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FORMATION OF REACTIVE TRICYCLIC INTERMEDIATES VIA THE INTRAMOLECULAR CYCLOPROPANATION OF DIHYDROPYRANS. SYNTHESIS OF EUCALYPTOL

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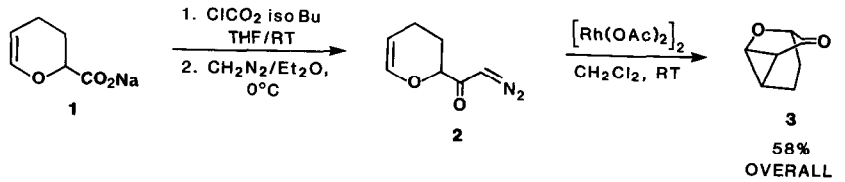
Summary: Tricyclic compound 3 was synthesized via a cyclopropanation reaction promoted by $[Rh(OAc)_2]_2$. This highly strained compound was found to undergo selective chemical transformations to give [2.2.2] oxa-bicyclic ketones. This methodology was applied in a total synthesis of the monoterpene, eucalyptol.

The reaction of α-diazo carbonyl compounds with olefins, mediated by transition metal catalysts, provides a useful route to cyclopropanes.[1] Mechanistically, the reaction involves the addition of the keto-carbene to a carbon-carbon double bond. The intermolecular reaction of keto-carbenes and olefins requires a high concentration of the olefin (usually as the solvent) since dimerization of the carbene is usually a faster reaction than cyclopropanation.[2] Due to this limitation many researchers have chosen to exploit this reaction in an intramolecular sense, thus obviating the carbene dimerization problem. Upon surveying the literature we noted that the vast majority of the intramolecular cyclopropanations studies to date have been systems which produce bi- or tricyclic carbocycles.[3] This paper describes our efforts to produce novel oxygen heterocycles by the intramolecular cyclopropanation of cyclic enol ethers. Furthermore, the reactivity of the strained oxa-tricyclic system was explored under a variety of reaction conditions, to produce regiospecific fragmentation of the cyclopropane ring to unveil novel [2.2.2] oxabicyclooctanones.

Beginning with the commercially available 3,4-dihydro-2H-pyran-2-carboxylic acid, sodium salt 1, we were able to produce the corresponding α-diazo ketone 2 by a two-step procedure outlined in Scheme I. Addition of a catalytic amount (2 weight %) of $[Rh(OAc)_2]_2$ in CH_2Cl_2 at room temperature produced an efflux of nitrogen gas and provided the desired tricyclic cyclopropyl ketone 3.[4]

SCHEME I



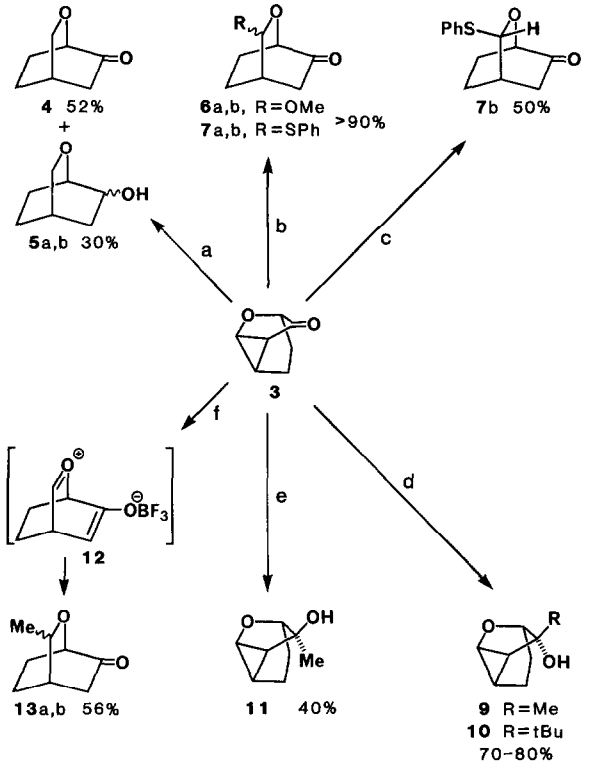
1 2 3

58% OVERALL

The ease of cyclopropanation underscores the mildness of the rhodium II catalyst. Attempts with traditional copper catalysts provided only decomposition products. Another factor promoting the reaction is that the double bond is electron rich (due to the α-oxygen) and the keto-carbene is electronically deficient (due to the carbonyl).

Catalytic hydrogenation of 3 cleanly reduced the cyclopropane ring to give the bicyclic ketone 4 as the major product along with a mixture of epimeric alcohols 5a,b resulting from a subsequent reduction of 4. Bicyclic compound 4 has been described only once before in an 8-step synthesis.[5]

SCHEME II

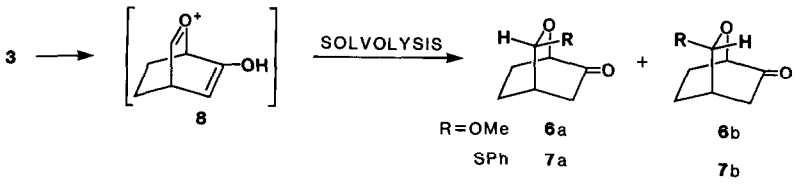


a) H_2 / 10% Pd·C, EtOAc, 50psi; b) MeOH/cat pTsOH or PhSH/THF cat pTsOH; c) PhSNa/THF, 110°C 4h; d) MeLi,tBuLi or MeMgCl/Et_2O, -78°C 10min; e) Me_2CuLi/Et_2O, 0°C 2h; f) $Me_2CuLi/BF_3Et_2O/Et_2O$ -78°C 5min ⟶ 0°C 30min.

Dissolution of oxa-tricycle 3 in acidic (catalytic pTsOH) MeOH cleanly produced a mixture of epimeric cyclic methyl acetals 6a and 6b in a ratio of 3:1. The corresponding reaction was seen to occur using thiophenol (catalytic pTSOH/THF), to give a 5:1 mixture of thio-acetals 7a and 7b. We reasoned that this mechanism occurs via an acid catalyzed unimolecular fragmentation of 3 to form the oxonium enol 8 which reacts with the nucleophile preferentially on the less hindered side (the enol).[6] However, when thiolate anion was used (thiophenol, NaH/THF, 110°C, sealed tube) nucleophilic opening via an SN_2 mechanism produced only 7b, with the thiophenyl group on the side opposite the carbonyl.

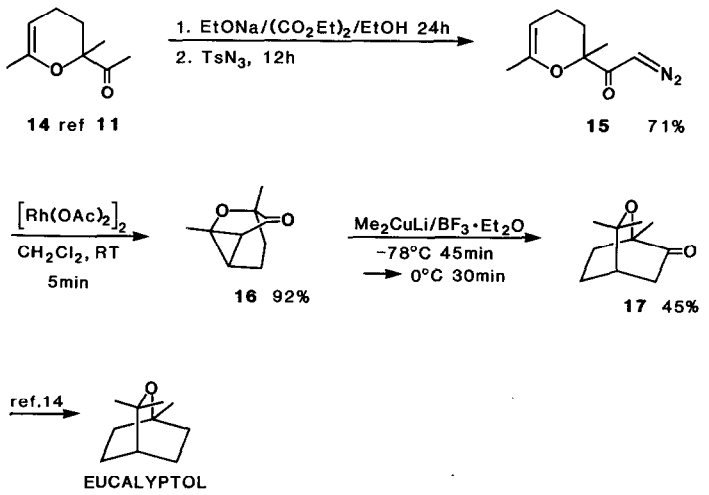
Attempts to achieve nucleophilic opening reactions using carbon nucleophiles in homo-conjugate fashion resulted only in 1,2 addition to the carbonyl.[7] Organometallic reagents MeLi, MeMgBr and tBuLi reacted on the less hindered face of the carbonyl (exo) giving carbinols 9 and 10, while Me_2CuLi delivered a methyl group on the more hindered concave part of the molecule affording exclusively carbinol 11.[8] A rationalization for the opposite stereoselection of the cuprate reaction lies in the belief that the ring ether oxygen serves to complex the copper cation masking the convex face of the molecule and the nucleophile is delivered from the opposite side. Homo-conjugate opening of the cyclopropane ring with Me_2CuLi was finally achieved in the presence of $BF_3.Et_2O$.[9] This reaction probably proceeds via an oxonium-boron enolate zwitterion 12,[10a] which is alkylated to give a 1:1 mixture of epimers 13a,b.

SCHEME III



This reaction allowed us to design a short synthesis of the monoterpene, eucalyptol[10] (Scheme IV). Beginning with the known dihydropyran 14,[11] the diazoketone 15 was prepared using the modified procedure of Harmon et al.[12] Cyclization, mediated by $[Rh(OAc)_2]_2$ proceeded very smoothly to produce oxa-tricyclanone 16. Homo-conjugate addition of $Me_2CuLi/BF_3.Et_2O$ afforded bicyclic ketone 17, itself an oxidative metabolite of eucalyptol.[13,4] This constitutes a formal synthesis of eucalyptol since the Clemmensen reduction of 17 has been reported.[14]

SCHEME IV: SYNTHESIS OF EUCALYPTOL



In conclusion, the formation of strained tricyclic heterocycles such as 3 or 16 provides a useful entry into oxa-bicyclic compounds by relying on the regioselective fragmentation of the cyclopropane ring. We are also interested in expanding this approach to different ring sizes, and will soon report syntheses of substituted 7- and 8-membered rings.

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2. a) A.J. Anciaux, A.J. Hubert, A.F. Noels, N. Petiniot and P. Teyssié, J. Org. Chem., 45, 695 (1980), b) M.P. Doyle, D. Van Lensen, and W.H. Tamblyn, Synthesis, 10, 787 (1981), c) M.P. Doyle, R.L. Dorow, W.H. Tamblyn and W.E. Buhro, Tetrahedron Lett., 23, 2261 (1982), d) M.P. Doyle, J.H. Griffin, V. Bugheri and R.L. Dorow, Organometallics, 3, 53 (1984.
3. For example: a) T. Hudlicky, F.F. Koszyk, T.M. Kutchan and J.P. Sheth, J. Org. Chem., 45, 5020 (1980), b) D. Becker and H.J.E. Loewenthal, Isr. J. Chem., 10, 375 (1972), c) C.J.V. Scanio and D.L. Lickei, Tetrahedron Lett., 14, 1363 (1972).
4. Satisfactory spectral data were obtained, including: 250 MHz ^{1}H NMR IR and high resolution mass spectra. For key compounds 3, 16 and 17, ^{13}C-NMR spectra were also recorded.
5. Joan K. Glascock, Ph.D. dissertation 1980, Duke University..
6. The stereochemical assignments were made by comparing the ^{1}H NMR chemical shifts of the β-proton adjacent to the ketones, 6a and 6b. In 6a but not 6b the proton in question experiences a profound downfield chemical shift due to the electronegative methoxy substituent. A similar but less pronounced effect is observed for 7a and 7b.
7. Homoconjugate additions with carbon nucleophiles usually require 2 activating groups. For example see a) E.J. Corey and P.L. Fuchs, J. Am. Chem. Soc., 94, 4014 (1972), b) B.M. Trost, D.F. Taber and J.B. Alper, Tetrahedron Lett., 18, 3857 (1976).
8. Stereochemical assignments between 9 and 11 were made by ^{1}H NMR analysis of their chemical shifts of the cyclopropyl methine adjacent to the 3°y alcohol. The methine proton in 11 appears at 1.53 ppm, deshielded by the electronegative oxygen atom relative to the same proton in 9 which appears at 1.40 ppm.
9. For experimental conditions see: A.B. Smith III and J. Jerris, J. Am. Chem. Soc., 103, 194 (1981).
10. Eucalyptol is also referred to as 1,8-cineole. Recent syntheses include: a) J.P. Bégué, M. Charpantier-Morize, D. Bonnet-Delpon and J. Sansoulet, J. Org. Chem. 45, 3357 (1980), b) C.M. Link, D.K. Jansen and C.N. Sukenik, J. Am. Chem. Soc., 102, 7798 (1980), c) R.M. Scarborough Jr., A.B. Smith III, W.E. Barnette and K.C. Nicolaou, J. Org. Chem., 44, 1742 (1979), d) J.M. Coxan, M.P. Hartshorn, J.W. Mitchell and K.E. Roberts, Chem. and Ind., 652 (1968).
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