The Cyclisation of Secondary Allenic Alcohols

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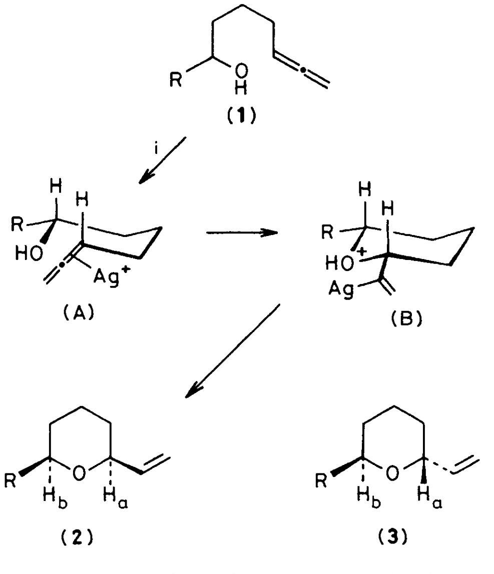
The silver-mediated cyclisation of secondary allenic alcohols is stereoselective giving predominantly *cis*-2,6-disubstituted tetrahydropyrans; this methodology has been applied to the synthesis of the civet constituent (**4**).

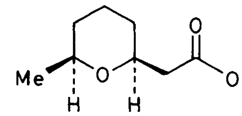
The development of new stereocontrolled approaches to substituted tetrahydropyrans and tetrahydrofurans is currently of interest, principally because these heterocyclic units are found in a wide range of biologically important natural products, *e.g.* polyether antibiotics.[1] One important route to these heterocycles involves the cyclisation between a hydroxy group or alkyl ether and an appropriately placed alkene, mediated by a suitable electrophile.[2] In principle an analogous reaction may be carried out using an allenic substrate to give an alkenyl substituted product as illustrated in Scheme 1. This process has recently been reported for a series of simple allenic alcohols (**1**, R=H) promoted by either silver(I) or mercury(II), to give monosubstituted tetrahydropyrans in good yield.[3] The distinct advantage of incorporating an allenic unit into this type of cyclisation is that the product, *i.e.* (**2**) or (**3**), retains a synthetically useful alkene residue. Thus, following the initial ring-forming reaction, the second π bond of the original allene may then be used for further elaboration.



Scheme 1. *Reagents and conditions*, i, $AgNO_3$ (1—2 equiv.), 40—50 °C, acetone–H_2O, 4—8 h.

As part of an investigation into the synthetic applications of allene chemistry we describe here a study of the stereoselectivity of the silver(I)-mediated cyclisation of hydroxyallenes (**1**, R≠H) to give 2,6-disubstituted tetrahydropyrans. In addition this methodology has been applied to the synthesis of (*cis*-6-methyltetrahydropyran-2-yl)acetic acid (**4**), a minor constituent of civet, the glandular secretion of *Viverra civetta*.[4]

The required hydroxyallenes (**1a—e**) are readily available from hepta-5,6-dien-1-ol[5] by oxidation to the corresponding aldehyde followed by treatment with the appropriate Grignard reagent.† Cyclisations of (**1a—e**) were carried out with silver nitrate (2 equiv.) in aqueous acetone (50 °C; 5 h) (Scheme 1) and the products were readily separated by flash chromatography.‡ The yields of the tetrahydropyran *cis*- and



(4)

Table 1

(1)	% Yield (2)	% Yield (3)
a; R = Me	71	4
b; R = $\mathrm{Bu^t}$	50	[a]
c; R = c-C_6H_{11}	90	7
d; R = Ph	90	3
e; R = CH=CH_2	50	[a]

[a] Traces of the presumed *trans*-isomer were observed (t.l.c.) but could not be isolated in pure form.

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† All new compounds gave satisfactory spectral data (i.r., ^1H and ^{13}C n.m.r.) and elemental analysis or high resolution mass measurement; yields refer to isolated material, homogenous by t.l.c.

‡ These reactions may be carried out with catalytic amounts of silver nitrate (0.1 equiv.) but reaction times are increased substantially (3 days). In any event the silver may be efficiently recovered.

trans-isomers are shown in Table 1. In all cases examined the major component was shown (*vide infra*) to be the *cis*-2,6-disubstituted tetrahydropyran, compounds (**2a—e**).[6] Although the formation of *cis*-(**2**) may be rationalised in terms of an intermediate chair conformation such as (A), it is not clear that the high selectivity observed is a function of kinetic control. It is possible that a reversible cyclisation step, followed by an irreversible protonation of the resulting silver complex (B) (to regenerate Ag^I), occurs to give *cis*-(**2**). In addition no isomerisation, *cis*-(**2**)$\rightleftharpoons$*trans*-(**3**), was observed under these conditions.

Assignment of the stereochemistry of the tetrahydropyran products is based upon ^{1}H n.m.r. evidence (difference nuclear Overhauser effect involving H_a and H_b). Only the *cis*-products (**2a—e**) showed, upon irradiation of H_a, an enhancement of H_b, which was of the order of 6%. For (**2e**) and (**3e**) confirmation of the stereochemical assignment was obtained by correlation with compounds of known configuration.[7]

An example of the utility of this cyclisation process is illustrated by the synthesis of the civet constituent (**4**). Hydroboration of (**3a**) followed by Jones oxidation gave (**4**) [m.p. 49—50 °C, 60% from (**3a**)] which was identical with previously synthesised material.§ This procedure also confirms the *cis*-stereochemistry of (**2a**).

These studies therefore complement and extend related routes to tetrahydropyrans, providing highly stereoselective access to usefully functionalised 2,6-disubstituted systems. Stereocontrolled approaches to other heterocycles involving allene chemistry and their subsequent use in synthesis are currently under investigation.

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§ We thank Professor S. V. Ley for this comparison.