α,β-Unsaturated Carboxylic Acid Derivatives. VIII. The Synthesis and Reaction of Esters *N*-Acyl-*N*-bromo-α-dehydroamino Acid[1]

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The addition of bromine to *t*-butyl 2-(*N*-acylamino)-2-alkenoate (**3**) was accompanied by the elimination of hydrogen bromide and the decomposition of the ester group to give 2-(*N*-acylamino)-3-bromo-2-alkenoic acid, while the bromination of **3** with NBS gave the corresponding *N*-bromo derivative (**7**), whose bromine atom gradually migrates to give *t*-butyl 2-(*N*-acylamino)-3-bromo-2-alkenoate. The substitution of the bromine of **7** with nucleophiles gave, successively, the corresponding *N*-methoxy, *N*-benzyloxy and *N*-cyano derivatives, while that with sodium azide gave the corresponding migration products. The structures of the new compounds were assigned.

In previous papers, we reported the new syntheses of alkyl 2-(*N*-acylamino)-2-alkenoate (**3**) by the condensation of alkyl 2-oxoalkanoate with chloroacetamide[2] or chloroacetonitrile[3] and by the elimination of acetic acid from alkyl 2-(*O*-acetyl-*N*-acyl-hydroxyamino)alkanoate, which had itself been derived by the acetylation of alkyl 2-hydroxyaminoalkanoate (**1**) or alkyl 2-(*N*-acyl-hydroxyamino)alkanoate (**2**).[4,5]

Because of the possible synthetic utility of the *N*-bromo derivative of **3** in the preparation of α-dehydrohydroxyamino acids, cyclic hydroxamic acids such as mycelianamide,[6] and other similar substances, the facile synthesis of *t*-butyl 2-(*N*-bromoacetamido)-2-alkenoate (**7**) was pursued, and it was briefly communicated that the bromination of **3** with bromine or *N*-bromosuccinimide (NBS) gave 2-(*N*-acylamino)-3-bromo-2-alkenoic acids (**5**) or **7** respectively.[7] However, no available method of synthesizing **7** or **5** has ever been reported, except for the preparation of β-halo-*sec*- and -*tert*-enamines.[8–10]

In the present paper, we wish to report the syntheses of **5** and **7** in detail, together with the replacement of the bromine atom of **7** with nucleophiles. A few substitutions were accompanied by the rearrangement of substituents, and the structures of the products were assigned by means of IR and NMR spectroscopies.

Results and Discussion

Bromination of 1 and 3. Attempts at the addition of bromine to ethyl 2-(*N*-acylamino)-2-alkenoate (**3**; R^1=Et) in chloroform and the subsequent elimination of hydrogen bromide under several experimental conditions were unsuccessful, except for the direct conversion of **3a,c,d** (R=CH_3, R^1=*t*-Bu: **a**; X=CH_3, **c**; X=OC_2H_5, **d**; X=Phthalyliminomethyl) into 2-(*N*-acylamino)-3-bromo-2-butenoic acid (**6a,c,d**) in an about 50% yield at room temperature for 2 days. Besides, it was found that the treatment of ethyl 2-hydroxyaminobutanoate (**1e**) with bromoacetyl bromide in benzene in the absence of an alkali such as pyridine at room temperature gave ethyl 3-bromo-2-bromoacetamido-2-butenoate (**5e**) directly, though the yield was low. It was deduced that the formation of ethyl 2-bromoacetamido-2-butenoate (**3e**; R=CH_3, R^1=C_2H_5, X=CH_2Br) *via* the corresponding hydroxamic acid ester (**2e**)[5] was followed by the addition of bromine formed oxidatively from hydrogen bromide, and by the elimination of hydrogen bromide to afford **5e**. On the other hand, the reaction of **3** with bromine proceeded similarly through the addition of bromine and the elimination of hydrogen bromide to give **5**, which was subsequently converted into **6**.

On the other hand, the treatment of *t*-butyl 2-acetamido-2-alkenoate (**3a,b**: **b**; R=C_2H_5, R^1=*t*-Bu, X=CH_3) with NBS in tetrachloromethane at room temperature for 30 min gave **7a,b** as an unstable oily product in quantitative yield. It was found that the bromine on the nitrogen atom of **7a,b** gradually migrated at room temperature for 2 days to give **5a,b** as colorless crystals in about a 70% yield. The **5a,b** compound was composed of *E*- and *Z*-isomers, which were purely separated by chromatography on a silica gel column using benzene–ethyl acetate (5: 1 V/V). However, the unambiguous assignment of the geometric configuration of the products was difficult from only the spectroscopic data listed in Table 2.

The yields, the physical constants, and the spectral data of **5** and **7** are summarized in Tables 1 and 2 respectively.

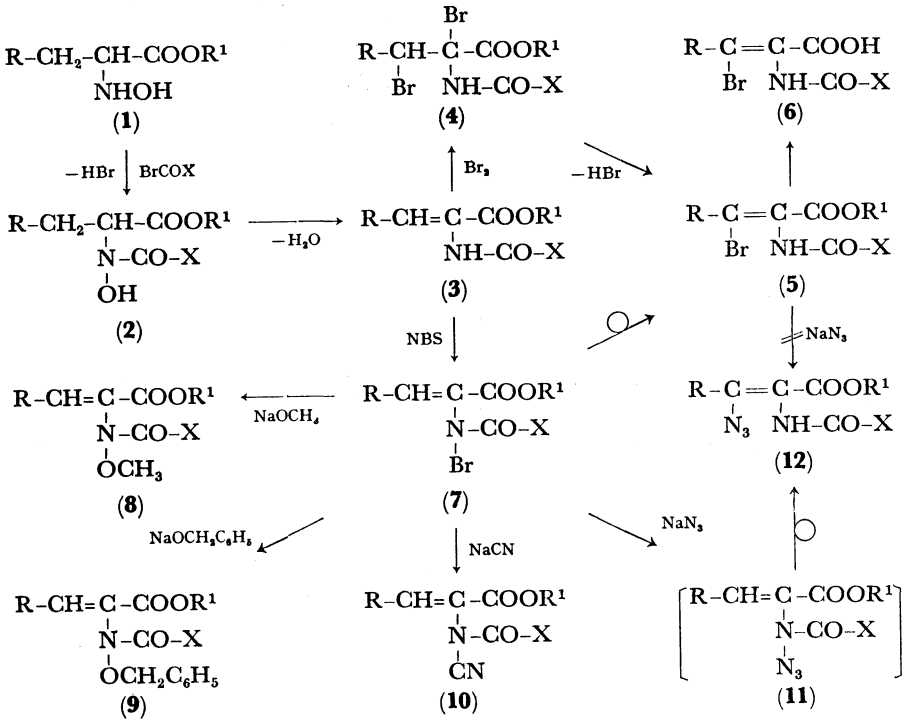
Reactions of 7 with Nucleophiles. The treatment of **7a,b** with sodium methoxide in methanol at room temperature for 2 hr afforded *t*-butyl 2-(*N*-acetyl-*O*-methyl-hydroxyamino)-2-alkenoate (**8a,b**). Moreover, in a similar manner, compound **7a,b** reacted with sodium benzyloxide in benzyl alcohol to give the expected *t*-butyl 2-(*N*-acetyl-*O*-benzyl-hydroxyamino)-2-alkenoate (**9a,b**). On the other hand, the reaction of **7a,b** with sodium cyanide in dimethyl formamide also occurred at room temperature for 2 hr to give *t*-butyl 2-(*N*-cyanoacetamido)-2-alkenoate (**10a,b**). It was found that the products obtained were more stable than **7a,b** and that the methoxy, benzyloxy, and cyano groups on the nitrogen atom do not migrate to the carbon atom in the β-position.

On the other hand, the treatment of **7a,b** with sodium azide in dimethyl formamide at room temperature for 2 hr unexpectedly gave the *t*-butyl 2-acetamido-3-azido-2-alkenoate (**12a,b**) as a colorless syrup or as needles in a good yield. In this case, the expected *N*-substituted compound (**11a,b**) could not be isolated. However,

the preparation of **12** by the reaction of **5** with sodium azide was unsuccessful. Consequently, it was deduced that the direct formation of **12** from **7** proceeded through the rearrangement reaction of the intermediate, **11a,b**.

All of the new compounds were obtained as syrups; some of them gradually crystallized in considerably good yields after purification on a silica gel column using benzene–ethyl acetate.

The structures of all the new compounds were characterized spectroscopically and gave satisfactory results in elemental analysis. From the NMR spectra, the vinyl proton signals of **7**, **8**, **9**, and **10** showed peaks in the δ 4.12—5.01 region as quartets or triplets, while the NH proton signals of **5** and **12** showed their peaks in the δ 6.86—8.35 region as broad singlets. On the other hand, the disappearance of the NH absorption band in the IR spectrum of **3** indicates the formation of **7**, while the appearance of the NH band in the region 3150—3340 cm^{-1} seems to support the formation of



a; R=CH_3, R^1=*t*-Bu, X=CH_3, **b**; R=C_2H_5, R^1=*t*-Bu, X=CH_3,
c; R=CH_3, R^1=*t*-Bu, X=OC_2H_5, **d**; R=CH_3, R^1=*t*-Bu, X=Phthalyliminomethyl,
e; R=CH_3, R^1=Et, X=CH_2Br

Scheme 1.

TABLE 1. *t*-BUTYL 2-(*N*-SUBSTITUTED-ACETAMIDO)-2-ALKENOATES (R-CH=C-COOBu-*t*, N-$COCH_3$, X)

Compd. No.	X	Yield (%)	mp °C	Formula	Found (Calcd), % C	H	N	IR spectrum, cm^{-1} in KBr CN	COO	C=O	C=C	NMR spectrum,[d] β-H, δ
7a	Br	100	syrup[a]						1740	1720	1680	5.01
7b	Br	100	syrup[a]						1740	1725	1680	4.80
8a	OCH_3	96	syrup	$C_{11}H_{19}NO_4$	57.58 (57.62)	8.12 (8.35)	6.43 (6.11)		1745	1670		4.44
8b	OCH_3	66	syrup	$C_{12}H_{21}NO_4$	59.55 (59.24)	8.85 (8.70)	6.02 (5.76)		1740	1665		4.12
9a	$OCH_2C_6H_5$	72	58—59[b]	$C_{17}H_{23}NO_4$	66.83 (66.86)	7.63 (7.59)	4.58 (4.58)		1740	1670		4.53
9b	$OCH_2C_6H_5$	60	67—68[b]	$C_{18}H_{25}NO_4$	68.11 (67.69)	7.92 (7.89)	4.30 (4.39)		1740	1670		4.32
10a	CN	94	53—54[c]	$C_{11}H_{16}N_2O_3$	58.73 (58.91)	7.04 (7.19)	12.31 (12.49)	2240	1760	1660		4.98
10b	CN	99	syrup	$C_{12}H_{18}N_2O_3$	60.50 (60.48)	7.72 (7.61)	11.58 (11.76)	2240	1755	1660		4.66

a) Pale yellow syrup, structure of which was confirmed by means of IR and NMR spectra and conversion into following compounds. b) Colorless prisms from petroleum ether. c) Colorless tablets from petroleum ether. d) Measured in $CDCl_3$.

TABLE 2. *t*-BUTYL 3-SUBSTITUTED-2-ACETAMIDO-2-ALKENOATES $\left(\begin{matrix}R\text{-}C{=}C\text{-}COOBu\text{-}t\\ \quad\ |\quad\ \ |\\ \quad X\quad NHCOCH_3\end{matrix}\right)$

Compd No.	X	Yield (%)	Mp °C	Formula	Found (Calcd), % C	H	N	IR spectrum, cm^{-1} in KBr NH	N_3	COO	C=O	C=C	NMR spectrum,[d] NH, δ
5a (*E*+*Z*)	Br	54	138—139[a]	$C_{10}H_{16}NO_3Br$	43.58 (43.18	5.80 5.80	5.06 5.04)	3340		1715	1680	1645	7.06
	Br	36	101.5—102.5[a]	$C_{10}H_{16}NO_3Br$	43.09 (43.18	5.88 5.80	4.93 5.04)	3340		1715	1685	1640	7.94
5b (*E*+*Z*)	Br	45	84—87[b]	$C_{11}H_{18}NO_3Br$	45.44 (45.22	6.31 6.21	4.79 4.79)	3270		1725	1670	1635	7.16
	Br	18	suyrp	$C_{11}H_{18}NO_3Br$			5.13 (4.79)	3270		1730	1680	1630	8.35
12a	N_3	92	104[c]	$C_{10}H_{16}N_4O_3$	50.07 (49.99	6.71 6.71	23.32 23.32)	3150	2110	1720	1640		6.86
12b	N_3	85	94[a]	$C_{11}H_{18}N_4O_3$	51.88 (51.95	7.02 7.14	21.98 22.03)	3150	2100	1720	1640		7.06

a) Colorless needles from di-*n*-butyl ether. b) Colorless fibrous from di-*n*-butyl ether. c) Colorless fibrous from tetrachloromethane. d) Measured in $CDCl_3$.

5 and **12**. From either the presence or absence of the vinyl or NH proton respectively, the structures of the above compounds were confirmed.

The above rearrangement reaction, which seems to be an intramolecular anionic 1,3-shift, and the configurational assignment of the products are now under investigation.

Experimental

All the melting points are uncorrected. The IR spectra were recorded with a Hitachi EPI-S2 Spectrometer. The NMR spectra were measured with a JNM-4H-100 Spectrometer (Japan Electron Optics Laboratory Co., Ltd.), using tetramethyl silane as the internal standard.

Materials. Compounds **1e** and **3a**, **b**, **c**, **d** were prepared by a method previously reported.[4]

Reaction of 3 with Bromine A solution of bromine (0.078 mol) in chloroform (20 ml) was stirred drop by drop, into a solution of *t*-butyl 2-acetamido-2-butenoate (**3a**: 0.078 mol) in chloroform (15 ml) below 0 °C. The reaction solution was then allowed to stand at room temperature for 2 days. The colorless crystals which had thus been separated out were collected and recrystallized from acetone to give colorless tablets, which were identified as 3-bromo-2-acetamido-2-butenoic acid (**6a**); yield, 58.8%; mp 150 °C (decomp). IR (KBr): 3300, 1720, 1645, 1630 cm^{-1}.

Found: C, 32.86; H, 3.60; N, 6.37%. Calcd for $C_6H_8NO_3Br$: C, 32.50; H, 3.60; N, 6.37%.

In a similar manner, the treatment of an equimolar amount of *t*-butyl 2-(*N*-ethoxycarbonylamino)-2-butenoate (**3c**) with bromine in chloroform gave 3-bromo-2-(*N*-ethoxycarbonylamino)-2-butenoic acid (**6c**) as colorless needles; those needles were recrystallized from chloroform; yield, 59.3%; mp 154—156.5 °C (decomp). IR (KBr): 3260, 1700, 1630 cm^{-1}.

Found: C, 33.58; H, 3.98; N, 5.58%. Calcd for $C_7H_{10}NO_4Br$: C, 33.35; H, 3.97; N, 5.56%.

In a similar manner, the treatment of an equimolar amount of *t*-butyl 2-(*N*-phthaloylglycylamino)-2-butenoate (**3d**) with bromine in glacial acetic acid gave a residual reddish syrup after the removal of the excess acetic acid under reduced pressure. When a small quantity of ethanol was added to the residue, crude crystals were gradually separated out. The crystals were collected and recrystallized from glacial acetic acid to give colorless needles, which were identified as 3-bromo-2-(*N*-phthaloylglycylamino)-2-butenoic acid (**6d**); yield, 37.8 %; mp 188 °C (decomp). IR (KBr): 3260, 1735, 1680, 1630 cm^{-1}.

Found: C, 45.82; H, 3.10; N, 7.68%. Calcd for $C_{14}H_{11}N_2O_5Br$: C, 45.80; H, 3.00; N, 7.63%.

Reaction of 1e with Bromoacetyl Bromide. To a solution of ethyl 2-hydroxyaminobutanoate (**1e**: 0.027 mol) in dry benzene (20 ml), we stirred bromoacetyl bromide (0.033 mol), drop by drop at room temperature. Then the reaction solution was heated at 70—80 °C for 30 min. After cooling to room temperature, the insoluble substance which had been separated out was filtered off, and the filtrate was evaporated under reduced pressure. The residual reddish oil was purified on a silica gel column using benzene–methanol (40: 1 v/v). After the removal of the solvent, the crystals which had been separated out were collected and recrystallized from di-*n*-butyl ether to give colorless needles, which were identified as ethyl 3-bromo-2-bromoacetamido-2-butenoate (**5e**); yield, 6.7%; mp 118—119 °C. IR (KBr): 3250, 1730, 1660, 1535 cm^{-1}.

Found: C, 29.60; H, 3.40; N, 4.26%. Calcd for $C_8H_{11}NO_3Br_2$: C, 29.20; H, 3.35; N, 4.26%.

Reaction of 3 with NBS. Into a solution of **3a** (0.020 mol) in tetrachloromethane (20 ml), we stirred NBS (0.021 mol), portion by portion at room temperature. After stirring for 30 min, the succinimide which had thus been separated out was filtered off, and the filtrate was evaporated under reduced pressure to give pale yellow syrup in a quantitative yield. This syrup was identified as *t*-butyl 2-(*N*-bromoacetamido)-2-2-butenoate (**7a**).

In a similar manner, *t*-butyl 2-(*N*-bromoacetamido)-2-pentenoate (**7b**) was also obtained in a quantitative yield starting from the reaction of an equimolar amount of *t*-butyl 2-acetamido-2-pentenoate (**3b**) and NBS.

Rearrangement Reaction of 7. When **7a** (0.07 mol) was allowed to stand at room temperature for 2 days, the syrup gradually crystallized to give colorless crystals, which were composed of *E*- and *Z*-isomers. The geometric isomers were separated purely by chromatography on a silica gel column using benzene–ethyl acetate (5: 1 v/v). After the removal of the solvent under reduced pressure, *t*-butyl 3-bromo-2-acetamido-2-butenoate (**5a***E* and **5a***Z*) was obtained.

In a similar manner, *t*-butyl 3-bromo-2-acetamido-2-pentenoate (**5bE** and **5bZ**) was also obtained in a pure state by starting from **7b** through the migration of bromine atom (Table 2).

Reaction of 7 with Sodium Methoxide. After treating **7a**

(0.0151 mol) with sodium methoxide (made from sodium (0.018 mol) and methanol (30 ml)), with stirring, at room temperature for 2 hr, the reaction solution was concentrated under reduced pressure. The residual yellow syrup was dissolved in benzene (30 ml), and then the solution was washed with water twice. The benzene layer was dried over anhydrous magnesium sulfate and then evaporated under reduced pressure. The residual pale yellow syrup was purified on a silica gel column using benzene–ethyl acetate (50: 1 v/v). The effluent was then condensed under reduced pressure to give a colorless syrup, which was identified as *t*-butyl 2-(*N*-acetyl-*O*-methyl-hydroxyamino)-2-butenoate (**8a**).

In a similar manner, *t*-butyl 2-(*N*-acetyl-*O*-methyl-hydroxyamino)-2-pentenoate (**8b**) was also obtained starting from the reaction of **7b** and sodium methoxide.

Reaction of 7 with Sodium Benzyloxide. After treating **7a** (0.0151 mol) with sodium benzyloxide (made from sodium (0.018 mol) and benzyl alcohol (30 ml)), with stirring, at room temperature for 2 hr, the reaction solution was concentrated under reduced pressure. The residual yellow syrup was dissolved with benzene (30 ml), and then the solution was washed with water three times. The benzene layer was dried over anhydrous magnesium sulfate and then evaporated under reduced pressure to give a pale yellow syrup, which was subsequently purified on a silica gel column using benzene–ethyl acetate (50: 1 v/v). The effluent was evaporated under reduced pressure to give a colorless syrup, which was identified as *t*-butyl 2-(*N*-acetyl-*O*-benzyl-hydroxyamino)-2-butenoate (**9a**).

In a similar manner, *t*-butyl 2-(*N*-acetyl-*O*-benzyl-hydroxyamino)-2-pentenoate (**9b**) was also obtained starting from the reaction of **7b** and sodium benzyloxide.

Reaction of 7 with Sodium Cyanide. Into a solution of **7a** (0.010 mol) in dimethyl formamide (25 ml), sodium cyanide (0.013 mol) was stirred portion by portion at room temperature. After stirring for 2 hr, the reaction solution was poured into ice water (30 ml) and then extracted with benzene three times. The benzene extracts were washed with water twice, dried over anhydrous magnesium sulfate, and finally evaporated under reduced pressure. The residual yellow syrup thus obtained gradually crystallized to give colorless crystals, which were identified as *t*-butyl 2-(*N*-cyanoacetamido)-2-butenoate (**10a**).

In a similar manner, *t*-butyl 2-(*N*-cyanoacetamido)-2-pentenoate (**10b**) was also obtained as a syrup; the syrup was subsequently purified on a silica gel column using benzene–ethyl acetate (50: 1 v/v), starting from the reaction of **7b** with sodium cyanide.

Reaction of 7 with Sodium Azide. Into a solution of **7a** (0.010 mol) in dimethyl formamide (25 ml), sodium azide (0.013 mol) was stirred portion by portion at room temperature. After stirring for 2 hr, the reaction solution was poured into ice water (30 ml) and then extracted with benzene three times. The benzene extracts were washed with water twice, dried over anhydrous magnesium sulfate, and finally evaporated to give a yellow syrup. Purification on a silica gel column using benzene–ethyl acetate (10: 1 v/v) and the evaporation of the effluent solvent under reduced pressure gave a pale yellow syrup, which gradually crystallized and which was identified as *t*-butyl 3-azido-2-acetamido-2-butenoate (**12a**).

In a similar manner, *t*-butyl 3-azido-2-acetamido-2-pentenoate (**12b**) was also obtained as a syrup, starting from the reaction of **7b** with sodium azide.

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References

1) Part VII: C. Shin, Y. Yonezawa, Y. Sekine, and J. Yoshimura, This Bulletin, **48**, 1317 (1975).
2) C. Shin, M. Fujii, and J. Yoshimura, *Tetrahedron Lett.*, **1971**, 2499; C. Shin, K. Sato, A. Ohtsuka, K. Mikami, and J. Yoshimura, This Bulletin, **46**, 3876 (1973).
3) C. Shin, M. Masaki, and M. Ohta, *ibid.*, **42**, 191 (1968).
4) C. Shin, K. Nanjo, E. Ando, and J. Yoshimura, *ibid.*, **47**, 3109 (1974).
5) C. Shin, K. Nanjo, and J. Yoshimura, *Chem. Lett.*, **1973**, 1039.
6) W. K. Anslow and H. Raistrick, *Biochem. J.*, **25**, 39 (1931).
7) C. Shin, K. Nanjo, and J. Yoshimura, *Tetrahedron Lett.*, **1974**, 521.
8) S. J. Huang and M. T. Lessard, *J. Org. Chem.*, **35**, 1204 (1970).
9) H. Ahlbrecht and T. Reiner, *Tetrahedron Lett.*, **1971**, 4901.
10) L. Duhamel, P. Duhamel, and J.-M. Poirier, *ibid.*, **1973**, 4237.