

## 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*)- $\gamma$ -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,<sup>1</sup> thiols<sup>2</sup>) and carbon nucleophiles (*e.g.* Grignard reagents,<sup>3,4</sup> organocuprates,<sup>4,5</sup> enolates,<sup>6</sup> enediolates,<sup>7</sup> malonates and related reagents,<sup>1</sup> and Wittig reagents<sup>8</sup>) has been reported, the nucleophilic opening of activated aziridine-2-carboxylates [*e.g.* (**2**)] to provide substituted  $\alpha$ -amino-acids has so far been limited to heteroatomic nucleophiles [*e.g.* P(OMe)<sub>3</sub>,<sup>9</sup> thiols and thioacids,<sup>10</sup> alcohols,<sup>11</sup> amines,<sup>12</sup> halides<sup>13</sup>]. In an effort to develop new methods for the synthesis of unusual amino

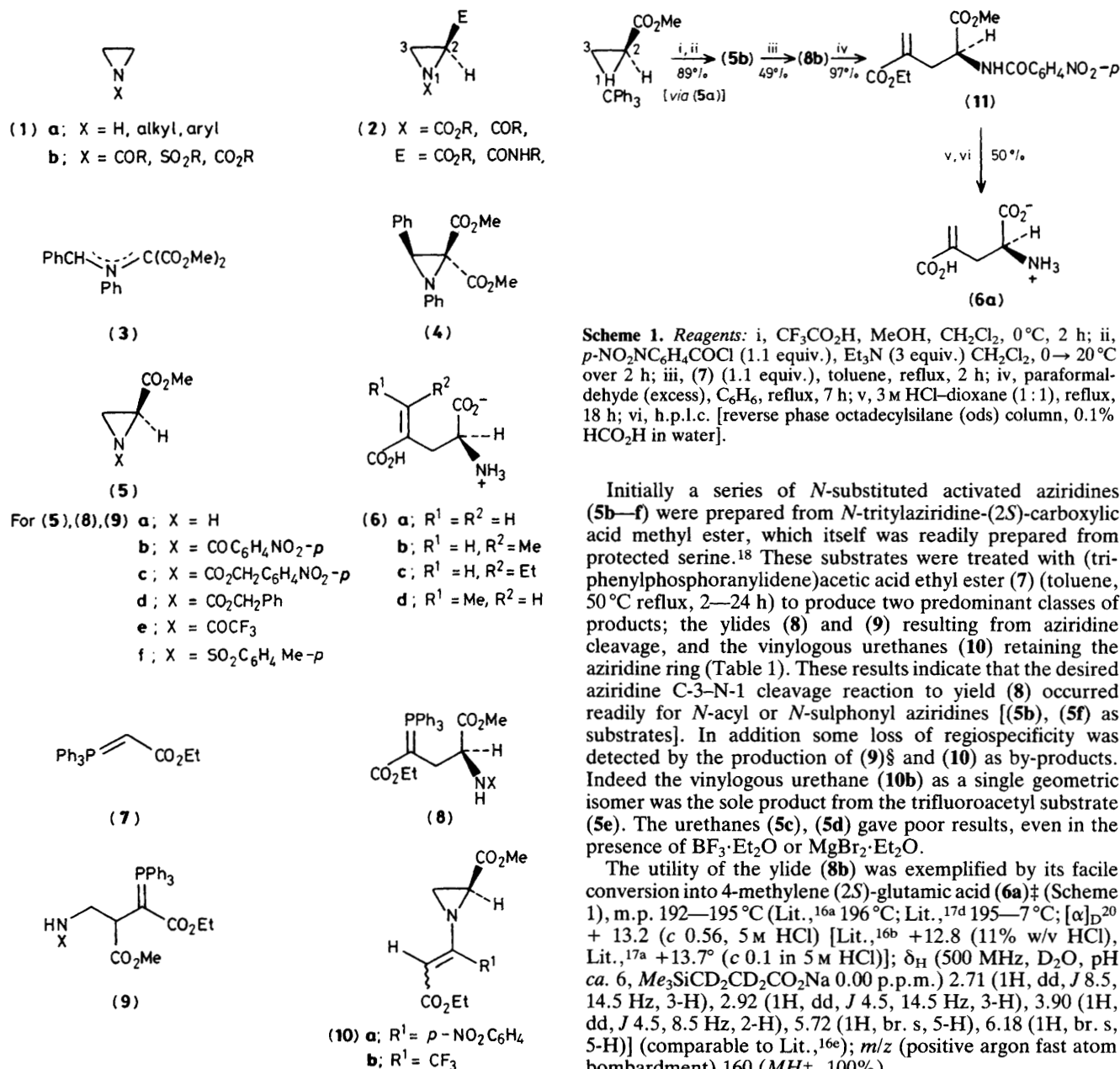
acids<sup>14</sup> we have examined the reaction of activated aziridine-(2*S*)-carboxylates with carbon nucleophiles. Herein we report that carbonyl stabilized Wittig reagents act as suitable nucleophiles enabling opening of the aziridine ring *via* C-3–N-1 $\dagger$  cleavage to provide an optically-pure ylide, suitable

$\dagger$  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.<sup>9,15</sup>

Table 1.

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

<sup>a</sup> Reactions performed in toluene under an inert atmosphere.



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.<sup>18</sup> 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 regioselectivity 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<sub>3</sub>·Et<sub>2</sub>O or MgBr<sub>2</sub>·Et<sub>2</sub>O.

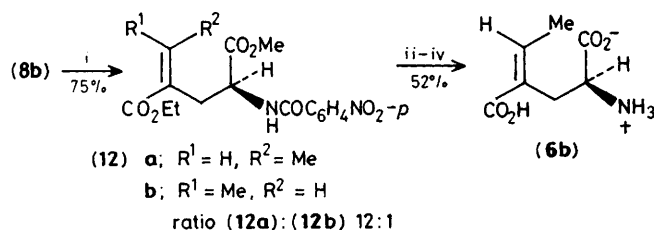
The utility of the ylide (8b) was exemplified by its facile conversion into 4-methylene (2*S*)-glutamic acid (6a)‡ (Scheme 1), m.p. 192–195 °C (Lit.,<sup>16a</sup> 196 °C; Lit.,<sup>17d</sup> 195–7 °C; [α]<sub>D</sub><sup>20</sup> + 13.2 (c 0.56, 5 M HCl) [Lit.,<sup>16b</sup> + 12.8 (11% w/v HCl), Lit.,<sup>17a</sup> + 13.7° (c 0.1 in 5 M HCl)]; δ<sub>H</sub> (500 MHz, D<sub>2</sub>O, pH ca. 6, Me<sub>3</sub>SiCD<sub>2</sub>CD<sub>2</sub>CO<sub>2</sub>Na 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.,<sup>16e</sup>); *m/z* (positive argon fast atom bombardment) 160 (MH<sup>+</sup>, 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

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

‡ Examples of this class of amino acid include (6a–c)<sup>16</sup> for which only racemic,<sup>17</sup> enzymatically resolved,<sup>17a</sup> or chemically resolved<sup>17b,c,d,e</sup> syntheses are reported.

§ Both types of regioselective aziridine ring openings have been observed in related systems.<sup>1</sup>



**Scheme 2.** Reagents: i, MeCHO, C<sub>6</sub>H<sub>6</sub>, 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<sub>2</sub>H in water).

(6b) (Scheme 2).<sup>¶</sup> For (6b), m.p. 175 °C (decomp.) [Lit.,<sup>16h</sup> 171–2 °C; Lit.,<sup>16g</sup> 198–201 °C]; [ $\alpha$ ]<sub>D</sub><sup>20</sup> +21° (c 0.35, H<sub>2</sub>O), [Lit.,<sup>16e</sup> +21° (c 2.8, H<sub>2</sub>O)];  $\delta_H$  (500 MHz, D<sub>2</sub>O, pH ca. 6.5, Me<sub>3</sub>SiCD<sub>2</sub>CD<sub>2</sub>CO<sub>2</sub>Na 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.,<sup>16d,e</sup>); *m/z* (positive argon fast atom bombardment) 174 (MH<sup>+</sup>, 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  $\gamma$ -alkylidene glutamates.

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<sup>¶</sup> The assignment of (6b) as the (*E*)-isomer followed from the relative chemical shift value of the olefinic proton of (6b) ( $\delta_H$  6.92) and (6d) ( $\delta_H$  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).<sup>16g</sup>

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