

Facile One-Pot Syntheses of Amidines and Enamines from Oximes via Beckmann Rearrangement Using Trifluoromethanesulfonic Anhydride

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Iminocarbocation intermediates were in situ-generated by treating various oximes with trifluoromethanesulfonic anhydride (Tf_2O) in the presence of triethylamine in toluene and nucleophilic trapping with amines or sodium enolates under mild conditions afforded the corresponding amidines and enamines. Some of the thus-obtained enamines were converted to 2-substituted 4-oxo-3-quinolinecarboxylic acid derivatives by subsequent intramolecular Friedel–Crafts acylation.

The Beckmann rearrangement is one of the most fundamental and frequently employed tools in organic synthesis for the construction of nitrogen-containing skeletons, such as amides or lactams.[1] Since this rearrangement was first discovered by Beckmann in 1886,[2] many useful modified methods have been developed and their reaction mechanisms have been studied in detail. The Beckmann rearrangement usually proceeds by treating oximes or oxime sulfonates with acids, including Lewis acids, such as hydrochloric acid,[1] sulfuric acid,[1] polyphosphoric acid,[3] formic acid, and boron trifluoride,[1] or dehydrating agents, such as phosphoryl chloride,[1] oxalyl chloride,[4] phosgene,[4] phosphorus pentachloride,[1] thionyl chloride,[1] and 1,1′-carbonyldiimidazole,[5] to form amides or lactams. The mechanism of the Beckmann rearrangement can be explained by considering the initial formation of an electron-deficient nitrogen atom by a partial ionization of the oxygen–nitrogen bond of the oxime along with a simultaneous intramolecular migration of the group anti to the departing hydroxy group to produce the iminocarbocation, which is then converted to the corresponding amides or lactams by a subsequent treatment with water. On the other hand, it was also known that α-alkylated amines are formed via imines,[6] amidines,[7] thioimidates,[8] imidoyl iodides,[9] iminonitriles,[8] aminophosphonates,[10] and enaminones[11] by trapping the iminocarbocation intermediates formed from oximes or oxime sulfonates via the Beckmann rearrangement with various nucleophiles. For example, amidines were synthesized by trapping iminocarbocations formed by the Beckmann rearrangement of oximes,[12,13] oxime sulfonates,[7] oxime carbonates,[1] and oxime phosphonates[14] with primary or secondary amines. Also, there are some reports on the formations of amines[6] or enamines[11] by trapping the intermediates with the carbon nucleophiles. In some cases, however, these reported procedures required the isolation of oxime sulfonates, or their products were obtained in low yields because of the high reaction temperature. Then, the Beckmann rearrangement of oximes having a strong leaving groups such as trifluoromathanesulfonate, was considered to proceed smoothly under mild condition to produce the carbocation intermediate; however, there have been no examples reported on the reaction to trap the iminocarbocation intermediates with amines or carbon nucleophiles.[15]

A preliminary result on the syntheses of amidines and enamines by trapping the iminocarbocation intermediates of the Beckmann rearrangement derived from oximes was reported in a previous communication.[16] After screening the reaction conditions of the above-mentioned reaction, various oximes were found to react smoothly with trifluoromethanesulfonic anhydride under mild conditions to generate the iminocarbocations via the Beckmann rearrangement, and successive reactions with amines or carbon nucleophiles afforded the amidines or enamines. Some of the thus-formed enamines were converted to 2-substituted 4-oxo-3-quinolinecarboxylic acid derivatives that possessed antibacterial activities[17] by the subsequent intramolecular Friedel–Crafts acylation.[18] Here, we would like to describe in detail the facile one-pot syntheses of amidines and enamines by trapping iminocarbocation intermediates formed in situ by the Beckmann rearrangement of oximes with amines or carbon nucleophiles.

Results and Discussion

Syntheses of Amidines. In the first place, the formation of amidine was tried by trapping the carbocation intermediate generated by the Beckmann rearrangement of benzophenone oxime with trifluoromethanesulfonic anhydride and *N*-methylaniline. The iminocarbocation intermediate was generated by adding trifluoromethanesulfonic anhydride to the benzophenone oxime in the presence of triethylamine in toluene at -78 °C. After stirring the mixture for 5 min, *N*-methylaniline was added and the reaction mixture was slowly warmed up to room temperature. After an aqueous work up, *N*-methyl-*N*,*N*′-diphenylbenzamidine was obtained in 95% yield. Similarly, various amidines were prepared by the above-mentioned one-pot procedure from the corresponding oximes. For example, a treatment of benzophenone with aliphatic amines, such as *N*-methylbenzylamine or morpholine, gave the corresponding amidines in good yields (Table 1, Entries 2 and 3). In the

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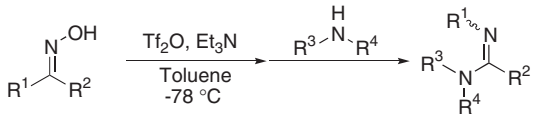
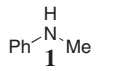
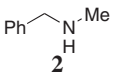
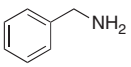
Table 1. Syntheses of Amidines by Trapping with Amines



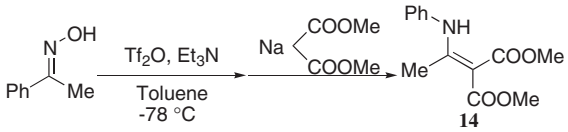
Entry	R^1	R^2	R^3R^4NH	Product	Yield/%[a,b]
1	Ph	Ph	 **1**	**3**	95[c]
2	Ph	Ph	 **2**	**4**	99
3	Ph	Ph		**5**	87
4	Ph	Me	**1**	**6**	89
5	Ph	Me	**2**	**7**	86
6	Ph	Me		**8**	60
7	Ph	Me		**9**	38
8	Me	Me	**1**	**10**	93
9	Et	Et	**1**	**11**	99
10			**2**	**12**	99
11	–$(CH_2)_5$–		**1**	**13**	83

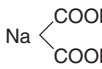
a) Isolated yields. b) All products were obtained as a single isomer and the geometry of them were not determined. c) The yield was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

case of acetophenone oxime, the reaction proceeded to give the corresponding amidines in good yields by trapping the carbocation intermediates with secondary amines (Table 1, Entries 4 and 5), while the desired products were obtained in low-to-moderate yields when the primary amines were used. This was probably because the produced amidines also reacted as nucleophiles with iminocarbocation intermediates (Table 1, Entries 6 and 7). Although aliphatic oximes are generally considered to be less reactive, they reacted smoothly while also giving the desired products in high yields (Table 1, Entries 8–10). According to this procedure, the yield of the rearranged product of cyclic oxime was improved compared with those by the conventional methods (Table 1, Entry 11).[7]

Syntheses of Enamines. Next, the trapping of iminocarbocation intermediates with carbon nucleophiles, such as sodium enolates, was tried in order to established a new method for the formation of enamines by a one-pot procedure: that is, an in-situ formation of iminocarbocations by a Beckmann rearrangement of oximes, and a successive reaction of the thus-formed carbocations with carbon nucleophiles afforded the enamines under mild conditions. A similar example was reported by Yamamoto and co-workers in which enamines were obtained from oxime sulfonates and enol silyl ethers by using a Lewis acid, such as diethylaluminum chloride.[11] In the present experiment, the carbocation intermediate was formed from acetophenone and 1.5 equivalents of trifluoromethanesulfonic anhydride in the presence of 2.0 equivalents of triethylamine in toluene at −78 °C. After stirring the mixture for 5 min, 2.0 equivalents of sodium enolate of dimethyl malonate dissolved in tetrahydrofuran were added and the reaction mixture was slowly warmed up to room temperature. After an aqueous work-up, the desired enamine was obtained in 41% yield. Next, the effect of the amount of nucleophile on the yield was studied and the enamine turned out to be obtained in 3% yield only when 1.5 equivalents of nucleophile were used. When 3.0 equivalents of nucleophile were used (Table 2), on the other hand, the desired product was obtained in high yield. After screening the effect of still other solvents, such as dichloromethane, acetonitrile, hexane, ethyl acetate, *N*,*N*-dimethylformamide, and diethyl ether, on the above model reaction, toluene and diethyl ether were found to be effective, and the desired products were obtained in high yield (Table 3, Entries 7 and 8). Regarding the effects of the bases, the generation of an iminocarbocation intermediate and facile trapping with carbon nucleophiles were examined in the presence of several organic and inorganic bases in toluene or diethyl ether. Then, the desired enamines were obtained in low yields when pyridine was used (Table 4, Entries 3 and 8). In the case with potassium carbonate, the rearranged products were obtained in 67% yield (toluene) and 49% (ether), respectively (Table 4, Entries 4 and 9). The desired product was obtained in high yield when triethylamine was used in toluene (Table 4, Entry 1). On the other hand, the reaction did not proceed at all, and no products were obtained when other dehydrating agents, such as trifluoroacetic anhydride, toluenesulfonic anhydride, toluenesulfonyl chloride, *p*-nitrotoluenesulfonyl chloride, methanesulfonic anhydride, and methanesulfonyl chloride, were used in place of trifluoro-

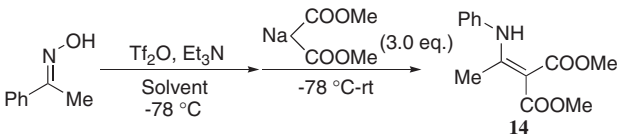
Table 2. Amount of Nucleophile



Entry	Nucleophile	Equivalent	Yield/%[a]
1		1.5	3[b]
2		2.0	41
3		3.0	96

a) Isolated yields. b) The yield was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

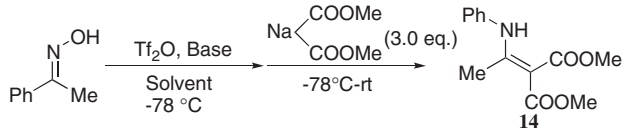
Table 3. Effects of Solvents



Entry	Solvent	Yield/%[a]	Entry	Solvent	Yield/%[a]
1	CH_2Cl_2	53	5	DMF	ND
2	CH_3CN	50[b]	6	THF	58
3	Hexane	41	7	Toluene	96
4	AcOEt	65	8	Et_2O	91

a) Isolated yields. b) Reaction was proceeded at −50 °C.

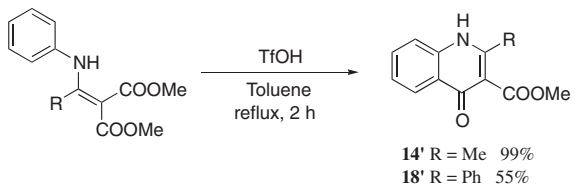
Table 4. Effect of Bases



14

Entry	Solvent	Base	Yield/%[a]
1	Toluene	Et_3N	96
2	Toluene	$^iPr_2EtN$	72
3	Toluene	Pyridine	8[b]
4	Toluene	K_2CO_3	67
5	Toluene	DBU	18[b]
6	Et_2O	Et_3N	91
7	Et_2O	$^iPr_2EtN$	66
8	Et_2O	Pyridine	37[b]
9	Et_2O	K_2CO_3	49
10	Et_2O	DBU	19

a) Isolated yields. b) The yield was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.



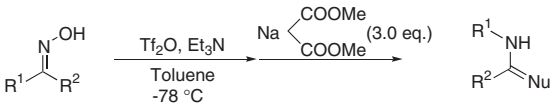
Scheme 1.

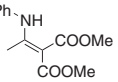
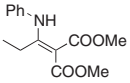
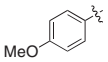
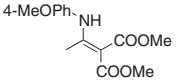
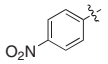
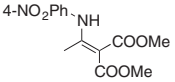
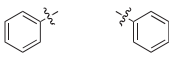
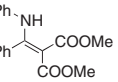
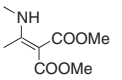
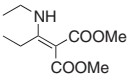
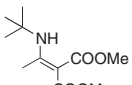
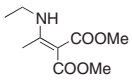
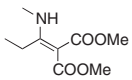
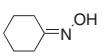
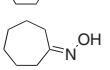
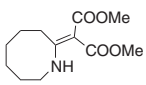
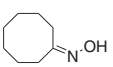
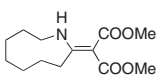
methanesulfonic anhydride shown in the above reaction.

The reaction was further examined by using various aromatic and aliphatic oximes (Table 5). As a result, the reactions smoothly proceeded to afford the corresponding enamines in good-to-high yields under mild conditions. When aromatic oximes having electron-donating or electron-withdrawing groups were used, the desired products were obtained in excellent yields (Table 5, Entries 3 and 4). The reaction of aliphatic oximes gave the corresponding oximes in good yields (Table 5, Entries 6, 7, and 8). When an *EZ* mixture of butanone oxime was used, the corresponding enamines were obtained in 89% yields as a mixture of **22a** formed by the migration of the ethyl group of oxime to nitrogen, and **22b** formed by the migration of the methyl group of oxime to nitrogen (Table 5, Entry 9). Concerning the cyclic oximes, seven- and eight-membered ring oximes gave the corresponding enamines in good yields while no products were obtained when six-membered ring oxime was used (Table 5, Entries 10–12). It was thus considered that the thus-obtained enamines would be converted to 2-substituted 4-oxo-3-quinolinecarboxylic acid derivatives that possess antibacterial activities by the subsequent intramolecular Friedel–Crafts acylation. Actually, the intramolecular Friedel–Crafts acylation of **14** and **18** proceeded to afford cyclized **14′** and **18′**, respectively, by treating with 2.0 equivalents of trifluoromethanesulfonic acid in refluxing toluene for two hours (Scheme 1).

Next, the reaction of the iminocarbocation intermediate derived from acetophenone oxime with various sodium enolates was tried. The iminocarbocation intermediates were smoothly

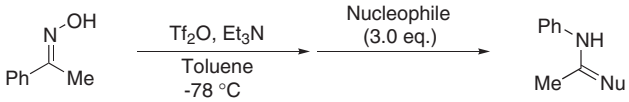
Table 5. Syntheses of Enamines by Trapping with Carbon Nucleophiles

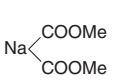
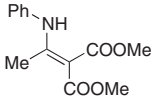
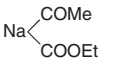
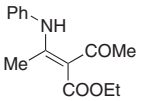
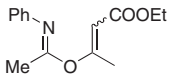
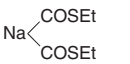
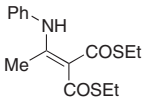
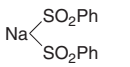
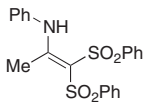
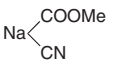
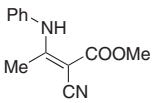
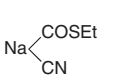
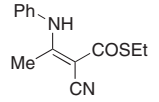
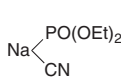
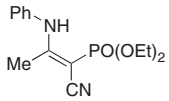
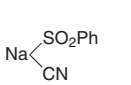
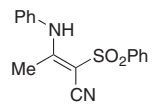
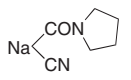
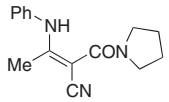
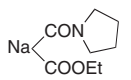
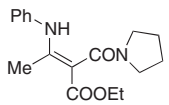
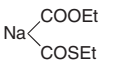
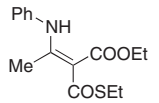


Entry	R^1	R^2	Product	Yield/%[a]
1		Me	 **14**	96
2		Et	 **15**	84
3		Me	 **16**	95
4		Me	 **17**	95
5			 **18**	81
6	Me	Me	 **19**	78
7	Et	Et	 **20**	73
8		Me	 **21**	84[b]
9	 *E*/*Z* = 74/26		 **22a**  **22b**	89[b,c]
10			—	ND
11			 **23**	74
12			 **24**	60[b]

a) Isolated yields. b) The yield was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. c) The proportion of product was **22a**/**22b** = 77/23.

Table 6. Syntheses of Enamines by Trapping with Carbon Nucleophiles



Entry	Nucleophile	Product	Yield/%[a]
1		 **14**	96
2		 **25a**  **25b**	94[b]
3		 **26**	99
4		 **27**	83
5		 **28**	99
6		 **29**	78[c]
7		 **30**	50
8		 **31**	69[c]
9		 **32**	89
10		 **33**	99[c]
11		 **34**	74[d]

a) Isolated yields. b) The proportion of product was C(**25a**)/O(**25b**) = 71/29. c) The yield was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. d) The proportion of product was 31/69.

trapped by the nucleophiles to afford the corresponding enamines in good-to-high yields (Table 6). In the case of using sodium enolate of the β-keto ester for a nucleophile, a mixture of *C*- and *O*-alkylated products was obtained in 94% combined yield (Table 6, Entry 2). The reaction smoothly proceeded when nucleophiles, such as sodium enolates of dithiomalonic acid di-*S*-ethyl ester and bis(phenylsulfonyl)methane, were used, and the desiresd products were obtained in high yields (Table 6, Entries 3 and 4). When the sodium enolates of methyl cyanoacetate, cyanothioacetic acid *S*-ethyl ester, cyanomethylphosphonic acid diethyl ester, benzenesulfonylacetonitrile, and 3-oxo-3-pyrrolidine-1-yl-propiononitrile were used, the corresponding enamines were obtained as a single product in moderate-to-high yield, respectively (Table 6, Entries 5–9). Similarly, a single product was obtained in the case of ethyl 3-oxo-3-pyrrolidin-1-ylpropanoate, though its geometry has not yet been determined (Table 6, Entry 10). The reaction of *O*,*S*-diethyl monothiomalonate gave a mixture of two isomers, which were not separated by thin-layer chromatography (Table 6, Entry 11). Next, the trapping of an iminocarbocation intermediate, derived from less reactive acetoxime with various carbon nucleophiles, was examined, and the reaction turned out to proceed smoothly and afforded the corresponding enamines as a single product in moderate-to-high yields (Table 7). Furthermore, when phenylsulfonylacetonitrile was employed as a nucleophile together with DBU, the desired product was obtained in 72% yield (Table 7, Entry 3).

In the case of using ketone enolates, the yields of the corresponding products were low (Table 8). When sodium enolates derived from several ketones were used, the desired products were obtained in yields of between 14 to 35% (Table 8, Entries 2, 7, and 8). In the case of lithium enolate, the product was obtained in only 20% yield (Table 8, Entry 4), while still no products were obtained when the other metal enolates and ammonium enolate, such as potassium and tetrabutyl ammonium, were used.

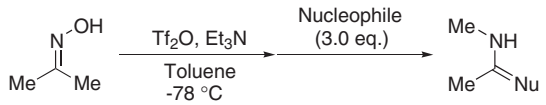
A proposed reaction mechanism is shown in Scheme 2. Initially, the oxime was activated with trifluoromethanesulfonic anhydride to form a reactive oxime trifluoromethanesulfonate (1). The successive elimination of a triflate anion from (1) caused a rearrangement of R^1 to the nitrogen atom to form iminocarbocation (2), which in turn was trapped with amine to give the corresponding amidine (3), or imine (4) upon a treatment with a carbon nucleophile, such as sodium malonate. The

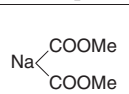
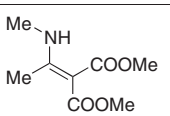
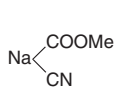
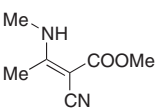
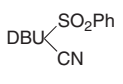
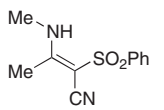
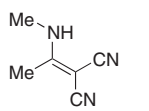
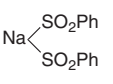
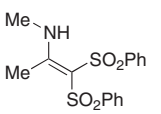
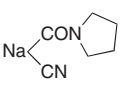
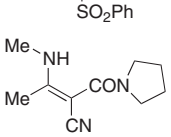
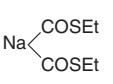
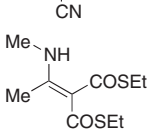
thus-formed imine (4) was converted to enamine (5) via 1,3-proton-shift. The geometry of enamines such as **28**, **29**, **30**, **31**, **32**, **35**, **36**, and **39** was determined by observations of the broadened signal in the lower magnetic field (9.78–12.4 ppm) due to the hydrogen-bonded NH proton in the ^{1}H NMR spectra of the products.

Conclusion

A new and efficient method for the one-pot syntheses of amidines and enamines was established by trapping iminocarbocation intermediates, generated in situ via a Beckmann rearrangement of ketoximes using trifluoromethanesulfonic anhydride, with amines and carbon nucleophiles under mild conditions without using Lewis acids. Some enamines formed by the above reactions were converted to 2-substituted 4-oxo-3-quinolinecarboxylic acid derivatives upon a treatment with trifluoromethanesulfonic acid.

Table 7. Syntheses of Enamines by Trapping with Carbon Nucleophiles



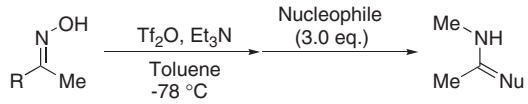
Entry	Nucleophile	Product		Yield/%[a]
1			**19**	78
2			**35**	99
3			**36**	72
4			**37**	71
5			**38**	57
6			**39**	70
7			**40**	49[b]

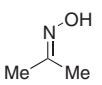
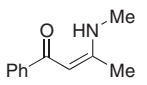
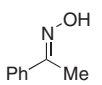
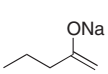
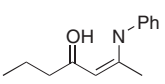
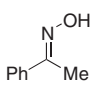
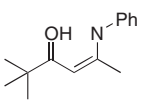
a) Isolated yields. b) The yield was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

Experimental

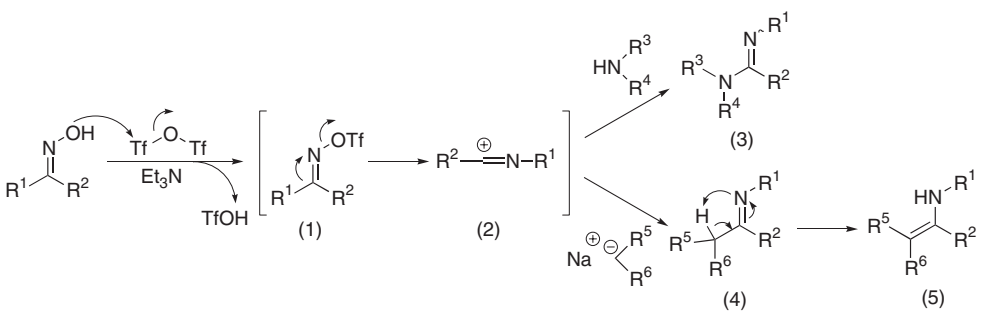
General. All of the melting points were determined on a Yanagimoto micro melting-point apparatus (Yanaco MP-S3) and were uncorrected. Infrared (IR) spectra were recorded on a Horiba FT 300 FT-IR spectrometer. ^{1}H NMR spectra were recorded on a JEOL EX270 (270 MHz) spectrometer; chemical shifts (δ) are reported in parts per million relative to tetramethylsilane. Splitting

Table 8. Syntheses of Enamines by Trapping with Carbon Nucleophiles



Entry	Oxime	Nucleophile	Product	Yield/%[a]
1				18
2				30[b]
3				30[c,d]
4				20
5			**41**	ND
6				ND
7			 **42**	14
8			 **43**	35[d]

a) Isolated yields. b) 4.0 eq. of nucleophile was used. c) 5.0 eq. of nucleophile was used. d) The yield was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.



Scheme 2.

patterns are designed as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C NMR spectra were recorded on a JEOL EX270 (68 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million relative to tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$; δ 77.0). High-resolution mass spectra (HRMS) were recorded on a JEOL-700T mass spectrometer. Elemental analysis were performed on vario EL III (elementar), DX-500 (DIONEX), and UV2200 (SHIMADZU). Analytical TLC was performed on Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm). Silica-gel columm chromatography was carried out on a Merck silica gel 60 (0.063–0.200 mm). Preparative thin-layer chromatography (PTLC) was carried out on a silica-gel Wacogel B-5F. Solvents were freshly distilled when dry solvents were needed. Some oximes were purchased from Tokyo Kasei Kogyo, Kanto Chemical, Aldrich Chemical or Merck, and were used after purification by distillation or recrystallization. Other oximes were prepared according to literature procedures.[19]

General Procedure for Syntheses of Amidines (Table 1). To a solution of benzophenone oxime (0.25 mmol) and triethylamine (0.50 mmol) in toluene (3.0 mL) was added a trifluoromethanesulfonic anhydride (0.38 mmol) under an argon atmosphere at −78 °C. After stirring for 5 min, *N*-methylaniline (0.50 mmol) was added and the reaction mixture was slowly warmed up to room temperature. After stirring for 1 h, the reaction mixture was quenched with water (5.0 mL), and the aqueous layer was extracted with ethyl acetate (30 mL). The organic layer was dried (Na_2SO_4), filtrated and evaporated, and the resulting residue was purified by preparative TLC to afford *N*-methyl-*N*,*N*′-diphenylbenzamidine (**3**)[7] in 95% yield as a colorless oil: IR (neat, cm^{-1}) 3910, 3424, 2360, 1581, 1357, 694; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.57 (s, 3H), 6.61 (d, $J = 7.8$ Hz, 2H), 6.77 (t, $J = 7.3$ Hz, 1H), 6.97–7.14 (m, 12H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 40.2, 121.1, 122.7 (×2), 124.9, 126.9 (×2), 127.4 (×2), 128.0, 128.1 (×2), 128.5 (×2), 130.1 (×2), 133.3, 146.0, 150.5, 159.4.

***N*-Benzyl-*N*-methyl-*N*′-phenylbenzamidine (4):** Colorless oil; IR (neat, cm^{-1}) 3023, 2915, 2360, 1581, 1072; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.90 (br, 3H), 4.45 (br, 2H), 6.54–6.57 (m, 2H), 6.65–6.71 (m, 1H), 6.91–6.99 (m, 2H), 7.08–7.35 (m, 10H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 35.9, 53.8, 120.76, 122.84 (×2), 127.0 (×2), 127.3, 127.9 (×2), 128.0 (×2), 128.3, 128.4 (×2), 128.7 (×2), 133.5, 138.0, 151.1, 160.8; HRMS (FAB) Calcd for $C_{21}H_{21}N_2$: $[M + H]^+$ 301.1699. Found: m/z 301.1705.

***N*-(α-Morpholin-4-ylbenzylidene)aniline (5):**[14] White solid; mp 85–87 °C; IR (KBr, cm^{-1}) 3880, 3718, 3208, 2715, 2591, 1866; ^{1}H NMR (270 MHz, $CDCl_3$) δ 3.47 (br, 4H), 3.76 (t, $J =$ 4.9 Hz, 4H), 6.58 (dd, $J = 8.2$, 1.0 Hz, 2H), 6.76 (t, $J = 7.4$ Hz, 1H), 7.01 (t, $J = 7.6$ Hz, 2H), 7.11–7.15 (m, 2H), 7.22–7.27 (m, 3H); ^{13}C NMR (68 MHz, C_6D_6) δ 66.7 (×4), 121.6, 123.1 (×2), 127.6 (×2), 128.0 (×2), 128.6 (×2), 129.3, 133.6, 151.6, 160.2.

***N*-Methyl-*N*,*N*′-diphenylacetamidine (6):**[14] Colorless oil; IR (neat, cm^{-1}) 3964, 3617, 3563, 1581, 1373, 694; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.67 (s, 3H), 3.33 (s, 3H), 6.75 (d, $J = 7.7$ Hz, 2H), 6.91 (t, $J = 7.3$ Hz, 1H), 7.13–7.56 (m, 7H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 16.9, 39.5, 122.0, 122.2, 125.9, 126.5, 127.4, 128.3, 128.7 (×2), 129.0, 129.3 (×2), 146.0, 160.2.

***N*-Benzyl-*N*-methyl-*N*′-phenylacetamidine (7):**[20] Colorless oil; IR (neat, cm^{-1}) 3903, 2360, 2329, 1612, 1481, 1226, 732; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.88 (s, 3H), 2.98 (s, 3H), 4.62 (s, 2H), 6.72 (d, $J = 7.3$ Hz, 2H), 6.91 (t, $J = 6.5$ Hz, 1H), 7.18–7.35 (m, 7H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 15.0, 36.1, 53.2, 121.3, 122.3 (×2), 125.8, 126.8, 126.9, 128.5 (×2), 128.6 (×2), 138.3, 151.8, 156.9.

***N*,*N*′-Diphenylacetamidine (8):**[21] White solid; mp 133–134 °C; IR (neat, cm^{-1}) 3433, 3401, 3356, 3000, 1712, 1365, 1219; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.92 (s, 3H), 6.95–7.00 (m, 2H), 7.14–7.27 (m, 8H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 18.8, 121.0, 122.6, 128.8, 145.1, 152.4.

***N*-Benzyl-*N*′-phenylacetamidine (9):** Colorless oil; IR (neat, cm^{-1}) 3433, 3401, 3356, 3000, 1712, 1365, 1219; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.82 (br, 3H), 4.50 (br, 2H), 6.79 (d, $J = 7.6$ Hz, 2H), 6.93–6.99 (m, 1H), 7.21–7.35 (m, 7H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.7, 45.8, 121.9 (×2), 122.1 (×2), 127.2 (×2), 127.9, 128.5 (×2), 128.7, 138.9, 151.2, 155.1; HRMS (FAB) Calcd for $C_{15}H_{17}N_2$: $[M + H]^+$ 225.1386. Found: m/z 225.1405.

***N*,*N*′-Dimethyl-*N*-phenylacetamidine (10):**[22] Colorless oil; IR (neat, cm^{-1}) 3679, 2352, 1643, 1272, 1164; ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.05 (s, 3H), 3.19 (s, 3H), 3.50 (s, 3H), 7.25 (d, $J = 5.6$ Hz, 2H), 7.39–7.50 (m, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 16.6, 31.6, 40.9, 126.2 (×2), 129.5, 130.5 (×2), 142.5, 164.8.

***N*′-Ethyl-*N*-methyl-*N*-phenylpropionamidine (11):** Colorless oil; IR (neat, cm^{-1}) 3224, 3170, 2352, 1635, 1272, 1257; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.04 (t, $J = 7.7$ Hz, 3H), 1.38 (t, $J = 7.3$ Hz, 3H), 2.36 (q, $J = 7.7$ Hz, 2H), 3.47 (s, 3H), 3.51–3.61 (m, 2H), 7.22–7.25 (m, 2H), 7.42–7.47 (m, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 10.8, 15.0, 21.9, 40.3, 41.3, 126.2 (×2), 129.7, 130.4 (×2), 141.9, 167.4; HRMS (FAB) Calcd for $C_{12}H_{19}N_2$: $[M + H]^+$ 191.1543. Found: m/z 191.1547.

***N*-Benzyl-*N*′-ethyl-*N*-methylpropionamidine (12):** Colorless oil; IR (neat, cm^{-1}) 3540, 2360, 1241, 1157, 1033; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.11–1.21 (m, 6H), 2.56 (q, $J = 7.8$ Hz, 2H), 3.03 (s, 3H), 3.41 (q, $J = 7.9$ Hz, 2H), 4.59 (s, 2H), 7.02 (d, $J =$ 6.6 Hz, 2H), 7.15–7.29 (m, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 10.6, 21.0, 34.2, 40.1, 54.4, 128.2, 128.5, 128.6, 129.0, 129.2, 134.7, 167.4; HRMS (FAB) Calcd for $C_{13}H_{21}N_2$: $[M + H]^+$ 205.1699. Found: m/z 205.1721.

Methylphenyl[4,5,6,7-tetrahydroazepin-2(3*H*)-yl]amine (13):[23] Colorless oil; IR (neat, cm^{-1}) 3332, 3293, 3255, 2923, 1635, 1272, 1257; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.59–1.78 (m, 6H), 2.50 (t, $J = 5.1$ Hz, 2H), 3.53 (s, 3H), 3.62 (br, 2H), 7.21–7.26 (m, 2H), 7.44–7.52 (m, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 23.1, 27.2, 29.5, 29.8, 41.3, 45.2, 126.1 (×2), 129.5, 130.5 (×2), 142.4, 169.6.

General Procedure for Syntheses of Enamines (Table 6–8). To a solution of acetophenone oxime (0.25 mmol) and triethylamine (0.50 mmol) in toluene (3.0 mL) was added trifluoromethanesulfonic anhydride (0.38 mmol) under an argon atmosphere at −78 °C. After stirring for 5 min, freshly prepared sodium enolate of methyl malonate dissolved in THF (0.30 M, 2.5 mL) was added and the reaction mixture was slowly warmed up to room temperature. After stirring for 1 h, the reaction mixture was quenched with water (5.0 mL), and the aqueous layer was extracted with ethyl acetate (30 mL). The organic layer was dried (Na_2SO_4), filtrated and evaporated, and the resulting residue was purified by preparative TLC to afford 2-(1-phenylaminoethylidene)malonic acid dimethyl ester (**14**) in 96% yield as a colorless oil; IR (neat, cm^{-1}) 2360, 2329, 1720, 1658, 1581, 1249; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.95 (s, 3H), 3.62 (s, 3H), 3.66 (s, 3H), 6.97 (d, $J = 7.8$ Hz, 2H), 7.12 (t, $J = 7.4$ Hz, 1H), 7.21–7.27 (m, 2H), 11.18 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 18.1, 51.2, 51.9, 93.7, 125.7 (×2), 126.3, 129.1 (×2), 137.7, 162.0, 168.78, 168.82; HRMS (FAB) Calcd for $C_{13}H_{16}NO_4$: $[M + H]^+$ 250.1074. Found: m/z 250.1096.

2-(1-Phenylaminopropylidene)malonic Acid Dimethyl Ester (15): Colorless oil; IR (neat, cm^{-1}) 3980, 1712, 1650, 1581, 1442, 1249; ^1H NMR (270 MHz, $CDCl_3$) δ 0.91 (t, $J = 7.5$ Hz, 3H), 2.35 (q, $J = 7.5$ Hz, 2H), 3.63 (s, 3H), 3.68 (s, 3H), 7.04 (d, $J = 7.4$ Hz, 2H), 7.14–7.29 (m, 3H), 11.0 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 13.1, 23.1, 51.2, 52.0, 92.9, 126.5 (×2), 126.7, 129.2 (×2), 137.8, 167.3, 168.9, 169.1; HRMS (FAB) Calcd for $C_{14}H_{18}NO_4$: $[M + H]^+$ 264.1230. Found: m/z 264.1255.

2-[1-(4-Methoxyphenylamino)ethylidene]malonic Acid Dimethyl Ester (16): Colorless oil; IR (neat, cm^{-1}) 2360, 2329, 1712, 1650, 1581, 1241; ^1H NMR (270 MHz, $CDCl_3$) δ 1.98 (s, 3H), 3.71 (s, 3H), 3.74 (s, 3H), 3.78 (s, 3H), 6.85 (d, $J = 8.7$ Hz, 2H), 7.00 (d, $J = 8.6$ Hz, 2H), 11.1 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 18.1, 51.1, 51.9, 55.4, 92.9, 114.3 (×2), 127.4 (×2), 130.5, 158.1, 163.0, 168.9, 169.0; HRMS (FAB) Calcd for $C_{14}H_{18}NO_5$: $[M + H]^+$ 280.1180. Found: m/z 280.1201.

2-[1-(4-Nitrophenylamino)ethylidene]malonic Acid Dimethyl Ester (17): White solid; mp 111–112 °C; IR (KBr, cm^{-1}) 2854, 2360, 1697, 1589, 1272; ^1H NMR (270 MHz, $CDCl_3$) δ 2.19 (s, 3H), 3.74 (s, 3H), 3.78 (s, 3H), 7.17 (dd, $J = 7.3$, 2.0 Hz, 2H), 8.21 (dd, $J = 7.0$, 2.1 Hz, 2H), 11.5 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 18.4, 51.7, 52.3, 98.2, 123.6 (×2), 125.0 (×2), 144.1, 144.3, 158.6, 168.0, 168.4; Found: C, 53.02; H, 4.87; N, 9.42%. Calcd for $C_{13}H_{14}N_2O_6$: C, 53.06; H, 4.80; N, 9.52%.

2-[Phenyl(phenylamino)methylene]malonic Acid Dimethyl Ester (18): White solid; mp 113–114 °C; IR (KBr, cm^{-1}) 3910, 2360, 2329, 1712, 1596; ^1H NMR (270 MHz, $CDCl_3$) δ 3.28 (s, 3H), 3.77 (s, 3H), 6.62–6.65 (m, 2H), 6.90–7.09 (m, 3H), 7.20–7.30 (m, 5H), 11.1 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 51.5, 51.7, 96.8, 123.5 (×2), 124.4, 128.2 (×2), 128.3 (×2), 128.5 (×2), 129.4, 133.6, 138.6, 161.2, 167.9, 168.2; Found: C, 69.04; H, 5.46; N, 4.48%. Calcd for $C_{18}H_{17}NO_4$: C, 69.44; H, 5.50; N, 4.50%.

2-(1-Methylaminoethylidene)malonic Acid Dimethyl Ester (19): Colorless oil; IR (neat, cm^{-1}) 3247, 2946, 2360, 1650, 1596, 1257; ^1H NMR (270 MHz, $CDCl_3$) δ 2.06 (s, 3H), 2.91 (d, $J = 5.1$ Hz, 3H), 3.63 (s, 3H), 3.69 (s, 3H), 9.71 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 16.6, 30.0, 50.8, 51.7, 91.0, 165.6, 169.17, 169.24; HRMS (FAB) Calcd for $C_8H_{14}NO_4$: $[M + H]^+$ 188.0917. Found: m/z 188.0936.

2-(1-Ethylaminopropylidene)malonic Acid Dimethyl Ester (20): Colorless oil; IR (neat, cm^{-1}) 3625, 2969, 2345, 1712, 1650, 1596, 1257; ^1H NMR (270 MHz, $CDCl_3$) δ 1.16 (t, $J = 7.5$ Hz, 3H), 1.23 (t, $J = 7.3$ Hz, 3H), 2.38 (q, $J = 7.5$ Hz, 2H), 3.24–3.34 (m, 2H), 3.64 (s, 3H), 3.70 (s, 3H), 9.58 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 12.7, 15.4, 23.3, 37.6, 50.8, 51.7, 90.0, 168.8 (×2), 169.4; HRMS (FAB) Calcd for $C_{10}H_{18}NO_4$: $[M + H]^+$ 216.1231. Found: m/z 216.1251.

2-(1-*t*-Butylaminoethylidene)malonic Acid Dimethyl Ester (21): Colorless oil; IR (neat, cm^{-1}) 3617, 3292, 2360, 2321, 1735, 1604, 1218; ^1H NMR (270 MHz, $CDCl_3$) δ 1.36 (s, 9H), 2.14 (s, 3H), 3.69 (s, 6H), 10.1 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 18.0, 30.9 (×3), 41.1, 52.5, 52.8, 91.3, 164.1 (×2), 166.7; HRMS (FAB) Calcd for $C_{11}H_{20}NO_4$: $[M + H]^+$ 230.1387. Found: m/z 230.1414.

2-(1-Ethylaminoethylidene)malonic Acid Dimethyl Ester (22a) and 2-(1-Methylaminopropylidene)malonic Acid Dimethyl Ester (22b): Isolated as a mixture of **22a** and **22b** (**22a**/**22b** = 77/23): Colorless oil; IR (neat, cm^{-1}) 3571, 2977, 2352, 2321, 1712, 1650, 1596, 1257; ^1H NMR (270 MHz, $CDCl_3$) δ 1.12–1.23 (m, 3H), 2.06 (s, 2.31H), 2.39 (q, $J = 7.4$ Hz, 0.46H), 2.94 (d, $J = 5.1$ Hz, 0.69H), 3.22–3.32 (m, 1.54H), 3.63 (s, 0.69H), 3.70 (s, 2.31H), 9.69 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 12.3, 15.1, 16.7, 23.1, 29.4, 38.1, 41.1, 50.8, 51.7, 52.5, 90.3, 90.7, 164.4 (×2), 166.7, 169.1, 169.3, 169.8; HRMS (FAB) Calcd for $C_9H_{16}NO_4$: $[M + H]^+$ 202.1074. Found: m/z 202.1095.

2-(Azocan-2-ylidene)malonic Acid Dimethyl Ester (23): White solid; mp 53–55 °C; IR (KBr, cm^{-1}) 2923, 2908, 1812, 1643, 1103; ^1H NMR (270 MHz, $CDCl_3$) δ 1.50–1.60 (m, 6H), 1.77 (br, 2H), 2.55 (t, $J = 6.5$ Hz, 2H), 3.38–3.45 (m, 2H), 3.66 (s, 3H), 3.71 (s, 3H), 9.96 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 25.0, 25.4, 27.1, 29.8, 32.3, 41.8, 50.8, 51.7, 89.9, 169.2, 169.4, 169.5; HRMS (FAB) Calcd for $C_{12}H_{20}NO_4$: $[M + H]^+$ 242.1387. Found: m/z 242.1401.

2-(Azonan-2-yliden)malonic Acid Dimethyl Ester (24): White solid; mp 51 °C; IR (KBr, cm^{-1}) 3856, 3648, 3340, 3000, 1735, 1635, 1249; ^1H NMR (270 MHz, $CDCl_3$) δ 1.24–1.72 (m, 10H), 2.53 (t, $J = 6.1$ Hz, 2H), 3.36–3.46 (m, 2H), 3.64 (s, 3H), 3.69 (s, 3H), 9.95 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 22.0, 25.3, 26.2, 28.7, 29.6, 30.2, 43.7, 50.8, 51.7, 89.9, 169.5, 169.6, 169.9; HRMS (FAB) Calcd for $C_{13}H_{22}NO_4$: $[M + H]^+$ 256.1543. Found: m/z 256.1549.

2-Acetyl-3-phenylaminobut-2-enoic Acid Ethyl Ester (25a):[24] Colorless oil; IR (neat, cm^{-1}) 3293, 2977, 2360, 1697, 1573, 1226; ^1H NMR (270 MHz, $CDCl_3$) δ 1.23 (t, $J = 7.1$ Hz, 3H), 2.04 (s, 3H), 2.22 (s, 3H), 4.15 (q, $J = 7.1$ Hz, 2H), 7.00 (d, $J = 7.8$ Hz, 2H), 7.16 (t, $J = 7.2$ Hz, 1H), 7.24–7.30 (m, 2H), 13.8 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.3, 18.7, 29.6, 60.4, 104.8, 125.7 (×2), 126.8, 129.1 (×2), 137.4, 164.9, 169.8, 195.7.

3-(*N*-Phenylacetimidoyloxy)but-2-enoic Acid Ethyl Ester (25b):[24] Colorless oil; IR (neat, cm^{-1}) 3980, 3810, 3702, 2360, 2329, 1689, 1195; ^1H NMR (270 MHz, $CDCl_3$) δ 1.26 (t, $J = 7.1$ Hz, 3H), 1.99 (s, 3H), 2.12 (d, $J = 1.0$ Hz, 3H), 4.14 (q, $J = 7.1$ Hz, 2H), 5.59 (d, $J = 1.0$ Hz, 1H), 6.74 (dd, $J = 8.3$, 1.0 Hz, 2H), 6.99–7.05 (m, 1H), 7.22–7.32 (m, 2H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.2, 21.1, 21.7, 60.4, 107.7, 120.8 (×2), 123.2, 128.8 (×2), 147.9, 162.5, 163.9, 170.9.

2-(1-Phenylaminoethylidene)dithiomalonic Acid Di-*S*-ethyl Ester (26): Colorless oil; IR (neat, cm^{-1}) 2969, 2931, 1658, 1581; ^1H NMR (270 MHz, $CDCl_3$) δ 1.14–1.27 (m, 6H), 1.92 (s, 3H), 2.79–2.92 (m, 4H), 7.00 (d, $J = 7.6$ Hz, 2H), 7.13–7.30 (m, 3H), 11.9 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.3, 14.9, 17.6, 23.4, 25.2, 112.1, 125.6 (×2), 126.6, 129.1, (×2), 137.2, 157.2, 186.2, 194.5; HRMS (FAB) Calcd for $C_{15}H_{29}NO_2S_2$: $[M + H]^+$ 310. 0930. Found: m/z 310.0938.

[2,2-Bis(phenylsulfonyl)-1-methylvinyl]aniline (27): Brown solid; mp 125–130 °C; IR (KBr, cm^{-1}) 3239, 3054, 1558, 1365; ^1H NMR (270 MHz, $CDCl_3$) δ 2.23 (s, 3H), 7.08–8.13 (m, 15H), 11.2 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.6, 106.7 (×2), 126.3 (×2), 126.7 (×2), 127.0 (×2), 128.6 (×2) 128.8 (×2), 129.5 (×2), 132.5, 132.7, 136.1, 144.4, 164.8; HRMS (FAB) Calcd for $C_{21}H_{20}NO_4S_2$: $[M + H]^+$ 414.0828. Found: m/z 414.0821.

2-Cyano-3-phenylaminobut-2-enoic Acid Methyl Ester (28):[25] White solid; mp 119–120 °C; IR (KBr, cm^{-1}) 3201, 2198, 1681, 1658, 1596, 1295; ^1H NMR (270 MHz, $CDCl_3$) δ 2.14 (s, 3H), 3.68 (s, 3H), 7.01 (d, $J = 7.6$ Hz, 2H), 7.21–7.64 (m, 3H), 11.3 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 18.9, 51.7, 73.5, 118.4, 125.5 (×2), 127.5, 129.4 (×2), 136.5, 168.3, 168.4.

2-Cyano-3-phenylaminobut-2-enethioic Acid *S*-Ethyl Ester

(29): Brown solid; mp 73–75 °C; IR (KBr, cm^{-1}) 2190, 1604, 1581, 1558, 1226; ^1H NMR (270 MHz, $CDCl_3$) δ 1.14–1.27 (m, 6H), 1.92 (s, 3H), 2.79–2.92 (m, 4H), 7.00 (d, $J = 7.6$ Hz, 2H), 7.13–7.30 (m, 3H), 11.9 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.3, 14.9, 17.6, 23.4, 25.2, 112.1, 125.6 (×2), 126.6, 129.1 (×2), 137.2, 157.2, 186.2, 194.5; HRMS (FAB) Calcd for $C_{13}H_{15}N_2OS$: $[M + H]^+$ 247.0900. Found: m/z 247.0918.

(1-Cyano-2-phenylamino-1-propenyl)phosphonic Acid Diethyl Ester (30): White solid; mp 99–100 °C; IR (KBr, cm^{-1}) 3224, 2985, 2183, 1604, 1025; ^1H NMR (270 MHz, $CDCl_3$) δ 1.291 (t, $J = 7.1$ Hz, 3H), 1.294 (t, $J = 7.0$ Hz, 3H), 2.16 (s, 3H), 4.02–4.13 (m, 4H), 6.98 (dd, $J = 7.7$, 0.5 Hz, 2H), 7.15–7.29 (m, 3H), 10.6 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 16.2, 16.3, 19.7, 19.9, 62.9, 63.0, 119.0, 125.6 (×2), 127.0, 129.3 (×2), 137.3, 170.4; Found: C, 56.96; H, 6.51; N, 9.65; P, 10.27%. Calcd for $C_{14}H_{19}N_2O_3P$: C, 57.14; H, 6.51; N, 9.52; P, 10.53%.

3-Phenylamino-2-phenylsulfonylbut-2-enenitrile (31): White solid; mp 175–176 °C; IR (KBr, cm^{-1}) 3278, 2345, 2190, 1573, 1389, 1141; ^1H NMR (270 MHz, $CDCl_3$) δ 2.11 (s, 3H), 7.07 (d, $J = 7.6$ Hz, 2H), 7.28–7.41 (m, 3H), 7.49–7.63 (m, 3H), 7.91–7.95 (m, 2H), 10.1 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.9, 116.2, 126.0, 126.7, 128.2, 129.3, 129.7, 133.6, 136.2, 141.4, 164.1; Found: C, 64.17; H, 4.80; N, 9.37; S, 10.69%. Calcd for $C_{16}H_{14}N_2O_2S$: C, 64.41; H, 4.73; N, 9.39; S, 10.75%.

3-Phenylamino-2-(1-pyrrolidinecarbonyl)but-2-enenitrile (32): White solid; mp 107–109 °C; IR (KBr, cm^{-1}) 2969, 2877, 2190, 1581, 1434, 1373; ^1H NMR (270 MHz, $CDCl_3$) δ 1.85 (br, 4H), 2.20 (s, 3H), 3.48–3.69 (m, 4H), 7.03 (d, $J = 7.8$ Hz, 2H), 7.17–7.34 (m, 3H), 12.4 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 18.9, 24.1, 26.8, 47.0, 48.8, 74.1, 120.6, 125.2 (×2), 126.6, 129.2, 137.5, 166.8, 167.4; HRMS (FAB) Calcd for $C_{15}H_{18}N_3O$: $[M + H]^+$ 256.1444. Found: m/z 256.1453.

3-Phenylamino-2-(1-pyrrolidinecarbonyl)but-2-enoic Acid Ethyl Ester (33): Colorless oil; IR (neat, cm^{-1}) 1735, 1643, 1441, 1250; ^1H NMR (270 MHz, $CDCl_3$) δ 1.18 (t, $J = 7.2$ Hz, 3H), 1.81–1.87 (m, 4H), 1.90 (s, 3H), 3.29–3.47 (m, 4H), 4.10 (q, $J = 7.2$ Hz, 2H), 6.99 (d, $J = 7.6$ Hz, 2H), 7.07–7.27 (m, 3H), 10.8 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.7, 17.2, 24.8, 25.9, 45.5, 47.8, 59.4, 97.4, 125.2 (×2), 125.6, 129.0 (×2), 138.3, 157.7, 167.1, 167.3; HRMS (FAB) Calcd for $C_{17}H_{23}N_2O_3$: $[M + H]^+$ 303.1703. Found: m/z 303.1727.

2-(1-Phenylaminoethylidene)monothiomanonic Acid *S*-Ethyl Ester (34): Obtained as *EZ* mixture; Colorless oil; IR (neat, cm^{-1}) 1697, 1651, 1573, 1250, 1173, 1172; ^1H NMR (270 MHz, $CDCl_3$) δ 1.24–1.61 (m, 3H), 2.03 (s, 0.93H), 2.13 (s, 2.07H), 2.81–2.96 (m, 2H), 4.15–4.32 (m, 2H), 7.06–7.11 (m, 2H), 7.19–7.39 (m, 3H), 11.2 (br, 0.31H), 12.8 (br, 0.69H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.3, 14.4, 14.7, 14.8, 17.7, 19.1, 23.5, 24.7, 59.9, 60.8, 101.6, 103.5, 125.6 (×2), 125.9 (×2), 126.3, 126.9 (×2), 129.1, 129.2 (×2), 137.3, 137.8, 160.0, 163.0, 167.7, 168.4, 189.8, 193.6; HRMS (FAB) Calcd for $C_{15}H_{20}NO_3S$: $[M + H]^+$ 294.1158. Found: m/z 294.1172.

2-Cyano-3-methylaminobut-2-enoic Acid Methyl Ester (35):[26] White solid; 119–122 °C; IR (KBr, cm^{-1}) 3810, 3494, 2198, 1666, 1280; ^1H NMR (270 MHz, $CDCl_3$) δ 2.22 (s, 3H), 2.99 (d, $J = 5.3$ Hz, 3H), 3.67 (s, 3H), 9.78 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.6, 30.7, 51.3, 71.0, 119.2, 168.9, 170.2.

3-Methylamino-2-phenylsulfonylbut-2-enenitrile (36): Colorless oil; IR (neat, cm^{-1}) 3363, 2329, 1604, 1126; ^1H NMR (270 MHz, $CDCl_3$) δ 2.19 (s, 3H), 3.00 (d, $J = 5.1$ Hz, 3H), 7.47–7.59 (m, 3H), 7.87–7.90 (m, 2H), 8.57 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 18.7, 31.3, 80.9, 117.0, 126.3 (×2), 129.1 (×2), 133.2, 141.8, 166.0; HRMS (FAB) Calcd for $C_{11}H_{11}N_2O_2S$: $[M - H]^-$ 235.0547. Found: m/z 235.0556.

2-(1-Methylaminoethylidene)malononitrile (37):[27] Colorless oil; IR (neat, cm^{-1}) 3409, 3224, 2815, 2360, 2321, 2198, 1604, 1403; ^1H NMR (270 MHz, $CDCl_3$) δ 2.18 (s, 3H), 2.97 (d, $J = 4.9$ Hz, 3H), 7.20 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.0, 31.1, 100.4, 115.2, 115.9, 172.1.

[1-Methyl-2,2-bis(phenylsulfonyl)vinyl]methylamine (38): White solid; mp 113–114 °C; IR (KBr, cm^{-1}) 3317, 1589, 1450, 1358, 1303, 1141, 1079; ^1H NMR (270 MHz, $CDCl_3$) δ 2.26 (s, 3H), 2.93 (d, $J = 4.9$ Hz, 3H), 7.46–8.02 (m, 10H), 9.56 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.6, 31.0, 103.9, 126.4, 126.7, 128.4, 128.7, 128.9, 129.2, 129.4, 129.6, 132.0, 132.3, 144.4, 145.0, 167.0; HRMS (FAB) Calcd for $C_{16}H_{18}NO_4S_2$: $[M + H]^+$ 352.0672. Found: m/z 352.0666.

3-Methylamino-2-(1-pyrrolidinecarbonyl)but-2-enenitrile (39): Colorless oil; IR (neat, cm^{-1}) 2939, 2869, 2183, 1643, 1604, 1581, 1434, 1389; ^1H NMR (270 MHz, $CDCl_3$) δ 1.81 (br, 4H), 2.19 (s, 3H), 2.91 (d, $J = 5.1$ Hz, 3H), 3.45 (br, 4H), 10.6 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 17.6, 24.3, 26.1, 30.4, 46.0, 47.6, 71.4, 121.5, 167.4,169.7; HRMS (FAB) Calcd for $C_{10}H_{16}N_3O$: $[M + H]^+$ 194.1288. Found: m/z 194.1301.

2-(1-Methylaminoethylidene)dithiomalonic Acid Di-*S*-ethyl Ester (40): Colorless oil; IR (neat, cm^{-1}) 2924, 1643, 1589, 1219; ^1H NMR (270 MHz, $CDCl_3$) δ 1.26 (t, $J = 7.2$ Hz, 6H), 2.01 (s, 3H), 2.86–2.97 (m, 6H), 10.4 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.7 (×2), 16.6, 23.6, 24.4, 29.9, 110.6, 161.0; HRMS (FAB) Calcd for $C_{10}H_{18}NO_2S_2$: $[M + H]^+$ 248.0774. Found: m/z 248.0778.

3-Methylamino-1-phenylbut-2-en-1-one (41):[28] Colorless oil; IR (neat, cm^{-1}) 2360, 2329, 1604, 1319,740; ^1H NMR (270 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.95 (d, $J = 5.3$ Hz, 3H), 5.62 (s, 1H), 7.28–7.34 (m, 3H), 7.74–7.80 (m, 2H), 11.3 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 19.4, 29.8, 91.9, 126.7 (×2), 128.0, (×2), 130.2, 140.3, 165.8, 187.4.

2-Phenylaminohept-2-en-4-one (42):[29] Colorless oil; IR (neat, cm^{-1}) 2954, 2931, 2877, 1604, 1573; ^1H NMR (270 MHz, $CDCl_3$) δ 0.90 (t, $J = 7.3$ Hz, 3H), 1.53–1.67 (m, 2H), 1.94 (s, 3H), 2.25 (t, $J = 7.6$ Hz, 2H), 5.11 (s, 1H), 7.02–7.29 (m, 5H), 12.5 (s, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 14.2, 19.5, 20.1, 44.4, 97.2, 124.5 (×2), 125.3, 129.0 (×2), 138.7, 160.0, 199.0.

2,2-Dimethyl-5-phenylaminohex-4-en-3-one (43):[30] Colorless oil; IR (neat, cm^{-1}) 2962, 1604, 1296, 1126; ^1H NMR (270 MHz, $CDCl_3$) δ 1.10 (s, 9H), 1.96 (s, 3H), 5.27 (s, 1H), 7.01–7.27 (m, 5H), 12.6 (br, 1H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 20.5, 27.9 (×2), 41.7, 92.9, 124.4, 125.2 (×2), 128.9 (×2), 138.8, 160.7. 204.7.

General Procedure for Syntheses of 2-Substituted 4-Oxo-3-quinolinecarboxylic Acid Derivatives (Scheme 1). To a solution of **14** (0.16 mmol) in toluene (1.0 mL) was added a trifluoromethanesulfonic acid (0.32 mmol) under an argon atmosphere at room temperature. The reaction mixture was gently refluxed for 2 h. After the reaction mixture was cooled down to room temperature, the reaction was quenched with water (5.0 mL), and the precipitate was filtrated and washed with ethyl acetate to afford 2-methyl-4-oxo-1,4-dihydroquinoline-3-carboxylic acid methyl ester (**14′**) as a white solid; mp 189–192 °C; IR (KBr, cm^{-1}) 1651, 1458, 1411, 1296, 1219, 1173; ^1H NMR (270 MHz, DMSO-d_6) δ 2.39 (s, 3H), 3.75 (s, 3H), 7.35 (t, $J = 7.1$ Hz,

1H), 7.54 (d, $J = 8.2$ Hz, 1H), 7.65–7.71 (m, 1H), 8.05 (dd, $J = 8.2$, 1.5 Hz, 1H), 12.0 (br, 1H); ^{13}C NMR (68 MHz, DMSO-d_6) δ 18.4, 51.8, 114.2, 118.0, 123.9, 124.2, 124.9, 132.3, 139.0, 149.5, 167.0, 172.9; HRMS (FAB) Calcd for $C_{12}H_{12}NO_3$: $[M + H]^+$ 218.0812. Found: m/z 218.0832.

4-Oxo-2-phenyl-1,4-dihydroquinoline-3-carboxylic Acid Methyl Ester (18′): White solid; mp 175–178 °C; IR (KBr, cm^{-1}) 1666, 1643, 1450, 1427, 1288, 1234, 1157; ^{1}H NMR (270 MHz, DMSO-d_6) δ 3.49 (s, 3H), 7.39–7.42 (m, 1H), 7.56 (br, 5H), 7.70 (s, 2H), 8.11 (d, $J = 7.9$ Hz, 1H), 12.1 (br, 1H); ^{13}C NMR (68 MHz, DMSO-d_6) δ 51.7, 115.2, 118.7, 124.1, 124.4, 124.8, 128.0 (×2), 128.6 (×2), 130.3, 132.4, 133.5, 139.4, 149.2, 166.8, 173.4; HRMS (FAB) Calcd for $C_{17}H_{14}NO_3$: $[M + H]^+$ 280.0968. Found: m/z 280.0959.

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