Unexpected formation of bicyclo[3.3.1]nonenyl methanesulfonate from tricyclo[4.3.0.02•9]nonan-8-ol†

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Attempted methanesulfonylation reaction of the tricyclo[4.3.0.02•9]nonan-8-ol under standard conditions led to the selective cleavage of the C\textsubscript{1}-C\textsubscript{6} cyclopropane bond resulting in the formation of bicyclo[3.3.1]nona-2,8-diene 10 instead of the expected methanesulfonate 9 of the starting alcohol or the fragmentation product bicyclenic diene 17.

The bicyclo[3.3.1]nonane ring system 1 has received considerable attention from both synthetic as well as theoretical chemists. The bicyclic framework 1 is present as part structure in several natural products, particularly in alkaloids and terpenoids such as limonoid xylocaripin, sesquiterpenes clovanediol, upial, trifarienols etc. In addition, bicyclo[3.3.1]nonanes have also been utilized as synthons for the construction of a variety of complex ring systems, enroute to natural products.

The synthetic utility of reactions involving long-range orbital interaction over more than three σ-bonds is not fully exploited. One of the important reactions that involves orbital interactions over more than three σ-bond is the heterolytic Grob fragmentation. Molecules containing electrophilic as well as nucleophilic moieties spaced with two carbons undergo regulated cleavage (fragmentation) into three fragments. In the general formulation (eq. 1), A-B denotes an electrophilic group, which leaves as A-B without the bonding electron pair. The middle group C-D affords the unsaturated fragment C=D, while the nucleophilic group X leaves with bonding electrons. There are three different mechanisms possible for such reactions, although the structure, electronic requirements and the number of bonds broken are same, the sequence with which bond rupture occurs may be different. Quite obviously in polycyclic systems, this kind of fragmentation leads to cleavage of one or two rings.

\[ \text{A-B-C-D-X} \rightarrow \text{[A-B]⁺ + C=D + [X]⁻} \]  

During our exploratory studies towards the development of a methodology for the enantiospecific synthesis of pinguisanes, we have come across an interesting fragmentation reaction which resulted in the enantiospecific generation of bicyclo[3.3.1]nonanes. Attempted synthesis of the methanesulfonate 2 starting from the tricyclic alcohol lead to a 1,4-homoelimination product 4, similar to the Grob fragmentation. Formation of the bicyclic compound 4 can be rationalized either via an E\textsubscript{2}-type concerted 1,4-homoelimination similar to the Grob fragmentation as shown in 5 or via the corresponding cyclopropylmethyl carbonium ion 6 (E\textsubscript{1}-type) of the methanesulfonate 2. In an attempt to establish the mechanism, the reaction was also carried out with the epimeric exo-alcohol 7, obtained from 3 employing a Mitsunobu protocol, which also resulted in the formation of the same bicyclic diene 4, suggesting the intermediary of the cyclopropylmethyl carbonium ion in the transformation of 2 \rightarrow 4. The reaction was investigated with a reasonable number of 1-methyltricyclo[4.3.0.02•9]nonan-8-ols and found to be general.

Subsequently, to investigate the role of the angular methyl group in the fragmentation reaction, the reaction was explored with the tricyclic alcohol, which lacks a methyl group on the C-1 carbon and contains a methyl group at C-6 carbon. As the methyl group at the C-1 position is absent in the tricyclic alcohol, it was anticipated that it will generate either the simple methanesulfonate or the fragmentation product bicyclo[4.3.0]nona-2,8-diene analogous to the formation of 4 from the tricyclic alcohol. The tricyclic alcohol was prepared from 3-methylcyclohexenol employing a combination of Johnson's orthoester variant of the Claisen rearrangement and intramolecular diazoketone
cyclopropanation\textsuperscript{9} based methodology as depicted in Scheme 1.

Thus, thermal activation of the allyl alcohol 11 with triethyl orthoacetate and a catalytic amount of propionic acid furnished the ester 12 in 77% yield. Hydrolysis of the ester 12 with sodium hydroxide in aqueous methanol furnished the acid 13. Reaction of the acid 13 with oxalyl chloride in benzene at room temperature furnished the acid chloride 14, which on treatment with an excess of ethereal diazomethane generated the diazo ketone 15. Copper sulfate catalysed decomposition of the diazoketone 15 followed by intramolecular cyclopropanation of the resultant ketocarbenoid generated the tricyclic ketone\textsuperscript{10} 16 in a stereospecific manner. Reduction of the tricyclic ketone 16 with sodium borohydride in methanol and tetrahydrofuran at ice temperature furnished a 6 : 1 mixture of the tricyclic alcohol 8 in 88% yield, whose structure rests secured from the spectral data. Presence of a peak at 151 (C\textsubscript{10}H\textsubscript{15}O, M\textsuperscript{+}-1) in the mass spectrum and a strong absorption band at 3400 cm\textsuperscript{-1} due to the hydroxy group in the IR spectrum, presence of a ddd signal at 4.81 (J 12.6, 6.3 and 2.7 Hz) due to the methine attached to the hydroxy group, a singlet at 1.14 due to the tertiary methyl group for the major isomer in the \textsuperscript{1}H NMR spectrum established the structure of the alcohol 8, which was further confirmed by the \textsuperscript{13}C NMR spectrum.

Reaction of the alcohol 8 with methanesulfonyl chloride in methylene chloride and an excess of pyridine, in contrast to the expected diene 10 or the simple methanesulfonate 9, furnished an olefin containing methanesulfonate 17 in 65% yield, whose structure was deduced from its spectral data. In the IR spectrum presence of absorption bands at 3020 and 1560 cm\textsuperscript{-1} due to olefin and at 1350 and 1170 due to a sulfonate group revealed formation of a rearranged methanesulfonate. In the \textsuperscript{1}H NMR spectrum presence of a triplet of a doublet resonance at \(\delta\) 5.77 (J 9.6 and 3.3 Hz) and a multiplet at 5.45–5.55 due to two olefinic protons, a doublet at 4.7 (J 3.9 Hz) due to the methine attached to the methanesulfonyloxy group, a singlet at 3.04 due to methyl of the methanesulfonyl group, a multiplet at 2.75–2.80 due to the bridgehead proton, triplets of an AB quartet at 2.18 and 2.10 (J 18.3 and 2.0 Hz) due to the allylic methylene group, a singlet at 1.01 due to the tertiary methyl group established the structure of the rearranged bicyclic methanesulfonate 17. It was further confirmed by the \textsuperscript{13}C NMR spectrum, which exhibited resonances at \(\delta\) 128.7 and 126.7 (two similar olefinic carbons), at 86.3 (methine carbon attached to methanesulfonyloxy group), at 38.5 (methine carbon of the methanesulfonyl group), at 33.7 (C-5 quaternary carbon), at 17.5 (tertiary methyl group) in addition to other aliphatic carbon resonances. The stereochemistry of the methanesulfonyloxy group was tentatively assigned on the basis of the coupling constant of the methine proton attached to the oxygen, as the other epimer is expected to show less coupling (based on the PCMODEL minimized structure). The other logical bicyclic structure 18 was ruled out on the basis of the multiplicity and coupling constants of the methine group attached to methanesulfonyloxy group. Formation of such a methanesulfonate under solvolytic conditions is quite normal, however formation of the methanesulfonate 17 under the typical methanesulfonylation conditions is quite surprising.

Experimental

Ethyl 2-(1-methylcyclohex-2-en-1-yl)acetate (12) :
A solution of 3-methylcyclohexenol 11 (7.4 g, 67 mmol), triethyl orthoacetate (15 ml, 82 mmol) and propionic acid (catalytic) in toluene (15 ml) was placed in four Carius tubes under nitrogen atmosphere and heated at 180°C for four days. The Carius tubes were cooled and the contents were pooled. The reaction mixture was diluted with ether, washed with aqueous NaHCO₃ solution followed by brine and dried (Na₂SO₄). Evaporation of the solvent furnished the acid 13 (4.2 g, 95%) 11. IR (neat) : v max 1734 (O-C=O), 1452, 1368, 1338, 1323, 1242, 1161, 1035 cm⁻¹; 1H NMR (90 MHz, CDCl₃) : δ 5.68 (1 H, t of d, J 10.8 and 3 Hz, CH₂-C=H), 5.50 (1H, d, J 10.8 Hz, CH₂=CHCH₃), 4.41 (2H, q, J 7.2 Hz, O-CH₂CH₃), 2.30 (2H, s, CH₂C=O), 1.96 (2H, br s, allylic CH₃), 1.19-1.85 (4H, m, H-5 and 6), 1.30 (3H, t, J 7.2 Hz, O-CH₂CH₂CH₃), 1.14 (3H, s, tert-CH₃); 13C NMR (22.5 MHz, CDCl₃) : δ 171.31 (s, O-C=O), 134.7 (d, C-2'), 125.6 (d, C-3'), 59.4 (t, OCH₂CH₃), 46.3 (t, CH₂C=O), 34.8 (t, C-6'), 33.7 (s, C-1'), 26.9 (q, tert-CH₃), 24.7 (t, C-4'), 18.7 (t, C-5'), 14.0 (q, OCH₂CH₃).

2-(1-Methylcyclohex-2-yl)acetic acid (13) :

To a magnetically stirred solution of the ester 12 (5.25 g, 28.8 mmol) in methanol (5 ml) was added sodium borohydride (12.7 mg, 0.34 mmol) and stirred for 30 min. The solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1 : 10) as eluent furnished the 13 (4.2 g, 95%) 11. IR (neat) : v max 2900 (C=O), 1734, 1695, 1452, 1368, 1338, 1323, 1242, 1161, 1089, 1035 cm⁻¹; 1H NMR (90 MHz, CDCl₃) : δ 5.68 (1 H, t of d, J 10.8 and 3 Hz, CH₂-C=H), 5.50 (1H, d, J 10.8 Hz, CH₂=CHCH₃), 4.41 (2H, q, J 7.2 Hz, O-CH₂CH₃), 2.30 (2H, s, CH₂C=O), 1.96 (2H, br s, allylic CH₃), 1.19-1.85 (4H, m, H-5 and 6), 1.30 (3H, t, J 7.2 Hz, O-CH₂CH₂CH₃), 1.14 (3H, s, tert-CH₃); 13C NMR (22.5 MHz, CDCl₃) : δ 171.31 (s, O-C=O), 134.7 (d, C-2'), 125.6 (d, C-3'), 59.4 (t, OCH₂CH₃), 46.3 (t, CH₂C=O), 34.8 (t, C-6'), 33.7 (s, C-1'), 26.9 (q, tert-CH₃), 24.7 (t, C-4'), 18.7 (t, C-5'), 14.0 (q, OCH₂CH₃).

To a magnetically stirred, refluxing suspension of anhydrous copper sulfate (8 g) in dry cyclohexane (150 ml) was added, a solution of the diazoketone 15 (2.00 g, 11.2 mmol) in cyclohexane (20 ml) dropwise over a period of 30 min and refluxed for 5 h. The reaction mixture was cooled and filtered through a sintered funnel. Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1 : 10) as eluent furnished the tricyclic ketone 16 (927 mg, 55%) as oil 10. IR (neat) : v max 2900, 1722 (C=O), 1458, 1413, 1383, 1320, 1263, 1155, 879 cm⁻¹; 1H NMR (60 MHz, CDCl₃) : δ 2.20 and 1.86 (2H, 2 x d, J 16 Hz, CH₂C=O), 0.90-2.10 (9H, br m), 1.23 (3H, s, tert-CH₃); 13C NMR (100 MHz, CDCl₃) : δ 214.9 (s, C=O), 56.4 (t, CH₂C=O), 35.4 (d, C-9), 35.3 (t, C-5), 32.7 (d, C-1), 32.4 (s, C-6), 30.3 (q, tert-CH₃), 24.3 (d, C-2), 20.3 (C-3), 18.1 (t, C-4). 24-DNP derivative m.p. 193°C. 1H NMR (90 MHz, CDCl₃) : δ 9.14 (1H, d, J 2.5 Hz), 8.80 (1H, dd, J 10.0 and 2.5 Hz) and 7.86 (1H, d, J 10.0 Hz) [aromatic H], 2.92 and 2.48 (2H, 2 x d, J 16.2 Hz, H-7), 2.20-1.00 (9H, m), 1.36 (3H, s, tert-CH₃).

(Found : C, 58.25; H, 5.54; N, 16.85. Calcd. for C₁₆H₁₈N₄O₄ : C, 58.17; H, 5.49; N, 16.96%).

6-Methyltricyclo[4.3.0.0²⁷]nonan-8-ol (8) :

To an ice-cold magnetically stirred solution of the tricyclic ketone 16 (100 mg, 0.67 mmol) in THF (5 ml) and methanol (5 ml) was added sodium borohydride (12.7 mg, 0.34 mmol) and stirred for 30 min. The solvent was evaporated under reduced pressure, the residue was taken in methylene chloride (3 x 15 ml). The methylene chloride extract was washed with brine and dried (Na₂SO₄). Evaporation of the solvent furnished the acid 13 (4.2 g, 95%) 11. IR (neat) : v max 3300 (OH), 3000, 2950, 1540, 1355 cm⁻¹; 1H NMR (300 MHz, CDCl₃) : δ 4.81 (1H, ddd, J 12.6, 6.3 and 2.7 Hz, CH-OH), 2.11 (2H, dd, J 14.7 and 9.9 Hz), 2.05-1.70 (3H, m), 1.45-1.60 (4H, m), 1.19-1.35 (3H, m), 1.14 (3H, s, tert-CH₃); 13C NMR (75 MHz, CDCl₃) : Peaks due to major isomer : δ 74.8 (CH-OH), 52.1, 38.2 (C-6), 34.6, 31.5, 29.7, 29.4, 19.2, 18.6, 17.5. Peaks due to minor isomer : 73.4, 57.5, 37.3, 35.7, 32.5, 30.8, 27.1, 19.4, 19.1, 15.6. Mass : m/z 151 (M⁻-1, 9%), 134 (44), 119 (39), 95.
To a magnetically stirred solution of the tricyclic alcohol 8 (50 mg, 0.33 mmol) in CH₂Cl₂ (1 ml) was added pyridine (0.13 ml, 1.60 mmol) and methanesulfonyl chloride (0.028 ml, 0.36 mmol) and the reaction mixture was stirred at room temperature for 7 h. The reaction mixture was diluted with methylene chloride, washed with dilute HCl followed by brine and dried (Na₂SO₄). Evaporation of the solvent and purification of the residue over a silica gel column using ethyl acetate-hexane (1:10) as eluent furnished the bicyclic methanesulfonate 17 (54 mg, 72%).

IR (neat): \( \nu_{\text{max}} \) 3020, 2940, 1560, 1450, 1350, 1170, 945, 925, 980 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl₃): \( \delta \) 5.77 (1H, t of d, \( J = 9.9 \) and 3.3 Hz) and 5.45-5.55 (1H, m) [\( \text{CH} = \text{CH} \)], 4.7 (1H, d, \( J = 3.9 \) Hz, CHOMs), 3.04 (3H, s, SO₂CH₃), 2.75-2.80 (1H, m), 2.18 and 2.10 (2H, t of AB q, \( J = 18.3 \) and 2.0 Hz), 1.50-1.90 (6H, m), 1.01 (3H, s, tert-CH₃); \(^{13}\)C NMR (75 MHz, CDCl₃): \( \delta \) 128.7 and 126.7 (HC=CH), 86.3 (CHOMs), 41.4, 38.5, 36.2, 34.8, 33.7 (C-5), 28.1, 22.0, 17.5.

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