Pergamon

Tetrahedron Letters 39 (1998) 5853–5856

TETRAHEDRON LETTERS

Radical Cyclisation from Alkenyl Oxaziridines

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Received 7 May 1998; accepted 1 June 1998

Abstract

Some 6-oxa-1-azabicyclo[3.1.0]hexanes have been prepared by photoisomerisation of alkenyl nitrone esters and peracid oxidation of pyrrolines Their ring-opening reactions with iron(II) sulfate, tri-*n*-butyl tin hydride and copper(I)triphenylphosphine chloride in many cases afford the related pyrrolines, but some *trans* oxaziridines give products derived from the trapping of aminyl radicals by the pendant alkenes.

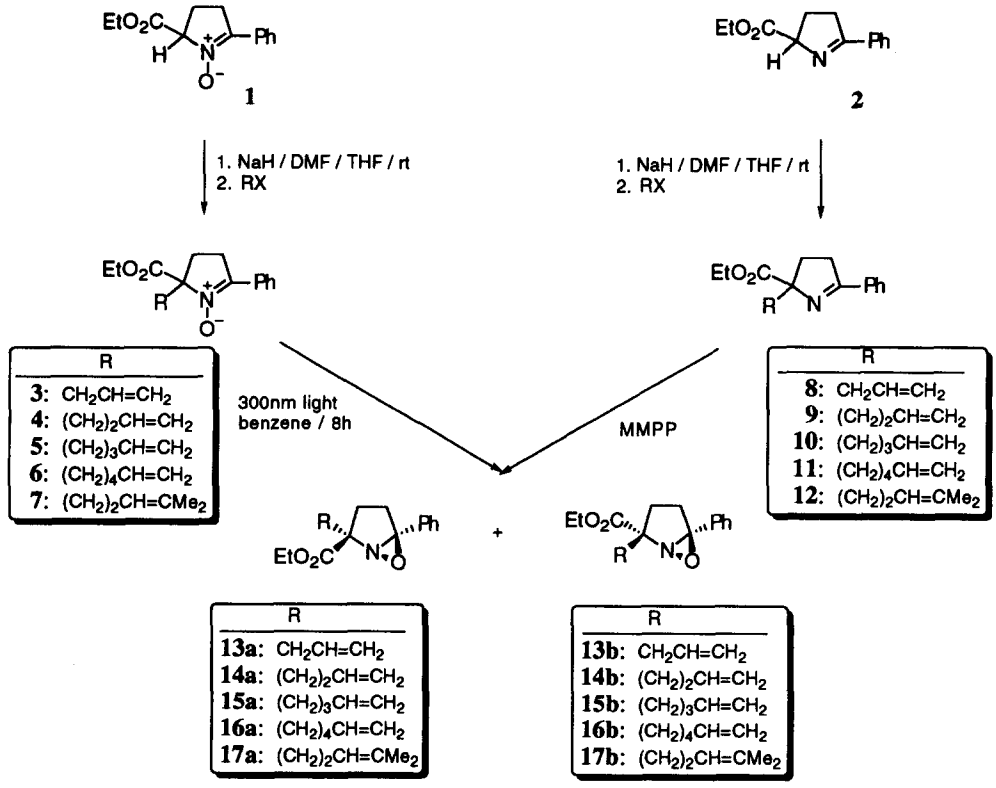
Keywords: oxaziridines; radicals and radical reactions; copper and compounds; pyrrolizines/pyrrolizidines

We wish to report that aminyl radicals generated from oxaziridines can undergo cyclisation onto pendant alkenes, provided that the stereochemical environment is suitable. Free radical cyclisation reactions have been widely investigated [1] and in particular, nitrogen centred radicals can interact with unsaturated groups to generate heterocyclic rings [1-4] such as pyrrolidines [5]. Aminyl radicals have been produced from a wide variety of substrates, but the oxaziridine ring system has been somewhat under-utilised for this purpose [6-10]. Initial reports of the ring-opening of oxaziridines with iron (II) sulfate implicated alkoxy radical intermediates, but the alternative aminyl radicals have subsequently been proposed [11]. We therefore decided to investigate the radical ring-opening reactions of a series of oxaziridines with pendant alkenyl groups.

The 5-alkenyl-1-pyrroline 1-oxide-5-carboxylic esters **3-7** and the 5-alkenyl-1-pyrroline-5-carboxylic esters **8-12** were prepared by base-catalysed alkylation of the 1-pyrroline 1-oxide **1** and 1-pyrroline **2** respectively [12]. The related 6-oxa-1-azabicyclo[3.1.0]hexanes **13-17** were synthesised by photoisomerisation of the nitrones **3-7** in benzene, and the action of magnesium monoperphthalate on the pyrrolines **8-12** in methanol. In all cases two isomeric oxaziridines were obtained, with photoisomerisation favouring those (**13a-17a**) with the oxaziridine ring and alkenyl groups *trans* with respect to the pyrrolidine ring, and peroxidation favouring those (**13b-17b**) with the oxaziridine ring and alkenyl groups *cis* . The observed selectivities are consistent with a consideration of the various steric factors involved. The structures of isomers **14a,b** were established by a NOESY experiment, in which the minor isomer from photoisomerisation showed a signal enhancement between the phenyl ring *ortho* protons and the methyl group of the ester: no such interaction was observed for the major isomer. The

0040-4039/98/$19.00
PII: S0040-4039(98)01160-5

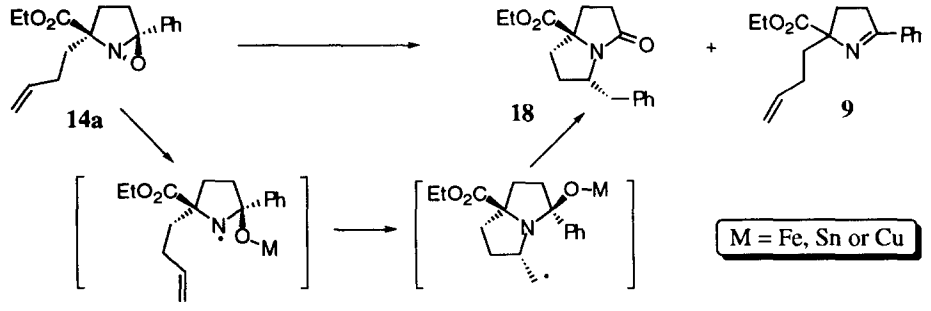
remaining structures were determined by NMR comparison, as well as being confirmed by the subsequent chemical outcome of the ring-opening reactions.



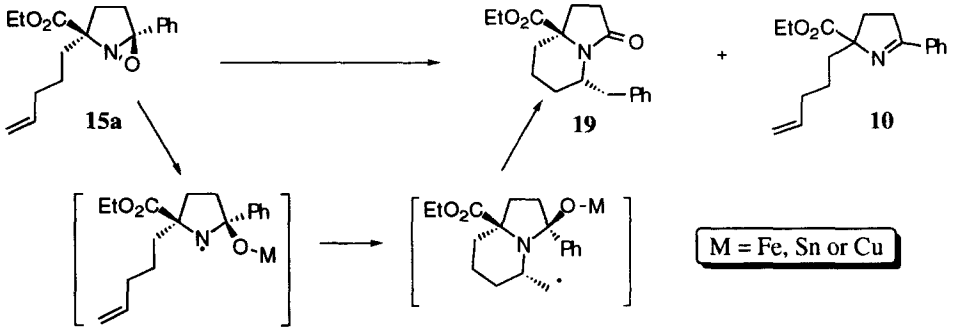
Reaction of iron(II) sulfate with both *trans* and *cis* isomers of the 2-allyl-6-oxa-1-azabicyclo[3.1.0]hexanes **13a,b** gave similar results and yielded the allylpyrroline **8** and ethyl 2-phenylpyrrole-5-carboxylate in yields of ~40% and ~30% respectively. Deoxygenation is a common outcome of such reactions, and formation of the pyrrole is clearly the result of the favourable loss of an allyl radical. Only in the reaction of the *trans* isomer **13a** was there an indication of the formation of a trace of unidentified bicyclic products. Similar reaction of oxaziridines **13a,b** with tri-*n*-butyl tin hydride and 2,2'-azobisisobutyronitrile in refluxing benzene [1] gave only poor yields (~15%) of the pyrroline **8**, together with unchanged starting material. However, use of the tetrameric copper(I)triphenylphosphine chloride [13] in refluxing tetrahydrofuran reversed the yields of the pyrroline **8** and ethyl 2-phenylpyrrole-5-carboxylate, and indicated the formation of ~15% of bicyclic products from *trans* isomer **13a**.

Reaction of the *trans* butenyl oxaziridine **14a** with iron(II) sulfate gave the pyrroline **9** in 14% yield, together with the bicyclic lactam **18** in 46% yield. The *cis* isomer **14b** gave only an 83% yield of pyrroline **9**. Tributyl tin hydride converted **14a** into pyrroline **9** (44%) and lactam **18** (20%), and **14b** into pyrroline **9** (71%). However, copper(I)triphenylphosphine chloride converted **14a** cleanly into the lactam **18** in 82% yield, while giving a high yield of only the

pyrroline **9** from *cis* isomer **14b**. The structure of the lactam **18** was established after extensive NMR spectroscopic correlations, including the use of COSY, HMQC and HMBC techniques. The stereochemistry at the benzyl-substituted carbon is that resulting from the more favoured chair-like transition state. The lactam **18** presumably results from the closure of an aminyl radical on to the alkene to give a pyrroline ring with an exocyclic methylene radical, to which the phenyl radical migrates with concomitant formation of the amide carbonyl group. The work of Aubé provides precedence for such phenyl migration [13].



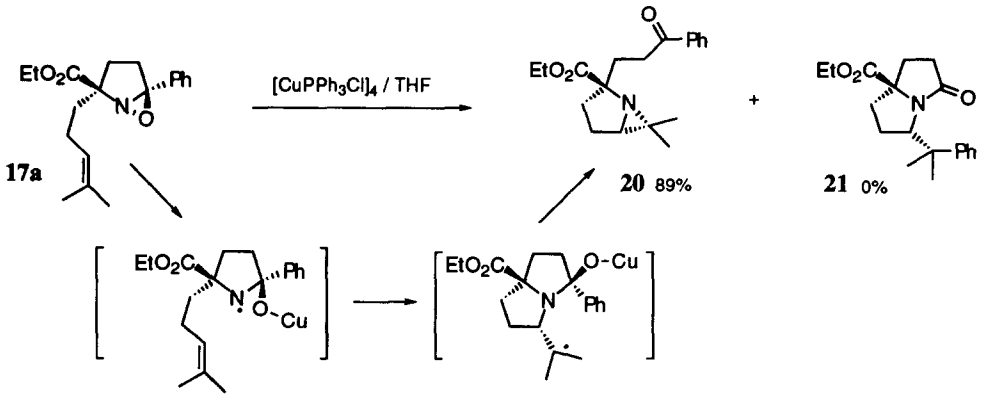
Treatment of the *trans* pentenyl oxaziridine **15a** with iron(II) sulfate gave the pyrroline **10** in 66% and the lactam **19** in 26%. The *cis* isomer **15b** gave only the pyrroline **10** as expected. Reaction of either isomer with tributyl tin hydride also gave only the pyrroline in ~80% yield. The yield of lactam **19** was increased to 40% and that of the pyrroline **10** fell to 41% when *trans* isomer **15a** was reacted with copper(I)triphenylphosphine chloride: *cis* isomer **15b** gave only pyrroline **10**. The lower yield of lactam **19** compared with lactam **18** is understandable, as 5-endo ring closure is favoured over 6-exo [1]. The lower yield also made the separation and characterisation of the product **19** difficult and it could not be obtained analytically pure.



Iron(II) sulfate cleanly converted each of the hexenyl oxaziridines **16a,b** into the pyrroline **11** in >90% yield.

In view of the cyclisation of the butenyl oxaziridine **14a,** reaction of the dimethyl analogs **17a,b** with copper(I)triphenylphosphine chloride was investigated. The *trans* isomer **17a** gave an 89% yield of the aziridine **20**, and the *cis* isomer **17b** yielded pyrroline **12** in 87%.

Formation of aziridine **20** presumably arises by attack of the intermediate tertiary alkyl radical on to nitrogen, in preference to the sterically hindered migration of the phenyl radical to it, which would have yielded lactam **21**.



The formation of cyclisation products from the *trans* oxaziridines **14a**, **15a** and **17a** clearly implicate aminyl rather than alkoxy radicals. Furthermore, the trapping of these aminyl radicals by the pendant alkenes establishes the stereochemical requirement for bond formation from the side opposite the departing oxygen atom. The high yielding formation of the pyrrolizidine **18** indicates that this route could provide a useful synthetic entry to numerous important pyrrolizidine alkaloid structures.

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