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(*Z*)-Selective β-Bromination of *N*-Formyl-α,β-dehydroamino Acid Esters

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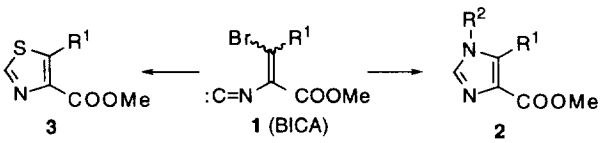
Abstract: Stereoselective β-bromination of *N*-formyl-α,β-dehydroamino acid esters **5** was investigated. A reaction of **5** with NBS afforded α-bromo-*N*-formylimines **10** which successively isomerized to give β-bromo-*N*-formyl-α,β-dehydroamino acid esters **4**. The migration of the double bond of the intermediates **10** with bulky substituents at the β-position resulted in highly stereoselective formation of (*Z*)-**4**, while that of the substrates with less bulky substituents proceeded non-stereoselectively. A mechanism of the stereoselective bromination was proposed on the basis of semiempirical calculations using AM1.

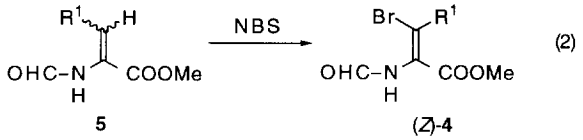
Introduction

As part of our synthetic studies[1-3] on chemically and biologically interesting amino acids and heterocyclic compounds using methyl 3-substituted 3-bromo-2-isocyanoacrylates **1** (BICA), we recently reported novel syntheses of methyl 1,5-disubstituted imidazole-4-carboxylates **2**[2] and methyl 5-substituted thiazole-4-carboxylates **3**[3] (eq 1). These facile and regioselective synthetic methods provided not only **2** and **3**, useful intermediates for pharmaceuticals and agricultural products, but a variety of 1,5-disubstituted imidazoles for which only two direct synthetic methods have been reported.[4]



(1)

During the course of these synthetic efforts, highly stereoselective formation of (*Z*)-β-bromo-*N*-formyl-α,β-dehydroamino acid methyl esters **4** was observed in the bromination of (*E*)- and/or (*Z*)-*N*-formyl-α,β-dehydroamino acid methyl esters **5** with NBS.[1-3] (eq 2).



5 (*Z*)-**4** (2)

Though several other research groups have already reported[5-15] that β-halogenation of *N*-acyl-α,β-dehydroamino acid esters proceeds with *Z*-selectivity, there has been no description so far of the correlation of either substrates or reaction conditions with the stereoselectivity. Das and co-workers[5] recently reported a 10:90 *E*/*Z* ratio in the bromination of *N*-acyldehydroalanine derivatives with Br_2 and Et_3N. Danion and co-workers[6] described *Z*-selective bromination of ethyl 2-(methoxycarbonylamino)cinnamate using NBS and Et_3N. Chlorination of *N*-acetyldehydroalanine derivatives was reported by Kolar and Olsen[7] to proceed in a 20:80 *E*/*Z* ratio with Cl_2 and DABCO, and in a 10:90 *E*/*Z* ratio with Cl_2 and DBU or *t*-BuOK. Stammer and co-workers,[8] Olsen and co-workers,[9] and Shin and co-workers[10] also reported *Z*-selective halogenation under similar conditions. On the other hand, two groups[16,17] have reported *E*-selective bromination using the substrates with a particular substituent attached to the double bond. In order to understand the stereochemistry of the bromination of common *N*-acyl-α,β-dehydroamino acid esters, we wish herein to demonstrate the bromination of *N*-formyl-α,β-dehydroamino acid esters **5** possessing various β-substituents and to propose a rationale for the stereoselective bromination of **5**.

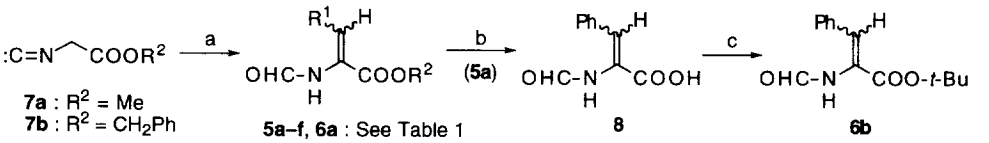
Results and Discussion

The key substrates in this study, *N*-formyl-α,β-dehydroamino acid esters **5**, **6** were synthesized, as shown in Scheme 1. Methyl and benzyl 3-substituted 2-(formylamino)acrylates **5a–f**, **6a** were prepared by a condensation reaction of methyl and benzyl isocyanoacetates (**7a,b**) with an appropriate aldehyde in the presence of sodium hydride.[18] *Tert*-butyl 2-(formylamino)-3-phenylacrylate (**6b**) was synthesized by an esterification of 2-(formylamino)-3-phenylacrylic acid (**8**), which was prepared by hydrolysis of the corresponding methyl ester **5a**, with *tert*-butyl bromide in the presence of benzyltriethyl ammonium chloride and potassium carbonate.[19] Each geometric isomer of **5a–f**, **6a,b** thus obtained was isolated by column chromatography on silica gel.

First, bromination was performed by the treatment of (*E*)- or (*Z*)-**5**, **6** with NBS (1.1 equiv) in $CHCl_3$ or CCl_4. Subsequent addition of an amine base (DABCO or Et_3N, 1.0 equiv, 10 min) to the reaction mixture afforded a mixture of (*E*)- and (*Z*)-β-bromo-*N*-formyl-α,β-dehydroamino acid esters **4**, **9**. Isomer ratios were determined by the integration of ester proton signals of the products in ^1H NMR spectra

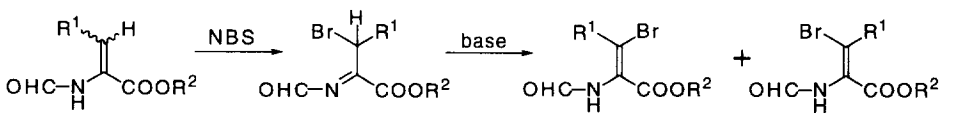
and are listed in Table 1. The substrates with bulky substituents, in particular isopropyl or 1-ethylpropyl, at the β-position showed a propensity to undergo highly *Z*-selective bromination under the above reaction conditions (entries 8, 12). In contrast, non-selective bromination was observed in the substrates with less bulky substituents such as methyl[20] and ethyl groups at the β-position (entries 6, 7). In the case of the bromination of (*E*)-**5**, similar results to that observed for (*Z*)-**5** were obtained (entries 2, 10). When the size of the ester groups increased, a significantly higher Z-selectivity was observed (entries 13, 14). The use of DABCO instead of Et_3N as a base improved Z-selectivity (entries 1 vs 3, 9 vs 11). Additionally, lower reaction temperature induced a slightly higher *Z*-selectivity in the bromination of **5a** (entries 4, 5)

Scheme 1



a) R^1-CHO, NaH, THF b) NaOH, MeOH-H_2O c) *t*-BuBr, $Et_3(PhCH_2)N^+Cl^-$, K_2CO_3 , *N,N*-dimethylacetamide

Table 1. Bromination of 5 and 6 with NBS.



5, 6 **10** **(*E*)-4, 9** **(*Z*)-4, 9**

entry	compound no.	R^1	R^2	base	temp (°C)	*E*/*Z* ratio of **4, 9** [1]	isolated yield (%) [2]	product
1	(*Z*)-**5a**	Ph	Me	Et_3N	24	33:67	66	**4a**
2	(*E*)-**5a**	Ph	Me	Et_3N	24	32:68	70	**4a**
3	(*Z*)-**5a**	Ph	Me	DABCO	24	20:80	72	**4a**
4	(*Z*)-**5a**	Ph	Me	DABCO	-20	14:86	65	**4a**
5	(*Z*)-**5a**	Ph	Me	DABCO	-60	7:93	51	**4a**
6	(*Z*)-**5b**	Me	Me	DABCO	24	46:54	44	**4b**
7	(*Z*)-**5c**	Et	Me	DABCO	24	50:50	59	**4c**
8	(*Z*)-**5d**	*i*-Pr	Me	DABCO	24	3:97	65	**4d**
9	(*Z*)-**5e**	*i*-Bu	Me	Et_3N	24	35:65	74	**4e**
10	(*E*)-**5e**	*i*-Bu	Me	Et_3N	24	33:67	71	**4e**
11	(*Z*)-**5e**	*i*-Bu	Me	DABCO	24	23:77	81	**4e**
12	(*Z*)-**5f**	$CHEt_2$	Me	DABCO	24	3:97	76	**4f**
13	(*Z*)-**6a**	Ph	CH_2Ph	DABCO	24	16:84	77	**9a**
14	(*Z*)-**6b**	Ph	*t*-Bu	DABCO	24	4:96	76	**9b**

1) The ratios were determined by ^1H NMR. 2) Isolated yields were calculated as a mixture of (*E*)- and (*Z*)-isomers.

Next, in order to characterize the intermediates in the bromination reaction, the reaction process was monitored by ^{1}H NMR using (*Z*)-methyl 2-formylamino-3-phenylacrylate (**5a**) as a typical example. When (*Z*)-**5a** was treated with NBS in $CDCl_3$ at 24 ℃ for 1 h in the absence of an amine base, the ^{1}H NMR spectrum indicated that the methylene proton signal of NBS at 2.95 ppm completely faded out and the methylene proton signal of succinimide appeared at 2.75 ppm. The NH proton signal of **5a** simultaneously disappeared and the proton signal which was assigned to the C^3-H of methyl 3-bromo-2-formylimino-3-phenylpropanoate (**10a**) appeared at 6.09 ppm. When an equimolar amount of an amine base (Et_3N or DABCO) was added to the reaction mixture at 24 ℃, the proton signal of the C^3-H of **10a** at 6.09 ppm and the ester proton signal at 3.89 ppm faded out in 10 minutes and the new signals appeared at 3.92 and 3.67 ppm which were assigned to be the ester proton signals of (*E*)- and (*Z*)-3-bromo-2-formylamino-3-phenylacrylate (**4a**) subsequently. The isomer ratios were determined to be 33:67 *E/Z* (with Et_3N) and 20:80 *E/Z* (with DABCO) by the integration of product resonances in the ^{1}H NMR. In the case of the reaction of (*E*)-**5a** with NBS, a similar result to that of (*Z*)-**5a** was observed. The bromination of **5**, **6** with a variety of substituents at the β-position was carried out under the same conditions to afford α-bromoimines **10**[21] of which the characteristic ^{1}H NMR spectral data are summarized in Table 2.

Table 2. Typical ^{1}H NMR Data of α-Bromoimine 10

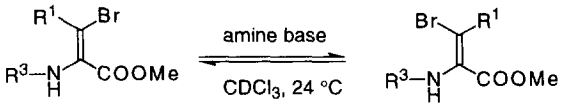
compd no.	R^1	R^2	H^1 NMR (δ in $CDCl_3$)		
			CHBr	CHO	ester
10a	Ph	Me	6.09 (s)	9.36	3.89
10b	Me	Me	5.10 (q)	9.33	3.92
10c	Et	Me	4.88 (m)	9.35	3.93
10d	*i*-Pr	Me	4.71 (d)	9.34	3.92
10e	*i*-Bu	Me	5.01 (dd)	9.33	3.93
10f	$CHEt_2$	Me	4.77 (d)	9.34	3.92
10g	Ph	CH_2Ph	6.08 (s)	9.37	-----[1)]
10h	Ph	*t*-Bu	6.04 (s)	9.37	1.45

1) 5.25 (s, CH_2Ph)

We examined the isomerization of the double bond of (*E*)- and (*Z*)-β-bromo-*N*-formyl-α,β-dehydroamino acid methyl esters **4** in the presence of an amine base. As isolated (*E*)-**4** or (*Z*)-**4** was treated again with an equimolar amount of DABCO or Et_3N in $CDCl_3$ at 24 ℃, isomer ratios were periodically determined by the integration of product resonances in the ^{1}H NMR. The results were presented in Table 3. In the case of *N*-formylated vinyl bromide, very slow isomerization of (*E*)-**4a** for instance to thermodynamically more stable (*Z*)-**4a** was detected in the presence of DABCO (entry 2)[22] while no isomerization was observed in the presence of Et_3N (entry 1). The isomerization ratios of (*E*)-**4a** to (*Z*)-**4a** were 4% after 24 hours and 28% after 7 days.[23] Whereas the vinyl bromides (**4b,e**) substituted with an alkyl group at the β-position, no isomerization was detected even after 24 hours under either conditions (DABCO or Et_3N) (entries 5–10). These results indicated that the interconversion between (*E*)- and (*Z*)-**4** under the reaction conditions which were used for the bromination of α,β-

dehydroamino acid esters as described in the previous section, was not relevant to the results shown in Table 1.

Table 3. Conversion of (*E*)- and (*Z*)-4, 11 in the presence of an amine base



(*E*)-**4**, **11** (*Z*)-**4**, **11**

entry	vinyl bromide	R^1	R^3	amine base	time	*E*/*Z* ratio of vinyl bromide
1	(*E*)-**4a**	Ph	CHO	Et_3N	24 h	100 : 0
2				DABCO	24 h	96 : 4
					7 d	72 : 28
3	(*Z*)-**4a**	Ph	CHO	Et_3N	24 h	0 : 100
4				DABCO	24 h	0 : 100
5	(*E*)-**4b**	Me	CHO	DABCO	24 h	100 : 0
6	(*Z*)-**4b**	Me	CHO	DABCO	24 h	0 : 100
7	(*E*)-**4e**	*i*-Bu	CHO	Et_3N	24 h	100 : 0
8				DABCO	24 h	100 : 0
9	(*Z*)-**4e**	*i*-Bu	CHO	Et_3N	24 h	0 : 100
10				DABCO	24 h	0 : 100
11	(*E*)-**11**	*i*-Bu	$COOCH_3$	DABCO	24 h	71 : 29
					4 d	28 : 72
12	(*Z*)-**11**	*i*-Bu	$COOCH_3$	DABCO	24 h	0 : 100

Coleman and Carpenter reported the rapid isomerization of (*E*)-methyl 4-(benzyloxy)-3-bromo-2-[*N*-(methoxycarbonyl)amino]-2-pentenoate to corresponding *Z*-isomer by treatment with DABCO. In this regard, their results were much different from ours. In order to investigate the effect of *N*-substituent on the isomerization of the double bond, we treated *N*-methoxycarbonyl vinyl bromides (**11**) with the bases. The substrates were prepared essentially by means of the procedure previously described[24,25]. In the case of *N*-methoxycarbonyl substrate **11**, much faster isomerization was observed in comparison with the case of *N*-formylated substrates (entries 11, 12). These results indicated that the isomerization was influenced by the chemical characteristics of *N*-substituents, and we believe that *N*-methoxycarbonyl group and benzyloxymethyl group at the β-position of their substrate synergetically contributed to the rapid isomerization of the double bond.

The geometric structures of the series of **4**, **9**, **11** were determined primarily based on the correlation of ^1H NMR spectral data.[26] In the case of **4b–f**, **11** which have alkyl substituents at the β-position, the chemical shift of the allylic C4-H protons of the *E*-isomers was observed at a higher field relative to that of the corresponding *Z*-isomers ($\Delta\delta$ = 0.15–0.66 ppm).[27] The configuration of (*E*)-**4b–f**, **11** was confirmed by the observation of a reciprocal positive NOE of the NH and C4-H resonances in the NOE difference spectrum, and by the absence of equivalent enhancements for their isomers. In the case of **4a** which have aromatic rings at the β-position, the chemical shift of the methyl ester proton of the *Z*-isomer appeared at a higher field (δ = 3.51–3.53 ppm in DMSO-d_6) than that of the corresponding *E*-isomer (δ = 3.88–3.91 ppm in DMSO-d_6), because of the shielding anisotropic effect of the adjacent

benzene ring.[1,2] Likewise, in the series of aromatic bromides **9a,b** the chemical shifts of benzyl and *t*-butyl ester protons of the *Z*-isomer appeared at a higher field than that of the corresponding *E*-isomer.

To account for the stereoselectivity of the bromination of *N*-formyl-α,β-dehydroamino acid esters (**5**, **6**) described above, we propose the following mechanistic rationale. As Coleman and Carpenter reported[17] the base-catalyzed isomerization of an α-bromoimine to the corresponding vinyl bromide occurs via a transition state wherein the sp^3 orbital of the C^3-H bond is aligned with the π-orbital of the double bond of the imine. Although geometric isomerism is possible for imines, there is no evidence for the determination of such isomers.[28] As a typical example, the four possible conformers of **10b,d** in the ground-state from **A** to **D** which directly lead to such transition states are depicted in Figure 1.

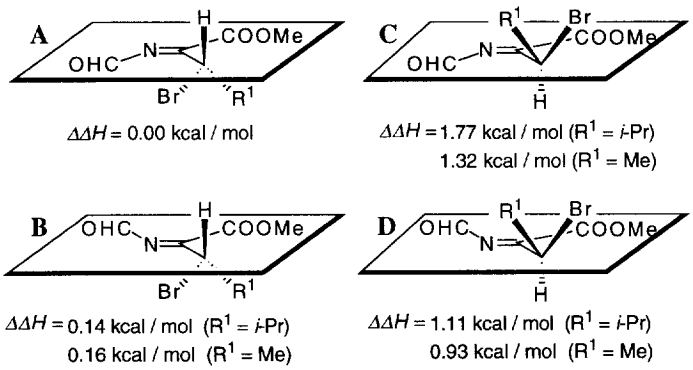


Figure 1. AM1 calculation of conformers 10b (R^1 = Me) and 10d (R^1 = *i*-Pr)

Hydrogen transfer of rotamers **A** and **B** gives the *Z*-vinyl bromide, whereas rotamers **C** and **D** give the *E*-vinyl bromide. Semiempirical calculations were performed on **A**, **B**, **C**, and **D** to estimate the potential energy of these four ground-state conformers by restricting the H-C^3-C^2-N dihedral angle to 90° and the C(O)-N-C^1 angle to ±120° using AM1.[29] The energy differences ($\Delta\Delta H$) between **A**, a standard, and other conformers are presented in Figure 1. In the case of bulky substituent (**10d**, R^1 = *i*-Pr) at the α-position, the calculation indicated a value of $\Delta\Delta H$ = 1.77 kcal/mol favoring **A** over **C** for anti-imine and a value of $\Delta\Delta H$ = 0.97 kcal/mol favoring **B** over **D** for syn-imine. However, in the case of less bulky substituent (**10b**, R^1 = Me), **A** and **B** are favored with a smaller value of $\Delta\Delta H$ = 1.32 and 0.77 kcal/mol, over **C** and **D** respectively. These results are well in accord with the *Z*-selectivity which was observed in the bromination of **5**.[33]

It has been elucidated that base-catalyzed migration of the double bond occurs partially intramolecularly in some cases.[30,31] The intramolecularity has been ascribed to a conducted tour mechanism[32] in which the base leads the proton from one carbanionic site to the other. The *Z*-selectivity of DABCO-promoted isomerization was higher than that of Et_3N-promoted isomerization would due to their ratios of intramoleculer hydrogen transfer process to intermolecular process based on their

basicity.[34,35] This analysis provides a reasonable explanation for the observed Z-selectivity in the base-promoted isomerization of **10**, and increase of Z-selectivity accompanied with increased bulkiness of the substituent at the β-position, and also the influence of the base.

Conclusion

Bromination of *N*-formyl-α,β-dehydroamino acid esters (**5**) with NBS immediately afforded α-bromoimines **10** which were stereoselectively isomerized to the corresponding (*Z*)-β-bromo-*N*-formyl-α,β-dehydroamino acid esters (**4**). The *Z*-selectivity of the isomerization improved according to the increase of a bulkiness of the β-substitutent and ester group of **5** and a base employed. Semiempirical calculations of four ground-state conformers of **10** using AM1 supported this rationalization for the geometrical selective bromination of **5**.

Experimental Section

General. Melting points were determined on a Büchi 535 capillary melting point apparatus and are uncorrected. Elemental analyses were performed on a Perkin-Elmer 2400II. IR spectra were recorded on a Perkin-Elmer 1640 spectrophotometer. ^{1}H NMR spectra were obtained on a Bruker AC-200 (200 MHz) spectrometer with TMS as an internal standard. Mass spectra were recorded on a Hitachi M-2000A. Column chromatography was performed on silica gel (E. Merck, No. 7734 or 9385 kieselgel 60) with the indicated solvent system. Radial chromatography was performed on a Chromatotron (Harrison Research Model 7924T) using 1-, 2-, and 4-mm silica gel coated (E. Merck kieselgel 60 PF_{254}) plates. All reactions with air- and moisture-sensitive compounds were conducted in oven-dried glassware under an atmosphere of dry nitrogen.

Preparation of *N*-Formyl-α,β-dehydroamino Acid Esters 5 and 6. Methyl and benzyl 3-substituted 2-(formylamino)acrylates (**5a–f**, **6a**) were synthesized essentially by means of the procedure previously described.[1,2] Physical properties of the new compounds are as follows.

(Z)-Methyl 2-(Formylamino)-2-pentenoate [(Z)-5c]: syrup; ^{1}H NMR (δ in $CDCl_3$) 1.05–1.15 (m, 3H), 2.13–2.39 (m, 2H), 3.79 (s each, total 3H) and 3.82 (miner isomer[36]), 6.74 (q each, total 1H, J = 7.6 Hz) and 6.63 (miner isomer), 7.09 (br, total 1H), 8.25 (s, total 1H) and 8.18 (miner isomer, d, J = 11.3 Hz); IR (film) 3280, 2970, 1725, 1680, 1500, 1440, 1300 cm^{-1}; SIMS *m/z* 158 (M+H, base), 130, 125.

(*E*)-Methyl 2-(Formylamino)-2-pentenoate [(*E*)-5c]: mp 30–34 ℃ (AcOEt/hexane); ^{1}H NMR (δ in $CDCl_3$) 1.09 (t, 3H, J = 7.6 Hz), 2.63 (q, 2H, J = 7.6 Hz), 3.86 (s each, total 3H) and 3.83 (miner isomer,[36]), 7.30 (t each, total 1H, J = 7.6 Hz) and 6.04 (miner isomer), 7.45 (br, 1H), 8.32 (s, total 1H) and 8.25 (miner isomer, d, J = 11.0 Hz); IR (KBr) 3300, 2970, 1710, 1520, 1440, 1365 cm^{-1}; SIMS *m/z* 158 (M+H), 125, 68 (base); Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.33; H, 7.27; N, 8.88.

(*Z*)-Benzyl 2-(Formylamino)-3-phenylacrylate [(*Z*)-6a]: mp 104–106 ℃ (AcOEt/hexane); ^{1}H NMR (δ in $CDCl_3$) 5.31 (s, 2H), 7.05 (br, 1H), 7.37–7.50 (m, 11H), 8.23 (br-m, 1H); IR (KBr) 3240, 1720, 1665, 1635, 1520 cm^{-1}; SIMS *m/z* 282 (M+H), 264, 253, 91 (base); Anal. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.49; H, 5.42; N, 5.16.

2-(Formylamino)-3-phenylacrylic Acid (8). A mixture of (*Z*)- and (*E*)-**5a** (2.19 g, 10 mmol) and NaOH (440 mg, 12 mmol) in MeOH (15 ml) was stirred at room temperature for 3 h. Water was then added, and the aqueous solution was washed with ether, and acidified with $KHSO_4$. The solution was extracted with ethyl acetate. The extract was washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo affording a solid which was crystallized from MeOH–ether to afford a mixture of (*Z*)- and (*E*)-**8** (1.96 g) in 93 % yield as a colorless crystalline solid: mp 191–193 ℃ (MeOH/ether); ^{1}H NMR (δ in DMSO-d_6) 7.30 (br-s, 1H), 7.38–7.41 (m, 3H), 7.60–7.64 (m, 2H), 8.17 (br-s, total 1H) and 8.01 (miner isomer,[36] d, J = 11.0 Hz), 9.69 (br-s, total 1H) and 9.29 (miner isomer, d, J = 11.0 Hz), 12.9 (br, 1H); IR (KBr) 3240, 1670, 1655, 1430 cm^{-1}; SIMS *m/z* 192 (M+H, base), 174, 163. Anal. Calcd for $C_{10}H_9NO_3$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.56; H, 4.79; N, 7.54.

***t*-Butyl 2-(Formylamino)-3-phenylacrylate (6b).** According to the procedures reported by Chevallet and co-workers,[19] a mixture of carboxylic acid (*Z*)- and (*E*)-**8** (1.91 g, 10 mmol) was dissolved in dimethylacetamide (75 ml) in the presence of benzyltriethylammonium chloride (2.3 g, 10 mmol). Anhydrous potassium carbonate (35.9 g, 260 mmol) and tert-butyl bromide (65.7 g, 480 mmol) were added to the mixture and stirred at 55 ℃ for 24 h. After cooling, cold water (1000 ml) was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous $MgSO_4$ and concentrated in vacuo. The resultant oil was chromatographed on silica gel with AcOEt–hexane to give (*Z*)-**6b** and (*E*)-**6b**. (*Z*)-**6b**: syrup; ^{1}H NMR (δ in DMSO-d_6) 1.46 (s, 9H), 7.14 (s, 1H), 7.21–7.43 (m, 2H), 7.59–7.63 (m, 3H), 8.17 (s, 1H), 9.76 (br, 1H); IR (film) 3200, 1720, 1665, 1520, 1350 cm^{-1}; SIMS *m/z* 248 (M+H), 192 (base), 174, 163. (*E*)-**6b**: mp 87–88 ℃ (AcOEt/hexane); ^{1}H NMR (δ in DMSO-d_6) 1.30 (s, 9H), 6.92 (s, 1H), 7.21–7.38 (m, 5H), 8.13 (s, 1H), 10.00 (br, 1H); IR (KBr) 3225, 1720, 1665, 1525, 1400, 1355 cm^{-1}; SIMS *m/z* 248 (M+H), 192 (base), 174, 163; Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.14; H, 6.64; N, 5.71.

General Procedure for the Preparation of β-Bromo-α,β-dehydroamino Acid Esters 4, 9. The title compounds (**4**, **9**) were synthesized essentially by means of the procedures previously described.[1,2] To a solution of **5**, **6** (20 mmol) in CCl_4 or $CHCl_3$ (50 ml) was added NBS (3.93 g, 22 mmol) under ice cooling. After stirring for 3 h, triethylamine (2.0 g, 20 mmol) was added dropwise to

the reaction mixture. After stirring for 10 min, the mixture was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The residue was subjected to column chromatography on silica gel with $CHCl_3$–AcOEt to give (*Z*)-**4**, **9** and/or (*E*)-**4**, **9**. Physical properties of the new compounds are as follows:

(*Z*)-Methyl 3-Bromo-2-(formylamino)-2-pentenoate [(*Z*)-4c]: syrup; ^1H NMR (δ in $CDCl_3$) 1.20 (t, 3H, J = 7.3 Hz), 2.77 (q, 2H, J = 7.3 Hz), 3.84 (s, 3H), 7.05 (br, 1H), 8.19 (s, 1H); IR (film) 3285, 2975, 1730, 1670, 1470, 1430, 1390, 1310 cm^{-1}; SIMS *m/z* 236/238 (M+H, base), 204/206, 176/178.

(*E*)-Methyl 3-Bromo-2-(formylamino)-2-pentenoate [(*E*)-4c]: syrup; ^1H NMR (δ in $CDCl_3$) 1.20 (m, 3H), 2.55–2.78 (m, 2H), 3.83 (s each, total 3H) and 3.84 (miner isomer[36]), 6.74 (br, 1H), 8.20 (s, total 1H) and 8.04 (miner isomer, d, J = 11.2 Hz); IR (film) 3240, 2980, 1735, 1655, 1510, 1390, 1300 cm^{-1}; SIMS *m/z* 236/238 (M+H, base), 208/210, 204/206.

(*Z*)-Benzyl 3-Bromo-2-(formylamino)-3-phenylacrylate [(*Z*)-9a]: mp 120–122 ℃ (AcOEt/hexane); ^1H NMR (δ in $CDCl_3$) 4.99 (s, 2H), 6.94–6.98 (m, 2H), 7.23–7.33 (m, 9H), 8.31 (s, total 1H) and 8.43 (miner isomer,[36] d, J = 11.2 Hz); IR (KBr) 3220, 1725, 1660, 1305 cm^{-1}; EIMS *m/z* 359/361 (M^+), 331/333, 280, 91 (base); Anal. Calcd for $C_{17}H_{14}NO_3Br$: C, 56.69; H, 3.92; N, 3.89. Found: C, 56.63; H, 3.93; N, 3.66.

(*E*)-Benzyl 3-Bromo-2-(formylamino)-3-phenylacrylate [(*E*)-9a]: mp 161–163 ℃ (AcOEt/hexane); ^1H NMR (δ in $CDCl_3$) 5.35 (s, 2H), 6.87 (br, 1H), 7.34–7.50 (m, 10H), 7.97 (s, 1H); IR (KBr) 3185, 1740, 1690, 1665, 1520, 1310 cm^{-1}; EIMS *m/z* 359/361 (M^+), 331/333, 280, 91 (base); Anal. Calcd for $C_{17}H_{14}NO_3Br$: C, 56.69; H, 3.92; N, 3.89. Found: C, 56.70; H, 3.95; N, 3.66.

(*Z*)-*t*-Butyl 3-Bromo-2-(formylamino)-3-phenylacrylate [(*Z*)-9b]: mp 60–62 ℃ (AcOEt/hexane); ^1H NMR (δ in $CDCl_3$) 1.19 (s, 9H), 7.30 (br, 1H), 7.36 (s, 5H), 8.30 (s, total 1H) and 8.48 (miner isomer,[36] d, J = 11.7 Hz); IR (KBr) 3295, 2980, 1720, 1475, 1390, 1370, 1320 cm^{-1}; SIMS *m/z* 326/328 (M+H), 270/272, 252/254, 57 (base); Anal. Calcd for $C_{14}H_{16}NO_3Br$: C, 51.54; H, 4.95; N, 4.29. Found: C, 51.36; H, 5.01; N, 4.20.

(*E*)-*t*-Butyl 3-Bromo-2-(formylamino)-3-phenylacrylate [(*E*)-9b]: mp 108–110 ℃ (AcOEt/hexane); ^1H NMR (δ in $CDCl_3$) 1.81 (s, 9H), 6.80 (br, 1H), 7.43 (s, 5H), 7.95 (s, total 1H) and 8.15 (miner isomer,[36] d, J = 11.7 Hz); IR (KBr) 3200, 2980, 1730, 1675, 1520, 1390, 1335, 1125 cm^{-1}; SIMS *m/z* 326/328 (M+H), 270/272, 252/254, 57 (base); Anal. Calcd for $C_{14}H_{16}NO_3Br$: C, 51.54; H, 4.95; N, 4.29. Found: C, 51.48; H, 4.99; N, 4.21.

General Procedure for the Preparation of α-Bromoimines 10. To a solution of **5**, **6** (2 mmol) in CCl_4 (5 ml) was added NBS (393 mg, 2.2 mmol) under room temperature. The reaction mixture was stirred for 3 h and washed with saturated aqueous $NaHCO_3$ and brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo giving **10** as an oil. The α-bromoimines **10g,h** were not isolated but were identified by NMR studies on the bromination of **6a,b**. NMR spectrum of the compounds are as follows.

Physical properties of the new compounds are as follows.

Methyl 3-Bromo-2-(*N*-formylimino)-3-phenylpropanoate (10a): syrup; ^{1}H NMR (δ in $CDCl_3$) 3.89 (s, 3H), 6.09 (s, 1H), 7.30–7.52 (m, 5H), 9.36 (s, 1H); ^{13}C NMR (δ in $CDCl_3$) 47.8, 54.1, 155.8, 165.1, 172.2; IR (film) 3295, 2230, 1735, 1690, 1475, 1320 cm^{-1}; EIMS *m/z* 283/285 (M^+), 256/258, 203, 116 (base).

Methyl 3-Bromo-2-(*N*-formylimino)butanoate (10b): syrup; ^{1}H NMR (δ in $CDCl_3$) 1.88 (d, 3H, *J* = 6.7 Hz), 3.92 (s, 3H), 5.10 (q, 1H, *J* = 6.7 Hz), 9.33 (s, 1H); ^{13}C NMR (δ in $CDCl_3$) 20.7, 40.6 , 54.0, 156.4, 159.1, 172.8; IR (film) 3295, 1735, 1710, 1670, 1480, 1430 cm^{-1}; EIMS *m/z* 221/223 (M^+), 207/209, 179/181, 54 (base).

Methyl 3-Bromo-2-(*N*-formylimino)pentanoate (10c): syrup; ^{1}H NMR (δ in $CDCl_3$) 0.95 (m, 3H), 1.94–2.26 (m, 2H), 3.93 (s, 3H), 4.88 (m, 1H), 9.35 (s, 1H); ^{13}C NMR (δ in $CDCl_3$) 12.1, 27.3, 49.3, 54.0, 155.7, 160.5, 177.7; IR (film) 3290, 2975, 1740, 1680, 1490, 1455, 1440 cm^{-1}; EIMS *m/z* 235/237 (M^+), 221/223, 194, 124 (base).

Methyl 3-Bromo-2-(*N*-formylimino)-4-methylpentanoate (10d): syrup; ^{1}H NMR (δ in $CDCl_3$) 1.09 and 1.20 (d, 3H each, *J* = 6.6 Hz), 2.41 (m, 1H), 3.92 (s, 3H), 4.71 (d, 1H, *J* = 8.3 Hz), 9.34 (s, 1H); ^{13}C NMR (δ in $CDCl_3$) 22.1, 32.6, 42.5, 52.7, 158.0, 158.1, 172.8; IR (film) 3290, 2970, 1735, 1680, 1485, 1430, 1390, 1305 cm^{-1}; SIMS *m/z* 250/252 (M+H), 222/224, 189, 147, 86 (base).

Methyl 3-Bromo-2-(*N*-formylimino)-5-methylhexanoate (10e): syrup; ^{1}H NMR (δ in $CDCl_3$) 0.97 (dd, 6H, *J* = 6.2 and 7.4 Hz), 1.79–2.14 (m, 3H), 3.93 (s, 3H), 5.01 (dd, 1H, *J* = 5.7 and 8.9 Hz), 9.33 (s, 1H); ^{13}C NMR (δ in $CDCl_3$) 21.5, 22.7, 26.0, 42.3, 46.0, 54.1, 155.8, 159.1, 172.8; IR (film) 2960, 1745, 1700, 1675, 1435 cm^{-1}; EIMS *m/z* 263/265 (M^+), 235/237, 232/234, 192/194, 152 (base).

Methyl 3-Bromo-2-(*N*-formylimino)-4-ethylhexanoate (10f): syrup; ^{1}H NMR (δ in $CDCl_3$) 0.72 and 0.92 (t, 3H each, *J* = 7.4 Hz), 1.35–1.73 (m, 4H), 2.76 (m, 1H), 3.92 (s, 3H), 4.77 (d, 1H, *J* = 8.3 Hz), 9.34 (s, 1H) ; IR (film) 2965, 1745, 1710, 1675, 1435 cm^{-1}; EIMS *m/z* 277/279 (M^+), 249/251, 152 (base).

Benzyl 3-Bromo-2-(*N*-formylimino)-3-phenylpropanoate (10g): ^{1}H NMR (δ in $CDCl_3$) 5.25 (s, 2H), 6.08 (s, 1H), 7.24–7.47 (m, 10H), 9.37 (s, 1H).

***t*-Butyl 3-Bromo-2-(*N*-formylimino)-3-phenylpropanoate (10h)**: ^{1}H NMR (δ in $CDCl_3$) 1.45 (s, 9H), 6.04 (s, 1H), 7.23–7.50 (m, 5H), 9.37 (s, 1H).

General Procedure for the NMR Study on the Bromination of 5 and 6. A solution of (*Z*)- or (*E*)-**5**, **6** (0.1 mmol) in $CDCl_3$ (0.7 ml) was treated with NBS (0.11 mmol) at 24 ℃ under argon atmosphere by inverting the tube 20 times. The reaction was monitored by ^{1}H NMR for 3 h at the same temperature. After analysis by ^{1}H NMR showed an α-bromoimines **10**, then triethylamine or DABCO (0.1 mmol) was added to the mixture and the tube was again inverted 20 times. After 10 min at the indicated temperature, the ratio of *E*/*Z* isomers was calculated with the integration of the ester proton signals.

General Procedure for the NMR Study on the Isomerization of 4 and 11. A solution of pure (*Z*)- or (*E*)-**4**, **11** (0.1 mmol) in $CDCl_3$ (0.7 ml) was treated with triethylamine or DABCO (0.1 mmol) at 24 ℃ under argon atmosphere by inverting the tube 20 times. The reaction was monitored by ^1H NMR until judged to be complete. The results are presented in Table 4.

Preparation of Methyl 3-Bromo-2-(methoxycarbonylamino)-5-methyl-2-hexenoate (11). (*Z*)-Methyl 2-(methoxycarbonylamino)-5-methyl-2-hexenoate (**12**) were synthesized by Horner-Emmons olefination[23,24] of an aldehyde with methyl *N*-methoxycarbonyl-α-dimethoxyphosphinyl-glycinates. (*Z*)-Methyl 2-(Methoxycarbonylamino)-5-methyl-2-hexenoate [(*Z*)-**12**]: syrup; ^1H NMR (δ in $CDCl_3$) 0.94 (d, 6H, J = 6.6 Hz), 1.77 (m, 1H), 2.12 (t, 2H, J = 7.1 Hz), 3.73 (s, 3H), 3.78 (s, 3H), 6.07 (br, 1H), 6.69 (t, 1H, J = 7.3 Hz); IR (film) 3325, 2960, 1725, 1510, 1300 cm^{-1}; SIMS *m/z* 216 (M+H, base), 184, 156.

The bromination of **12** were carried out essentially by means of the procedures previously described.[1,2]

(*Z*)-Methyl 3-Bromo-2-(methoxycarbonylamino)-5-methyl-2-hexenoate [(*Z*)-11]: syrup; ^1H NMR (δ in $CDCl_3$) 0.92 (d, 6H, J = 6.7 Hz), 2.03 (m, 1H), 2.62 (d, 2H, J = 7.1 Hz), 3.74 (s, 3H), 3.83 (s, 3H), 6.50 (br, 1H); IR (film) 2960, 1735, 1490, 1315, 1250, 1230, 1210, 775 cm^{-1}; SIMS *m/z* 294/296 (M+H), 262/264 (base), 230/232.

(*E*)-Methyl 3-Bromo-2-(methoxycarbonylamino)-5-methyl-2-hexenoate [(*E*)-11]: syrup; ^1H NMR (δ in $CDCl_3$) 0.95 (d, 6H, J = 6.6 Hz), 2.12 (m, 1H), 2.47 (d, 2H, J = 7.1 Hz), 3.73 (s, 3H), 3.83 (s, 3H), 6.08 (br, 1H); IR (film) 3315, 2960, 1735, 1505, 1460, 1340, 1245, 775 cm^{-1}; SIMS *m/z* 294/296 (M+H), 284 (base), 262/264.

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33. Though Coleman and Carpenter, on the other hand, reported that the ground state rotamer leading to the *E*-product is more stable than that leading to the *Z*-product, *N*- and β-substituents of their substrate and molecular mechanics calculations were not specified. We believe that this discrepancy is due to the substituents at the *N*- and β-positions which synergetically contributed to the potential energy of their ground-state conformers.
34. It is known that the degree of intramolecularity varies with pk_a of a base employed.[30c]

35. The double bond of the imines (**10a,d,f**) with a bulky substituent at the α-position isomerized predominantly to (*Z*)-**4a**, (*Z*)-**4d**, and (*Z*)-**4f** respectively, with elongation of the reaction time without the addition of an amine base, while no change was observed in the other imines (**10b,c,e**). In this case, the hydrogen transfer reaction should mainly proceed intramolecularly via a six-membered transition state[32] in which the formyl carbonyl group interacted with the hydrogen, and the steric repulsion would be amplified in the transition state.
36. Rotational isomer about the *N*-formylamine.

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