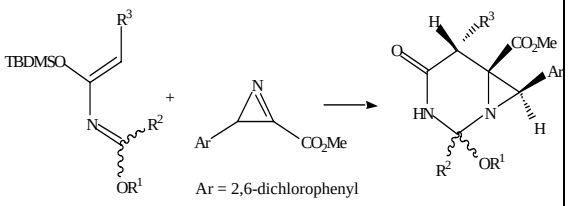
Graphical Abstract

Cycloaddition of methyl 2-(2,6- dichlorophenyl)-2*H*-azirine-3- carboxylate to electron rich 2-azadienes.

M. José Alves*, M. Miguel Durães, A. Gil Fortes
Departamento de Química, Universidade do Minho, Campus de Gualtar, 4700-320 Braga, Portugal

t-Butyldimethylsyliloxy-2-aza-dienes were reacted with 3-methyl-2-(2,6-dichlorophenyl)-2*H*-azirine carboxylate to form pyrimidones.	

Cycloaddition of methyl 2-(2,6-dichorophenyl)-2*H*-azirine-3-carboxylate to electron rich 2-azadienes

M. José Alves*, M. Miguel Durães, A. Gil Fortes

Departamento de Química, Universidade do Minho, Campus de Gualtar, 4710-057 Braga, Portugal

Abstract— *tert*-Butyldimethylsililoxy-2-aza-1,3-butadienes react with 2*H*-azirine **3** leading to Diels-Alder cycloadducts in moderate yields. The reactions are *endo*- and *regio*- selective with the azirine being added by its less hindered face. There is only one product in the case of **1b**, **4b**. There are two isomers (**4** and **5**) from **1a**, **1c** and **1d**. A different result was obtained with the diene **1e**. Diene **1e** formed products **4e** and **8**. Some of compounds **4** and **5** have been hydrolysed leading to functionalized aziridines **7**. Compound **8** gave aziridine **9**.

Keywords: 2-azadienes; 2*H*-azirines; Diels-Alder reactions.

Methyl 2-(2,6-dichorophenyl)-2*H*-azirine-3-carboxylate **3** has been synthesised by pyrolysis of methyl α-azidocinnamate [1] and used as a dienophile in Diels-Alder cycloadditions to commercial dienes, cyclic and acyclic, both symmetrical or non symmetrical.[2,3] Furan and diphenylisobenzofuran were also found to react well to give cycloadducts in excellent yields.[4] *tert*-Butyldimethylsyliloxy-2-aza-1,3-butadienes **1** have been easily prepared by Ghosez[5] and reacted with a range of electron poor dienophiles.[6-9] We prepared the 2-azadienes **1** and **2** from acylimidates and *tert*-butyldimethylsilyltriflates according to scheme 1.

We wish now to report the reaction of methyl 2-(2,6-dichorophenyl)-2*H*-azirine-3-carboxylate **3** with the 2-azadienes **1** and **2**. This is the first normal electron demand cycloaddition of a 2*H*-azirine to 2-azadienes. The literature contains an example of cycloaddition of an azirine to an electron poor 2-azadiene.[10]

Compounds **1a** and **1b** have been prepared previously. Compound **1b** was shown to have the configuration in scheme 1, with (*Z*) for the C-3 to C-4 bond. Compounds **1c** and **1d** are new compounds and the same configuration is assigned. In solution compounds (**1b**)-(**1d**) were found to consist of mixtures of stereomers in relation to C-1. The major isomers were deduced to have the *EZ* configuration and the minor isomers the *ZZ* configuration, based on spectroscopic evidence for cycloadducts obtained as discussed later. Stereomer **2** is formed in the series **e** and its assignment was made on the basis of spectroscopic analysis and hydrolysis of adducts formed.

2-Azadienes of type **1a**, **b**, **c** and **d** react at room temperature with the azirine **3** to give the bicyclic structures **4** and **5**. Usually the desilylated compound precipitated out of the reaction mixture as a solid that was isolated by simple filtration. Addition of commercial DCM to the reaction mixture, with redissolution of the solid in suspension followed by stirring with silica for 1 to several days at room temperature gave after flash chromatography poorer yieds of products **4**/**5** in all cases, compared with the direct filtration. Also treatment of the reaction mixture with tetramethylammonium fluoride gave the desilylated compound **4b** in a poorer

* Corresponding author. Tel.: +00-351-253-604376; fax: +00-351-253-678983; e-mail: mja@quimica.uminho.pt.

yield (41%). The primary cycloadduct could never be isolated or even identified in the reaction mixture by ^{1}H NMR analysis. Cycloadducts obtained from **1a** (a single isomer) proved to be a mixture of isomers **4a** and **5a** (1:1 ratio) obtained by filtration of the solid suspended in the reaction mixture in 53% yield. Treatment of a solution of **4a**/**5a** in DCM with silica gave **4a** quantitatively after 24 h. A single isomer **4b** was obtained in 51% yield by filtering the suspension of the reaction mixture. The starting diene **1b** contained only traces of the minor isomer. Reaction of the diene **1c** (4:1 mixture of isomers) with the azirine **3** afforded two diastereomers **4c** and **5c** (1:1 mixture) observed by ^{1}H NMR after treatment of the reaction mixture with silica for 3 days. After flash chromatography the isomer **4c** was partially separated (25%) together with a mixture of diastereomers (33%), in a total yield of 58%, the isomeric ratio being changed from 1:1 in the crude material to 4.5(**4c**): 1 (**5c**) after flash chromatography. Reaction of **1d** (2:1 isomeric ratio of isomers) with the azirine **3** formed two diastereomers **4d** and **5d** observed by ^{1}H NMR after treatment with silica for 7 days at room temperature as a 3:1 ratio of isomers. After flash chromatography the two isomers were fully separated **4d** (27%) and **5d** (11%); in a total yield of 38% (scheme 2)[*].

The expected relationship between the proportion of diene stereomers and the ratio of the diastereomeric products **4**/**5** is not observed. This is probably due to isomerization of product **5** into **4** in the presence of silica, according to scheme 3, although rotation about the C=N bond of dienes **1** during the reaction cannot be excluded. A crystal structure was determined for compound **4c**[§]; this is shown in figure 1. Also, NOESY spectra for both **4c** and **5c**, respectively the major and the minor isomers, gave valuable information about these structures. For compound **4c** the NOESY spectrum showed that H-5 and Me-2 were on the same side of the molecule. On the other hand the minor isomer **5c** showed H-7 to be on the same side of Me-2 (Fig 2). Structures **4c** and **5c** would be formed by an *endo* approach of the azirine from its less hindered face to the *EZ* and *ZZ* diene configurations, respectively. Further support for this was obtained by hydrolysis of compound **4c** and **5c** which gave the same product **7c**.

^{1}H NMR spectra of compounds **4c** and **5c** showed the influence of the ethoxy group on protons H-5 and H-7 when they are close in space. In compound **5c** the 1,4- relationship of proton H-5 with the ethoxy oxygen can account for its lower field resonance (+ 0.35 ppm), compared to the same proton in compound **4c**. The lower field resonance of H-7 in compound **4c** (+ 0.31 ppm), when compared to **5c**, can be due to the neigbourhood of the oxygen atom of the ethoxy group at C-2 on the same face.

Comparison of ^{1}H NMR chemical shifts of H-5 and H-7 in these two structures with values of chemical shifts of these protons in other diastereomeric pairs, showed that the same pattern applies in all cases (table 1).

Heating an ether solution of **4a** afforded the hydrolysis product **7a** in trace amounts. The same compound **7a** could be obtained pure in 74% yield upon treatment of a solution of **5a** in THF with HCl. Treatment of a mixture of **4c**/**5c** (1:1 ratio) with HCl in THF gave a single product **7c** in 87% yield. A significant conclusion is that the same hydrolysis product is forming from isomers **4** and **5** (scheme 4). This finding is in accordance with the diastereomeric structures assigned for compounds **4c** and **5c**, whose difference between isomers was stated to be at the C-2 stereogenic centre. As C-2 turns into a sp^2 hybridized carbon, this will be lost as a stereogenic centre in the hydrolysis product. A possible mechanism for the hydrolysis can be

[*] All compounds are achiral, and structure drawing show relative stereochemistry.

[§] Crystallographic data (excluding structure factors) for the structure in this paper, have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 207150. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

envisage from compounds **4** and **5**, structure **6** being the intermediate formed between the pyrimidones and compound **7** (scheme 3).
Reacting a mixture of dienes **2e** and **1e** (in a ratio 4:1) with azirine **3**, afforded a white solid after stirring at room temperature for 7 days. The solid was analysed by ^{1}H NMR, showing it to be a mixture of diastereomers identified as **4e** and **8**, in a 1.2 (**4e**) : 1 (**8**) ratio. Flash chromatography partially separated **4e** (30%) that was obtained as a white solid and a mixture of both **4e** and **8** (21%) also as a solid. Cycloadducts **4e** and **8** were obtained in a total yield of 51%. The NOESY spectrum of **4e** showed that the methoxy group at C-2 is close in space to H-7 and the methyl group at C-5 is also close to H-7. On the other hand the NOESY spectrum of the minor diastereomer showed proximity between H-5 and H-7, which would rule out structure **5** and strongly suggests structure **8** instead. Structure **8** should be formed from attack of the less hindered face of the azirine on the less stable diene configuration *EE*. When a mixture of the diastereomeric pair **4e**/**8** (in a ratio 1.1:1) was treated with HCl in THF two hydrolysis products (**7e** and **9** in 1.1:1 ratio) were obtained and separated after chromatography (scheme 5). Since **7e** and **9** are different compounds, **1e** and **2e** must differ in configuration at C-4. Major features for the assignment of structures **7** and **9** are the two doublets due to the NH-CH moiety of the aziridine ring coupling, *J c a* 9Hz, at δ_H 2.5-3.5 p.p.m. (table 2). Addition of D_2O causes exchange of the mobile proton and the CH then shows up as a sharp singlet. Also, the imide proton exchanges slowly, within some hours with deuterium. The *EE* diene **2e** seems to be the kinetic product of silylation of the acylimidate (scheme 1). Compounds **1e** and **2e** are formed in 1:4 ratio when neat TBDMSOTf is added to the acylimidate solution. A 1:1 ratio of isomers is formed when TBDMSOTf is added dropwise diluted in ether. In both cases cycloaddition with the azirine **3** produced cycloadducts **4e** and **8** in a *c a* 1:1 ratio, which means that an isomerisation process is taking place about C-3 to C-4, during the course of the reaction.

Conclusion

This is the first example of a reaction between an activated 2-azadiene and an electron deficient 2*H*-azirine **3**. The products are a new system and are formed with an excellent selectivity. The hydrolysis products are aziridine esters **7** and **9**, α-aminoesters with functionalized side chain that have potential biological value and are generally produced in good yields.

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

1-Knittel D., *Synthesis*, 1985, 186.
2-Bhullar P; Gilchrist T.L.; Maddocks P., *Synthesis*, 1997, 271.
3-Alves M.J.; Gilchrist T.L., *J. Chem. Soc., Perkin Trans. I* 1998, 299.
4-Alves M.J.; Azoia N.G.; Bickley J.F.; Gil Fortes A.; Gilchrist T.L.; Mendonça R., *J. Chem. Soc. Perkin 1*, 2001, 2969.
5-Ghosez L.; Bayard Ph.; Nshimyumkisa P.; Gouverneur V.; Sainte F.; Beaudegnies R.; Rivera M.; Frisque-Hesbain A.-M.; Wynants C., *Tetrahedron*, 1995, 51,11021.
6-Sainte F.; Serckx-Poncin B.; Hesbain-Frisque A-M.; Ghosez L., *J. Am. Chem. Soc*., 1982, 104, 1428.
7-Bayard Ph.; Sainte F.; Beardegnies R.; Ghosez L., *Tetrahedron Lett.*, 1988, 3799.
8-Gouverneur V.; Ghosez L., *Tetrahedron Lett.*, 1991, 5349.
9-Ntirampebura D.; Ghosez L., *Tetrahedron Lett.*, 1999, 7079.
10-Steglich W.; Jeschke R.; Buschmann E., *Gazz. Chim. Ital*., 1986, 116, 36.

Table 1. Some data for pyrimidones **4** and **5**.

compound	Mp (ºC)	^{1}H NMR [a], δ_H in p.p.m., *J* in Hz
4a	173.5-176.0	H-5 3.16 (1H, d, *J* 18.3); H-7 3.32 (1H, s), R^3 3.40 (1H, d, *J* 18.3)
5a	176.0-177.5	H-5 3.08 (1H, d, *J* 18); H-7 3.58 (1H, s); 3.34 (1H, d, *J* 18)
4b	140.5-146.5	H-5 3.19 (1H, d, *J* 7.2); H-7 3.59 (1H, s)
4c	181.2-183.2	H-5 4.40 (1H, s); H-7 4.13 (1H, s)
5c	134.5-137.5	H-5 4.75 (1H, s); H-7 3.82 (1H, s)
4d	175.5-177.5	H-5 4.41 (1H, s); H-7 3.80 (1H, s)
5d	189.1-190.1	H-5 5.09 (1H, s); H-7 3.66 (1H, s)
4e	212.0-214.0	H-5 2.59 (1H, q, *J* 6.9); H-7 3.77 (1H, s)
6e	187.0-188.4	H-5 3.82 (1H, q, *J* 7.2); H-7 3.48 (1H, s)

a) selected peaks

Table 2. Some data for aziridines **7** and **9**.

compound	Mp (ºC)	yield (%)	^{1}H NMR (CH and NH of the aziridine ring), δ_H in p.p.m., *J* in Hz
7a[a]	164.3-165.1	74	CH 3.21 (1H, d, *J* 8.4); NH 2.87 (1H, br d, *J* 8.4)
7b[b]	116.3-117.4	42	CH 3.37 (1H, *J* 9, CH); NH 2.85 (1H, d, *J* 9)
7c[c]	191.1-191.6	87	CH 2.40 (1H, d, *J* 9.9); NH 3.08 (1H, d, *J* 9.9)
7d[d]	180.2-181.2	68	CH 2.51 (1H, d, *J* 9.9); NH 3.02 (1H, d, *J* 9.9)
7e[e]	189.3-190.0	29[f]	CH 3.39 (1H, br d); NH 2.83 (1H, d, *J* 9.3)
9[e]	139.5-139.9	25[f]	CH 3.38 (1H, d, *J* 9.0), NH 2.97 (1H, d, *J* 9)

a) obtained from hydrolysis of compound **5a**; b) obtained from hydrolysis of compound **4b**; c) obtained from hydrolysis of an isomeric mixture (1:1) of compounds **4c** and **5c**; d) obtained from hydrolysis of compound **4d**; e) **7e** was obtained from hydrolysis of compound **4e**, and compound **9** was characterised by ^{1}H-NMR spectroscopy comparing the spectra of a pure sample of **7e** with a mixture of **7e** and **9**; f) partially separated after flash chromatography; total yield of **7e** and **9** is 75%.

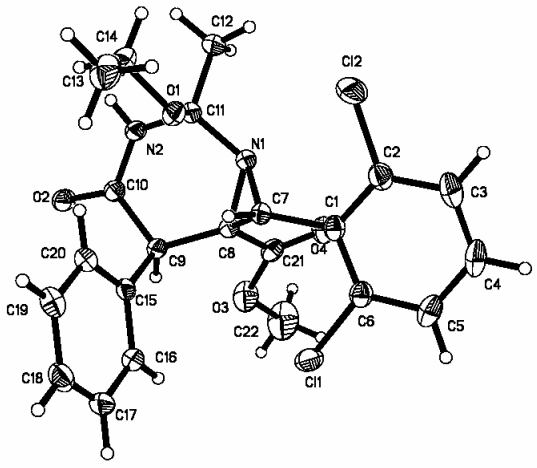


Figure 1- X-ray crystal structure for **4c**.

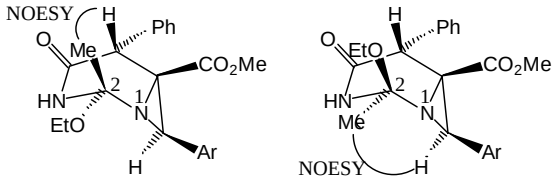


Figure 2- Compounds **4c** and **5c** showing the interaction through space (NOESY).

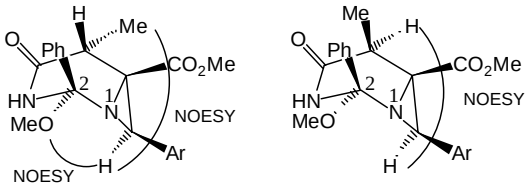
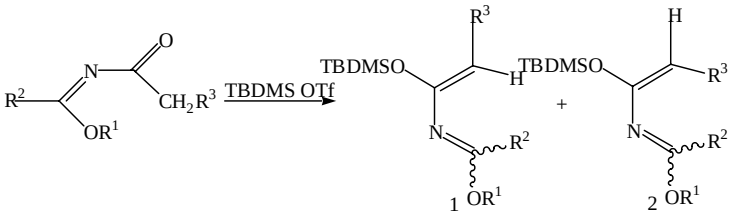
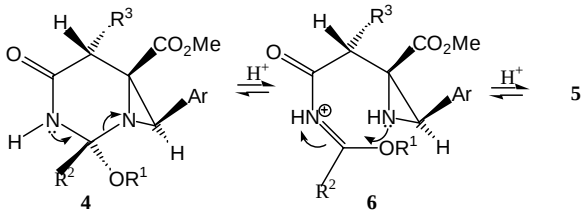


Figure 3- Compounds **4e** and **8** showing the interaction through space (NOESY).

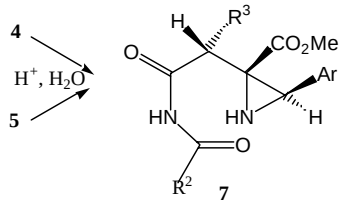


	R^1	R^2	R^3	Yield (%)	Ratio 1:2
a	Et	Me	H	65	100:0
b	"	"	Me	87	100:0
c	"	"	Ph	86	100:0
d	Me	Ph	"	88	100:0
e	"	"	Me	82	20:80

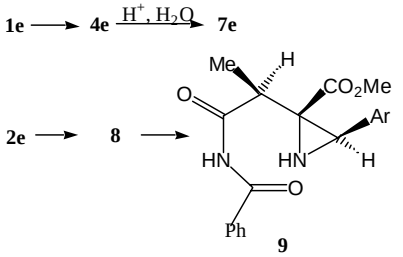
Scheme 1



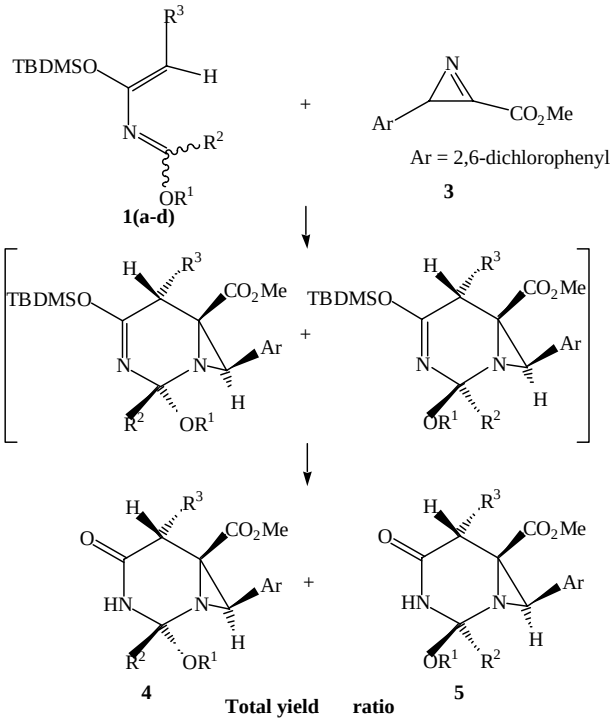
Scheme 3



Scheme 4



Scheme 5



	Total yield	ratio 4:5
a	**%** 53	1:1
b	51	isomer 4 only
c	58	4.5:1
d	38	3:1

Scheme 2