Ylides from dihalocarbenes and esters of *N*-benzhydrylidene amino acids: halogen-dependent reaction pathways

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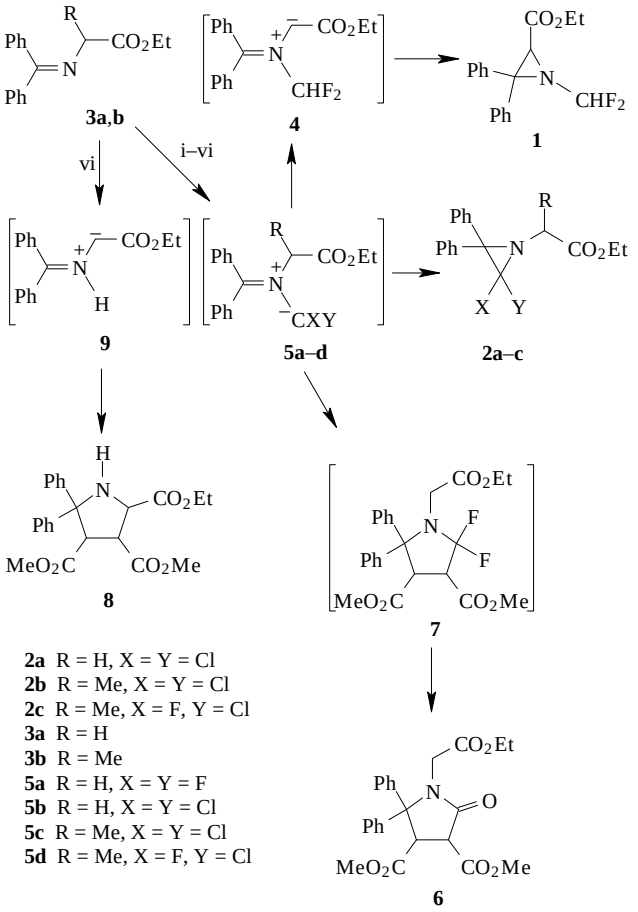
The nature of the halogen dramatically affects the properties of azomethine ylides derived from dihalocarbenes and the benzophenone Schiff bases of amino acid esters: dichloro- and chlorofluoroylides cyclise to give *gem*-dihaloaziridines **2a**–**e**, while difluoroylides characteristically undergo ylide–ylide isomerisation and 1,3-dipolar cycloaddition.

Immonium ylides formed by the reaction of imines with dihalocarbenes are convenient synthetic blocks for preparing various nitrogen- and halogen-containing compounds.[1,2] Azomethine ylides derived from dihalocarbenes and azomethines generally cyclise to give *gem*-dihaloaziridines,[1–4] except for ylides from *N*-alkylazomethines which prefer to undergo cycloaddition reactions with dipolarophiles.[1,5] However, increased steric bulk around the C=N bond encourage this latter type of ylide to undergo ring closure to aziridines as well.[5]

In contrast, McCarthy *et al.*[6] reported the formation of ethyl 1-(difluoromethyl)-3,3-diphenylaziridine-2-carboxylate **1** instead of the expected *gem*-dihaloaziridine of the type **2** in the reaction of ethyl *N*-benzhydrylideneglycinate **3a** with difluorocarbene generated from chlorodifluoromethane and 10% aqueous NaOH under ion-pair extraction conditions (method A). The authors[6] proposed that aziridine **1** arises from cyclisation of ylide **4**, the latter resulting from a prototropic shift in the initially formed azomethine ylide **5a**.†

Change in the reactivity of ylide **5** with fluorine atoms in place of chlorine atoms could be responsible for unusual results in the mentioned reaction. In addition, under the non-typical conditions of difluorocarbene generation[7] aziridine **1** may arise from substrate **3a** (which is a strong enough CH acid[8]) by a non-carbene mechanism, analogous to that reported by Rao *et al.*[9] Unfortunately, there is hardly any information in the literature on the reaction of difluorocarbene with imines[7,10] and other dihalocarbenes with Schiff bases derived from amino acids.[1–4] All this has prompted us to study the effect of halogen atom nature on the path of the dihalocarbene reaction with imines derived from amino acids and the reasons for the effect.

We established that glycinate **3a** reacts with dichlorocarbene generated by the thermocatalytic decomposition of sodium trichloroacetate to yield *gem*-dichloroaziridine **2a**.‡ The same result was obtained when the reaction was performed in the



Scheme 1 *Reagents and conditions:* i, Cl_3CCO_2Na, $PhCH_2N^+Et_3Cl^-$ (cat.), $CHCl_3$, reflux, 2 h, 64% yield of **2a**; ii, $CHCl_3$, KOH, $PhCH_2N^+Et_3Cl^-$ (cat.), 18–20 °C, 2 h, 98% yield of **2b**; iii, $CHCl_2F$, 60% aq. KOH, $PhCH_2N^+Et_3Cl^-$ (cat.), CH_2Cl_2, 8 °C, 4 h, 79% yield of **2c**; iv, CBr_2F_2, Pb, $Bu_4N^+Br^-$, CH_2Cl_2, sealed tube, ultrasonic bath, 25–35 °C, 4.5 h, 12% yield of **1**; v, CBr_2F_2, 10% aq. NaOH, $Bu_4N^+HSO_4^-$, CH_2Cl_2, 10 °C, 3 h, 17% yield of **1**, vi, CBr_2F_2, Pb, $Bu_4N^+Br^-$, *cis*-$MeO_2CCH{=}CHCO_2Me$, CH_2Cl_2, sealed tube, 45 °C, 22 h, 17% yield of **6** and 10% yield of **8**.

† Ylide–ylide isomerisation of azomethine ylides derived from imines and dihalocarbenes was not known previously. Only recently it was reported on a formal 1,3-H-shift in keteneiminium dichloromethanides (derived from *N*-alkylketeneimines and dichlorocarbene), giving rise to isomeric azomethine ylides.[14]

‡ All new compounds were characterised by C, H, N elemental analysis and spectral data.

For **2a**: mp 86 °C (hexane), IR (CCl_4, ν/cm^{-1}): 1764 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.34 (t, *J* 7.1 Hz, 3H, CH_3), 3.55 (s, 2H, CH_2N), 4.32 (q, *J* 7.1 Hz, 2H, CH_2O), 7.27–7.55 (m, 10H, H_{Ph}); ^{13}C NMR ($CDCl_3$) δ: 14.2 (CH_3), 50.6 (CH_2N), 58.4 (CPh_2), 61.4 (CH_2O), 81.9 (CCl_2), 128.0 (4-C_{Ph}), 128.3, 129.2 (2- and 3-C_{Ph}), 136.3 (1-C_{Ph}), 169.2 (C=O).

For **2b**: mp 100–102 °C (pentane), IR (CCl_4, ν/cm^{-1}): 1740 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.32 (t, *J* 7.3 Hz, 3H, CH_3), 1.73 (t, *J* 7.2 Hz, 3H, CH_3), 3.17 (q, *J* 7.2 Hz, 1H, CH), 4.21–4.39 (m, 2H, CH_2O), 7.25–7.65 (m, 10H, H_{Ph}); ^{13}C NMR ($CDCl_3$) δ: 14.2 (CH_3), 18.5 (CH_3), 57.9 (CH), 58.9 (CPh_2), 61.4 (CH_2O), 81.5 (CCl_2), 127.8 (4-C_{Ph}), 128.1, 128.4, 128.9, 129.6 (2- and 3-C_{Ph}), 135.5, 137.9 (1-C_{Ph}), 172.6 (C=O).

For **2c** (diastereomer mixture, 1:1.2): mp 74–77 °C (pentane), IR (CCl_4, ν/cm^{-1}): 1760 (C=O); ^{1}H NMR (CCl_4) δ: 1.22 and 1.25 (t, *J* 7 Hz, 3H, CH_3), 1.58 (d, *J* 7 Hz, 3H, CH_3), 3.08 (q, *J* 7 Hz, 1H, CH), 4.15 and 4.18 (q, *J* 7 Hz , 2H, CH_2O), 7.15–7.75 (m, 10H, H_{Ph}).

For **6**: mp 122–124 °C (ether), IR (CCl_4, ν/cm^{-1}): 1755, 1722 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.01 (t, *J* 7.1 Hz, 3H, CH_3), 3.44 (s, 3H, CH_3O), 3.45 (d, *J* 17.0 Hz, 1H, CHN), 3.67–3.80 (m, 2H, CH_2O), 3.86 (s, 3H, CH_3O), 4.03 (d, *J* 11.2 Hz, 1H, 4-H), 4.34 (d, *J* 17.0 Hz, 1H, CHN), 4.86 (d, *J* 11.2 Hz, 1H, 3-H), 7.02–7.58 (m, 10H, H_{Ph}); ^{13}C NMR ($CDCl_3$) δ: 13.8 (CH_3), 43.1 (CH_2N), 48.8 (4-C) 52.1 and 52.2 (CH_3O), 53.1 (3-C), 61.1 (CH_2O), 73.0 (5-C), 127.7, 128.3, 128.6, 128.7, 128.9, 129.8, 137.7 and 137.8 (C_{Ph}), 166.9, 168.2, 168.6 and 168.9 (C=O).

For **8**: mp 146–148 °C (ether–CH_2Cl_2), IR (CCl_4, ν/cm^{-1}): 1760 (C=O); ^{1}H NMR ($CDCl_3$) δ: 1.27 (t, *J* 7.4 Hz, 3H, CH_3), 3.41 (dd, *J* 7.1, 10.7 Hz, 1H, 3-H), 3.45 (s, 3H, CH_3O), 3.64 (s, 3H, CH_3O), 4.12 (d, *J* 10.7 Hz, 1H, 2-H), 4.21 (d, *J* 7.1 Hz, 1H, 4-H), 4.16–4.31 (m, 2H, CH_2O), 7.12–7.68 (m, 10H, H_{Ph}); ^{13}C NMR ($CDCl_3$) δ: 14.6 (CH_3), 50.9, 51.7, 52.1, 55.6, 60.2, (CH_3O, 2-4-C), 75.4 (5-C), 125.2, 125.6, 127.0, 127.2, 128.5, 128.9, 143.2 and 143.6 (C_{Ph}), 170.2, 170.4 and 170.7 (C=O).

presence of dimethyl maleate as a dipole trap. Moreover, 'normal' *gem*-dihaloaziridines **2b**,**c** also arise from reaction of ethyl *N*-benzhydrylidenealaninate **3b** with dichloro- and chlorofluorocarbenes generated by basic hydrolysis of chloroform and dichlorofluoromethane, respectively. In these cases no ylide–ylide isomerisation products were found.

Unexpectedly, the conversion **3a** → **1** proved possible to accomplish using method A, with dibromodifluoromethane instead of chlorodifluoromethane. This result is also best explained in terms of an ylide **5a** formation–1,3-H-shift–cyclisation sequence, where difluorocarbene is likely to be generated as in the $CBr_2F_2/CHBr_3/KOH/Bu_4N^+HSO_4^-$ system.[11] In our case, a bromophilic anion is presumably generated from glycinate **3a** as a CH-acid.

Attempted trapping of ylide **5a**, with the aim of providing evidence for its intermediacy in method A, by 1,3-dipolar cycloaddition to dimethyl maleate failed because of the rapid base hydrolysis of the dipolarophile. This result compelled us to try a nonbasic method of generating difluorocarbene. We treated glycinate **3a** with difluorocarbene generated by reduction of dibromodifluoromethane with lead[12] (method B) and found that here, too, aziridine **1** is formed. The poor yield of the product can be explained by the instability of **1** under the reaction conditions. This conclusion derives from the fact that the yield of **1** falls as the conversion of the starting glycinate increases. Nevertheless, the reaction of imine **3a** with difluorocarbene (method B) in the presence of dimethyl maleate results in formation of pyrrolidinone **6**. The latter compound arises from hydrolysis of pyrrolidine **7**, which is the primary cycloaddition product of ylide **5a** to the olefin. Along with pyrrolidinone **6** pyrrolidine **8** was isolated, which is formed by cycloaddition to the dimethyl maleate of ylide **9** resulting from a prototropic shift in imine **3a**. Reactions of this type are well documented.[13] Aziridine **1** is not formed under these conditions.

The results reported above are supportive of the assumption that difluorocarbene reacts with imine **3a** with initial formation of difluoroylide **5a**; the latter can further undergo a formal 1,3-H-shift to ylide **4** followed by cyclisation to yield aziridine **1**. In the presence of dimethyl maleate, ylide **5a** prefers to undergo a cycloaddition reaction than to undergo an H-shift. However, unlike ylides **5b**–**d**, difluoro derivative **5a** fails to cyclise into a *gem*-difluoroaziridine of the type **2** or this process is easily reversible. Cyclisation barriers of ylides $H_2C{=}N^+H{-}C^-Cl_2$ (23.8 kcal mol^{-1}), $H_2C{=}N^+H{-}C^-ClF$ (23.3 kcal mol^{-1}), $H_2C{=}N^+H{-}C^-F_2$ (33.1 kcal mol^{-1}) into the corresponding *gem*-dihaloaziridines and barriers of ring opening of the aziridines to the ylides (47.2, 47.2, 52.4 kcal mol^{-1}, respectively), estimated by the MNDO method,[§] count in favour of the first hypothesis. The great barrier to cyclisation in the latter ylide is mainly associated with stabilisation of the ylide form by the two geminal fluorines.

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[§] MOPAC (Version 6.00) has been used.

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