A Novel Synthesis of Methyl 1,5-Disubstituted Imidazole-4-carboxylates Using 3-Bromo-2-isocyanoacrylates

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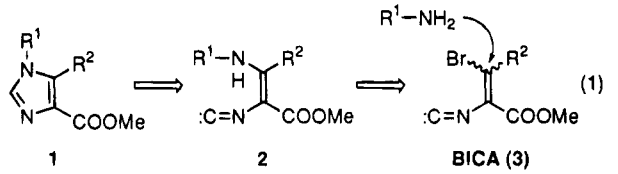
Methyl 1,5-disubstituted imidazole-4-carboxylates **1** were synthesized using methyl 3-substituted 3-bromo-2-isocyanoacrylates **3** (BICA), and the reaction mechanism was elucidated. Reactions of **3**, which were prepared by bromination of 3-substituted 2-(formylamino)acrylates **6** followed by dehydration of the formylamino group, with a variety of primary amines gave imidazoles **1** in good overall yields. A mechanistic study suggested a Michael reaction of an amine with **3** followed by β-elimination of hydrogen bromide exclusively afforded (*E*)-*N*,3-disubstituted 3-amino-2-isocyanoacrylates **2**. Geometric isomerization to (*Z*)-**2** with a base and subsequent cyclization gave imidazoles **1**.

Imidazoles are biologically important heterocyclic compounds, and a variety of useful therapeutic agents containing the imidazole moiety have been developed.[1] As part of our synthetic studies[2] on biologically interesting amino acids and heterocyclic compounds using multifunctional 3-substituted 3-bromo-2-isocyanoacrylates **3** (BICA), we briefly reported a facile synthesis of methyl 1,5-disubstituted imidazole-4-carboxylates **1**. A survey of the literature reveals that, since van Leusen[3] reported the synthesis of 1,4,5-trisubstituted imidazoles using tosylmethyl isocyanates (TosMIC), few synthetic strategies[4] have appeared for the preparation of the imidazole skeleton. In this paper we wish to report the extension of the reactivity of BICA to an efficient synthesis of various types of methyl 1,5-disubstituted imidazole-4-carboxylates **1**, useful intermediates for pharmaceuticals and agricultural products, for which only a couple of direct synthetic methods have been reported.[3,4a] We will also propose a detailed reaction mechanism.

We envisioned the following strategy for the synthesis of 1,5-disubstituted imidazole-4-carboxylates **1** using BICA (eq 1).

In this strategy, a Michael reaction of a primary amine with α,β-unsaturated ester **3** and successive β-elimination of hydrogen bromide would occur as the first step. The resulting *Z*-enamine **2** has an acidic NH proton, removal



(1)

of which would precipitate an intramolecular α-addition reaction to the isonitrile group[5] affording imidazoles **1**. It was expected that this approach could be applied to the synthesis of imidazoles having a range of substituents at the 1- and 5-positions, especially those with an aromatic ring at 1-position, which has been difficult to prepare so far.[6]

Result and Discussion

Synthesis of Methyl 3-Substituted 3-Bromo-2-isocyanoacrylates (BICA) (3). The key compounds in this study, methyl 3-substituted 3-bromo-2-isocyanoacrylates **3**, were synthesized as shown in Scheme 1. Namely, 3-substituted 2-(formylamino)acrylates **6** were prepared *via* two different routes: (1) a condensation reaction[7] of methyl isocyanoacetate (**4**) with an appropriate aldehyde in the presence of sodium hydride (method A) and (2) *N*-chlorination followed by dehydrochlorination[8] of *N*-formyl-α-amino acid methyl esters **5**, which were derived from commercially available α-amino acid methyl esters (method B). In both cases thermodynamically more stable (*Z*)-**6** was predominantly formed.[9]

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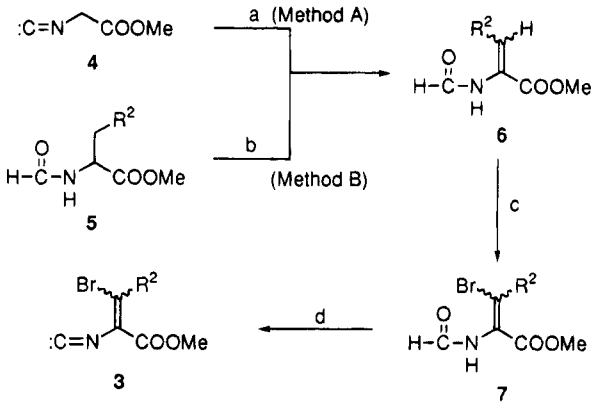
Scheme 1[a]



[a] (a) R^2CHO, NaH, THF (b) (1) *t*-BuOCl, toluene (2) DABCO, $CHCl_3$ (c) NBS, CCl_4 (d) $POCl_3$, Et_3N, −20 °C, CH_2Cl_2.

Table 1. Yields and Physical Properties of BICA (3)

compd	R	yield (%)[a]	mp (°C)
(*Z*)-**3a**	Ph	79	48−51
(*E*)-**3a**	Ph	66	syrup
(*Z*)-**3b**	Ph(2-Cl)	73	84−86
(*E*)-**3b**	Ph(2-Cl)	77	syrup
(*Z*)-**3c**	Ph(2-Br)	74	92−93
(*Z*)-**3d**	Ph(3-Me)	71	syrup
(*Z*)-**3e**	Ph(3-OPh)	87	syrup
(*Z*)-**3f**	Ph(4-Cl)	70	79−81
(*Z*)-**3g**	Ph(4-Me)	74	66−68
(*Z*)-**3h**	Ph(4-OMe)	69	95−97
(*Z*)-**3i**	Ph(4-OCH_2Ph)	75	68−70
(*Z*)-**3j**	Ph(2,4-Cl_2)	95	syrup
(*Z*)-**3k**	Ph(3,4-OCH_2O-)	89	116−118
(*E*)-**3k**	Ph(3,4-OCH_2O-)	73	72−73
(*Z*)-**3l**	CH_3	54	syrup
(*E*)-**3l**	CH_3	NI[b]	NI[b]
(*Z*)-**3m**	$(CH_3)_2CH$-	82	50−51
(*E*)-**3m**	$(CH_3)_2CH$-	60	syrup
(*Z*)-**3n**	$(CH_3)_2CHCH_2$-	92	syrup
(*E*)-**3n**	$(CH_3)_2CHCH_2$-	54	syrup
(*Z*)-**3o**	$(CH_3CH_2)_2CH$-	94	syrup

[a] Isolated yield of **3** from **7**. [b] NI = not isolated. (*E*)-**3l** was unstable under the reaction conditions.

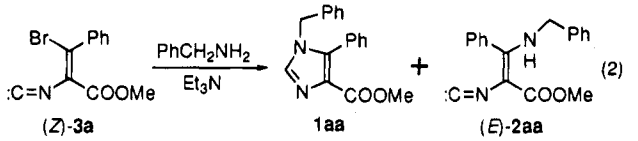
Then, bromination[10] of **6** with NBS resulted in the predominant formation of (*Z*)-3-substituted 3-bromo-2-(formylamino)acrylates **7**. Coleman and Carpenter reported[10a] bromination of methyl 4-(benzyloxy)-2-[*N*-(methoxycarbonyl)amino]-2-pentanoate predominantly gave (*E*)-3-bromo-2-pentanoate derivative, which could only be converted to *Z*-isomer by treatment with DABCO. In this regard, their results were much different than ours. The detailed reaction mechanism is now under investigation in this laboratory. Each geometric isomer of **7** isolated by column chromatography was converted to the corresponding BICA by dehydration of the *N*-(formylamino) group with $POCl_3$ and triethylamine by means of the procedure reported by us.[7a] The yields and melting points of **3** are summarized in Table 1.

Synthesis of Methyl 1,5-Disubstituted Imidazole-4-carboxylates (1). We examined the reaction of (*Z*)-methyl 3-bromo-2-isocyano-3-phenylacrylate [(*Z*)-**3a**] with benzylamine in the presence of an equimolar amount of triethylamine as a typical example (eq 2) (Table 2).

Table 2. Reaction of (*Z*)-3a with Benzylamine

run[a]	$PhCH_2NH_2$ (equiv)	solvent	temp (°C)	time (h)	yield (%)[e] **1aa**	yield (%)[e] (*E*)-**2aa**
1	1.0	DMF	10	24	17	60
2	1.0	DMF	25	6	50	27
3	1.2	DMF	25	6	80	trace
4	1.2	DMF	50	4	63	nd[f]
5	1.0	HMPA	10	24	20	57
6	1.0	HMPA	25	24	65	20
7	1.2	HMPA	25	6	80	trace
8	1.2	THF	25	24	38	42
9[b]	1.2	toluene	25	24	27	36
10[c]	1.2	chloroform	25	24	19	32
11[d]	1.2	DMF	25	6	70	trace

[a] The reaction was carried out in a 0.5 M DMF solution of **3a**. [b] (*Z*)-**3a** was recovered in 11% yield. [c] (*Z*)-**3a** was recovered in 23% yield. [d] (*E*)-**3a** was used instead of (*Z*)-**3a**. [e] Isolated yield. [f] Not detected.



When (*Z*)-**3a** was treated with an equimolar amount of benzylamine at 10 °C for 24 h in DMF, the desired methyl 1-benzyl-5-phenylimidazole-4-carboxylate (**1aa**) and uncyclized amine adduct (*E*)-methyl 3-(benzylamino)-2-isocyano-3-phenylacrylate [(*E*)-**2aa**] were obtained in 17 and 60% yields (run 1), respectively, whereas the reaction at 25 °C increased the yield of **1aa** to 50% (run 2). On the other hand, the reaction of (*Z*)-**3a** with 1.2 equiv of benzylamine in DMF at 25 °C for 6 h afforded exclusively **1aa** in 80% yield (run 3). Increasing the reaction temperature accelerated the reaction rate but reduced the chemical yield (run 4) because of the thermal lability of **3a**. Next, the solvent effect was investigated under the second set of reaction conditions (benzylamine 1.2 equiv, 25 °C). The use of HMPA gave imidazoles in good yields (runs 5−7), but the use of THF, toluene, or chloroform suppressed the reaction rate. In these cases, even when the reaction was continued for 24 h, *E*-enamine (*E*)-**2aa** was predominantly obtained with recovery of (*Z*)-**3a** in trace, 11%, or 23% yield, respectively (runs 8−10). In the case of the reaction of (*E*)-**3a** with benzylamine, a result similar to that observed for (*Z*)-**3a** (run 11) was obtained.

The geometric structures of a series of 3-bromo-2-(formylamino)acrylates **7**, BICA (**3**), and enamines **2** were determined on the basis of correlation of the chemical shifts and NOE studies in the ^1H NMR spectra and by X-ray analysis. In the case of bromides **7a−k**, which have aromatic rings at the 3-position, the chemical shift of the methyl ester proton of the *E*-isomer appeared at higher field (δ = 3.38−3.50 ppm in DMSO-d_6) than that of the corresponding *Z*-isomer (δ = 3.73−3.78 ppm in DMSO-d_6) because of the deshielding anisotropic effect of the adjacent benzene ring.[2] Likewise, in the series of aromatic BICA (**3a−k**), the chemical shift of the methyl ester proton of the *Z*-isomer appeared at higher field (δ = 3.63−3.72 ppm in $CDCl_3$) than that of the corresponding *E*-isomer (δ = 3.92−3.93 ppm in $CDCl_3$). The chemical shift of the methyl ester of enamine **2aa** appeared at δ 3.83 ppm in $CDCl_3$, and therefore the

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Scheme 2

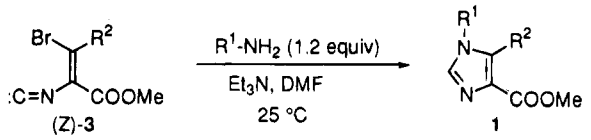


Table 3. Synthesis of Methyl 1,5-Disubstituted Imidazole-4-carboxylates (1) using (Z)-3

entry	R^2	R^1-NH_2	time (h)	yield (%)	product
1	Ph	$PhCH_2NH_2$	6	80	**1aa**
2[a]	Ph	$PhCH_2NH_2$	6	70	**1aa**
3	Ph	$MeOCOCH_2NH_2$	6	77	**1ac**
4	Ph	$HOCH_2CH_2NH_2$	6	74	**1ad**
5	Ph	$PhNH_2$	48	52	**1ae**
6	Ph	(4-OMe)$PhNH_2$	48	62	**1af**
7	Ph	[3,4,5-$(OMe)_3$]$PhNH_2$	48	64	**1ag**
8	Ph	(4-Cl)$PhNH_2$	48	38	**1ah**
9	Ph	(4-COOMe)$PhNH_2$	48	0	**1ai**
10	Ph(4-Cl)	$PhCH_2NH_2$	6	83	**1fa**
11	Ph(4-Me)	$PhCH_2NH_2$	6	78	**1ga**
12	Me_2CH	$PhNH_2$	48	63	**1me**
13	Me_2CH	$Ph(CH_3)CHNH_2$	20	70	**1mj**
14	Me_2CHCH_2	$Ph(CH_3)CHNH_2$	6	84	**1nj**
15	Me_2CHCH_2	2-pyridylmethylamine	18	85	**1nk**
16	Et_2CH	$PhNH_2$	48	34	**1oe**
17	Et_2CH	(4-COOMe)$PhNH_2$	48	0	**1oi**
18	Et_2CH	$MeNH_2$	15	78	**1ol**

[a] (*E*)-**3a** was used instead of (*Z*)-**3a**.

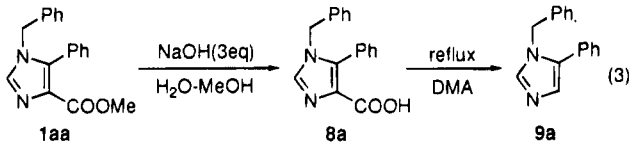
configuration of **2aa** was determined to be *E*. In the series of bromides **7l–n** and BICA (**3m,n**), which have alkyl substituents at the 3-position, the chemical shift of the allylic C4-H proton of the *E*-isomer was observed at higher field.[11] The configuration of *E*-bromides **7l–n** was 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 the *Z*-isomers. The geometry of *Z*-BICA (**3m**) was confirmed by X-ray analysis.

On the basis of the above results, a variety of methyl 1,5-disubstituted imidazole-4-carboxylates **1** were synthesized by the reaction of **3** with 1.2 equiv of a primary amine in the presence of triethylamine in DMF at 25 °C, as shown in Scheme 2, and the results are summarized in Table 3. BICA (**3**) reacted with a range of primary amines to afford desired imidazoles **1** in good yields.[12] Only the reactions with weak nucleophiles, such as anilines with an electron-withdrawing group at the 4-position, did not proceed (entries 9, 17). In addition, conversion of 1,5-disubstituted imidazole-4-carboxylates **1** to 1,5-disubstituted imidazoles **9** was examined. For instance, saponification of ester **1aa** with NaOH (3 equiv) in MeOH–H_2O afforded carboxylic acid **8a** in 95% yield. Decarboxylation[13] of **8a** proceeded in refluxing *N,N*-dimethylacetamide (DMA) for 3 h to give 1-benzyl-5-phenylimidazole (**9a**) in 68% yield (eq 3). The results indicated that this synthetic strategy is efficient for the preparation not only of 1,5-disubstituted imidazole-4-carboxylates **1** but also of 1,5-disubstituted imidazoles **9**.

Table 4. Reaction of (Z)-3a with Benzylamine

run	$PhCH_2NH_2$ (equiv)	time (h)	yield (%)[b] **1aa**	yield (%)[b] (*E*)-**2aa**
1	1.0	1	trace	88
2	1.0	6	trace	82
3	1.8	1	23	64
4	1.8	10	27	60
5	1.8	24	31	50
6	2.2	1	55	40
7	2.2	3	65	29
8	2.2	10	83	9
9	2.2	24	86	nd[c]
11	3.0	1	95	trace
12	3.0	6	95	nd
13[a]	1.0	6	trace	80
14[a]	1.8	2	9	74
15[a]	2.2	24	75	trace

[a] (*E*)-**3a** was used instead of (*Z*)-**3a**. [b] Isolated yield. [c] Not detected.



The Mechanism of the Reaction of BICA (3) with Amines. As described above, the yields of the desired imidazole compounds were drastically affected by the reaction conditions, especially the amount of a primary amine. In order to clarify the mechanism of the reaction of **3** with an amine, (*Z*)-**3a** was treated with varying amounts of benzylamine in the absence of a base[14] in DMF, and the results are summarized in Table 4. The reaction of (*Z*)-**3a** with 1.0 equiv of benzylamine exclusively gave *E*-enamine **2aa**, and the yield did not change upon elongation of the reaction time (runs 1, 2). Addition of 1.8 equiv of benzylamine resulted in the formation of 23-31% yields of imidazoles **1**, and the yields depended on the reaction time (runs 3–5). In contrast, in the case of the reaction with 2.2 equiv of benzylamine, the yields of **1** increased along with the reaction time (runs 6–9). The reaction with a large excess of benzylamine proceeded smoothly to afford **1** in 95% yield (runs 11, 12). The reaction of (*E*)-**3a** with benzylamine gave a result similar to that of (*Z*)-**3a** (runs 13–15).

On the basis of these results, we proposed the reaction mechanism shown in Scheme 3. This reaction consisted of two steps. In the first step, independent the geometry of **3**, a Michael reaction of benzylamine with **3** followed by β-elimination of hydrogen bromide exclusively gave (*E*)-**2**,[15] which could not cyclize because the amino and the isonitrile groups were on the opposite site of the double bond. This result suggested that the stereoselectivity was caused by an electrostatic attraction between the NH proton and the carbonyl of ester at the transition state (A).[15b,16] In the second step, an isomerization from

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(12) The reaction of (*Z*)-**3l** with benzylamine did not afford the corresponding imidazole compound because of the instability of (*Z*)-**3l** under the reaction conditions. Optimization of the reaction conditions is needed.

(13) (a) Takahashi, K.; Mitsuhashi, K. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 557. (b) O'Connell, J. F.; Parquette, J.; Yelle, W. E.; Wang, W.; Rapoport, H. *Synthesis* **1988**, 767.

(14) Benzylamine not only serves as a reactant but also acts as an acid scavenger.

(15) Nucleophilic vinylic substitution of β-bromo-α,β-unsaturated esters and nitriles under analogous conditions affords β-substituted derivatives with retention of the geometry: (a) Truce, W. E.; Gobarty, M. L. *J. Org. Chem.* **1970**, *35*, 2113. (b) Rappoport, Z. *Acc. Chem. Res.* **1981**, *14*, 7. (c) Ancos, B.; Maestro, C. M.; Martin, F. F. *Synthesis* **1988**, 136.

(16) Herbig, K.; Huisgen, R.; Huber, H. *Chem. Ber.* **1966**, 2546.

Scheme 3

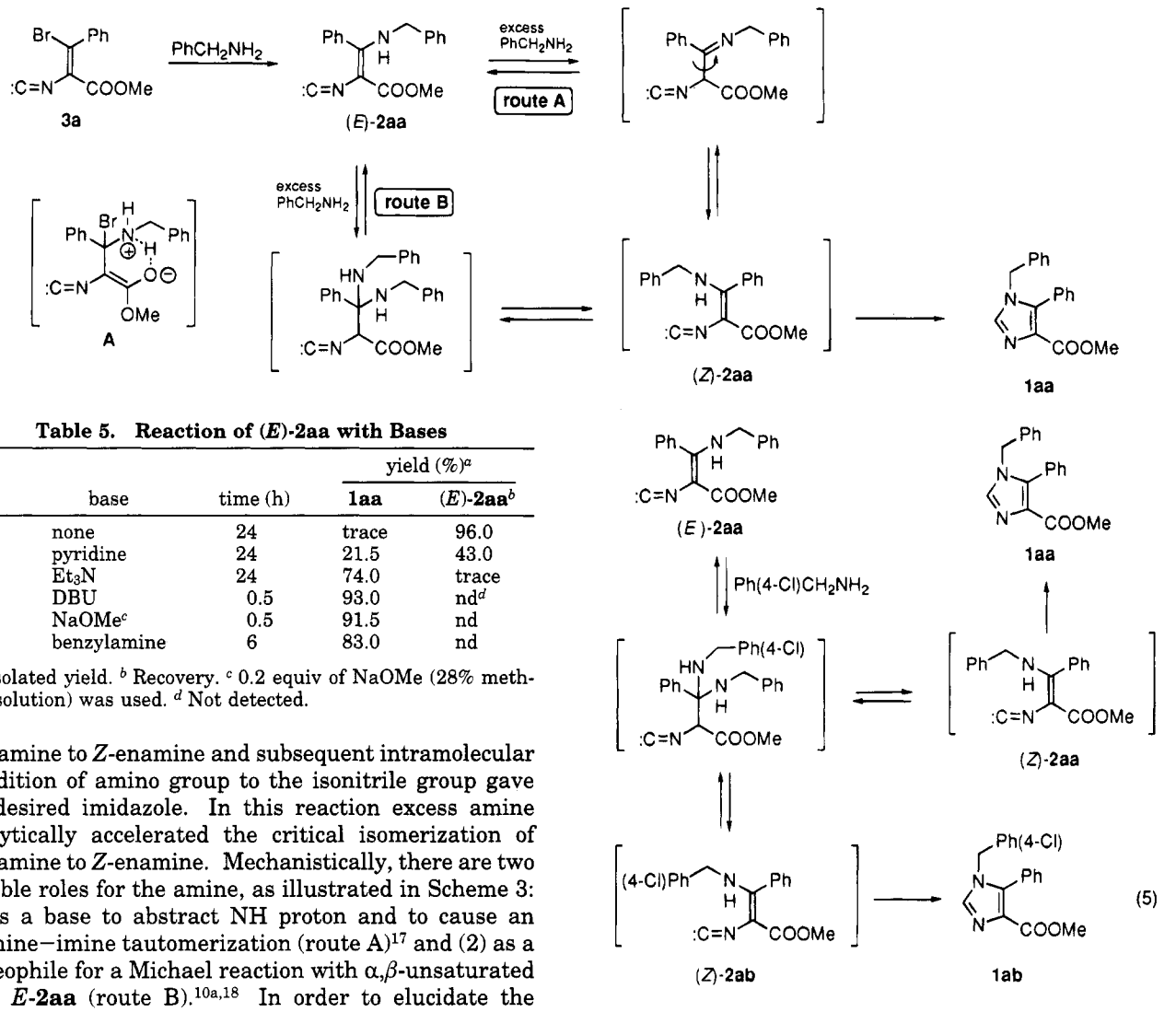
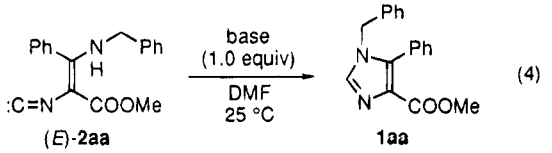


Table 5. Reaction of (*E*)-2aa with Bases

run	base	time (h)	yield (%)[a] 1aa	yield (%)[a] (*E*)-2aa[b]
1	none	24	trace	96.0
2	pyridine	24	21.5	43.0
3	Et_3N	24	74.0	trace
4	DBU	0.5	93.0	nd[d]
5	NaOMe[c]	0.5	91.5	nd
6	benzylamine	6	83.0	nd

[a] Isolated yield. [b] Recovery. [c] 0.2 equiv of NaOMe (28% methanol solution) was used. [d] Not detected.

E-enamine to *Z*-enamine and subsequent intramolecular α-addition of amino group to the isonitrile group gave the desired imidazole. In this reaction excess amine catalytically accelerated the critical isomerization of *E*-enamine to *Z*-enamine. Mechanistically, there are two possible roles for the amine, as illustrated in Scheme 3: (1) as a base to abstract NH proton and to cause an enamine–imine tautomerization (route A)[17] and (2) as a nucleophile for a Michael reaction with α,β-unsaturated ester *E*-**2aa** (route B).[10a,18] In order to elucidate the reaction mechanism at the second step, isolated enamine *E*-**2aa** was treated with bases, as shown in eq 4, and the results are summarized in Table 5. All the bases, except



(4)

pyridine, afforded imidazole **1aa** in a good yield. The fact that triethylamine and DBU, which have no nucleophilicity, gave imidazoles suggested the predominance of route A. To confirm this suggestion the reaction of (*E*)-**2aa** with 2 equiv of 4-chlorobenzylamine was examined in DMF at 25 °C for 24 h. If the reaction proceeded *via* route B, methyl 1-(4-chlorobenzyl)-5-phenylimidazole-4-carboxylate (**1ab**) was expected to contaminate **1aa**. However, **1aa** was isolated in 93% yield, and the formation of **1ab** was not detected. These results indicated that the imidazoles were formed *via* route A.

(5)

Summary

Useful intermediates, methyl 3-substituted 3-bromo-2-isocyanoacrylate **3** (BICA), which were easily derived from α-isocyanoacetate **4** or *N*-formyl amino acid ester **5** were utilized for the novel synthesis of methyl 1,5-disubstituted imidazole-4-carboxylates **1** and 1,5-disubstituted imidazoles **9**. A mechanistic study elucidated that the reaction of BICA with amines proceeded regioselectively to afford (*E*)-*N*,3-disubstituted 3-amino-2-isocyanoacrylates **2**, which underwent base-catalyzed isomerization to *Z*-form and subsequent cyclization to imidazoles (**1**). Efforts to further expand the utility of BICA are under investigation in this laboratory.

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. ^1H 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

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(18) (a) Basavaiah, D.; Gowriswari, V. V. L.; Sarma, P. K. S.; Dharma Rao, P. *Tetrahedron Lett.* **1990**, *31*, 1621. (b) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron* **1988**, *44*, 6095.

with air- and moisture-sensitive compounds were conducted in oven-dried glassware under an atmosphere of dry nitrogen.

Preparation of Methyl 3-Substituted 2-(Formylamino)acrylates (6). 3-Substituted 2-(formylamino)acrylates **6b–h,j–l,n,o** were synthesized essentially by means of the procedure previously described[7] (method A), and the other acrylates **6a,i,m** were prepared by method B.[8] Physical properties of the new compounds are as follows.

(*Z*)-Methyl 2-(Formylamino)-3-(3-methylphenyl)acrylate [(*Z*)-6d]: mp 113–114 °C (AcOEt/hexane); ^{1}H NMR (δ in $CDCl_3$) 2.35 (s, 3H), 3.89 (s, 3H), 7.03 (br, 1H), 7.16 (br-s, 1H), 7.26–7.31 (m, 4H), 8.28 (br-d like, total 1H) and 8.21 (minor isomer,[19] s); IR (KBr) 3240, 1720, 1655 cm^{-1}; SIMS *m/z* 220 (M + H, base), 191, 188. Anal. Calcd for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.89; H, 6.08; N, 6.34.

(*Z*)-Methyl 2-(Formylamino)-3-(3-phenoxyphenyl)acrylate [(*Z*)-6e]: mp 82–84 °C (AcOEt/hexane); ^{1}H NMR (δ in $CDCl_3$) 3.88 (s, 3H), 6.97–7.15 (m, 6H), 7.33–7.41 (br-m, 5H), 8.21 (br-s, 1H); IR (KBr) 3240, 1725, 1670 cm^{-1}; SIMS *m/z* 298 (M + H), 284, 266, 69 (base). Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71. Found: C, 68.60; H, 5.10; N, 4.65.

(*Z*)-Methyl 3-(4-(Benzyloxy)phenyl)-2-(formylamino)acrylate [(*Z*)-6i]: mp 122–126 °C (MeOH); ^{1}H NMR (δ in $CDCl_3$) 3.83 (s, total 3H) and 3.86 (minor isomer,[19] s), 5.09 (s, total 2H) and 5.04 (minor isomer, s), 6.90–7.00 (m, 2H), 7.30–7.58 (m, 8H), 7.8 and 8.63 (br each, 1H), 8.11 and 8.30 (br each, 1H); IR (KBr) 3230, 1710, 1665, 1600 cm^{-1}; SIMS *m/z* 312 (M + H), 238, 177, 85 (base). Anal. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50. Found: C, 69.34; H, 5.45; N, 4.45.

(*Z*)-Methyl 2-(Formylamino)-2-butenoate [(*Z*)-6l]: syrup; ^{1}H NMR (δ in DMSO-d_6) 1.68 (d, total 3H, J = 7.2 Hz) and 1.79 (minor isomer,[19] d, J = 7.2 Hz), 3.67 (s, total 3H) and 3.72 (minor isomer, s), 6.58 (q, total 1H, J = 7.2 Hz) and 6.66 (minor isomer, q, J = 7.2 Hz), 8.10 (s, total 1H) and 8.01 (minor isomer, d, J = 11.1 Hz), 9.42 (br, total 1H) and 9.11 (minor isomer, br-d, J = 11.1 Hz); IR (film) 3265, 1725, 1690, 1500 cm^{-1}; EIMS *m/z* 143 (M$^+$), 111 (base).

(*E*)-Methyl 2-(Formylamino)-2-butenoate [(*E*)-6l]: syrup; ^{1}H NMR (δ in DMSO-d_6) 1.90 (d, total 3H, J = 7.4 Hz) and 1.96 (minor isomer,[19] d, J = 7.4 Hz), 3.70 (s, total 3H) and 3.73 (minor isomer, s), 6.36 (q, total 1H, J = 7.4 Hz) and 6.14 (minor isomer, q, J = 7.4 Hz), 8.05 (s like, 1H), 9.58 (br, total 1H) and 9.24 (minor isomer, br-d like); IR (film) 3305, 1720, 1695, 1535 cm^{-1}; EIMS *m/z* 143 (M$^+$), 111, 45 (base).

(*Z*)-Methyl 2-(Formylamino)-4-methyl-2-pentenoate [(*Z*)-6m]: syrup; ^{1}H NMR (δ in $CDCl_3$) 1.08 (dd, 6H, J = 4.5 and 6.5 Hz), 2.69 (m, 1H), 3.79 (s, total 3H) and 3.81 (minor isomer,[19] s), 6.49 and 6.59 (d each, 1H, J = 10.7 Hz), 7.01 and 7.40 (br each, 1H), 8.27 (s, total 1H) and 8.17 (minor isomer, d, J = 11.3 Hz); IR (film) 3275, 2965, 1725, 1690, 1510 cm^{-1}; SIMS *m/z* 172 (M + H), 158, 140 (base).

(*E*)-Methyl 2-(Formylamino)-4-methyl-2-pentenoate [(*E*)-6m]: syrup; ^{1}H NMR (δ in $CDCl_3$) 1.08 (d, 6H, J = 6.6 Hz), 3.25–3.49 (m, 1H), 3.83 (s, total 3H) and 3.86 (minor isomer,[19] s), 7.13 (d, total 1H, J = 10.0 Hz) and 5.85 (minor isomer, d, J = 10.0 Hz), 7.44 (br, 1H), 8.20–8.37 (s and d like, 1H); IR (film) 3310, 2965, 1730, 1695, 1520 cm^{-1}; SIMS *m/z* (M + H) was not detected, 140, 111, 43 (base).

(*Z*)-Methyl 2-(Formylamino)-5-methyl-2-hexenoate [(*Z*)-6n]: syrup; ^{1}H NMR (δ in $CDCl_3$) 0.95 (dd, 6H, J = 4.0 and 6.6 Hz), 1.79 (m, 1H), 2.05–2.22 (m, 2H), 3.80 and 3.82 (s each, 3H), 6.68 and 6.80 (t each, 1H, J = 7.6 Hz), 7.08 (br, 1H), 8.16–8.34 (s and d like, 1H); IR (film) 3270, 2960, 1725, 1680, 1500 cm^{-1}; EIMS *m/z* 185 (M$^+$), 153, 114, 54 (base).

(*E*)-Methyl 2-(Formylamino)-5-methyl-2-hexenoate [(*E*)-6n]: syrup; ^{1}H NMR (δ in $CDCl_3$) 0.95 (d, 6H, J = 6.6 Hz), 1.76 (m, 1H, J = 6.6 Hz), 2.50 (dd, 2H, J = 6.6 and 7.8 Hz), 3.85 (s, 3H), 7.33 (d, total 1H, J = 7.8 Hz) and 6.07 (minor isomer,[19] t, J = 7.8 Hz), 7.50 (br, 1H), 8.16–8.33 (s and d like, 1H); IR (film) 3310, 2960, 1720, 1700, 1520 cm^{-1}; EIMS *m/z* 185 (M$^+$), 153, 114, 54 (base).

General Procedure for the Preparation of Methyl 3-Substituted 3-Bromo-2-(formylamino)acrylates (7). 3-Substituted 3-bromo-2-(formylamino)acrylates **7** were synthesized essentially by means of the procedures previously described.[2] To a solution of 3-substituted 2-(formylamino)acrylates **6** (20 mmol) in carbon tetrachloride (50 mL) was added NBS (3.93 g, 22 mmol) under ice cooling. After stirring was continued for 3 h, triethylamine (2.0 g, 20 mmol) was added dropwise to the reaction mixture. The mixture was washed with saturated aqueous $NaHCO_3$ and brine, dried over anhyd $MgSO_4$, and concentrated in vacuo. The residue was subjected to column chromatography on silica gel with $CHCl_3$–AcOEt to afford (*Z*)-**7** and/or (*E*)-**7**.

Physical properties of the new compounds are as follows:

(*Z*)-Methyl 3-Bromo-3-(2-chlorophenyl)-2-(formylamino)acrylate [(*Z*)-7b]: mp 109–110 °C (AcOEt/hexane); ^{1}H NMR (δ in DMSO-d_6) 3.38 (s, 3H), 7.30–7.46 (m, 3H), 7.51–7.55 (m, 1H), 8.19 (s, 1H), 10.2 (br, 1H); IR (Nujol) 3150, 1735, 1665 cm^{-1}; EIMS *m/z* 318 (M$^+$), 280, 172 (base). Anal. Calcd for $C_{11}H_9NO_3BrCl$: C, 41.47; H, 2.85; N, 4.40. Found: C, 41.17; H, 2.85; N, 4.30.

(*E*)-Methyl 3-Bromo-3-(2-chlorophenyl)-2-(formylamino)acrylate [(*E*)-7b]: syrup; ^{1}H NMR (δ in DMSO-d_6) 3.78 (s, 3H), 7.36–7.60 (m, 4H), 7.85 (s, 1H), 9.75 (br, 1H); IR (film) 3300, 3250, 1740, 1680 cm^{-1}; EIMS *m/z* 318 (M$^+$), 280, 172 (base).

(*Z*)-Methyl 3-Bromo-3-(2-bromophenyl)-2-(formylamino)acrylate [(*Z*)-7c]: mp 157–159 °C (*i*-Pr_2O); ^{1}H NMR (δ in DMSO-d_6) 3.38 (s, 3H), 7.3–7.4 (m, 3H), 7.63–7.75 (m, 1H), 8.20 (s, 1H), NH was not detected; IR (Nujol) 3210, 1740, 1670 cm^{-1}; EIMS *m/z* 363 (M$^+$), 330, 172 (base). Anal. Calcd for $C_{11}H_9NO_3Br_2$: C, 36.40; H, 2.50; N, 3.86. Found: C, 36.33; H, 2.45; N, 3.68.

(*E*)-Methyl 3-Bromo-3-(2-bromophenyl)-2-(formylamino)acrylate [(*E*)-7c]: mp 128–129 °C (*i*-Pr_2O); ^{1}H NMR (δ in DMSO-d_6) 3.77 (s, 3H), 7.3–7.6 (m, 3H), 7.72–7.8 (m, 1H), 7.83 (s, 1H), 9.66 (br, 1H); IR (Nujol) 3300, 1720, 1695 cm^{-1}; EIMS *m/z* 363 (M$^+$), 330, 172 (base). Anal. Calcd for $C_{11}H_9NO_3Br_2$: C, 36.40; H, 2.50; N, 3.86. Found: C, 36.25; H, 2.40; N, 3.65.

(*Z*)-Methyl 3-Bromo-2-(formylamino)-3-(3-methylphenyl)acrylate [(*Z*)-7d]: mp 136–137 °C (AcOEt/hexane); ^{1}H NMR (δ in DMSO-d_6) 2.30 (s, 3H), 3.41 (s, 3H), 7.05–7.32 (m, 4H), 8.16 (s, 1H), 10.1 (br, 1H); IR (KBr) 3255, 1740, 1670, 1620 cm^{-1}; SIMS *m/z* 298/300 (M + H), 266/268, 238/240, 186 (base). Anal. Calcd for $C_{12}H_{12}NO_3Br$: C, 48.34; H, 4.06; N, 4.70. Found: C, 48.10; H, 4.06; N, 4.60.

(*Z*)-Methyl 3-Bromo-2-(formylamino)-3-(3-phenoxyphenyl)acrylate [(*Z*)-7e]: syrup; ^{1}H NMR (δ in DMSO-d_6) 3.57 (s, 3H), 6.95–7.45 (m, 9H), 8.25 (s, 1H), NH was not detected; IR (film) 3280, 1730, 1670 cm^{-1}; EIMS *m/z* 375/377 (M$^+$, base), 343/245.

(*Z*)-Methyl 3-(4-(Benzyloxy)phenyl)-3-bromo-2-(formylamino)acrylate [(*Z*)-7i]: mp 137–141 °C (AcOEt/hexane); ^{1}H NMR (δ in $CDCl_3$) 3.58 (s, 3H), 5.08 (s, 2H), 6.94 (d, 2H, J = 8.8 Hz), 7.20–7.50 (m, 8H), 8.28 (s, 1H); IR (KBr) 3250, 1740, 1665, 1600 cm^{-1}; SIMS *m/z* 390/392 (M + H), 358/360, 310, 91 (base). Anal. Calcd for $C_{18}H_{16}NO_4Br$: C, 55.40; H, 4.13; N, 3.59. Found: C, 55.35; H, 4.08; N, 3.62.

(*Z*)-Methyl 3-Bromo-3-(2,4-dichlorophenyl)-2-(formylamino)acrylate [(*Z*)-7j]: mp 151–153 °C (*i*-Pr_2O); ^{1}H NMR (δ in $CDCl_3$) 3.53 (s, 3H), 7.22 (m, 2H), 7.38–7.55 (br-m, 1H), 8.30 (br-s, 1H), NH was not detected; IR (Nujol) 3310, 1720, 1685 cm^{-1}; SIMS *m/z* 354 (M + H), 278, 186 (base). Anal. Calcd for $C_{11}H_8NO_3BrCl_2$: C, 37.43; H, 2.28; N, 3.97. Found: C, 37.35; H, 2.08; N, 3.72.

(*Z*)-Methyl 3-Bromo-2-(formylamino)-3-(3,4-(methylenedioxy)phenyl)acrylate [(*Z*)-7k]: mp 154–156 °C (AcOEt); ^{1}H NMR (δ in DMSO-d_6) 3.49 (s, 3H), 6.10 (s, 2H), 6.75–7.0 (m, 3H), 8.20 (s like, 1H), 10.1 (br, 1H); IR (Nujol) 3250, 1735, 1710, 1680 cm^{-1}; EIMS *m/z* 327/329 (M$^+$), 299/301, 296/298, 216 (base). Anal. Calcd for $C_{12}H_{10}NO_5Br$: C, 43.93; H, 3.07; N, 4.27. Found: C, 43.70; H, 3.15; N, 4.18.

(*E*)-Methyl 3-Bromo-2-(formylamino)-3-(3,4-(methylenedioxy)phenyl)acrylate [(*E*)-7k]: syrup; ^{1}H NMR (δ in DMSO-d_6) 3.73 (s, 3H), 6.06 (s, 2H), 6.92 (s, 3H), 7.86 (s like, 1H), 9.80 (br, 1H); IR (film) 3370, 1725, 1670 cm^{-1}; EIMS *m/z* 327/329 (M$^+$), 299/301, 216 (base).

(19) Rotational isomer about the *N*-formyl amine.

(Z)-Methyl 3-Bromo-2-(formylamino)-2-butenoate [(Z)-7l]: mp 82−83 °C (AcOEt/hexane); ^{1}H NMR (δ in $CDCl_3$) 2.60 (s, total 3H) and 2.76 (minor isomer,[19] s), 3.83 (s, 3H), 7.09 (br, total 1H) and 6.9 (minor isomer, br), 8.19 (s, total 1H) and 8.25 (minor isomer, br); IR (KBr) 3265, 1730, 1665, 1505 cm^{-1}; EIMS m/z 221/223 (M^+), 193/195, 161/163, 110 (base). Anal. Calcd for $C_6H_8NO_3Br$: C, 32.46; H, 3.63; N, 6.31. Found: C, 32.71; H, 3.55; N, 6.36.

(E)-Methyl 3-Bromo-2-(formylamino)-2-butenoate [(E)-7l]: mp 97−99 °C (AcOEt/hexane); ^{1}H NMR (δ in $CDCl_3$) 2.43 (s, total 3H) and 2.54 (minor isomer,[19] s), 3.83 (s, total 3H) and 3.84 (minor isomer, s), 7.05 (br, total 1H) and 6.9 (minor isomer, br), 8.19 (s, total 1H) and 8.05 (minor isomer, d, J = 11.2 Hz); IR (KBr) 3345, 1725, 1695 cm^{-1}; EIMS m/z 221/223 (M^+), 193/195, 190/192, 161/163, 110 (base). Anal. Calcd for $C_6H_8NO_3Br$: C, 32.46; H, 3.63; N, 6.31. Found: C, 32.42; H, 3.42; N, 6.59.

(Z)-Methyl 3-Bromo-2-(formylamino)-4-methyl-2-pentenoate [(Z)-7m]: syrup; ^{1}H NMR (δ in $CDCl_3$) 1.12 (d, 6H, J = 6.5 Hz), 3.20 (m, 1H, J = 6.5 Hz), 3.85 (s, 3H), 7.18 (br, 1H), 8.18 (s, 1H); IR (film) 3290, 2975, 1735, 1680 cm^{-1}; SIMS m/z 250/252 (M + H, base), 218/220, 190/192.

(E)-Methyl 3-Bromo-2-(formylamino)-4-methyl-2-pentenoate [(E)-7m]: syrup; ^{1}H NMR (δ in DMSO-d_6) 1.10 (d, 6H, J = 6.5 Hz), 3.02 (m, 1H, J = 6.5 Hz), 3.63 (s, 3H), 8.00 (s, 1H), 8.49 (br, 1H); IR (film) 3250, 2965, 1730, 1685, 1500 cm^{-1}; EIMS m/z 249/251 (M^+), 218/220, 206/208, 138 (base).

(Z)-Methyl 3-Bromo-2-(formylamino)-5-methyl-2-hexenoate [(Z)-7n]: syrup; ^{1}H NMR (δ in DMSO-d_6) 0.86 (d, 6H, J = 6.6 Hz), 1.95 (m, 1H), 2.60 (d, 2H, J = 7.2 Hz), 3.67 (s, 3H), 8.01 (s, 1H), 9.86 (br, 1H); IR (film) 3300, 2959, 1736, 1695, 1467 cm^{-1}; EIMS m/z 263/265 (M^+), 232/234, 192/194, 152 (base).

(E)-Methyl 3-Bromo-2-(formylamino)-5-methyl-2-hexenoate [(E)-7n]: syrup; ^{1}H NMR (δ in DMSO-d_6) 0.89 (d, 6H, J = 6.6 Hz), 1.96 (m, 1H), 2.45 (d, 2H, J = 7.2 Hz), 3.67 (s, 3H), 8.00 (s, 1H), 9.97 (br, 1H); IR (film) 3300, 2960, 1730, 1680, 1495 cm^{-1}; EIMS m/z 263/265 (M^+), 231/233, 204/206, 43 (base).

Typical Procedure for the Preparation of Methyl 3-Substituted 3-Bromo-2-isocyanoacrylates (BICA). (Z)-Methyl 3-Bromo-2-isocyano-3-phenylacrylate [(Z)-3a]. $POCl_3$ (1.7 g, 11 mmol) was added dropwise to a solution of (Z)-methyl 3-bromo-2-(formylamino)-3-phenylacrylate [(Z)-**7a**] (2.8 g, 10 mmol) and Et_3N (2.5 g, 25 mmol) in CH_2Cl_2 (30 mL) at −20 °C under vigorous stirring. The mixture was stirred at 0 °C for 2 h and then poured into aqueous K_2CO_3 (3.5 g, 25 mmol, 30 mL). The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was chromatographed on silica gel with $CHCl_3$ as an eluent to give a yellow syrup, which was crystallized from hexane to afford (Z)-**3a** (2.4 g, 79%) as yellow prisms: mp 48−51 °C (AcOEt/hexane); ^{1}H NMR (δ in $CDCl_3$) 3.67 (s, 3H), 7.26−7.43 (m, 5H); IR (KBr) 2120, 1745 cm^{-1}; EIMS m/z 265/267 (M^+), 234/236, 207/209, 127 (base). Anal. Calcd for $C_{11}H_8NO_2Br$: C, 49.65; H, 3.03; N, 5.26. Found: C, 49.46; H, 2.77; N, 5.24.

In the same manner, other BICAs were obtained; yields and melting points are presented in Table 1. Physical properties are as follows:

(E)-Methyl 3-Bromo-2-isocyano-3-phenylacrylate [(E)-3a]: syrup; ^{1}H NMR (δ in $CDCl_3$) 3.92 (s, 3H), 7.3−7.5 (m, 5H); IR (film) 2100, 1740 cm^{-1}; EIMS m/z 265/267 (M^+), 234/236, 207/209, 127 (base).

(Z)-Methyl 3-Bromo-3-(2-chlorophenyl)-2-isocyanoacrylate [(Z)-3b]: mp 84−86 °C (hexane); ^{1}H NMR (δ in $CDCl_3$) 3.65 (s, 3H), 7.20−7.45 (m, 4H); IR (KBr) 2120, 1745 cm^{-1}; EIMS m/z 300 (M^+), 238, 206 (base). Anal. Calcd for $C_{11}H_7NO_2BrCl$: C, 43.96; H, 2.35; N, 4.66. Found: C, 43.76; H, 2.25; N, 4.64.

(E)-Methyl 3-Bromo-3-(2-chlorophenyl)-2-isocyanoacrylate [(E)-3b]: syrup; ^{1}H NMR (δ in $CDCl_3$) 3.92 (s, 3H), 7.20−7.45 (m, 4H); IR (film) 2110, 1740 cm^{-1}; EIMS m/z 300 (M^+), 238, 206 (base).

(Z)-Methyl 3-Bromo-3-(2-bromophenyl)-2-isocyanoacrylate [(Z)-3c]: mp 92−93 °C (hexane); ^{1}H NMR (δ in $CDCl_3$) 3.72 (s, 3H), 7.18−7.35 (m, 3H), 7.64 (dd like, 1H); IR (KBr) 2120, 1740 cm^{-1}; SIMS m/z 346 (M + H), 332, 318, 183 (base). Anal. Calcd for $C_{11}H_7NO_2Br_2$: C, 38.30; H, 2.05; N, 4.06. Found: C, 38.15; H, 2.00; N, 4.06.

(Z)-Methyl 3-Bromo-2-isocyano-3-(3-methylphenyl)-acrylate [(Z)-3d]: syrup; ^{1}H NMR (δ in $CDCl_3$) 2.35 (s, 3H), 3.63 (s, 3H), 7.05−7.24 (m, 4H); IR (film) 2110, 1745 cm^{-1}; EIMS m/z 279/281 (M^+), 248/250, 140 (base).

(Z)-Methyl 3-Bromo-2-isocyano-3-(3-phenoxyphenyl)-acrylate [(Z)-3e]: syrup; ^{1}H NMR (δ in $CDCl_3$) 3.65 (s, 3H), 6.90−7.10 (m, 5H), 7.26−7.40 (m, 4H); IR (film) 2110, 1745 cm^{-1}; EIMS m/z 357/359 (M^+), 127 (base).

(Z)-Methyl 3-Bromo-2-isocyano-3-(4-chlorophenyl)-acrylate [(Z)-3f]: mp 79−81 °C (dec) (hexane); ^{1}H NMR (δ in $CDCl_3$) 3.68 (s, 3H), 7.25 (d, 2H, J = 9.0 Hz), 7.40 (d, 2H, J = 9.0 Hz); IR (Nujol) 2100, 1735cm^{-1}; EIMS m/z 300 (M^+), 238, 206 (base). Anal. Calcd for $C_{11}H_7NO_2BrCl$: C, 43.96; H, 2.35; N, 4.66. Found: C, 43.86; H, 2.30; N, 4.50.

(Z)-Methyl 3-Bromo-2-isocyano-3-(4-methylphenyl)-acrylate [(Z)-3g]: mp 66−68 °C (hexane); ^{1}H NMR (δ in $CDCl_3$) 2.38 (s, 3H), 3.67 (s, 3H), 7.22 (s, 4H); IR (Nujol) 2110, 1730cm^{-1}; EIMS m/z 279/281 (M^+), 248/250, 221/223, 200, 156, 140 (base). Anal. Calcd for $C_{12}H_{10}NO_2Br$: C, 51.45; H, 3.60; N, 5.00. Found: C, 51.31; H, 3.81; N, 4.77.

(Z)-Methyl 3-Bromo-2-isocyano-3-(4-methoxyphenyl)-acrylate [(Z)-3h]: mp 95−97 °C (hexane); ^{1}H NMR (δ in $CDCl_3$) 3.72 (s, 3H), 3.86 (s, 3H), 6.94 (d, 2H, J = 9.0 Hz), 7.34 (d, 2H, J = 9.0 Hz); IR (KBr) 2120, 1730 cm^{-1}; SIMS m/z 296/298 (M + H), 275/277, 91 (base). Anal. Calcd for $C_{12}H_{10}NO_3Br$: C, 48.67; H, 3.40; N, 4.73. Found: C, 48.55; H, 3.44; N, 4.67.

(Z)-Methyl 3-(4-(Benzyloxy)phenyl)-3-bromo-2-isocyanoacrylate [(Z)-3i]: mp 68−70 °C (hexane); ^{1}H NMR (δ in $CDCl_3$) 3.69 (s, 3H), 5.09 (s, 2H), 6.90−7.00 (m, 2H), 7.20−7.50 (m, 7H); IR (KBr) 2120, 1735cm^{-1}; SIMS m/z 372/374 (M + H), 211, 91 (base). Anal. Calcd for $C_{18}H_{14}NO_3Br$: C, 58.08; H, 3.79; N, 3.76. Found: C, 58.31; H, 3.91; N, 3.67.

(Z)-Methyl 3-Bromo-3-(2,4-dichlorophenyl)-2-isocyanoacrylate [(Z)-3j]: syrup; ^{1}H NMR (δ in $CDCl_3$) 3.70 (s, 3H), 7.18−7.30 (m, 2H), 7.35−7.43 (m, 1H); IR (film) 2110, 1735 cm^{-1}; EIMS m/z 335 (M^+), 254, 91 (base).

(Z)-Methyl 3-Bromo-2-isocyano-3-(3,4-(methylenedioxy)phenyl)acrylate [(Z)-3k]: mp 116−118 °C dec (hexane); ^{1}H NMR (δ in $CDCl_3$) 3.70 (s, 3H), 6.01 (s, 2H), 6.80 (s, 3H); IR (Nujol) 2110, 1730 cm^{-1}; EIMS m/z 309/311 (M^+), 230, 170, 59 (base). Anal. Calcd for $C_{12}H_8NO_4Br$: C, 46.48; H, 2.60; N, 4.52. Found: C, 46.31; H, 2.55; N, 4.67.

(E)-Methyl 3-Bromo-2-isocyano-3-(3,4-(methylenedioxy)phenyl)acrylate [(E)-3k]: mp 72−73 °C (hexane); ^{1}H NMR (δ in $CDCl_3$) 3.93 (s, 3H), 6.03 (s, 2H), 6.8−7.25 (m, 3H); IR (Nujol) 2110, 1730 cm^{-1}; EIMS m/z 309/311 (M^+), 230, 170, 59 (base). Anal. Calcd for $C_{12}H_8NO_4Br$: C, 46.48; H, 2.60; N, 4.52. Found: C, 46.41; H, 2.65; N, 4.47.

(Z)-Methyl 3-Bromo-2-isocyano-2-butenoate [(Z)-3l]: syrup; ^{1}H NMR (δ in $CDCl_3$) 2.90 (s, 3H), 3.87 (s, 3H); IR (film) 2120, 1735 cm^{-1}; SIMS m/z (M + H) was not detected, 149 (base).

(Z)-Methyl 3-Bromo-2-isocyano-4-methyl-2-pentenoate [(Z)-3m]: mp 50−51 °C (hexane); ^{1}H NMR (δ in $CDCl_3$) 1.15 (d, 6H, J = 6.5 Hz), 3.88 (s, 3H), 4.10 (q, 1H, J = 6.6 Hz); IR (KBr) 2120, 1735 cm^{-1}; SIMS m/z 233 (M + H), 149, 69 (base). Anal. Calcd for $C_8H_{10}NO_2Br$: C, 41.40; H, 4.34; N, 6.04. Found: C, 41.53; H, 4.42; N, 5.82.

(E)-Methyl 3-Bromo-2-isocyano-4-methyl-2-pentenoate [(E)-3m]: syrup; ^{1}H NMR (δ in $CDCl_3$) 1.17 (d, 6H, J = 6.6 Hz), 3.44 (q, 1H, J = 6.6 Hz), 3.88 (s, 3H); IR (film) 2115, 1745 cm^{-1}; SIMS m/z 233 (M + H), 149, 110, 69 (base).

(Z)-Methyl 3-Bromo-2-isocyano-5-methyl-2-hexenoate [(Z)-3n]: syrup; ^{1}H NMR (δ in $CDCl_3$) 0.97 (d, 6H, J = 6.7 Hz), 2.13 (m, 1H), 3.12 (d, 2H, J = 7.2 Hz), 3.86 (s, 3H); IR (film) 2115, 1735 cm^{-1}; SIMS m/z 246/248 (M + H), 219, 43 (base).

(E)-Methyl 3-Bromo-2-isocyano-5-methyl-2-hexenoate [(E)-3n]: syrup; ^{1}H NMR (δ in $CDCl_3$) 1.02 (d, 6H, J = 6.7 Hz), 2.20 (m, 1H), 2.79 (d, 2H, J = 7.3 Hz), 3.89 (s, 3H); IR (film) 2115, 1745 cm^{-1}; SIMS m/z 246/248 (M + H), 219, 43 (base).

(Z)-Methyl 3-Bromo-4-ethyl-2-isocyano-2-hexenoate [(Z)-3o]: syrup; ^{1}H NMR (δ in $CDCl_3$) 0.82 (t, 6H, J = 7.4 Hz), 1.34–1.74 (m, 4H), 3.56–3.96 (m, 1H), 3.82 (s, 3H); IR (film) 2110, 1735 cm^{-1}; EIMS m/z 259/261 (M^+), 228/230, 91 (base).

Typical Procedure for the Preparation of Methyl 1,5-Disubstituted Imidazole-4-carboxylates. Methyl 1-Benzyl-5-phenylimidazole-4-carboxylate (1aa).[2b] To a mixture of (Z)-methyl 3-bromo-2-isocyano-3-phenylacrylate [(Z)-**3a**] (1.33 g, 5 mmol) and triethylamine (0.55 g, 5 mmol) in DMF (15 mL) was added dropwise benzylamine (0.64 g, 6 mmol) at 25 °C. After stirring was continued for 6 h at the same temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and then extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was chromatographed on silica gel with $CHCl_3$-AcOEt (1:1) as an eluent to give **1aa** as a yellow syrup, which was crystallized from i-Pr_2O to afford **1aa** (2.4 g, 79%) as colorless needles: mp 112–113 °C (AcOEt/i-Pr_2O); ^{1}H NMR (δ in $CDCl_3$) 3.76 (s, 3H), 4.96 (s, 2H), 6.84–7.52 (m, 10H), 7.56 (s, 1H); IR (Nujol) 1700, 1500, 1450, 1350 cm^{-1}; EIMS m/z 292 (M^+), 261, 233, 91 (base). Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.70; H, 5.44; N, 9.50.

In the same manner, other imidazoles (**1**) were obtained; yields are presented in Table 3. Physical properties are as follows:

Methyl 1-[(Methoxycarbonyl)methyl]-5-phenylimidazole-4-carboxylate (1ac): syrup; ^{1}H NMR (δ in $CDCl_3$) 3.71 (s, 3H), 3.77 (s, 3H), 4.56 (s, 2H), 7.29–7.36 (m, 2H), 7.43–7.50 (m, 3H), 7.62 (s, 1H); IR (film) 2900, 1755, 1720, 1500, 1300 cm^{-1}; EIMS m/z 274 (M^+), 243 (base).

Methyl 1-(2-Hydroxyethyl)-5-phenylimidazole-4-carboxylate (1ad): mp 127–129 °C (AcOEt/i-Pr_2O); ^{1}H NMR (δ in $CDCl_3$) 3.67 (s, 3H), 3.74 (br, 2H), 3.93 (t, 2H, J = 5.1 Hz), 5.52 (br, 1H), 7.24–7.35 (m, 2H), 7.41–7.48 (m, 3H), 7.67 (s, 1H); IR (Nujol) 3300, 1700, 1510, 1460 cm^{-1}; EIMS m/z 246 (M^+), 215 (base), 188. Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73; N, 11.38. Found: C, 63.37; H, 5.63; N, 11.28.

Methyl 1,5-Diphenylimidazole-4-carboxylate (1ae): mp 153–155 °C (AcOEt/i-Pr_2O); ^{1}H NMR (δ in $CDCl_3$) 3.83 (s, 3H), 6.98–7.43 (m, 5H), 7.26 (s, 5H), 7.70 (s, 1H); IR (Nujol) 1715, 1500, 1360 cm^{-1}; EIMS m/z 278 (M^+, base), 247, 219. Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.41; H, 4.81; N, 9.92.

Methyl 1-(4-Methoxyphenyl)-5-phenylimidazole-4-carboxylate (1af): mp 179–181 °C (AcOEt); ^{1}H NMR (δ in $CDCl_3$) 3.76 (s, 3H), 3.81 (s, 3H), 6.80 (d, 2H, J = 6.8 Hz), 6.98 (d, 2H, J = 6.8 Hz), 7.19–7.30 (m, 5H), 7.66 (s, 1H); IR (Nujol) 1715, 1520, 1490 cm^{-1}; EIMS m/z 308 (M^+), 277 (base), 248. Anal. Calcd for $C_{18}H_{16}N_2O_3$: C, 70.12; H, 5.23; N, 9.09. Found: C, 69.91; H, 5.13; N, 8.92.

Methyl 5-Phenyl-1-(3,4,5-trimethoxyphenyl)imidazole-4-carboxylate (1ag): mp 146–147 °C (AcOEt/i-Pr_2O); ^{1}H NMR (δ in $CDCl_3$) 3.65 (s, 6H), 3.82 (s, 3H), 3.84 (s, 3H), 6.25 (s, 2H), 7.25–7.36 (m, 5H), 7.76 (s, 1H); IR (Nujol) 1730. 1710, 1600, 1510, 1460 cm^{-1}; EIMS m/z 368 (M^+), 237, 209 (base). Anal. Calcd for $C_{20}H_{20}N_2O_5$: C, 65.21; H, 5.47; N, 7.60. Found: C, 65.10; H, 5.30; N, 7.44.

Methyl 1-(4-Chlorophenyl)-5-phenylimidazole-4-carboxylate (1ah): mp 182–184 °C (AcOEt); ^{1}H NMR (δ in $CDCl_3$) 3.84 (s, 3H), 6.99–7.06 (d-like, 2H), 7.21–7.35 (m, 7H), 7.72 (s, 1H); IR (Nujol) 1720, 1550, 1495 cm^{-1}; EIMS m/z 312 (M^+), 281 (base), 253. Anal. Calcd for $C_{17}H_{13}N_2O_2Cl$: C, 65.29; H, 4.19; N, 8.96. Found: C, 65.29; H, 3.96; N, 8.86.

Methyl 1-Benzyl-5-(4-chlorophenyl)imidazole-4-carboxylate (1fa): mp 190–192 °C (AcOEt); ^{1}H NMR (δ in $CDCl_3$) 3.79 (s, 3H), 4.98 (s, 2H), 6.91–6.96 (m, 2H), 7.19 (d, 2H, J = 8.6 Hz), 7.26–7.30 (m, 3H), 7.38 (d, 2H, J = 8.6 Hz), 7.61 (s, 1H); IR (Nujol) 1705, 1485, 1355 cm^{-1}; EIMS m/z 326 (M^+), 295, 268, 91 (base). Anal. Calcd for $C_{18}H_{15}N_2O_2Cl$: C, 66.16; H, 4.63; N, 8.57. Found: C, 65.92; H, 4.57; N, 8.34.

Methyl 1-Benzyl-5-(4-methylphenyl)imidazole-4-carboxylate (1ga): mp 110–112 °C (AcOEt/hexane); ^{1}H NMR (δ in $CDCl_3$) 2.36 (s, 3H), 3.76 (s, 3H), 4.95 (s, 2H), 6.88–6.98 (br-m, 2H), 7.17 (s, 5H), 7.24–7.30 (m, 2H), 7.54 (s, 1H); IR (Nujol) 1700, 1500, 1350 cm^{-1}; EIMS m/z 306 (M^+), 275, 247, 91 (base). Anal. Calcd for $C_{19}H_{18}N_2O_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.45; H, 5.88; N, 8.94.

Methyl 5-Isopropyl-1-phenylimidazole-4-carboxylate (1me): mp 119–122 °C (AcOEt/hexane); ^{1}H NMR (δ in $CDCl_3$) 1.27 (d, 6H, J = 7.1 Hz), 3.30 (m, 1H, J = 7.1 Hz), 3.93 (s, 3H), 7.26–7.33 (m, 2H), 7.44 (s, 1H), 7.49–7.57 (m, 3H) ; IR (Nujol) 2970, 1705, 1545, 1500, 1330 cm^{-1}; EIMS m/z 244 (M^+), 212 (base), 197, 183. Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.73; H, 6.60; N, 11.50.

Methyl 5-Isopropyl-1-(1-phenylethyl)imidazole-4-carboxylate (1mj): mp 126–128 °C (AcOEt/hexane); ^{1}H NMR (δ in $CDCl_3$) 1.13 and 1.31 (d each, 3H each, J = 7.1 Hz), 1.90 (d, 3H, J = 7.1 Hz), 3.37 (m, 1H) 3.89 (s, 3H), 5.45 (q, 1H, J = 7.1 Hz), 7.02–7.06 (m, 2H), 7.26–7.39 (m, 3H), 7.54 (s, 1H); IR (KBr) 3095, 2945, 1715, 1540, 1330 cm^{-1}; EIMS m/z 272 (M^+), 241, 167, 105 (base). Anal. Calcd for $C_{16}H_{20}N_2O_2$: C, 70.56; H, 7.40; N, 10.29. Found: C, 70.43; H, 7.33; N, 10.50.

Methyl 5-Isobutyl-1-(1-phenylethyl)imidazole-4-carboxylate (1nj): syrup; ^{1}H NMR (δ in $CDCl_3$) 0.92 (d, 6H, J = 6.6 Hz), 1.88 (d, 3H, J = 7.1 Hz), 1.86 (m, 1H), 2.79 (ABq-like, 2H), 3.88 (s, 3H), 5.35 (q, 1H, J = 7.1 Hz), 7.02–7.06 (m, 2H), 7.29–7.39 (m, 3H), 7.58 (s, 1H); IR (film) 2960, 1705, 1555, 1495 cm^{-1}; SIMS m/z 287 (M + H), 255, 183, 151, 105 (base).

Methyl 5-Isobutyl-1-(2-pyridylmethyl)imidazole-4-carboxylate (1nk): syrup; ^{1}H NMR (δ in $CDCl_3$) 0.91 (d, 6H, J = 6.6 Hz), 1.89 (m, 1H), 2.80 (d, 2H, J = 7.5 Hz), 3.89 (s, 3H), 5.24 (s, 2H), 6.80 (d, 1H, J = 7.8 Hz), 7.25 (dd like, 1H), 7.66 (ddd like, 1H), 8.60 (dd like, 1H); IR (film) 2960, 1710, 1560, 1510, 1435 cm^{-1}; EIMS m/z 273 (M^+), 258, 230, 93 (base).

Methyl 5-(1-Ethylpropyl)-1-phenylimidazole-4-carboxylate (1oe): syrup; ^{1}H NMR (δ in $CDCl_3$) 0.74 (t, 6H, J = 7.4 Hz), 1.64 and 1.84 (m, 2H each), 2.84 (br, 1H), 3.91 (s, 3H), 7.23–7.29 (m, 2H), 7.46 (s, 1H), 7.48–7.55 (m, 3H); IR (film) 2950, 1710, 1505, 1460 cm^{-1}; EIMS m/z 272 (M^+), 257, 240, 225, 211 (base).

Methyl 5-(1-Ethylpropyl)-1-methylimidazole-4-carboxylate (1ol): syrup; ^{1}H NMR (δ in $CDCl_3$) 0.72 (t, 6H, J = 7.4 Hz), 1.73 (m, 4H), 3.22 (br, 1H), 3.57 (s, 3H), 3.79 (s, 3H), 7.26 (s, 1H); IR (film) 2950, 1710, 1520, 1370 cm^{-1}; EIMS m/z 210 (M^+), 195, 163 (base).

Mechanistic Study of the Reaction of Methyl 3-Bromo-2-isocyano-3-phenylacrylate (3a) with Benzylamine. Typical Procedure: To a mixture of (Z)-**3a** (1.33 g, 5 mmol) and triethylamine (0.55 g, 5 mmol) in DMF (15 mL) was added dropwise benzylamine (0.54 g, 5 mmol) at 25 °C. After stirring was continued for 24 h at the same temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and then extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was chromatographed on silica gel with $CHCl_3$-AcOEt (4:1 to 1:1) as an eluent to give (E)-Methyl 3-benzylamino-2-isocyano-3-phenylacrylate [(E)-**2aa**] (0.26 g, 20%) as a yellow syrup and methyl 1-benzyl-5-phenylimidazole-4-carboxylate (**1aa**) as a yellow syrup which was crystallized from i-Pr_2O to afford **1aa** (0.85 g, 65%) as colorless needles: mp 112–113 °C (AcOEt/i-Pr_2O). [(E)-**2aa**]: ^{1}H NMR (δ in $CDCl_3$) 3.83 (s, 3H), 4.20 (d, 2H, J = 6.3 Hz), 7.07–7.11 (m, 2H), 7.26–7.37 (m, 5H), 7.46–7.50 (m, 3H), 9.51 (br-s, 1H); IR (film) 3230, 2120, 1660 cm^{-1}; EIMS m/z 292 (M^+), 261, 233, 91 (base).

Reaction of Methyl 3-(Benzylamino)-2-isocyano-3-phenylacrylate [(E)-2aa] with a Base. Typical Procedure: To a solution of (E)-**2aa** (292 mg, 1 mmol) in DMF (15 mL) was added dropwise DBU (152 mg, 1 mmol) at 25 °C. After stirring was continued for 0.5 h at the same temperature, the reaction mixture was poured into saturated aqueous $NaHCO_3$ and then extracted with AcOEt. The organic layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was chromatographed on silica gel with $CHCl_3$–AcOEt (1:1) as an eluent to give methyl 1-benzyl-5-phenylimidazole-4-carboxylate (**1aa**) as a yellow syrup, which was crystallized from i-Pr_2O to afford **1aa** (280 mg, 96%) as colorless needles: mp 112–113 °C (AcOEt/i-Pr_2O).

1-Benzyl-5-phenylimidazole-4-carboxylic acid (8a). A mixture of methyl 1–benzyl-5-phenylimidazole-4-carboxylate (**1aa**) (2.92 g, 10 mmol) and NaOH (1.2 g, 30 mmol) in MeOH–

H_2O (1:1, 50 mL) was stirred for 18 h at rt. The reaction mixture was neutralized with $KHSO_4$ and then extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was crystallized from MeOH/H_2O to afford **8a** (2.64 g, 95%) as colorless needles: mp >230 °C (MeOH/H_2O); ^1H NMR (δ in DMSO-d_6) 5.07 (s, 2H), 6.82–6.89 (m, 2H), 7.22–7.26 (m, 5H), 7.35–7.40 (m, 3H), 7.96 (s, 1H), 12.9 (br, 1H); IR (KBr) 3120, 2500(br), 1705, 1495, 1220 cm^{-1}; EIMS m/z 278 (M^+), 233, 91 (base). Anal. Calcd for $C_{17}H_{14}N_2O_2$: C, 73.37; H, 5.07; N, 10.07. Found: C, 73.35; H, 5.22; N, 10.04.

1-Benzyl-5-phenylimidazole (9a). A suspension of 1-benzyl-5-phenylimidazole-4-carboxylic acid (**8a**) (2.0 g, 7.2 mmol) in DMA (20 mL) was refluxed for 3 h. The reaction mixture was poured into water and then extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The resulting oil was chromatographed on silica gel with $CHCl_3$–MeOH (20:1) as an eluent to give **9a** as a yellow syrup, which was crystallized from hexane to afford **9a** (1.14 g, 68%) as colorless prisms: mp 112–113 °C (AcOEt/hexane) (lit.[20] mp 111 °C); ^1H NMR (δ in $CDCl_3$) 5.16 (s, 2H), 7.01–7.05 (m, 2H), 7.17 (s, 1H), 7.26–7.40 (m, 8H), 7.65 (s, 1H); IR (KBr) 3450(br), 1495, 1480, 1455, 1240 cm^{-1}; EIMS m/z 234 (M^+), 91 (base). Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 81.87; H, 6.23; N, 11.85.

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