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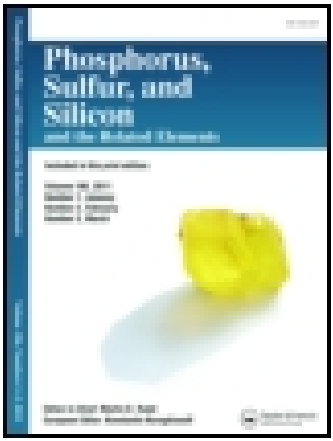

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Published online: 04 Oct 2006.

To cite this article: Virginia R. Ward , Matthew A. Cooper & A. David Ward (2001) The Synthesis of N-Benzoyl Aziridines from β-Benzamidoalkyl Phenyl Selenides, Phosphorus, Sulfur, and Silicon and the Related Elements, 172:1, 195-201, DOI: 10.1080/10426500108046651

To link to this article: http://dx.doi.org/10.1080/10426500108046651

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Phosphorus, Sulfur and Silicon, 2001, Vol. 172, pp. 195-201
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The Synthesis of *N*-Benzoyl Aziridines from β-Benzamidoalkyl Phenyl Selenides

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β-Benzamidoalkyl phenyl selenides can be oxidised, using mCPBA, to the corresponding selenones which can be cyclised to oxazolines or aziridines depending on the reaction conditions. In neutral or weakly basic conditions the oxazoline is the major product but if the oxidation is conducted at -60°C then the corresponding aziridine is formed in high yields using strongly basic conditions. The synthesis of a range of bicyclic *N*-benzoyl aziridines is described.

Keywords: selenides; selenones; oxazolines; aziridines

INTRODUCTION

In the presence of excess *m*-chloroperbenzoic acid (mCPBA) selenides can be oxidised to the corresponding selenones. The ability of the phenylselenonyl group to act as a leaving group has been utilised for both inter- and intramolecular reactions [1,2,3,4,5] and it has been shown to be a better leaving group than bromide and iodide [1]. With cyclic systems, and some non-cyclic ones, the reaction can also produce significant quantities of rearranged products [2]. With non-cyclic amides the oxidation and nucleophilic displacement leads to oxazolines or pyrrolidines depending upon which atom of the amide group can

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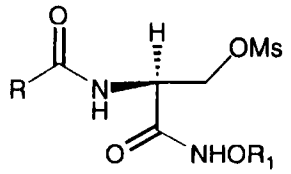
provide the more stable ring system [3]. In this conference report we present our preliminary results which show that *trans*-2-benzamidocycloalkyl phenyl selenides cyclise exclusively to aziridines, rather than oxazolines, under the appropriate conditions.

Aziridines are valuable synthetic intermediates due to their ability to undergo regio- and stereocontrolled ring-opening reactions [6]. *N*-acyl aziridines are of particular value as activation of the nitrogen by an electron-withdrawing group enhances their susceptibility to ring-opening [6-12]. *N*-acyl aziridines are usually prepared by acylation of the already formed aziridine [13-15]. The alternative approach, *via* cyclisation of β-substituted amides, has often been employed in the formation of oxazolines [16-25], which result from ring-closure by oxygen rather than by nitrogen, but rarely when the desired product is an aziridine [13]. Some β-hydroxy amides, particularly those of *threo*-stereochemistry [26] such as threonine-containing peptides [27-29], have been found to give aziridines under Mitsunobu conditions while the same treatment of *allo*-threonine derivatives leads to oxazolines [27].

N-alkylation of an amide is most effectively achieved by generation of the amide anion followed by reaction with the alkylating agent [30]. For this reason cyclisation to an aziridine does not occur unless



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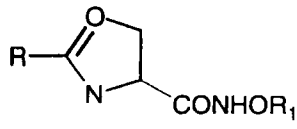

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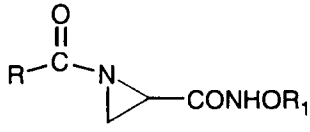

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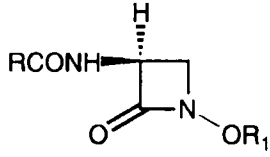

4

$R = R_1 = CH_2C_6H_5$

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the conditions are at least moderately basic. Thus Wipf and Miller [27] found that oxazolines were the sole products when threonine-containing peptides were subjected to buffered Mitsunobu cyclisation.

Krook and Miller [31] have shown that cyclisation of the mesylate **1** can be directed to oxazoline **2** formation under weakly basic conditions, with bicarbonate in hot dichloroethane, and to aziridine **3** and β-lactam **4** formation with potassium *tert*-butoxide (tBuOK) in THF.

Toshimitsu *et al.* [32] cyclised the β-benzamido selenide **5** to the oxazoline in 84% yield through its oxidation to the selenone with 2 equivalents of mCPBA in methanol. We have been investigating the oxidation of a range of β-amido selenides and report herein that the oxidation of β-benzamidocycloalkyl phenyl selenides under strongly basic conditions at low temperature gives the aziridines as the exclusive products, generally in high-yielding, clean reactions.

RESULTS AND DISCUSSION

We had previously carried out the oxidation of the benzamide **6b** with 3 equivalents of mCPBA and 1.5 equivalents of KOH in isopropanol and were afforded the oxazoline **8b**. However, with an excess of base, the aziridine **7b** was afforded in 73% yield. Investigation of the reaction with benzamides **6a**, **6c** and **6d** showed that the product composition depended on the basicity of the reaction conditions, with neutral or acidic conditions favouring the oxazoline and an excess of base giving the aziridine as the predominant product. The use of NaH or tBuOK instead of KOH improved the ratio of aziridine to oxazoline, presumably due to more effective generation of isopropoxide ion (Table, method a). However, except for the benzamides **6b** and **6c**, we were unable to effect a clean transformation to the aziridine. Oxidation of the acyclic selenide **5** under strongly basic conditions gave the oxazoline in 87% yield, a replication of the result of Toshimitsu *et al.* [32].

Following the lead provided by the work of Krook and Miller [31], we found that by carrying out the oxidation of the cyclic selenides at -60°C in THF followed by addition of tBuOK, the aziridines were afforded as the exclusive products (Table, method b). The acyclic compound **5** also predominantly formed the aziridine under these conditions.

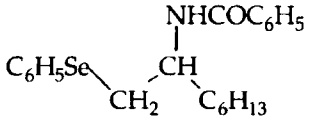
TABLE: Products from the reaction of **5** and **6** with mCPBA in basic conditions.

selenide	product (ratio)[a]	yield[a] %	product (ratio)[b]	yield[b] %
5	**10**	87	**9, 10** (73:27)	55
6a	**7a, 8a** (51:49)	77	**7a**	75
6b	**7b**	85	**7b**	83
6c	**7c**	70	**7c**	94
6d	**7d, 8d, 11** (74:12:14)[c]	55	**7d**	81
6e	-	-	**7e**	87

a 4 eq. mCPBA, 6-8 eq. NaH or tBuOK in iPrOH, R. T.

b 3.2 eq. mCPBA, 6 eq. tBuOK, THF. -60°C.

c Some of the corresponding elimination product **11** was also formed



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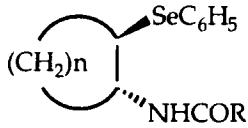

6

(a) n = 3, R = C_6H_5
(b) n = 4, R = C_6H_5
(c) n = 4, R = *p*-Br-C_6H_4
(d) n = 5, R = C_6H_5
(e) n = 6, R = C_6H_5

Since we were uncertain whether the selenone was being generated at this low temperature, we sought confirmation that the intermediate was in fact the selenone and not the selenoxide. To this end, the cyclopentanebenzamide **6a** was oxidised with 1.1 equivalents of

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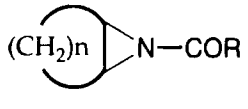

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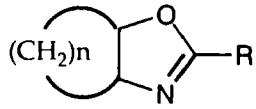
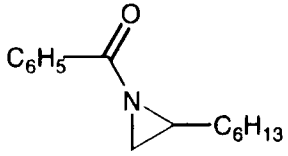


8

(a) n = 3, R = C_6H_5
(b) n = 4, R = C_6H_5
(c) n = 4, R = *p*-Br-C_6H_4
(d) n = 5, R = C_6H_5
(e) n = 6, R = C_6H_5



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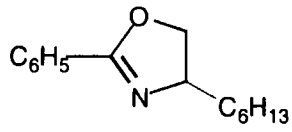

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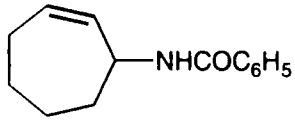

11

mCPBA (sufficient to give the selenoxide) with other parameters kept constant. This reaction gave predominantly the selenoxide *syn*-elimination product.

When the reaction was conducted on **6d** at higher temperatures (-15, 0°C) aziridine formation decreased with a concomitant increase in the syn elimination product **11**. At both temperatures only traces of oxazoline were observed. These results indicate that although it may have little effect on the mode of cyclisation, the low temperature is necessary to ensure that the selenoxide is sufficiently long-lived to enable its further oxidation to the selenone.

The oxidation of the selenoxide to the selenone is presumably much faster in protic solvents as there is little elimination product when the reaction is conducted in alcohol solvents. Indeed, we have found in other

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work that the oxidation of selenides to selenones is 50 to 60 times faster in alcohols than in THF. However, the more facile formation of oxazolines in hydroxylic solvents may be explained by the reduction in the nucleophilicity of the amide nitrogen anion through hydrogen-bonding, rendering attack by oxygen more competitive.

In summary, we have determined the conditions under which *N*-benzoyl aziridines **7** can be prepared in reasonable to very good yield from β-amido selenides. Considering the ease of formation of these selenides from alkenes (*via* addition of phenylselanyl halides to alkenes in benzonitrile followed by treatment with aqueous trifluoromethanesulfonic acid), our procedure represents an efficient and mild alternative preparation of bicyclic *N*-benzoyl aziridines, with overall yields at least comparable to, and in one case a six-fold improvement on, those reported with other methods [11,12].

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