Exploiting azafulvenium methides chemistry

Teresa M. V. D. Pinho e Melo

Departamento de Química, Universidade de Coimbra, 3004-535 Coimbra, Portugal
E-mail: tmelo@ci.uc.pt

Abstract

The synthesis of heterocycles via reactive intermediates, (*e.g.* azadienes, münchnones, aza- and diazafulvenium methides) generated from 1,3-thiazolidines is described. The use of thiazolidines' diastereoselective reactions for the synthesis of chiral heterocyclic compounds is also reported.

Keywords: Thiazolidines, bis(enamines), 1,3-thiazolidine-annulated systems, pyrrolo-[1,2-*c*]thiazoles, azadienes, azafulvenium methides, diazafulvenium methides

Table of Contents

Introduction

1,3-Thiazolidine-4-carboxylic acids have proven to be useful building blocks in organic synthesis. The most interesting aspect of their reactivity is the possibility of carrying out diastereoselective reactions thus allowing the development of synthetic routes to chiral heterocycles. Of particular interest is also the use of 1,3-thiazolidine-4-carboxylic acids as precursors of reactive intermediates (*e.g.* azadienes or dipoles), which widen the type of structures that can be made available from these heterocycles. In the recent past, we have explored both approaches to new heterocyclic compounds and some illustrative examples of this chemistry will be presented in this paper. Particular emphasis will be given to our more recent research work, the generation and reactivity of azafulvenium methide systems.

1. 2-Aza-1,3-butadienes or their tautomers from 1,3-thiazolidine-4-carboxylic acids

The Diels-Alder reaction of acyclic 2-azadienes is a useful method for the preparation of pyridines, dihydropyridines and tetrahydropyridines. *N*-Arylidenedehydroalanine methyl esters had already been prepared in 1979 by Öhler and Schmidt, by the reaction of thiazolidine esters with silver carbonate and DBU.[1] This synthetic strategy for the generation of the 2-azadienes **2a**–**2f** from the corresponding thiazolidines **1a**-**1f** was further explored (Scheme 1). These intermediates can participate as 2-azadienes in Diels-Alder reactions with a range of dienophiles. The azadiene **2a** show a particular reactivity pattern since it reacts with both electron deficient and electron rich dienophiles.[2]

a R = Ph
b R = *p*-Me$_2$NC$_6$H$_4$
c R = *p*-NO$_2$C$_6$H$_4$
d R = 4-pyridyl
e R = COPh
**f** R = CO$_2$Et
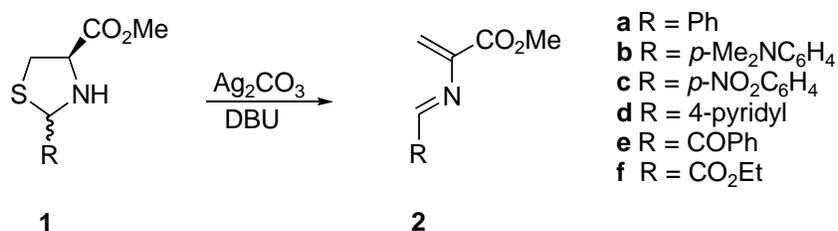
Scheme 1

In fact, the azadiene **2a**, generated *in situ* from the thiazolidine **1a** in the presence of a large excess of but-3-en-2-one, leads to the formation of three compounds in an overall yield of 76%. On the other hand, the same azadiene reacts with *N*-cyclohex-1-enylpyrrolidine with the formation of the cycloadducts **6** (37%) and **7** (20%) (Scheme 2).[2]

3 (20%)   **4** (5%)   **5** (51%)

6 (37%)   **7** (20%)
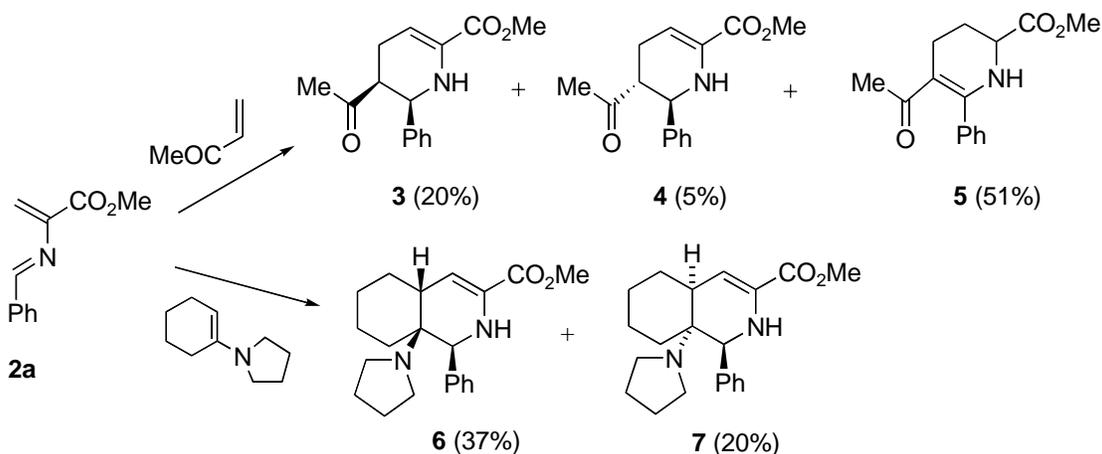
Scheme 2

The unusual reactivity of azadiene **2a**, characterized by the participation in both the *normal* and *inverse* Diels-Alder reaction, can be attributed to the fact that the HOMO and LUMO energy levels are rather close as indicate by AM1 calculations. The AM1 calculated polarization of the relevant frontier orbitals of azadiene **2a** shows a higher contour value at C-4 than at C-1 in both LUMO and HOMO orbitals. This polarization explains the observed regioselectivity in the *normal* and *inverse* Diels-Alder reactions of this compound. On the other hand, the calculations predict both orbitals to be nearly symmetrical with respect to the C=N-C=C plane, a result which is in agreement with the fact that no *endo/exo* selectivity has been experimentally observed.[3]

The azadienes (**1a** and **8**) exclusively act as dienophiles in the reaction with cyclopentadiene and these compounds then undergo an aza Cope rearrangement (a 2-aza-[3,3]-sigmatropic shift) at room temperature, followed by prototropy to give **11**. The cycloadditions of 1-(benzylideneamino)acrylates **2a** with cyclopentadiene gives two products the norbornene ester **10a** and the tetrahydropyridine ester **11a**. When allowed to stand in solution at room temperature for 10 days the product was found to consist of only a single component, compound **11a**. A similar result was obtained starting from thiazolidine **8**. In fact, compound **11b** was also prepared by heating a solution of the Schiff base **10b** in toluene (Scheme 3).[4]
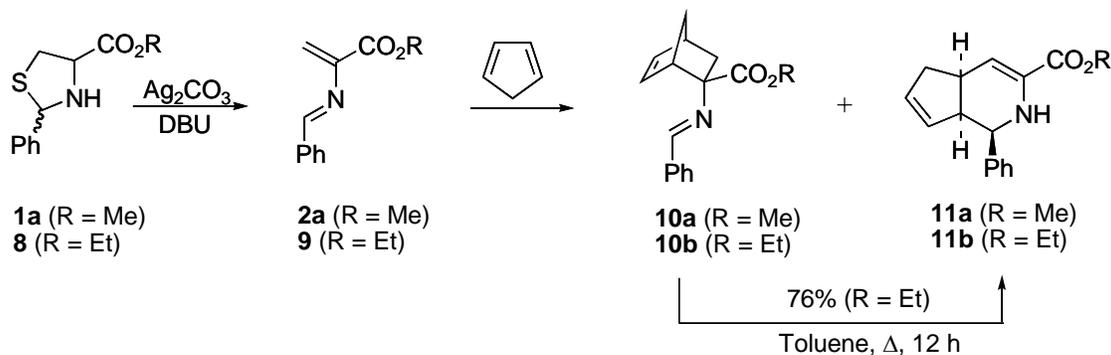
Scheme 3

Thiazolidines **12** react with silver carbonate and DBU to give isolable cross-conjugated bis(enamines) **14**, the more stable tautomers of the azadienes **13** (Scheme 4).[5] The diester **14a** has been also prepared from methyl β-halo-α-aminopropionate hydrohalides by reaction with bases.[6] Other cross-conjugated bis(enamines) of this type have been produced by thermal rearrangement of vinylaziridines.[7] These compounds undergo an interesting photocyclization to 3,4-dihydropyrroles which can be intercepted, as 1,3-dipoles, in cycloaddition reactions with alkenes and alkynes.[6,7,8] Compound **14a** is also reported to react as an electrophile with hydrazines[9] and with primary amines,[10] giving hydrazones and imines of methyl pyruvate as products. The diester **14a** reacts with DDQ to give a single product in high yield, a 1:1 adduct of the diester and DDQ (**15**), which structure was established by X-ray crystallography. Reaction of the diester **14a** with methyl vinyl ketone gives the tetrahydropyridine **16** in moderate yield. The

formation of this product can be rationalized as a conjugate addition–cyclization sequence, somewhat analogous to the Hantzsch dihydropyridine synthesis (Scheme 4).[5]
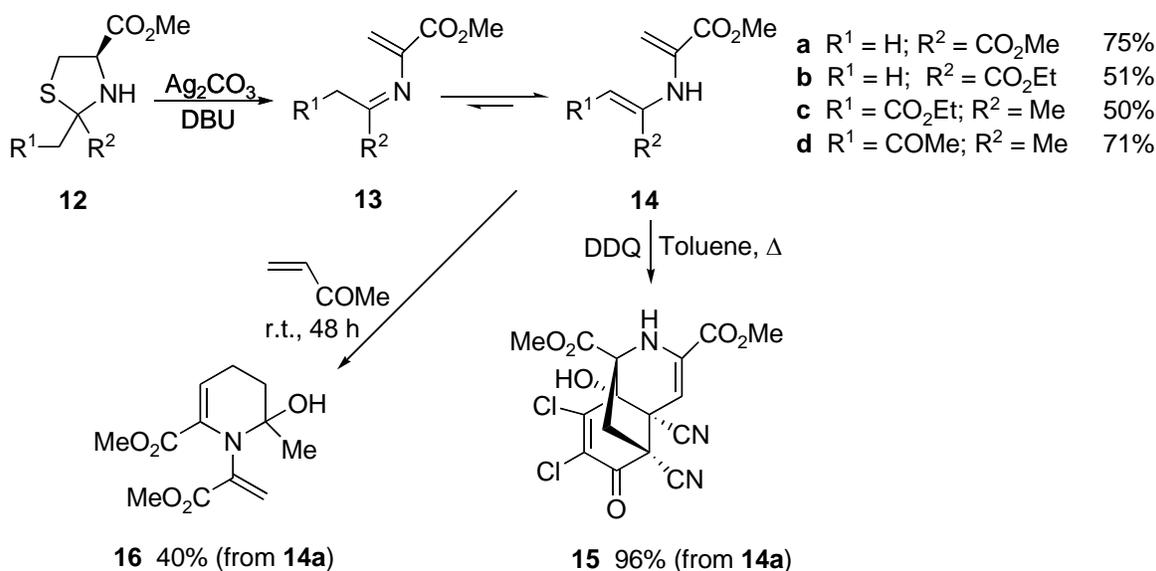
Scheme 4

2. Synthesis of 1,3-thiazolidine-annulated systems

The synthesis of tricyclic isoindole derivatives from *L*-cysteine has been reported. The reaction of *L*-cysteine methyl ester with 2-carboxybenzaldehyde or 2-acetylbenzoic acid results in the direct diastereoselective synthesis of (3*R*,9b*S*)-5-oxo-2,3,5,9b-tetrahydro-thiazolo[2,3-*a*]isoindole-3-carboxylate **18a** and (3*R*,9b*S*)-9b-methyl-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindole-3-carboxylate **18b**, respectively (Scheme 5).[11] These compounds can be converted into the corresponding acids (**19**). The synthesis of compound **18a** has also been reported by Allin and co-workers using more drastic reaction conditions[12] and compound **19a** can also be obtain directly from the reaction of 2-carboxybenzaldehyde with cysteine hydrochloride in the presence of pyridine.[13] The sealed tube thermolysis of **19** in acetic anhydride gives 3-methylene-2,5-dioxo-3*H*,9b*H*-oxazolo[2,3-*a*]isoindoles **20**. The isoindole derivatives (**20**) represent a new member of a class of compounds having a significant number of applications.[14] On flash vacuum pyrolysis compounds **19** undergo decarboxylation to the corresponding chiral (9b*S*)-5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindoles (**21**) in moderate yields.[11b] Compounds **21** have been prepared before from the reaction of carboxybenzaldehyde or 2-acetylbenzoic acid with 2-aminoethanethiol. However, they were obtained as racemic mixtures.[12,13,15] Some 5-oxo-2,3,5,9b-tetrahydrothiazolo[2,3-*a*]isoindoles substituted at C-9 with aryl and heteroaromatic groups have also been prepared as racemic mixtures although the separation of both enantiomers can be achieved by chromatography on cellulose triacetate.[14b]
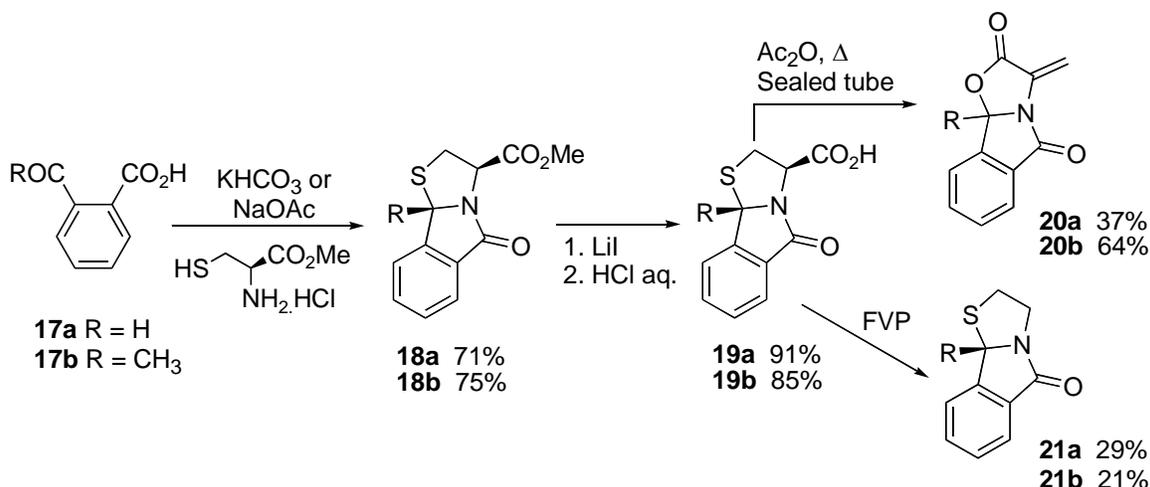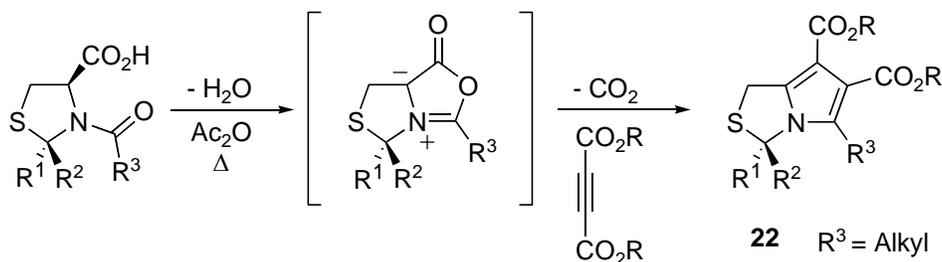
Scheme 5

3. Dipoles from 1,3-thiazolidine-4-carboxylic acids

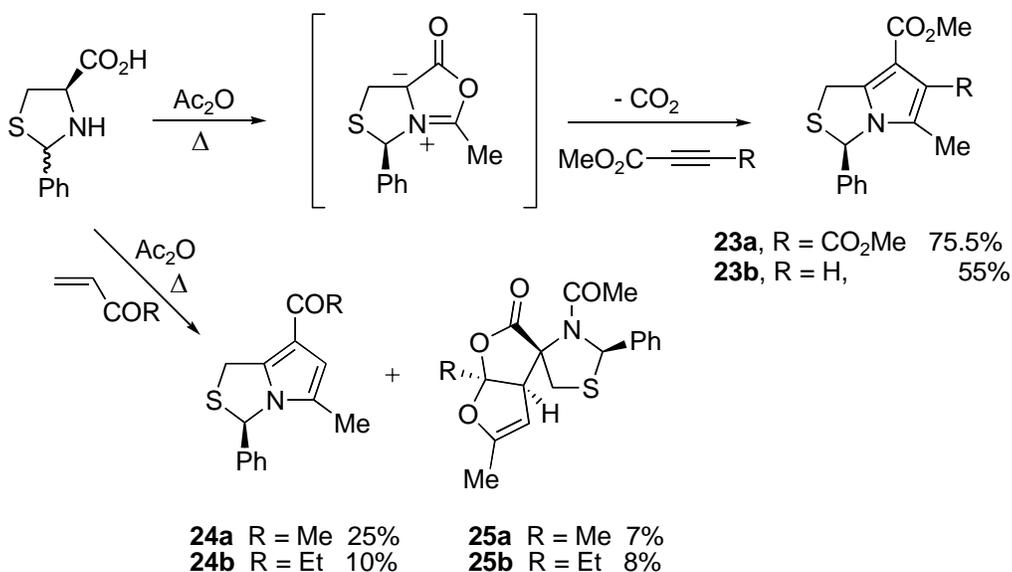### 3.1 Cycloaddition strategy to chiral pyrrolo[1,2-*c*]thiazoles

2-Substituted-1,3-thiazolidine-4-carboxylates are obtained from the reaction of aldehydes and *L*-cysteine esters in a process where a new chiral center at the C-2 position of the thiazolidine is created leading to a mixture of the (*2S,4R*)- and (*2R,4R*)-diastereoisomers. The acylation of the diastereoisomeric mixture can lead to the selective synthesis of *N*-acyl-2-substituted-1,3-thiazolidine-4-carboxylates as pure stereoisomers with (*2R,4R*) or (*2S,4R*) stereochemistry depending on the reaction conditions. In fact 2-substituted-1,3-thiazolidine-4-carboxylates can undergo selective inversion at C-2 through a mechanism involving the opening of the ring but the protection with the acyl group prevents this epimerization and allows the isolation of pure diastereoisomers.[16] The existing chiral center(s) in 1,3-thiazolidine-4-caboxylic acids allows diastereoselective reactions to occur, and these have been widely used for various synthetic purposes.

Györgydeák and co-workers[17] have shown that chiral 3-substituted pyrrolo[1.2-*c*]thiazole-6,7-dicarboxylates (**22**) can be obtained from 2-substituted-*N*-acyl-1,3-thiazolidine-4-carboxylic acids with high enantiomeric excess. The chirality at C-4 of the thiazolidine is lost and the chirality at C-2 (C-3 in the product) is retained (Scheme 6).
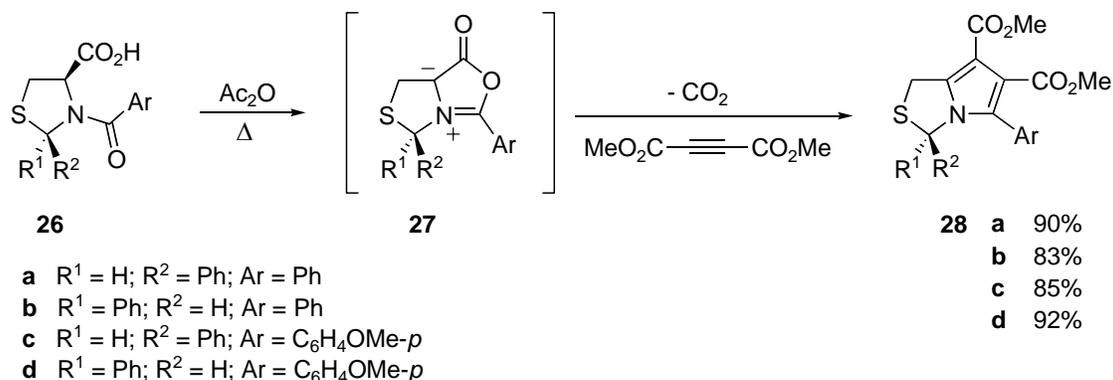

Scheme 6

The münchnones cycloaddition strategy to chiral pyrrolo[1,2-*c*]thiazoles, a class of compounds with potential biological activity, has been further explored.[18] In our work we observed that starting from 2-phenylthiazolidine-4-carboxylic acid as a mixture of 2*R*,4*R*- and 2*S*,4*R*-diastereoisomers, chiral 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivatives were obtained. The thiazolidine was heated in a solution of acetic anhydride in the presence of a dipolarophile. Under these reaction conditions the stereoselective *N*-acylation occurs *in situ*, followed by the intermolecular dipolar cycloaddition giving chiral products with *R* configuration (**23**). The reaction with methyl propiolate gave the regioisomer **23b** exclusively. Heating 2-phenylthiazolidine-4-carboxylic acid in acetic anhydride in the presence of alkyl vinyl ketones two products are obtained, the expected (3*R*)-7-acetyl-3-phenyl-5-methyl-1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles **24** and the spiro compounds **25** (Scheme 7).


23a, R = CO$_2$Me   75.5%
23b, R = H,   55%

24a R = Me 25%   **25a** R = Me 7%
24b R = Et 10%   **25b** R = Et 8%

Scheme 7

N-Benzoyl-1,3-thiazolidines can also be used as precursors of 1*H*,3*H*-pyrrolo[1,2-*c*]thiazole derivatives. In fact, the dipolar cycloadditions of (5*R*)-3-aryl- and (5*S*)-3-aryl-5-phenyl-5*H*,7*H*-thiazolo-[3,4-*c*]oxazol-4-ium-1-olates **27** with dimethyl acetylene-dicarboxylate leads to the synthesis of 1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles (**28**) in very high yield (Scheme 8).[19]

26

a R^1 = H; R^2 = Ph; Ar = Ph
b R^1 = Ph; R^2 = H; Ar = Ph
c R^1 = H; R^2 = Ph; Ar = C$_6$H$_4$OMe-*p*
d R^1 = Ph; R^2 = H; Ar = C$_6$H$_4$OMe-*p*

27

28 a 90%
   **b** 83%
      c 85%
      d 92%

Scheme 8

The synthetic strategy can be applied to the synthesis of chiral tricyclic pyrrolo[1,2-*c*]thiazoles. The generation of 5-substituted-*5H,7H*-thiazolo[3,4-*c*]oxazol-4-ium-1-olates containing internal dipolarophiles involves the *N*-acylation of 2-substituted-thiazolidine-4-carboxylates with the appropriate acid chloride as illustatred by the examples shown in Scheme 9. The reaction conditions used allowed the selective synthesis of *N*-acylthiazolidines **29** with (2*R*,4*R*) stereochemistry which leads to the synthesis of pyrrolo[1,2-*c*]thiazole derivatives **32** with *R* configuration.[20]

29

30

31

32

a n =1; R = Ph; X = O
b n =1; R = Ph; X = S
c n =1; R = Me; X = O
d n = 2; R = Ph; X = O
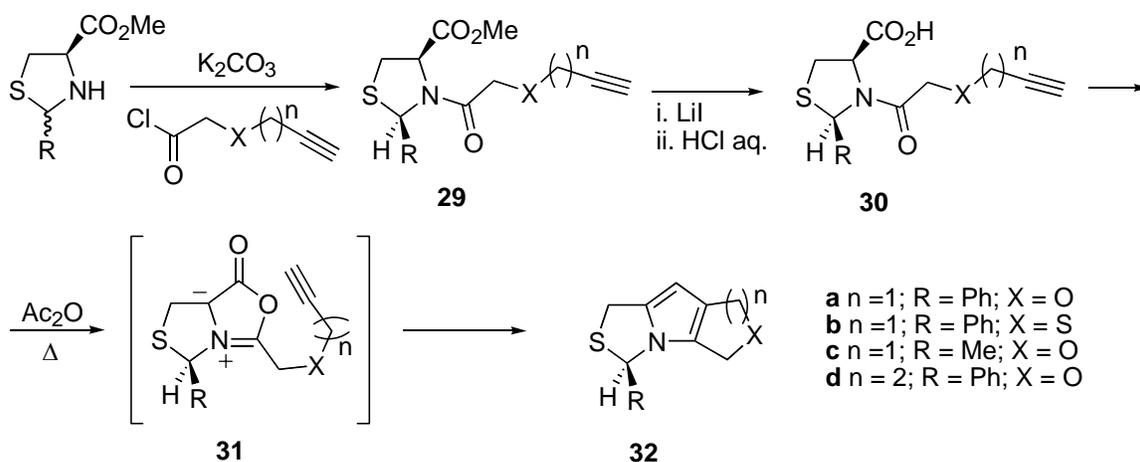
Scheme 9

The reaction of (*p*-methoxyphenyl)glyoxal and *L*-cysteine methyl ester gives as expected a thiazolidine as a mixture of the (2*S*,4*R*)- and (2*R*,4*R*)-diastereoisomers. However, in this case the two diastereoisomers of methyl 2-(*p*-methoxyphenyl)thiazolidine-4-carboxylate can be separated by selective crystallisation proving that the interconversion of these isomers through a reversible ring opening mechanism is difficult. The reaction of each thiazolidine with prop-2-ynyloxyacetic acid chloride in presence of potassium carbonate leads to the corresponding *N*-acylthiazolidines (**33** and **36**) with retention of configuration at C-2. Using our synthetic strategy the chiral 5-(*p*-

methoxyphenyl)-*1H*-pyrrolo[1,2-*c*]thiazole **35** was obtained with *R* configuration from **33** and its enantiomer, 5-(*p*-methoxyphenyl)-*1H*-pyrrolo[1,2-*c*]thiazole **38**, from thiazolidine **36** (Scheme 10).[20b]
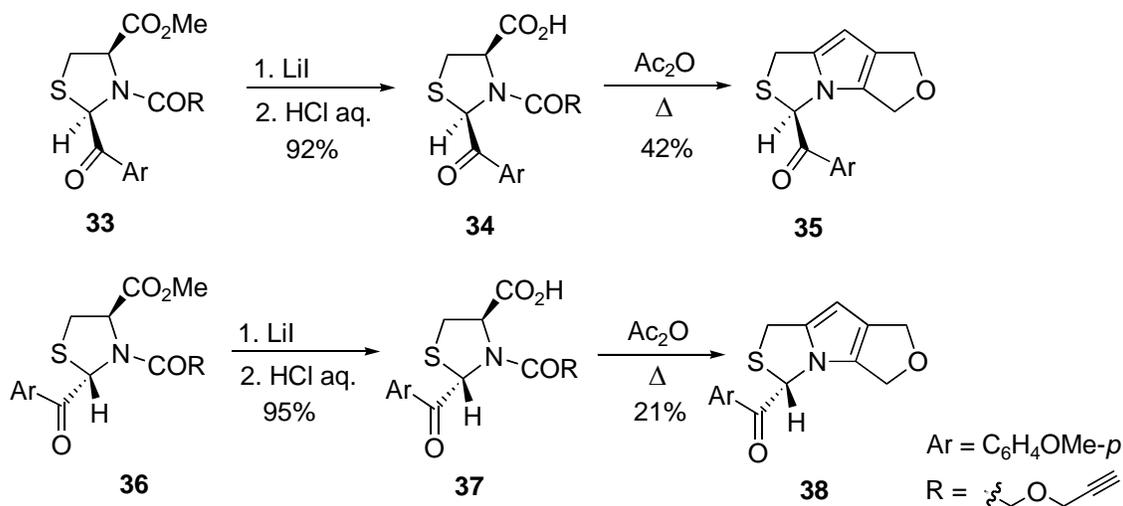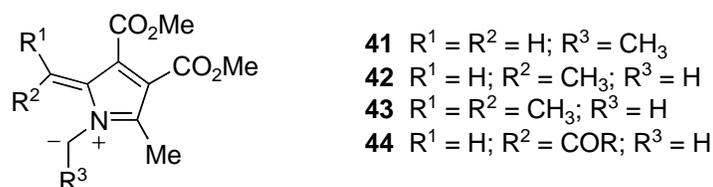

Scheme 10

3.2 Generation and Reactivity of Azafulvenium Methides

The study of pericyclic reactions of extended dipoles (with more than 4π electrons) is an almost unexplored research area. However, Storr and co-workers explored the reactivity of pyrrolo[1,2-*c*]thiazole-2,2-dioxides and pyrazolo[1,5-*c*]thiazole-2,2-dioxides and proved that they can be considered as masked aza- and diazafulvenium methides (**39** and **40**).[21] Earlier, Padwa and co-workers described unsuccessful attempts to extrude SO_2 from pyrrolo[1,2-*c*]thiazole-2,2-dioxides for the generation of an azafulvenium methide, both thermally (300 °C) and photochemically.[22] These systems can be considered as "higher-order" azomethine ylides (**39**) or azomethine imines (**40**) and, in principle, can act as 4π 1,3-dipoles or as 8π 1,7-dipoles.


Storr and co-workers found that the generation of 1-azafulvenium methides (**41**-**44**) by the thermal extrusion of sulfur dioxide from pyrrolo[1,2-*c*]thiazole-2,2-dioxides could be achieved under flash vacuum pyrolysis (FVP) reaction conditions. They described the first evidence for trapping of transient 1-azafulvenium methide systems (**41**-**44**) in pericyclic reactions. These extended dipolar systems **41**-**43** undergo sigmatropic [1,8]H shifts giving vinylpyrroles and the acyl derivatives **44** electrocyclise to give pyrrolo[1,2-*c*]-[1,3]oxazines.[21]

41 $R^1 = R^2 = H$; $R^3 = CH_3$
42 $R^1 = H$; $R^2 = CH_3$; $R^3 = H$
43 $R^1 = R^2 = CH_3$; $R^3 = H$
44 $R^1 = H$; $R^2 = COR$; $R^3 = H$

In relation with our ongoing research on the synthesis of chiral 1*H*,3*H*-pyrrolo[1,2-*c*]thiazoles, we became interested in exploring the generation of azafulvenium methides in order to get further knowledge on the reactivity of these transient 8π 1,7-dipoles.[23,24]

We found that the vinylpyrrole **46a** could be obtained in 61% yield via azafulvenium methide **41** carrying out the reaction in a sealed tube allowing us to conclude that sulfone **45a** extrudes sulfur dioxide without the need of FVP conditions. The flash vacuum pyrolysis of sulfone **45a** was also studied. Interestingly our FVP conditions led to a different outcome than the previously reported result,[21] the synthesis of methyl 1,3-dimethyl-5-oxo-5*H*-pyrrolizine-2-carboxylate **47a**. The pyrolysis of vinylpyrrole **46a** also led to the efficient synthesis of compound **47a** (79%). Therefore, vinylpyrrole **46a** is an intermediate in the formation of methyl 1,3-dimethyl-5-oxo-5*H*-pyrrolizine-2-carboxylate **17a** from sulfone **45a**. The thermolysis of **45b** carried out in a sealed tube led to *N*-vinylpyrrole **46b** in 43% yield. On the other hand, compound **46b** was converted into 5-oxo-5*H*-pyrrolizine **47b** on FVP (44%). The same product was obtained from the FVP of **45b** (Scheme 11).[23,24]
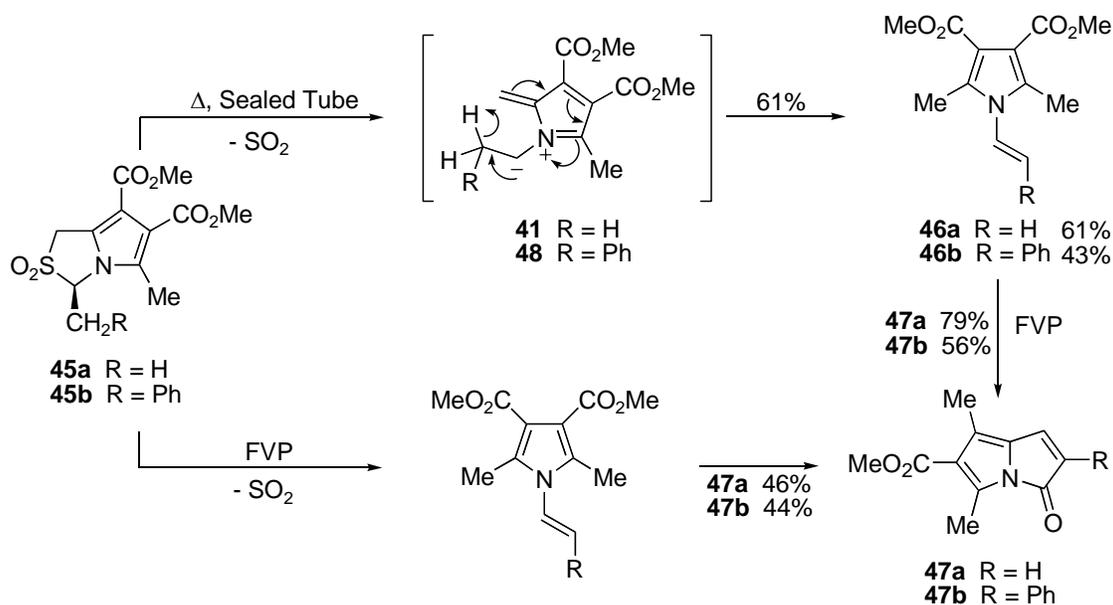
Scheme 11

The study was extended to other 3-alkyl pyrrolo[1,2-*c*]thiazole-2,2-dioxide derivatives.[24] In the case of pyrrolo[1,2-*c*]thiazole **45c** bearing an isopropyl group at C-3, the sealed tube

thermolysis leads to pyrrole **49** in moderate yield. The two substituents at the terminus of the double bond of **49** preclude its conversion into a pyrrolizine. Thus, under FVP reactions conditions two products are obtained, the *N*-vinylpyrrole **49** and 6-oxo-cyclopenta[*b*]pyrrole **50**, which structure was determined by X-ray crystallography (Scheme 12).
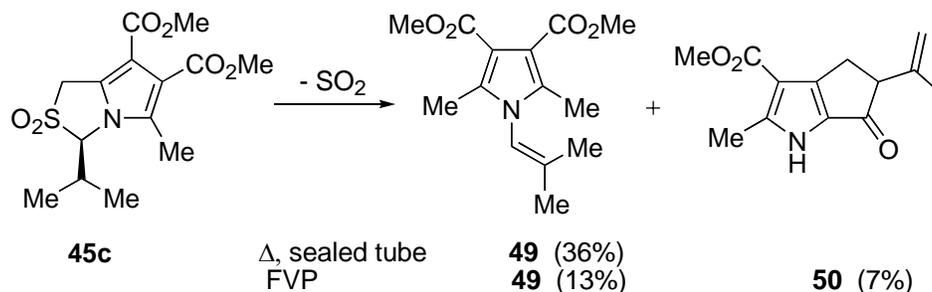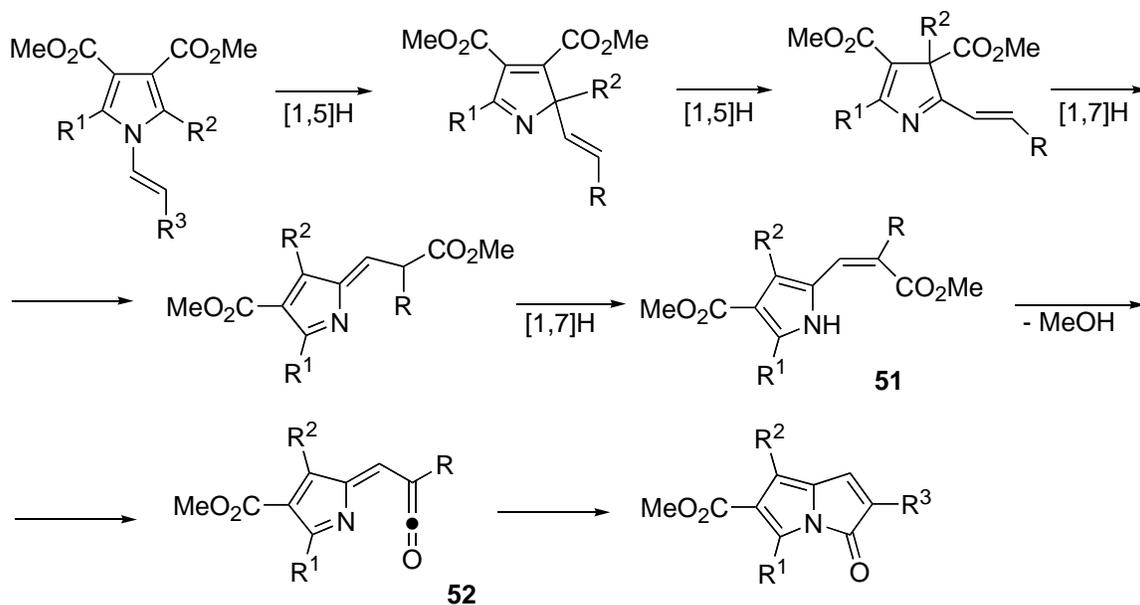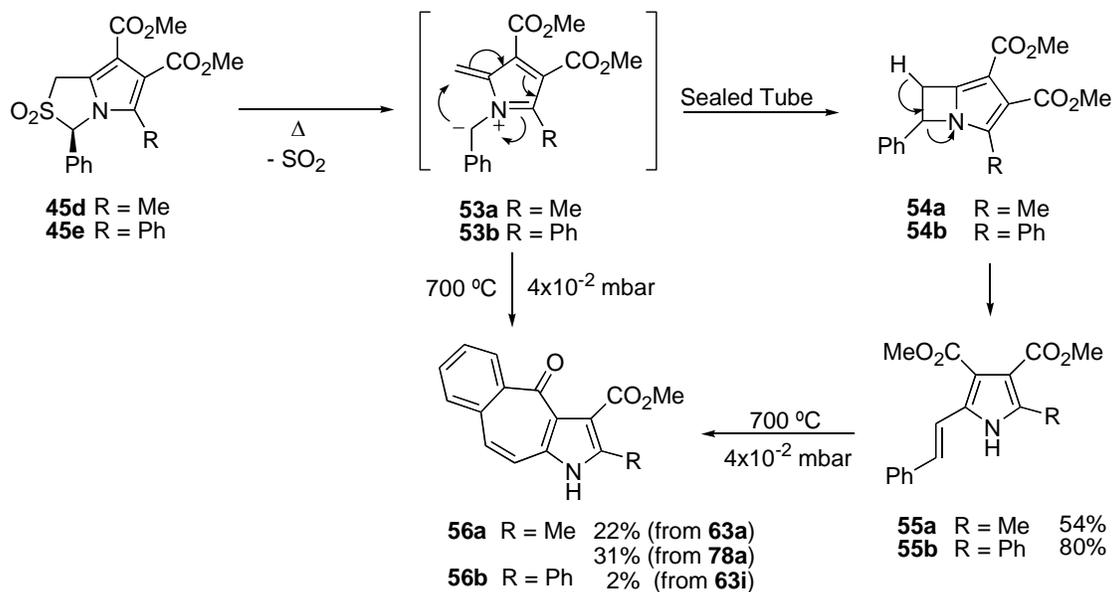

Scheme 12

The mechanism of conversion of pyrrolo[1,2-*c*]thiazole-2,2-dioxides into *N*-vinylpyrroles was proposed by Storr *et al.* who first reported the synthesis of *N*-vinylpyrrole **46a** from the 1-azafulvenium methide **41**.[21] It is an allowed, suprafacial [1,8]H shift in the 8π 1,7-dipolar system (Scheme 11).

The formation of 5-oxo-5*H*-pyrrolizines from *N*-vinylpyrroles can be rationalized as outlined in Scheme 13. It is known that 2-substituted 3-(pyrrol-2-yl)propionate methyl esters undergo concerted elimination of methanol on FVP to give pyrrol-2-ylideneketene intermediates which give pyrrolizinones by electrocyclisation.[25] Thus, pyrrol-2-ylpropionates **51** must be intermediates in the synthesis of the 5-oxo-5*H*-pyrrolizines, formed from the *N*-vinylpyrroles through a sequence of sigmatropic shifts. The pyrrol-2-ylpropionates undergo concerted elimination of methanol giving pyrrol-2-ylideneketenes **52**, which are converted into pyrrolizinones by electrocyclisation.

The thermolysis of 3-phenyl-1*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxides **45d** and **45e** was also studied (Scheme 14). We found that the cheletropic extrusion of SO_2 from these sulfones could be carried out in a sealed tube leading to styryl-1*H*-pyrroles (**55**). The formation of styryl-1*H*-pyrroles **55** can be explained considering the generation of azafulvenium methides (**53**) followed by an 1,7-electrocyclic reaction giving **54**, which rearrange to the final products. Sulfone **45d** is converted into methyl 2-methyl-4-oxo-1,4-dihydro-1-aza-benzo[*f*]azulene-3-carboxylate **56a** on flash vacuum pyrolysis. Under these reaction conditions styryl-1*H*-pyrrole **55a** is formed and converted into a pyrrole fused to a benzocyclohepten-5-one ring system. This was confirmed by promoting the FVP of styryl-1*H*-pyrrole **55a**, which also gave compound **56a** (31%). 3-Phenyl-1*H*-pyrrolo[1,2-*c*]thiazole-2,2-dioxide **45e** and styryl-1*H*-pyrrole **55b** showed similar chemical behavior when compared with **45d** and **55a** respectively, and the corresponding 4-oxo-1,4-dihydro-1-aza-benzo[*f*]azulene-3-carboxylate **56b** could be obtained on FVP, although in low yield.
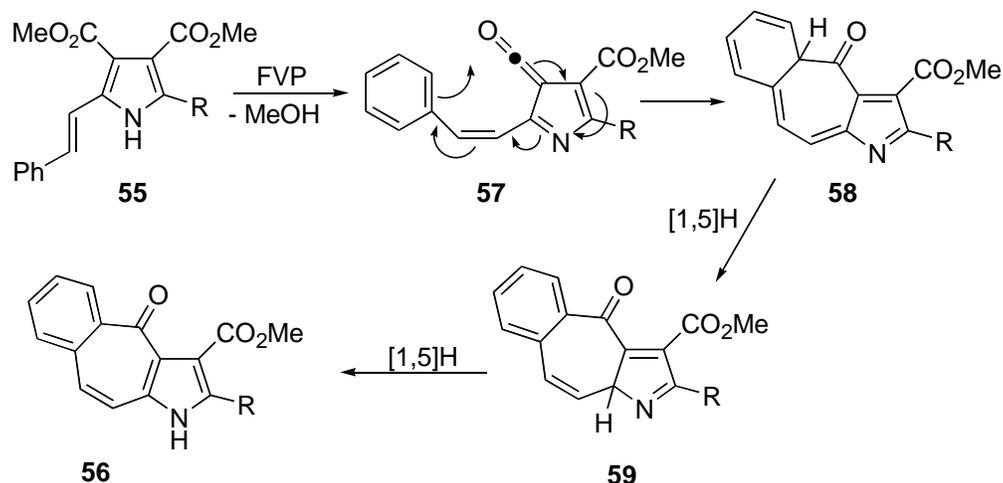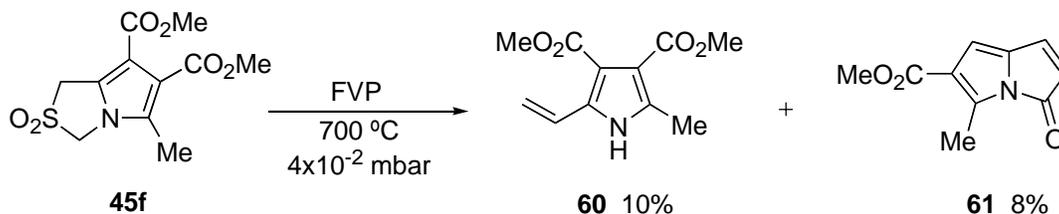
Scheme 13

Scheme 14

The mechanism for the formation of **56** is shown in Scheme 15. The styryl-1*H*-pyrrole **55** generates pyrrol-3-ylketene **57** on eliminating methanol. Electrocyclisation of **57** followed by two sigmatropic H-shifts gives compounds **56**.
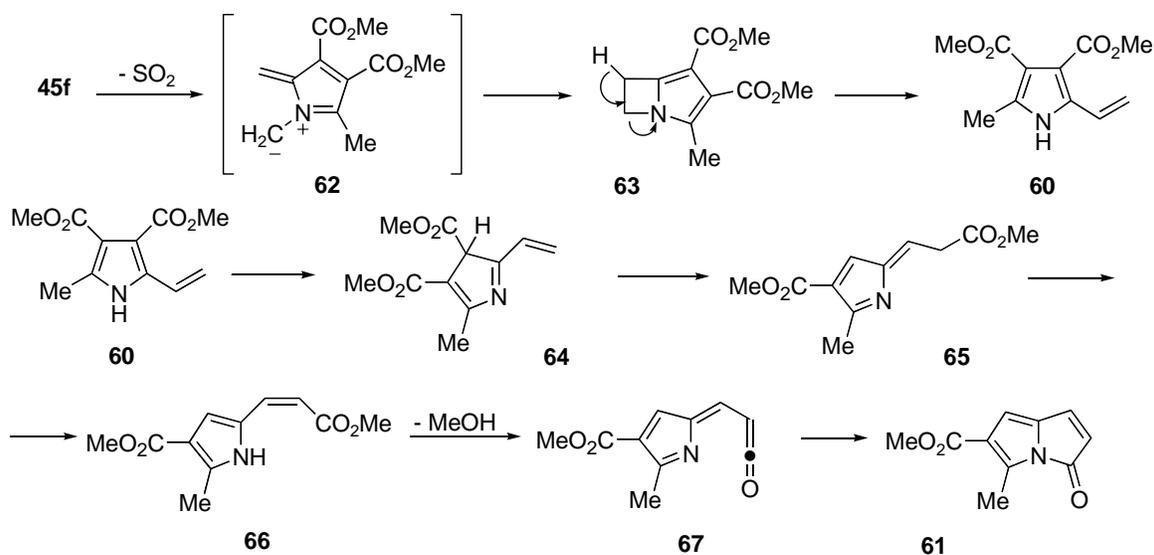
Scheme 15

Padwa *et al.* reported unsuccessful attempts to extrude sulfur dioxide from pyrrolo[1,2-*c*]thiazole-2,2-dioxide **45f** by solution-phase thermolysis (300 ºC).[22] Storr *et al.* considering that this unsuccessful result was due to the high thermal stability of this sulfone, characterized by low bond order of the 3,4-bond of the sulfolene moiety, attempted the flash vacuum pyrolysis.[21] Although sulfur dioxide was eliminated from sulfone **45f** no identifiable products were detected. However, we observed that under our FVP conditions two products are obtained from pyrrolo[1,2-*c*]thiazole-2,2-dioxide **45f**, the *C*-vinylpyrrole **60** and 5-oxo-5*H*-pyrrolizine **61**, although in low yield (Scheme 16).[24]
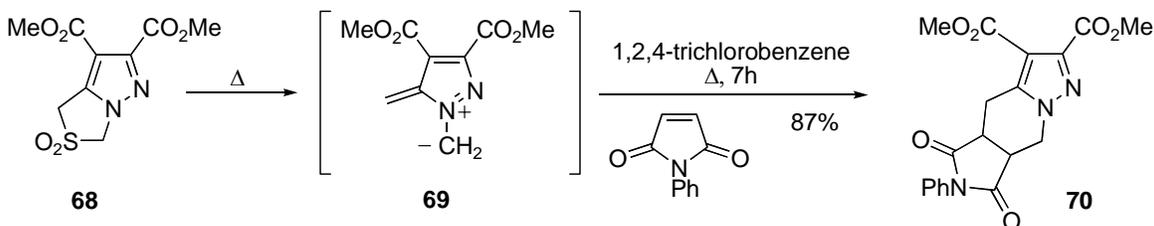

Scheme 16

The 1-azafulvenium methide (**62**) does not have a proton in the appropriate position to allow the suprafacial [1,8]H shift of the type described in Scheme 11 for the synthesis of *N*-vinylpyrroles. Therefore, the process occurs *via* an alternative route, an 1,7-electrocyclic reaction gives **63** which undergoes a rearrangement to pyrrole **60**. This is in fact, a mechanism pathway similar to the one described for the phenyl derivatives **55**. The mechanistic interpretation for the synthesis of 5-oxo-5*H*-pyrrolizine **61** from **60** is also outlined in Scheme 17.[24]
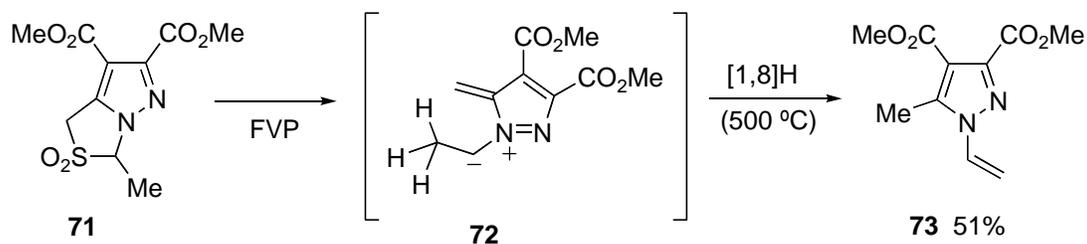
Scheme 17

It has been reported that pyrazole derivative **68** undergoes SO_2 extrusion in solution and the corresponding 1,2-diazafulvenium methide **69** does not react with *N*-phenylmaleimide or dimethyl acetylenedicarboxylate but can be intercepted in $8\pi+2\pi$ cycloaddition with silylated acetylenes giving adducts resulting from the addition across the 1,7-position.[21] We also observed that 1,2-diazafulvenium methide **69** can be trapped by reacting with bis(trimethylsilyl)acetylene, confirming the reported result. However, the dipolar system **69** also participates in the cycloaddition with *N*-phenylmaleimide giving the corresponding cycloadduct in 87% yield (Scheme 18).[26]

Scheme 18

We decided to explore the possibility of generating new diazafulvenium methides systems and study their reactivity in the absence of dipolarophiles. Carrying out flash vacuum pyrolysis of 3-methyl-pyrazolo[1,5-*c*]thiazole-2,2-dioxide **71** at 500 ºC we obtained 1-vinyl-1*H*-pyrazole **73** selectively *via* the diazafulvenium methide **72**, which was trapped in an intramolecular sigmatropic [1,8]H shift (Scheme 19).[26]

Scheme 19

The 3-methyl-pyrazolo[1,5-*c*]thiazole-2,2-dioxide **71** undergoes also SO$_2$ extrusion by solution-phase thermolysis to give **72**, which can be intercepted in $8\pi+2\pi$ cycloadditions with *N*-phenylmaleimide and dimethyl acetylenedicarboxylate giving adducts resulting from the addition across the 1,7-positions in high yields. An attempt to react **72** with bis(trimethylsilyl)acetylene led only to the synthesis of 1-vinyl-1*H*-pyrazole **73** in 16% yield.[26]

Conclusions

1,3-Thiazolidines are interesting precursors of reactive intermediates namely azadienes, and dipoles, which in turn are useful heterocycles building blocks. Exploring thiazolidines' diastereoselective reactions allows the development of routes to chiral heterocyclic compounds, including 1,3-thiazolidine-annulated systems and pyrrolo[1,2-*c*] thiazoles.

Pyrrolo[1,2-*c*]thiazole-2,2-dioxides and pyrazolo[1,5-*c*]thiazole-2,2-dioxides are masked aza- and diazafulvenium methides. The intramolecular trapping of the transient azafulvenium methides in pericyclic reaction, namely sigmatropic [1,8]H shifts and 1,7-electrocyclization, leads to the synthesis of *N*-vinylpyrroles and *C*-vinylpyrroles. Under FVP conditions the vinylpyrroles are converted into heterocycles where another ring system is annulated to pyrrole, such as 5-oxo-5*H*-pyrrolizines and 4-oxo-1,4-dihydro-1-aza-benzo[*f*]azulenes. The synthesis of these heterocycles can also be directly achieved from the flash vacuum pyrolysis of pyrrolo[1,2-*c*]thiazole-2,2-dioxides. The SO$_2$ extrusion of pyrazolo[1,5-*c*]thiazole-2,2-dioxides occurs more easily than from the analogous pyrrolo sulfones and can be carried out in refluxing 1,2,4-trichlorobenzene. The diazafulvenium methides, generated by this way, can be intercepted in $8\pi+2\pi$ cycloadditions giving adducts resulting from the addition across the 1,7-position. In the absence of dipolarophiles the 1-methyl-diazafulvenium methide, generated under FVP reaction conditions, undergoes an intramolecular sigmatropic [1,8]H shift giving a 1-vinyl-1*H*-pyrazole derivative.

Acknowledgements

References

1. Öhler, E.; Schmidt, U. *Chem. Ber.* **1979**, *112*, 107.
2. (a) Gilchrist, T. L.; Gonsalves, A. M. d'A. R.; Pinho e Melo, T. M. V. D. *Tetrahedron Lett.* **1993**, *34*, 4097. (b) Gilchrist, T. L.; Gonsalves, A. M. d'A. R.; Pinho e Melo, T. M. V. D. *Tetrahedron* **1994**, *50*, 13709. (c) Gilchrist, T. L.; Gonsalves, A. M. d'A. R.; Pinho e Melo, T. M. V. D. *Pure & Appl. Chem.* **1996,** *68*, 859.
3. Pinho e Melo, T. M. V. D.; Fausto, R.; Gonsalves, A. M. d'A. R.; Gilchrist, T. L. *J. Org. Chem.* **1998**, *63*, 5350.
4. Gilchrist, T. L.; Gonsalves, A. M. d'A. R.; Pinho e Melo, T. M. V. D. *Tetrahedron Lett.* **1993**, *34*, 6945.
5. Pinho e Melo, T. M. V. D.; Cabral, A. M. T. D. P. V.; Gonsalves, A. M. d'A. R.; Beja, A. M.; Paixão, J. A.; Silva, M. R.; Alte da Veiga, L. *J. Org. Chem.* **1999**, *64*, 7229.
6. Zaima, T.; Matsunaga, Y.; Mitsuhashi, K. *J. Heterocycl. Chem.* **1983**, *20*, 1.
7. Gelas–Mialhe, Y.; Mabiala, G.; Vessière, R. *J. Org. Chem.* **1987**, *52*, 5395.
8. (a) Zaima, T.; Matsuno, C.; Matsunaga, Y.; Mitsuhashi, K. *J. Heterocycl. Chem.* **1984**, *21*, 445. (b) Zaima, T.; Matsuno, C.; Matsunaga, Y.; Mitsuhashi, K. *Nippon Kagaku Kaishi* **1984**, 1293; *Chem. Abstr.* **1984**, *101*, 230340.
9. Zaima, T.; Mitsuhashi, K. *Nippon Kagaku Kaishi* **1979**, 901; *Chem. Abstr.* **1979**, *91*, 140303.
10. Zaima, T.; Matsuno, C.; Mitsuhashi, K. *Nippon Kagaku Kaishi* **1983**, 152; *Chem. Abstr.* **1983**, *98*, 179141.
11. (a) Pinho e Melo, T. M. V. D.; Santos, C. I. A.; Rocha Gonsalves, A. M. d'A.; Paixão, J. A.; Beja, A. M.; Silva, M. R. *Tetrahedron Lett.* **2003**, 44, 8285. (b) Pinho e Melo, T. M. V. D.; Santos, C. I. A.; Rocha Gonsalves, A. M. d'A.; Paixão, J. A.; Beja, A. M. *Tetrahedron* **2004**, *60*, 3949.
12. Allin, S. M.; Vaidya, D. G.; Page, M. I.; Slawin, A. M. Z. *ARKIVOC* **2000**, *1*, 151.
13. Oliver, G. L.; Gates, Jr., J. W. *J. Am. Chem. Soc.* **1958**, 702.
14. (a) Takahashi, I.; Kawakami, T.; Hirano, E.; Yokota, H.; Kitajima, H. *Synlett* **1996**, 353. (b) Mertens, A.; Zilch, H.; König, B.; Schäfer, W.; Poll, T.; Kampe, W.; Seidel, H.; Leser, U.; Leinert, H. *J. Med. Chem.* **1993**, *36*, 2526. (c) Schäfer, W.; Friebe, W.-G.; Leinert, H.; Mertens, A.; Poll, T.; Saal, von der W.; Zilch, H.; Nuber, B.; Ziegler, M. L. *J. Med. Chem.* **1993**, *36*, 726. (d) Clercq, E. *J. Med. Chem.* **1995**, *38*, 2491. (e) Allin, S. M.; Vaidya, D. G.; Page, M. I.; Slawin, A. M. Z.; Smith, T. *Tetrahedron Lett.* **2000**, *41*, 2219.

15. Hiskey, R. G.; Dominianni, S. J. *J. Org. Chem.* **1965**, *30*, 1506.

16. *1,3-Thiazolidine-4-carboxylic Acids as Building Blocks in Organic Synthesis*, Teresa M. V. D. Pinho e Melo In *Targets in Heterocyclic Systems – Chemistry and Properties*, Attanasi, A.; Spinelli, D., Eds., Italian Society of Chemistry, 2004; Vol.8, pp 288-329.

17. Györgydeák, Z.; Szilágyi, L.; Kajtár, J.; Argay, G.; Kálmán, A. *Monatsh. Chem.* **1994**, *125*, 189.

18. Pinho e Melo, T. M. V. D.; Soares, M. I. L.; Barbosa, D. M.; Rocha Gonsalves, A. M. d'A.; Matos Beja, A.; Paixão, J. A.; Ramos Silva, M.; Alte da Veiga, L. *Tetrahedron* **2000**, *56*, 3419.

19. Pinho e Melo, T. M. V. D.; Gomes, C. S. B.; Rocha Gonsalves, A. M. d'A.; Paixão, J. A.; Matos Beja, A.; Ramos Silva, M.; Alte da Veiga, L. *Tetrahedron* **2002**, *58*, 5093.

20. (a) Pinho e Melo, T. M. V. D.; Barbosa, D. M.; Ramos, P. J. R. S.; Rocha Gonsalves, A. M. d'A.; Gilchrist, T. L.; Matos Beja, A.; Paixão, J. A.; Ramos Silva, M.; Alte da Veiga, L.; *J. Chem. Soc. Perkin Trans. I* **1999**, 1219. (b) Pinho e Melo, T. M. V. D.; Soares, M. I. L.; Rocha Gonsalves, A. M. d'A.; Paixão, J. A.; Matos Beja, A.; Ramos Silva, M. *J. Org. Chem.* **2002**, *67*, 4045.

21. (a) Sutcliffe, O. B.; Storr, R. C.; Gilchrist, T. L.; Rafferty, P.; Crew, A. P. A. *Chem.Comm.* **2000**, 675-676; (b) Sutcliffe, O. B.; Storr, R. C.; Gilchrist, T. L.; Rafferty, P. *J. Chem. Soc. Perkin Trans. 1* **2001**, 1795-1806.

22. Padwa, A.; Fryxell, G. E.; Gasdaska, J. R.; Venkatramanan, M. K.; Wong, G. S. K. *J. Org. Chem.* **1989**, *54*, 644-652.

23. Pinho e Melo, T. M. V. D.; Soares, Maria I. L.; Rocha Gonsalves, A. M. d'A. McNab, H. *Tetrahedron Lett.* **2004**, *45*, 3889-3893.

24. Pinho e Melo, T. M. V. D.; Soares, Maria I. L.; Rocha Gonsalves, A. M. d'A.; Paixão, J. A.; Matos Beja, A,; Ramos Silva, M. *J. Org. Chem.* **2005**, *70*, 6629-6638.

25. McNab, H.; Parson, S.; Stevenson, E. *J. Chem. Soc. Perkin Trans. I* **1999**, 2047-2048.

26. Pinho e Melo, T. M. V. D.; Soares, M. I. L.; Rocha Gonsalves, A. M. d'A. *Tetrahedron Lett*. **2006**, 791-794.