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# A New Synthesis of Didehydroamino Acid Esters

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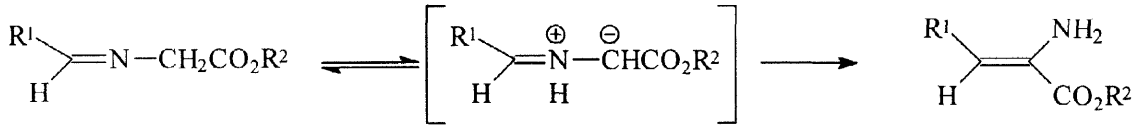
***Abstract:*** A novel synthesis of didehydroamino acid (DDAA) esters **4** is described, starting from aldimines **1**. The mechanism for this reaction involves the cycloaddition of an azomethine ylide **2** to an imine **1**, followed by the base-catalysed ring-opening of the imidazolidine intermediate **6**. This method has also been extended to the synthesis of DDAA esters **4h-j** catalysed by an imine **1a**. 

Due to their importance as components of both natural[1] and synthetic dehydropeptides,[2] and as synthetic intermediates,[3] the synthesis of didehydroamino acids (DDAA) and their derivatives has attracted much attention.[4] We wish to report here a simple and mild preparative route to DDAA esters starting from simple aldimines.



**1** **2** **4**

**a** $R^1$=$Ph_2C$=CH, $R^2$=Et
**b** $R^1$=$Ph_2C$=CH, $R^2$=Me
**c** $R^1$=$(4\text{-}ClC_6H_4)_2C$=CH, $R^2$=Et
**d** $R^1$=$(4\text{-}ClC_6H_4)_2C$=CH, $R^2$=Me
**e** $R^1$=$Me_2C$=CH, $R^2$=Et
**f** $R^1$=$3\text{-}O_2NC_6H_4$, $R^2$=Et
**g** $R^1$=$4\text{-}O_2NC_6H_4$, $R^2$=Et
**h** $R^1$=Ph, $R^2$=Et
**i** $R^1$=$4\text{-}ClC_6H_4$, $R^2$=Et
**j** $R^1$=$4\text{-}MeOC_6H_4$, $R^2$=Et

**Scheme 1**

Our initial studies involved the generation of azomethine ylides with α,β-unsaturation **2a-e**. These azomethine ylides were generated by the 1,2-prototropy[5] of the corresponding aldimine **1**, itself easily generated *via* the condensation of glycine ethyl or methyl ester with an aldehyde. Upon refluxing a solution of the imines **1a-e** and triethylamine in toluene the azomethine ylides **2a-e**, Scheme 1, were generated and this was confirmed by trapping of ylide **2a** with *N*-phenylmaleimide to give the adducts **3a-c**, Scheme 2. The stereochemistry of these cycloadducts was established by NOE, and by X-ray crystallography, Figure 1, for

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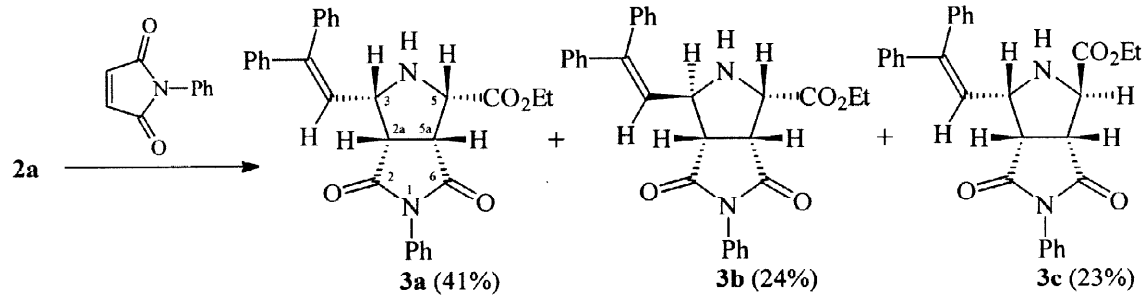
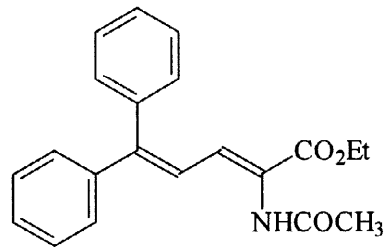
adduct **3a**. As can be seen from Figure 1, cycloadduct **3a** arises, as expected,[6] from the endo cycloaddition of the kinetically generated *syn* configuration of the azomethine ylide.




**Scheme 2**




**5**

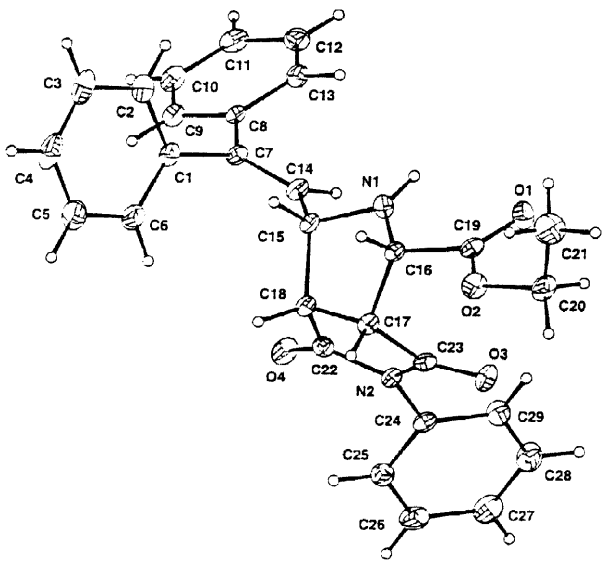



**Figure 1** Crystal Structure of **3a**

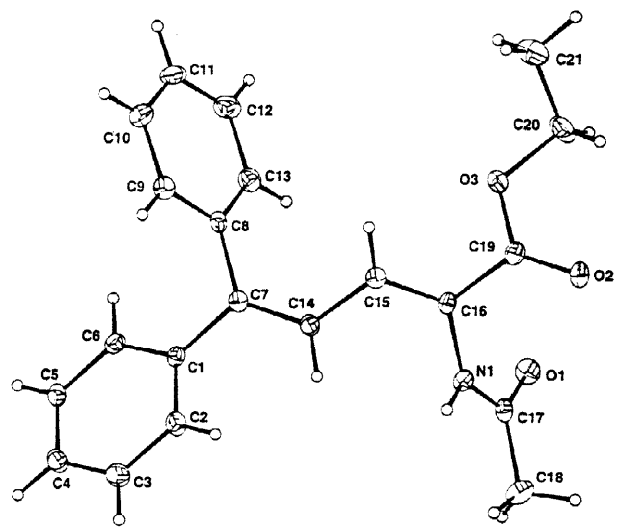



**Figure 2** Crystal Structure of **5**

In the absence of trapping agent however, the azomethine ylides **2a,c**, generated under the same conditions, are converted to the dehydroamino acid esters **4a,c**, Scheme 1. The stereochemistry of the product dehydroamino acid esters was again confirmed by NOE, and by X-ray crystallography of the *N*-acetyl derivative **5** of dehydroamino acid ester **4a**, Figure 2. Spectral analysis of the reaction mixture indicates the presence of only this geometrical isomer. For the aliphatic derivative **1e** no reaction was observed under these conditions and an alternate set of conditions, stirring in acetonitrile at room temperature for 2 days, in the presence of DBU and LiBr (to aid formation of the lithio azomethine ylide corresponding to **2e**), was employed to give the dehydroamino acid ester **4e** in low yield, after chromatography. The synthesis of a range of other didehydroamino acid esters **4** was then investigated using this methodology — but under differing reaction conditions, Table 1. For imines **1h-j** no reaction was observed under either of the standard sets of conditions — toluene / reflux, or DBU / acetonitrile / room temperature.

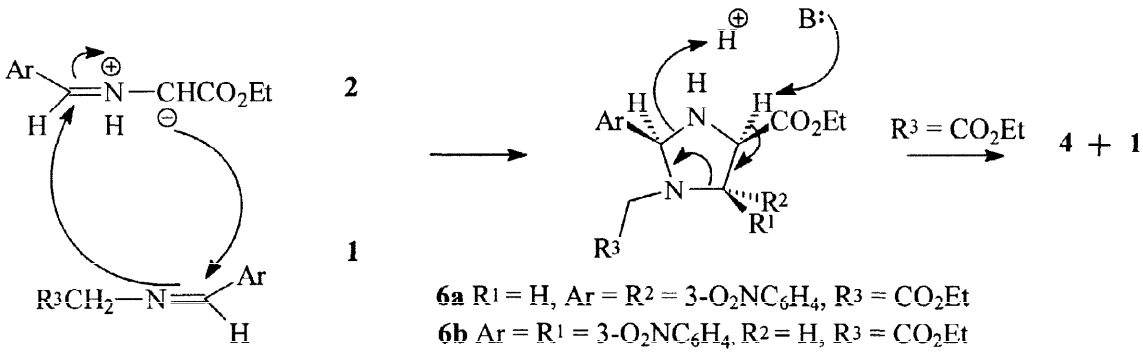
**Table 1** Synthesis of DDAA Esters

| Entry | Imine | $R^1$= | DDAA Ester | % Isolated yield | Reaction conditions |
|---|---|---|---|---|---|
| 1 | **1a** | $Ph_2C$=CH— | **4a** | 75 | PhMe/$Et_3N$/reflux |
| 2 | **1a** | | **4a** | 81 | PhMe/ $Et_3N$/reflux, then AcOH |
| 3 | **1a** | | **4a** | 61 | hν |
| 4 | **1c** | $(4\text{-}ClC_6H_4)_2C$=CH— | **4c** | 62 | PhMe/$Et_3N$/reflux |
| 5 | **1e** | $Me_2C$=CH— | **4e** | 22 | THF/$Et_3N$, then DBU/LiBr/MeCN/r.t. |
| 6 | **1f** | $3\text{-}O_2NC_6H_4$ | **4f** | 55 | DBU/MeCN/r.t. |
| 7 | **1g** | $4\text{-}O_2NC_6H_4$ | **4g** | 60 | DBU/MeCN/r.t. |
| 8 | **1h** | Ph | **4h** | 34 | **1a** (5 mol%)/PhMe/$Et_3N$/reflux |
| 9 | **1i** | $4\text{-}ClC_6H_4$ | **4i** | 35 | **1a** (5 mol%)/PhMe/$Et_3N$/reflux |
| 10 | **1j** | $4\text{-}MeOC_6H_4$ | **4j** | 15 | **1a** (5 mol%)/PhMe/$Et_3N$/reflux |

In order to establish the mechanism for this reaction, we initially performed a crossover experiment by heating a mixture of imines **1b** and **1c** and in dry toluene. A mixture of all four possible dehydroamino acid esters **4a-d** was obtained. The methyl esters **4b,d** were separated from the ethyl esters **4a,c** by column chromatography on silica gel and all the esters were identified by $^1$H NMR and mass spectrometry. This result suggested that the dehydroamino acid esters **4** are formed *via* an intermolecular reaction, presumably involving the initial cycloaddition of an azomethine ylide **2** to the precursor imine **1** to give an imidazolidine **6**, followed by ring opening to give the dehydroamino acid ester **4**, Scheme 3. In addition, if the substituent on the α-carbon of the amino acid ester is not hydrogen then this reaction fails, although the azomethine ylide is generated in this case, since it can be trapped by a dipolarophile.

Grigg has reported the metal salt-catalysed, 'crossed' cycloaddition of 2-naphthyl azomethine ylides **2** (Ar = 2-naphthyl) to imines **1** (Ar = 2-naphthyl, $R^3$ = $CO_2Me$ or Ph) to give imidazolidines **6c,d**,[7] Scheme 3. Using this method we have prepared a mixture of imidazolines **6a** (*syn*-exo) and **6b** (*syn*-endo), in the ratio

3:1, by the $Mg(ClO_4)_2$-catalysed cycloaddition of azomethine ylide **2f** (Ar = 3-$O_2NC_6H_4$, $R^3$ = $CO_2Et$) to its precursor imine **1f**. Further confirmation of the mechanism for didehydroamino acid ester formation was then obtained from the base-catalysed ring-opening of the mixture of imidazolines **6a,b**, which gave only the one isomer of the didehydroamino acid ester **4f**.




**6a** $R^1$ = H, Ar = $R^2$ = 3-$O_2NC_6H_4$, $R^3$ = $CO_2Et$
**6b** Ar = $R^1$ = 3-$O_2NC_6H_4$, $R^2$ = H, $R^3$ = $CO_2Et$
**6c** Ar = $R^2$ = 2-naphthyl, $R^1$ = H, $R^3$ = $CO_2Me$ or Ph
**6d** Ar = $R^1$ = 2-naphthyl, $R^2$ = H, $R^3$ = $CO_2Me$ or Ph

**Scheme 3**

Our understanding of the intermolecular nature of the mechanism for this reaction suggested the possibility of the imine-catalysed synthesis of DDAA esters and this was investigated for the 3 imines **1h-j** (entries 8-10, Table 1) for which the standard conditions were unsuccessful. Accordingly, treatment of these imines **1h-j** with **1a** (5 mol%) in refluxing toluene gave the corresponding DDAA esters **4h-j** in low yield after chromatography, Table 1. In addition to providing further proof for the mechanism for this process, these results, taken in conjunction with the others in Table 1, represent a new synthetic route to a range of didehydroamino acid esters.

**References**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