Using Morita–Baylis–Hillman Acetates of 2-Azidobenzaldehydes for the Synthesis of 2-Alkoxy-3-Cyanomethylquinolines and Alkyl Quinoline-3-Carboxylates

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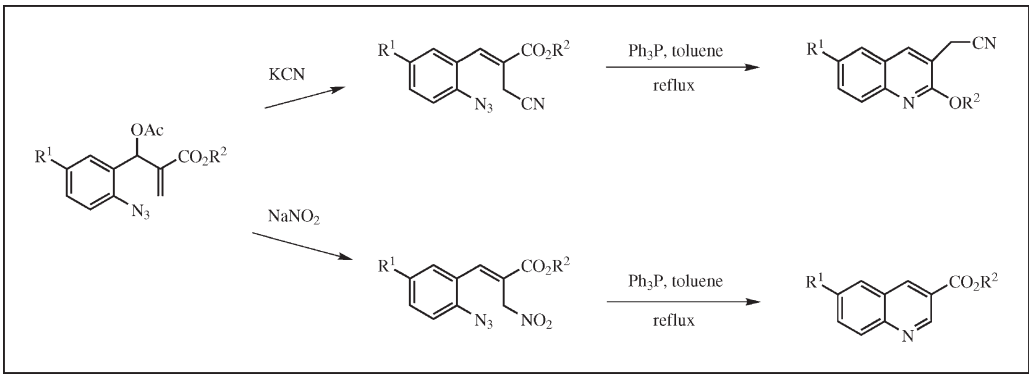

A simple method for the synthesis of several 2-alkoxy-3-cyanomethylquinolines and alkyl quinoline-3-carboxylates using iminophosphorane-mediated cyclization reactions of 3-(2-azidophenyl)-2-cyanomethylpropenoates and 3-(2-azidophenyl)-2-nitromethylpropenoates has been developed. These compounds were readily obtained from the Morita–Baylis–Hillman acetates of 2-azidobenzaldehydes using potassium cyanide or sodium nitrite, respectively.

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INTRODUCTION

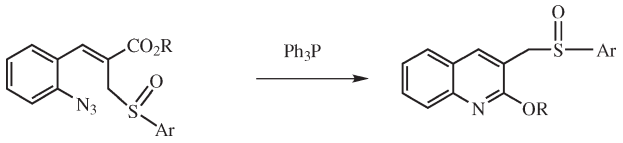
The Morita–Baylis–Hillman reaction [1] has attracted the attention of organic chemists in recent years. This reaction provides useful multifunctional molecules that have been successfully used in the synthesis of various heterocyclic compounds including quinolines [1(h)]. Quinolines and their derivatives occur in numerous natural products [2] show interesting physiological activities and have attractive applications as pharmaceuticals and agrochemicals [3]. Many methods for the synthesis of quinolines have been developed [4]; however, the development of new synthetic methods remains an active research area.

Recently, we reported [5] the synthesis of 2-alkoxy-3-arylsulfinylmethylquinolines using an intramolecular aza–Wittig type reaction of (*Z*)-3-(2-azidophenyl)-2-(arylsulfinylmethyl)propenoates, which were readily obtained from the Morita–Baylis–Hillman acetates of 2-azidobenzaldehydes, with triphenylphosphine via *E*/*Z* isomerization, as shown in Scheme 1. To continue our work on the Morita–Baylis–Hillman reaction [6], we wanted to incorporate a cyano or nitro group in the allylic position of 3-(2-azidophenyl)propenoates and aimed to examine the feasibility of their conversions to the corresponding 2-alkoxyquinoline derivatives involving an intramolecular aza–Wittig ring closure process between an ester carbonyl and an iminophosphorane. Herein, we describe the syntheses of 2-alkoxy-3-cyanomethylquinolines from 3-(2-azidophenyl)-2-cyanomethylpropenoates and the unexpected quinoline-3-carboxylic acid alkyl esters from 3-(2-azidophenyl)-2-nitromethylpropenoates.

RESULTS AND DISCUSSION

We initiated our studies by preparing the key intermediate 3-(2-azidophenyl)-2-cyanomethylpropenoates **2** from known Morita–Baylis–Hillman acetates of 2-azidobenzaldehydes previously reported in the literature [7]. The S_N2' displacement reaction of the acetates **1** with potassium cyanide in aqueous dimethyl sulfoxide at room temperature afforded 3-(2-azidophenyl)-2-cyanomethylpropenoates **2** with (*E*)-stereoselectivity as the sole product in good to excellent yields (Table 1 and Scheme 2). The stereochemistry of product **2** was determined by comparing the ^{1}H-NMR values of the olefinic proton ($\delta = 7.84$–8.01) with published values for similar compounds [7]. The reaction of azide **2a** with

Scheme 1



triphenylphosphine in anhydrous toluene at room temperature for 4 h gave the iminophosphorane **3a** in a 98% yield. Treatment of **3a** in toluene at reflux temperature for 30 h produced, after column chromatography, an 89% yield of 3-cyanomethyl-2-methoxyquinoline (**5a**) with triphenylphosphine oxide (90%). *In situ* generation of iminophosphoranes **3** and subsequent aza–Wittig ring closure of other 3-(2-azidophenyl)-2-cyanomethylpropenoates **2** were very successful, resulting in the corresponding 2-alkoxy-3-cyanomethylquinoline derivatives **5** in 75–95% yields (Table 1 and Scheme 2).

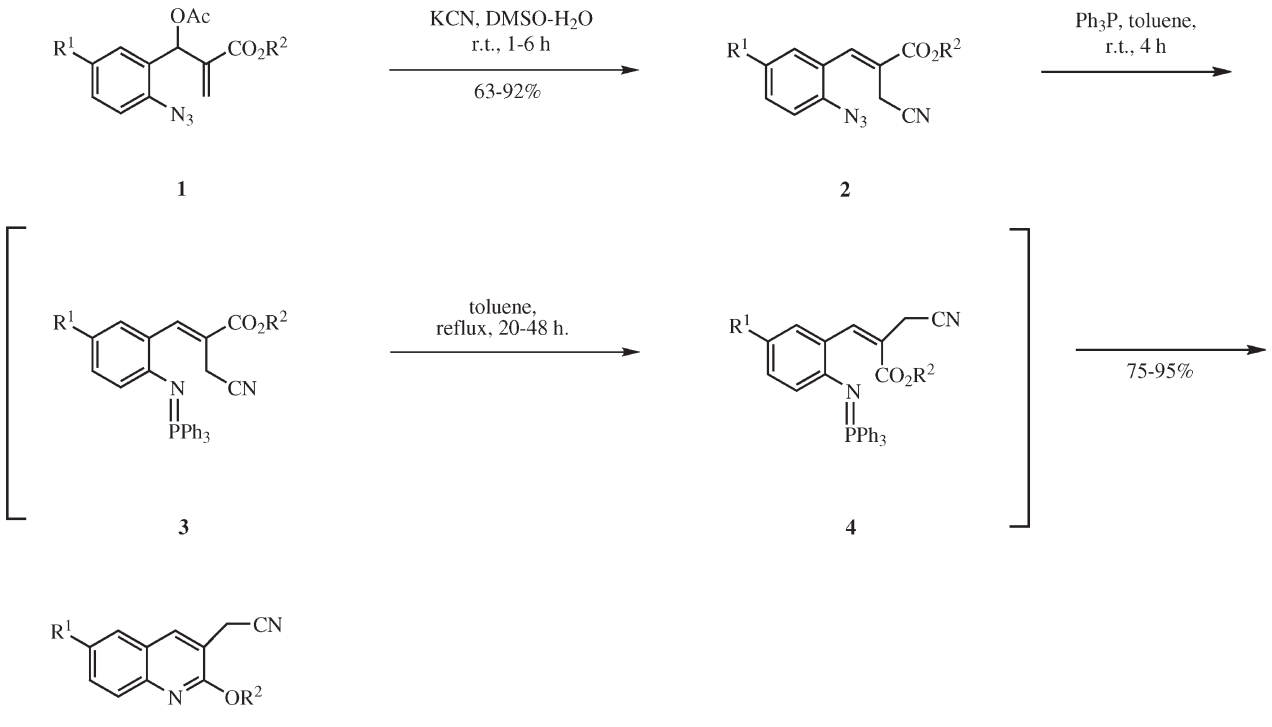
Table 1

2-Cyanomethylpropenoates **2** and 2-alkoxy-3-cyanomethylquinolines **5**.

Entry	**2** [Yield (%)/time (h)]	**5** [Yield (%)/time (h)]
1	**2a** (88/1)	**5a** (87/30)
2	**2b** (74/5)	**5b** (83/25)
3	**2c** (92/1)	**5c** (75/20)
4	**2d** (87/3)	**5d** (95/48)
5	**2e** (63/6)	**5e** (87/28)

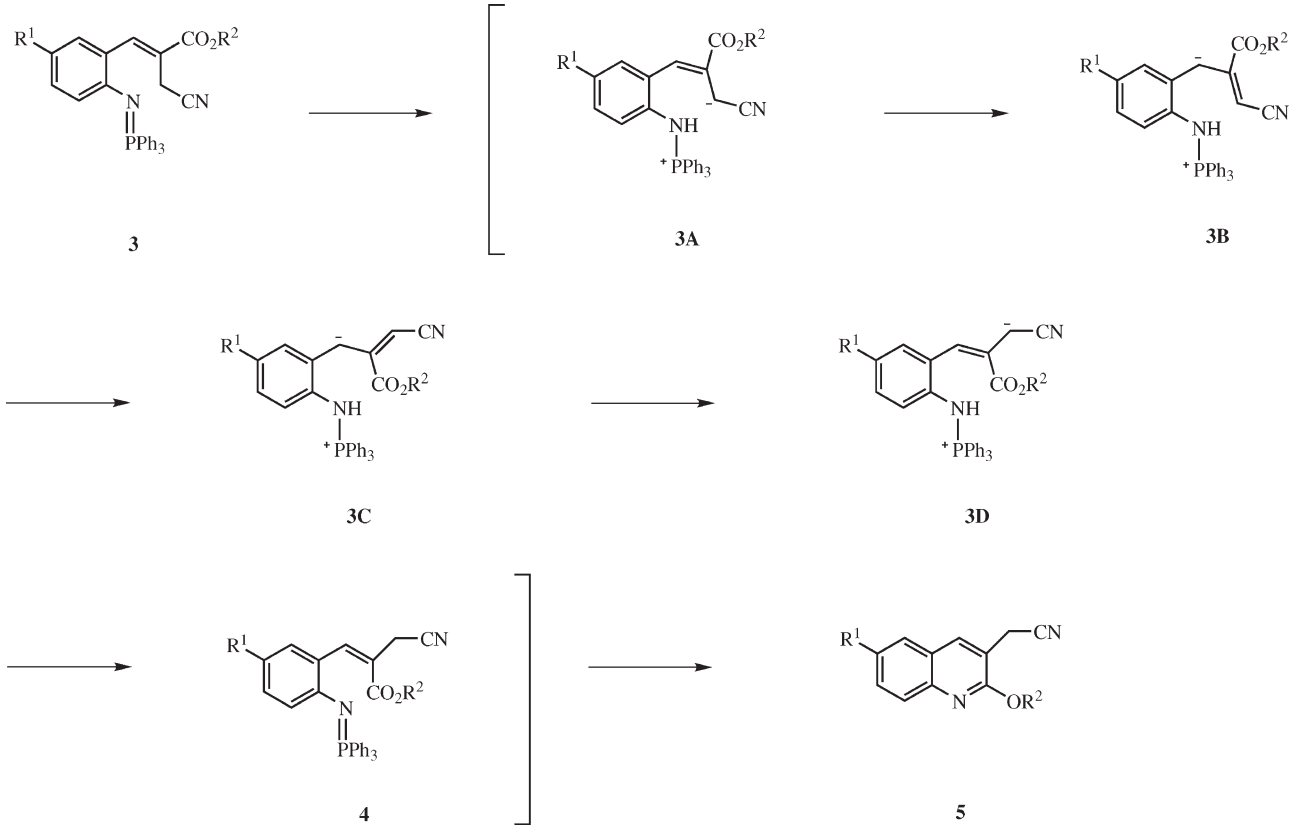
A possible mechanism for the transformation of **3** into **5** is shown in Scheme 3 based on our previous study [5]. The mechanistic sequence involves an abstraction of the acidic α-hydrogen of nitrile by the nitrogen anion of (*E*)-iminophosphorane **3** to give several zwitterionic intermediates (**3A–3D**). The formula **3B,** corresponding to a negative charge located on C-3,

Scheme 2



1, 2, 3, 4, 5	R^1	R^2
a	H	Me
b	Cl	Me
c	MeO	Me
d	H	Et
e	H	Bu

Scheme 3



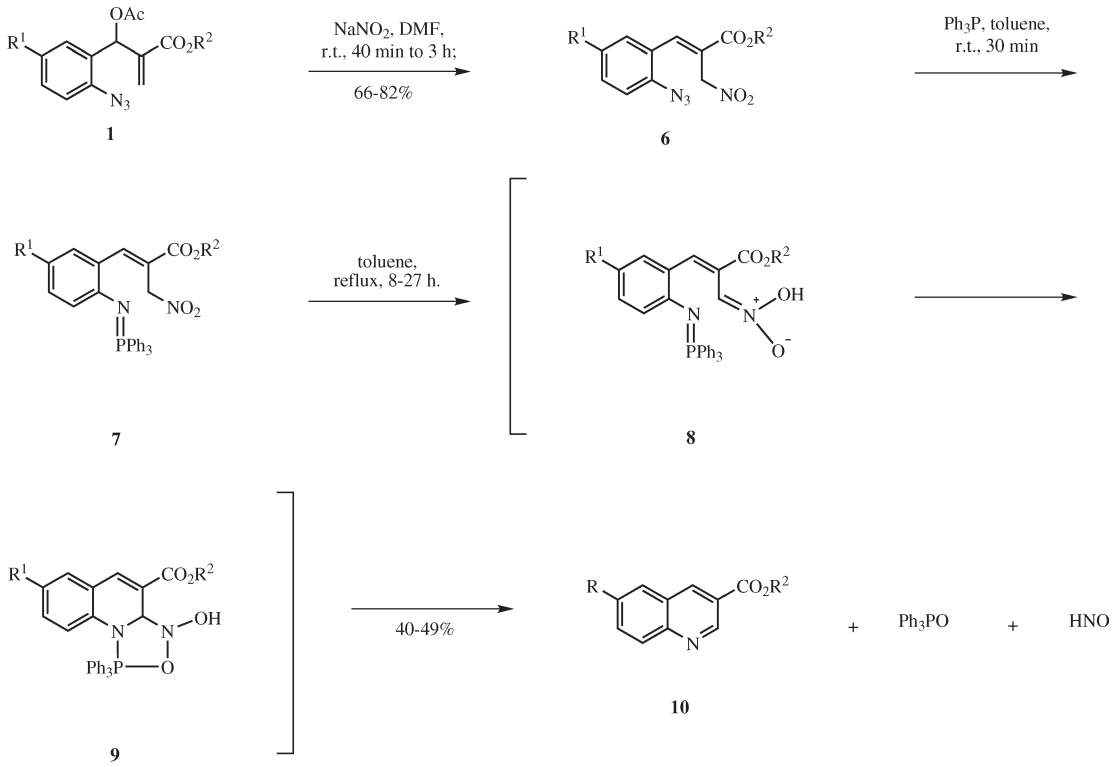
enabled rotation about the C-2–C-3 bond, and subsequent proton migration through the zwitterionic intermediates gave (*Z*)-iminophosphorane **4**, followed by an aza–Wittig reaction at the ester carbonyl group to produce quinoline **5**.

Encouraged by these results, we used the same method for the synthesis of 2-alkoxy-3-nitromethylquinolines from the substrate afforded by the S_N2' reaction of the acetates **1** with nitrite ions [8]. The acetates **1** were treated with sodium nitrite in dimethylformamide at room temperature to give the corresponding 3-(2-azidophenyl)-2-nitromethylpropenoates **6** with (*E*)-stereoselectivity as the sole product in moderate yields (Scheme 4 and Table 2). The stereochemistry of product **6** was determined by comparing the ^{1}H-NMR values of the olefinic proton (δ = 8.04–8.16) with the values of similar compounds published in ref. 8. Again, the reaction of **6a** with triphenylphosphine in toluene at room temperature for 30 min gave the iminophosphorane **7a** (91%). Treatment of **7a** in toluene at reflux temperature resulted in the formation of an unexpected quinoline-3-carboxylic acid methyl ester **10a** (54%) along with triphenylphosphine oxide (63%), whereas the expected 2-methoxy-3-nitromethylquinoline was not produced at all. *In situ* generation of iminophosphoranes **7** and subsequent ring closure were successful, producing the corresponding quinoline-3-carboxylic acid alkyl esters **10** in 40–49% yields. A plausible mechanism for the formation of the quinoline derivative **10** involved initial migration of the acidic α-hydrogen of the nitro group with the assistance of the iminophosphorane **7** nitrogen anion to form the nitronic acid **8**. Nucleophilic attack by the nitrogen anion on the nitronic acid **8**, followed by a loss of triphenylphosphine oxide and an unstable hyponitrous acid (HNO) [9] through the cyclic intermediate **9**, resulted in the quinoline **10** [10].

CONCLUSIONS

In summary, we prepared several 2-alkoxy-3-cyanomethylquinolines and quinoline-3-carboxylic acid alkyl esters from the reaction of 3-(2-azidophenyl)-2-cyanomethylpropenoates and 3-(2-azidophenyl)-2-nitromethylpropenoates, respectively, which were readily obtained from the Morita–Baylis–Hillman acetates of 2-azidobenzaldehydes, using triphenylphosphine at reflux temperature in toluene. In particular, we discovered an unusual behavior of the nitro group when it acted as a leaving group after nucleophilic attack of the iminophosphorane.

Scheme 4



1, 6, 7, 10	R^1	R^2
a	H	Me
b	Cl	Me
c	MeO	Me
d	H	Et
e	H	Bu

EXPERIMENTAL

Melting points were measured using an electrothermal melting point apparatus and were uncorrected. TLC analyses were conducted on Merck silica gel $60F_{254}$, and spots were visualized under UV light. Chromatography on the silica gel was conducted on Merck silica (70–230 mesh ASTM), and IR spectra were determined using a Nicolet Magna 550 FTIR spectrometer with KBr discs. The ^{1}H-NMR spectra were recorded using a Varian 300 spectrometer in $CDCl_3$ at 300 MHz, and all chemical shifts are given in parts per million (ppm) using δ_H $Me_4Si = 0$ ppm as reference and the coupling constants (*J*) are given in Hertz. The Varian spectrophotometer was used to measure both ^{13}C-NMR spectra, at 75.4 MHz using the solvent peak as an internal reference, and ^{31}P-NMR spectra at 121 MHz using $(PhO)_3PO = 0$ as the reference. Low-resolution mass spectra were recorded using a ThermoQuest Polaris Q mass spectrometer operating at 70 eV. Elemental analyses were conducted on a Thermo Electron Corporation Flash EA 1112 instrument.

The known Morita–Baylis–Hillman acetates, methyl 3-acetoxy-3-(2-azidophenyl)-2-methylenepropanoates **1a–c** [7,11], ethyl 3-acetoxy-3-(2-azidophenyl)-2-methylenepropanoate (**1d**) [7], and butyl 3-acetoxy-3-(2-azidophenyl)-2-methylenepropanoate (**1e**) [5] were prepared according to published procedures.

Table 2

2-Nitromethylpropenoates **6** and alkyl quinoline-3-carboxylates **10**.

Entry	**6** [Yield (%)/time (h)]	**10** [Yield (%)/time (h)]
1	**6a** (74/1)	**10a** (48/22)
2	**6b** (76/40 min)	**10b** (49/27)
3	**6c** (66/100 min)	**10c** (41/8)
4	**6d** (67/3)	**10d** (42/12)
5	**6e** (82/2)	**10e** (40/20)

General procedure for the synthesis of (E)-alkyl 3-(2-azidophenyl)-2-cyanomethylpropenoates 2. Potassium cyanide (6 mmole) was added to a stirred solution of Morita–Baylis–Hillman acetates **1** (4 mmole) in 20 mL of dimethyl sulfoxide and 10 mL of water at room temperature. After stirring for 1–6 h, the mixture was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified via column chromatography with silica gel by elution with hexane and ethyl acetate (3:1) to produce **2**.

(E)-Methyl 3-(2-azidophenyl)-2-cyanomethylpropenoate (2a). Reaction time: 1 h; yield: 88%; yellow solid: mp 66–67°C (hexane–EtOAc); IR (potassium bromide) 2250, 2128, 2088, 1716 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 3.42 (s, 2H, CH_2), 3.91 (s, 3H, CH_3), 7.24–7.27 (m, 2H, aromatic), 7.33–7.35 (m, 1H, aromatic), 7.45–7.48 (m, 1H, aromatic), 7.95 (s, 1H, CH); ^{13}C-NMR (deuteriochloform) δ 17.2, 52.8, 117.2, 118.7, 123.3, 125.0, 125.2, 129.8, 131.1, 139.1, 139.7, 165.8 [7].

(E)-Methyl 3-(2-azido-5-chlorophenyl)-2-cyanomethylpropenoate (2b). Reaction time: 5 h; yield: 74%; brown solid: mp 101–102°C (hexane–EtOAc); IR (potassium bromide) 2252, 2135, 2098, 1699 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 3.41 (s, 2H, CH_2), 3.91 (s, 3H,CH_3), 7.19 (d, J = 8.5 Hz, 1H, aromatic), 7.28 (d, J = 2.5 Hz, 1H, aromatic), 7.44 (dd, J = 8.5 and 2.5 Hz, 1H, aromatic), 7.84 (s, 1H, CH); ^{13}C-NMR (deuteriochloform) δ 17.1, 52.9, 116.6, 119.9, 124.5, 126.5, 129.4, 130.4, 130.9, 137.6, 138.3, 165.4; ms: *m/z* (%) 250 (19), 248 (55) [M^+–N_2], 235 (34), 233 (100), 218 (26), 216 (60), 188 (34), 164 (10), 162 (29). Anal. Calcd. for $C_{12}H_9ClN_4O_2$: C, 52.09; H, 3.28; N, 20.25. Found: C, 51.87; H, 3.12; N, 20.04.

(E)-Methyl 3-(2-azido-5-methoxyphenyl)-2-cyanomethylpropenoate (2c). Reaction time: 1 h; yield: 92%; brown solid: mp 72–73°C (hexane–EtOAc); IR (potassium bromide) 2251, 2126, 2100, 1713 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 3.78 (s, 2H, CH_2), 3.90 (s, 3H, CH_3), 4.08 (s, 3H, CH_3), 7.06 (d, J = 3.0 Hz, 1H, aromatic), 7.30 (dd, J = 9.1 and 2.8 Hz, 1H, aromatic), 7.76 (d, J = 9.1 Hz, 1H, aromatic), 8.01 (s, 1H, CH); ^{13}C-NMR (deuteriochloform) δ 17.3, 52.8, 55.7, 114.3, 117.2, 117.3, 119.8, 123.5, 126.0, 131.3, 139.9, 156.7, 165.7; ms: *m/z* (%) 244 (89) [M^+–N_2], 229 (100), 212 (85), 201 (28), 184 (47). Anal. Calcd. for $C_{13}H_{12}N_4O_3$: C, 57.35; H, 4.44; N, 20.58. Found: C, 57.09; H, 4.67; N, 20.28.

(E)-Ethyl 3-(2-azidophenyl)-2-cyanomethylpropenoate (2d). Reaction time: 3 h; yield: 87%; yellow solid: mp 59–60°C (hexane–EtOAc); IR (potassium bromide) 2251, 2129, 2094, 1709 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 1.40 (t, J = 7.2 Hz, 3H, CH_3), 3.41 (s, 2H, CH_2), 4.36 (q, J = 7.2 Hz, 2H, CH_2), 7.24–7.28 (m, 2H, aromatic), 7.32–7.35 (m, 1H, aromatic), 7.45–7.47 (m, 1H, aromatic), 7.94 (s, 1H, CH); ^{3}C-NMR (deuteriochloform) δ 14.2, 17.2, 61.9, 117.2, 118.6, 123.6, 125.0, 125.3, 129.8, 131.0, 139.1, 139.4, 165.2 [7].

(E)-Butyl 3-(2-azidophenyl)-2-cyanomethylpropenoate (2e). Reaction time: 6 h; yield: 63%; yellow oil; IR (neat) 2253, 2128, 2094, 1711 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 0.98 (t, J = 7.4 Hz, 3H, CH_3), 1.42–1.54 (m, 2H, CH_2), 1.71–1.80 (m, 2H, CH_2), 3.41 (s, 2H, CH_2), 4.31 (t, J = 6.6 Hz, 2H, CH_2), 7.21–7.27 (m, 2H, aromatic), 7.33–7.35 (m, 1H, aromatic), 7.45–7.50 (m, 1H, aromatic), 7.94 (s, 1H, CH); ^{13}C-NMR (deuteriochloform) δ 13.7, 17.2, 19.2, 30.6, 65.8, 117.2, 118.6, 123.6, 125.0, 125.3, 129.8, 131.0, 139.1, 139.5, 165.3; ms: *m/z* (%) 256 (20) [M^+–N_2], 199 (100), 183 (33), 155 (20), 128 (18). Anal. Calcd. for $C_{15}H_{16}N_4O_2$: C, 63.37; H, 5.67; N, 19.71. Found: C, 63.21; H, 5.40; N, 19.58.

Two-step synthesis of 3-cyanomethyl-2-methoxyquinoline (5a). ***(Z)-Methyl 2-cyanomethyl-3-[2-N-(triphenylphosphoranylidene)phenyl]- propenoate (3a).*** A mixture of 2-cyanomethylazide **2a** (0.97 g, 4 mmole) and Ph_3P (1.15 g, 4.4 mmole) in 10 mL of anhydrous toluene was stirred at room temperature for 4 h. The mixture was concentrated under reduced pressure, and the residue was purified using column chromatography with silica gel and eluted with hexane and ethyl acetate (3:1) providing 1.87 g (98%) of **3a** as a yellow solid: mp 165–166°C (hexane–EtOAc); IR (potassium bromide) 2248, 1704, 1589, 1470 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 3.53 (s, 2H, CH_2), 3.92 (s, 3H, CH_3), 6.50–6.53 (m, 1H, aromatic), 6.70–6.75 (m, 1H, aromatic), 6.93–6.98 (m, 1H, aromatic), 7.27–7.76 (m, 16H, aromatic), 8.73 (s, 1H, CH); ^{13}C-NMR (deuteriochloform) δ 17.3, 52.3, 117.3, 117.9, 118.4, 127.0, 128.4, 128.5, 128.6, 128.7, 128.8, 129.3, 129.9, 130.4, 131.2, 131.8, 131.9, 132.0, 132.1, 132.4, 132.5, 145.5, 151.5, 167.2; ^{31}P-NMR [deuteriochloform/$(PhO)_3PO$] δ 20.57. ms: *m/z* (%) 277 (100), 201 (11), 199 (50). Anal. Calcd. for $C_{30}H_{25}N_2O_2P$: C, 75.62; H, 5.29; N, 5.88. Found: C, 75.40; H, 5.11; N, 5.62.

3-Cyanomethyl-2-methoxyquinoline (5a). Iminophosphorane (0.95 g, 2 mmole) in 10 mL of anhydrous toluene was stirred at reflux temperature for 26 h. The mixture was concentrated under reduced pressure, and the residue was chromatographed on silica gel and eluted with hexane and ethyl acetate (2:1) providing 0.35 g (89%) of **5a** and 0.50 g (90%) of triphenylphosphine oxide in the order of elution: mp 103–104°C (hexane–EtOAc); IR (potassium bromide) 2243, 1629 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 3.80 (d, J = 1.1 Hz, 2H, CH_2), 4.12 (s, 3H, CH_3), 7.39–7.44 (m, 1H, aromatic), 7.62–7.68 (m, 1H, aromatic), 7.73–7.76 (m, 1H, aromatic), 7.84–7.87 (m, 1H, aromatic), 8.09 (s, 1H, aromatic); ^{13}C-NMR (deuteriochloform) δ 19.1, 53.9, 114.8, 117.1, 124.6, 124.8, 127.0, 127.3, 129.9, 137.0, 146.1, 159.1; ms: *m/z* (%) 198 (86) [M^+], 183 (19), 169 (27), 158 (100), 130 (26). Anal. Calcd. $C_{12}H_{10}N_2O$: C, 72.71; H, 5.08; N, 14.13. Found: C, 72.88; H, 4.82; N, 14.03.

General procedure for one-pot synthesis of 2-alkoxy-3-cyanomethylquinoline 5. A mixture of 2-cyanomethylazide **2** (4 mmole) and Ph_3P (1.15 g, 4.4 mmole) in 10 mL of toluene was stirred at reflux temperature for 20–48 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The resulting mixture was chromatographed on silica gel and eluted with hexane and ethyl acetate (2:1) to produce pure quinoline **5**.

3-Cyanomethyl-2-methoxyquinoline (5a). Reaction time: 30 h; yield: 87%; white solid: mp 103–104°C (hexane–EtOAc). The spectral data were the same as previously described.

6-Chloro-3-cyanomethyl-2-methoxyquinoline (5b). Reaction time: 25 h; yield: 83%; white solid: mp 159–160°C (hexane–EtOAc); IR (potassium bromide) 2262, 1632 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 3.80 (d, J = 1.1 Hz 2H, CH_2), 4.11 (s, 3H, CH_3), 7.59 (dd, J = 9.1 and 2.2 Hz, 1H, aromatic), 7.72 (d, J = 2.2 Hz, 1H, aromatic), 7.79 (d, J = 9.1 Hz, 1H, aromatic), 8.01 (s, 1H, aromatic); ^{13}C-NMR (deuteriochloform) δ 19.2, 54.1, 116.0, 116.7, 125.4, 126.1, 128.6, 130.0, 130.6, 136.0, 144.5, 159.3; ms: *m/z* (%) 234 (14), 232 (47) [M^+], 194

(31), 192 (100). Anal. Calcd. for $C_{12}H_9ClN_2O$: C, 61.95; H, 3.90; N, 12.04. Found: C, 61.79; H, 3.73; N, 11.81.

3-Cyanomethyl-2,6-dimethoxyquinoline (5c). Reaction time: 20 h; yield: 75%; white solid: mp 119–120°C (hexane–EtOAc); IR (potassium bromide) 2261, 1619 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 3.78 (d, J = 1.1 Hz, 2H, CH_2), 3.90 (s, 3H, CH_3), 4.08 (s, 3H, CH_3), 7.06 (d, J = 2.8 Hz, 1H, aromatic), 7.30 (dd, J = 9.1 and 2.8 Hz, 1H, aromatic), 7.76 (d, J = 9.1 Hz, 1H, aromatic), 8.01 (s, 1H, aromatic); ^{13}C-NMR (deuteriochloform) δ 19.1, 53.7, 55.5, 105.9, 114.9, 117.1, 121.6, 125.4, 128.3, 136.0, 141.5, 156.4, 157.8; ms: *m*/*z* (%) 228 (93) [M^+], 213 (30), 188 (100), 185 (29). Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.20; H, 5.09; N, 12.41.

3-Cyanomethyl-2-ethoxyquinoline (5d). Reaction time: 48 h; yield: 95%; white solid: mp 79–80°C (hexane–EtOAc); IR (potassium bromide) 2259, 1628 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 1.46 (t, J = 7.2 Hz, 3H, CH_3), 3.80 (d, J = 1.1 Hz, 2H, CH_2), 4.57 (q, J = 7.2 Hz, 2H, CH_2), 7.38–7.43 (m, 1H, aromatic), 7.61–7.66 (m, 1H, aromatic), 7.72–7.75 (m, 1H, aromatic), 7.81–7.84 (m, H, aromatic), 8.09 (s, 1H, aromatic); ^{13}C-NMR (deuteriochloform) δ 14.5, 19.2, 62.4, 114.8, 117.1, 124.5, 124.7, 127.0, 127.3, 129.8, 136.9, 146.2, 158.8; ms: *m*/*z* (%) 212 (24) [M^+], 197 (13), 184 (100), 166 (21), 158 (22). *Anal*. Calcd. for $C_{13}H_{12}N_2O$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.40; H, 5.54; N, 13.07.

2-Butoxy-3-cyanomethylquinoline (5e). Reaction time: 28 h; yield: 87%; white solid: mp 45–46°C (hexane–EtOAc); IR (potassium bromide) 2255, 1625 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 1.01 (t, J = 7.4 Hz, 3H, CH_3), 1.47–1.59 (m, 2H, CH_2), 1.79–1.88 (m, 2H, CH_2), 3.79 (d, J = 1.1 Hz, 2H, CH_2), 4.52 (t, J = 6.6 Hz, 2H, CH_2), 7.38–7.43 (m, 1H, aromatic), 7.61–7.66 (m, H, aromatic), 7.72–7.75 (m, 1H, aromatic), 7.82–7.85 (m, 1H, aromatic), 8.08 (s, 1H, aromatic); ^{13}C-NMR (deuteriochloform) δ 13.9, 19.2, 19.4, 30.9, 66.3, 114.9, 117.1, 124.5, 124.7, 127.0, 127.3, 129.8, 136.9, 146.2, 159.0; ms: *m*/*z* (%) 240 (2) [M^+], 184 (100), 166 (18). Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.78; H, 6.56; N, 11.38.

General procedure for the synthesis of (E)-methyl 3-(2-azidophenyl)-2-nitromethylpropenoates 6. Sodium nitrite (4.4 mmole) was added to a stirred solution of Morita–Baylis–Hillman acetates **1** (4 mmole) in 15 mL of dimethyl formamide at room temperature. After stirring for 40 min to 3 h, the mixture was extracted with diethyl ether (3 × 20 mL). The combined organic layers were dried over anhydrous magnesium sulfate, and the solvent was evaporated under reduced pressure. The residue was purified using column chromatography with silica gel and was eluted with hexane and ethyl acetate (6:1) to produce **6**.

(E)-Methyl 3-(2-azidophenyl)-2-nitromethylpropenoate (6a). Reaction time: 1 h; yield: 74%; light yellow solid: mp 101–102°C (hexane–EtOAc); IR (potassium bromide) 2143, 2102, 1710, 1555, 1302 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 3.88 (s, 3H, CH_3), 5.26 (s, 2H, CH_2), 7.16–7.27 (m, 3H, aromatic), 7.46–7.51 (m, 1H, aromatic), 8.16 (s, 1H, CH); ^{13}C-NMR (deuteriochloform) δ 52.8, 71.8, 118.7, 123.1, 124.9, 125.1, 129.5, 131.5, 139.4, 143.3, 165.8; ms: *m*/*z* (%) 188 (100) [M^+–N_2–NO_2], 156 (55), 128 (31). Anal. Calcd. for $C_{11}H_{10}N_4O_4$: C, 50.38; H, 3.84; N, 21.37. Found: C, 50.07; H, 3.72; N, 21.16.

(E)-Methyl 3-(2-azido-5-chlorophenyl)-2-nitromethylpropenoate (6b). Reaction time: 40 min; yield: 76%; yellow solid: mp 94–95°C (hexane–EtOAc); IR (potassium bromide) 2137, 2102, 1706, 1550, 1298 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 3.88 (s, 3H, CH_3), 5.24 (s, 2H, CH_2), 7.18 (d, J = 8.8 Hz, 1H, aromatic), 7.22 (d, J = 2.5 Hz, 1H, aromatic), 7.44 (dd, J = 8.8 and 2.5 Hz, 1H, aromatic), 8.04 (s, 1H, CH); ^{13}C-NMR (deuteriochloform) δ 52.9, 71.6, 119.9, 124.2, 126.2, 129.2, 130.4, 131.2, 137.8, 141.8, 165.4; ms: *m*/*z* (%) 223 (25), 222 (12) [M^+–N_2–NO_2], 221 (76), 192 (33), 190 (100), 164 (21), 162 (59). Anal. Calcd. for $C_{11}H_9ClN_4O_4$: C, 44.53; H, 3.06; N, 18.89. Found: C, 44.37; H, 2.85; N, 18.67.

(E)-Methyl 3-(2-azido-5-methoxyphenyl)-2-nitromethylpropenoate (6c). Reaction time: 100 min; yield: 66%; yellow solid: mp 95–96°C (hexane–EtOAc); IR (potassium bromide) 2140, 2130, 1700, 1551, 1299 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 3.77 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 5.27 (s, 2H, CH_2), 6.76 (d, J = 2.8 Hz, 1H, aromatic), 7.02 (dd, J = 8.8 and 2.8 Hz, 1H, aromatic), 7.16 (d, J = 9.1 Hz, 1H, aromatic), 8.12 (s, 1H, CH); ^{13}C-NMR (deuteriochloform) δ 52.8, 55.6, 71.9, 114.0, 117.4, 119.8, 123.3, 125.6, 131.5, 143.3, 156.7, 165.7; ms: *m*/*z* (%) 218 (15) [M^+–N_2–NO_2], 217 (100), 186 (72), 158 (52). Anal. Calcd. for $C_{12}H_{12}N_4O_5$: C, 49.32; H, 4.14; N, 19.17. Found: C, 49.14; H, 3.98; N, 18.89.

(E)-Ethyl 3-(2-azidophenyl)-2-nitromethylpropenoate (6d). Reaction time: 3 h; yield: 67%; light yellow solid: mp 104°C (hexane–EtOAc); IR (potassium bromide) 2142, 2101, 1701, 1553, 1299 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 1.36 (t, J = 7.2 Hz, 3H, CH_3), 4.33 (q, J = 7.2 Hz, 2H, CH_2), 5.25 (s, 3H, CH_3), 7.16–7.27 (m, 3H, aromatic), 7.45–7.51 (m, 1H, aromatic), 8.15 (s, 1H, CH); ^{13}C-NMR (deuteriochloform) δ 14.1, 61.9, 71.9, 118.7, 123.5, 125.0, 125.1, 129.5, 131.4, 139.3, 143.0, 165.2; ms: *m*/*z* (%) 202 (12) [M^+–N_2–NO_2], 201 (77), 173 (92), 156 (100), 128 (80). Anal. Calcd. for $C_{12}H_{12}N_4O_4$: C, 52.17; H, 4.38; N, 20.28. Found: C, 52.28; H, 4.31; N, 20.04.

(E)-Butyl 3-(2-azidophenyl)-2-nitromethylpropenoate (6e). Reaction time: 2 h; yield: 82%; brown oil; IR (neat) 2129, 1713, 1558, 1294 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 0.97 (t, J = 7.2 Hz, 3H, CH_3), 1.36–1.49 (m, 2H, CH_2), 1.66–1.75 (m, 2H, CH_2), 4.28 (t, J = 6.6 Hz, 2H, CH_2), 5.25 (s, 2H, CH_2), 7.16–7.26 (m, 3H, aromatic), 7.45–7.51 (m, 1H, aromatic), 8.15 (s, 1H, CH); ^{13}C-NMR (deuteriochloform) δ 13.7, 19.1, 30.5, 65.7, 71.9, 118.7, 123.5, 125.0, 125.1, 129.5, 131.4, 139.4, 143.0, 165.3; ms: *m*/*z* (%) 229 (10), 228 (22), 173 (100), 156 (40), 155 (51), 128 (39). Anal. Calcd. for $C_{14}H_{16}N_4O_4$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.02; H, 5.07; N, 18.26.

Two-step synthesis of methyl quinoline-3-carboxylate (10a). ***(Z)-Methyl 2-nitromethyl-3-[2-N-(triphenylphosphoranylidene)phenyl]-propenoate (7a).*** A mixture of 2-nitromethylazide **6a** (1.05 g, 4 mmole) and Ph_3P (1.15 g, 4.4 mmole) in 10 mL of anhydrous toluene was stirred at room temperature for 30 min. The mixture was concentrated under reduced pressure, and the residue was purified using column chromatography with silica gel and was eluted with hexane and ethyl acetate (2:1) providing 1.81 g (91%) of **7a** as a yellow solid: mp 153°C (hexane–EtOAc); IR (potassium bromide) 1707, 1553, 1469, 1436 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 3.89 (s, 3H, CH_3), 5.37 (s, 2H, CH_2), 6.49–6.52 (m, 1H, aromatic), 6.63–6.68 (m, 1H, aromatic), 6.93–6.99 (m, 1H, aromatic),

7.09–7.13 (m, 1H, aromatic), 7.43–7.59 (m, 9H, aromatic), 7.69–7.76 (m, 6H, aromatic), 8.95 (s, 1H, CH); ^{13}C-NMR (deuteriochloform) δ 52.2, 72.9, 117.4, 118.0, 128.1, 128.4, 128.6, 128.8, 128.9, 129.8, 130.9, 131.1, 131.9, 132.0, 132.4, 132.5, 149.3, 151.8, 167.3; ^{31}P-NMR [deuteriochloform/$(PhO)_3PO$] δ 20.94. ms: *m*/*z* (%) 277 (100), 199 (45). Anal. Calcd. for $C_{29}H_{25}N_2O_4P$: C, 70.15; H, 5.08; N, 5.64. Found: C, 69.91; H, 4.79; N, 5.43.

Methyl quinoline-3-carboxylate (10a). Iminophosphorane **7a** (0.98 g, 2 mmole) in 5 mL of anhydrous toluene was stirred at reflux temperature for 22 h. The mixture was concentrated under reduced pressure, and the residue was chromatographed on silica gel and was eluted with hexane and ethyl acetate (2:1) providing 0.20 g (54%) of **10a** as a white solid and 0.35 g (63%) of triphenylphosphine oxide in the order of elution: mp 76–77°C (hexane–EtOAc); IR (potassium bromide) 1723 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 4.02 (s, 3H, CH_3), 7.60–7.65 (m, 1H, aromatic), 7.81–7.87 (m, 1H, aromatic), 7.93 (d, J = 8.0 Hz, 1H, aromatic), 8.17 (d, J = 8.5 Hz, 1H, aromatic), 8.85 (d, J = 1.7 Hz, 1H, aromatic), 9.45 (d, J = 2.2 Hz, 1H, aromatic); ^{13}C-NMR (deuteriochloform) δ 52.5, 122.9, 126.7, 127.4, 129.1, 129.4, 131.8, 138.7, 149.7, 149.9, 165.8; ms: *m*/*z* (%) 187 (52) [M$^+$], 156 (80), 128 (100) [5,12].

General procedure for one-pot synthesis of alkyl quinoline-3-carboxylates 10. A mixture of 2-nitromethylazide **6** (4 mmole) and Ph_3P (1.15 g, 4.4 mmole) in 10 mL of toluene was stirred at reflux temperature for 8–50 h. The mixture was cooled to room temperature and concentrated under reduced pressure. The resulting mixture was chromatographed on silica gel and was eluted with hexane and ethyl acetate (2:1) to produce pure quinoline **10**.

Methyl quinoline-3-carboxylate (10a). Reaction time: 22 h; yield: 48%; white solid: mp 76–77°C (hexane–EtOAc). The spectral data were the same as previously described.

Methyl 6-chloroquinoline-3-carboxylate (10b). Reaction time: 27 h; yield: 49%; white solid: mp 169–170°C (hexane–EtOAc); IR (potassium bromide) 1723 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 4.03 (s, 3H, CH_3), 7.76 (dd, J = 9.0 and 2.2 Hz, 1H, aromatic), 7.91 (d, J = 2.2 Hz, 1H, aromatic), 8.10 (d, J = 9.0 Hz, 1H, aromatic), 8.75 (d, J = 1.7 Hz, 1H, aromatic), 9.43 (d, J = 1.9 Hz, 1H, aromatic),^{13}C-NMR (deuteriochloform) δ 52.6, 123.7, 127.4, 127.5, 131.0, 132.7, 133.3, 137.7, 148.1, 150.1, 165.4 [5,12(a)].

Methyl 6-methoxyquinoline-3-carboxylate (10c). Reaction time: 8 h; yield: 41%; light yellow solid: mp 119–120°C (hexane–EtOAc); IR (potassium bromide) 1710 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 3.95 (s, 3H, CH_3), 4.01 (s, 3H, CH_3), 7.15 (d, J = 2.8 Hz, 1H, aromatic), 7.47 (dd, J = 9.3 and 2.8 Hz, 1H, aromatic), 8.04 (d, J = 9.3 Hz, 1H, aromatic), 8.72 (d, J = 1.7 Hz, 1H, aromatic), 9.29 (d, J = 2.2 Hz, 1H, aromatic); ^{13}C-NMR (deuteriochloform) δ 52.4, 55.6, 105.9, 123.1, 124.7, 127.9, 130.7, 137.3, 146.0, 147.5, 158.2, 166.0 [5].

Ethyl quinoline-3-carboxylate (10d). Reaction time: 12 h; yield: 42%; white solid: mp 63–65°C (hexane–EtOAc); IR (potassium bromide) 1713 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 1.47 (t, J = 7.2 Hz, 3H, CH_3), 4.49 (q, J = 7.2 Hz, 2H, CH_2), 7.60–7.65 (m, 1H, aromatic), 7.81–7.87 (m, 1H, aromatic), 7.94 (d, J = 8.3 Hz, 1H, aromatic), 8.17 (d, J = 8.3 Hz, 1H, aromatic), 8.85 (d, J = 1.9 Hz, 1H, aromatic), 9.46 (d, J = 2.2 Hz, 1H, aromatic); ^{13}C-NMR (deuteriochloform) δ 14.3, 61.5, 123.2, 126.8, 127.4, 129.1, 129.4, 131.7, 138.6, 149.8, 150.0, 165.3 [13].

Butyl quinoline-3-carboxylate (10e). Reaction time: 20 h; yield: 40%; yellow oil; IR (neat) 1720 cm^{-1}; ^{1}H-NMR (deuteriochloform) δ 1.02 (t, J = 7.4 Hz, 3H, CH_3), 1.47–1.59 (m, 2H, CH_2), 1.78–1.88 (m, 2H, CH_2), 4.43 (t, J = 6.6 Hz, 2H, CH_2), 7.61–7.66 (m, 1H, aromatic), 7.82–7.87 (m, 1H, aromatic), 7.96 (d, J = 8.0 Hz, 1H, aromatic), 8.18 (d, J = 8.5 Hz, 1H, aromatic), 8.85 (d, J = 2.2 Hz, 1H, aromatic), 9.46 (d, J = 2.2 Hz, 1H, aromatic); ^{13}C-NMR (deuteriochloform) δ 13.8, 19.2, 30.7, 65.4, 122.3, 126.8, 127.4, 129.1, 129.4, 131.8, 138.7, 149.8, 150.1, 165.4; ms: *m*/*z* (%) 229 (8) [M$^+$], 228 (13), 173 (100), 155 (47), 128 (32). Anal. Calcd. for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.21; H, 6.38; N, 6.03.

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REFERENCES AND NOTES

[1] For reviews of the Morita–Baylis–Hillman reaction, see: (a) Drewes, S. E.; Roos, G. H. P. Tetrahedron 1988, 44, 4653; (b) Basavaiah, D.; Rao, P. D.; Hyma, R. S. Tetrahedron 1996, 52, 8001; (c) Ciganek, E. Org React 1997, 51, 201; (d) Langer, P. Angew Chem Int Ed 2000, 39, 3049; (e) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. Chem Rev 2003, 103, 811; (f) Kataoka, T.; Kinoshita, H. Eur J Org Chem 2005, 45; (g) Basavaiah, D.; Rao, K. V.; Reddy, R. J Chem Soc Rev 2007, 36, 1581; (h) Singh, V.; Batra, S. Tetrahedron 2008, 64, 4511; (i) Declerck, V.; Martinez, J.; Lamaty, F. Chem Rev 2009, 109, 1; (j) Ma, G.-N.; Jiang, J.-J.; Shi, M.; Wei, Y. Chem Commun 2009, 5496.

[2] Michael, J. P. Nat Prod Rep 1997, 14, 605.

[3] (a) McAteer, C. H.; Balasubramanian, M.; Murugan, R. In Comprehensive Heterocyclic Chemistry III; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Pergamon Press: Oxford, 2008; Vol. 7, pp 309–336; (b) Gray, N. M.; Dappen, M. S.; Cheng, B. K.; Cordi, A. A.; Biesterfeldt, J. P.; Hood, W. F.; Monahan, J. B. J Med Chem 1991, 34, 1283; (c) Baston, E.; Palusczak, A.; Hartmann, R. W. Eur J Med Chem 2000, 35, 931; (d) Hazeldine, S. T.; Polin, L.; Kushner. J.; White, K.; Corbett, T. H.; Biehl, J.; Horwitz, J. P. Bioorg Med Chem 2005, 13, 1069; (e) Upadhayaya, R. S.; Vandavasi, J. K.; Vasireddy, N. R.; Sharma, V.; Dixit, S. S.; Chattopadhyaya, J. Bioorg Med Chem 2009, 17, 2830.

[4] For a recent review of the synthesis of substituted quinolines and quinoline-annulated ring systems, see: (a) Madapa, S.; Tusi, Z.; Batra, S. Curr Org Chem 2008, 12, 1116, and references cited therein; For other examples, see: (b) Keller, P. A. In Comprehensive Heterocyclic Chemistry III; Katritzky, A. R., Ramsden, C. A., Scriven, E. F. V., Taylor, R. J. K., Eds.; Pergamon Press: Oxford, 2008; Vol. 7, pp 217–308; (c) Qiang, L. G.; Baine, N. H. J Org Chem 1988, 53, 4218; (d) Meanwell, N. A.; Roth, H. R.; Smith, E. C. R.; Wedding, D. L.; Wright, J. J. K.; Fleming, J. S.; Gillespie, E. J Med Chem 1991, 34, 2906; (e) Radl, S.; Bouzard, D. Heterocycles 1992, 34, 2143; (f) Dow, R. L.; Bechle, B. M.; Chou, T. T.; Goddard, C.; Larson, E. R. Bioorg Med Chem Lett 1995, 5, 1007; (g) Ruhland, T.; Kunzer, H. Tetrahedron Lett 1996, 37, 2757; (h) Katritzky, A. R.; Arend, M. J Org Chem 1998, 63, 9989; (i) Suginome, M.; Fukuda, T.; Ito, Y. Org Lett 1999, 1, 1977; (j) Cacchi, S.; Fabrizi, G.; Marinelli, F. Synlett 1999, 401; (k) Cho, C. S.; Oh, B. H.; Shim, S. C. Tetrahedron Lett 1999, 40, 1499; (l) Ranu, B. C.; Hajra, A.; Jana, U. Tetrahedron Lett 2000, 41, 531; (m) Kim, J. N.; Lee, H. J.; Lee, K. Y.; Kim, H. S. Tetrahedron Lett 2001, 42, 3737; (n) Familoni, O. B.; Klaas, P. J.; Lobb, K. A.; Pakade, V. E.; Kaye, P. T. Org Biomol Chem 2006, 4, 3960; (o) Basavaiah, D.; Reddy, R. J.; Rao,

J. S. Tetrahedron Lett 2006, 47, 73; (p) Narender, P.; Srinivas, U.; Ravinder, M.; Ananda Rao, B.; Ramesh, C.; Harakishore, K.; Gangadasu, B.; Murthy, U. S. N.; Jayathirtha Rao, V. Bioorg Med Chem 2006, 14, 4600; (q) Madapa, S.; Singh, V.; Batra, S. Tetrahedron 2006, 62, 8740; (r) Pathak, R.; Madapa, S.; Batra, S. Tetrahedron 2007, 63, 4511; (s) Gowrisankar, S.; Lee, H. S.; Kim, J. M.; Kim, J. N. Tetrahedron Lett 2008, 49, 1670; (t) Colacino, E.; André, C.; Martinez, J.; Lamaty, F. Tetrahedron Lett 2008, 49, 4953; (u) Singh, V.; Singh, V.; Batra, S. Eur J Org Chem 2008, 5446; (v) Singh, V.; Hutait, S.; Batra, S. Eur J Org Chem 2009, 3454; (w) Amarante, G. W.; Benassi, M.; Pascoal, R. N.; Eberlin, M. N.; Coelho, F. Tetrahedron 2010, 66, 4370; (x) Ramesh, C.; Kavala, V.; Kuo, C.-W.; Yao, C.-F. Tetrahedron Lett 2010, 51, 5234.

[5] Han, E.-G.; Kim, H. J.; Lee, K.-J. Tetrahedron 2009, 65, 9616.

[6] For our recent examples, see: (a) Song, Y. S.; Lee, C. H.; Lee, K.-J. J Heterocycl Chem 2003, 40, 939; (b) Ko, S. H.; Lee, K.-J. J Heterocycl Chem 2004, 41, 613; (c) Park, J. B.; Ko, S. H.; Kim, B. G.; Hong, W. P.; Lee, K.-J. Bull Korean Chem Soc 2004, 25, 27; (d) Park, J. B.; Ko, S. H.; Hong, W. P.; Lee, K.-J. Bull Korean Chem Soc 2004, 25, 927; (e) Hong, W. P.; Lim, H. N.; Park, H. W.; Lee, K.-J. Bull Korean Chem Soc 2005, 26, 655; (f) Hong, W. P.; Lee, K.-J. Synthesis 2006, 963; (g) Song, Y. S.; Lee, K.-J. J Heterocycl Chem 2006, 43, 1721; (h) Lim, H. N.; Ji, S.-H.; Lee, K.-J. Synthesis 2007, 2454; (i) Song, Y. S.; Lee, K.-J. Synthesis 2007, 3037; (j) Lim, H. N.; Song, Y. S.; Lee, K.-J. Synthesis 2007, 3376; (k) Jeon, K. J.; Lee, K.-J. J Heterocycl Chem 2008, 45, 615; (l) Ahn, S. H.; Lim, H. N.; Lee, K.-J. J Heterocycl Chem 2008, 45, 1701; (m) Park, S. P.; Song, Y. S.; Lee, K.-J. Tetrahedron 2009, 65, 4703; (n) Park, S. P.; Ahn, S.-H. Tetrahedron 2010, 66, 3490.

[7] Lee, C. H.; Song, Y. S.; Cho, H. I.; Yang, J. W.; Lee, K.-J. J Heterocycl Chem 2003, 40, 1103.

[8] For early our reports on the displacement reaction of the Morita–Baylis–Hillman acetates with nitrite ion, see: (a) Hong, W. P.; Lee, K.-J. Synthesis 2005, 33; (b) Ji, S.-H.; Hong, W. P.; Ko, S. H.; Lee, K.-J. J Heterocycl Chem 2006, 43, 799.

[9] (a) Atkinson, R. N.; Storey, B. M.; King, S. B. Tetrahedron Lett 1996, 37, 9287; (b) Cohen, A. D.; Zeng, B.-B.; King, S. B.; Toscano, J. P. J Am Chem Soc 2003, 125, 1444.

[10] For recent reports on the cyclization reactions employing nitro compounds as a leaving group due to the loss of hyponitrous acid, see: (a) Singh, V.; Kanojiya, S.; Batra, S. Tetrahedron 2006, 62, 10100; (b) Singh, V.; Batra, S. Eur J Org Chem 2007, 2970.

[11] Yi, H.-W.; Park, H. W.; Song, Y. S.; Lee, K.-J. Synthesis 2006, 1953.

[12] (a) O'Dell, D. K.; Nicholas, K. M. J Org Chem 2003, 68, 6427; (b) Cain, M.; Weber, R. W.; Guzman, F.; Cook, J. M.; Barker, S. A.; Rice, K. C.; Crawley, J. N.; Paul, S. M.; Skolnick, P. J Med Chem 1982, 25, 1081.

[13] Chung, Y. M.; Lee, H. J.; Hwang, S. S.; Kim, J. N. Bull Korean Chem Soc 2001, 22, 799.