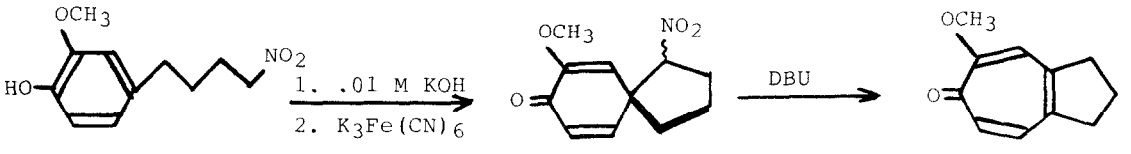
1a 2a

The course of this rearrangement was clarified by studies of the homologous nitro compound **1b**, mp 40-42°C.[2] Treatment of **1b** as above produced mainly the crystalline spirocyclic dienone **3b**,[4] mp 89-91°C, accompanied by varying amounts (15-30%) of a byproduct identified as the cyclic nitronate ester **4b**.[5] We found that the ratios of these two isomers depended on the base strength and rate of acidification of the reaction mixture. Indeed, by use of only 2.1 eqts. of .01 M KOH in the oxidation, followed by direct extraction (after 10 min at 0°C) without any acid quench, the spirocyclic dienone **3b** could be cleanly isolated in 83% yield. On redissolving **3b** in an excess of dilute base, followed by rapid addition of glacial acetic acid, the cyclic nitronate ester **4b** was formed in 76% yield; no tropone was observed under these conditions. However, several hours of treatment of **3b** or **4b** with 3 M KOH, or better with DBU in CH_3CN for 12 hours at 25°C, gave the C_{11} tropone **2b**[6] in up to 66% yield. These transformations are summarized in the following equations.



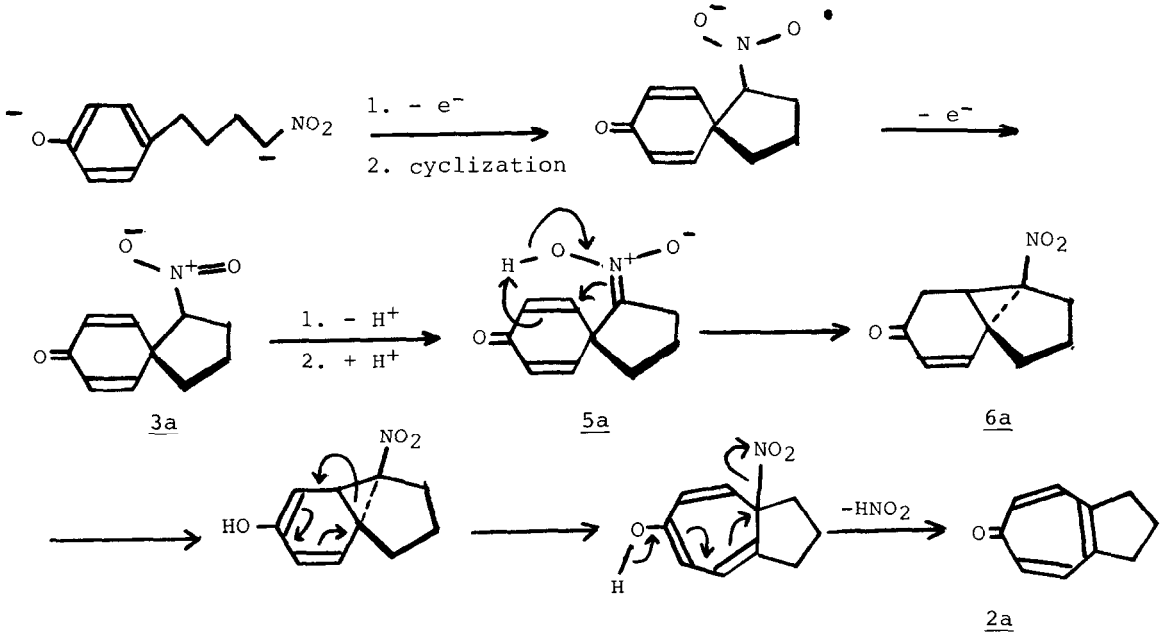
1b **3b** **4b** **2b**

These reactions can be extended to the synthesis of a tropolone derivative. Thus, the o-methoxyphenol **1c**[7] reacts smoothly under the above conditions to produce the (isolable) spirocyclic dienone diastereomers **3c** which can be converted (DBU, 25°C, 3 hrs) to the annelated tropolone methyl ether **2c**[8] in 45-50% overall yield.



1c **3c** **2c**

We propose some preliminary mechanistic conclusions on the overall reaction sequence based on the following results. Reactant **1a** is not cyclized below pH 11, indicating that deprotonations of both the phenol ($pK_a \approx 10.1$) and of the nitroalkane ($pK_a \approx 8.8$) are required. When the reaction of **1a** is carried out with 2.1 eqts. of base, direct $CHCl_3$ extraction permits isolation of spirocyclic C_{10} intermediate **3a**[9] in 83% yield; a dilute alkaline solution of **3a** on acidification rapidly produces tropone **2a** in nearly quantitative yield. Kinetic studies at fixed base strength (.01 M KOH) and pseudo-first order conditions of excess $K_3Fe(CN)_6$, ranging from 2.5 to 9 molar eqts., indicate that the rate for **1a** cyclization (as measured by extent of **2a** formation after acid quench, using NMR analysis) is proportional to ferricyanide concentration. The simplest interpretation of these data[10] is that the dianion of **1a** undergoes one-electron transfer to the oxidant, and that the subsequent fast steps are cyclization to the radical anion[11] of **3a** followed by a second electron transfer to yield neutral **3a** itself. The rearrangement of **3a** to tropone **2a**, though very slow in base, occurs rapidly on acidification of the corresponding nitronate and thus presumably involves the nitronic acid **5a**, possibly by the "ene" reaction shown below. In the C_{11} series, the nitronic acid corresponding to **3b** must kinetically close to the cyclic ester **4b** rather than undergo the electrocyclic reaction sequence leading to tropones. Once the putative cyclopropane intermediate (cf. **6a**) is formed, the subsequent rearrangement to a tropone system has good precedent.[12]



The possible application of this chemistry for the synthesis of colchicine derivatives is under study.

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References.

1. Kende, A.S.; Ebetino, F.H.; Ohta, T. Tetrahedron Lett. 1985, 26, 3063.

2. Nitro compounds 1a and 1b were prepared from the corresponding p-MeO-aryl carbinols by mesylation, displacement of OMs by iodide (NaI, Me_2CO, reflux), displacement of I by NO_2 using Amberlyst A-26 polymer-supported nitrite reagent (Fluka, C_6H_6, r.t., 8 hrs) and demethylation (4 eqts. BBr_3, CH_2Cl_2, -78° to 0°C, 2 hrs). All new compounds gave satisfactory elemental or mass spectrometric analyses and both IR and ^{1}H-NMR are in agreement with the structures shown.

3. Chapman, O.L.; Koch, T.H. J. Org. Chem. 1966, 24, 2289.

4. 3b: IR($CHCl_3$): 1665, 1625 cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.34(1H,dd,J=11, 4Hz), 6.80(1H,dd,J=11, 4), 6.35(1H,dd,J=11, 2), 6.28(1H,dd,J=11, 2), 4.67(1H,dd,J=5, 12), 2.39-2.16(2H,m), 2.15-2.07(1H,br d), 1.80-1.46(5H,m). Found: C, 63.54; H, 6.51; N, 6.61.

5. 4b: mp 186°C(dec); IR($CHCl_3$): 1685, 1645 cm^{-1}; ^{1}H-NMR(300 MHz, $CDCl_3$): δ 6.69(1H,dd,J=10.5, 2Hz), 6.18(1H,d,J=10.5), 4.67(1H,br s), 2.94(1H,dd,J=17, 1.5), 2.85(1H,dd,J=17, 4)), 2.68(1H,dd,J=17, 4), 2.33-2.17(1H,m), 2.15-2.00(2H,m), 1.91(1H,d,J=12), 1.72-1.4(3H,m). Found: C, 63.35; H, 6.39; N, 6.65.

6. 2b: mp 96-97°C; IR($CHCl_3$): 1645, 1563, 1512 cm^{-1}; ^{1}H-NMR(300 MHz, $CDCl_3$): δ 6.92(2H,d,J=12 Hz), 6.83(2H,d,J=12), 2.65(4H,m), 1.72(4H,m).

7. 1c was prepared from 4-t-butyldimethylsiloxy-3-methoxycinnamic acid which was chain extended following the precedent of Evans, D.A.; Tanis, S.P.; Hart, D.J. J. Am. Chem. Soc. 1981, 103, 5813. The side chain was modified as in reference 2 above, followed by Bu_4NF desilylation.

8. 2c: IR($CHCl_3$): 1611, 1555, 1489 cm^{-1}; ^{1}H-NMR(300 MHz, $CDCl_3$): δ 7.19(1H,d,J=12 Hz), 7.11(1H,d,J=12), 6.74(1H,s), 3.91(3H,s), 3.03(2H,t,J=7), 2.96(2H,t,J=7), 2.03(2H,quintet).

9. 3a: mp 87-88°C; IR($CHCl_3$): 1661, 1625 cm^{-1}; ^{1}H-NMR(300 MHz, $CDCl_3$): δ 6.84(1H,dd,J=10, 4 Hz), 6.77(1H,dd,J=10, 4), 6.31(2H,m), 4.89(1H,t,J=9), 2.72(1H,m), 2.45(1H,m), 2.26(1H,m), 2.1-2.0(3H,m).

10. For a similar analysis, see McDonald, P.D.; Hamilton, G.A. J. Am. Chem. Soc. 1973, 95, 7752.

11. For a detailed discussion of the key role of radical anion intermediates in the chemistry of aliphatic nitroalkanes, see Kornblum, N. in "The Chemistry of Amino, Nitroso and Nitro Compounds and their Derivatives, Supplement F, Part 1", ed. Patai, S. (John Wiley & Sons Ltd., Chichester, 1982), pp 361-393. See also Gilbert, B.C.; Norman, R.O.C. Canad. J. Chem. 1982, 60, 1379.

12. E.g., Iwata, C.; Yamada, M.; Shinoo, Y.; Kobayashi, K.; Okada, H. J.C.S. Chem. Commun. 1977, 888.

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