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*Short communication*



# Some Cyclisations of *N*-(*o*-Nitrophenyl)amino Acid Esters

**Colin S. French* and David M. Smith**

School of Chemistry, Purdie Building, University of St Andrews, St Andrews, Fife, KY16 9ST, Scotland; Phone: +44-1334-463851; Fax: +44-1334-463808 (csf@st-andrews.ac.uk)

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**Abstract**

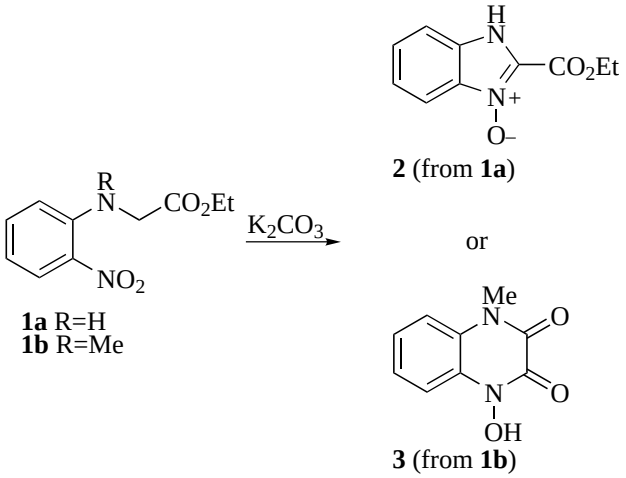
The *N*-(*o*-nitrophenyl) derivatives of glycine and sarcosine esters **1a** and **1b** are cyclised in basic media to benzimidazole *N*-oxides **2** and 1-hydroxyquinoxaline-2,3-diones **3** respectively. Since the formation of the hydroxyquinoxalinedione is anomalous given the previously accepted mechanism for this reaction an alternative mechanism has been proposed, which can account for both types of cyclisation.

**Keywords:** Benzimidazole *N*-oxides, *N*-(*o*-nitrophenyl)amino acid esters, cyclisation mechanisms, benzoxadiazines

## Introduction

The *N*-(*o*-nitrophenyl) derivatives of glycine and sarcosine esters **1a** and **1b** are cyclised in basic media to benzimidazole *N*-oxides **2** and 1-hydroxyquinoxaline-2,3-diones **3** respectively [1] (Scheme 1). Certain *N*-(*o*-nitrophenyl)glycine derivatives also cyclise to compounds of type **3** (substituting NH for NMe); for example, *N*-(2,6-dinitrophenyl)glycine esters.

The formation of the hydroxyquinoxalinedione is anomalous given the previously accepted mechanism [2] for the reaction **1a**→**2** (Scheme 2). In this mechanism, the N-H is involved only after the cyclisation has taken place (the final product being deprotonated by the base), and so it is not obvious why the sarcosine derivative is cyclised




**1a** R=H
**1b** R=Me

**2** (from **1a**)

**3** (from **1b**)

**Scheme 1**

* *To whom correspondence should be addressed*

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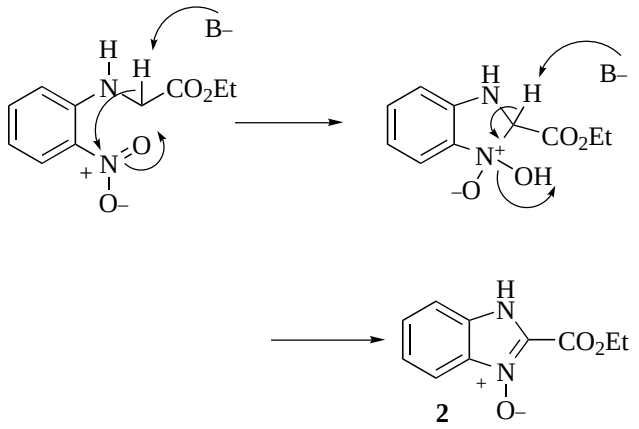
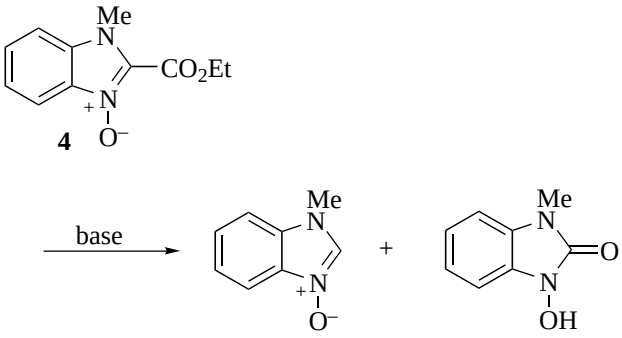


**Scheme 2**



**Scheme 3**

to a completely different heterocycle, *viz*. 1-hydroxyquinoxaline-2,3-dione.

It could be argued that the benzimidazole *N*-oxide **4** is the primary product of this reaction, which on further treatment with base, undergoes nucleophilic attack at C-2 followed by ring opening and recyclisation. However, the reaction of **4** with NaOH is known [3] to lead to complete loss of the ester function (Scheme 3) and not to ring opening.

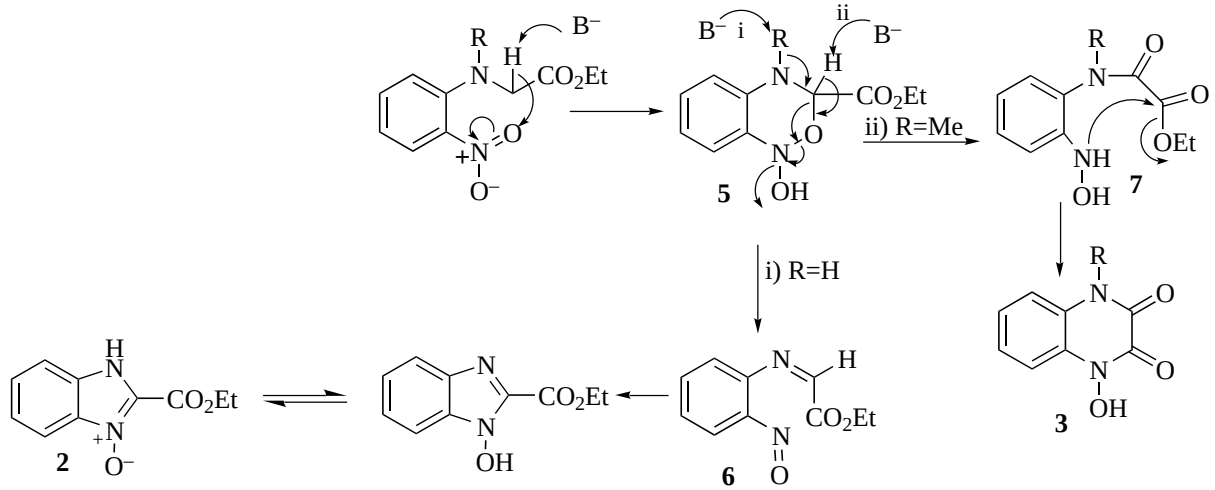
In view of the disparity between the glycine and sarcosine results, an alternative mechanism has been proposed (Scheme 4) which can account for both types of cyclisation. This mechanism, whereby a common benzoxadiazine intermediate **5** is formed, could rationalise the different courses of the cyclisations in the glycine and sarcosine series. When R=H, the benzoxadiazine intermediate is attacked by base to form the *o*-nitrosoanil **6** which is known [4] to cyclise spontaneously to the benzimidazole *N*-oxide **2**. When R=Me, or when access to the amino proton is hindered (for example in the 2,6-disubstituted derivatives) the α-hydrogen is removed instead and the intermediate **7** is formed. The latter may then undergo recyclisation to the quinoxalinedione **3**.

It was hoped that support (or otherwise) for the proposed mechanism might be provided by adding extra substituents to the amino acid, whereby one step in the mechanism might be blocked.

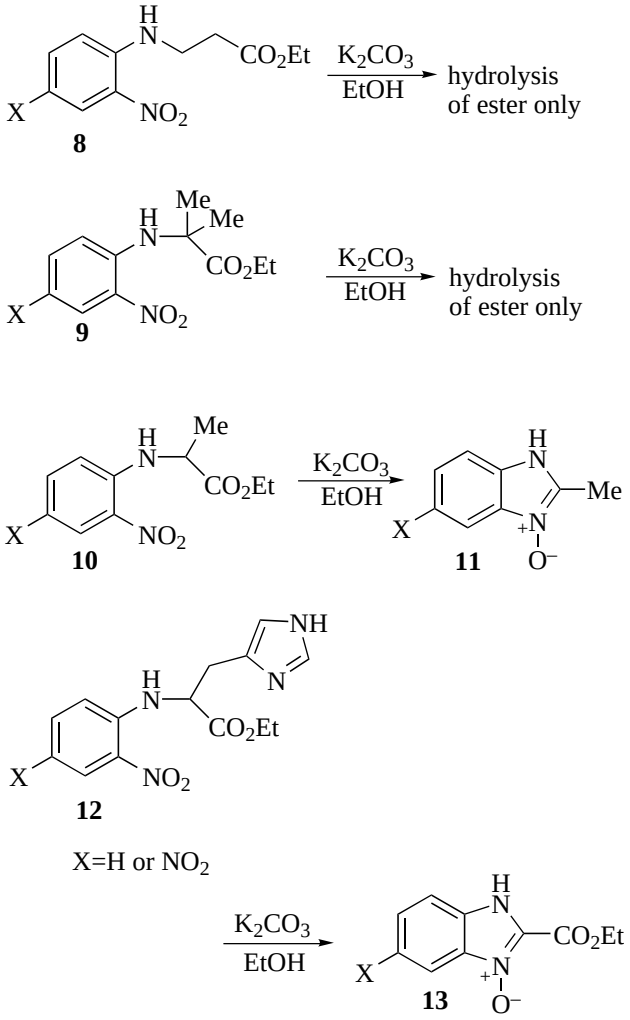
## Results and Discussion

To date, the following amino acid derivatives **8**-**10** and **12** have been reacted with base (potassium carbonate, Scheme 5).

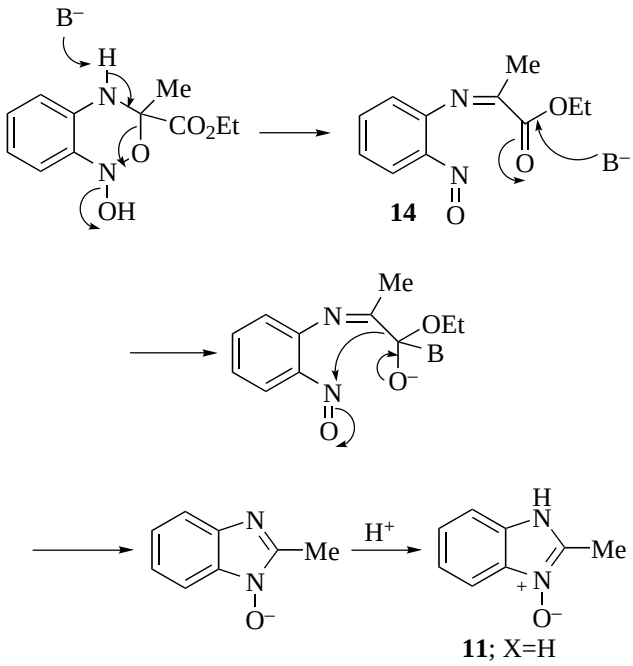
In the reaction of the alanine derivative **10**, the formation of the 2-methylbenzimidazole *N*-oxide **11** can be rationalised by nucleophilic attack of the base on the *o*-nitrosoanil followed by recyclisation (Scheme 6).



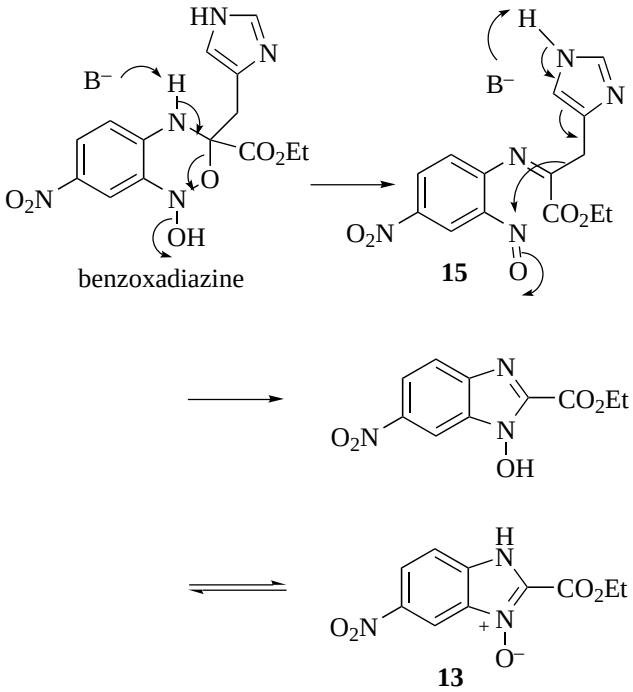
**Scheme 4**




**Scheme 5**




**Scheme 6**

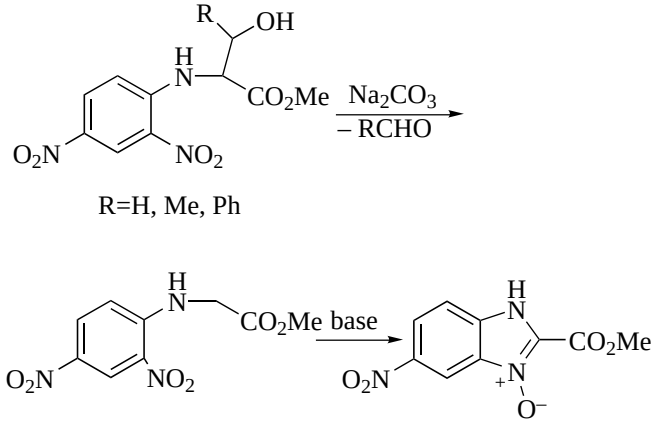



**Scheme 7**

Loss of the imidazolyl moiety in the reaction of the histidine derivative could be accounted for by recyclisation of the *o*-nitrosoanil **15** at the same time as the loss of the imidazole (Scheme 7).

An alternative to the cleavage of the imidazolyl moiety by the above mechanism is cleavage *before* the cyclisation takes place, *cf.* the findings of Luetzow and Vercellotti [5] with serine and threonine derivatives (Scheme 8).

The reactions with base of other *N*-(*o*-nitrophenyl)amino acid esters, such as those of *N*-methylalanine, other common amino acids, and *N*-(2,6-dinitrophenyl)amino acid esters are currently under investigation.




**Scheme 8**

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