Budapest University of Technology and Economics
Department of Organic Chemical Technology

Cycloadditions and electrocyclisations of azomethine ylides

PhD thesis

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Introduction

The chemistry of azomethine ylides was investigated by many research groups worldwide. These reactive intermediates were used in the synthesis of many important compounds (pharmaceuticals, alkaloids etc.). These facts suggested us to continue the work on this field, which gives the body of my PhD thesis. This can be divided to the following sections:

Experiments on 1,3-dipolar cycloadditions:

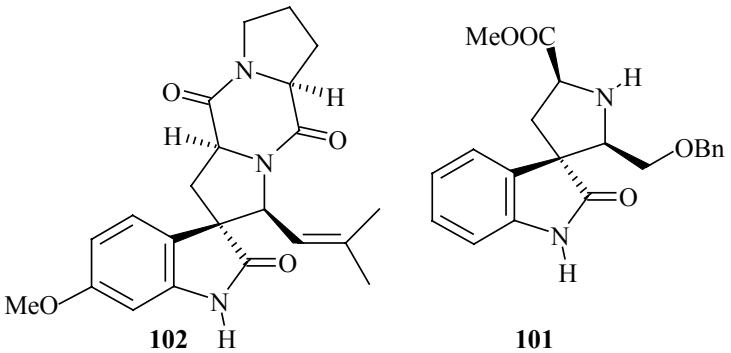
1. Synthesis of spiro-oxindole alkaloid analogues
2. Synthesis of tricyclic core of martinelline alkaloids
3. Preparation of highly substituted pyrroles
4. Tandem in situ Generation of Azomethine Ylides and Base Sensitive Nitroethylene Dipolarophiles
5. Cycloadditons of 4H-pyran-4-one derivatives
6. Synthesis of oxazolidnes and 1-aryl-2-dimethylaminoethanols

Experiments on 1,7-electrocyclisations:

7. Electrocyclisations with ester-stabilised azomethine ylides and with the participation of a nitro-group

Results:

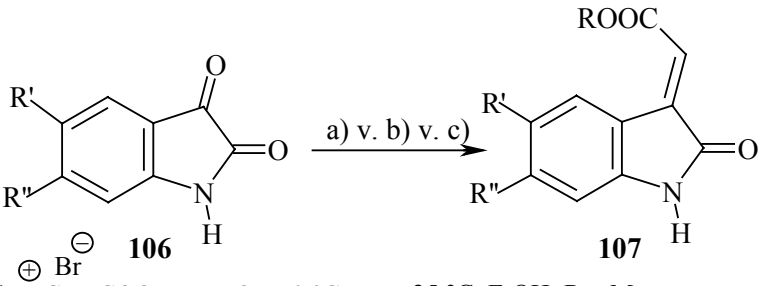
1.1. The spiro-oxindole alkaloids isolated mainly from plants indigenous to south east Asia. A number of pharmacologically active compounds contains this skeleton, for example the spyrotyprostatine **102**. This molecule and more interestingly some of its synthesis intermediates (*e.g.* **101**) inhibited the growths of several tumors.



102 **101**

Figure 1

The dipolarophiles for the cycloadditions were synthesized by the Wittig-reaction of the appropriately substituted isatines (**106**):



a) Ph_3P-CH_2-COOMe; NaOEt; 0 °C ⟶ 25 °C; EtOH; R = Me;

b) Ph_3P=CH-COOMe; 25 °C; dioxane; 30 min; R = Me;

c) $(EtO)_2P(O)CH_2COOEt$; NaOEt; EtOH; 0 °C ⟶ 25 °C ⟶ heating; 1 h; R= Et;

Figure 2

The dipolarphiles easily reacted with different azomethine ylides:

1.2. Reactions with dipoles generated by decarboxylation of amino acids:

The non-stabilized azomethine ylide, generated from sarcosine and carbonyl compounds easily reacted with 2-oxoindolin-3-ylidene derivatives. The best carbonyl reactants were the aromatic and heteroaromatic aldehydes. In these reaction mainly (or sometimes exclusively) the *endo* cycloadducts were formed. In other experiments acrolein derivateves were succesfully reacted as aldehyde component. Instead of sarcosine N-benzyl-glycine and proline were used as amino acids (**117, 119, 120,** *Figure 3)*.

1.3. Reactions with dipoles generated by N-metallation

Azomethine ylides generated from the Schiff base of aromatic aldehydes in the presence of lithium bromide or silver acetate with triethylamine smoothly reacted with the dipolarophiles investigated. In this reactions **121** and **122** formed as a single isomer, while **123** was a mixture of *endo* and *exo* products.

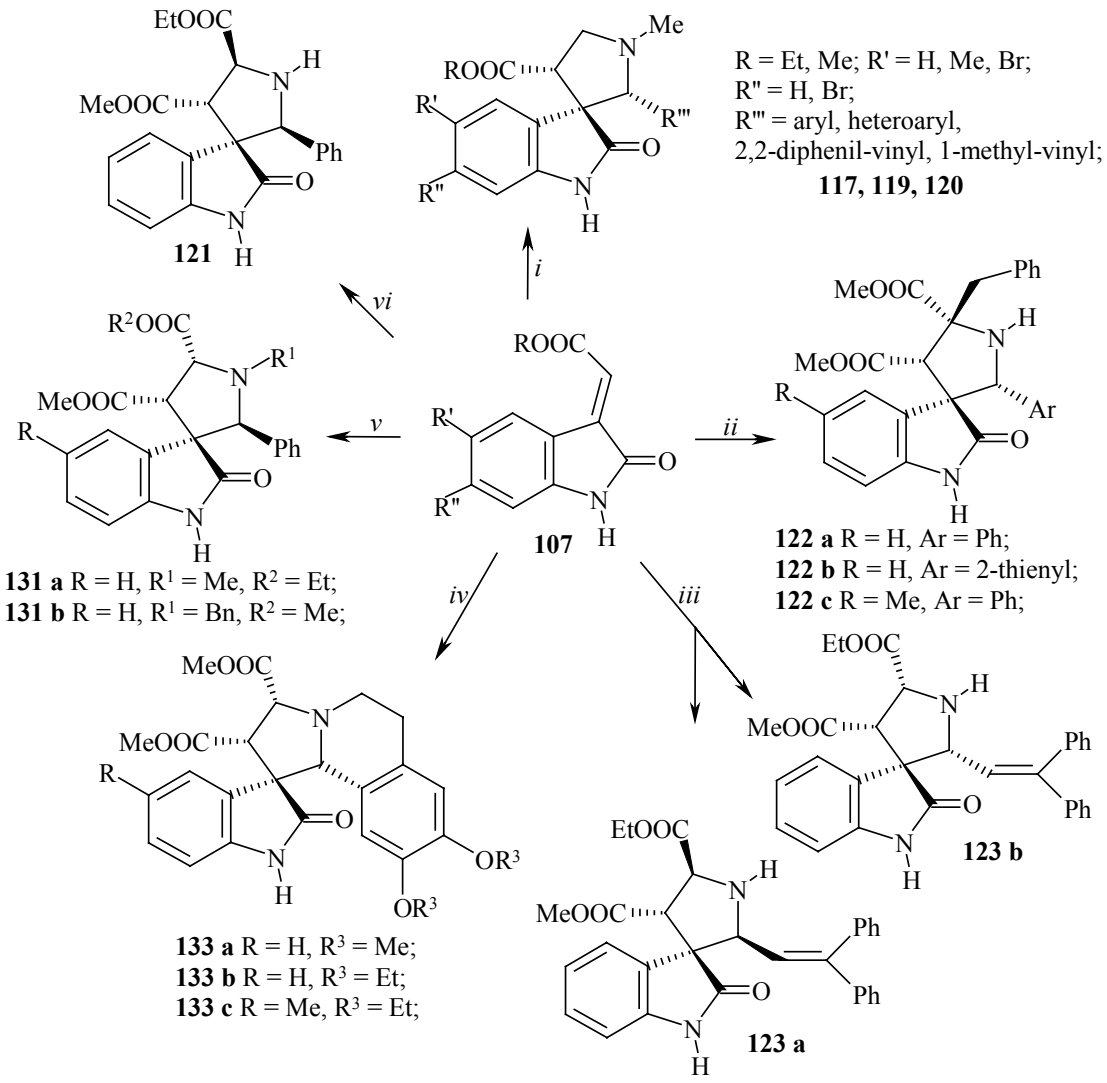


Figure 3

i. R‴-CHO, sarcosine, toluene, heating;
ii. Ph-CH_2-CH(COOMe)N=CH-Ar; AgOAc, toluene, Et_3N, 25 °C;
iii. Ph_2C=CH-CH=N-CH_2-COOEt; AgOAc, toluene, Et_3N, 25 °C;
iv. 3,4-di(m)ethoxy-6,7-dihydro-*N*-(metoxicarbonyl-methy)-isoquinolinium-bromide; Et_3N, MeOH;
v. R^1-NH-CH_2-$COOR^2$, Ph-CHO, toluene, heating;
vi. Ph-CH=N-CH_2-COOEt; LiBr, MeCN, Et_3N, 25 °C;

2 Martinellic acid (**135**) and martinelline (**134**) isolated from the roots of the tropical plant *Martinella iquitosensis* are the first alkaloids with the pyrrolo[3,2-*c*]quinoline ring system. These compounds show unique biological activity, as they are the first naturally occurring nonpeptide bradykinin B_1 and B_2 receptor antagonists.

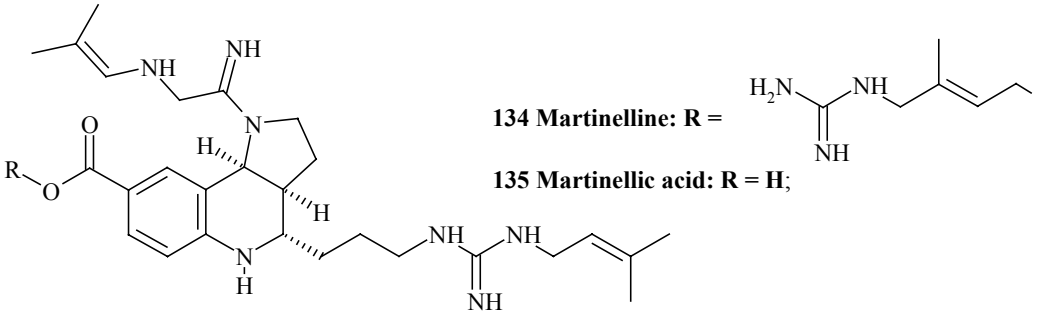


Figure 4

In our work we have targeted the simple synthesis of pyrrolo[3,2-*c*]quinoline ring system. We have achieved this starting from the imines **152,** which were reacted with dipolarophiles in the presence of silver or lithium catalysts in a stereoselecitve 1,3-dipolar cycloaddition. These reactions were followed by a reductive cyclisation to **162** with good yields, which could be a novel building block for combinatorial chemistry applications or a starting material for synthesis of the natural product itself (*Figure 107*).

To our surprise, the reduction of cycloadducts formed from methyl vinyl ketone as a dipolarophile did not give us the expected cyclised product, but we could isolate quantitatively the α-amino acid esters **158**.

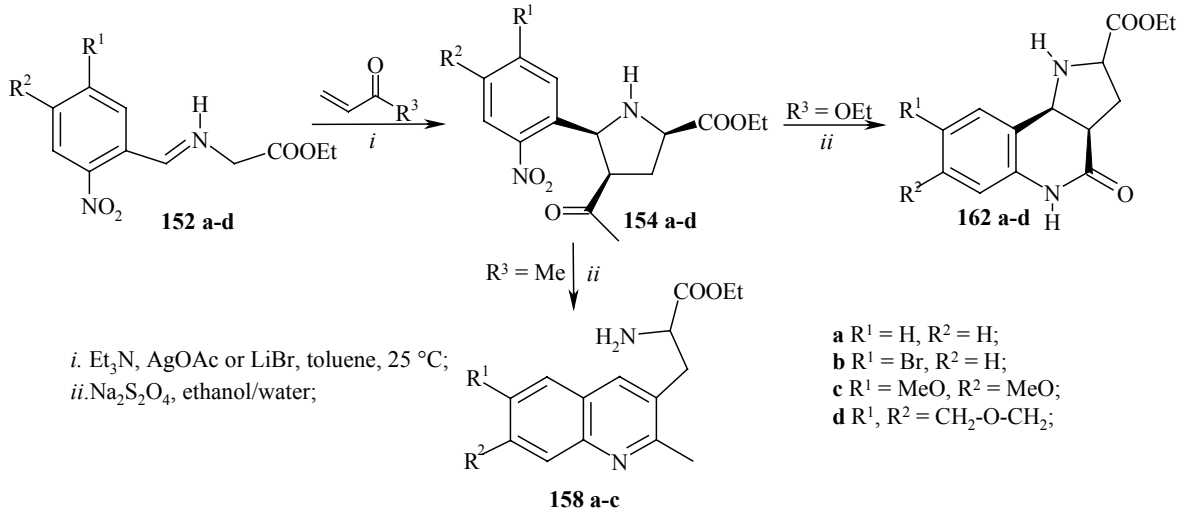
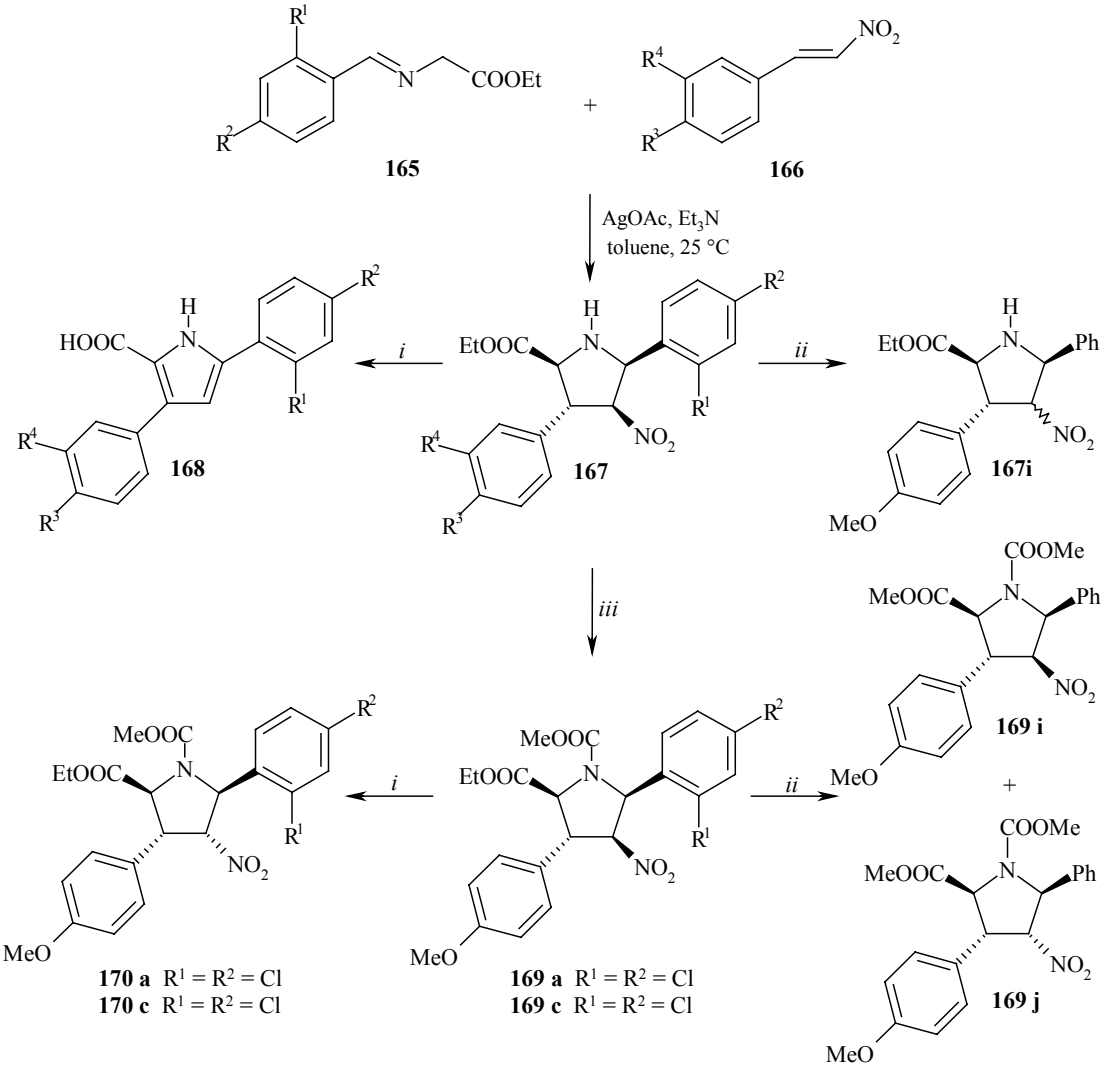


Figure 5

3. The biological importance of pyrrole-containing natural products has stimulated extensive research on the synthesis and reactivity of pyrrole derivatives. There are many methods for the synthesis of these important heterocycles, including the 1,3-dipolar cycloaddition of azomethine ylides to alkynes, followed by aromatization of the intermediate pyrrolines. However, the preparation of pyrroles by dehydrogenation of pyrrolidines has found little application due to the lack of general methods, and to the forcing conditions required in most cases.

We have found that a variety of substituted nitro-pyrrolidines, prepared in a 1,3-dipolar cycloaddition, can be converted into pyrroles using alkaline hydrogen peroxide to promote a cascade oxidation-elimination process (Figure 6).

We originally attempted to find a feasible method for the Nef-type conversion of highly substituted nitro-pyrrolidines **167** when we tried the oxidation of nitronate anion by NaOMe. In all cases the reactions, using two equivalents of base, were complete after stirring for 1 day, giving the diarylpyrrole-2-carboxylic acids **168** in virtually quantitative yield. No aromatization occurred in the case of the *N*-protected derivatives **169**.



i. NaOMe, MeOH, H_2O_2; *ii.*a) NaOMe, MeOH; b) H^+; *iii.* ClCOOMe, pyridine, CH_2Cl_2, 25 °C;

Figure 6

4. The potential of the simplest nitro-olefin, nitroethylene as a versatile reagent for organic synthesis has found limited application. Nitroethylene, which was first described early this century by Wieland and Sakkelarios1 is known to polymerise readily in the presence of any trace of water and reacts violently with base. This behaviour prevents its use in many types of reaction. In order to avoid the difficulty in handling and storing these nitroethylenes, we considered the possibility of employing some more convenient surrogates.

We have studied the behaviour of 2-acetoxynitroethane in the presence of triethylamine and of an azomethine ylide generated also by the action of this base. Under the basic reaction conditions, β-elimination of the acetate group would generate the required nitroethylene in situ, and the concentration of the latter could be maintained sufficiently low to minimise base-induced polymerisation. The 2-acetoxy-nitroethane was obtained by the acylation of 2-nitroethanol with acetic anhydride, and reacted easily with 1,3-dipoles in the presence of triethylamine to yield pyrrolidine derivatives **187**. We have also investigated the possible replacement of the nitromethylene-oxindole in similar base mediated cycloadditions.

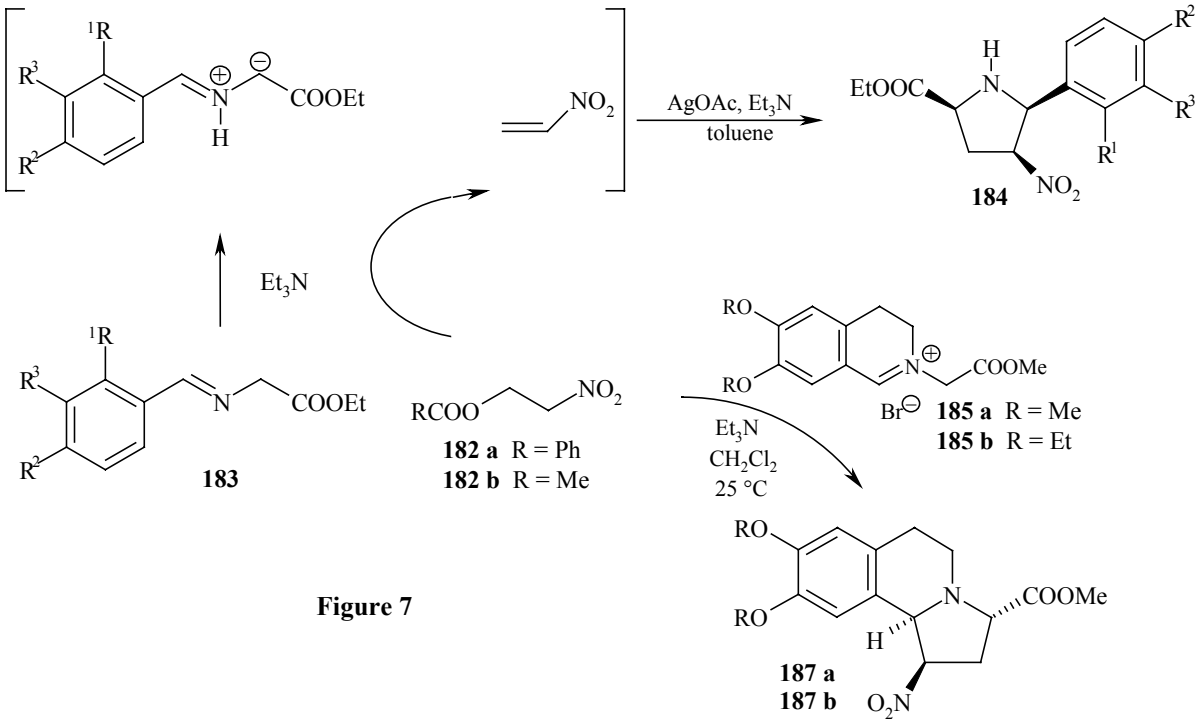


Figure 7

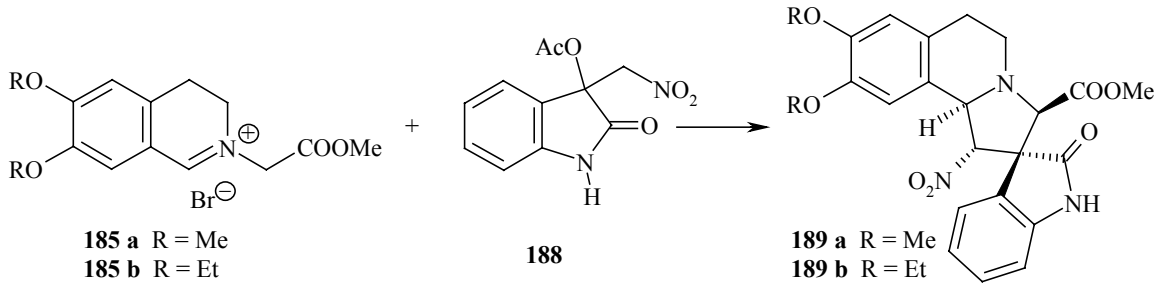


Figure 8

5.-6. In the search for non-cytotoxic antitumour agents, which act *via* the inhibition of protein tyrosine kinases we have recently prepared a number of pyranoacridones which exhibited good activity in biological assays for the inhibition of growth factor mediated cell proliferation. As part of our investigation into the synthesis of biologically active compounds, we became interested in the reactivity of the 4*H*-pyran-4-ones in a variety of cycloaddition reactions. In contrast to the well documented reactivity of 4*H*-benzopyran-4-ones the cycloadditions of simple pyrones have received rather limited attention. The results showed the different reactivity of the C=C double bond of **195** and **196** ester derivatives, while the

197 aldehyde to our surprise in all cases reacted on the C=O double bond. Selected examples collected on Figure 9.

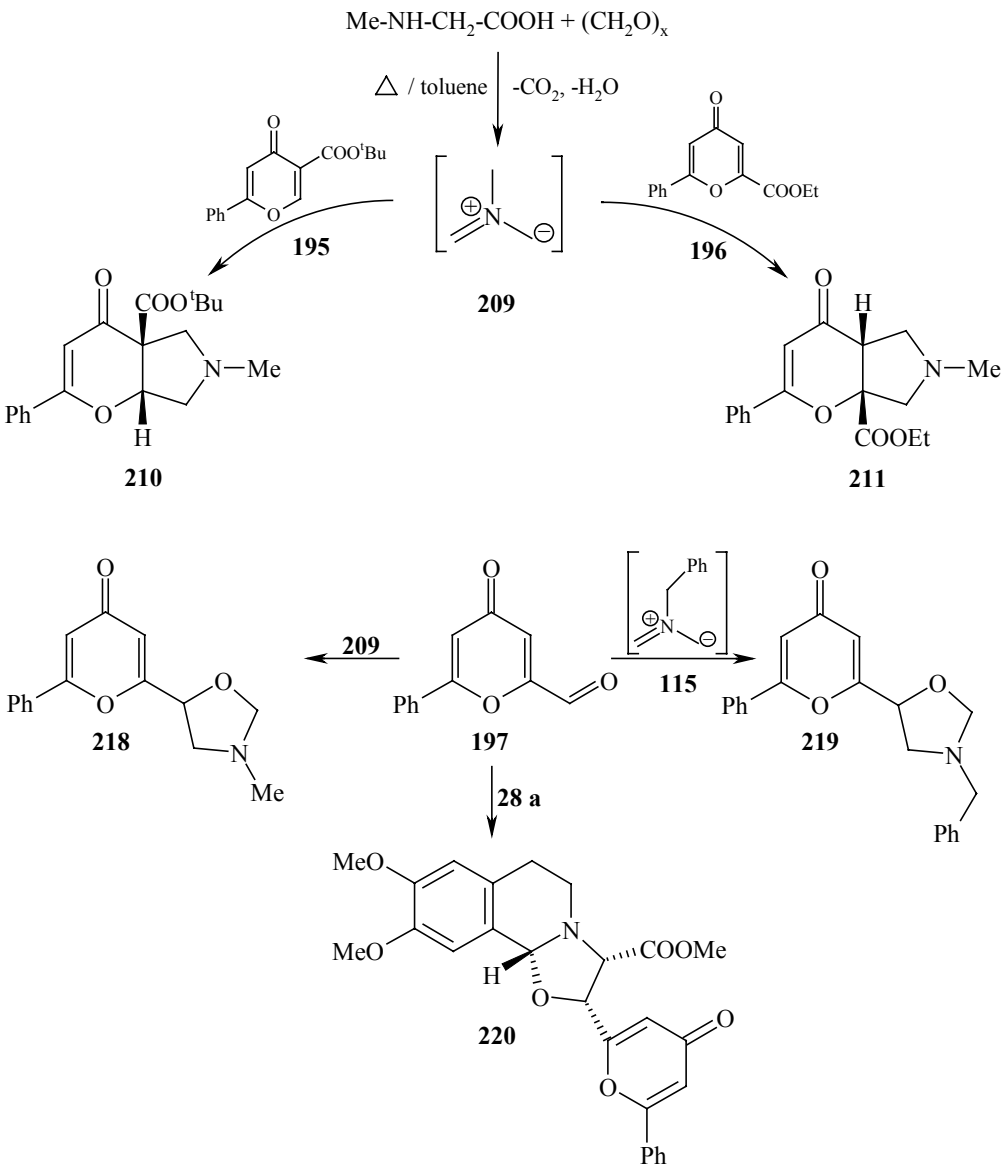


Figure 9

We have used aldehydes as heterodipolarophiles in the new and convenient synthesis of 1-aryl-2-dimethylaminoethanols. The importance of β-hydroxyamines as β-blockers in medicine is well-known and some of their uses include nervous system stimulants, bronchodilators, appetite suppressants and, most significantly, combating heart disease. An efficient two-step synthesis of 1-aryl-2-dimethylaminoethanols is achieved, consisting of oxazolidine **231** generation from the cycloaddition of an azomethine ylide **209** to an aldehyde, followed by reductive ring-opening (Figure 10).

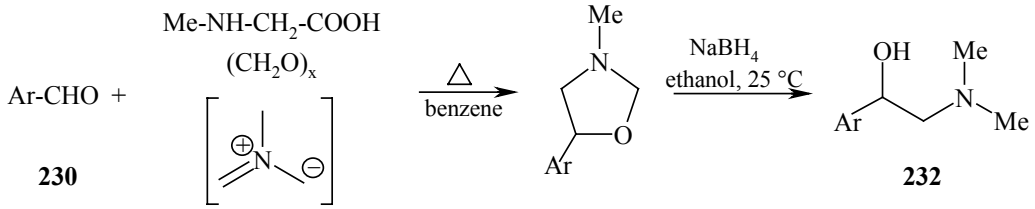


Figure 10

7. The 1,7-electrocyclisation of dipolar intermediates constitutes a general route to a variety of seven-membered heterocycles. In this work we have investigated the reactivity of the conjugated azomethine ylides formed from β-phenyl-cinnamic aldehyde and sarcosine esters. The reactions of the 2-nitro-phenyl substituted azomethine ylides also were studied.
When we have studied the formation and reactions of the non-stabilised azomethine ylide **277** formed in the reaction of *o*-nitrobenzaldehyde with sarcosine to our surprise, in spite of the presence of a large excess of active dipolarophiles,we could not observe any trace of the expected cycloadducts **276**, however, two products, an indazole-*N*-oxide **275** and an oxazolidine **274** were isolated (Figure 11).

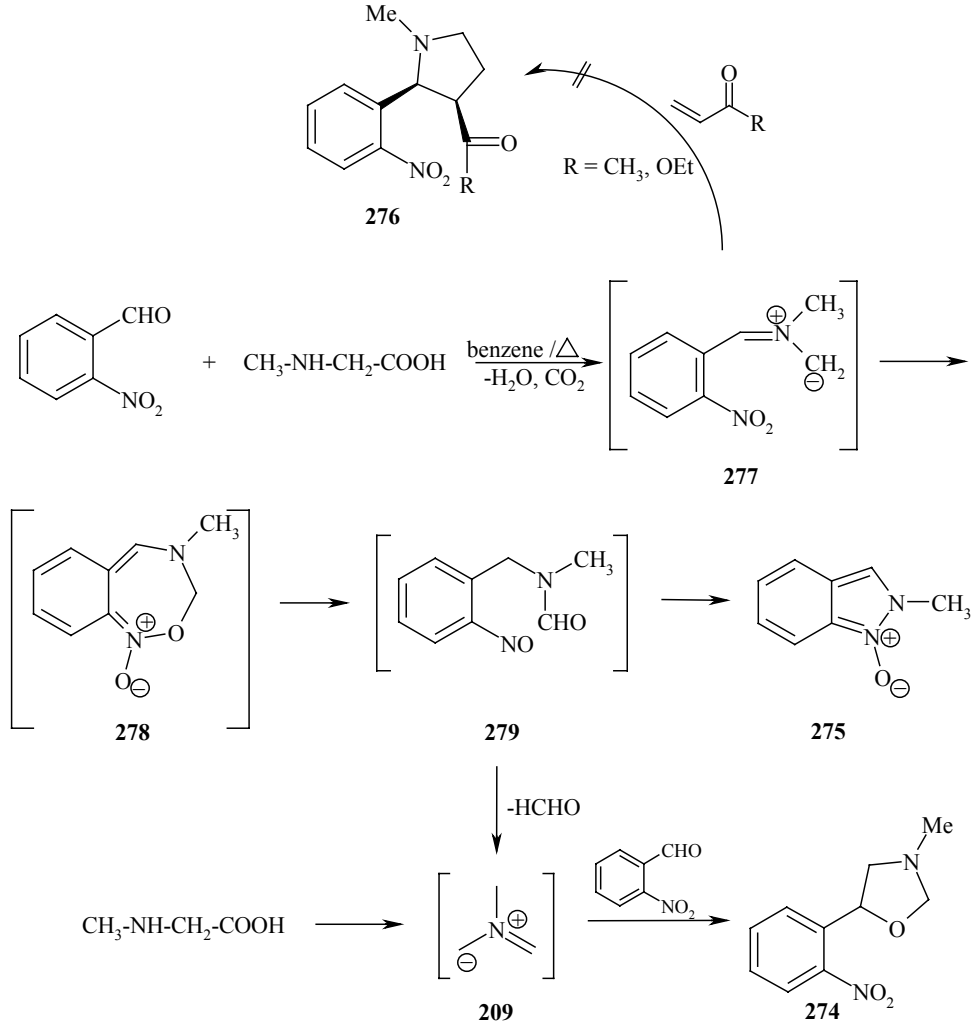


Figure 11

The formation of these products could be explained with an 1,7-electrocyclisation of an azomethine ylide onto the nitro group. With regard to the proposed mechanism we performed the next series of experiments with further conjugated ylide systems to get similar products like **289** and **295** *(Figure 12)*.

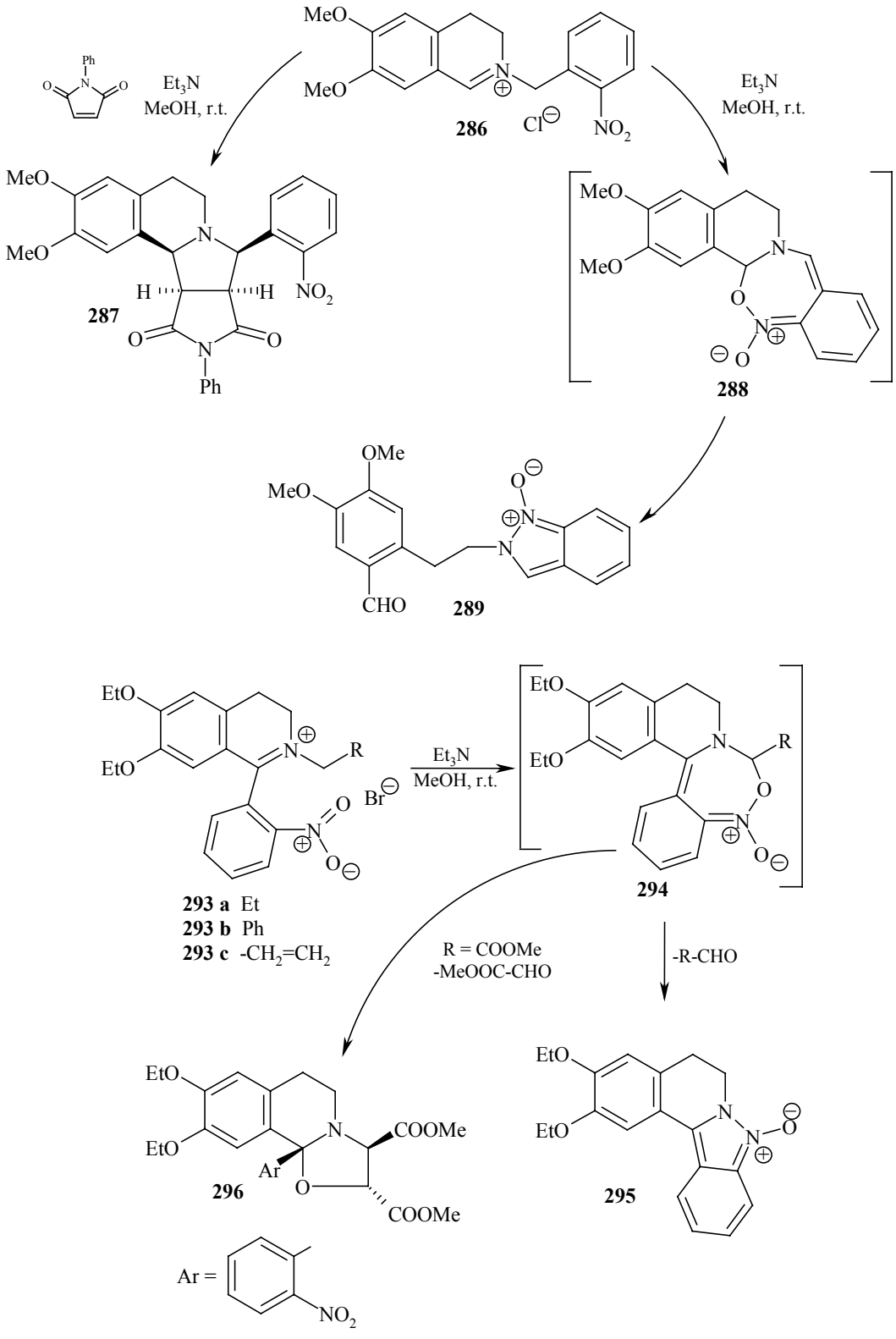


Figure 12

Summary of the PhD Thesis

The chemistry of azomethine ylides was investigated by many research groups worldwide and these reactive intermediates were used in the synthesis of many important compounds These facts suggest the importance of the further study of the chemistry of these dipoles.
In my work I have studied the cycloadditions and electrocyclisations of azomethine ylides. I have investigated the generation of these reactive species and the use of them in the synthesis of biologically important compounds and the stereoselectivity of these reactions.

We have successfully prepared for example the analogues of some spiro-oxindole alkaloids,[6] the tricyclic core of martinelline alkaloids,[4] diaryl-pyrrol carboxylic acids,[5] aryl-oxazolidnes and 1-aryl-2-dimethylaminoethanols[7] using the 1,3-dipolar cycloadditions of azomethine ylides as a key step. We have investigated the reactivity of the 4*H*-pyran-4-ones in a variety of cycloaddition reactions,[1] and we have found a new method for the use of some nitro-ethylene derivatives under basic conditions generated *in situ*.2
We have explored the first 1,7-electrocyclisation of an azomethine ylide onto a nitro group.[8] and we have investigated the reactivity of other conjugated stabilized azomethine ylides.[9]

Publications

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