A Facile Synthesis of New Ketenimine Derivatives of α-Amino Acids

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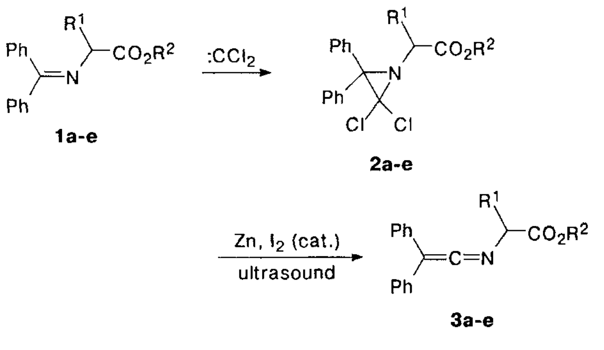
Abstract: N-Vinylidene α-amino acid derivatives have been prepared from the benzophenone Schiff bases of α-amino acid esters via dichlorocarbene addition to give *gem*-dichloroaziridine followed by ring opening and dechlorination.

New synthesis of α-amino acid derivatives are important because of the widespread use of these compounds in physical and life sciences. Nevertheless, N-vinylidene α-amino acids, which can be useful starting compounds for preparation of a wide range of heterocycles,[1] are practically unknown.[1, 2]

A possible synthetic approach to ketenimine derivatives of this type might involve preparation of *gem*-dihaloaziridines by addition of dihalocarbene across the carbon-nitrogen double bond[3] of a Schiff base derived from an amino acid ester followed by transformation of the resulting aziridine to ketenimine under the action of NaI[4, 5] or Zn.[5] Surprisingly, until now the sole known reaction of dihalocarbene with a Schiff base derivative of an α-amino acid was the reaction of difluorocarbene with ethyl N-benzhydrylideneglycinate.[6]

There are a number of potentially complicating factors one may face when realising this two-step methodology. Glycine derivatives **1a, b** are acidic enough so that the proton alpha to the nitrogen could be removed under basic conditions of dichlorocarbene generation;[7] on the other hand, in non-basic thermic conditions azetidinone derivatives can arise.[8] Additionally, the thermal rearrangement of ketenimines to nitriles can occur (the reaction is well documented for N-benzyl ketenimines[9]) during transformation of aziridine to ketenimine.

With this in mind, we examined the viability of the approach to N-[1-(alkoxycarbonyl)alkyl]ketenimines via *gem*-dichloroaziridines. We found that *gem*-dichloroaziridines can be prepared from alkyl N-benzhydrylideneglycinates **1a,b** using only non-basic carbene generation conditions, namely, thermic decomposition of sodium trichloroacetate in boiling chloroform with benzyltriethylammonium chloride as catalyst. In contrast, application of this method of carbene generation proved to be less successful for preparing aziridines from imines **1c-e** with R ≠ H because of competing formation of azetidinones. In this case, the reaction of chloroform with solid potassium hydroxide under PTC conditions is the method of choice for dichlorocarbene generation.[10]



Attempted conversion of the aziridines to ketenimines by treatment with NaI in acetone, which requires prolonged boiling, failed as the resulting ketenimines underwent rearrangement to nitriles. Therefore, to effect a more successful aziridine → ketenimine transformation another dehalogenation method was tried. 1,2,2-Triaryl-3,3-dichloroaziridines are known to be transformed to ketenimines in 10 min by treatment with Zn powder in boiling THF. But, with the aziridines in study no reaction occurred under these conditions, even when ultrasound irradiation was applied. We, however, found that addition of a catalytic amount of iodine in the reaction mixture provided the desired ketenimines. The results of extension of this protocol to a series of amino acid derivatives are listed in the Table.

Table. Compounds **2** and **3** Prepared

Starting material	R^1	R^2	Yield (%) of **2**	mp((C) of **2**	Yield (%) of $\mathbf{3}^a$
1a	H	Me	71	66-68	85
1b	H	Et	64	86	80
1c	Me	Me	81	100-102	95
1d	Me	Et	98	100-102	95
1e	$PhCH_2$	Me	79	124-125	97

a) Oil.

A typical experimental procedure was as follows:[11] **Methyl 2-(2,2-dichloro-3,3-diphenylaziridin-1-yl)propanoate (2c)**. A mixture of imine **1c** (1.5 g, 5.6 mmol), benzyltriethylammonium chloride (0.227 g, 1 mmol) and KOH pellets (2 g, 35.6 mmol) in $CHCl_3$ (20 mL) was stirred vigorously at 18-20 °C (cooling) for 1 h. Pentane (200 mL) and $MgSO_4$ (2 g) were added, the reaction mixture was stirred for 0.5 h and then filtered through celite. The filtrate was concentrated *in vacuo*, and the residue was crystallized from ether - hexane to give pure aziridine **2c** as colourless prisms; yield 1.6 g (81%). IR (KBr) ν max: 1744 (C=O) cm^{-1}. ^1H-NMR ($CDCl_3$, 250 MHz) δ: 1.74 (d, 3H, J = 6.8 Hz, MeC), 3.21 (q, 1H, J = 6.8 Hz, CH), 3.83 (s, 3H, MeO), 7.22-7.65 (m, 10H, Ph). ^{13}C-NMR ($CDCl_3$, 62.9 MHz) δ: 18.5 (Me), 52.4 (MeO), 57.7 (CH), 58.9 (CPh_2), 81.4 (CCl_2), 127.8 (4-C_{Ph}), 128.1, 128.4, 128.8 and 129.6 (2, 3-C_{Ph}), 135.5 and 137.8 (1-C_{Ph}), 173.1 (C=O). Anal. Calcd for $C_{18}H_{17}NO_2Cl_2$: C, 61.72; H, 4.89; N, 4.00. Found: C, 61.83; H, 4.72; N, 4.12.

Methyl N-(2,2-diphenylvinylidene)alaninate (3c). A mixture of aziridine **2c** (0.558 g, 1.59 mmol), Zn powder (0.260 g, 3.98 mmol), iodine (0.015g, 0.06 mmol) and anhydrous THF (10 mL) in a round-bottomed thoroughly stopped flask was immersed in a sonic cleaner and the mixture was irradiated with ultrasound for 4 h, the temperature of the bath during ultrasound irradiation was 40-50 °C (TLC control, alumina plates, 25% ether/pentane as eluent). The reaction mixture was concentrated *in vacuo*, extracted with ether/pentane (60 mL; 1:1, v : v), the extract was filtered, washed with water (2 x 20 mL) and dried ($MgSO_4$). After filtration, the solution was evaporated *in vacuo*, the residue was extracted with pentane and the extract was concentrated on a rotary evaporator, and the residual solvent was removed in high vacuum to give practically pure ketenimine **3c** as a pale yellow oil; yield 0.425 g (95%). IR (Film) ν max: 2011 (C=C=N), 1745 (C=O) cm^{-1}. ^1H-NMR ($CDCl_3$, 250 MHz) δ: 1.59 (d, 3H, J = 7.0 Hz, MeC), 3.72 (s, 3H, MeO), 4.44 (q, 1H, J = 7.0 Hz, CH), 7.16-7.36 (m, 10H, Ph). ^{13}C-NMR

($CDCl_3$, 62.9 MHz) δ: 18.7 (Me), 52.4 (MeO), 60.1 (CH), 77.3 (CPh_2), 126.2 (4-C_{Ph}), 127.7, 128.6 (2, 3-C_{Ph}), 133.9 (1-C_{Ph}), 171.1 (C=O), 189.6 (C=N). MS (high resolution) *m/z* 279.1259 (M^+) ($C_{18}H_{17}NO_2$ requires 279.1259).

To conclude, the present approach makes it possible convenient and efficient preparation of ketenimine derivatives of α-amino acids.

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