COMMUNICATION

Synthesis of *N*-acylaziridines from β-amido selenides

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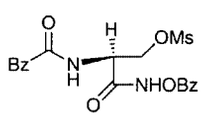
Received 15th March 2001, Accepted 16th March 2001
First published as an Advance Article on the web 30th March 2001

The low temperature oxidation of β-amido selenides with MCPBA affords the corresponding β-amido selenones. *In situ* treatment of the selenones with KOtBu gives *N*-acylaziridines in good to excellent yield.

Aziridines are valuable compounds due to the regio- and stereocontrolled ring-opening reactions which are central to their chemistry.[1] *N*-Acylaziridines are of particular value in such reactions as substitution at the nitrogen atom with an electron-withdrawing group enhances the susceptibility of the aziridine ring to open.[1–3]

N-Acylaziridines are usually prepared by acylation of the unsubstituted aziridine.[4–6] The alternative approach, *via* cyclisation of β-substituted amides, often forms oxazolines,[7–11] as a result of ring-closure by oxygen rather than by nitrogen, and only rarely produces an aziridine.[4] Krook and Miller[12] have shown that cyclisation of the mesylate **1** can be directed to give the oxazoline **2** under weakly basic conditions (potassium bicarbonate in hot dichloroethane) and the aziridine **3** and



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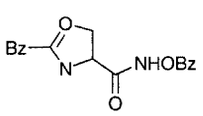

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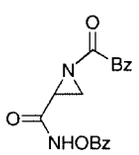

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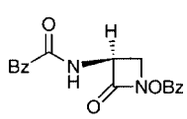

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β-lactam **4** under strongly basic conditions (potassium *tert*-butoxide (tBuOK) in tetrahydrofuran (THF)), thus demonstrating that cyclisation of amides to aziridines requires generation of the amide anion prior to alkylation, as does *N*-alkylation of amides in general.[13] β-Hydroxy amides of *threo*-stereochemistry, such as threonine-containing peptides, have been found to give aziridines under Mitsunobu conditions in which the reduced diisopropyl azodicarboxylate anion is believed to act as the base.[14–17] The same treatment of *allo*-threonine derivatives, however, leads to oxazolines.[15]

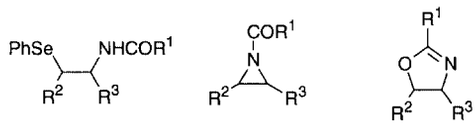
Toshimitsu[18] cyclized β-amido selenide **5a** to the oxazoline **7a** in 84% yield through its oxidation to the selenone with MCPBA in methanol in the absence of base. We report herein that the cyclisation of β-amido selenides under strongly basic conditions at low temperature can be directed predominantly to aziridine formation and that where the alkyl group is cyclic, aziridines are formed as the exclusive products.

Initially the cycloalkyl phenyl selenides were oxidised under conditions similar to those used by Toshimitsu,[18] with an excess of MCPBA in isopropanol (propan-2-ol) in the presence of potassium hydroxide (KOH). Thus the reaction of selenide **8b** using 1.5 equivalents of KOH and 3 equivalents of MCPBA gave the oxazoline in 94% yield. However, with 7.5 equivalents of base the aziridine was afforded in 73% yield. Investigation of

Table 1 Products from the reaction of **5** and **8** with MCPBA under basic conditions

Selenide	Product[a] (ratio)	Yield[a] (%)	Product[b] (ratio)	Yield[b] (%)
5a	**7a**	87	**6a**,**7a** (74 : 26)	73
5b		—	**6b**,**7b** (61 : 39)	72
5c		—	**6c**,**7c** (83 : 11)[c]	83
8a	**9a**,**10a** (51 : 49)	77	**9a**	75
8b	**9b**	85	**9b**	83
8c	**9c**	70	**9c**	94
8d		—	**9d**	66
8e	**9e**,**10e** (74 : 12)[c]	55	**9e**	81
8f		—	**9f**	67
8g		—	**9g**	87

[a] 4 eq. MCPBA, 6–8 eq. NaH or tBuOK in iPrOH, RT. [b] 3.3 eq. MCPBA, 4.5–9 eq. tBuOK in THF, −60 °C. [c] Some of the corresponding elimination product was also formed.



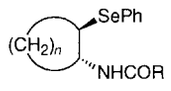
5 **6** **7**

a $R^1 = C_6H_5$; R^2 = H,H; $R^3 = C_6H_{13}$
b $R^1 = p$-Br-C_6H_4; R^2 = H,H; $R^3 = C_6H_{13}$
c approx. 1:1 mixture of
$R^1 = C_6H_5$; $R^2 = CH_3$; $R^3 = C_3H_7$ and
$R^1 = C_6H_5$; $R^2 = C_3H_7$; $R^3 = CH_3$

the oxidation of other cyclic benzamido selenides confirmed that neutral or acidic conditions favoured the oxazoline with an excess of base giving the aziridine as the predominant product. The use of sodium hydride (NaH) or tBuOK instead of KOH improved the ratio of aziridine to oxazoline, presumably due to generation of the stronger base, isopropoxide ion (Table 1, conditions a). However, except with the cyclohexanebenzamides **8b** and **8c**, we were unable to effect a clean transformation to the aziridines. Oxidation of acyclic selenoamide **5a** under these conditions gave the oxazoline in 87% yield, a replication of Toshimitsu's result.[18]

The work of Krook and Miller[12] suggested that cyclisation to the aziridine might be more favoured by the use of an aprotic solvent such as THF at a lower temperature. We were unaware of any precedent for the generation of selenones at temperatures below zero degrees; neither did we know of any reports of the generation of selenones with MCPBA in solvents other than alcohols or dichloromethane. Indeed, we have found the oxidation of other selenides to be 50 to 60 times slower in THF than in alcohols and we expected the reaction at low temperature in THF to be very slow, if it proceeded at all. We were therefore surprised to find that oxidation of the cyclic amido selenides for one hour at −60 °C in THF followed by addition of tBuOK and allowing the mixture to warm to *ca.* 0 °C over 1 hour, afforded the aziridines as the exclusive products, often in excellent yield (Table 1, conditions b).[19] The acyclic compounds

 DOI: 10.1039/b102468j



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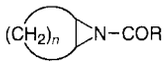

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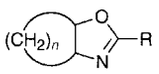
a $n = 3$, R = C_6H_5
b $n = 4$, R = C_6H_5
c $n = 4$, R = p-Br-C_6H_4
d $n = 4$, R = CH_3
e $n = 5$, R = C_6H_5
f $n = 5$, R = CH_3
g $n = 6$, R = C_6H_5



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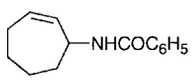

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5a–**c** also predominantly formed the corresponding aziridines **6a**–**c** under these conditions.

The oxidation of **8e** with 1 equivalent of MCPBA (sufficient to give the selenoxide) and 3 equivalents of tBuOK with other parameters constant gave the selenoxide *syn*-elimination product **11** (58%) and starting material (13%). This confirmed that the intermediate was the selenone and not the selenoxide. In addition, the ^{77}Se NMR spectrum of a mixture of **8b** and MCPBA in THF at −60 °C showed a peak at δ 1010, consistent with the presence of a selenone.[20]

When the reaction was conducted on **8e** at higher temperatures (−15 °C, 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 β-amido selenides were prepared *via* established procedures in two steps from the corresponding alkenes,[21,22] with overall yields of aziridine from the starting alkene at least comparable to, and in one case a six-fold improvement on, yields reported using other methods.[23,24] Thus our methodology represents an efficient and mild alternative route to *N*-acylaziridines.

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19 In a typical procedure, to a solution of the selenide **8d** (250 mg, 0.84 mmol) in tetrahydrofuran (20 ml) cooled to −60 °C was added dropwise, with stirring, a solution of MCPBA (594 mg, 80%, 2.75 mmol) in tetrahydrofuran (20 ml) and the mixture was stirred at −60 °C for 1 h. Potassium *tert*-butoxide (571 mg, 5.1 mmol) was added and the resulting mixture stirred for a further 1 h. Aqueous sodium thiosulfate (0.5 M, 15 ml) and saturated aq. sodium bicarbonate (10 ml) were added and the aqueous phase extracted with diethyl ether (30 ml). The organic extract was washed with 10% aq. sodium hydroxide (10 ml) and saturated aq. sodium chloride (10 ml) and dried ($MgSO_4$) and the solvent evaporated at reduced pressure. Chromatography using a gradient of 0 to 10% diethyl ether in dichloromethane as eluent gave the aziridine **9d** as a clear liquid (77 mg, 66%).
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