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OXIDATION OF FURANS II. USE OF FURANS AS MASKED DIENOPHILES IN THE INTRAMOLECULAR DIELS-ALDER REACTION

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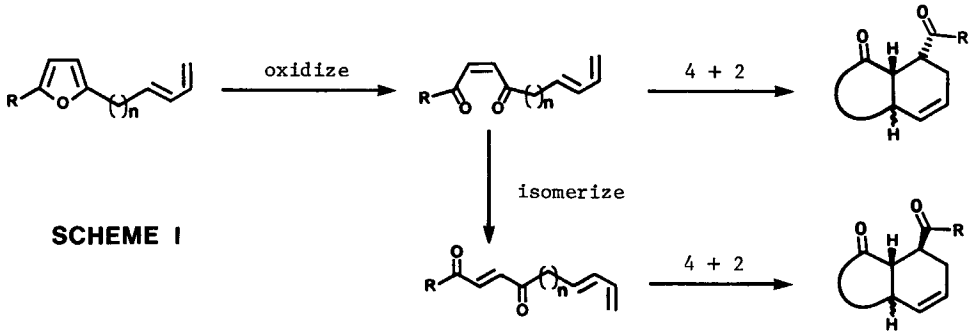
Summary: Chemoselective oxidation of alkadienylfurans using m-chloroperoxybenzoic acid gave trienes which underwent intramolecular Diels-Alder cycloaddition to hydrindenones.

In a previous report we had demonstrated the efficacy of furan oxidation using m-chloroperoxybenzoic acid (MCPBA) by synthesizing a number of enedione-functionalized macrocycles from macrocyclic furan precursors.[1] With the advent of this mild, one-step procedure for the stereospecific conversion of 2,5-dialkylfurans to the corresponding cis-enediones,[2] we investigated other situations in which this transformation might be of preparative synthetic value. With the expectation that enediones should function well as dienophiles in the Diels-Alder reaction, attention was turned to the oxidation of alkadienylfurans (Scheme I). Chemoselective attack of the peracid at the electron-rich furan nucleus would give a triene which could then undergo intramolecular Diels-Alder cycloaddition.[3] The synthetic utility of such a scheme might be further

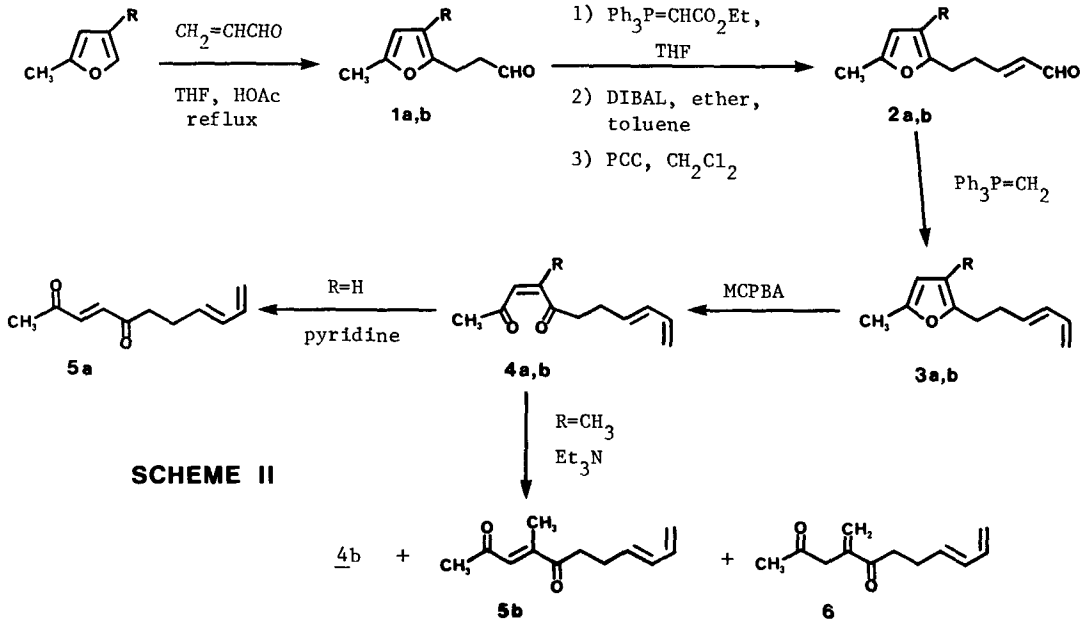


SCHEME I

enhanced by the possibilities for incorporation of additional substituents on the furan ring, and by control of the dienophile double bond geometry through isomerization of the kinetically produced cis-enedione. Herein we report implementation of this strategy for the synthesis of hydrindenones.[4]

Synthesis of the requisite hexadienylfurans **3a,b** (Scheme II) was accomplished in a straightfoward manner using furylpropionaldehydes **1a,b**, which

are readily prepared in multigram quantities by acid-catalyzed addition[5] of 2-methylfuran or 2,4-dimethylfuran[6] to acrolein. Homologation to the unsaturated aldehydes **2a,b** was brought about by Wittig olefination (97-99%), reduction to the allylic alcohol (92-96%), and oxidation (2 eq. PCC, CH_2Cl_2, 0°C to r.t., 2h, 58-68%). In this last operation it is noteworthy that there is selective oxidation of the allylic alcohol, as it is known that alkylfurans are oxidized by PCC to give trans-enediones.[7] Methylenation (81-88%) provided **3a,b** exclusively as their E-isomers as judged by 250 MHz ^1H NMR.[8]

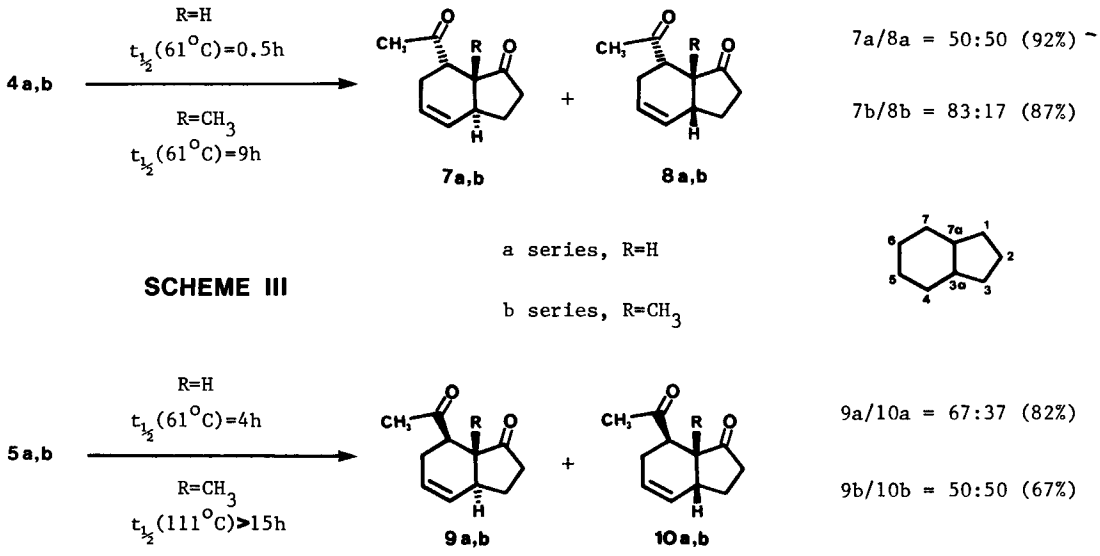


SCHEME II

The oxidation chemoselectivity of these substrates using MCPBA was then examined. Treatment of **3a** with a slight deficiency of peracid (0.9 eq. MCPBA, CH_2Cl_2, -10°C to r.t., 2h) gave triene **4a** in 61% isolated yield (70% yield based on 13% recovered starting material). Diene oxidation had occurred only to the extent of 8% (the isolated yield of a mixture of internal and terminal allylic epoxides). Oxidation of **3b** using similar reaction conditions produced triene **4b** in 87% isolated yield (96% yield based on 10% recovered starting material), with diene oxidation being undetectable! This latter result no doubt stems from the electronic effect of increased alkyl substitution on the furan ring which renders it even more susceptible to electrophilic attack by the peracid. Secondary Baeyer-Villiger products, which form very rapidly during the MCPBA oxidation of certain tri- and tetrasubstituted furans,[9,10] were not observed with **3b**.

Previous experience with the isomerization of cis-enediones[11] suggested that **4a** might be converted to **5a** upon exposure to pyridine. In the event

(excess pyridine, CH_2Cl_2, r.t., 18h), trans-enedione **5a** was obtained in 40% yield, with intramolecular Diels-Alder products derived from **4a** accounting for the remainder of the mass balance. Similar conditions with **4b** using pyridine or 4-(N,N-dimethylamino)pyridine gave no reaction. Triethylamine however, gave an equilibrium mixture of **4b**, **5b**, and deconjugated isomer **6** in a ratio of 1:1.2:1.8. The trans isomer **5b** was easily separated by column chromatography, and the remaining two components could be recycled to give more **5b**.



SCHEME III

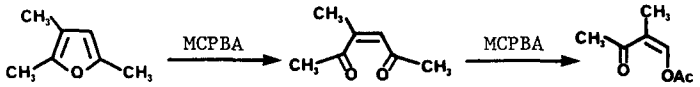
The Diels-Alder chemistry of the four trienes was then studied, and the results are summarized in Scheme III.[12] As indicated above, cis-enedione **4a** cyclized even at room temperature, giving equal amounts of the trans- and cis-fused hydrindenones **7a** (J_{7a-3a}=13.6Hz) and **8a** (J_{7a-3a}=7.7Hz). The trans-fused product **7a** was easily epimerized to the more stable cis-fused hydrindenone **10a** (J_{7a-3a}=7.3Hz) by weak acid or base.[13] The trans-enedione **5a** cyclized more slowly[14] to give a mixture favoring to a small extent the trans-fused product **9a** (J_{7a-3a} obscured). Not unexpectedly, methyl substitution on the dienophile slowed the rate of cyclization. Cis-enedione **4b**, however, exhibited the best selectivity, giving predominantly the trans-fused product (**7b**: δCH_3-7a= 0.89ppm[4a]; **8b**: δCH_3-7a=1.14ppm[4a]). Trans-enedione **5b** cyclized at a much slower rate, even at higher temperature (111°C, toluene), giving equal amounts of trans- and cis-fused products. For preparative purposes, cyclization of **5b** was conducted at higher temperatures (195°C, sealed tube, toluene, 8h). The results of this study indicate that dienophile 1,2-diactivation, while having a favorable effect upon the rate of cyclization relative to other monoactivated systems,[4a,b,e-g] does not divert to a great extent the established preference[4a-d,g] for exo cyclization of substrates possessing terminal dienophile activation.

During this study, a spectroscopic feature which aided in differentiating the cis- and trans-fused hydrindenones emerged from the ^{13}C NMR spectra: for each pair of products, the trans-fused isomer exhibited a C-1 chemical shift which was 4-5 ppm upfield of the corresponding resonance for the cis-fused isomer.[15]

Acknowledgement is made to Dow Chemical for fellowship support of P.D.W.

REFERENCES

1. P.D. Williams, E. LeGoff, J.Org.Chem.,(1981), **46**, 4143.
2. Previously, a two-step procedure had been employed: J.H. Hirsch, A.J. Szur, J.Heterocyclic Chem.,(1972), **9**, 523.
3. For recent reviews, see: A.G. Fallis, Can.J.Chem.,(1984), **62**, 183; Ciganek, E., Organic Reactions (1984), **32**, 1-374.
4. For other IMDA approaches to hydrindenes, see: (a) W.R. Roush, H.R. Gillis, A.I. Ko, J.Am.Chem.Soc.,(1982), **104**, 2269; (b) W.R. Roush, S.M. Peseckis, Ibid.,(1981), **103**, 6696; (c) R.K. Boeckman, Jr., T.R. Alessi, Ibid.,(1982), **104**, 3216; (d) R.K. Boeckman, Jr., S.S. Ko, Ibid.,(1982), **104**, 1033; (e) M.E. Jung, K.M. Halweg, Tetrahedron Lett.,(1981), 3929; (f) P. Helquist, A.B. Swati, Ibid.,(1981), 3933; (g) D.F. Taber, C. Campbell, B.P. Gunn, I.C. Chiu, Ibid.,(1981), 5141.
5. I.D. Webb, G.T. Borherdt, J.Am.Chem.Soc.,(1951), **73**, 752; J. ApSimon, V.S. Srinivasan, M.R. L'Abbe, R. Seguin, Heterocycles,(1981), **15**, 1079.
6. T. Morel, P.E. Verkade, Rec.Trav.Chim.,(1951), **70**, 35.
7. G. Piancatelli, A. Scettri, M. D'Auria, Tetrahedron,(1980), 661.
8. Wittig olefination of **1a** using allylidenetriphenylphosphorane gave a mixture of E- and Z-**3a** which were readily distinguished by 250 MHz ^1H NMR.
9. S.B. Gingerich, P.W. Jennings, J.Org.Chem.,(1984), **49**, 1284; S.B. Gingerich, P.W. Jennings, Ibid.,(1983), **48**, 2606; S.B. Gingerich, W.H. Campbell, C.E. Bricca, P.W. Jennings, C.F. Campana, Ibid.,(1981), **46**, 2590.
10. In this regard, we have found that 2,3,5-trimethylfuran is converted to the cis-enedione in high yield using 1 eq. MCPBA. Addition of a second equivalent resulted in regio- and stereospecific Baeyer-Villiger oxidation to give the enol acetate shown below: P.D.Williams, Ph.D. Dissertation, Michigan State Univ., 1982.



11. Cis-3-octene-2,5-dione was isomerized by pyridine in chloroform (r.t., 8h) to the trans isomer in virtually quantitative yield: P.D. Williams, Ph.D. Dissertation, Michigan State University, 1982.
12. Cyclizations were performed in refluxing chloroform-d_1 (bp 61°C) or toluene-d_8 (bp 111°C) and the reaction progress was monitored by integration of appropriately resolved signals in the 250 MHz ^1H NMR spectra of aliquots.
13. It is well known that cis-fused hydrindenones are more stable than the trans isomers: H.O. House, G.H. Rasmusson,J.Org.Chem.,(1963),**28**, 27; A. Ichihara, R. Kimura, V. Seiichiro, S. Sadao, J.Am.Chem.Soc.,(1980), **102**, 6353.
14. A slower rate of cyclization for trans-1,2-diactivated substrates compared to the cis isomers has been noted: J.D. White, B.G. Sheldon, J.Org.Chem.,(1981), **46**, 2273.
15. This might be ascribed to the γ-gauche shielding effect of C-3: G.C. Levy, R.L. Lichter, G.L. Nelson in "Carbon-13 Nuclear Magnetic Resonance Spectroscopy " 2nd Edition, Wiley-Interscience, N.Y., 1980, p.33. The C-1 chemical shifts are: **7a**,214.3ppm; **8a**,218.0ppm; **9a**,214.1ppm; **10a**,219.5ppm; **7b**,217.9ppm; **8b**,222.5ppm; **9b**,217.5ppm; **10b**,221.5ppm.

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