## Ene Reaction of the Active Imino Group. A Novel Synthesis of a-Amino-Acids<sup>1</sup>

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The thermal (120 °C) and catalytic (SnCl<sub>4</sub>, BF<sub>3</sub>, and AlCl<sub>3</sub>) ene addition reactions of butyl N-(p-tolylsulphonyl)iminoacetate with alkenes give adducts which are readily convertible into  $\gamma\delta$ -unsaturated  $\alpha$ -amino-acids.

THE ene reaction involves the addition of an alkene possessing an allylic hydrogen atom to a multiple bond (enophile) (Scheme 1),<sup>2</sup> and is of theoretical and synthetic



SCHEME 1

interest.<sup>‡</sup> Because enophilic activity is exhibited by different types of electron-deficient multiple bonds (C=C, C=C, C=O, N=N, *etc.*) the ene reaction is a convenient route to compounds with diverse structures and

functional groups, often in a highly stereoselective fashion.§ We have now examined its utility for the synthesis of  $\alpha$ -amino-acids.<sup>1</sup>

The addition of alkenes (1) to butyl N-(p-tolylsulphonyl)iminoacetate (2) which could be readily prepared by the reaction of butyl glyoxylate with Nsulphinyltoluene-p-sulphonamide,<sup>4</sup> is the first example of an ene reaction involving an active C=N group. It gives the adducts (3), which can be easily converted into  $\alpha$ amino- or  $\gamma$ 8-unsaturated  $\alpha$ -amino-acids. Therefore the reaction offers a new approach to the synthesis of this class of compounds.

TABLE 1	
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	Reaction	Molar Temperature ratio			M.p.	ν <sub>max</sub> ./cm <sup>-1</sup>			
Adduct	time/h	(t/°C)	(2) to $(1)$	Yield (%)	$(t/^{\circ}C)$	SO,	C=CH,	C=0	NH
(3a)	24	120	1:7	70	47-48	1 160	1 640	1 740	3 300
(3b)	16	120	1:5	78	39—40	1 160		1 730	3 340
(3c)	16	120	1:5	75	(170 at 10 <sup>-4</sup> Torr)	1 160	1 640	1 740	3 340
(3d)	10	120	1:3	79	(170 at 10 <sup>-4</sup> Torr)	1 160	1 650	1 740	3 300
(3e)	8	120	1:3	90	(170 at 10 <sup>-4</sup> Torr)	$1170 \\ 1350$		1 740	3 300
(3f)	8	120	1:3	91	(170 at 10 <sup>-4</sup> Torr)	$1160 \\ 1350$		1 740	3 350
(3g)	8	120	1:3	88	(170 at 10 <sup>-4</sup> Torr)	1 170		1 745	3 350
(3h)	4	120	1:1	92	63	1 160	1 630	1 740	3 300
(3i)	4	130	1:2	82	b	1 160		1 730	3 300
(4)	20	120	1:5	56	72	1 160		1 710	3 300
(5)	16	120	1:3	81	61	1 160		1 740	3 300
(6)	0.5	125	1:2	76	(170 at 10 <sup>-4</sup> Torr)	1 160		1 735	3 300
(7)	0.5	125	1:1	74	79	1 160		1 740	3 300

<sup>a</sup> Air-bath temperature. <sup>b</sup> Not distilled.



#### RESULTS AND DISCUSSION

The thermal (120 °C) reaction of the iminoacetate  $(2)^{4}$  with a series of alkenes with terminal or di- and trisubstituted double bonds gave in each case the ene adducts (3)—(7) in good to excellent yields (Table 1) essentially as a single product as indicated by t.l.c.

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<sup>+</sup> The ene reaction, though lacking appropriate elements of symmetry, could be considered as a  $\pi^2_s + \pi^2_a + \sigma^2_a$  pericyclic process. Establishing experimentally its concerted or non-concerted character for particular cases is therefore of theoretical significance.

§ Notably for the intramolecular variant of an ene reaction.<sup>8</sup>

Their structures were confirmed by elemental analyses and spectral data. The i.r. spectra contained bands corresponding to the appropriate C=O, SO<sub>2</sub>, C=C, and NH



functional groups and the <sup>1</sup>H n.m.r. spectra contained signals for all the expected protons (Table 2). For compounds (3e), (3f), (3g), and (3i) where geometric isomers are possible values of the coupling constants for the olefinic protons of ca. 15 Hz proved their E

## TABLE 2

100 MHz <sup>1</sup>H n.m.r. data for the adducts (3)-(7)

Chemical shift <sup>a</sup> ( $\delta$  relative to Me<sub>4</sub>Si = 0) and Adduct coupling constants (J/Hz)

- 5.62 (1 H, m, 4-H), 5.04 (2 H, m, 5-H<sub>2</sub>), 3.99 (1 H, dt,  $J_{\rm NH, 2}$  7.1,  $J_{2, 3}$  6.5, 2-H), and 2.50 (2 H, m, 3-H<sub>2</sub>), 5.28 (3 H, m, 4-H, 5-H, NH), 2.42 (2 H, m, 3-H<sub>2</sub>), (3a)
- (3b)
- and 1.61 (3 H, d,  $J_{5.6}$ , 5.75, 6-H<sub>3</sub>) 5.61 (1 H, m,  $J_{4,5}$  17.5,  $J_{4,5}$  9.75,  $J_{3,4}$  8.25 4-H), 5.00 (2 H, m, 5-H<sub>2</sub>), 3.79 (1 H, dd,  $J_{NH,2}$  10.0,  $J_{2,3}$  6.0, 2-H), 2.50 (1 H, m, 3-H), and 1.04 (3 H, d,  $J_{3,ME}$ (3c) 6.0, 3-Me)
- (3d)
- 6.0, 3-Me) 4.74 (2 H, m, 5-H<sub>2</sub>), 4.04 (1 H, dt,  $J_{NH,2}$  9.5  $J_{2,3}$  7.0, 2-H), 2.41 (2 H, m, 3-H<sub>2</sub>), and 1.65 (3 H, s, 4-Me) 5.50 (1 H, dt,  $J_{4,5}$  15,  $J_{5,6}$  6.0, 5-H), 5.16 (1 H, dt,  $J_{3,4}$  7.75, 4-H), 3.95 (1 H, dt,  $J_{NH,2}$  9.5,  $J_{2,3}$ 5.5, 2-H), 2.41 (2 H, m, 3-H<sub>2</sub>), 1.94 (2 H, dq,  $J_{6,7}$ 7.58, 6-H<sub>2</sub>), and 0.94 (3 H, t, 7-H<sub>3</sub>). 5.29 (3 H, m, 4-H, 5-H, NH), 2.43 (1 H, m, 3-H), 1.59 (3 H, d, 4.60, 6-H) and 1.01 (3 H, d, 4.60) (3e)
- (3f) 1.59 (3 H, d, J 6.0, 6-H<sub>3</sub>), and 1.01 (3 H, d, J 6.0, 3-Me)
- 3-Me) 3-Me) 5.46 (1 H, dt,  $J_{4.5}$  15.5  $J_{3,4}$  6.25, 4-H), 5.16 (1 H, dt,  $J_{5.6}$  6.25, 5-H), 3.96 (1 H, dt,  $J_{NH,2}$  9.0  $J_{2.3}$  5.5, 2-H), 2.65 (2 H, m, 3-H<sub>2</sub>), 1.93 (2 H, dt,  $J_{6.7}$  7.5, 6-H<sub>2</sub>), and 0.90 (3 H, t,  $J_{7,8}$  6.5, 8-H<sub>3</sub>) 5.29 (1 H, s, 5-H), 5.09 (1 H, s, 5'-H), 3.93 (1 H, dt,  $J_{NH,2}$  9.5  $J_{2.3}$  7.0, 2-H), and 2.85 (2 H, d, 3-H<sub>2</sub>) 6.39 (1 H, d,  $J_{4.5}$  15.5, 5-H), 5.96 (1 H, dt,  $J_{3.4}$  6.75, 4-H), 4.09 (1 H, dt,  $J_{5.75}$ ,  $J_{2.3}$  5.75, 2-H), and 2.63 (2 H, dd,  $J_{5.75}$ ,  $J_{2.3}$  5.75, 2-H), and 2.63 (2 H, dd,  $J_{5.75}$ ,  $J_{-2.3}$  5.75, 2-H), and 2.63 (2 H, dd,  $J_{5.75}$ ,  $J_{-2.3}$  5.75, 2-H), and 2.63 (2 H, dd,  $J_{5.75}$ ,  $J_{-2.3}$  5.89 (1 H, dd), 5.38 (1 H, dd), 3.10 (3 H, m), and 1.66 (2 H, m) (ring protons); 3.86 (1 H, dd,  $J_{NH,2}$  10.75  $J_{2.3}$  4.75, 2-H) 5.80 (1 H, m), 5.34 (1 H, d), and 2.49 (1 H, m) (ring protons); 3.80 (dd,  $J_{NH,2}$  10.0  $J_{2.3}$  6.5, 2-H) (3g)
- (3h) (3i)
- (4)
- (5)
- (ring protons); 3.80 (dd,  $J_{NH,2}$  10.0  $J_{2,3}$  6.5, 2-H) 5.41br (1 H, s) and 1.85 (4 H, m) (ring protons); 3.98 (1 H, dt,  $J_{NH,2}$  9.0,  $J_{2,3}$  7.0, 2-H), and 2.39 (6) 8  $(2 H, m, 3-H_2)$ 5.34 (2 H, m, C=CH and NH), 2.17 (6 H, m, 3-H<sub>2</sub>
- (7) \* and 4 ring protons), and 1.56 (1 H, t, J 6.25, 2-H)

<sup>a</sup> Signals corresponding to the C<sub>6</sub>H<sub>4</sub>Me, NH, and OC<sub>4</sub>H<sub>9</sub> groups appeared at typical chemical shifts which were ap-proximately the same for all the adducts (3—7); *e.g.* (3e): 7.73 and 7.25 (2 × 2 H, 2 × d, ArH), 5.28 (1 H, d,  $J_{\rm NH,2}$  9.5, NH), 3.88 (2 H, t, *J* 6.0,  $-OCH_2-$ ), 2.38 (3 H, s, ArMe), 1.39 (4 H, m, CH<sub>2</sub>CH<sub>2</sub>), and 0.90 (3 H, t, *J* 6.0, Me). <sup>b</sup> Remaining ring proton signals overlap with these of the battery correspondence. proton signals overlap with those of the butoxy-group protons.

configuration. The marked preponderance of the Eover the Z-isomer indicates that in both modes of addition with an endo- or exo-butoxycarbonyl group (Scheme 2 depicts only endo-addition) the transition state (A) is favoured. In (A) the alkene adopts a conformation in which the steric interaction of the alkyl group R and the hydrogen atom at C-1, cis to the -CH<sub>2</sub>R substituent, is avoided. This result could be construed as evidence in favour of a concerted process and militating against a biradical intermediate which should lead to an equilibrium ratio of E- and Z-isomers and the formation of side-products. Analogous stereoselectivity was observed previously in the ene reaction of diethyl mesoxalate and butyl glyoxylate with alkenes for which independent evidence for a concerted mechanism was



obtained.<sup>5</sup> A comparison of reaction time, temperature, and yields of the thermal ene reaction of butyl glyoxylate,<sup>6</sup> diethyl mesoxalate,<sup>7</sup> and the iminoacetate (2)indicates that the sulphonate-activated imino-group is more reactive than the carbonyl group even when the carbonyl group is activated by two alkoxycarbonyl substituents.

The iminoacetate (2) also exhibited a higher reactivity than carbonyl enophiles in electrophilic substitution. It

$$(3) Z = 0$$

$$(9) Z = S$$

reacted readily with furan and thiophen to give the aminoacid derivatives (8) and (9) whereas the analogous reaction of butyl glyoxylate 8,9 and diethyl mesoxalate 8 with furan required the presence of an acid catalyst and that with thiophen proceeded only in poor yield.<sup>10</sup>

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Numerous ene reactions that require an elevated temperature have been carried out successfully at room temperature in the presence of Lewis acid catalysts.<sup>11-13</sup> These catalysts were particularly effective for enophiles with an active carbonyl group.<sup>12,13</sup> The reactions proceeded in much higher yield and with greater stereo-specificity.<sup>13</sup>

The reaction of the iminoacetate (2) with alkenes (pent-1-ene, hex-1-ene, and isobutene) in the presence of SnCl<sub>4</sub>, AlCl<sub>3</sub>, and BF<sub>3</sub> was examined. The reactions were accelerated and similar yields of the adducts to those in the absence of catalyst were obtained in only 10 min at room temperature. The catalysed reaction could also be carried out at temperatures as low as -78 °C which is convenient for handling the volatile alkenes propene and butene. The application of the imine ene reaction to the synthesis of  $\alpha$ -amino-acids or  $\gamma\sigma$ -unsaturated  $\alpha$ -aminoacids was demonstrated by the conversion of the adduct (3e) into the saturated tosylated amino-acid butyl ester (12) and the (E)-2-aminohept-4-enoic acid (11). Basic hydrolysis of the adduct (3e) and subsequent detosylation with sodium in liquid ammonia gave (11) in 85% overall

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a sealed tube for 0.5—24 h. The solvent and excess of alkene were evaporated under reduced pressure and a benzene-hexane solution of the residue was filtered through

TABLE 3

	El	emental	analy	vses a						
		Elemental analyses								
Molecular		Fo	und (	%)	Required (%)					
Compound	l formula	С	Н	Ν	С	н	Ν			
(3a)	C <sub>16</sub> H <sub>23</sub> NO <sub>4</sub> S	59.2	7.3	4.1	59.1	7.1	4.3			
(3b)	C <sub>17</sub> H <sub>25</sub> NO <sub>4</sub> S	60.5	7.5	3.8	60.1	7.4	4.1			
(3c)	C <sub>17</sub> H <sub>25</sub> NO <sub>4</sub> S	60.0	7.5	4.1	60.1	7.4	4.1			
(3d)	C <sub>17</sub> H <sub>25</sub> NO <sub>4</sub> S	60.3	7.5	4.1	60.1	7.4	4.1			
(3e)	C <sub>18</sub> H <sub>27</sub> NO <sub>4</sub> S	61.1	7.9	4.2	61.2	7.7	4.0			
(3f)	C <sub>18</sub> H <sub>27</sub> NO <sub>4</sub> S	61.1	7.6	3.6	61.2	7.7	4.0			
(3i)	C <sub>22</sub> H <sub>27</sub> NO <sub>4</sub> S	61.5	7.2	3.8	61.5	7.2	4.0			
(4)	C <sub>18</sub> H <sub>25</sub> NO <sub>4</sub> S	62.4	7.4	3.6	62.4	7.5	3.8			
(5)	C <sub>19</sub> H <sub>27</sub> NO <sub>4</sub> S	66.0	6.8	3.3	65.8	6.8	3.5			
(6)	C <sub>20</sub> H <sub>29</sub> NO <sub>4</sub> S	63.1	7.7	3.6	62.8	7.6	4.0			
(7)	$C_{22}H_{31}NO_6S$	60.3	7.1	3.3	60.4	7.1	<b>3.2</b>			
" Com spectros	pounds (3g), copically.	(3h), an	d (11	) were	charact	erized	onl			

a short silica gel (Merck 60, 230-400 mesh) column. Reaction conditions, yields, m.p.s, b.p.s, and spectral data are in Tables 1 and 2.



yield. Catalytic hydrogenation of the adduct (3e) afforded the tosyl derivative (12) in 90% yield. Of particular interest is the easy access to the unsaturated compounds since several  $\alpha$ -amino-acids of non-protein origin have a double bond at the  $\gamma\delta$ -position <sup>14</sup> or a functional group which could be derived from the latter; <sup>15</sup> e.g. the adduct (7) has the carbon skeleton of the antibiotic  $\alpha$ -amino-acid anticapsine. The foregoing ene reaction opens a new approach to the synthesis of these natural  $\alpha$ -amino-acids.

### EXPERIMENTAL

I.r. spectra were recorded with a Unicam SP-200, Beckman Acculab TM1 or Beckman IR 4240 spectrophotometer. <sup>1</sup>H N.m.r. spectra were measured with a Jeol JNM-4H-100 spectrometer in [<sup>2</sup>H]chloroform with Me<sub>4</sub>Si as internal standard, unless otherwise specified. Elemental analyses are in Table 3.

Thermal Reaction of Butyl N-(p-Tolylsulphonyl)iminoacetate <sup>4</sup> (2) with Alkenes. General Procedure.—A solution of (2) (1 mmol) and the alkene (1) (1—7 mmol, freshly distilled from lithium aluminium hydride) in dry benzene (0.5 ml) was flushed with nitrogen and heated at 120 °C in Catalysed Reaction of the Iminoacetate (2) with Pent-1-ene. —To a solution of (2) (283 mg, 1 mmol) and pent-1-ene (350 mg, 5 mmol) in dichloromethane (1 ml) chilled to 0 °C tin(IV) chloride (0.1 ml, 1 mmol) was added. After 30 min the mixture was diluted with dichloromethane (10 ml), washed with water (10 ml), dried (MgSO<sub>4</sub>), and evaporated. A solution of the residue in benzene-ether (4 : 1) was filtered through a short silica gel (Merck 60, 230—400 mesh) column and evaporated again. Distillation furnished (3e) (307 mg, 87%) identical (t.l.c., i.r., <sup>1</sup>H n.m.r.) with the sample obtained in the thermal reaction.

Reaction of the Iminoacetate (2) with Thiophen.—A mixture of (2) (0.5 g, 1.7 mmol) and thiophen (440 mg, 5.1 mmol) was heated in a sealed tube at 110 °C for 4 h. The excess of thiophen was evaporated off and a solution of the residue in benzene–ether (7:3) chromatographed on a silica gel (Serva, 200—300 mesh) column to yield butyl 2-thienyl-(toluene-p-sulphonamido)acetate (9) (518 mg, 80%), m.p. 68 °C (from benzene–hexane, 1:10),  $v_{max}$  (KBr) 3 300 (NH), 1 720 (C=O), 1 340, and 1 160 (SO<sub>2</sub>) cm<sup>-1</sup>;  $\delta$  6.73 (1 H, dd,  $J_{3,4}$  3.5,  $J_{3,5}$  1.25 Hz, 3-H), 6.71 (1 H, dd,  $J_{4,5}$  5.25 Hz, 5-H), 6.50 (1 H, dd, 4-H), and 5.45 (1 H, d,  $J_{NH,CH}$  8.5 Hz, -CH $\leq$ ) (Found: C, 55.6; H, 5.8; N, 3.6. C<sub>17</sub>H<sub>21</sub>NO<sub>4</sub>S<sub>2</sub> requires C, 55.6; H, 5.8; N, 3.8%).

Reaction of the Iminoacetate (2) with Furan.-A mixture of (2) (0.5 g, 1.7 mmol) and furan (350 mg, 5.1 mmol) was heated in a sealed tube at 110 °C for 4 h. Evaporation of furan and recrystallization of the residue from benzenehexane (1:10) afforded the 2-furylacetate (8) (502 mg, 81%), m.p. 75 °C,  $\nu_{max.}({\rm KBr})$  3 320 (NH), 1 735 (C=O), 1 130, and 1 165 (SO<sub>2</sub>) cm<sup>-1</sup>;  $\delta$  6.82 (1 H, dd,  $J_{3,5}$  1,  $J_{4,5}$  2 Hz, 5-H), 6.04 (1 H, dd,  $J_{3,4}$  3.25 Hz, 3-H), 5.85 (1 H, dd, 4-H), and 5.31 (1 H, d, J<sub>NH, CH</sub> 8.5 Hz, -CH<) (Found: C, 58.0; H, 6.1; N, 3.9.  $C_{17}H_{21}NO_5S$  requires C, 58.1; H, 6.0; N, 4.0%).

(E)-2-Aminohept-4-enoic Acid (11) Hydrochloride.—A solution of the adduct (3e) (0.483 g, 1.37 mmol) and potassium hydroxide (0.75 g, 13.4 mmol) in ethanol-water 1:1 (15 ml) was heated at 60 °C for 1 h. The ethanol was evaporated off, and the residue brought to pH 3 with concentrated hydrochloric acid and extracted with chloroform  $(3 \times 20 \text{ ml})$ . Evaporation gave a thick oil which was dissolved in ether (20 ml) and saturated with gaseous ammonia to afford the ammonium salt of (10) (0.335 g, 78%). The ammonium salt of (10) (0.24 g, 0.76 mmol) was treated with sodium (0.20 g, 8.7 mmol) in liquid ammonia (20 ml) at reflux for 3 h. The mixture was then evaporated to dryness and to the residue 10% hydrochloric acid (5 ml) was added. The water layer was extracted with ether  $(8 \times 15)$ ml) and evaporated and the residue extracted with warm ethanol  $(2 \times 2 \text{ ml})$ . Removal of the solvent and drying *in* vacuo afforded the hydrochloride of (11) (0.220 g, 85%),  $\delta$ 5.80 (1 H, dt,  $J_{4,5}$  15.3,  $J_{3,4}$  6.2 Hz, 4-H), 5.35 (1 H, dt,  $J_{5, 6}$  7.1 Hz, 5-H), 4.11 (1 H, t,  $J_{2, 3}$  6.0 Hz, 2-H), 2.66 (2 H, dd, 3-H<sub>2</sub>), 2.04 (2 H, dq, J<sub>6.7</sub> 7.3 Hz, 6-H<sub>2</sub>), and 0.99 (3 H, t, Me).

Butyl 2-N-(p-Tolylsulphonyl)aminoheptanoate (12).—A solution of the adduct (3e) (1.0 g, 2.83 mmol) in acetic acid (5 ml) was hydrogenated at atmospheric pressure in the presence of 5% Pd-C catalyst (0.5 g). When the absorption of hydrogen ceased the catalyst was filtered off and the solvent evaporated. Recrystallization of the residue from hexane afforded the saturated amino-ester (12) (0.905 g, 90%), m.p. 48 °C,  $v_{max}$ (KBr), 3 330 (NH), 1 740 (C=O),

1 340, and 1 160 (SO<sub>2</sub>) cm<sup>-1</sup>,  $\delta$  7.71 (1 H, d,  $J_{\rm NH,2}$  9.0 Hz, NH), 3.85 (1 H, dt,  $J_{2,3}$  6.0 Hz, 2-H), 3.84 (2 H, t, J 6.2 Hz, OCH<sub>2</sub>), 2.40 (3 H, s, ArMe), 1.84-1.04 (12 H, m,  $6 \times CH_2$ ), and 1.01–0.71 (6 H, m,  $2 \times Me$ ) (Found: C, 60.7; H, 8.5; N, 3.8. C<sub>18</sub>H<sub>29</sub>NO<sub>4</sub>S requires C, 60.8; H, 8.2; N, 3.9%).

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