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NOVEL OXIDATIVE CYCLIZATION OF BRIDGED SECONDARY ALCOHOLS WITH CERIC AMMONIUM NITRATE

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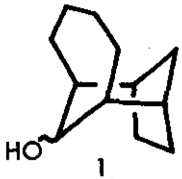
The formation of 5-membered ring ether, an unprecedented reaction of ceric ammonium nitrate on secondary alcohols, has been observed in five cases. Possible mechanisms were proposed.

Utilization of ceric ammonium nitrate (CAN) to oxidation of alcohols has recently been documented:[1,2] Cyclic secondary alcohols generally undergo oxidative cleavage to afford unsaturated or substituted aldehydes. By application of this oxidation to tricyclic alcohols of general carbon skeleton 1, we have found specific oxidative cyclization giving tetrahydrofurane derivatives, a novel behavior of secondary alcohols towards to the reagent.



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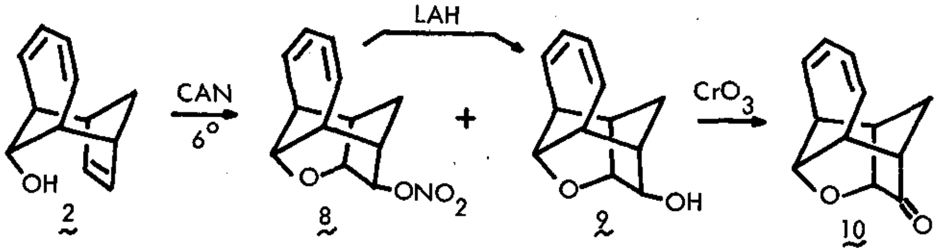
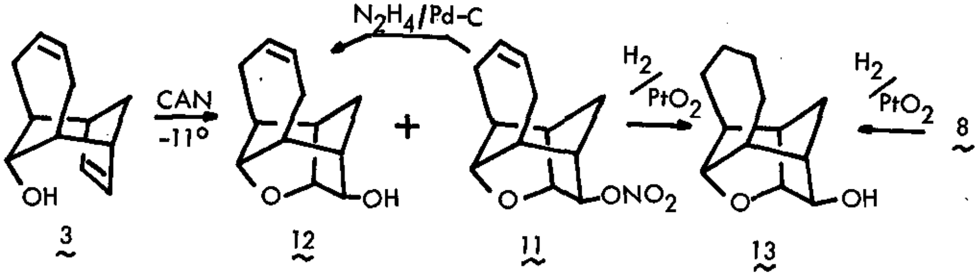
In general reactions, the secondary alcohols 2-7 synthesized previously[3] was submitted to the oxidation at various temperatures with 2-2.8 moles of CAN in acetonitrile-water solvent, monitoring the reaction by the disappearance of the characteristic red color of cerium-alcohol complex.[1b,4] Products were separated by preparative TLC on silica gel.

Oxidation of alcohol 2 at 6°C afforded nitrate 8, m.p. 78.8-79.8°, and alcohol 9, oil, in 38% and 28% yields, respectively. Structure of 8 was deduced from its spectra shown in Table: The presence of a diene system, a nitrate group



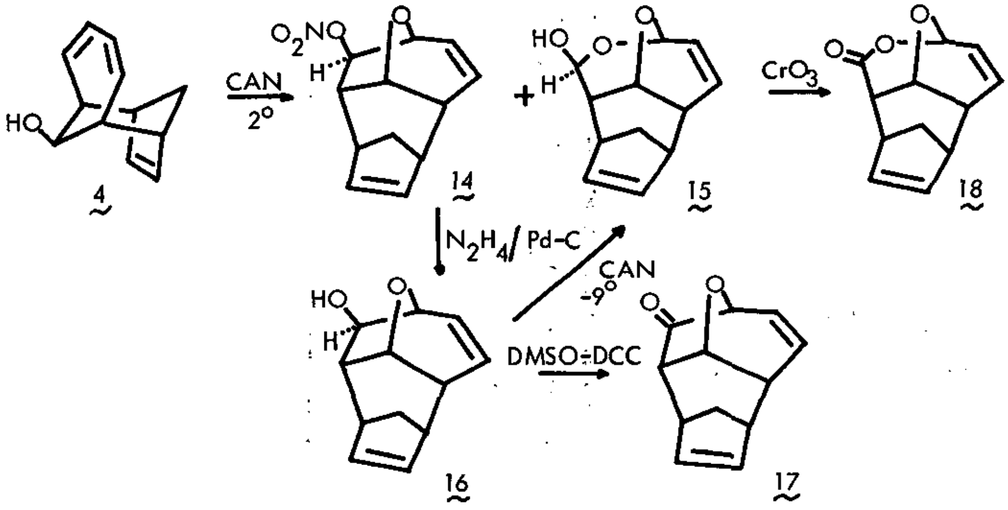
and three carbinyl protons are clearly shown. Singlet nature of the carbinyl proton at 5.24 ppm in NMR spectrum suggested trans disposition of two vicinal oxygens. Furthermore, the alcohol 9 was derived from 8 by $LiAlH_4$ reduction and oxidized by CrO_3 to the 5-membered ring ketone 10, oil, ν^{CHCl_3} 1755 cm^{-1} (no OH).

The alcohol 3 behaves similarly, the products being nitrate 11, m.p. 83-84.5° (33%) and alcohol 12, m.p. 92-94.5° (36%). The structures of these compounds were deduced by their spectra (Table) and established by chemical correlations: 11 was converted by hydrazine-Pd-charcoal reduction to 12 and by catalytic (PtO_2) reduction to the hydroxy ether 13, oil, which was also obtained by the same procedure from 8.



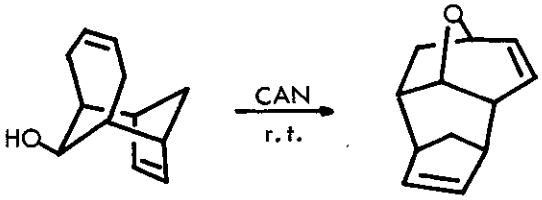
Thus, unprecedented formation of ether linkage from secondary alcohol was observed in two cases. The reaction pathway can be rationalized as follows, involving rapid formation of CAN-alcohol complex at the initial stage. The complex would then collapse by two consecutive one-electron transfers,[5] first forming O-radical which with the participation of double bond affords a tetrahydrofurane ring and C-radical. The latter can be oxidized to carbonium ion to which nucleophilic attack of water or nitrate ion takes place. Alternative pathway involving O-cation is conceivable but less likely.

When the corresponding epimeric alcohols were subjected to the oxidation, similar oxidative cyclization took place at the different site. The alcohol 4 gave at 2°C two monomeric products, nitrate 14, oil, and lactol 15, m.p. 124-127°, in 30% *and 26% yields, respectively.*[6] *For both 14 and 15, the absence of diene system and*



the presence of cyclopentadiene (m/e 66) and pyrone (m/e 81) moieties were indicated by their spectra (Table). Furthermore, 14 was reduced by hydrazine-Pd-charcoal to alcohol 16, m.p. 116-118°, detailed analysis of whose PMR spectrum allowed the assignment of the Structure. δ_{CDCl_3} 1.57 (1H, ddd, J=11.0, 3.8, 4.2), 1.70 (1H, d, J=11.0), 2.26 (1H, m), 2.37-2.70 (3H, m), 2.79 (1H, br.td, J=3.8, 2.8), 3.95 (1H, d, J=3.0), 4.25 (1H, d, J=5.0), 4.31 (1H, br.t, J=5.0), 5.70 (1H, ddd, J=9.8, 2.8, ~1), 5.92 (1H, dd, J=5.7, 2.5), 6.08 (1H, dd, J=5.7, 2.8), 6.16 (1H, ddd, J=9.8, 5.0, 1.0). The alcohol 16 can be oxydized with DMSO-DCC to keto ether 17, oil, ν 1752 cm^{-1}. Lactol 15 must be formed from 16 by normal mode of CAN oxidation. In fact, reaction of 16 at -9° afforded 15 quantitatively. Structure of 15 was suggested from its spectra (Table) and its conversion ($CrO_3 \cdot 2$ Py) to lactone 18, m.p. 115-116°, ν 1728, 1232 cm^{-1}.

The CAN oxidation of 5 at room temperature gave ether 19, oil, in 39% yield. The structure is based on its PMR spectral analysis (Table). Spectrum is very similar with those of 14 and 16.



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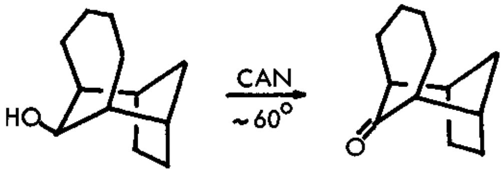
Formation of 14 and 19 can be understood by the same mechanisms as before.

The ether formation occurs also in a saturated system, although under more drastic conditions. Thus, while alcohol 6 at ~60° yielded known ketone 20[7] in



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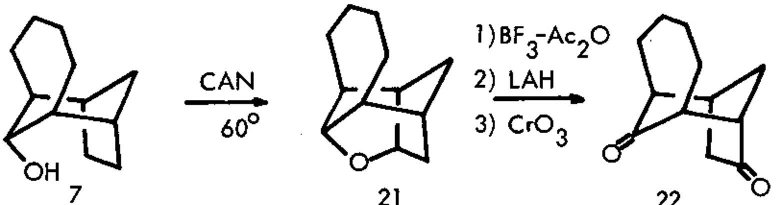
95% yield (no C-C bond cleavage), epimeric alcohol 7 afforded ether 21, oil, in 85% yield under the same conditions. Structure of 21 is based on the spectra of



7 21 22

diketone 22, oil, MS m/e 192 (M^+), 164, 135, 121, 110, 79, ν^{CHCl_3} 1735, 1722, 1702 cm^{-1}, derived from 21 by ether cleavage (BF_3-Ac_2O and then $LiAlH_4$) and subsequent CrO_3 oxidation. These reactions can be understood by the abstraction of neighboring hydrogens by complexing Ce.

Thus, unprecedented oxidative cyclization observed in the present cases appears to be common for the secondary alcohols with double bond or CH bond in the proximity of a hydroxyl group, and find some synthetic application.

Table. Spectroscopic Data of CAN Oxidation Products

8 : m/e 235 (M^+), 143, 128, 111, 91, 83 (b), 55; λ_{max}^{MeOH} 245 (ϵ 4472), 253.5 (5799), 263 (5809), 272 nm (3172); ν^{KBr} 1623, 1284, 996, 945, 860, 705 cm^{-1}; δ_{CDCl_3} 1.76 (1H, m), 2.21 (1H, br.d, J=12.6), 2.59 (1H, br.s), 2.65-3.00 (3H, m), 4.16 (1H, br.t, J=3.0), 4.64 (1H, dd, J=4.9, 2.5), 5.24 (1H, s), 5.3-6.1 (4H, complex).

9 : m/e 190 (M^+), 143, 131, 112, 107, 91 (b); λ_{max}^{MeOH} 246.5 (ϵ 3610), 254 (4694), 263 (4532), 274 (2400); ν^{oil} 3400, 2960, 1610, 1005, 940, 700 cm^{-1}; δ_{CDCl_3} 1.55-2.12 (2H, m), 2.28 (1H, m), 2.43-3.05 (4H, m), 4.09 (1H, br.t, J=3), 4.22 (1H, s), 4.42 (1H, dd, J=4.5, 2.5), 5.32-5.93 (4H, m).

11 : m/e 191 (M^+-NO_2), 175, 145, 117, 91 (b), 79, 67; ν^{KBr} 1635, 1615, 1280, 1005, 955, 880 cm^{-1}; δ_{CDCl_3} 1.61 (1H, m), 2.03-2.88 (9H, m), 4.12 (1H,

br.t, J=3.0), 4.60 (1H dd, J=4.9, 2.3), 5.11 (1H, s), 5.45 (1H, m), 5.57 (1H, m).

12 : m/e 192 (M^+), 131, 117, 92, 79 (b), 67; ν^{KBr} 3350, 1430, 1100, 1020, 985, 980, 880 cm^{-1}; δ_{CDCl_3} 1.53-2.78 (1H, m), 3.95-4.15 (2H, m), 4.38 (1H, dd, J=5.0, 2.5), 5.47-5.67 (2H, m).

14 : m/e 189 (M^+-NO_2), 107, 91, 81 (b), 66; ν^{oil} 1625, 1280, 1075, 1050, 860 cm^{-1}; δ_{CDCl_3} 1.70 (1H, ddd, J=11.2, 4.0, 2.5), 1.83 (1H, d, J=11.2), 2.35-2.65 (3H, m), 2.84 (1H, ddd, J=3.2, 2.8, 2.5), 4.26 (1H, br.td, J= 6.4, 1.2), 4.35 (1H, ddd, J=5.3, 1.0, 0.5), 4.89 (1H, d, J=3.2), 5.77 (1H, ddd, J=9.8, 3.0, 1.2), 5.95 (1H, dd, J=5.7, 2.5), 6.09 (1H, dd, J=5.7, 2.8), 6.19 (1H, ddd, J=9.8, 5.3, 1.0).

15 : m/e 206 (M^+), 160, 131, 91, 81 (b), 66; ν^{KBr} 3325, 1640, 1340, 1115, 967, 765 cm^{-1}; δ_{CDCl_3} 1.49 (1H, br.dt, J=11.0, 4.5), 1.88 (1H, m), 1.92 (1H, br.d, J=11.0), 2.60 (1H, m), 2.75-2.95 (2H, m), 3.25 (1H, br.-OH), 4.13 (1H, br.t, J=6.5), 5.27 (1H, br.dd, J=3.5, 1), 5.39 (1H, br.d, J=9.0), 5.81-6.11 (4H, m).

19 : m/e 174 (M^+), 156, 117, 91, 81 (b), 79, 66; ν^{oil} 2930, 1460, 1340, 1040, 1015, 720 cm^{-1}; δ_{CDCl_3} 1.49 (1H, ddd, J=12.0, 4.5, 1.0), 1.55 (1H, m), 1.87 (1H, d, J=10.8), 2.04 (1H, ddd, J=12.0, 10.9, 7.2), 2.31-2.75 (4H, m), 4.11 (1H, br.t, J=6.4), 4.44 (1H, br.dd, J=7.2, 4.5), 5.61 (1H, ddd, J=9.4, 2.8, 0.5), 5.88 (1H, ddd, J=5.7, 2.8, 0.5), 6.08 (1H, ddd, J=5.7, 2.5, 0.7), 6.21 (1H, ddd, J=9.4, 4.5, 1.1).

21 : m/e 178 (M^+), 134 (b), 91, 79, 67; ν^{oil} 2920, 1025, 1003, 986, 858 cm^{-1}, δ_{CDCl_3} 4.01 (1H, br.s), 4.57 (1H, br.s).

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6 A trace of dimeric compound, m.p. 202-204°, was also obtained. Its spectra suggests it to be a dehydration product between **15** and **4**.

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