Metal(IV) phosphate catalysed retro-Prins reaction involving an oxetane intermediate

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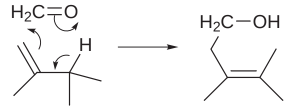
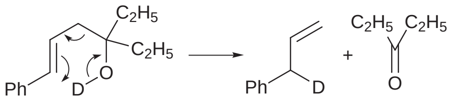
Dehydration of 1,3-diols over metal(IV) phosphate catalysts has given retro-Prins reactions.

Introduction

The Prins reaction of an alkene with an aldehyde to yield a β-hydroxyalkene provides a mechanistic conundrum.[1] The uncatalysed reaction (1) is believed to proceed through an 'ene' mechanism,[2] but various substrates undergoing acid-catalysed Prins reactions have been reported to proceed through a carbocation,[3] through a mechanism not involving a carbocation,[4] and through the formation of an oxetane intermediate,[5] as well as an ene reaction.[6] The retro-Prins reaction has proved useful synthetically,[7] but it is known only as a thermal elimination. One mechanistic study has shown clearly that the thermal retro-Prins elimination can proceed through an uncatalysed concerted reaction with hydrogen transfer [reaction (2).][8] In the present work, the discovery of a metal(IV) phosphate catalysed retro-Prins reaction is reported, which appears to proceed *via* a Lewis acid promoted mechanism on the surface of the heterogeneous catalyst.



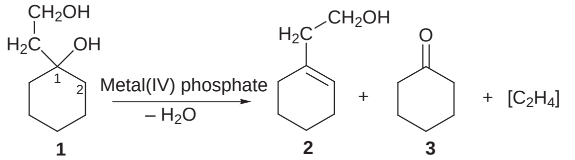
(1)



(2)

Results and discussion

When 1-(2-hydroxyethyl)cyclohexanol **1**[9] is refluxed over zirconium phosphate for 15 minutes, a highly selective retro-Prins reaction (3) occurs to produce an 11% yield[10] of cyclohexanone **3** plus 88% of 1-(2′-hydroxyethyl)cyclohexene **2** (Table 1). With tin(IV) phosphate as catalyst, a similar reaction time yields 18% of cyclohexanone with 80% of alkenol **2**. Using a smaller ring compound, 1-(2-hydroxyethyl)cyclopentanol **4**,[9] again with tin(IV) phosphate as catalyst, a 78% yield of cyclopentanone was obtained, together with 22% of alkenol **5** [reaction (4)]. On refluxing the diol **4** with phosphoric acid for 15 minutes, a 32% conversion into cyclopentanone was observed, with no other products being identified.

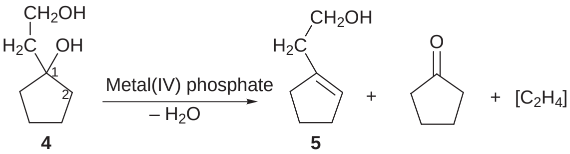


(3)

Table 1 Compositions of reaction mixtures after refluxing the indicated diols with different catalysts for 15 minutes

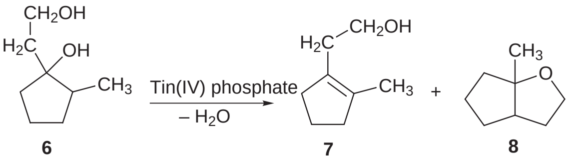
Diol[a]	Catalyst[b]	Percentage conversion	Yield[c] (%)	
			alkenol[d]	ketone[e]
1	ZrP	65	88 (**2**)	11 (**H**)
1	SnP	70	80 (**2**)	18 (**H**)
4	H_3PO_4	82	none	32 (**P**)
4	ZrP	37	89 (**5**)	10 (**P**)
4	SnP	30	22 (**5**)	78 (**P**)
6[f]	SnP	10	3 (**7**)	none[g]

[a] Diol structures are shown in the text. [b] ZrP = zirconium(IV) phosphate, SnP = tin(IV) phosphate. [c] The percentage yield is based on the amount of material converted to products in the standard 15 minute reaction time. [d] The structure of the isolated alkenol is shown in parentheses after each yield. [e] **H** = cyclohexanone; **P** = cyclopentanone. [f] One component amounting to 13% was identified only by mass spectrometry as the diene, 1-ethenyl-2-methylcyclopentene. [g] The yield of cyclic ether **8** in this experiment was 64%.



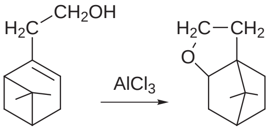
(4)

The results suggested that reactions (3,4) might be proceeding through an oxetane, possibly *via* a carbocation formed at position 1 of either structure **1** or **4**. Therefore, an alternative ring closure onto position 2, which should give a stable product, was provided by refluxing 1-(2-hydroxymethyl)-2-methylcyclopentanol **6** with tin(IV) phosphate for 15 minutes; it was expected that a carbocation might be produced at either position 1 or 2. Only 3% of the dehydration product **7** was found, the major component being 6*a*-methylperhydrocyclopenta[*b*]furan **8**, formed in 64% yield [reaction (5)]. No product of a retro-Prins reaction (2-methylcyclopentanone) was observed.



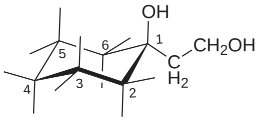
(5)

It is possible that the cyclohexanone or cyclopentanone respectively could have been formed from alkenol **2** or **5** following an initial dehydration step over the phosphate catalyst. Accordingly, a sample of alkenol **2** was prepared independently through a Prins reaction of paraformaldehyde with methylenecyclohexane. When compound **2** was refluxed with zirconium phosphate for 15 minutes under the same conditions as for the *retro*-reaction (3), no trace of cyclohexanone was formed and the starting material was recovered unchanged. To examine the possibility that reaction (4) could be forced to proceed *via* alkenol **2**, the latter was reacted with the much stronger Lewis acid, $AlCl_3$, in dichloromethane for 30 minutes at room temperature. Reaction took place but only produced a complex mixture of products, none of which was cyclohexanone. Because it might be deemed uncertain that a carbocation had indeed been generated by the action of $AlCl_3$ on alkenol **2**, it was decided to check for its formation by carrying out the same reaction with nopol **9**, an analogous alkenol that is known to be sensitive to acid.[1] It was hoped that nopol would undergo a more selective rearrangement. In fact, when refluxed with phosphate catalysts for 15 minutes, no change at all was observed in nopol but with the stronger Lewis acid, $AlCl_3$, in dichloromethane at room temperature a cyclic ether [**10**; reaction (6)] was formed, characteristic of expansion of the pinene ring proceeding through a carbocation process. The tetrahydrofuran **10** has also been found as a product of acid-catalysed reaction of paraformaldehyde with camphene.[11] No product of retro-Prins reaction, nopinnone, was found. Thus, both nopol **9** and alkenol **2** can clearly generate carbocations but these do not undergo a retro-Prins reaction. It is reasonable to suggest that the diols **1** and **4** do not react with zirconium or tin phosphate through a carbocation mechanism. There appear to be alternative pathways.[12] If the side-chain in **1** or **4** can cyclise to a tertiary carbocation centre after a hydride shift so as to form a five-membered ring cyclic ether, then it does so. When a hydride shift would produce only a secondary carbocationic centre, then cyclisation through an oxetane is preferred and the latter decomposes to give the retro-Prins products of cyclohexanone or cyclopentanone.



9 **10** (6)

Cyclisation of an equatorial side-chain to form an oxetane is hindered by axial hydrogen atoms at C-2 and C-6 in the cyclohexyl material **11**. If the side-chain is considered to cyclise from an axial position there will be a lesser inhibition from hydrogens on C-3 and C-5. Therefore, any cyclisation reaction to form an oxetane from the diol **1** will be impeded, whether it proceeds through a formal carbocation or *via* an intramolecular displacement process. With nopol, the bridging groups severely inhibit oxetane formation. In the case of the cyclopentyl system, the steric effects are greatly reduced (structure **12**) and oxetane formation to C-1 is more favourable. Calculation of the energies of intermediates and transition states confirm these deductions.[13] In proceeding from the tertiary carbocation **13** to produce the oxetane **14**, there is a small increase in enthalpy of formation of 0.6 kcal mol^{-1}; the transition state has similar energy to the enthalpies of formation of both **13** and **14**, suggesting a very easy shift of the side-chain with subsequent decomposition to the retro-Prins product (cyclopentanone). In contrast, for the cyclohexyl carbocation **15**, formation of the oxetane **16** is accompanied by an increase in the enthalpy of formation of 10 kcal mol^{-1} and a transition state energy barrier of about 50 kcal mol^{-1}, *viz*. the process of oxetane formation is not favourable and presumably explains the lower yields observed for the retro-Prins reaction.



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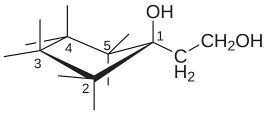

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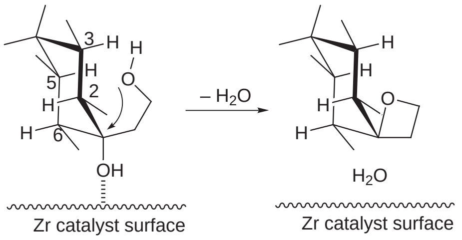

Fig. 1

13 **14** **15** **16**

The calculated enthalpies and transition state energies make it surprising that oxetane formation occurs at all when dehydrating the cyclohexyl diol **1** over metal(IV) phosphates. However, it has been shown recently that the gas phase dehydration of tertiary alcohols proceeds through synchronous removal of OH and a neighbouring H atom rather than through a formal carbocation mechanism.[12] Bonding of the primary alcohol in **1** to the catalyst surface would presumably inhibit its cyclisation but similar bonding of the tertiary hydroxy group would allow the side-chain to cyclise from a more favourable equatorial orientation, displacing the bound tertiary hydroxy group at the same time (Fig. 1). The diol **4** would be expected to react similarly. The presence of a methyl group at C-2 in compound **6** should assist displacement of the hydroxy group by a synchronous shift of a hydride so as to leave a tertiary carbocation centre ready to form a five-membered ring ether rather than an oxetane. Thus, the observation of a retro-Prins reaction of the cyclohexyl and cyclopentyl series appears to depend critically on (a) the ease of oxetane formation and its subsequent decomposition, (b) the lack of a formal carbocation centre during dehydration with the metal(IV) phosphates and, (c) on the lack of a suitably favourable 1,2-hydride shift to produce a tertiary carbocationic centre that favours five-membered ring ether formation.

Experimental

Preparation of metal(IV) phosphates

Amorphous zirconium phosphate and tin phosphate catalysts were prepared by published methods.[14,15] After washing the phosphates well with water and separating them by centrifugation, they were dried in an oven at 100 °C at atmospheric pressure for 18 h.

Preparation of diols

The diols **1** and **4** were prepared by published methods and had similar properties to those reported.[9]

Preparation of 6a-methylperhydrocyclopenta[*b*]furan 8

A sample of this material was supplied by Dr G. Carr, having been prepared[9] by cyclisation of the diol **6** in fluorosulfuric acid. It was characterised through its mass spectrum: *m*/*z* 126 ([M^+], 34%), 95 (87), 93 (100), 81 (52), 79 (83), 67 (59).

Preparation of 1-(2-hydroxyethyl)cyclohexene 2

This was prepared by a published method[1] and was purified by chromatography over alumina (Aldrich, Brockman Grade 1 -

weakly acidic), using a mixture of petroleum ether (40–60 °C) and dichloromethane (30:70 v/v) as eluant. The sample was similar to that reported more fully in a later reported preparation.[16] It was further characterised through its mass spectrum: *m*/*z* 126 ([M$^+$], 6%), 95 (27), 81 (32), 79 (100), 67 (46), 41 (42).

Identification of products of reaction

Comparison with standard samples was used for all except two products. (i) A sample of 1-hydroxyethylcyclopentene **5** was obtained by dehydration of compound **4** over zirconium phosphate exchanged with copper acetate,[17] which gave the hydroxyalkene **5** in 85% yield after distillation:[16] *m*/*z* 112 ([M$^+$]); δ_H ($CDCl_3$) 1.8–2.0 (4H, m), 2.2–2.4 (4H, m), 3.7 (2H, t, *J* 6.4 Hz), 5.48 (1H). (ii) 2-Methyl-1-hydroxyethylcyclopentene **7** was identified through its mass spectrum: *m*/*z* 126 ([M$^+$], 42%), 108 (3), 95 (100), 93 (49), 81 (19), 80 (10), 79 (45), 77 (16), 67 (40), 55 (10), 39 (12).

Reactions

In a typical experiment, 1-(2-hydroxyethyl)cyclopentenol (**4**; 5.5 mmol), n-dodecane (internal standard; 3.4 mmol) and zirconium phosphate (0.135 g) were refluxed in air for 15 min at 305 °C. On cooling, a sample of the reaction mixture was removed by pipette, filtered and analysed on a Dani 3800 gas chromatograph using a 25 m × 0.25 mm (id) capillary OV1 column connected to a VG 7070E mass spectrometer operating in electron ionization mode at 70 V. Product yields were calculated from the internal standard peak after calibration against authentic materials, with the exception of compound **7** (see above).

Acknowledgements

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References

1 D. R. Adams and S. P. Bhatnagar, *Synthesis*, 1977, 661.
2 H. M. R. Hofmann, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 556.
3 K. B. Schowen, E. E. Smissman and R. L. Schowen, *J. Org. Chem.*, 1968, **33**, 1873.
4 H. Kwart and M. W. Brechbiel, *J. Org. Chem.*, 1982, **47**, 3353 and 5409.
5 J. P. Bain, *J. Am. Chem. Soc.*, 1946, **68**, 638.
6 O. Meresz, K. P. Leung and A. S. Denes, *Tetrahedron Lett.*, 1972, 2797.
7 K. H. Schulte-Elte and H. Pamingle, *Helv. Chim. Acta*, 1989, **72**, 1158.
8 R. T. Arnold and G. Smolinsky, *J. Org. Chem.*, 1960, **25**, 129; *J. Am. Chem. Soc.*, 1960, **82**, 4918.
9 G. Carr and D. Whittaker, *J. Chem. Soc., Perkin Trans. 2*, 1989, 359.
10 'Yield' refers to the percentage of each product in the reaction mixture after 15 minutes and allowing for the percentage conversion of starting material.
11 E. A. Kobzar, D. V. Korchagina, N. F. Salakhutdinov, K. G. Ione and V. A. Barkhash, *Zh. Org. Khim.*, 1992, **28**, 1309; *Chem. Abstr.*, 1993, **118**, 192023j.
12 R. A. W. Johnstone, J.-Y. Liu and D. Whittaker, personal communication.
13 J. J. P. Stewart, MOPAC 6.00, QCPE No. 455; supplied by CACHe WorksSystem, ver. 3.0, Oxford Molecular, Oxford Science Park, Oxford, UK OX4 4GA.
14 A. Clearfield and S. P. Pack, *J. Inorg. Nucl. Chem.*, 1975, **37**, 1283.
15 A. Clearfield and J. A. Stynes, *J. Inorg. Nucl. Chem.*, 1964, **26**, 559.
16 B. B. Snider, D. J. Rodini, T. C. Kirk and R. Cordova, *J. Am. Chem. Soc.*, 1982, **104**, 555.
17 M. C. Cruz Costa, R. A. W. Johnstone and D. Whittaker, *J. Mol. Catal. A*, 1996, **104**, 251.

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