

## The use of 2-azadienes in the Diels–Alder reaction

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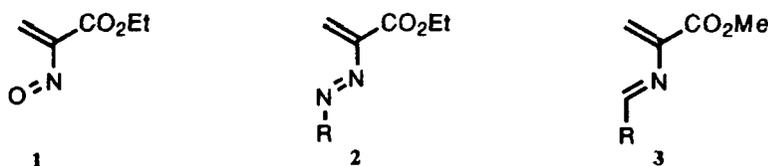
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### Abstract

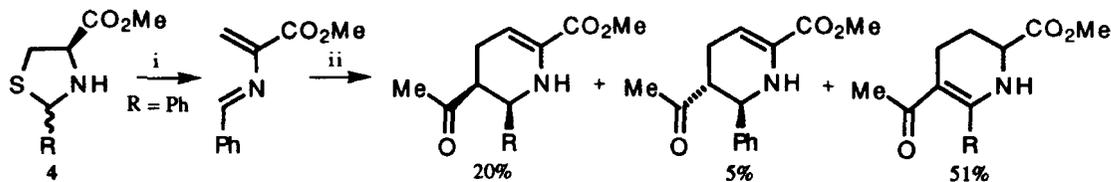
Cysteine methyl ester has been converted into a series of 2-substituted methyl thiazolidine-4-carboxylates by reaction with carbonyl compounds including aromatic aldehydes and  $\alpha$ - and  $\beta$ -oxoesters. These thiazolidines react with silver carbonate with the elimination of the elements of  $\text{H}_2\text{S}$  and with the formation of transient 1-substituted 2-azadiene carboxylate esters. The Diels–Alder reactions of these azadienes have been shown to take place with both electron rich dienophiles (enamines) and with electron deficient dienophiles (enones). The cycloaddition reactions are regioselective but not stereoselective. Exceptionally, the intermediates act as dienophiles when reacted with cyclopentadiene. Some of the 2-azadienes derived from oxoesters tautomerise to isolable enamines. A new example of intramolecular 1,3-dipolar cycloaddition of a Schiff base of a *S*-allylcysteine methyl ester derivative is described.

We have previously reported the generation of ethyl 2-nitrosopropenoate **1** (1) and the analogous azo esters **2** ( $\text{R} = t$ -butoxycarbonyl, 2,4-dinitrophenyl, tosyl) (2). These transient heterodienes undergo cycloaddition reactions with a range of electron rich alkenes. We therefore set out to investigate methods of generation of 2-azadienes having the general structure **3**, which we hoped would also be useful as partners in the Diels–Alder reaction.



2-Azadienes of the general structure **3** ( $\text{R} = \text{aryl}$ ) had first been reported by Öhler and Schmidt, who had generated them from Schiff bases of cysteine methyl ester by reaction with silver carbonate and DBU (3). Wulff and co-workers later reported that the same compounds could be produced from Schiff bases of serine methyl ester by dehydration (4). The compounds prepared were much longer lived than the heterodienes **1** and **2**, and some were characterised spectroscopically. Although no intermolecular cycloaddition reactions were reported some of these compounds were shown to dimerise by what is formally a Diels–Alder process (5).

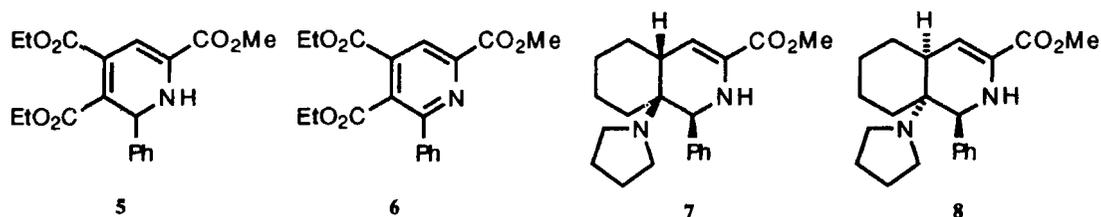
The Schiff base formed from cysteine methyl ester and benzaldehyde exists predominantly as the tautomeric thiazolidine ester **4** ( $\text{R} = \text{Ph}$ ). This compound was treated with silver carbonate and DBU in order to generate the 2-azadiene **3** ( $\text{R} = \text{Ph}$ ). Reactions which were carried out in the presence of electron rich alkenes such as ethyl vinyl ether failed to produce any cycloadducts. However a reaction carried out in the presence of an electron deficient dienophile, but-3-en-2-one, was successful (Scheme 1).



Scheme 1 i,  $\text{Ag}_2\text{CO}_3$ , DBU; ii,  $\text{MeCOCH}=\text{CH}_2$ .

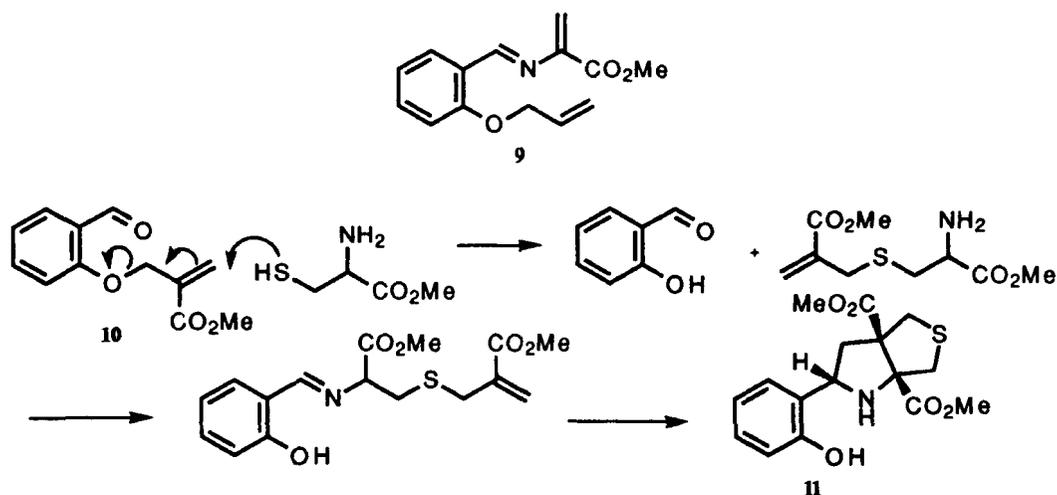
The reaction led to the isolation of three cycloadducts in good overall yield. All show the same regioselectivity but the cycloaddition apparently shows little *endo/exo* selectivity. The major product has undergone extensive prototropy but it is not formed from either of the two minor products; this was established by subjecting each independently to the reaction conditions.

A survey of the reaction of the 2-azadiene **1** ( $R = \text{Ph}$ ) with other electron deficient dienophiles was then undertaken (6). This confirmed the picture derived from the reaction with but-3-ene-2-one: the cycloaddition reactions were regioselective but showed little other selectivity. In several cases the reaction products isolated resulted from further oxidation of the adducts to dihydropyridines or to pyridines; for example, the reaction with diethyl acetylenedicarboxylate led to the formation of the esters **5** and **6** in an overall yield of 35%. It was then discovered that this azadiene would also undergo cycloaddition reactions with enamines; for example, the reaction with 1-cyclohexenylpyrrolidine led to the formation of the isolation of the adducts **7** (37%) and **8** (20%).



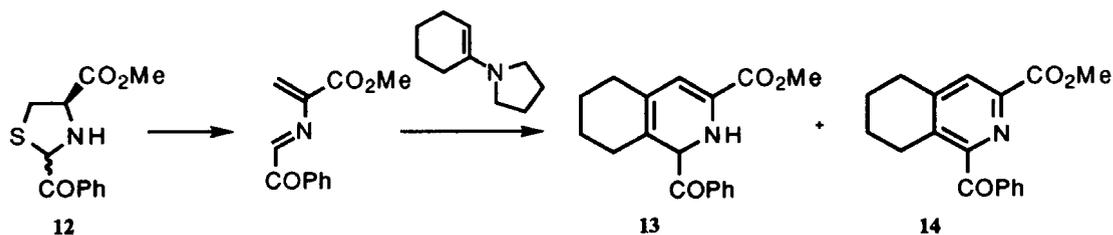
The 2-azadiene **3** ( $R = \text{Ph}$ ) thus forms cycloadducts with strongly electron deficient and strongly electron rich dienophiles, but not with those intermediate in character. This behaviour, which is uncommon with dienes but which is observed with some 1,3-dipoles, indicates that the cycloaddition is changing in character from a diene HOMO controlled reaction with electron deficient dienophiles to a diene LUMO controlled reaction with electron rich dienophiles. We tried to improve the efficiency of the addition to dienophiles of the two types by varying the aryl group in the azadiene **3**. Thus, the 2-azadiene **3** ( $R = 4$ -dimethylaminophenyl) was generated and was reacted with electron deficient dienes and the intermediates **3** ( $R = 2$ -pyridyl and 4-nitrophenyl) were reacted with electron rich dienes. The effects on the yields of products were not large and no new types of cycloadduct were formed (for example, the azadienes bearing electron deficient aryl substituents still failed to react with ethyl vinyl ether).

It is well known that intramolecular Diels-Alder reactions can often proceed even when the internal dienophile has little or no activation so attempts were made to carry out cycloadditions of this type. The azadiene **9** was first generated but this failed to undergo intramolecular cycloaddition; only hydrolysis products were isolated. The dienophile was then activated and an attempt was made to generate the corresponding azadiene from the precursor aldehyde **10**. However, its reaction with cysteine methyl ester took an unexpected pathway (Scheme 2). The activated allyl group was transferred to sulfur by a nucleophilic addition-elimination sequence and the resulting *S*-allylcysteine then formed a Schiff base. This could be isolated but it smoothly underwent an internal 1,3-dipolar cycloaddition at room temperature to give the cycloadduct **11**. An X-ray crystal structure of the final product confirmed its structure. Two examples of internal dipolar cycloadditions of this type involving Schiff bases of *S*-allylcysteine have been recorded by Grigg and his co-workers (7).



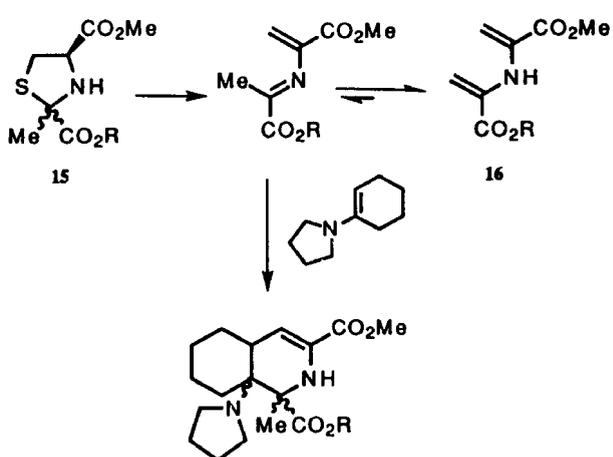
Scheme 2

The relative stability of thiazolidines in comparison with acyclic imines allows a wider range of carbonyl compounds to be condensed with cysteine methyl ester than with most aliphatic primary amines. We therefore attempted to extend the range of 2-azadienes by making use of this characteristic. Thiazolidines were prepared from simple aliphatic aldehydes including 2,2-dimethylacetaldehyde and formaldehyde, and from an aromatic ketone, acetophenone. The corresponding azadienes were generated in the usual way. These intermediates failed to form cycloadducts either with electron rich or with electron deficient dienophiles, and only hydrolysis products were detected. The reactions of thiazolidines derived from activated aldehydes and ketones were more successful. Phenylglyoxal reacted with cysteine methyl ester to give the thiazolidine **12**; this was converted into the 2-azadiene in the standard way and the azadiene was intercepted in fair to good yield by reaction with enamines. For example, the compounds **13** (35%) and **14** (14%) were isolated from the reaction with 1-cyclohexenylpyrrolidine (Scheme 3). Ethyl glyoxylate reacted with cysteine methyl ester in a similar way and the derived 2-azadiene also gave adducts with enamines.

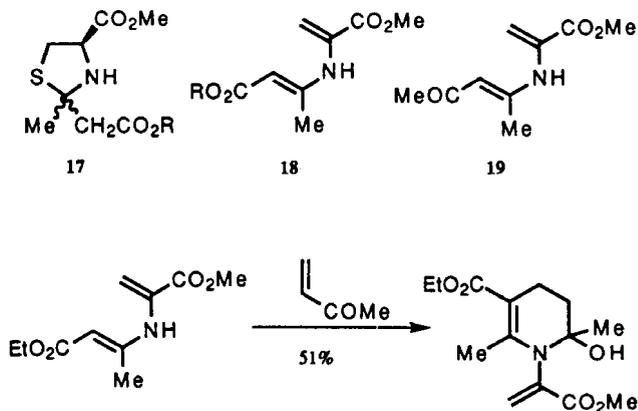


Scheme 3

The reaction of cysteine methyl ester with ethyl pyruvate and with methyl pyruvate led to the formation of the corresponding thiazolidines **15**. These compounds reacted with silver carbonate and DBU in the absence of dienophiles to give isolable products in good yield. These compounds proved to be stable for extended periods and they were fully characterised. Their structures were established as the bis(enamines) **16**; evidently they were produced from the 2-azadienes by prototropy (Scheme 4). This process proved to be a reversible one, because when the esters **16** were allowed to react with 1-cyclohexenylpyrrolidine, products were isolated in moderate yield which correspond to those expected for a cycloaddition of the enamine to the 2-azadienes (the stereochemistry of the products has not been established).



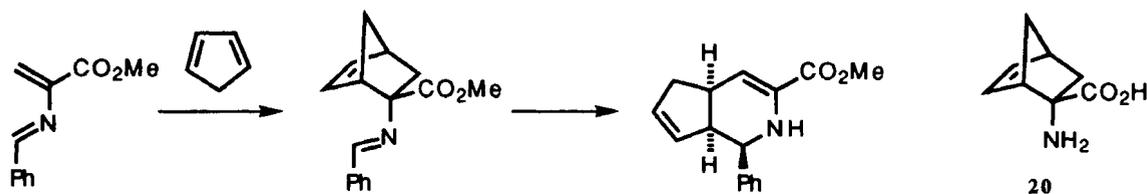
Scheme 4



Scheme 5

The thiazolidines derived from the reactions of  $\beta$ -ketoesters and 1,3-diketones also gave stable bis(enamines) upon treatment with silver carbonate and DBU. For example, the thiazolidines **17** formed from ethyl acetoacetate and methyl acetoacetate gave the bis(enamines) **18** and compound **19** was prepared in a similar way starting from acetylacetone. Compounds of the type **16**, **18** and **19** are, potentially, useful building blocks for heterocyclic synthesis. We have started to explore their reactions; one example, shown in Scheme 5, is a Hantzsch type tetrahydropyridine synthesis with an enone as the reaction partner. A reaction sequence analogous to this has also been carried out with the bis(enamines) **16**.

The thiazolidines derived from cysteine methyl ester and carbonyl compounds are thus a source of a wide variety of 2-azadienes or their tautomers. The Diels-Alder reactions of the 2-azadienes are not as selective, nor as high yielding, as those of the heterodienes **1** and **2** which we have studied earlier. These intermediates may ultimately prove to be more useful in other types of reaction, such as that shown in Scheme 5. A further illustration is provided by the reaction of the 2-azadiene **3** (R = Ph) with cyclopentadiene in which the intermediate **3** acts initially as a dienophile (Scheme 6) (8). The adduct then undergoes an aza Cope rearrangement at room temperature. The initial reaction provides a route to the amino acid **20** and related compounds which complements those previously reported (9).



Scheme 6

**Acknowledgements:** The majority of the work described here was carried out while Teresa Pinho e Melo was on a study visit to the University of Liverpool. We thank JNICT, Chymiotecnon and Fundação Calouste Gulbenkian for financial support. We also thank Mr J. V. Barkley for carrying out the X-ray crystal structure determination of compound **11**.

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