Graphical Abstract

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

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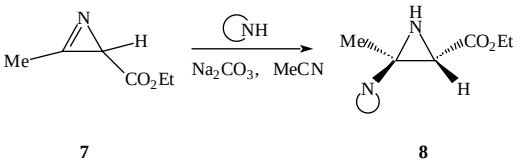

7 **8**

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

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

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

We have previously found that 2*H*-azirine-3-carboxylic esters **1** and **2** are useful precursors for functionalized aziridines **3** that are formed by simple nucleophilic addition to the respective 2*H*-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 2*H*-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, 2*H*-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 2*H*-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 2*H*-azirine-2-carboxylic esters firstly reported by Zwanenburg and co-workers [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^1 = Me, R^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 ^{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.[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_2CO_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 ^{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.[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. ^{1}HNMR, ^{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 δ_H 1.82-2.12 ppm that couples with the neighbouring CH at δ_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**, [1,2] *e.g*. aziridine **9** for the NH-CH moiety. ^{13}C spectra are also indicative, in all cases consistently showing two sp^3 carbons at δ_C 42-43 ppm and 62 ppm, assigned to C-2 and C-3, respectively.[6]

According to NOe experiment on compound **8f** and **8g**, the stereochemistry of addition seems to be *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 2*H*-azirine-2-carboxylates, [7] although in the case of Grignard ragents, *syn* addition has been reported instead. [3,6]

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

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References

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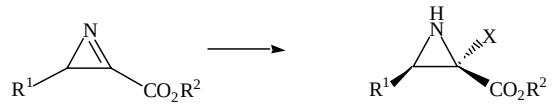
Table 1. Some physical and spectroscopic characteristics for aziridines **8**.

Nº	Yield (%)	m.p. (ºC)	$[\alpha]_D^{20}$ ($CHCl_3$)	^{1}H NMR ($CDCl_3$)	^{13}C NMR ($CDCl_3$) C-2	C-3
8a	60	>70 (dec.) (EtOAc: Pet. ether 40-60)	-36	1.96 (bd, 1H, N-H, *J*8.7Hz) 2.95 (d, 1H, C-H, *J*8.7Hz)	42.62	62.44
8b	83	oil	-91	1.97 (bs, 1H, N-H) 2.86 (d, 1H, C-H, *J*8.7Hz)	42.63	62.37
8c	59	oil	-83	1.86 (b, 1H, N-H) 2.79 (d, 1H, C-H, *J*9.0Hz)	42.83	62.32
8d [a]	---	---	---	1.85 (bd, 1H, N-H, *J*9.0Hz) [b] 3.04 (d, 1H, C-H, *J*9.0Hz)	---	---
8e	60	>65 (dec.) (Et_2O: Pet. ether 40-60)	-22	1.82 (bs, 1H, N-H) 2.85 (bs, 1H, C-H)	43.16	62.20
8f	41 (major)	90-92 (EtOAc)	-53	1.99 (d, 1H, N-H, *J*9.0 Hz) 2.94 (d, 1H, C-H, *J*9.0Hz)	41.93	62.69
8g	27 (minor)	oil	-47	2.12 (d, 1H, N-H, *J*8.7Hz) 2.96 (d, 1H, C-H, *J*8.7Hz)	42.72	62.63
8h	62	oil	-67	1.88 (d, 1H, N-H, *J*9.0Hz) 2.89 (d, 1H, C-H, *J*9.0Hz)	42.76	62.38
8i	---	---	---	1.85 (d, 1H, N-H, *J*9.0Hz) 2.97 (d, 1H, C-H, *J*9.0Hz)	---	---

[a] Crude material *ca* 100% yield. Decomposition after flash chromatography.
[b] 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.

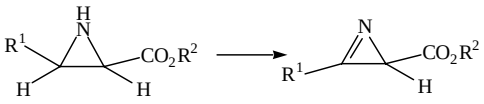


1- R^1 = 2,6-dichlorophenyl; R^2= Me

2- R^1 = H; R^2 = (*N*,*N*-diethylsulfamoyl)isobornyl

3- X = SAr , NR_2

Scheme 1

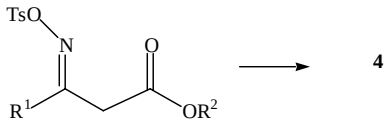


5 **4**

R^1 = alkyl, phenyl

R^2 = Me

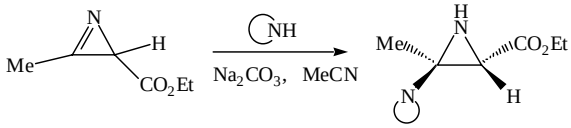
Scheme 2



6

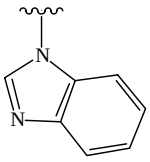
R^1 , R^2 = alkyl

Scheme 3

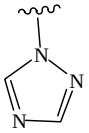


7 **8**

N-Het =



8a



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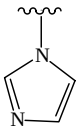

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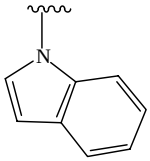

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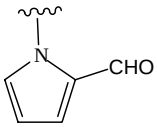

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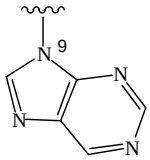

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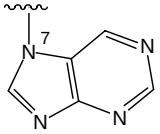
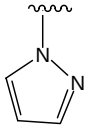
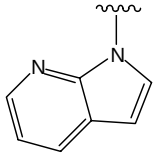


8g

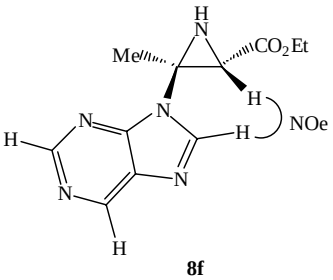


8h



8i

Scheme 4



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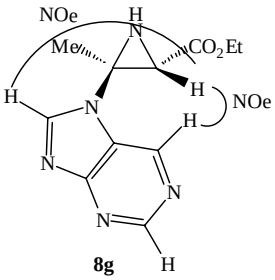

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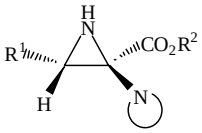
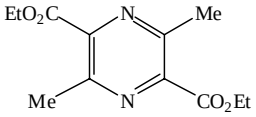


R^1 = H ; R^2 = (*N*,*N*-diethylsulfamoyl)isobornyl

9



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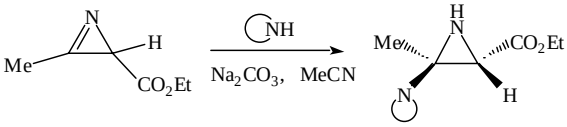

7 **8**