α,β-Unsaturated Carboxylic Acid Derivatives. XVII. The Facile Synthesis of Ethyl α-Azido-α-alkenoates and Reduction to Ethyl α-Amino-α-alkenoates[1]

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Several pathways leading to ethyl α-azido-α-alkenoates (**8**) by the β-elimination to ethyl α-azido-β-substituted (hydroxy-, acetoxy-, or mesyloxy)-alkanoates with NaN_3 or Et_3N have been examined. The optimized procedure, in combination with subsequent reduction provides a general synthetic route to α-amino-α-alkenoic acid esters (**9**). The configuration of **8** and **9** have been shown to be of (*Z*)-geometry.

α,β-Unsaturated α-amino acid (α-dehydroamino acid; DHA) or the α-imino form has been postulated as the intermediate in the biological epimerization of the L-α-amino acid into the enantiomer by the process of dehydrogenation-hydrogenation.[2] In addition, DHA is of great importance as a starting material for the incorporation and synthesis of dehydropeptides and peptide antibiotics.[2-5]

In previous papers,[6,7] the facile synthesis of ethyl 2-amino-2-alkenoates (**9**) by reduction of the corresponding 2-azido compounds (**8**) with aluminium-amalgam (Al–Hg) have been reported. Schmidt *et al.* reported the preparation of methyl 2-amino-2-alkenoates by the elimination of methanol from the corresponding α-methoxy α-amino acids[8] or the dehydrochlorination of α-chloro amino acid derivatives.[9]

The synthesis of **8** and the subsequent selective reduction of **8** into **9** will be reported in detail. The

TABLE 1. ETHYL 2-BROMO-3-SUBSTITUTED ALKANOATES (**2**, **3**, AND **4**)

Compound No.	Yield (%)	Bp °C/mmHg[a] (Mp °C)	Formula	Found (Calcd), % C	Found (Calcd), % H	IR spectrum,[b] cm^{-1} OH	IR spectrum,[b] cm^{-1} COOEt	IR spectrum,[b] cm^{-1} $COCH_3$	IR spectrum,[b] cm^{-1} SO_2O	NMR spectrum,[c] δ 2-proton (Hz)	NMR spectrum,[c] δ 3-proton (Hz)	NMR spectrum,[c] δ SCH_3
2a	58	65—70/3	$C_6H_{11}O_3Br$	34.11 (34.12)	5.43 (5.21)	3450,	1750			4.15d(7.6),	4.01—4.22m	
2b	51	67—71/1.5	$C_7H_{13}O_3Br$	37.39 (37.33)	5.66 (5.78)	3440,	1743			4.15d(7.6),	3.85—4.08m	
2c	48	72—75/0.5	$C_8H_{15}O_3Br$	39.98 (40.17)	6.23 (6.28)	3440,	1743			4.14d(7.6),	3.85—4.09m	
2d	50	70—73/0.5	$C_8H_{15}O_3Br$	40.11 (40.17)	6.15 (6.28)	3450,	1740			4.19d(7.9),	3.86dd(4.0)	
2e	45	(72—73)[d]	$C_{11}H_{13}O_3Br$	48.40 (48.35)	4.80 (4.76)	3400,	1720			4.34d(8.0),	5.05dd(5.1)	
3a	83	67—73/1.5	$C_8H_{13}O_4Br$	37.85 (37.94)	5.19 (5.14)		1755			4.29d(7.7),	5.23dq(6.0)	
3b	85	78—80/1	$C_9H_{15}O_4Br$	41.08 (40.70)	5.40 (5.62)		1750			4.32d(7.8),	5.12—5.56m	
3c	86	82—86/1	$C_{10}H_{17}O_4Br$	42.27 (42.70)	6.15 (6.05)		1755			4.32d(7.1),	5.26—5.36m	
3d	84	80—85/1	$C_{10}H_{17}O_4Br$	42.78 (42.70)	6.18 (6.05)		1755			4.28d(9.0),	5.35dd(3.7)	
3e	90	syrup	$C_{13}H_{15}O_4Br$	49.66 (49.52)	4.78 (4.76)		1750			4.48d(10.0),	6.16d(10.0)	
4a	59	110—115/1	$C_7H_{13}O_5SBr$	29.10 (29.06)	4.56 (4.50)		1741,	1365	1180	4.32d(8.0),	4.95—5.22m,	3.06s
4b	51	120—122/1	$C_8H_{15}O_5SBr$	31.74 (31.68)	4.87 (4.95)		1740,	1360	1180	4.41d(8.0),	4.91—5.08m,	3.06s
4c	53	120—125/0.8	$C_9H_{17}O_5SBr$	34.13 (34.07)	5.42 (5.36)		1740,	1360	1175	4.46d(7.0),	4.95—5.12m,	3.04s
4d	46	121—125/0.8	$C_9H_{17}O_5SBr$	34.12 (34.07)	5.56 (5.36)		1745,	1360	1175	4.36d(8.3),	4.96—5.10m,	3.05s
4e	81	(70—71)[e]	$C_{12}H_{15}O_5SBr$	41.00 (41.08)	4.30 (4.29)		1750,	1368	1180	4.50d(10.0),	5.90d(10.0),	2.71s

a) Colorless oil. b) Recorded in KBr. c) Measured in $CDCl_3$. d) Colorless needles from benzene–cyclohexane (1 : 4 v/v). e) Colorless needles from hexane.

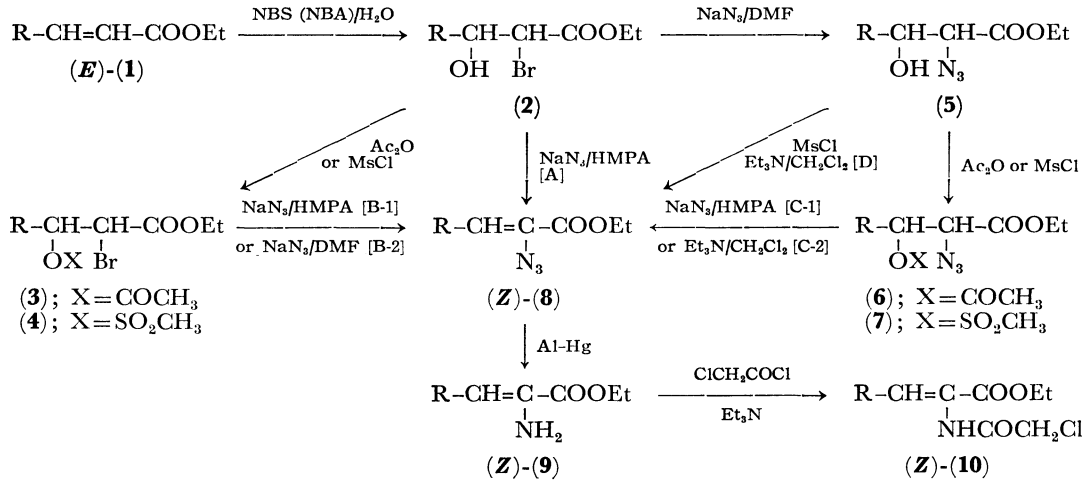
geometric structure of **8** and **9** has been shown to be of (*Z*)-configuration.

Results and Discussion

The starting material, ethyl 2-bromo-3-hydroxyalkanoate (**2**) were readily prepared by treating ethyl (*E*)-2-alkenoates (**1**) with *N*-bromosuccinimide (NBS) or *N*-bromoacetamide (NBA) and water.[6]

The direct reaction of **2** with 3M NaN_3 in hexamethylphosphoric triamide (HMPA) gave **8** in low yield (Procedure A).

To effect β-elimination after azidation, **2** was converted into ethyl 3-acetoxy-2-bromo (**3**)- and 2-bromo-3-mesyloxyalkanoates (**4**) by conventional means, and subjected to a similar substitution-elimination. The



a; R=CH_3, **b**; R=C_2H_5, **c**; R=*n*-C_3H_7, **d**; R=*i*-C_3H_7, **e**; R=C_6H_5

Scheme 1. Alphabet in brackets is the type of procedure.

TABLE 2. ETHYL 2-AZIDO-3-SUBSTITUTED ALKANOATES (**5**, **6**, AND **7**)

Compd No.	Yield (%)	Bp °C/mmHg[a] (Mp °C)	Formula	Found (Calcd), % C	H	N	IR spectrum,[b] cm^{-1} OH	N_3	COOEt $COCH_3$	SO_2O	NMR spectrum,[c] δ 2-proton (Hz)	3-proton (Hz)	SCH_3
5a	75	72—75/1.5	$C_6H_{11}N_3O_3$	41.71 (41.61)	6.45 (6.40)	24.30 (24.27)	3450,	2100,	1750		3.79d(4.0),	4.02—4.32m	
5b	80	75—80/1.7	$C_7H_{13}N_3O_3$	45.12 (44.91)	7.10 (7.00)	22.39 (22.45)	3450,	2100,	1740		3.84d(3.5),	3.85—4.20m	
5c	75	81—83/1	$C_8H_{15}N_3O_3$	47.79 (47.75)	7.70 (7.51)	20.90 (20.88)	3450,	2100,	1740		3.85d(3.4),	3.81—4.18m	
5d	72	80—82/1.5	$C_8H_{15}N_3O_3$	47.61 (47.75)	7.56 (7.51)	20.92 (20.88)	3450,	2100,	1740		3.86d(3.0),	3.70dd(6.9)	
5e	70	syrup	$C_{11}H_{13}N_3O_3$	56.18 (56.16)	5.65 (5.57)	17.76 (17.86)	3450,	2100,	1740		3.98d(4.0),	4.50d(4.0)	
6a	92	73—76/1	$C^8H_{13}N_3O_4$	44.58 (44.64)	6.12 (6.09)	19.61 (19.53)		2100,	1750		3.72d(3.5),	5.36dq(6.6)	
6b	91	75—81/1	$C_9H_{15}N_3O_4$	47.19 (47.15)	6.70 (6.60)	18.43 (18.33)		2100,	1750		3.78d(3.5),	5.26dt(6.9)	
6c	95	80—82/0.2	$C_{10}H_{17}N_3O_4$	49.43 (49.37)	7.10 (7.04)	17.32 (17.28)		2100,	1750		3.74d(3.2),	5.36dt(6.5)	
6d	92	80—82/0.5	$C_{10}H_{17}N_3O_4$	49.56 (49.37)	6.98 (7.04)	17.33 (17.28)		2100,	1750		3.18d(3.0),	5.12dd(7.8)	
6e	89	syrup	$C_{13}H_{15}N_3O_4$	56.58 (—)	5.44 (—)	15.31 (—)		2100,	1755		4.02d(5.0),	6.23d(5.0)	
7a	75	135—140/1.5	$C_7H_{13}O_5SN_3$	33.56 (33.47)	5.19 (5.18)	16.77 (16.73)		2110,	1750,	1370 1190	3.85d(3.8),	5.20dq(6.2),	3.05s
7b	82	135—137/1	$C_8H_{15}O_5SN_3$	36.32 (36.23)	5.78 (5.66)	15.86 (15.85)		2110,	1750,	1370 1185	3.89d(3.2),	5.04dt(6.9),	3.06s
7c	81	138—139/1	$C_9H_{17}O_5SN_3$	38.88 (38.71)	5.87 (6.09)	15.23 (15.05)		2110,	1755,	1370 1190	3.87d(3.2),	5.14dt(6.8),	3.06s
7d	80	140—142/1.5	$C_9H_{17}O_5SN_3$	38.75 (38.71)	6.11 (6.09)	14.98 (15.05)		2110,	1760,	1380 1190	3.87d(3.2),	4.86dd(7.8),	3.08s
7e	76	(68—69)[d]	$C_{12}H_{15}O_5SN_3$	45.79 (46.01)	4.77 (4.79)	13.45 (13.42)		2100,	1745,	1370 1187	4.16d(5.9),	5.94d(5.9),	2.88s

a) Colorless oil. b) Recorded in KBr. c) Measured in $CDCl_3$. d) Colorless needles from hexane.

Table 3. The percentage yields and NMR spectra (δ) of **8**

Compound No.	Procedures and yields (%)						NMR spectrum,[a] δ	
	A	B		C		D	3-proton (Hz)	3-alkyl (Hz)
		1	2	1	2			
8a	45	90	68	90	92	91	6.18qa[a] (7.0)	1.80d (7.0)
8b	40	81	71	81	90	92	6.15t (7.2)	2.24qi[c] (7.2)
8c	35	74	69	74	89	96	6.16t (7.6)	2.21qa[b] (7.6)
8d	37	75	69	75	88	93	5.96d (7.4)	2.80m[d] (6.3)
8e	41	95	43	95	90	85	6.96s —	(7.32—7.52m 7.80—7.92m)[e]

a) Measured in $CDCl_3$. b) Quartet. c) Quintet. d) Multiplet. e) Phenyl protons.

Table 4. The percentage yietds and NMR spectra of **9** and **10**

Compound No.	Yield (%)	NMR spectrum, δ in $CDCl_3$			Compound No.	Yield (%)
		3-proton (Hz)	NH_2	3-alkyl		
9a	75.6	5.65q[a] (7.2)	3.50	1.68q	**10a**	86
9b	85.7	5.56t[b] (7.1)	3.45	2.07t	**10b**	87
9c	80.0	5.59t[b] (7.3)	3.50	2.04t	**10c**	79
9d	84.5	5.46d[c] (9.1)	3.52	2.45m[c]	**10d**	85
9e	70.9	6.50s[d]	4.30	7.20—7.55m[e]	**10e**	65

a) Quartet. b) Triplet. c) Doublet. d) Singlet. e) Multiplet.

reaction of **4** in *N,N*-dimethylformamide (DMF) gave **8** in *ca.* 65% yield together with the direct β-elimination product, the ethyl 2-bromo-2-alkenoates (Procedure B-2). **3** was completed in HMPA in *ca.* 80% yield (Procedure B-1).

In subsequent experiment, **2** was firstly conversted into ethyl 2-azido-3-hydroxyalkanoate (**5**), and subsequently into ethyl 3-acetoxy-2-azido (**6**)- and 2-azido-3-mesyloxyalkanoates (**7**) in good yields. The similar elimination reaction of **6** in HMPA in the presence of NaN_3 (Procedure C-1) and **7** in CH_2Cl_2 in the presence of Et_3N (Procedure C-2) proceeded more smoothly to give **8** in *ca.* 85 and 90% yields respectively. The reaction of **5** with mesyl chloride in CH_2Cl_2 in the presence of Et_3N was completed immediately to give **8** quantitatively (Procedure D).

Procedure D is the most satisfactory method for the preparation of **8** from **2** and is generally applicable for the conversion of α-hydroxy azides into the corresponding azido olefin, the results of which will be published elsewhere.

The reduction of **8** with Al–Hg in ether readily gave the expected **9** in *ca.* 80% yield.[7] In order to determine the geometric configuration of **9**, chloroacetylation was performed to give ethyl 2-(chloroacetylamino)-2-alkenoates (**10**). All physical constants and spectral data of **10** were in good agreement with the authentic samples of the (*Z*)-configuration.[10] Therefore, the structures of **8**, **9**, and **10** have been unambiguously assigned the (*Z*)-configuration.

The configuration of the addition products (**2**—**4**), have been the erythro-isomer from the observed $J_{2,3}$ values of over 7.0 Hz. Similarly, from the $J_{2,3}$ values (*ca.* 3.5 Hz), the configuration of **5**, **6**, and **7** has been assigned to the threo-isomer.

Consequently it is considered that the stereospecific *trans* addition to (***E***)-**1**[11] gave the erythro-isomer, which was converted into the threo-isomer by substitution and *trans* β-elimination of the two isomers above proceeded to give (***Z***)-**8**.

Experimental

All boiling and melting points are uncorrected. The IR and NMR spectra were recorded with Hitachi EPI-G3 and JNM-PS-100 Spectrometers with tetramethylsilane as the internal standard respectively.

Preparation of **2**. To a solution of **1** (0.5 mol) in H_2O (300 ml) and tetrahydrofuran (300 ml) was added portionwise NBS or NBA (0.6 mol) below 10 °C. After reaction at the same temperature for 12 h, the resulting solution was allowed to stand for 24 h at room temperature. The solution was extracted four times with ether (200 ml) and the ethereal extracts washed twice with water and dried over anhydrous $MgSO_4$. Evaporation of the ether gave a syrup, which was distilled under reduced pressure to give **2**.

Preparation of **5**. A mixture of **2** (0.1 mol) and NaN_3 (0.25 mol) in DMF (150 ml) was heated with stirring at 60—70 °C for 20 h. The reaction solution was poured into ice-

water (400 ml) and the aqueous solution extracted three times with benzene (100 ml). The combined benzene extracts were washed twice with water and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave **5**.

Preparation of 3 and 6. Two drops of concentrated H_2SO_4 were added to a solution of **2** (0.1 mol) in acetic anhydride (0.15 mol). After stirring at 50—60 °C for 30 min, the reaction mixture was diluted with benzene (60 ml). The benzene solution was washed once with aqueous $NaHCO_3$ and twice with water and dried over anhydrous Na_2SO_4. Concentration of the benzene solution gave a syrupy residue, which was distilled under reduced pressure to give **3**. A similar reaction of **5** gave **6**.

Preparation of 4 and 7. To a solution of **2** (0.05 mol) and mesyl chloride (0.05 mol) in CH_2Cl_2 (50 ml) was added Et_3N (0.05 mol) under nitrogen at 0—3 °C. The chilled solution was allowed to stand at room temperature and the reaction solution continuously stirred at room temperature for 30 min. The reaction solution was washed three times with water and the solution dried over anhydrous Na_2SO_4 and evaporated. The syrup obtained was distilled under reduced pressure to give **4**. A similar reaction of **5** gave **7**.

Preparation of 8. Procedure A. A solution of **2** (0.05 mol) and NaN_3 (0.15 mol) in HMPA (70 ml) was stirred at 30—35 °C for 24 h. The reaction solution was poured into ice-water (300 ml) and the aqueous solution extracted three times with benzene (60 ml). The benzene extracts were washed twice with water, dried over anhydrous $MgSO_4$, and evaporated under reduced pressure. The syrupy residue obtained was purified on a silica gel column using a mixture of hexane and benzene (2: 1 v/v) as eluentent to give **8**.

Procedure B. B-1: A solution of **3** (0.05 mol) and NaN_3 (0.15 mol) in HMPA (70 ml) was stirred at room temperature for 20 h. The reaction solution was poured into ice-water (300 ml) and the aqueous solution similarly worked up to give **8**. *B-2*: Similarly, **4** (0.05 mol) was treated with NaN_3 in DMF (70 ml) at 40—45 °C for 48 h to give **8**.

Procedure C. C-1: Similarly, **6** (0.05 mol) and NaN_3 (0.1 mol) in HMPA (70 ml) was worked up for 12 h to give **8**. *C-2*: To a solution of **7** (0.05 mol) in CH_2Cl_2 (50 ml) was added dropwise Et_3N (0.08 mol) with stirring under nitrogen below 5 °C. After stirring at room temperature for 30 min, the reaction solution was washed once with 3 M HCl and three times with water and dried over anhydrous $MgSO_4$. A similar work-up of the residual syrup gave pure **8**.

Procedure D. To a solution of **5** (0.05 mol) and mesyl chloride (0.06 mol) in CH_2Cl_2 (50 ml) was added dropwise Et_3N (0.15 mol) with stirring under nitrogen below 3 °C. After stirring at room temperature for 40 min, the precipitated salt was filtered off and the filtrate washed once with 3 M HCl and three times with water and dried over anhydrous $MgSO_4$. Finally, a similar purification gave **8**.

Preparation of 9. A solution of **8** (0.05 mol) in ether (30 ml) was added dropwise to a suspension of Al-Hg (made from 4 g of Al) in ether (50 ml) with vigorous stirring at room temperature. After a few minutes, the ether began to reflux, and the refluxing was maintained by the addition of a few drops of water at 20 min intervals. After the addition of the solution was completed, stirring was continued for 3 h. The mixture was extracted several times with an ether-ethyl acetate mixture (1: 3 v/v). The combined extracts were evaporated and distilled under reduced pressure to give **9**.

Preparation of 10. To a solution of **9** (0.02 mol) and Et_3N (0.025 mol) in dry ether (20 ml) was added chloroacetyl chloride (0.025 mol) dropwise with stirring at room temperature. After stirring for 4 h, the salt separating out was filtered. The filtrate was washed once with 3 M HCl, once with aqueous $NaHCO_3$, and twice with water and dried over anhydrous Na_2SO_4. The ether solution was evaporated to give a viscous syrup, which was purified on a silica-gel column using a benzene-acetone mixture (8: 1 v/v) as the eluentent. The fraction obtained was concentrated under reduced pressure to give **10**.

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