Nucleophilic Ring Opening of Aziridine-2-carboxylates with Wittig Reagents; An Enantioefficient Synthesis of Unsaturated Amino Acids

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Reaction of *N*-tosyl- or *N*-acyl aziridine-(2*S*)-carboxylate esters with carbonyl stabilized Wittig reagents provides an isolable phosphorus ylide resulting from opening of the aziridine ring; this ylide reacts with carbonyl compounds to provide a novel synthesis of optically pure unsaturated amino acids, exemplified by enantioefficient syntheses of the naturally occurring (2*S*)-γ-methyleneglutamic acid and (*E*)-(2*S*)-4-ethylideneglutamic acid.

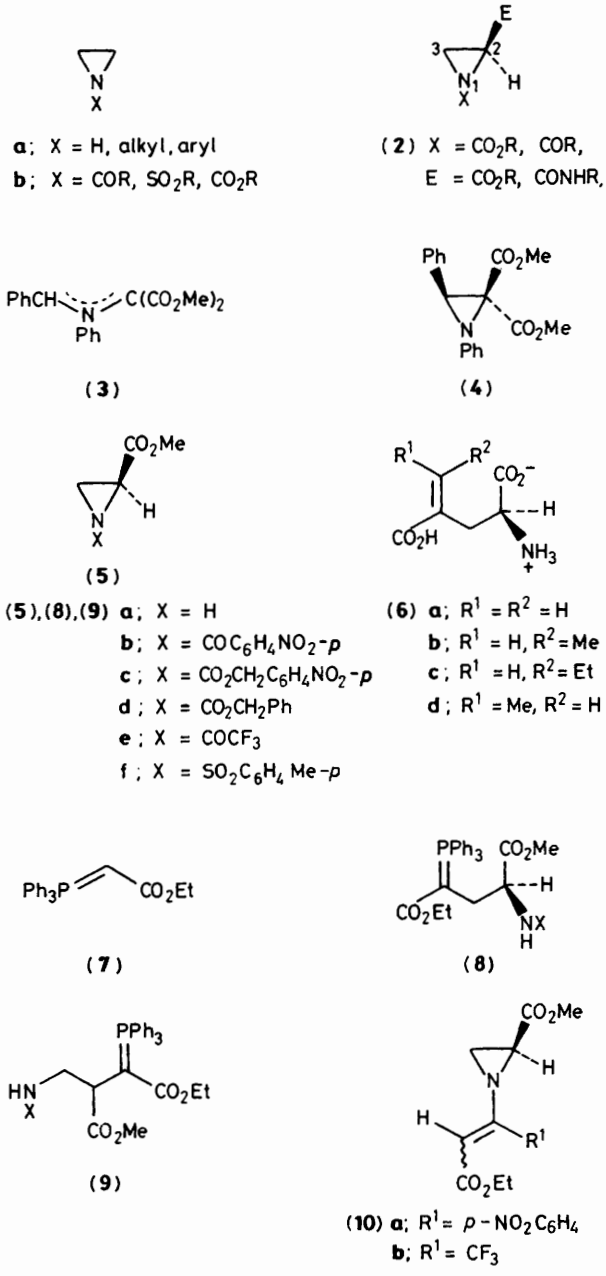
Although the opening of unactivated [*e.g.* (**1a**)] and activated aziridines [*e.g.* (**1b**)] by both hetero (*e.g.* amines,[1] thiols[2]) and carbon nucleophiles (*e.g.* Grignard reagents,[3,4] organocuprates,[4,5] enolates,[6] enediolates,[7] malonates and related reagents,[1] and Wittig reagents[8]) has been reported, the nucleophilic opening of activated aziridine-2-carboxylates [*e.g.* (**2**)] to provide substituted α-amino-acids has so far been limited to heteroatomic nucleophiles [*e.g.* $P(OMe)_3$,[9] thiols and thioacids,[10] alcohols,[11] amines,[12] halides[13]). In an effort to develop new methods for the synthesis of unusual amino acids[14] we have examined the reaction of activated aziridine-(2*S*)-carboxylates with carbon nucleophiles. Herein we report that carbonyl stabilized Wittig reagents act as suitable nucleophiles enabling opening of the aziridine ring *via* C-3–N-1† cleavage to provide an optically-pure ylide, suitable

† The reaction of Wittig reagents with azomethine ylides (**3**) obtained by the thermal ring opening of 2,2-dimethoxycarbonylarizidines (**4**) has been reported to occur by nucleophilic addition and cycloaddition pathways.[9,15]

Table 1.

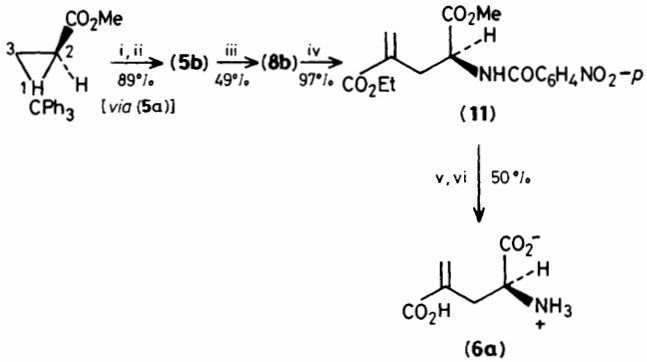
Arizidine (5)	Equiv. of Wittig reagent	Reaction conditions[a]	Isolated products (%)
b	1.1	Reflux, 2 h	(**8b**) (49), (**9b**) (12), (**10a**) (16)
c	2.0	Reflux, 24 h	(**8c**) (30)
d	2.0	Reflux, 24 h	(**8d**) (30)
e	1.0	50 °C, 6 h	(**10b**) (95)
f	1.1	Reflux, 2 h	(**8f**) (66), (**9f**) (13)

[a] Reactions performed in toluene under an inert atmosphere.



for subsequent modification to the 4-alkylidine-(2*S*)-glutamic acid family‡ of naturally occurring amino acids.

‡ Examples of this class of amino acid include (**6a**—**c**)[16] for which only racemic,[17] enzymatically resolved,[17a] or chemically resolved[17b,c,d,e] syntheses are reported.



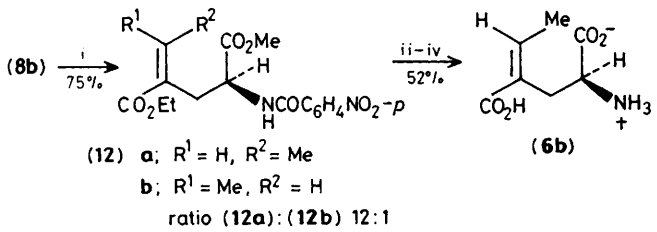
Scheme 1. *Reagents:* i, CF_3CO_2H, MeOH, CH_2Cl_2, 0 °C, 2 h; ii, *p*-$NO_2NC_6H_4COCl$ (1.1 equiv.), Et_3N (3 equiv.) CH_2Cl_2, 0→ 20 °C over 2 h; iii, (**7**) (1.1 equiv.), toluene, reflux, 2 h; iv, paraformaldehyde (excess), C_6H_6, reflux, 7 h; v, 3 M HCl–dioxane (1 : 1), reflux, 18 h; vi, h.p.l.c. [reverse phase octadecylsilane (ods) column, 0.1% HCO_2H in water].

Initially a series of *N*-substituted activated aziridines (**5b**—**f**) were prepared from *N*-tritylaziridine-(2*S*)-carboxylic acid methyl ester, which itself was readily prepared from protected serine.[18] These substrates were treated with (triphenylphosphoranylidene)acetic acid ethyl ester (**7**) (toluene, 50 °C reflux, 2—24 h) to produce two predominant classes of products; the ylides (**8**) and (**9**) resulting from aziridine cleavage, and the vinylogous urethanes (**10**) retaining the aziridine ring (Table 1). These results indicate that the desired aziridine C-3–N-1 cleavage reaction to yield (**8**) occurred readily for *N*-acyl or *N*-sulphonyl aziridines [(**5b**), (**5f**) as substrates]. In addition some loss of regiospecificity was detected by the production of (**9**)§ and (**10**) as by-products. Indeed the vinylogous urethane (**10b**) as a single geometric isomer was the sole product from the trifluoroacetyl substrate (**5e**). The urethanes (**5c**), (**5d**) gave poor results, even in the presence of $BF_3{\cdot}Et_2O$ or $MgBr_2{\cdot}Et_2O$.

The utility of the ylide (**8b**) was exemplified by its facile conversion into 4-methylene (2*S*)-glutamic acid (**6a**)‡ (Scheme 1), m.p. 192—195 °C (Lit.,[16a] 196 °C; Lit.,[17d] 195—7 °C; $[\alpha]_D^{20}$ + 13.2 (*c* 0.56, 5 M HCl) [Lit.,[16b] +12.8 (11% w/v HCl), Lit.,[17a] +13.7° (*c* 0.1 in 5 M HCl)]; δ_H (500 MHz, D_2O, pH *ca.* 6, $Me_3SiCD_2CD_2CO_2Na$ 0.00 p.p.m.) 2.71 (1H, dd, *J* 8.5, 14.5 Hz, 3-H), 2.92 (1H, dd, *J* 4.5, 14.5 Hz, 3-H), 3.90 (1H, dd, *J* 4.5, 8.5 Hz, 2-H), 5.72 (1H, br. s, 5-H), 6.18 (1H, br. s, 5-H)] (comparable to Lit.,[16e]); *m/z* (positive argon fast atom bombardment) 160 (MH^+, 100%).

Reaction of (**8b**) with acetaldehyde gave predominantly (12 : 1) the geometric isomer (**12a**) which after recrystallisation was similarly deprotected to the naturally occurring isomer

§ Both types of regiospecific arizidine ring openings have been observed in related systems.[1]



Scheme 2. *Reagents:* i, MeCHO, C_6H_6, reflux, 7 h; ii, recrystallise [diethyl ether–petroleum (40—60 °C)]; iii, 3 M HCl–dioxane (1:1), reflux, 20 h; iv, h.p.l.c. purification (reverse phase ods column, 0.1% HCO_2H in water).

(**6b**) (Scheme 2).¶ For (**6b**), m.p. 175 °C (decomp.) [Lit.,[16h] 171—2 °C; Lit.,[16g] 198—201 °C]; $[\alpha]_D^{20}$ +21° (*c* 0.35, H_2O), [Lit.,[16e] +21° (*c* 2.8, H_2O)]; δ_H (500 MHz, D_2O, pH *ca.* 6.5, $Me_3SiCD_2CD_2CO_2Na$ 0.00 p.p.m.) 1.63 (3H, d, *J* 7 Hz, 5-Me), 2.7—3.0 (2H, m, 3-H), 3.7—3.9 (1H, m, 2-H), 6.92 (1H, q, *J* 7 Hz, 5-H), (comparable to Lit., [16d,e]); *m/z* (positive argon fast atom bombardment) 174 (MH^+, 100%).

In summary we have shown that aziridine-2-carboxylates can be ring-opened with Wittig reagents in a preparatively useful manner to provide a simple synthesis of optically pure γ-alkylidene glutamates.

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¶ The assignment of (**6b**) as the (*E*)-isomer followed from the relative chemical shift value of the olefinic proton of (**6b**) (δ_H 6.92) and (**6d**) (δ_H 6.25), and is consistent with a previous study using the n.m.r. shift reagent. tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dionato)europium-(III).[16g]