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A NOVEL ROUTE TO OPTICALLY ACTIVE DIHYDROPYRANS AND 3-METHYLENETETRAHYDROFURANS

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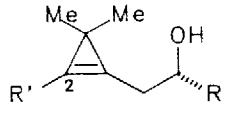
Reaction of 2-(cycloprop-1-en-1-yl)ethanol derivatives with bromine, acid or silver ion generally leads to ring expansion, either to 5,6-dihydro-2H-pyrans or to 3-methylenetetrahydrofurans.

2-(Cycloprop-2-en-1-yl)ethanol derivatives undergo thermal, photochemical or metal induced rearrangement to dihydropyrans.[1] Related 2-(cycloprop-1-en-1-yl)ethanol derivatives are reported to add bromine rapidly, although the product(s) were not discussed.[2] We now report that this reaction leads from cyclopropenes (1) and (7) to monobromo-dihydropyrans or to (bromomethylene)tetrahydrofurans, that the cyclisation can also occur on reaction with acid or with silver ion, and that these reactions can be used to produce optically active heterocycles.

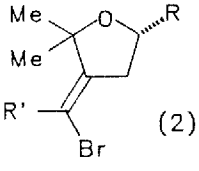
The 2-(cycloprop-1-en-1-yl)ethanol derivatives were prepared by reaction of the corresponding 1-lithiocyclopropene[3] with an oxirane for 3 - 4 h at 20 °C. Reaction of (1a) with bromine in dichloromethane for 30m at -40 °C gave (2a) (83%).[4] Reduction with lithium - t-butanol - THF led to (3, R = H), which was also obtained when (1a) was treated with either catalytic p-toluene sulphonic acid or silver trifluoromethanesulphonate in benzene for 12h at 20 °C (61, 47% respectively).[5]



(1)

Br_2, CH_2Cl_2
-40 to -50 °C

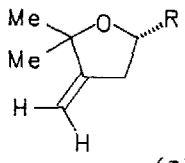
(a) R = R' = H
(b) R = Me, R' = H
(c) R = H, R' = $SiMe_3$



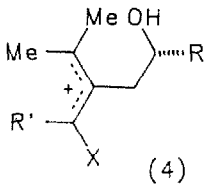
(2)

The E-stereochemistry about the double bond in (2a) was established by an n.O.e. study, which showed an enhancement in the alkene signal at δ 5.96 upon irradiation of the signal for the methyl groups. The racemic alcohol (1b) underwent similar cyclisations, leading to (2b) (67%) and (3, R = Me) (52%)[6] respectively on treatment with bromine in dichloromethane for 30m at -50 °C or with p-TsOH in benzene for 15h at 20 °C. In the same way the optically pure alcohol (1b), derived from R-(+)-methyloxirane,[7] led to optically active (2b).[8] Although there are a number of reports of acid and electrophile induced ring-opening of cyclopropenes to allylic systems,[9] few have examined the mechanism in detail. In general, it is assumed that addition to the π-bond occurs and that the resulting cyclopropyl cation ring-opens to an allyl cation, although the possibility of σ-attack was recognised at an early stage.[9b] Thus the products (2a),

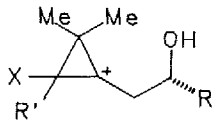
(2b) and (3) are formally derived by addition of H^+ or Br^+ to the cyclopropene to generate the cations (4, R = H, Me; R' = H; X = H, Br) either directly or through the cations (5),[9] and cyclisation at the dialkyl-substituted terminus.



(3)

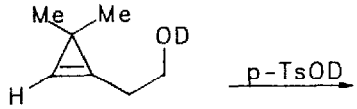


(4)

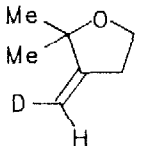


(5)

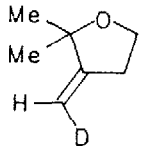
In the case of the bromination, a mole of HBr is apparently generated during the course of the reaction, but no products of protonation were observed; this may simply reflect the much greater rate of the bromination reaction. If the cation (5) were to be involved, the stereochemistry of (2a) would presumably reflect the preference for outward disrotation of bromine in the cyclopropyl - allyl ring opening, and electrophilic addition to cyclopropenes might provide a valuable probe of this process in the absence of the directing effect of the leaving group seen in solvolysis.[10] However, an examination of the acid induced cyclisation of (1a) using a D-label shows that the mechanism is probably more subtle; the results are summarised below:



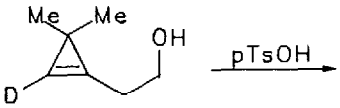
p-TsOD



2.7



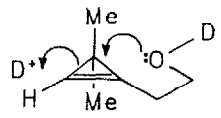
1



pTsOH

1

2.7

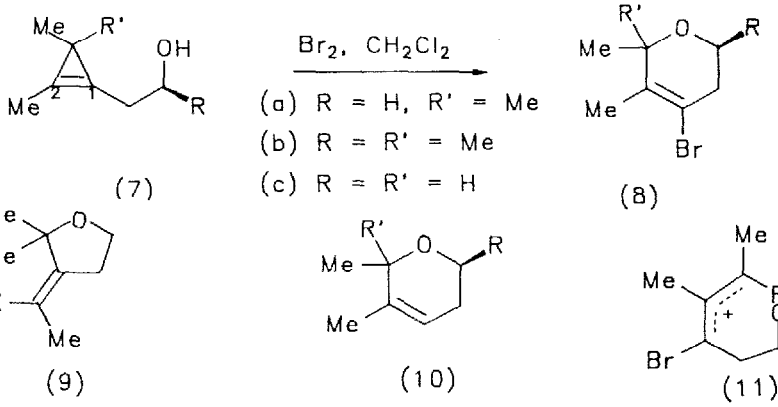


(6)

The isomer ratios, determined by deuterium n.m.r.,[5b] cannot be explained in terms of a planar cyclopropyl cation; it is not yet clear whether the results are best explained by π-attack concerted with ring-opening, by σ-attack predominantly from the side of the C_2-C_3 bond, or by a mixed mechanism. It is interesting to note, however, that the molecule is well arranged for σ-attack concerted with cyclisation as in (6).[11]

The cyclopropene (1c) underwent a similar cyclisation to produce (2c);[12] a minor product, the alkene (2a), was also obtained when (2c) was treated with hydrogen bromide in acetic acid, and is probably produced by reaction with acid generated during the bromination of (1c). The regiochemistry of (2c) may be explained by electrophilic attack of bromine at C-2 of (1c) leading to the development of positive charge β- to silicon. The origin of the E-stereochemistry is not clear; it is worth noting, however, that treatment of (1c) with p-toluene sulphonic acid as above leads to a 2:1 mixture of Z- and E-3-(trimethylsilylmethylene)- 2,2-dimethyltetrahydrofurans.

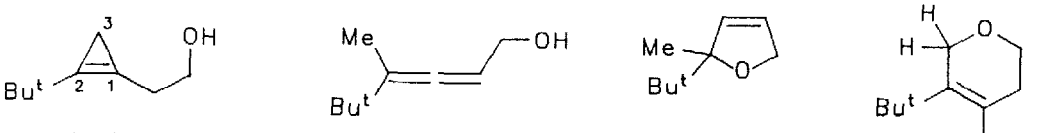
The introduction of a methyl group at C-2 of the cyclopropene caused an alternative cyclisation. Treatment of (7a) with bromine in CH_2Cl_2 led predominantly to the pyran (8a):



(7) (8) (9) (10) (11)

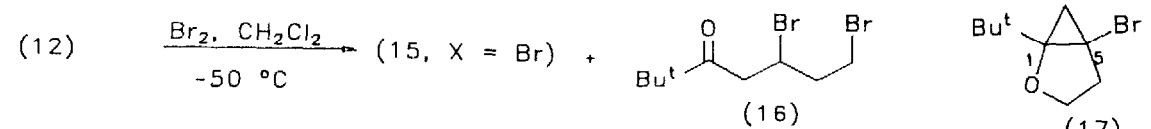
A minor product was (9, X = Br)[13] (ratio ca 1:6). Reduction with Li – t-BuOH – THF led to (10, R = H, R' = Me) and (9, X = H); the alkene hydrogen signal for (10, R = H, R' = Me) was a very broad multiplet ($W_{1/2}$ ca. 7 Hz), whereas that for (9, X = H) was a quartet of triplets, with a quartet coupling of 7 Hz. Once again, the optically pure alcohol (7b), in this case derived from S-(-)-methyloxirane, was converted to an optically active pyran (8b),[14] while the 2,3-dimethylcyclopropene (7c) gave only the pyran (8c).[15,16] The reason that bromine apparently adds only or largely to C-1 of the π-bond in (7) is not clear; however, related cyclopropene ring openings show subtle substituent effects.[17] It is not clear whether the cation (11), if it is an intermediate, is formed exclusively with the geometry required for cyclisation, or whether an isomerisation occurs.

Reaction of the alcohol (12) with p-toluene sulphonic acid in benzene led to three products:



(12) (13) (14) (15) X

The allene (13) (35%)[18] may arise by protonation of (12) at the methylene-end of the 1,3-bond with subsequent or concurrent elimination of a proton from the vinylic methylene group. The dihydrofuran (14) (10%) may arise by acid induced ring closure of (13),[19] while (15, X = H) (18%), is apparently derived by protonation at the less hindered end of the π-bond, ring opening and cyclisation. The reaction of (12) with bromine followed a different course. The minor product was the pyran (15, X = Br) (18%); the major product was the ketone (16) (61%).[20] The origin of this is not certain. Addition of Br^+ to the less hindered end of the π-bond followed by intramolecular trapping by the alcohol could lead to (17). Protonation of the 1,5-bond at C-5 by the acid generated and cleavage of the α-oxycation by bromide at C-3 could in turn lead to (16).



(16) (17)

We wish to thank the Government of Iraq for the Award of a grant to J.A-D.

1. A.Padwa, T.J.Blacklock and R.Loza, *J.Org.Chem.*, 1982, *47*, 3712; A.Padwa and T.J.Blacklock,

J.Amer.Chem.Soc., 1977, *99*, 2345.

2. A.J.Schipperijn and P.Smael, *Rec.Trav.Chim.Pays Bas*, 1971, *90*, 1298.
3. Prepared in situ by treatment of a 1,1,2-trihalocyclopropane with 2 mol.equiv. of MeLi in ether (M.S.Baird, H.H.Hussain and W.Nethercott, *J.Chem.Soc.PerkinTrans.I*, 1986, 1845).
4. This showed δ_H 5.96 (1H, t, J 2.7 Hz), 3.95 (2H, t, J 7.0 Hz), 2.69 (2H, dt, J 2.7, 7.0 Hz), 1.31 (6H, s); δ_C 153.5s, 97.5d, 82.3s, 63.9t, 34.0t, 27.3q.
5. (a) Compound (3, X = H) showed δ_H 4.92 (1H, t, J 2.1 Hz), 4.80 (1H, t, J 2.3 Hz), 3.85 (2H, t, J 7.0 Hz), 2.64 (2H, tt, J 2.2, 6.9 Hz), 1.29 (6H, s); δ_C 156.5s, 103.6t, 81.3s, 64.4t, 33.3t, 27.7q; ν_{max} 1649 cm^{-1};(b) irradiation of the signal at δ 1.29 caused an n.O.e. enhancement only in the alkene signal at δ 4.80.
6. This showed δ_H 4.86 (1H, dd, J 1.6, 2.5 Hz), 4.76 (1H, dd, J 1.7, 2.8 Hz), 4.05 (1H, m), 2.66 (1H, ddt, J 1.6, 5.5, 15.5 Hz), 2.26 (1H, ddt, J 2.8, 9.6, 15.5 Hz), 1.33 (3H, s), 1.28 (3H, d, J 5.9 Hz), 1.27 (3H, s).
7. M.K.Ellis and B.T.Golding, *Org.Synthesis, 63*, 140.
8. This showed δ_H 5.92 (1H, dd, J 2.1, 3.1 Hz), 4.16 (1H, m), 2.82 (1H, ddd, J 2.1, 5.8, 16.8 Hz), 2.22 (1H, ddd, J 3.1, 9.4, 16.8 Hz), 1.36 (3H, s), 1.31 (3H, d, J 6 Hz), 1.28 (3H, s); δ_C 154.6s, 97.2d, 82.7s, 71.4d, 41.7t, 28.9q, 27.4q, 21.1q; ν_{max} 1648 cm^{-1}; $[\alpha]_D^{25}$ -23.63 °.
9. See eg., B.Halton and M.G.Banwell, Cyclopropenes, in The Chemistry of the Cyclopropyl Group, Vol.2, Wiley, 1988; (b) G.L.Closs, Cyclopropenes, in Alicyclic Chemistry, Vol.1, 1966.
10. E.C.Friedrich, Chapter 11, Chemistry of the Cyclopropyl Group, Vol.1, Wiley, 1988.
11. Addition of DCl-AcOD to 1-methylcyclopropene is reported to give Z-3-deuterio-2-methylpropenyl derivatives (V.R.Kartashov, P.S.Afanas'ev, E.V.Skorobogatova, V.A.Chertkov, V.N.Ermolaeva, N.M.Sergeev and N.S.Zefirov, *Zh.Org.Khim.*, 1986, *22*, 868).
12. The stereochemistry of (2c) was established as E- on the basis of an n.O.e. enhancement in the signal for the methyl groups on irradiation of the signal for the trimethylsilyl-group.
13. The stereochemistry of (9, X = Br) is not yet certain.
14. Compound (8b) showed δ_H 3.94 (1H, complex m), 2.28 - 2.55 (2H, complex), 1.79 (3H, dd, J 1.5, 2.4 Hz), 1.32 (3H, s), 1.30 (3H, s), 1.19(3H, d, J 6.1 Hz); δ_C 137.5s, 116.4s, 77.0s, 65.3d, 44.2t, 28.3q, 24.5q, 21.3q, 18.9q; $[\alpha]_D$ = +115 °.
15. This showed δ_H 4.18 (1H, br.q, J 6.6 Hz), 3.96 (1H, dddd, J 0.4, 3.9, 5.4, 11.2 Hz), 3.68 (1H, ddd, J 11.2, 8.3, 4.3 Hz), 2.66 (1H, v.complex d, J 14.0 Hz), 2.44 (1H, v.complex d, J 14.0 Hz), 1.75 (3H, ddd, 0.95, 1.7, 2.2 Hz), 1.28 (3H, d, J 6.6 Hz).
16. Reaction (8, R = Me, R' = H) with bromine as above led to a 1:2 mixture of *cis*- and *trans*-2,6-dimethyl-4-bromo-5,6-dihydro[2H]pyrans.
17. T.Itoh and C.Djerassi, *J.Amer.Chem.Soc.*, 1983, *105*, 4407.
18. This showed δ_H 5.25 (1H, m), 4.03 (2H, d, J 6 Hz), 1.70 (3H, d, J 2.5 Hz), 1.45 (1H, br.s), 1.03 (9H, s); ν_{max} 1960, 3347 cm^{-1}.
19. (a) L.-I.Olsson and A.Claesson, *Synthesis*, 1979, 743; (b) J.Delaunay, A.Lebouc and O.Riobe, *Bull.Soc.Chim.France*, 1979, 547.
20. This showed δ_H 3.65 (1H, br.pent, J ca.6.3 Hz), 3.55 (1H, dd, J 7.0, 9.9 Hz), 3.42 (1H, br.dt, J 10.4, 6.8 Hz), 3.31 (2H, m), 2.23 (1H, dq, J 14.7, 7.0 Hz), 2.06 (1H, dq, J 14.7, 6.8 Hz); δ_C 214.7s, 46.3d, 44.8s, 34.8t, 31.7t, 30.1t, 26.4q; ν_{max} 1703 cm^{-1}.

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