Pergamon

Tetrahedron Letters 40 (1999) 5915–5918

TETRAHEDRON LETTERS

Activation of the Reverse-Cope Elimination by Allylic Oxygen Functions: Syntheses of (-)-Hygroline and (+)-Pseudohygroline

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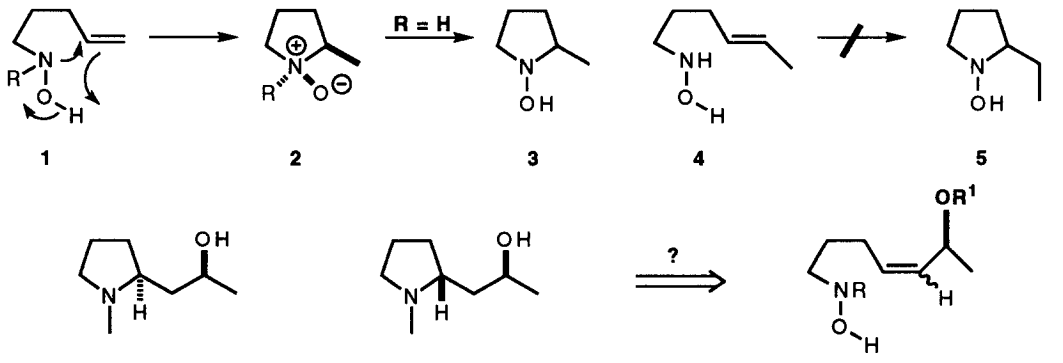
Received 30 April 1999; accepted 8 June 1999

Abstract:- *Reverse-Cope cyclisations of N-(4-alkenyl)hydroxylamines* ***8*** *are accelerated by the presence of the allylic oxygen function; this has been applied to a brief synthesis of the alkaloids (-)-hygroline* ***6*** *and (+)-pseudohygroline* ***7***

Keywords: Reverse-Cope; pyrrolidines; hydroxylamines; cyclisation.

In its simplest form, the reverse-Cope elimination, as the name suggests, is a thermal reaction in which an unsaturated hydroxylamine **1** undergoes cyclisation to give a cyclic *N*-oxide **2** and thence the corresponding hydroxylamine **3**, when R = H. The reaction was first discovered some twenty years ago;[1,2] more recently, many of its salient features have been defined by Ciganek[3] and excellent evidence has been provided that it is a concerted pericyclic process, related to the ene reaction.[4] The cyclisation is very sensitive to substitution effects, benefiting greatly from the Thorp-Ingold effect[3] but being slowed by the inclusion of substituents at the distal end of the participating alkene function. Indeed, early studies[5] revealed that inclusion of a methyl substituent was sufficient to suppress the cyclisation. Thus, although the simplest substrate [**1**; R = H] cyclises smoothly at 40°C,[2] the homologue **4** fails to give the pyrrolidine **5** but rather is eventually heated to destruction at around 120°C.[5] The reverse-Cope elimination is largely restricted to the formation of five-membered rings; thus far, piperidine formation is successful only with monosubstituted alkenes.[6,7]



1 **2** **3** **4** **5**

6; (-)-Hygroline **7; (+)-Pseudohygroline** **8**

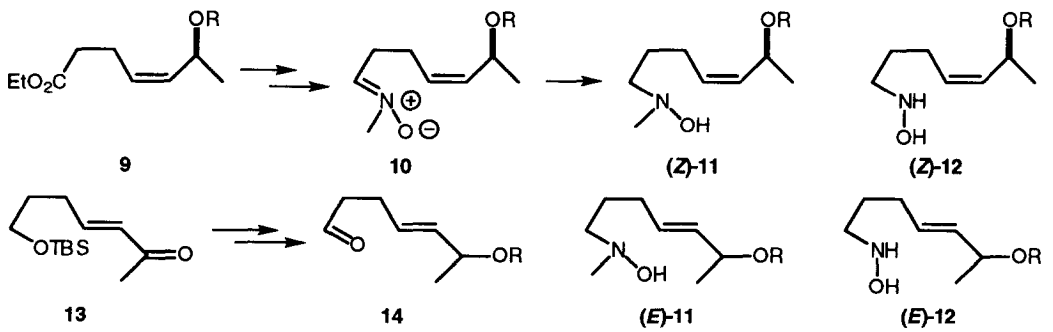
We were intrigued by the possibility that the stereochemistry of the cyclisation could be controlled by

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01131-4

functional groups adjacent to the alkene and reasoned that a suitable test of this idea would be in syntheses of the pyrrolidine hygroline **6** and the known diastereomer pseudohygroline **7**. The required precursors, hydroxylamines **8**, offered the opportunity for the inclusion of variations in both the alkene geometry and the allylic oxygen and hydroxylamine nitrogen substituents, which could promote or deter interaction by hydrogen bonding between these functions. However, in view of the reluctance of hydroxylamine **4** to undergo cyclisation,[5] we were uncertain at the outset if this approach was even viable. Herein, we report that it is, that some stereocontrol is achieved but, more significantly, that an activation effect has been uncovered.

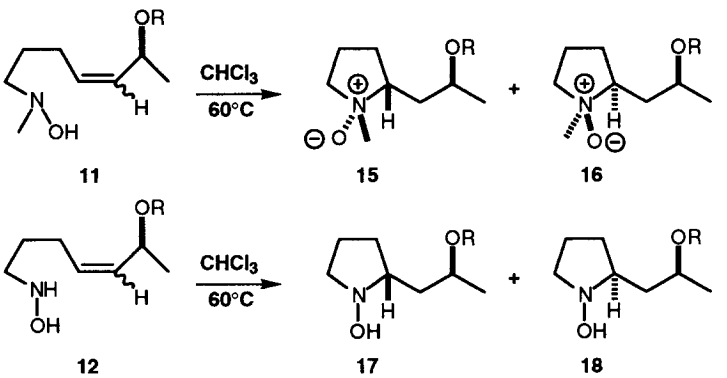
(-)-Hygroline **6** is the enantiomer of the naturally occurring compound; we chose to attempt the preparation of this enantiomer as the asymmetric carbon in precursors **8** is available from cheap (*S*)-lactic acid. (+)-Hygroline is a biosynthetic precursor to a range of homologous alkaloids and was first identified in *Erythoxylum coca*;[8] during this study, pseudohygroline **7** was first synthesized as part of the structural proof of hygroline. Isolated from other sources,[9] racemic hygroline was also synthesized in the early 1980s;[10] more recently, asymmetric approaches have been developed, based on [1,3]-dipolar cycloadditions between nitrones and either crotonates containing a chiral auxiliary[11] or homochiral vinyl sulphoxides[12] or on a 5-*exo* mercury-induced cyclisation of a suitable 4-alkenamide, in the case of (+)-pseudohygroline **7**.[13]

The (*Z*)-precursors [**(*Z*)-11**] were obtained from methyl (*S*)-lactate: introduction of the protecting groups 'R', followed by Dibal-H reduction [Et_2O, -78°C; ~85%] and Wittig reaction of the resulting lactaldehydes [$EtO_2C(CH_2)_3PPh_3Br$, $NaN(TMS)_2$, 0°C, THF; ~90%] to give the (*Z*)-alkenoates **9**. A second Dibal-H reduction [~ 90%] and reaction with MeNHOH.HCl [K_2CO_3, 20°C, CH_2Cl_2; ~quant.] then gave the nitrones **10**; reduction using sodium cyanoborohydride [pH 4, MeOH; ~quant.] gave the required alkenylhydroxyl-amines **(*Z*)-11**. Desilylation of **11c** [5% aq. HCl, MeOH, 20°C, 6h, 90%] gave the allylic alcohol **11b**. The primary hydroxylamines **(*Z*)-12** were obtained *via* the related oximes, again by cyanoborohydride reduction. The isomeric, racemic alkenylhydroxylamines [**(±)-(*E*)-11** and **(±)-(*E*)-12**] were obtained from 2-hydroxytetrahydrofuran: Wittig homologation [$Ph_3P{=}CHCOMe$, CH_2Cl_2, 40°C; 92%] and silylation [TBSCl, imidazole, THF; 72%] gave the enone **13**. Luche reduction , silylation, selective removal of the TBS group [AcOH, aq.THF; ~70%] and Swern oxidation then gave the aldehydes **14**. The hydroxylamines **(*E*)-11** and **(*E*)-12** were then obtained as above, *via* the corresponding nitrones and oximes respectively.



We were delighted to find that all these alkenylhydroxylamines underwent smooth and essentially quantitative reverse-Cope cyclisation upon heating in chloroform.[3] The *N*-methyl derivatives **(*Z*)-11** required

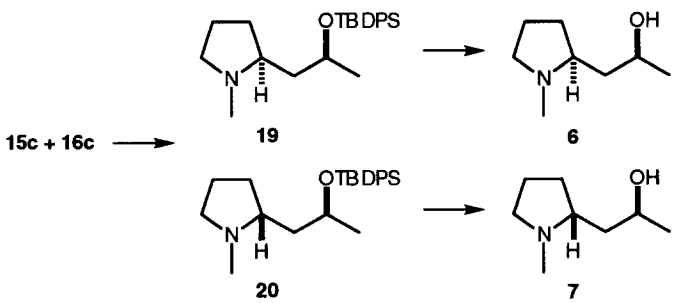
1-5h for complete conversion whereas the primary hydroxylamines **(*Z*)-12** reacted somewhat more slowly (6-8h). The cyclisations also occurred equally well but much more slowly at ambient temperature (times in parentheses). In view of the failure of hydroxylamine **4** to cyclize,[5] we reasoned that the adjacent oxygen group must be activating these cyclisations. It was therefore all the more curious to find relatively poor levels of stereoselection, as shown, which did not show great differences between the potentially strongly hydrogen-bonding functions (OH, OBn) and the correspondingly weak H-bonding function OTBDPS. Cyclisations of the corresponding (*E*)-isomers [**(*E*)-11** and **(*E*)-12**] were equally facile and essentially quantitative but, again, little stereoselection was observed, although the major isomers **16** and **18** were the minor obtained from the corresponding (*Z*)-isomers. Isomer ratios were determined by integration of ^{1}H NMR spectra and stereochemical assignments were made largely on the basis of the subsequent conversions into hygroline and pseudohygroline. It thus seems likely that the beneficial influence of the allylic oxygen functions is due to an electronic effect, rather than hydrogen bonding, which was expected to bring together the reacting centres.



FROM (*Z*)-11
a) R = Bn: <1.5h (60h); 2:1 (5:1);
b) R = H: <1h (48h); 1.8:1 (2:1);
c) R = TBDPS: 5h; 3:1;
FROM (*E*)-11
d) R = H: (18h); (1:2);
e) R = TBDPS: 3.5h; 1:2;
f) R = TIPS: 4h; 1:1.

FROM (*Z*)-12
a) R = Bn: 6h; 7:3;
b) R = TBDPS: 8h; 1:1;
FROM (*E*)-12
c) R = TBDPS: 3h; 1:2;

Completion of the (-)-hygroline **6** and (+)-pseudohygroline **7** syntheses was achieved by reduction of the mixed *N*-oxides **15c** and **16c** [H_2, 5%Pd-C, 20°C, EtOH; 99%], separation of the resulting pyrrolidines **19** and **20** [Silica; EtOAc:EtOH:Et_3N (90:9:1)] and desilylation [NH_4F, MeOH, 18h, 20°C; >70%] to give samples of the two isomers which exhibited spectral and analytical data identical to those previously reported (and see data associated with formulae).

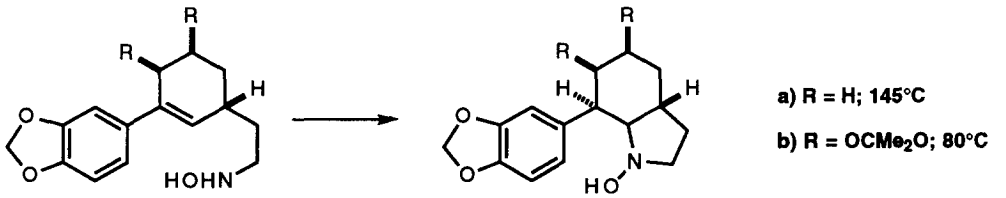


m.p. 29-31°C [lit.[11] m.p. 32.5-34.5°C]
$[\alpha]_D^{20}$ -50.2 (c 0.466, EtOH)
[lit.[11] $[\alpha]_D^{24}$ +50.7 (c 0.869, EtOH)]
[Lit. data for (+)-hygroline]

Oil [lit.[13] oil]
$[\alpha]_D^{20}$ +78.8 (c 0.939, EtOH)
[lit.[13] $[\alpha]_D^{20}$ +70. (c 2.0, EtOH)]

At this point, we realised that the rate enhancing effect of the allylic oxygens had, in effect, been previously observed. In their outstanding contribution to reverse-Cope chemistry,[4] during which excellent evidence was obtained which suggests it to be a genuine pericyclic process related to the ene reaction, the Oppolzer group applied the reaction to total syntheses of the alkaloids (-)-lycorane and (+)-trianthine. The

central reverse-Cope cyclisations of hydroxylamines **21** were found to proceed under significantly different conditions: the simpler substrate **21a** required prolonged thermolysis in refluxing xylene to effect cyclisation to the lycorane precursor **22a** whereas the related species **21b** containing an acetal function undergoes cyclisation in refluxing benzene. Although other factors may be involved, especially conformational ones, the presence of an allylic oxygen function could well be the source of this enhanced rate.



In summary, our results, together with those of of the Oppolzer group, suggest that an allylic oxygen function will be useful in providing significant rate enhancements in reverse-Cope cyclisations, in a manner which is seemingly rather insensitive to the nature of the oxygen substituents or their conformation. However, such a centre appears to have a poor capacity for influencing the stereochemical outcome of these cyclisations.

Acknowledgements

We are very grateful to Dr Patrick Perlmutter (Monash University) for providing spectral data of the final products, to the EPSRC Mass Spectrometry Service, Swansea University for the provision of high resolution Mass Spectral data and to the EPSRC for financial support (PDRA to RS).

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