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A New Synthesis of Didehydroamino Acid Esters

Paul W. Groundwater,*[a] Toqir Sharif,[b] Andrea Arany,[a] David E. Hibbs,[b] Michael B. Hursthouse,[b] and Miklòs Nyerges[a]

a School of Health Sciences, University of Sunderland, Sunderland SR2 3SD, U.K.

b Department of Chemistry, University of Wales, Cardiff, P.O. Box 912, Cardiff, CF1 3TB, U.K.

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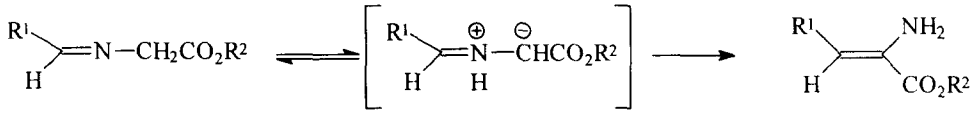
Abstract: A novel synthesis of didehydroamino acid (DDAA) esters **4** is described, starting from aldimines **1**. The mechanism for this reaction involves the cycloaddition of an azomethine ylide **2** to an imine **1**, followed by the base-catalysed ring-opening of the imidazolidine intermediate **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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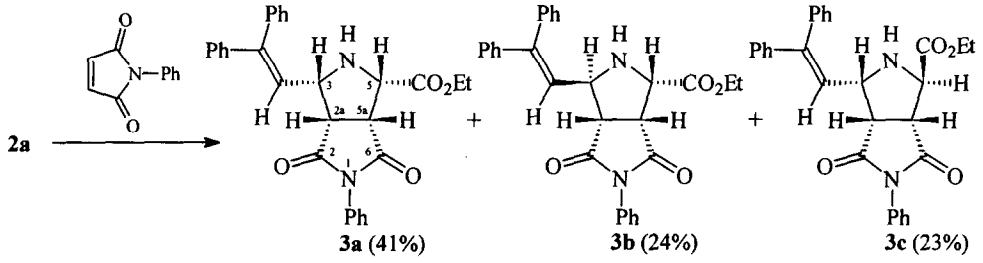
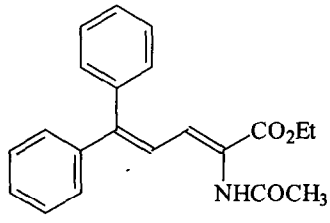
adduct **3a**. As can be seen from Figure 1, cycloadduct **3a** arises, as expected,[6] from the endo cycloaddition of the kinetically generated *syn* configuration of the azomethine ylide.



Scheme 2



5

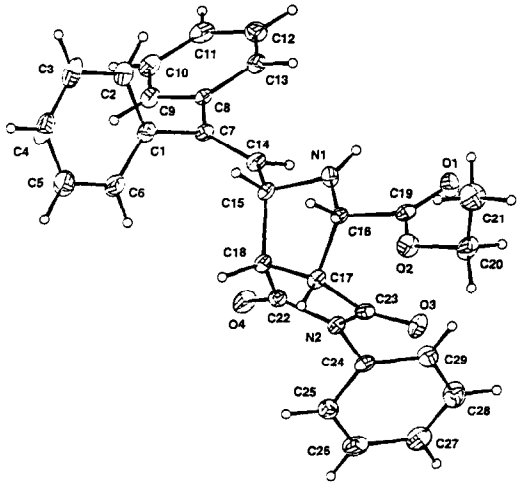


Figure 1 Crystal Structure of **3a**

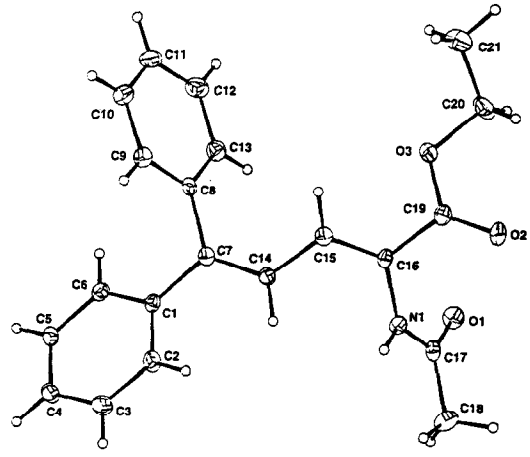


Figure 2 Crystal Structure of **5**

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.

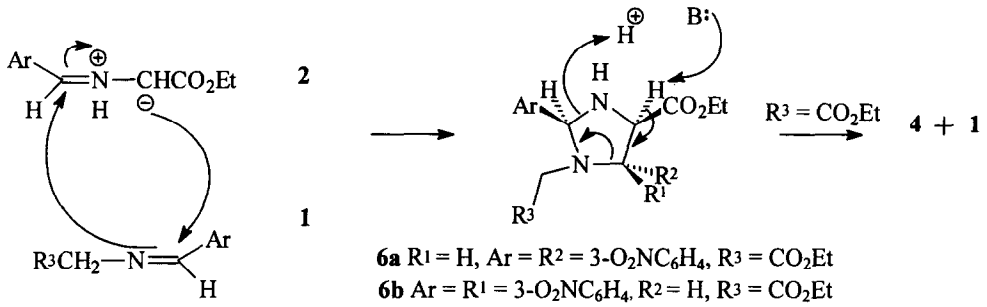
Table 1 Synthesis of DDAA Esters

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.

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