Pergamon

Tetrahedron Letters 42 (2001) 2597–2600

TETRAHEDRON LETTERS

The synthesis of *N*-hydroxyisoindolines by reverse-Cope chemistry

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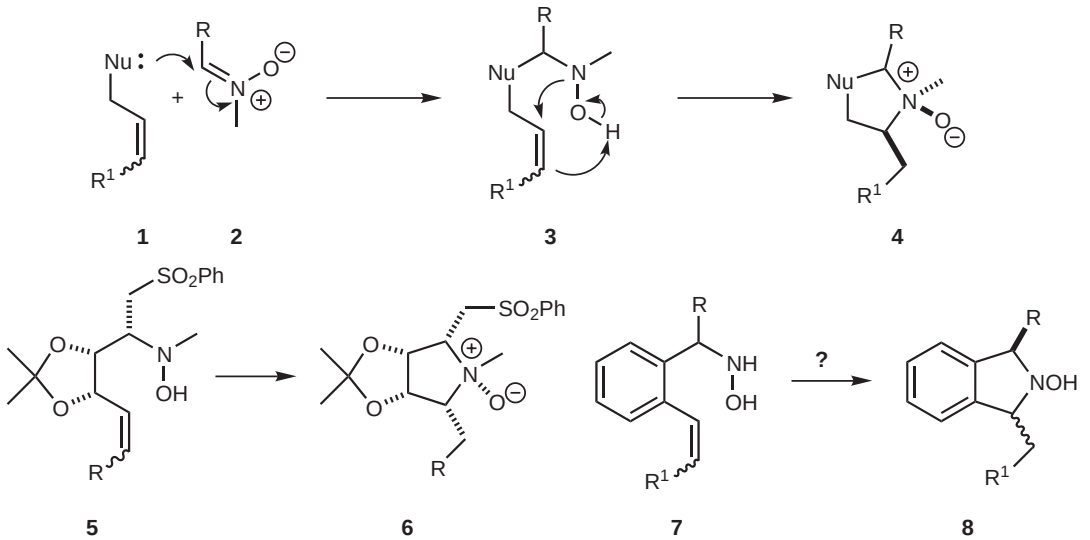
Received 23 October 2000; revised 26 January 2001; accepted 7 February 2001

Abstract—*N*-(2-Alkenylbenzyl)hydroxylamines undergo relatively facile reverse-Cope cyclisations to give good yields of *N*-hydroxyisoindolines.

During the past 10 years, the reverse- or retro-Cope cyclisation has been shown to be a useful method for the elaboration of a variety of saturated five-membered heterocycles,[1–3] having lain dormant in terms of any further development since its serendipitous discovery during the late 1970s.[4] Accumulated evidence[1,2,5] suggests these intramolecular cyclisations of *N*-alkenyl hydroxylamines are concerted processes belonging to the 2n+2o+2π family of 1,3-azaprotio cyclotransfer reactions (1,3-APT), as defined by Grigg.[6] Amongst our own contributions to this area are a series of examples wherein the required alkenyl hydroxylamines **3** are obtained by attack of a suitable nucleophile **1** onto a nitrone **2**; both secondary allylic amines,[7a] allylthiols[7b] and lithiated sulphones[7c] proved to be suitable nucleophilic partners.

Cyclisation to the final products **4** occurred at a variety of rates and, in line with previous observations,[1–3] was significantly slower when the alkene was disubstituted [i.e. **1**, **3**: $R^1 \neq H$]. Further, we found that *C*-arylnitrones [**2**; R = Ar] led to hydroxylamines **3** which were much less reactive towards cyclisation than the corresponding alkyl-substituted intermediates [**3**; R = alkyl].



1 2 3 4

5 6 7 8

Keywords: isoindolines; reverse-Cope; cyclisation; hydroxylamine; 1,3-APT.
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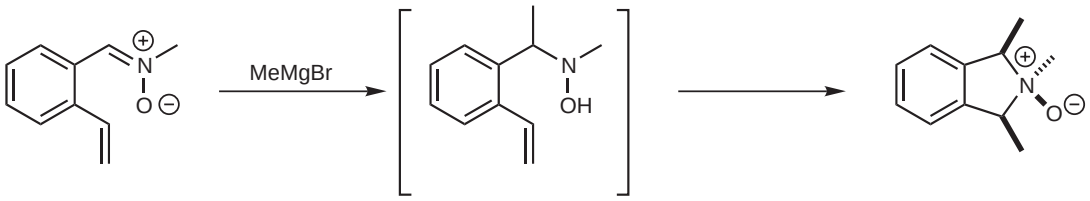
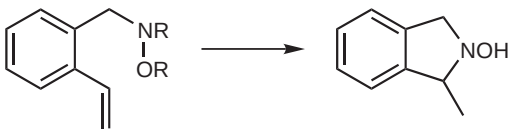
0040-4039/01/$ - see front matter
PII: S0040-4039(01)00237-4



9 **10** **11 (+ 10% *trans*)**



12 **13**

a) R = H: $CHCl_3$, 20°C, <14h, 100%;
b) R = $CO_2CH_2CH{:}CH_2$: $(Ph_3P)_4Pd$, dimedone, THF, 60°C, 2h, 71%;
c) R = $CO_2(CH_2)_2SiMe_3$: Bu_4NCl, KF, MeCN, 50°C, 12h, 70%;
d) R = $CO_2CH_2CCl_3$: Zn, EtOH, 80°C, 2h, ~30%.

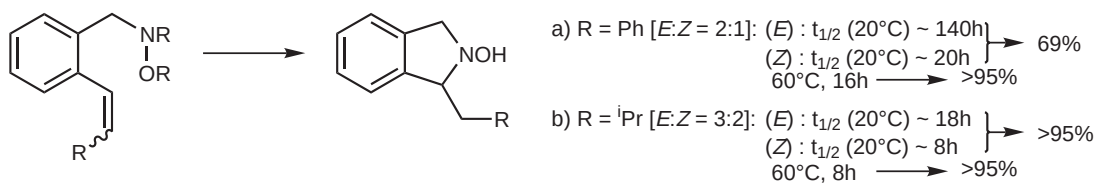
In contrast, and not unexpectedly for a cyclisation known to benefit greatly from the Thorpe–Ingold effect,[1] when the alkene and hydroxylamine functions were held as substituents on a dioxolane ring **5**, the reverse-Cope cyclisations were particularly facile, leading to the all-*cis*-pyrrolidines **6**.[8] The former deleterious effects of an aryl substituent appear to be due to electronic rather than steric factors,[7c] while the latter cyclisations may also benefit from the presence of an allylic oxygen.[9]

Against this background, we were interested to determine whether reverse-Cope cyclisations of the *ortho*-alkenylbenzyl hydroxylamines **7** could be used to prepare isoindolines **8**, as the two effects outlined above appeared to be in opposition. To the best of our knowledge, the only example of such a cyclisation was reported by Ciganek during his definitive study of the reverse-Cope cyclisation: when the nitrone **9** was treated with MeMgBr, the resulting hydroxylamine **10** underwent conversion to the isoindoline-*N*-oxide **11**, largely as the *cis*-isomer shown, in less than one hour at ambient temperature.[1] However, the product was reported to be unstable and no further examples were reported. The facility of this single cyclisation suggested that substituents might be successfully incorporated on the terminus of the alkene [i.e. $R^1 \neq H$], despite the rate retardation effect, and that primary hydroxylamines which, in general, are less reactive than the corresponding *N*,*N*-dialkyl derivatives [cf. **3**, **5**, **10**], might also cyclise under reasonably mild conditions. Herein, we report that such reverse-Cope cyclisations are indeed viable and quite general.

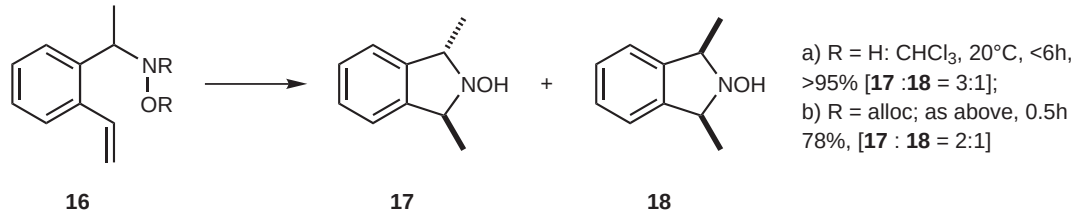
The simplest example **13**, available from reverse-Cope chemistry, was obtained from four separate precursors **12 a**–**d** and turned out to be a stable, crystalline solid, mp 112–113°C, although in solution it appeared to undergo facile aerial oxidation. The parent hydroxylamine **12a** was prepared by cyanoborohydride reduction of the corresponding oxime and underwent complete and essentially quantitative cyclisation in chloroform at ambient temperature in <14 h.

The three alternative precursors, **12b**–**d**, were all obtained from the corresponding alcohol by Mitsunobu reaction, as described in the foregoing paper.[10] Deprotection of each also delivered the isoindoline **13**, via hydroxylamine **12a**, in the overall yields shown. As each deprotection procedure necessitated heating, the reverse-Cope cyclisation was complete after this first step. Only in the case of the bis-Troc derivative **12d** was the yield poor, presumably because of partial N–O bond cleavage under these reducing conditions.

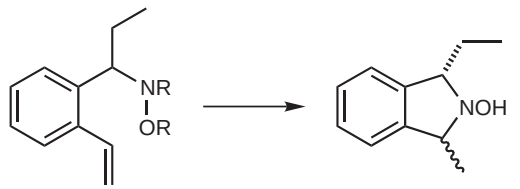
We were then delighted to find that distal alkene substituents could be successfully incorporated. Thus, both the phenyl and isopropyl derivatives **14a** and **14b**, obtained by oxime reduction, slowly cyclised to the *N*-hydroxyisoindolines **15** at ambient temperature; essentially quantitative yields were realised in gently refluxing chloroform. A notable feature of both cyclisa-



14 **15**

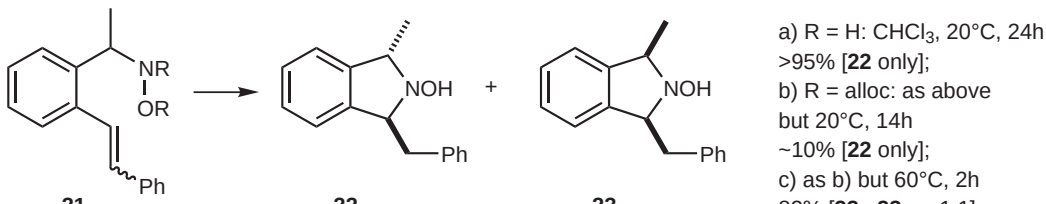


16 **17** **18**



19 **20**

tions was that the (*Z*)-isomers reacted faster than the corresponding (*E*)-isomers (^{1}H NMR monitoring). Possibly, this is because the alkene must twist out of conjugation to allow it to line up in parallel with the hydroxylamine function, seemingly a necessity for successful cyclisation.[5,8] This would require less energy in the case of an already slightly twisted (*Z*)-styrene function.



21 **22** **23**

As expected, reverse-Cope cyclisations in examples having a substituent at the benzylic position occurred somewhat more readily. Thus, the hydroxylamine **16a** derived by oxime reduction cyclised rapidly at 20°C to give a 3:1 mixture of the *trans*- and *cis*-dimethylisoindolines **17** and **18** in essentially quantitative yield; a similar 2:1 ratio was obtained even more rapidly at 60°C during deprotection of the Mitsunobu product **16b**.[10]Under similar conditions, but for 2 h, the bis-alloc derivative **19** was converted into a separable 1:1 mixture of the two possible products **20** in 79% isolated yield.[11]

The acceleration induced by a benzylic substituent was also evident when the stilbene derivative **21a** was kept in chloroform solution at 20°C: cyclisation was complete in 24 h to give only the *trans*-isomer **22**,[11] which was also obtained but in much poorer yield by partial deprotection of the Mitsunobu product **21b**. Deprotection at 60°C was complete in 2 h and gave the isoindolines **22** and **23** in the 1:1 ratio and an 82% isolated yield.

These examples serve to demonstrate that the reverse-Cope method is certainly useful for the synthesis of isoindolines and hence derivatives of these, especially isoindoles.[12] These observations also serve to emphasise the utility of the Mitsunobu methodology highlighted in the foregoing paper. In our hands, the oxime reductions used to obtain isolated hydroxylamines were especially capricious and exceptionally sensitive to small changes in the pH of the cyanoborohydride reaction mixture, particularly with aryl ketone derivatives. In these cases, the Mitsunobu approach was both more efficient and reliable. The origins of the lack of stereoselectivity in the cyclisations carried out at 60°C appear to reflect a relatively close similarity in the energies of the two conformations leading to such isomers. Calculations aimed at verifying this point are in progress, as are efforts to further extend this chemistry to the elaboration of enantiopure isoindolines and also of isoindoles.[13]

Acknowledgements

We thank the EPSRC Mass Spectrometry Service, UC Swansea for the provision of high resolution Mass Spectral data, Dr. David E. Hibbs for the X-ray determination of *cis*-**20** and the INTAS scheme and EPSRC for financial support.

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