New Pathway for the Reaction of Difluorocarbene with Imines

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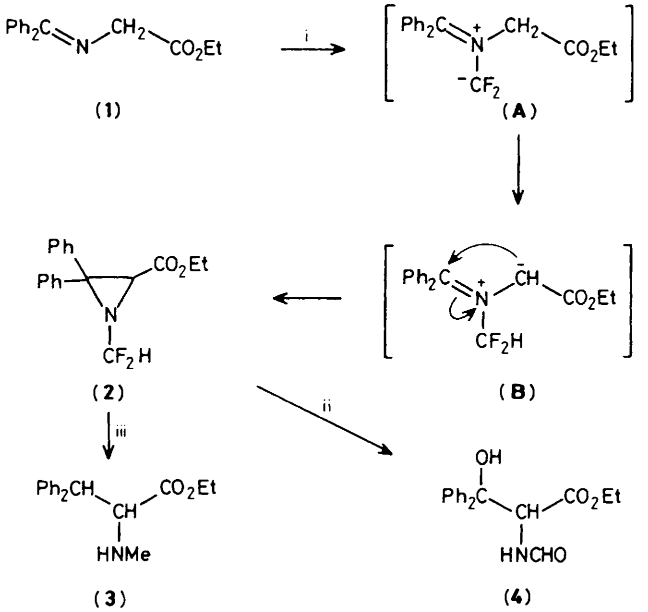
The reaction of chlorodifluoromethane with the benzophenone Schiff base of ethyl glycinate (**1**) provided the novel ethyl 1-difluoromethyl-2,2-diphenylaziridine-3-carboxylate (**2**), the crystal structure of which has been determined.

Difluorocarbene, the most selective electrophilic carbene,[1—3] has been used successfully to introduce a difluoromethyl group at tertiary carbon atoms of both esters[4] and protected amino acid derivatives.[5—7] Our interest in fluorinated amino acids[8] and other fluorinated time-dependent enzyme inhibitors[9—11] prompted us to investigate the reaction of chlorodifluoromethane[4] and the glycine equivalent (**1**) under basic conditions. This has led to the discovery of a new pathway for the reaction of difluorocarbene with imines.

Reaction of the Schiff base ester (**1**) and chlorodifluoromethane under ion-pair extraction conditions[8,12,13] provided the novel *N*-difluoromethylaziridine (**2**),‡ the crystal structure of which has been determined (see Figure 1).§ The aziridine (**2**) was transformed to the amino acid derivatives (**3**) and (**4**) by hydrogenation and dilute acid hydrolysis, respectively.

The addition of dihalogenocarbenes across the carbon–nitrogen double bond of *N*-alkyl or *N*-aryl Schiff bases to form the corresponding dihalogenoaziridines has been reviewed.[15,16] However, the formation of an *N*-dihalogenomethylaziridine from an imine or any other compound is, to our knowledge, novel. A mechanism consistent with formation of (**2**) from (**1**) proceeds *via* a prototropic shift to form the azomethine ylide (B) from the ylide (A) followed by ring formation.[17] It should be noted that there has been considerable interest recently in the generation of azomethine ylides from imines.[18]



Scheme 1. *Reagents:* i, $CHClF_2$, aq. NaOH, CH_2Cl_2, $Bu^n{}_4N^+ HSO_4^-$, 5 °C; ii, 1 M HCl, ether; iii, H_2, PtO_2, HCl, EtOH or $NaCNBH_3$, HOAc.

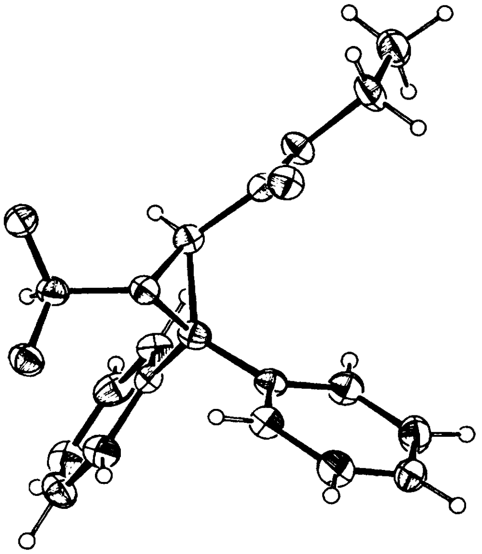


Figure 1. ORTEP drawing of (**2**).

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‡ The reaction was carried out as follows: to a solution of ethyl *N*-(diphenylmethylene)glycinate (**1**)[14] (7.5 mmol) and tetra-n-butylammonium hydrogen sulphate (8.2 mmol) in CH_2Cl_2 (50 ml) at 0 °C was introduced chlorodifluoromethane until saturation (balloon which remained slightly expanded). Aqueous NaOH (2.75 M; 135 ml) was added dropwise with rapid stirring keeping the reaction temperature below 5 °C. After 4 h, the organic layer was washed with brine, concentrated, dissolved in ether, washed with brine, and concentrated to provide crystalline (**2**) (4.4 mmol, 59%). Recrystallization from hexane gave 3.2 mmol of (**2**) as white crystals, m.p. 94.5—96 °C; ^1H n.m.r. (300 MHz, $CDCl_3$) δ 0.89 (3H, t), 3.78 (1H, d, J 1.47 Hz), 3.93 (1H, q), 3.99 (1H, q), 5.41 (1H, t, J_{HF} 69.1 Hz), and 7.05—7.56 (10H, m); ^{19}F n.m.r. (282.2 MHz, $CDCl_3$) δ (from $CFCl_3$) −92.98 (1F, dd, J_{FF} 222.8, J_{HF} 68.7 Hz) and −100.57 p.p.m. (1F, dd, J_{FF} 222.8, J_{HF} 70.2 Hz); *m/z* (chemical ionisation) 318 (MH^+).

§ *Crystal data:* $C_{18}H_{17}F_2NO_2$, monoclinic, space group $P2_1/n$, a = 13.525(9), b = 8.582(4), c = 14.181(10) Å, β = 105.04(5)°; U = 1589.75 Å^3, Z = 4, D_c = 1.325 g cm^{-3}. There were 2229 reflections (out of 2815 unique) with $F \geqslant 3\sigma(F)$ collected with a locally modified Picker diffractometer using graphite-monochromatized molybdenum Mo-K_α radiation. The diffractometer, data-handling techniques, and general procedures have been described previously: J. C. Huffman, L. N. Lewis, and K. G. Caulton, *Inorg. Chem.*, 1980, **19**, 2755. The structure was solved by direct methods and refined by full-matrix least squares. Final residuals are R 0.045 and R_w 0.047. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1. Complete crystallographic details are also available in microfiche form from the Chemistry Library, Indiana University, Bloomington, Indiana 47405, U.S.A. Request MSC Report 84707.

The mechanism, generality, and synthetic utility of this new reaction are being studied. All new compounds gave satisfactory elemental analyses and spectral data consistent with assigned structures.

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