**Optically active aziridine esters by nucleophilic addition of nitrogen heterocycles to a chiral 2$H$-azirine-2-carboxylic ester**

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Chirally enriched ethyl 3-methyl-2$H$-azirine-2-carboxylate acts as an efficient alkylating agent for a variety of five membered aromatic nitrogen heterocycles.
Optically active aziridine esters by nucleophilic addition of nitrogen heterocycles to a chiral 2H-azirine-2-carboxylic ester

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Abstract—Chiral enriched ethyl 3-methyl-2H-azirine-2-carboxylate acts as an efficient alkylating agent for a variety of five-membered aromatic nitrogen heterocycles.

Keywords: chiral 2H-azirines; nucleophilic additions; diastereoselectivity; aziridines.

We have previously found that 2H-azirine-3-carboxylic esters 1 and 2 are useful precursors for functionalized aziridines 3 that are formed by simple nucleophilic addition to the respective 2H-azirine. Reactions are stereoselective, the addition being on the less hindered face of the azirine to form the trans products 3 (scheme 1).1 The main drawback to this methodology as a route to α-amino esters 3 is that there is currently no method of obtaining the 2H-azirine-3-carboxylic ester 1 in an enantiopure form. As a first approach to a chiral aziridine, the azirine 2 bearing the (N,N-diethylsulfamoyl) isobornyl unit as the chiral auxiliary in the ester moiety, was obtained 2 and reacted with nucleophiles. The expected addition reactions took place, but diastereodifferentiation of the two faces of the azirine was generally not good.2 So, we concluded that it would be difficult to generate chiral adducts if the chirality of the compound is outside the ring. On the other hand, 2H-azirine-2-carboxylic esters of type 4 can be accessed in optically active form from ester aziridines 5 by Swern oxidation 3 (scheme 2) or from β-ketoester oxime p-toluenesulfonates 6, by a modified Neber elimination, using (+)-dihydroquinidine as a chiral tertiary base (scheme 3). 4 To our surprise we find that 2-alkoxycarbonylazirine compounds are electrophilic enough to react with nitrogen heterocycles at room temperature within some hours, showing a close relationship with the electrophilicity of 2H-azirine-3-carboxylic esters, despite their lower degree of activation. The reason why this behaviour was not expected is associated with lack of conjugation of the C=N bond with the carbonyl group in compounds 4.

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The chirally enriched 2H-azirine-2-carboxylic esters firstly reported by Zwanenburg and coworkers\textsuperscript{4} were used as electrophiles in addition reactions to five and five fused aromatic nitrogen heterocycles. The azirine was obtained by stirring a solution of 6 (R\textsuperscript{1} = Me, R\textsuperscript{2} = Et) in dry toluene in presence of (+)-dihydroquinidine (1 equiv.), which was removed in the end of the reaction by extraction with aq. citric acid (10%); the crude product was used without further purification. The \textsuperscript{1}H NMR spectrum of the reaction mixture in the presence of ytterbium chiral shift reagent (Yb(tfc)) (ee 70%) is in good agreement with the enantiomeric excess reported.\textsuperscript{4} Aziridines 8 are formed by stirring a solution of the azirine 7 with the nucleophile in acetonitrile at room temperature and in presence of Na\textsubscript{2}CO\textsubscript{3}. Adducts are generally stable enough to be isolated after flash chromatography. The only exceptions are the adducts 8d and 8i. The indole adduct 8d, proved to be a single compound in the crude mixture by \textsuperscript{1}H NMR analysis, although it reacts on silica during dry-flash chromatography, reverting back to azirine 7 and indole that were recovered in 80\% and 50\% yields respectively. 7-Azaindole adduct 8i, also reacts on silica, giving back the azaindole (78\%) and a dimer of the azirine, compound 10 obtained in 65\% yield. The nitrogen heteroaromatic eliminations of the aziridine adducts have been described before from aziridine adducts 9. Also the pyrazine of type 10 was observed before by decomposition of aziridine adducts 9 in the presence of acid (silica) or base. Reaction of the azirine 7 with purine, gave a mixture of N-7 (8g) and N-9 (8f) alkyl isomers in 1:2 ratio respectively, in agreement with the higher nucleophilicity of N-7 and N-9 compared with N-1 and N-3 in purine.\textsuperscript{5} The adducts were fully separated by dry flash chromatography. Addition products were isolated as oils (8b, 8c, 8g, 8h) or solids (8a, 8e, 8f) in 60-80\% yield. \textsuperscript{1}HNMR, \textsuperscript{13}C NMR and high resolution mass spectra of these compounds fit the proposed structures. The main features of the NMR spectra of the addition products are the NH doublet in a narrow region \(\delta_H 1.82-2.12\) ppm that couples with the neighbouring CH at \(\delta_H 2.85-3.05\). The coupling constant between them is of the order of 8.7 to 9 Hz (see table 1). A very similar interaction was described in other aziridines of type 8,\textsuperscript{12} e.g. aziridine 9 for the NH-CH moiety. \textsuperscript{13}C spectra are also indicative, in all cases consistently showing two sp\textsuperscript{3} carbons at \(\delta_C 42-43\) ppm and 62 ppm, assigned to C-2 and C-3, respectively.\textsuperscript{6}

According to NOe experiment on compound 8f and 8g, the stereochemistry of addition seems to be \textit{anti} to the ethoxycarbonyl group of the azirine. Irradiating H-2 (d) of the aziridine moiety at 2.9 ppm showed an enhancement (3.72\%) of the purine signal H-8 at 8.34 ppm. On the other hand, irradiation of H-2 (d) of the other isomer at 2.97 ppm gave an enhancement of
H-8 at 8.48 ppm (2.72%) and H-6 at 9.15 ppm (2.86%). Free rotation around C-N bond between the aziridine and purine tied moieties would explain the NOe of the aziridine H-2 over the purine H-8 and H-6 in isomer 8g, and H-2 of the aziridine over the purine H-8 in isomer 8f. The anti azirine addition was observed before in 2H-azirine-2-carboxylates, although in the case of Grignard reagents, syn addition has been reported instead. The ee of the products was established by further functionalisation of the NH in compound 8d with a chiral acylating agent ((1S)-(+)-camphorsulfonyl chloride). A mixture of two major diastereomers was obtained in a ratio between 4:1 to 5:1, which is approximately the same enantiomeric ratio observed in the starting chiral azirine. Two other minor diastereomers were also detected in a ratio about 4:1, due to the syn addition of indole to the azirine. The two major diastereomers represent 85% of the crude mixture, which indicates a good diastereoselectivity for the addition reaction.

The obvious extension of this work to carbon and sulfur nucleophiles did not give promising results. Reaction of 7 with phenylmagnesium bromide produced a 3:1 mixture of diastereomers, indicating that the addition is not stereoselective in this case. Careful studies of the reaction over a temperature range of −78 ºC to −20 ºC always gave products in the same isomeric ratio. On the other hand, 4-chlorothiophenol reacted in an undefined way and it was not possible to reproduce a clear procedure for the reaction. This was ascribed by us to be the result of easy addition/elimination of the sulfur nucleophile.

In conclusion, we found the relative non-activated azirine 7 to be a good alkylating agent for nitrogen heterocycles, opening the possibility of forming chiral aziridines of type 8 with excellent diastereoselectivity.

Acknowledgements

We thank Dr Thomas L. Gilchrist for helpful discussions of the work and Fundação Ciência e Tecnologia for project funding (POCTI/32723/QUI/2000).

References

**Table 1.** Some physical and spectroscopic characteristics for aziridines 8.

<table>
<thead>
<tr>
<th>No</th>
<th>Yield (%)</th>
<th>m.p. (°C)</th>
<th>[α]D&lt;sup&gt;20&lt;/sup&gt; (CHCl&lt;sub&gt;3&lt;/sub&gt;)</th>
<th>&lt;sup&gt;1&lt;/sup&gt;H NMR (CDCl&lt;sub&gt;3&lt;/sub&gt;)</th>
<th>&lt;sup&gt;13&lt;/sup&gt;C NMR (CDCl&lt;sub&gt;3&lt;/sub&gt;)</th>
</tr>
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<tbody>
<tr>
<td>8a</td>
<td>60</td>
<td>&gt;70 (dec.)</td>
<td>-36</td>
<td>1.96 (bd, 1H, N-H, J8.7Hz)</td>
<td>42.62  62.44</td>
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<tr>
<td></td>
<td></td>
<td>(EtOAc: Pet. ether 40-60)</td>
<td>2.95 (d, 1H, C-H, J8.7Hz)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8b</td>
<td>83</td>
<td>oil</td>
<td>-91</td>
<td>1.97 (bs, 1H, N-H)</td>
<td>42.63  62.37</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.86 (d, 1H, C-H, J8.7Hz)</td>
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<tr>
<td>8c</td>
<td>59</td>
<td>oil</td>
<td>-83</td>
<td>1.86 (b, 1H, N-H)</td>
<td>42.83  62.32</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>2.79 (d, 1H, C-H, J9.0Hz)</td>
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<tr>
<td>8d</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>1.85 (bd, 1H, N-H, J9.0Hz)</td>
<td>---  ---</td>
</tr>
<tr>
<td>a)</td>
<td></td>
<td></td>
<td></td>
<td>b)</td>
<td>3.04 (d, 1H, C-H, J9.0Hz)</td>
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<tr>
<td>8e</td>
<td>60</td>
<td>&gt;65 (dec.)</td>
<td>-22</td>
<td>1.82 (bs, 1H, N-H)</td>
<td>43.16  62.20</td>
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<tr>
<td></td>
<td></td>
<td>(Et&lt;sub&gt;2&lt;/sub&gt;O: Pet. ether 40-60)</td>
<td>2.85 (bs, 1H, C-H)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8f</td>
<td>41 (major)</td>
<td>90-92 (EtOAc)</td>
<td>-53</td>
<td>1.99 (d, 1H, N-H, J9.0 Hz)</td>
<td>41.93  62.69</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>2.94 (d, 1H, C-H, J9.0Hz)</td>
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<tr>
<td>8g</td>
<td>27 (minor)</td>
<td>oil</td>
<td>-47</td>
<td>2.12 (d, 1H, N-H, J8.7Hz)</td>
<td>42.72  62.63</td>
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<td>2.96 (d, 1H, C-H, J8.7Hz)</td>
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<tr>
<td>8h</td>
<td>62</td>
<td>oil</td>
<td>-67</td>
<td>1.88 (d, 1H, N-H, J9.0Hz)</td>
<td>42.76  62.38</td>
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<td></td>
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<td>2.89 (d, 1H, C-H, J9.0Hz)</td>
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<tr>
<td>8i</td>
<td>---</td>
<td>---</td>
<td>---</td>
<td>1.85 (d, 1H, N-H, J9.0Hz)</td>
<td>---  ---</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.97 (d, 1H, C-H, J9.0Hz)</td>
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</table>

* Crude material ca 100% yield. Decomposition after flash chromatography.
* Further characterization was made through the camphor sulfamoyl chloride derivative; the crude material displayed four doublets due to one of the methylenic sulfamoyl protons at  5.29, 5.23, 5.11 and 5.02 in a ratio 1:0:26:0:16:0:06.
Scheme 1

1. $R^1 = 2,6$-dichlorophenyl; $R^2 = \text{Me}$
2. $R^1 = \text{H}; R^2 = (N,N$-diethylsulfamoyl)$\text{isobornyl}$
3. $X = \text{SAr, NR}_2$

Scheme 2

5. $R^1 = \text{alkyl, phenyl}$
   $R^2 = \text{Me}$

Scheme 3

6. $R^1, R^2 = \text{alkyl}$

Scheme 4

$N$-Het =

8a
8b
8c
8d
8e
8f
8g
8h
8i
\[ \begin{align*}
8f & \quad \text{H N CO}_2\text{Et} \\
8g & \quad \text{H N CO}_2\text{Et} \\
9 & \quad \text{R}^1 = \text{H} \quad \text{R}^2 = (N,N\text{-diethylsulfamoyl})\text{isobornyl} \\
10 & \quad \text{EtO}_2\text{C}\text{Me} \\
7 & \quad \text{Me} \quad \text{CO}_2\text{Et} \xrightarrow{\text{NH}} \text{H} \\
8 & \quad \text{Me} \quad \text{CO}_2\text{Et} \quad \text{HN} \\
\end{align*} \]