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A convenient synthesis of quinolines by reactions of *o*-isocyano-β-methoxystyrenes with nucleophiles

Kazuhiro Kobayashi,* Keiichi Yoneda, Kazuna Miyamoto, Osamu Morikawa and Hisatoshi Konishi

Department of Materials Science, Faculty of Engineering, Tottori University, Koyama-minami, Tottori 680-8552, Japan

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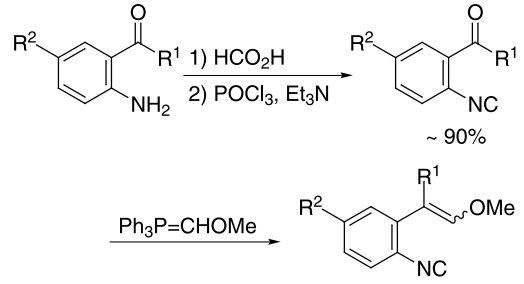
Abstract—2,4-Disubstituted quinolines have been synthesized by reactions of *o*-isocyano-β-methoxystyrenes, which can be easily prepared from commercially available *o*-aminophenyl ketones in three steps, with alkyl(or aryl)lithiums in generally good yields. Subsequently, *o*-isocyano-β-methoxystyrenes have also proved to react efficiently with lithium dialkylamides to afford the corresponding 4-substituted *N*,*N*-dialkylquinolin-2-amines in satisfactory yields.

There has been substantial interest in quinoline derivatives, because some of them are known to occur in nature,[1] and exhibit a wide variety of biological activities.[2] Moreover, they have been utilized as intermediates for the design of biologically active compounds.[3] Therefore, a large number of general methods for the preparation of substituted quinolines have recently been reported,[4] and any new general route to quinoline derivatives is of interest and value. In this paper we wish to report in full on the results of our investigation,[5,6] which offer a simple and general method for preparing 2,4-disubstituted quinolines and 4-substituted *N*,*N*-dialkylquinolin-2-amines by reactions of *o*-isocyano-β-methoxystyrenes with alkyl(or aryl)lithiums and lithium dialkylamides, respectively.[7] 2-Alkylated quinoline derivatives[8] and quinolin-2-amines[9] have been reported to exhibit notable biological activities.

1. Results and discussion

o-Isocyano-β-methoxystyrenes **1** were prepared in three steps from commercially available 2-aminophenylketones as shown in Scheme 1. Thus, formylation of 2-aminophenyl ketones with formic acid afforded the corresponding formamides, which were dehydrated by treatment with phosphoryl chloride/triethylamine to afford 2-isocyanophenyl ketones. Wittig reaction of these isocyano ketones with (methoxymethyl)triphenylphosphonium ylide gave *o*-isocyano-β-methoxystyrene derivatives **1**, as a mixture of stereoisomers in each case. The ratios of stereoisomers were determined by ^{1}H NMR spectral data (see Section 2).

The reactions of *o*-isocyano-β-methoxystyrenes **1** with aryl(or alkyl)lithiums **2** were conducted as shown in Scheme 2. Thus, after treatment of the isocyanides **1** with organolithiums **2** (1.5 equiv) at −78 °C in 1,2-dimethoxyethane (DME), the mixtures were allowed to warm to room temperature. Usual aqueous workup, followed by purification using preparative TLC on silica gel, gave 2,4-disubstituted quinolines **3**. The results summarized in Table 1 demonstrate that the good yields of the desired 2,4-disubstituted quinolines **3a**–**3i** were obtained in general (entries 1–9), though somewhat poorer yields of the desired products **3j** and **3k** were obtained by using *o*-isocyano-β-methoxy-α-methylstyrene (**1c**) (entries 10 and 11). When the reactions were conducted in THF, rather diminished



1a R^1 = Ph, R^2 = H 72% (*E*:*Z* = ~1:1)
1b R^1 = Ph, R^2 = Cl 67% (*E*:*Z* = ~1:1)
1c R^1 = Me, R^2 = H 70% (*E*:*Z* = ~7:3)

Scheme 1.

Keywords: Isocyanide; Lithium amide; Organolithium; Quinoline; Styrene.
* Corresponding author. Tel./fax: +81 857 31 5263;
e-mail: kkoba@chem.tottori-u.ac.jp

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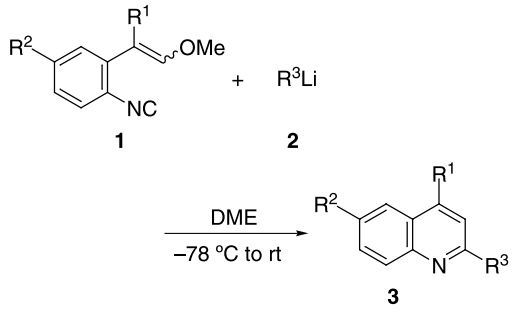


Scheme 2.

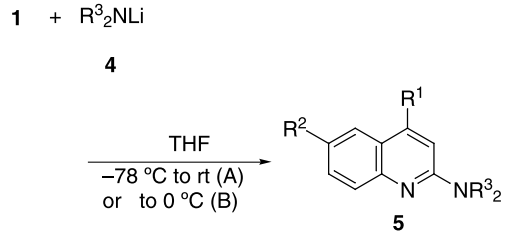
Table 1. Preparation of 2,4-disubstituted quinolines **3** according to Scheme 2

Entry	Isocyanide **1**	Organolithium **2**	**3** (Yield/%)[a]
1	**1a** (R^1=Ph, R^2=H)	**2a** (R^3=*n*-Bu)	**3a** (79)
2	**1a**	**2b** (R^3=*sec*-Bu)	**3b** (84)
3	**1a**	**2c** (R^3=*tert*-Bu)	**3c** (89)
4	**1a**	**2d** (R^3=Ph)	**3d** (91)
5	**1a**	**2e** (R^3=*p*-Tol)	**3e** (88)
6	**1a**	**2f** (R^3=2-thienyl)	**3f** (74)
7	**1a**	**2g** (R^3=2-furyl)	**3g** (75)
8	**1b** (R^1=Ph, R^2=Cl)	**2c**	**3h** (87)
9	**1b**	**2d**	**3i** (85)
10	**1c** (R^1=Me, R^2=H)	**2c**	**3j** (58)
11	**1c**	**2d**	**3k** (55)

[a] Isolated yields after purification by preparative TLC on silica gel.

yields of the desired products were obtained. For example, the reaction of **1a** with **2a** in THF under the same conditions as described above in DME led to the formation of rather complex reaction mixture and the desired product **3a** was obtained only in 41% yield. This is probably attributable to the lability of THF to organolithiums. It should be noted that the reaction of **1a** with PhMgBr gave an intractable mixture of products, from which no more than a trace amount of **3a** was obtained.

We anticipated that the use of lithium dialkylamide in place of alkyl(or aryl)lithiums would be expected to afford *N*,*N*-dialkylquinolin-2-amine derivatives, and the reactions of *o*-isocyano-β-methoxystyrenes **1** with lithium dialkylamides **4** were carried out as shown in Scheme 3. Thus, isocyanides **1** were treated with lithium amides **4** (1.2 equiv in general), generated by the treatment of secondary amines with butyllithium, in THF at −78 °C, and then the mixtures

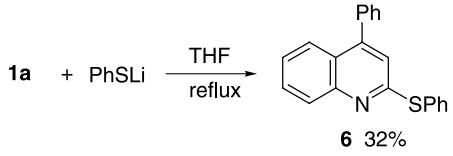


Scheme 3.

were allowed to warm to room temperature (Method A). Usual aqueous workup, followed by purification using preparative TLC on silica gel, gave 4-substituted *N*,*N*-dialkylquinolin-2-amines **5**. The results are summarized in Table 2. Two equivalents each of lithium dialkylamides generated from bulky secondary amines, such as diisopropylamine or dicyclohexylamine, were used for satisfactory production of the desired products (entries 2, 3 and 11). In order to obtain satisfactory yields of **5h** and **5i** (entries 9 and 10), the reaction temperature was raised to only 0 °C (Method B) considering the lability of chloride under the reaction conditions (entry 8). Although the reactions using *o*-isocyano-β-methoxy-α-phenylstyrenes **1a** and **1b** gave the desired quinoline-2-amines **5a**–**5i** in moderate to fair yields (entries 1–7, 9 and 10), the use of *o*-isocyano-β-methoxy-α-methylstyrene (**1c**) afforded the desired products **5j** and **5k** only in rather poor yields (entries 11 and 12). In these cases rather complex reaction mixtures including small quantities of the starting **1c** were obtained.

Subsequently, the possibility of the preparation of 2-sulfenylated quinoline derivatives was examined. Scheme 4 shows that benzenethiolate is usable as a nucleophile in the present method but under reflux conditions in THF to afford 2-phenylthio-4-phenylquinoline (**6**) in low yield. This reaction gave a rather complicated reaction mixture including a fair amount of the starting **1a**.

The production of quinoline derivatives **3**, **5**, and **6** may be

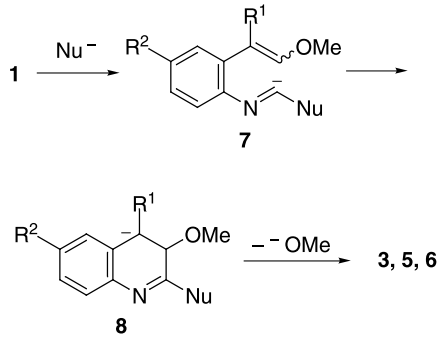


Scheme 4.

Table 2. Preparation of quinolin-2-amines **5** according to Scheme 3

Entry	Isocyanide **1**	Lithium amide **4**	Equiv	Method	**5** (Yield/%)[a]
1	**1a**	**4a** (NR^3_2=NEt_2)	1.2	A	**5a** (60)
2	**1a**	**4b** (NR^3_2=N*i*-Pr_2)	2.0	A	**5b** (61)
3	**1a**	**4c** (NR^3_2=N*c*-Hex_2)	2.0	A	**5c** (45)
4	**1a**	**4d** (NR^3_2=pyrrolidin-1-yl)	1.2	A	**5d** (64)
5	**1a**	**4e** (NR^3_2=piperidin-1-yl)	1.2	A	**5e** (72)
6	**1a**	**4f** (NR^3_2=morpholin-1-yl)	1.2	A	**5f** (55)
7	**1a**	**4g** (NR^3_2=4-methylpiperazin-1-yl)	1.2	A	**5g** (77)
8	**1b**	**4d**	1.2	A	**5h** (35)
9	**1b**	**4d**	1.2	B	**5h** (50)
10	**1b**	**4e**	1.2	B	**5i** (52)
11	**1c**	**4b**	2.0	A	**5j** (16)
12	**1c**	**4e**	1.2	A	**5k** (15)

[a] Isolated yields after purification by preparative TLC on silica gel.



Scheme 5.

interpreted as illustrated in Scheme 5. The α-addition of a nucleophile to the isocyano carbon of **1** resulted in formation of the imidoyl anion intermediate **7**. This anion attacks to the α-carbon atom of the methoxyvinyl moiety of **7** to afford the benzyl anion intermediate **8**, which, after a loss of methoxide, provides **3**, **5**, and **6**. The yields of the products are thought to depend upon the nucleophilicity of the nucleophiles. The poorer results of the reactions using **1c** is presumed to be ascribed to the lower stability of the corresponding intermediate benzyl anions compared to those from **1a** and **1b**.

In conclusion, we have demonstrated that the reactions of *o*-isocyano-β-methoxystyrene derivatives with nucleophiles, such as alkyl(or aryl)lithiums, lithium dialkylamides, or lithium benzenethiolate, provide a new method for the preparation of 2,4-disubstituted quinolines. The present method may find some value in organic synthesis because of its efficiency, the ready availability of the starting materials and the ease of operation.

2. Experimental

2.1. General

The melting points were determined on a Laboratory Devices MEL-TEMP II melting-point apparatus and are uncorrected. The IR spectra were recorded on a Perkin–Elmer 1600 Series FT IR spectrometer. The ^{1}H NMR spectra were determined using $SiMe_4$ as an internal reference with a JEOL JNM-GX270 FT NMR spectrometer operating at 270 MHz in $CDCl_3$. Low-resolution mass spectra were recorded on a JEOL AUTOMASS 20 spectrometer (Center for Joint Research and Development, this University). High-resolution mass spectra were performed on a JEOL JMS AX505 HA spectrometer (Faculty of Agriculture, this University). Thin-layer chromatography (TLC) was carried out on Merck Kieselgel 60 PF_{254}. All of the solvents used were dried over appropriate drying agents and distilled under argon prior to use.

2.2. Starting materials

2-Isocyanophenyl ketones were prepared from the corresponding commercially available 2-aminophenyl ketones by formylation with formic acid in toluene at reflux temperature, followed by dehydration with $POCl_3/Et_3N$ in THF at 0 °C. 2-Isocyanobenzophenone: 87% yield from 2-aminobenzophenone; a pale-yellow solid; mp 95–96 °C (hexane–CH_2Cl_2); IR (KBr disk) 2123, 1660 cm^{-1}; ^{1}H NMR δ 7.45–7.7 (7H, m), 7.81 (2H, dd, J=8.3, 1.6 Hz). Calcd for $C_{14}H_9NO$: C, 81.14; H, 4.38; N, 6.76. Found: C, 81.11; H, 4.33; N, 7.01. 5-Chloro-2-isocyanobenzophenone: 88% yield from 2-amino-5-chlorobenzophenone; a pale-yellow solid; mp 84–85 °C (hexane–CH_2Cl_2); IR (KBr disk) 2125, 1662 cm^{-1}; ^{1}H NMR δ 7.4–7.7 (6H, m), 7.82 (2H, dd, J=8.2, 1.3 Hz). Calcd for $C_{14}H_8ClNO$: C, 69.58; H, 3.34; N, 5.80. Found: C, 69.28; H, 3.51; N, 5.53. 2-Isocyanoacetophenone: 74% from 2′-aminoacetophenone; a yellow oil; IR (neat) 2124, 1696 cm^{-1}; ^{1}H NMR δ 2.72 (3H, s), 7.45–7.6 (3H, m), 7.78 (1H, dd, J=7.9, 1.6 Hz). The last isocyanide was rather unstable and used in the next step without any purification after workup. All other chemicals used in this study are commercially available.

2.3. Typical procedure for the preparation of isocyanostyrenes 1

2.3.1. 1-Isocyano-2-(2-methoxy-1-phenylethenyl)benzene (1a). To a stirred suspension of (methoxymethyl)triphenylphosphonium chloride (0.96 g, 2.9 mmol) in THF (15 mL) at 0 °C under argon was added butyllithium (2.9 mmol; 1.6 M solution in hexanes) dropwise; the mixture was stirred for 15 min. To this ylide solution 2-isocyanobenzophenone (0.50 g, 2.4 mmol) in THF (5 mL) was added. The mixture was allowed to warm to room temperature and stirring was continued for 30 min. The reaction was quenched by adding water (20 mL) and the organic materials were extracted with Et_2O three times (20 mL each). The combined extracts were washed with water three times and then brine, dried over anhydrous K_2CO_3, and evaporated. The crude product was purified by chromatography on silica gel to give **1a** (0.42 g, 72%) as a pale-yellow viscous oil; a mixture of stereoisomers (*E*/*Z*= ca. 1:1): R_f 0.66 (1:3 EtOAc–hexane); IR (neat) 2123, 1636 cm^{-1}; ^{1}H NMR δ 3.81 (1.5H, s), 3.83 (1.5H, s), 6.38 (0.5H, s), 6.69 (0.5 H, s), 7.05–7.5 (9H, m); MS *m*/*z* 235 (M^+, 97), 165 (100). Calcd for $C_{16}H_{13}NO$: M, 235.0997. Found: *m*/*z* 235.0994.

2.3.2. 4-Chloro-1-isocyano-2-(2-methoxy-1-phenylethenyl)benzene (1b). A pale-yellow viscous oil; a mixture of stereoisomers (*E*/*Z*=ca. 1:1): R_f 0.61 (1:3 EtOAc–hexane); IR (neat) 2123, 1636 cm^{-1}; ^{1}H NMR δ 3.82 (1.5H, s), 3.84 (1.5H, s), 6.40 (0.5 H, s), 6.69 (0.5H, s), 7.10 (1H, dd, J= 7.9, 1.6 Hz), 7.2–7.4 (7H, m); MS *m*/*z* 269 (M^+, 100). Calcd for $C_{16}H_{12}ClNO$: M, 269.0607. Found: *m*/*z* 269.0624.

2.3.3. 1-Isocyano-2-(2-methoxy-1-methylethenyl)benzene (1c). A pale-yellow oil; a mixture of stereoisomers (*E*/*Z*=*ca.* 7:3): R_f 0.31 (1:10 EtOAc–hexane); IR (neat) 2124, 1666 cm^{-1}; ^{1}H NMR δ 1.91 (2.1H, d, J=1.3 Hz), 2.00 (0.9H, d, J=1.3 Hz), 3.63 (2.1H, s), 3.73 (0.9 H, s), 6.13 (0.7H, q, J=1.3 Hz), 6.23 (0.3H, q, J=1.3 Hz), 7.15–7.4 (4H, m); MS *m*/*z* 173 (M^+, 60), 130 (100). Calcd for $C_{11}H_{11}NO$: M, 173.0841. Found: *m*/*z* 173.0861.

2.4. Typical procedure for the preparation of 2,4-disubstituted quinolines 3

2.4.1. 2-Butyl-4-phenylquinoline (3a). To a stirred solution of isocyanostyrene **1a** (0.12 g, 0.51 mmol) in DME (2.5 mL) at −78 °C under argon was added dropwise butyllithium (0.77 mmol; 1.57 M in hexane solution). After stirring for 30 min at this temperature, the mixture was allowed to warm to room temperature and stirring was continued for an additional 30 min. Saturated aqueous ammonium chloride (15 mL) was added and the mixture was extracted with Et_2O three times (15 mL each). The combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and evaporated. The residue was purified by preparative TLC on silica gel to give **3a** (0.11 g, 79%) as a pale-yellow viscous oil: R_f 0.67 (1:3 EtOAc–hexane); IR (neat) 3058, 2955, 1592, 1557, 1490, 765, 701 cm^{-1}; ^1H NMR δ 0.97 (3H, t, J=7.3 Hz), 1.47 (2H, sextet, J=7.3 Hz), 1.75–1.9 (2H, m), 3.01 (2H, t, J=7.9 Hz), 7.24 (1H, s), 7.43 (1H, ddd, J=8.2, 7.3, 1.3 Hz), 7.5–7.6 (5H, m), 7.68 (1H, ddd, J=8.2, 7.3, 1.3 Hz), 7.86 (1H, dd, J=8.2, 1.3 Hz), 8.11 (1H, dd, J=8.2, 1.3 Hz); MS m/z 261 (M^+, 1.1), 246 (6.9), 232 (19), 219 (100). Calcd for $C_{19}H_{19}N$: C, 87.31; H, 7.33; N, 5.36. Found: C, 87.09; H, 7.20; N, 5.36.

2.4.2. 2-(1-Methylpropyl)-4-phenylquinoline (3b). A pale-yellow viscous oil; R_f 0.74 (1:3 EtOAc–hexane); IR (neat) 3056, 2960, 1592, 1557, 1491, 772, 701 cm^{-1}; ^1H NMR δ 0.93 (3H, t, J=7.3 Hz), 1.40 (3H, d, J=6.9 Hz), 1.65–2.0 (2H, m), 2.95–3.15 (1H, m), 7.23 (1H, s), 7.43 (1H, ddd, J=8.2, 7.3, 1.3 Hz), 7.5–7.55 (5H, m), 7.68 (1H, ddd, J=8.2, 7.3, 1.3 Hz), 7.86 (1H, dd, J=8.2, 1.3 Hz), 8.12 (1H, dd, J=8.2, 1.3 Hz); MS m/z 261 (M^+, 3.3), 246 (45), 233 (100). Calcd for $C_{19}H_{19}N$: C, 87.31; H, 7.33; N, 5.36. Found: C, 87.07; H, 7.29; N, 5.20.

2.4.3. 2-(1,1-Dimethylethyl)-4-phenylquinoline (3c). A pale-yellow solid; mp 85–88 °C (hexane); IR (KBr disk) 3058, 1962, 1602, 1589, 1553, 1488, 778, 761, 706 cm^{-1}; ^1H NMR δ 1.50 (9H, s), 7.42 (1H, ddd, J=8.2, 7.3, 1.3 Hz), 7.44 (1H, s), 7.45–7.55 (5H, m), 7.66 (1H, ddd, J=8.2, 7.3, 1.3 Hz), 7.84 (1H, dd, J=8.2, 1.3 Hz), 8.12 (1H, dd, J=8.2, 1.3 Hz); MS m/z 261 (M^+, 43), 246 (100). Calcd for $C_{19}H_{19}N$: C, 87.31; H, 7.33; N, 5.36. Found: C, 87.48; H, 7.09; N, 5.27.

2.4.4. 2,4-Diphenylquinoline (3d). A pale-yellow solid; mp 120–122 °C (hexane) (lit.,[10] 114 °C); the spectral data for this product were identical to those reported previously.[11]

2.4.5. 2-(4-Methylphenyl)-4-phenylquinoline (3e). A pale-yellow solid; 116–117 °C (hexane–Et_2O) (lit.,[12] 106 °C); the spectral data for this product were identical to those reported previously.[11]

2.4.6. 4-Phenyl-2-(2-thienyl)quinoline (3f).[13a] A pale-yellow solid; mp 89–92 °C (hexane–Et_2O) (lit.,[13b] 83–85 °C); IR (KBr disk) 3065, 1590, 1548, 1489, 1428, 828, 772, 761, 712, 700 cm^{-1}; ^1H NMR δ 7.15 (1H, dd, J=5.0, 3.6 Hz), 7.35–7.6 (7H, m), 7.65–7.75 (3H, m), 7.83 (1H, dd, J=8.2, 1.3 Hz), 8.15 (1H, d, J=8.2 Hz); MS m/z 287 (M^+, 100).

2.4.7. 2-(2-Furyl)-4-phenylquinoline (3g).[13a] A pale-yellow solid; mp 109–111 °C (hexane–Et_2O) (lit.,[13b] 100–102 °C); IR (KBr disk) 3091, 1595, 1550, 1495, 1084, 1007, 776, 764, 742, 702 cm^{-1}; ^1H NMR δ 6.59 (1H, dd, J=3.3, 1.7 Hz), 7.23 (1H, dd, J=3.3, 1.0 Hz), 7.4–7.6 (6H, m), 7.63 (1H, dd, J=1.7, 1.0 Hz), 7.71 (1H, ddd, J=8.2, 7.3, 1.3 Hz), 7.77 (1H, s), 7.86 (1H, dd, J=8.2, 1.3 Hz), 8.19 (1H, dd, J=8.2, 1.3 Hz); MS m/z 271 (M^+, 100).

2.4.8. 6-Chloro-2-(1,1-dimethylethyl)-4-phenylquinoline (3h). A pale-yellow viscous oil; R_f 0.81 (1:3 hexane–AcOEt); IR (neat) 3060, 2961, 1590, 1550, 1484, 1137, 701 cm^{-1}; ^1H NMR δ 1.48 (9H, s), 7.4–7.6 (6H, m including s at δ 7.45), 7.60 (1H, dd, J=8.9, 2.3 Hz), 7.80 (1H, d, J=2.3 Hz), 8.05 (1H, d, J=8.9 Hz); MS m/z 295 (M^+, 37), 280 (100). Calcd for $C_{19}H_{18}ClN$: C, 77.15; H, 6.13; N, 4.74. Found: C, 76.96; H, 5.95; N, 4.55.

2.4.9. 6-Chloro-2,4-diphenylquinoline (3i).[14a] A pale yellow solid; mp 114–117 °C (hexane–Et_2O) (lit.,[14b] 127–129 °C); IR (KBr disk) 3026, 1590, 1544, 1483, 1357, 826, 776, 756, 704, 690 cm^{-1}; ^1H NMR δ 7.4–7.6 (8H, m), 7.66 (1H, dd, J=8.9, 2.3 Hz), 7.84 (1H, s), 7.86 (1H, d, J=2.3 Hz), 8.15–8.2 (3H, m); MS m/z 315 (M^+, 100).

2.4.10. 2-(1,1-Dimethylethyl)-4-methylquinoline (3j).[15] A pale-yellow viscous oil; R_f 0.84 (1:3 hexane–AcOEt); IR (neat) 3061. 2956, 1602, 1558, 1507, 1480, 1448, 758 cm^{-1}; ^1H NMR δ 1.46 (9H, s), 2.69 (3H, s), 7.35 (1H, s), 7.48 (1H, ddd, J=8.2, 6.9, 1.3 Hz), 7.65 (1H, ddd, J=8.2, 6.9, 1.3 Hz), 7.93 (1H, dd, J=8.2, 1.3 Hz), 8.05 (1H, dd, J=8.2, 1.3 Hz); MS m/z 199 (M^+, 54), 184 (100).

2.4.11. 4-Methyl-2-phenylquinoline (3k).[16] A pale-yellow viscous oil; R_f 0.65 (1:3 hexane–AcOEt); the spectral data for this compound were identical to those reported previously.[17]

2.5. Typical procedure for the preparation of quinolin-2-amine derivatives 5

2.5.1. 2-Diethylamino-4-phenylquinoline (5a). To a stirred solution of lithium diethylamide (0.51 mmol; generated by the standard method from diethylamine and butyllithium) at −78 °C under argon was added a solution of isocyanostyrene **1a** (0.10 g, 0.43 mmol) in THF (1.0 mL). After stirring for 30 min at this temperature, the mixture was allowed to warm to room temperature and stirring was continued for an additional 30 min. Similar workup as described for the above typical procedure followed by purification by preparative TLC on silica gel to give **5a** (71 mg, 60%) as a pale-yellow viscous oil; R_f 0.70 (1:3 EtOAc–hexane); IR (neat) 3060, 2969, 1610, 1597, 1548, 1450, 1426, 1360, 1246, 770, 701 cm^{-1}; ^1H NMR δ 1.26 (6H, t, J=6.9 Hz), 3.68 (4H, q, J=6.9 Hz), 6.74 (1H, s), 7.08 (1H, ddd, J=8.2, 6.9, 1.3 Hz), 7.4–7.55 (6H, m), 7.57 (1H, dd, J=8.2, 1.3 Hz), 7.72 (1H, dd, J=8.6, 1.3 Hz); MS m/z 276 (M^+, 29), 247 (100). Calcd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14. Found: C, 82.55; H, 7.49; N, 10.13.

2-Aminoquinoline derivatives **5b–k** were prepared according to the procedure described above, excepting that 2.0 mol amounts each of lithium diisopropylamide (for **5b** and **5j**)

and lithium dicyclohexylamide (for **5c**) were used and that the preparation of **5h** and **5i** were conducted at −78–0 °C.

2.5.2. 2-Diisopropylamino-4-phenylquinoline (5b). A pale-yellow solid; mp 104–105 °C (hexane); IR (KBr disk) 3056, 2928, 1607, 1593, 1544, 1491, 1478, 1373, 1350, 1244, 771, 706 cm^{-1}; ^1H NMR δ 1.41 (12H, d, J=6.9 Hz), 4.42 (2H, septet, J=6.9 Hz), 6.81 (1H, s), 7.07 (1H, ddd, J=8.2, 6.9, 1.3 Hz), 7.4–7.6 (7H, m), 7.72 (1H, dd, J=8.6, 1.3 Hz); MS m/z 304 (M^+, 29), 261 (100). Calcd for $C_{21}H_{24}N_2$: C, 82.85; H, 7.95; N, 9.20. Found: C, 82.59; H, 8.12; N, 9.39.

2.5.3. 2-Dicyclohexylamino-4-phenylquinoline (5c). A pale-yellow solid; mp 167–169 °C (hexane–Et_2O); IR (KBr disk) 3062, 2927, 2846, 1608, 1597, 1545, 1493, 1473, 1376, 1216, 758, 704 cm^{-1}; ^1H NMR δ 1.15–1.50 (6H, m), 1.65–1.9 (10H, m), 2.0–2.2 (4H, m), 3.75–3.9 (2H, m), 6.84 (1H, m), 7.06 (1H, ddd, J=8.2, 6.9, 1.3 Hz), 7.4–7.6 (7H, m), 7.70 (1H, dd, J=8.2, 1.3 Hz); MS m/z 384 (M^+, 25), 301 (100). Calcd for $C_{27}H_{32}N_2$: C, 84.33; H, 8.39; N, 7.28. Found: C, 84.28; H, 8.60; N, 7.23.

2.5.4. 4-Phenyl-2-(pyrrolidin-1-yl)quinoline (5d). A pale-yellow solid; mp 145–148 °C (hexane–Et_2O) (lit.,[18] mp 139.5 °C); IR (KBr disk) 3051, 2967, 2861, 1604, 1593, 1547, 1500, 1427, 1342, 785, 759, 713 cm^{-1}; ^1H NMR δ 2.0–2.1 (4H, m), 3.65–3.7 (4H, m), 6.65 (1H, s), 7.10 (1H, ddd, J=8.2, 6.9, 1.3 Hz), 7.4–7.55 (6H, m), 7.59 (1H, dd, J=8.2, 1.0 Hz), 7.77 (1H, d, J=8.6 Hz); MS m/z 274 (M^+, 39), 245 (100).

2.5.5. 4-Phenyl-2-(piperidin-1-yl)quinoline (5e). A pale-yellow solid; mp 121–123 °C (hexane–Et_2O); IR (KBr disk) 3050, 2929, 2825, 1610, 1596, 1547, 1492, 1429, 1230, 778, 761, 710 cm^{-1}; ^1H NMR δ 1.69 (6H, br s), 3.7–3.8 (4H, m), 6.90 (1H, s), 7.13 (1H, ddd, J=8.2, 6.9, 1.3 Hz), 7.4–7.55 (6H, m), 7.59 (1H, dd, J=8.2, 1.3 Hz), 7.74 (1H, d, J=8.2 Hz); MS m/z 288 (M^+, 96), 259 (100). Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99; N, 9.71. Found: C, 83.19; H, 7.08; N, 9.39.

2.5.6. 2-(Morpholin-1-yl)-4-phenylquinoline (5f). A pale-yellow solid; mp 124–126 °C (hexane–Et_2O); IR (KBr disk) 3060, 2965, 1605, 1594, 1548, 1491, 1425, 1229, 1125, 762 cm^{-1}; ^1H NMR δ 3.72–3.78 (4H, m), 3.82–3.88 (4H, m), 6.88 (1H, s), 7.19 (1H, ddd, J=8.2, 6.9, 1.3 Hz), 7.45–7.60 (6H, m), 7.64 (1H, dd, J=8.2, 1.3 Hz), 7.78 (1H, d, J=8.2 Hz); MS m/z 290 (M^+, 58), 259 (100). Calcd for $C_{19}H_{18}N_2O$: C, 78.59; H, 6.25; N, 9.65. Found: C, 78.48; H, 6.34; N, 9.66.

2.5.7. 2-(4-Methylpiperazin-1-yl)-4-phenylquinoline (5g). A pale-yellow solid; mp 124–126 °C (hexane–Et_2O) (lit.,[19] mp 123–129 °C); IR (KBr disk) 3057, 2832, 2847, 1609, 1595, 1547, 1492, 1424, 1424, 1231, 772, 699 cm^{-1}; ^1H NMR δ 2.36 (3H, s), 2.56 (4H, t, J=5.1 Hz), 3.80 (4H, t, J=5.1 Hz), 6.90 (1H, s), 7.16 (1H, ddd, J=8.2, 6.9, 1.3 Hz), 7.4–7.6 (6H. m), 7.61 (1H, dd, J=8.2, 1.3 Hz), 7.76 (1H, dd, J=8.2, 1.3 Hz); MS m/z 303 (M^+, 5.3), 233 (100).

2.5.8. 6-Chloro-4-phenyl-2-(pyrrolidin-1-yl)quinoline (5h). A pale-yellow solid; mp 158–160 °C (hexane–Et_2O); IR (KBr disk) 3068, 2852, 1605, 1543, 1471, 1438, 1413, 1347, 1072, 965, 858, 705 cm^{-1}; ^1H NMR δ 2.0–2.1 (4H, m), 3.6–3.65 (4H, m), 6.65 (1H, s), 7.4–7.55 (7H, m), 7.68 (1H, d, J=8.9 Hz); MS m/z 308 (M^+, 45), 279 (100). Calcd for $C_{19}H_{17}ClN_2$: C, 73.90; H, 5.55; N, 9.07. Found: C, 74.11; H, 5.53; N, 8.85.

2.5.9. 6-Chloro-4-phenyl-2-(piperidin-1-yl)quinoline (5i). A pale-yellow solid; mp 136–139 °C (hexane–Et_2O); IR (KBr disk) 3060, 2925, 2846, 1595, 1543, 1483, 1413, 1223, 953, 778, 708 cm^{-1}; ^1H NMR δ 1.65–1.7 (6H, m), 3.7–3.8 (4H, m), 6.91 (1H, s), 7.4–7.55 (7H, m), 7.66 (1H, d, J=8.9 Hz); MS m/z 322 (M^+, 100). Calcd for $C_{20}H_{19}ClN_2$: C, 74.41; H, 5.93; N, 8.68. Found: C, 74.40; H, 6.02; N, 8.66.

2.5.10. 2-Diisopropylamino-4-methylquinoline (5j). A pale-yellow solid; mp 60–62 °C (hexane); IR (KBr disk) 3059, 2966, 1606, 1552, 1493, 1469, 1428, 1353, 1238, 1150, 753 cm^{-1}; ^1H NMR δ 1.39 (12H, d, J=6.9 Hz), 2.57 (3H, s), 4.38 (2H, septet, J=6.9 Hz), 6.74 (1H, s), 7.15 (1H, ddd, J=8.2, 6.9, 1.3 Hz), 7.46 (1H, ddd, J=8.2, 6.9, 1.3 Hz), 7.63 (1H, dd, J=8.2, 1.3 Hz), 7.72 (1H, dd, J=8.2, 1.3 Hz); MS m/z 242 (M^+, 10), 199 (100). Calcd for $C_{16}H_{22}N_2$: C, 79.29; H, 9.15; N, 11.56. Found: C, 79.15; H, 9.16; N, 11.54.

2.5.11. 4-Methyl-2-(piperidin-1-yl)quinoline (5k).[20] A pale-yellow solid; mp 119–120 °C (hexane–AcOEt) (lit.,[21] mp 119–121 °C); the spectral data for this compound were identical to those reported previously.[21]

2.6. 4-Phenyl-2-(phenylthio)quinoline (6)

To a stirred solution of benzenethiol (86 mg, 0.55 mmol) in THF (1.5 mL) at −78 °C under argon was added butyllithium (0.55 mmol; 1.6 M in hexanes). After stirring for 15 min, isocyanostyrene **1a** (0.10 g, 0.43 mmol) was added and the mixture was allowed to warm to room temperature, then it was heated at reflux temperature for 7.5 h. After similar workup as described for the above typical procedure, followed by separation by preparative TLC on silica gel to give **6** (43 mg, 32%) as a pale-yellow solid; mp 99–101 °C (hexane–Et_2O); IR (KBr disk) 3062, 1609, 1578, 1540, 773, 745, 702, 690 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 6.96 (1H, s), 7.35–7.5 (9H, m), 7.6–7.7 (3H, m), 7.76 (1H, dd, J=8.4, 1.1 Hz), 8.00 (1H, dd, J=8.4, 0.7 Hz); MS m/z 313 (M^+, 100). Calcd for $C_{21}H_{15}NS$: C, 80.48; H, 4.82; N, 4.47; S, 10.23. Found: C, 80.50; H, 4.65; N, 4.37; S, 10.21.

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