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A HIGHLY EFFECTIVE ONE-POT SYNTHESIS OF QUINOLINES FROM 2-ALKYNYLNITROBENZENES

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Abstract – A highly effective one-pot synthesis of poly-substituted quinolines from 2-alkynylnitrobenzenes using inexpensive reagents has been developed. Reaction of 2-alkynylnitrobenzenes with Sn/HCl in EtOH resulted in the formation of 2-aminophenyl ketones and subsequently condensed in situ with ketones to form tri-substituted quinolines in 80-97% yields.

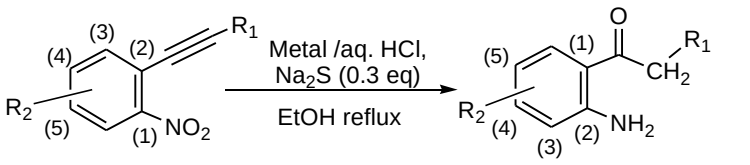
INTRODUCTION

Palladium-catalyzed cross-coupling reactions between terminal alkynes and aryl halides, known as the Sonogashira reaction, have been used extensively in natural products chemistry and materials science for the synthesis of substituted and conjugated alkynes.[1] If 2-alkynylnitrobenzenes (**1**) prepared from Sonogashira coupling reaction were reduced and hydrated in one-pot operation, the corresponding vinyl alcohols were easily rearranged to 2-aminophenyl ketones (**2**), which are useful intermediates for many heterocycles such as quinolines, imidazoles, benzotriazoles, and benzodiazepines.[2] Especially, quinolines and their derivatives are very important compounds because of their wide occurrence in natural products and biologically active compounds.[3] Amongst various methodologies reported for the preparation of quinolines, Friedländer annulation is one of the simplest and most straightforward protocols.[4] One of the drawbacks of this method remains the relative instability of the intermediate 2-aminobenzaldehydes or 2-aminophenyl ketones, which can readily undergo self-condensation. These results prompted us to investigate the one-pot synthesis of quinolines from 2-alkynylnitrobenzenes by reduction, hydration and acidic cyclization by Friedländer reaction. We report herein the one-pot synthesis of 2,3,4-trisubstituted quinolines from 2-alkynylnitrobenzenes.

RESULTS AND DISCUSSION

2-Alkynylnitrobenzenes were synthesized from 2-iodonitrobenzene and terminal alkynes by Sonogashira coupling reaction.[1] We first tried the reduction and hydration of 2-phenylethynylnitrobenzene (**1a**) (Scheme 1). Treatment of **1a** with Sn (1 eq) and Na_2S (0.3 eq) followed by the addition of conc. HCl (4

eq) resulted in the formation of 1-(2-aminophenyl)-2-phenylethanone (**2a**) in 50% yield (entry 1, Table 1). When conc. HCl (10 eq) was added to a suspension of **1a** and Sn (2 eq) and Na_2S (0.3 eq) in refluxing EtOH for 8 h, **2a** was obtained in 90% yield, indicating that reduction and hydration were performed in one-pot operation (entry 2). 0.3 eq of Na_2S is essential for the present reaction, because, in the absence of Na_2S, less than 10% of 2-phenylindole was obtained as a side product, suggesting that a very small amount of palladium chloride catalyzed the intramolecular cyclization (entry 3).[5] When Zn or Fe was used as a reducing reagent, **2a** was also obtained in 50% and 65% yields, respectively (entries 4 and 5). Thus, Sn found to be a better reducing reagent for the synthesis of 2-aminophenyl ketones. Other substituted 2-alkynylnitrobenzenes **1b-i** gave 2-aminophenyl ketones **2b-i** in good yields (entries 6-13).



1a: R_1 = Ph, R_2 = H
1b: R_1 = *n*-Bu, R_2 = H
1c: R_1 = *n*-pentyl, R_2 = H
1d: R_1 = *p*-BuC_6H_4, R_2 = H
1e: R_1 = $HOCH_2CH_2$, R_2 = H
1f: R_1 = *tert*-Bu, R_2 = H
1g: R_1 = Ph, R_2 = 5-Cl
1h: R_1 = Ph, R_2 = 5-OMe
1i: R_1 = Ph, R_2 = 4-Me

2a: R_1 = Ph, R_2 = H
2b: R_1 = *n*-Bu, R_2 = H
2c: R_1 = *n*-pentyl, R_2 = H
2d: R_1 = *p*-BuC_6H_4, R_2 = H
2e: R_1 = $HOCH_2CH_2$, R_2 = H
2f: R_1 = *tert*-Bu, R_2 = H
2g: R_1 = Ph, R_2 = 4-Cl
2h: R_1 = Ph, R_2 = 4-OMe
2i: R_1 = Ph, R_2 = 5-Me

Scheme 1

Table 1. Reaction of 2-Alkynylnitrobenzene **1** with Sn, Zn, or Fe/HCl

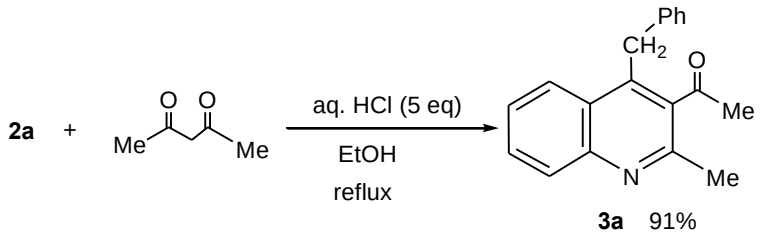
Entry	**1**	Metal (eq)	HCl /eq	**2**	Yield /%
1	**1a**	Sn (1)	4	**2a**	50
2	**1a**	Sn (2)	10	**2a**	82
3	**1a**	Sn (2)	10	**2a**	65[a]
4	**1a**	Zn (3)	10	**2a**	50
5	**1a**	Fe (3)	10	**2a**	65
6	**1b**	Sn (2)	10	**2b**	93
7	**1c**	Sn (2)	10	**2c**	98
8	**1d**	Sn (2)	10	**2d**	86
9	**1e**	Sn (2)	10	**2e**	74
10	**1f**	Sn (2)	10	**2f**	93
11	**1g**	Sn (2)	10	**2g**	73
12	**1h**	Sn (2)	10	**2h**	75
13	**1i**	Sn (2)	10	**2i**	84

a) The reaction was carried out in the absence of Na_2S (8% of 2-phenylindole was obtained as a side product).

Simple 2-aminophenylethanones, such as 2-aminoacetophenone and 2-aminobenozophenone, were commercially available; however, few reports on the synthesis of more complicated 2-aminophenyl

ketones **2** were known. Among them are photo Fries rearrangement, reduction of 2-nitrophenyl ketones, *o*-acylation of anilines, and addition of 2-cyanoanilines with Grignard reagents.[6] The present method provides a general method on the synthesis of **2**.

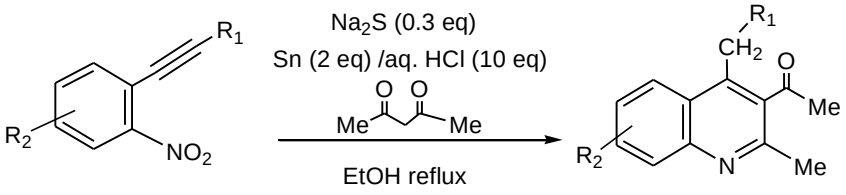
We then investigated tandem synthesis of quinolines from 2-alkynylnitrobenzenes, Sn/HCl, and acetylacetone by a combination of reduction/hydration and Friedländer reaction.[4] Acidic Friedlander reaction was generally carried out acetic acid as a solvent. If we want to synthesize quinolines in one-pot operation, other solvent should be required. Thus, we first tried the reaction of **2a** with acetylacetone under several reaction conditions to find an optimum condition. Treatment of **2a** with acetylacetone and sulfuric acid in acetic acid gave 2-methyl-3-acetyl-4-phenylquinoline (**3a**) in 96% yield. When the reaction was carried out by using HCl as acid in refluxing ethanol, **3a** was obtained in 91% yield (Scheme 2).



Scheme 2

Then one-pot reaction was carried out under these conditions (conc HCl in refluxing EtOH).

Treatment of **1a** with Sn (2 eq)/HCl (10 eq), Na_2S (0.3 eq), and acetylacetone (1.2 eq) in refluxing EtOH for 18 h gave 2-methyl-3-acetyl-4-benzylquinoline (**3a**) in 89% yield (entry 1, Table 2). As shown in Table 2, quinolines **3b**-**i** were obtained in 80-93% yields (Scheme 3). Thus, one-pot synthesis of quinolines from 2-alkynylnitrobenzenes was accomplished.



1a: R_1 = Ph, R_2 = H
1b: R_1 = *n*-Bu, R_2 = H
1c: R_1 = *n*-pentyl, R_2 = H
1d: R_1 = *p*-BuC_6H_4, R_2 = H
1e: R_1 = $HOCH_2CH_2$, R_2 = H
1f: R_1 = *tert*-Bu, R_2 = H
1g: R_1 = Ph, R_2 = 5-Cl
1h: R_1 = Ph, R_2 = 5-OMe
1i: R_1 = Ph, R_2 = 4-Me

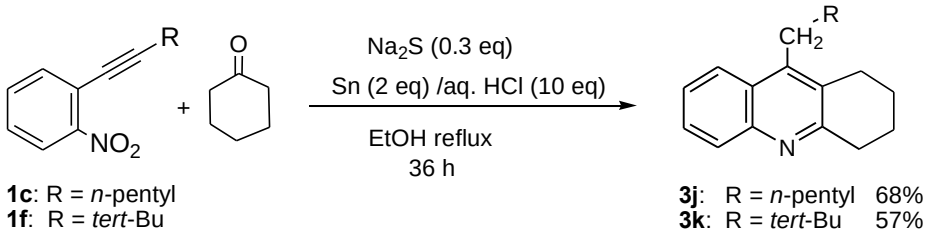
3a: R_1 = Ph, R_2 = H
3b: R_1 = *n*-Bu, R_2 = H
3c: R_1 = *n*-pentyl, R_2 = H
3d: R_1 = *p*-BuC_6H_4, R_2 = H
3e: R_1 = $HOCH_2CH_2$, R_2 = H
3f: R_1 = *tert*-Bu, R_2 = H
3g: R_1 = Ph, R_2 = 7-Cl
3h: R_1 = Ph, R_2 = 7-OMe
3i: R_1 = Ph, R_2 = 6-Me

Scheme 3

Table 2. One-pot synthesis of quinolines from **1**

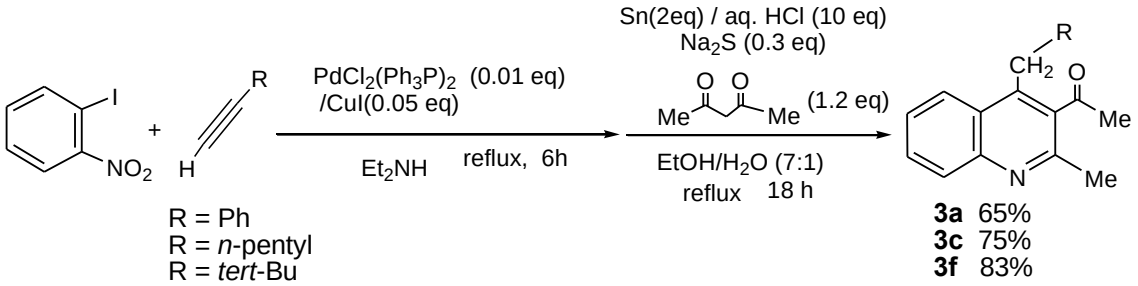
3	Time / h	Product	Yield / %
1a	18	**3a**	89
1b	18	**3b**	80
1c	15	**3c**	86
1d	18	**3d**	87
1e	20	**3e**	95
1f	21	**3f**	97
1g	27	**3g**	60
1h	27	**3h**	76
1i	27	**3i**	67

Similarly, one-pot synthesis of quinolines from cyclohexanone was accomplished (Scheme 4).



Scheme 4

While 2-alkynylnitrobenzenes were easily synthesized by the CuI-$PdCl_2$ catalyzed reaction of 2-iodonitrobenzene with terminal alkynes, we finally tried the one-pot synthesis of 2,3,4-trisubstituted quinolines from 2-iodonitrobenzene. Treatment of 2-iodonitrobenzene with ethynylbenzene in the presence of catalytic amount of $PdCl_2$-CuI in refluxing Et_3N, followed by the evaporation and addition of Sn/HCl and acetylacetone in refluxing ethanol resulted in the formation of **3a** in 65% yield (Scheme 5).



Scheme 5

In summary, we have accomplished the general synthesis of 2-aminophenyl ketones from 2-alkynylnitrobenzenes. One-pot reaction of 2-alkynylnitrobenzenes with ketones afforded the corresponding quinolines in high yields. Thus, general and convenient synthesis of polysubstituted quinolines from 2-nitroalkynylbenzenes was achieved.

EXPERIMENTAL

General

All chemicals were obtained from commercial suppliers and were used without further purification. Analytical TLC was carried out on precoated plates (Merck silica gel 60, F254) and flash column chromatography was performed with silica (Merck, 70-230 mesh). NMR spectra (^{1}H at 400 MHz; ^{13}C at 100 MHz) were recorded in $CDCl_3$, and chemical shifts are expressed in ppm relative to internal TMS for ^{1}H- and ^{13}C-NMR. Melting points were uncorrected.

Materials: 2-Alkynylnitrobenzenes were synthesized by Sonogashira coupling reaction.[1] 1-Butyl-4-(2-(2-nitrophenyl)ethynyl)benzene **1d**: red needles. mp 146-148 ^{o}C ^{1}H NMR ($CDCl_3$) δ = 0.92 (t, 3H, *J* = 7.4 Hz, CH_3), 1.33 (dt, 2H, *J* = 7.4 and 7.4 Hz, CH_2), 1.57-1.60 (m, 2H, CH_2), 2.61 (dd, 2H, *J* = 7.6 and 7.8 Hz, CH_2), 7.18 (d, 2H, *J* = 8.0 Hz, Ar), 7.42 (dd, 1H, *J* = 7.6 and 7.8 Hz, Ar), 7.50 (d, d, 2H, *J* = 8.0 Hz, Ar), 7.56 (dd, 1H, *J* = 7.6 and 8.0 Hz, Ar), 7.69 (d, 1H, *J* = 7.8 Hz, Ar), 8.06 (d, 1H, *J* = 8.0 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 14.15 (CH_3), 22.54 (CH_2), 33.58 (CH_2), 35.92 (CH_2), 84.92 (≡C), 97.84 (≡C), 119.75, 124.93, 128.51, 128.83, 132.19, 132.21, 132.99, 134.74, 144.83 (Ar). HRMS: Calcd for $C_{18}H_{17}NO_2$; 279.1259. Found; (M^+) 279.1258.

Synthesis of 1-(2-aminophenyl)-2-phenylethanone 2a

To a suspension of 2-phenylethynylnitrobenzene **1a** (0.11 g, 0.50 mmol), Sn (0.12 g, 1.0 mmol) and $Na_2S{\cdot}9H_2O$ (0.036 g, 0.15 mmol) in EtOH:H_2O (9:1, 5 mL) was added conc, HCl (0.42 mL, 5.0 mmol) in one portion. After refluxing for 8 h, the reaction mixture was washed with 5% aq. Na_2CO_3 (10 mL) and extracted with EtOAc (10 mL x 3). The combined extracts were dried over magnesium sulfate, filtered, and evaporated to give yellow crystals, which was chromatographed over silica gel by elution with hexane:EtOAc (5:1) to give yellow leaflets of 1-(2-aminophenyl)-2-phenylehanone **2a** (0.095 g, 0.41 mmol) was obtained in 82%. Compound **2a**: mp 99-100 ^{o}C (lit.,[7] mp 98-99 ^{o}C). ^{1}H NMR ($CDCl_3$) δ = 4.26 (s, 2H, CH_2), 6.29 (br, 2H, NH_2), 6.63-6.66 (m, 2H, Ar), 7.23-7.26 (m, 4H, Ar), 7.31 (dd, 2H, *J* = 7.4 Hz and 8.0 Hz, Ar), 7.82 (d, 1H, *J* = 8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 46.33 (CH_2), 116.04, 117.66, 117.74, 126.98, 128.83, 129.72, 131.81, 134.71, 135.62, 151.07 (Ar), 200.20 (CO).

Other 2-aminophenylethanones were obtained in a similar manner.

1-(2-Aminophenyl)-1-hexan-1-one **2b** (0.19 g, 0.93 mmol, 93%). Yellow oil,[8] ^{1}H NMR ($CDCl_3$) δ = 0.90 (dd, 3H, *J* = 6.0 Hz and 6.4 Hz, CH_3), 1.35-1.38 (m, 4H, CH_2), 1.70 (dt, 2H, *J* = 7.2 Hz and 7.4 Hz, CH_2), 2.91 (t, 2H, *J* = 7.5 Hz, CH_2), 6.25 (br, 2H, NH_2), 6.62-6.66 (m, 2H, Ar), 7.23-7.27 (m, 1H, Ar), 7.73 (d, 1H, *J* = 8.0 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 14.21 (Me), 22.80, 24.92, 31.88, 39.51 (CH_2), 115.94, 117.58, 118.26, 131.45, 134.33, 150.58 (Ar), 203.44 (C=O).

1-(2-Aminophenyl)-1-heptan-1-one **2c** (0.11 g, 0.49 mmol, 98%). Yellow oil,[9] ^{1}H NMR ($CDCl_3$) δ = 0.88 (dd, 3H, *J* = 6.8 Hz and 7.0 Hz, Me), 1.30-1.40 (m, 6H, CH_2), 1.68 (dt, 2H, *J* = 7.6 Hz and 7.6 Hz, CH_2), 2.91 (t, 2H, *J* = 7.5 Hz, CH_2), 6.26 (br 2H, NH_2), 6.67-6.70 (m, 2H, Ar), 7.24-7.28 (m, 1H, Ar), 7.74 (d, 1H, *J* = 8.0 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 14.27 (Me), 22.77, 25.18, 29.36, 31.93, 39.55 (CH_2), 115.92, 117.56, 118.26, 131.44, 134.30, 150.56 (Ar), 203.41 (C=O).

1-(2-Aminophenyl)-2-(4-butylphenyl)ethanone **2d** (0.16 g, 0.60 mmol, 86%). Colorless leaflets: mp 72-73 ^{o}C. ^{1}H-NMR ($CDCl_3$) δ = 0.90 (dd, 3H, *J* = 7.4 Hz and 7.4 Hz, Me), 1.32 (dt, 2H, *J* = 7.4 Hz and 7.6 Hz, CH_2), 1.57-1.60 (m, 2H, CH_2), 2.56 (dd, 2H, *J* = 7.6 Hz and 7.8 Hz, CH_2), 4.22 (s, 2H, CH_2), 6.23 (br, 2H, NH_2), 6.63-6.66 (m, 2H, Ar), 7.13 (d, 2H, *J* = 8.4 Hz, Ar), 7.16 (d, 2H, *J* = 8.4 Hz, Ar), 7.25-7.27 (m, 1H, Ar), 7.84 (d, 1H, *J* = 8.2 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 14.21 (Me), 22.65, 33.82, 35.53, 45.94, (CH_2), 116.01, 117.64, 117.81, 128.90, 129.55, 131.86, 132.70, 130.64, 141.56, 151.09 (Ar), 200.46 (C=O). Anal. Calcd for $C_{18}H_{21}NO$: C, 80.86; H, 7.92; N, 5.24. Found: C, 80.86; H, 7.78; N, 5.27.

1-(2-Aminophenyl)-4-hydroxy-1-butan-1-one **2e** (0.066 g, 0.37 mmol, 74%). Pale brown oil,[10] ^{1}H NMR ($CDCl_3$) δ = 1.99 (dt, 2H, *J* = 6.0 Hz and 6.8 Hz, CH_2), 3.09 (t, 2H, *J* = 6.8 Hz, CH_2), 3.73 (t, 2H, *J* = 6. 0 Hz), 6.66-6.68 (m, 2H, Ar), 7.26-7.27 (m, 1H, Ar), 7.76 (d, 1H, *J* = 8.0 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 27.67, 36.16, 62.60 (CH_2), 116.06, 117.64, 118.03, 131.45, 134.64, 150.65 (Ar), 203.14 (C=O). HRMS: Calcd for $C_{10}H_{13}NO_2$; 179.0946. Found; (M^+) 179.0942.

1-(2-Aminophenyl)-3,3-dimethyl-1-butan-1-one **2f** (0.18 g, 0.93 mmol, 93%). Yellow oil, ^{1}H NMR ($CDCl_3$) δ = 1.06 (s, 9H, 3Me), 2.82 (s, 2H, CH_2), 6.29 (br, 2H, NH_2), 6.58-6.62 (m, 2H, Ar), 7.19-7.23

(m, 1H, Ar), 7.73 (d, 1H, *J* = 8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 30.50 (Me), 31.96 ($C(Me)_3$), 50.77 (CH_2), 115.75, 117.57, 119.73, 132.24, 134.25, 150.59 (Ar), 203.40 (C=O). HRMS: Calcd for $C_{12}H_{17}NO$; 191.1310. Found; (M^+) 191.1315.

1-(2-Amino-4-chrolophenyl)-2-phenyletanone **2g** (0.090 g, 0.37 mmol, 73%). Yellow leaflets: mp 98-99 °C. ^{1}H NMR ($CDCl_3$) δ = 4.22 (s, 2H, CH_2), 6.37 (br, 2H, NH_2), 6.59 (d, 1H, *J* = 8.8 Hz, Ar), 6.65 (s, 1H, Ar), 7.23-7.35 (m, 5H, Ar), 7.74 (d, 1H, *J* = 8.8 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 46.43 (CH_2), 116.19, 116.49, 116.80, 127.13, 128.91, 129.63, 133.18, 135.29, 140.62, 151.90, (Ar), 199.50 (C=O). HRMS: Calc for $C_{14}H_{12}{}^{35}ClNO$; 245.0607. Found; (M^+) 245.0612.

1-(2-Amino-4-methoxyphenyl)-2-phenylethanone **2h** (0.054 g, 0.22 mmol, 75%). Yellow granules[11]: mp 92-93 °C. ^{1}H NMR ($CDCl_3$) δ = 3.79 (s, 3H, OMe), 4.19 (s, 2H, CH_2), 6.06 (s, 1H, Ar), 6.22 (d, 1H, *J* = 8.8 Hz, Ar), 6.42 (br, 2H, NH_2), 7.24-7.34 (m, 5H, Ar), 7.75 (d, 1H, *J* = 8.8 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 46.21 (CH_2), 55.47 (OMe), 99.55, 104.91, 112.33, 126.91, 128.84, 129.68, 134.00, 136.13, 153.74, 164.44 (Ar), 198.53 (C=O). HRMS: Calcd for $C_{15}H_{15}NO_2$; 241.1103. Found; (M^+) 241.1100.

1-(2-Amino-5-methylphenyl)-2-phenyletanone **2i** (0.094 g, 0.42 mmol, 84%). Colorless amorphous solid[12]: mp 95-96 °C. ^{1}H NMR ($CDCl_3$) δ = 2.26 (s, 3H, Me), 4.26 (s, 2H, CH_2), 6.13 (br, 2H, NH_2), 6.58 (d, 1H, *J* = 8.0 Hz, Ar), 7.09 (d, 1H, *J* = 8.0 Hz, Ar), 7.26-7.36 (m, 5H, Ar), 7.64 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ = 20.75 (Me), 46.25 (CH_2), 117.71, 117.79, 124.97, 126.95, 128.81, 134.00, 129.80, 131.33, 135.74, 135.96, 149.00 (Ar), 200.07 (C=O). HRMS: Calcd for $C_{15}H_{15}NO$; 225.1154. Found; (M^+) 225.1158.

Reaction of 2a with acetylacetone (acidic Friedländer reaction)

To a solution of **2a** (0.11 g, 0.50 mmol) in EtOH (8 mL) was added conc HCl (0.20 mL, 2.5 mmol) and acetylacetone (52 mL, 0.50 mmol). After refluxing for 18h, the reaction mixture was concentrated and 5% aq. Na_2CO_3 (10 mL) was added to this solution. The mixture was extracted with EtOAc (5 mL x 3). The combined extract was dried over sodium sulfate, filtered, and evaporated to give yellow solid, which was chromatographed over silica gel (hexane:EtOAc = 5:1) to give 3-acetyl-4-benzyl-2-methylquinoline (**3a)** (0.125 g, 0.45 mmol). **3a**: colorless amorphous solid. mp 84-86 °C. ^{1}H NMR ($CDCl_3$) δ = 2.42 (s, 3H, Me), 2.68 (s, 3H, Me), 4.37 (s, 2H, CH_2), 7.06 (d, 2H, *J* = 6.3 Hz, Ar), 7.16-7.24 (m, 3H, Ar), 7.44 (dd, 1H, *J* = 7.7 Hz and 8.4 Hz, Ar), 7.66 (dd, 1H, *J* = 7.7 Hz and 8.4 Hz, Ar), 7.87 (d, 1H, *J* = 8.4 Hz, Ar), 8.03 (d, 1H, *J* = 8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 23.92, 32.85 (Me), 34.92 (CH_2), 124.87, 125.83, 126.87, 126.88, 128.49, 128.99, 129.62, 130.15, 136.77, 138.62, 140.59, 147.85, 153.15 (Ar), 206.77 (CO). HRMS: Calc for $C_{19}H_{17}NO$; 275.1310. Found; (M^+) 275.1303.

One-pot Synthesis of Quinoline 6a from 1a

To a solution of **1a** (0.13 g, 0.60 mmol), Sn (0.14 g, 1.2 mmol), $Na_2S{\cdot}9H_2O$ (0.44 g, 0.18 mmol), and acetylacetone (0.072 mL, 0.72 mmol) in 10 mL of EtOH:H_2O (9:1) was added conc HCl (0.50 mL, 6.0 mmol). After refluxing for 18 h, 5% aq. Na_2CO_3 solution was added, and extracted with EtOAc (5 mL x 3). The combined extract was dried over magnesium sulfate, filtered, evaporated, and chromatographed over silica gel (hexane:EtOAc = 5:1) to give 3-acetyl-4-benzyl-2-methylquinoline (**3a)** (0.15 g, 0.53 mmol) in 89% yield.

Other reactions were carried out in a similar manner by using 0.3 mmol of **3**.

3-Acetyl-2-methyl-4-pentylquinoline **3b** (0.061 g, 0.24 mmol, 80%). Yellow oil. ^{1}H NMR ($CDCl_3$) δ = 0.90 (dd, 3H, *J* = 7.2 Hz and 7.6 Hz, Me), 1.34-1.46 (m, 4H, CH_2), 1.64-1.70 (m, 2H, CH_2), 2.60 (s, 3H, Me), 2.63 (s, 3H, Me), 2.87 (t, 2H, *J* = 8. 4 Hz, CH_2), 7.52 (dd, 1H, *J* = 7.6 Hz and 8.4 Hz, Ar), 7.67 (dd, 1H, *J* = 7.6 Hz and 8.4 Hz, Ar), 7.96 (d, 1H, *J* = 8.4 Hz, Ar), 8.01 (d, 1H, *J* = 8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 14.16 (Me), 22.58 (CH_2), 23.78 (Me), 30.04, 31.23, 32.53 (CH_2), 32.94 (Me), 124.01, 125.39, 126.52, 129.68, 129.86, 135.51, 143.73, 147.67, 152.86 (Ar), 206.72 (CO). HRMS: Calcd for $C_{17}H_{21}NO$; 255.1623. Found; (M^+) 255.1623.

3-Acetyl-4-hexyl-2-methylquinoline **3c** (0.069 g, 0.26 mmol, 86%). Yellow oil. ^{1}H NMR ($CDCl_3$) δ = 0.90 (dd, 3H, *J* = 6.6 Hz and 7.0 Hz, Me), 1.30-1.34 (m, 4H, CH_2), 1.44-1.48 (m, 2H, CH_2), 1.62-1.69 (m, 2H, CH_2), 2.59 (s, 3H, Me), 2.63 (s, 3H, Me), 2.86 (t, 2H, *J* = 8.2 Hz, CH_2), 7.52 (dd, 1H, *J* = 7.6 Hz and 8.4 Hz, Ar), 7.67 (dd, 1H, *J* = 7.6 Hz and 8.4 Hz, Ar), 7.96 (d, 1H, *J* = 8.4 Hz, Ar), 8.02 (d, 1H, *J* =

8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 14.26 (Me), 22.79 (CH_2), 23.71 (Me), 30.10, 30.14, 31.53, 31.68 (CH_2), 32.96 (Me), 124.03, 125.41, 126.59, 129.57, 129.94, 135.52, 143.94, 147.49, 152.84 (Ar), 206.64 (CO). HRMS: Calcd for $C_{18}H_{23}NO$; 269.1773. Found; (M^+) 269.1737.

3-Acetyl-(4-butylbenzyl)-2-methylquinoline **3d** (0.086 g, 0.26 mmol, 87%). Yellow oil. ^{1}H NMR ($CDCl_3$) δ = 0.87 (dd, 3H, *J* = 7.2 Hz and 7.4 Hz, Me), 1.26-1.34 (m, 2H, CH_2), 1.51-1.55 (m, 2H, CH_2), 2.40 (s, 3H, Me), 2.51 (t, 2H, *J* = 7. 6 Hz, CH_2), 2.68 (s, 3H, Me), 4.32 (s, 2H, CH_2), 6.96 (d, 2H, *J* = 7.8 Hz, Ar), 7.03 (d, 2H, *J* = 7.8 Hz, Ar), 7.42 (dd, 1H, *J* = 7.6 Hz and 8.4 Hz, Ar), 7.65 (dd, 1H, *J* = 7.6 Hz and 8.4 Hz, Ar), 7.88 (d, 1H, *J* = 8.4 Hz, Ar), 8.02 (d, 1H, *J* = 8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 14.16 (Me), 22.55 (CH_2), 23.89 (Me), 32.82, 33.78 (CH_2), 34.55 (Me), 35.38 (CH_2), 124.96, 125.90, 126.82, 128.36, 129.01, 129.57, 129.99, 135.75, 136.71, 140.95, 141.48, 147.84, 153.10 (Ar), 206.78 (CO). HRMS: Calcd for $C_{23}H_{25}NO$; 331.1936. Found; (M^+) 331.1937.

3-Acetyl-4-(3-hydroxylpropyl)-2-methylquinoline **3e** (0.069 g, 0.29 mmol, 95%). Pale brown oil. ^{1}H NMR ($CDCl_3$) δ = 1.65 (br, 1H, OH), 1.93-1.99 (m, 2H, CH_2), 2.62 (s, 3H, Me), 2.65 (s, 3H, Me), 3.05 (dd, 2H, *J* = 7.4 Hz and 7.6 Hz, CH_2), 3.67 (dd, 2H, *J* = 5.6 Hz and 5.6 Hz, CH_2), 7.54 (dd, 1H, *J* = 7.2 and 7.6 Hz, Ar), 7.70 (dd, 1H, *J* = 7.2 Hz and 7.6 Hz, Ar), 7.98 (d, 1H, *J* = 8.4 Hz, Ar), 8.02-8.05 (d, 1H, *J* = 8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 23.84 (Me), 26.29, 33.06 (CH_2), 33.90 (Me), 61.78 (CH_2), 124.16, 125.28, 126.73, 129.67, 130.08, 135.82, 143.05, 147.68, 152.78 (Ar), 207.62 (CO). HRMS: Calcd for $C_{15}H_{17}NO_2$; 243.1259. Found; (M^+) 243.1248.

3-Acetyl-2-methyl-4-neopentylquinoline **3f** (0.074 g, 0.29 mmol, 97% yield). Yellow oil. ^{1}H NMR ($CDCl_3$) δ = 0.93 (s, 9H, Me) 0.98 (s, 2H, CH_2), 2.54 (s, 3H, Me), 2.64 (s, 3H, Me), 7.51 (dd, 1H, *J* = 7.6 Hz and 8.0 Hz, Ar), 7.69 (dd, 1H, *J* = 7.2 Hz and 7.6 Hz, Ar), 8.01 (d, 1H, *J* = 8.4 Hz, Ar), 8.09 (d, 1H, *J* = 8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 24.30 (Me), 31.21 (3Me), 33.37 (CH_2), 34.17 (Me), 41.35 ($C(Me)_3$), 125.74, 125.88, 126.88, 129.41, 129.84, 136.95, 141.99, 147.63, 153.08 (Ar), 206.71 (CO). HRMS: Calcd for $C_{17}H_{21}NO$; 255.1623. Found; (M^+) 255.1621.

3-Acetyl-4-benzyl-7-chloro-2-methylquinoline **3g** (0.056 g, 0.18 mmol, 60%). Yellow granules: mp. 88-89 ^{o}C. ^{1}H NMR ($CDCl_3$) δ = 2.42 (s, 3H, Me), 2.67 (s, 3H, Me), 4.33 (s, 2H, CH_2), 7.04 (d, 2H, *J* = 7.4 Hz, Ar), 7.20-7.26 (m, 3H, Ar), 7.37 (d, 1H, *J* = 8.8 Hz, Ar), 7.78 (d, 1H, *J* = 8.8 Hz, Ar), 8.03 (s, 1H, Ar). ^{13}C NMR ($CDCl_3$) δ = 23.92, 32.78 (Me), 34.96 (CH_2), 124.29, 126.28, 127.02, 127.80, 128.40, 128.60, 129.08, 135.95, 136.88, 138.28, 140.73, 148.34, 154.56, (Ar), 206.29 (C=O). HRMS: Calcd for $C_{19}H_{16}{}^{35}ClNO$; 309.0920. Found; (M^+) 309.0925.

3-Acetyl-4-benzyl-7-methoxy-2-methylquinoline **3h** (0.070 g 0.23 mmol, 76%). Yellow amorphous solid: mp 132-133 ^{o}C. ^{1}H NMR ($CDCl_3$) δ = 2.39 (s, 3H, Me), 2.65 (s, 3H, Me), 3.94 (s, 3H, OMe), 4.33 (s, 2H, CH_2), 7.05 (d, 2H, *J* = 7.2 Hz, Ar), 7.08 (d, 1H, *J* = 9.2 Hz, Ar), 7.18-7.25 (m, 3H, Ar), 7.37 (s, 1H, Ar), 7.75 (d, 1H, *J* = 9.2 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 22.60, 31.67 (Me), 33.62 (CH_2), 55.49 (OMe), 106.34, 118.59, 119.59, 124.76, 125.55, 127.20, 127.69, 133.61, 137.47, 139.50, 148.49, 152.23, 159.87 (Ar), 205.65 (C=O). HRMS: Calcd for $C_{20}H_{19}NO_2$; 305.1416. Found; (M^+) 305.1408.

3-Acetyl-4-benzyl-2,6-dimethylquinoline **3i** (0.058 g 0.20 mmol) in 67% yield. Yellow granules: mp 123-124 ^{o}C. ^{1}H NMR ($CDCl_3$) δ = 2.37 (s, 3H, Me), 2.44 (s, 3H, Me), 2.65 (s, 3H, Me), 4.34 (s, 2H, CH_2), 7.06 (d, 2H, *J* = 7.2 Hz, Ar), 7.18-7.26 (m, 3H, Ar), 7.49 (d, 1H, *J* = 8.4 Hz, Ar), 7.64 (s, 1H, Ar), 7.92 (d, 1H, *J* = 8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 22.13, 23.75, 32.78 (Me), 34.70 (CH_2), 123.68, 123.70, 125.83, 126.80, 128.49, 128.95, 129.29, 132.28, 136.73, 138.72, 139..90, 146.42, 152.00 (Ar), 206.97 (C=O). HRMS: Calcd for $C_{20}H_{19}NO$; 289.1467. Found; (M^+) 289.1467.

9-Hexyl-5,6,7,8-tetrahydroacridine **3j** (0.055 g, 0.20 mmol, 68%). Yellow oil. ^{1}H NMR ($CDCl_3$) δ = 0.90 (dd, 3H, *J* = 6.8 Hz and 6.8 Hz, Me), 1.32-1.48 (m, 4H, CH_2), 1.48 (dt, 2H, *J* = 6.8 Hz and 7.0 Hz, CH_2), 1.56 (dt, 2H, *J* = 6.8 Hz and 8.0 Hz, CH_2), 1.93-1.98 (m, 4H, CH_2), 2.92 (dd, 2H, *J* = 7.6 Hz and 8.0 Hz, CH_2), 3.11 (dd, 2H, *J* = 6.0 Hz and 6.2 Hz, CH_2), 7.43 (dd, 1H, *J* = 7.6 Hz and 8.0 Hz, Ar), 7.57 (dd, 1H, *J* = 7.6 Hz and 8.4 Hz, Ar), 7.93 (d, 1H, *J* = 8.0 Hz, Ar), 7.96 (d, 1H, *J* = 8.4 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 14.33 (Me), 22.90, 23.04, 23.46, 26.57, 27.90, 29.84, 30.24, 31.91, 34.74 (CH_2), 123.54, 125.47, 126.41, 128.22, 128.25, 129.33, 145.94, 146.55, 159.04 (Ar). HRMS: Calcd for $C_{19}H_{25}N$; 267.1987. Found; (M^+) 267.1989.

9-Neopentyl-5,6,7,8-tetrahydroacridine **3k** (0.043 g, 0.17 mmol, 57%). Yellow oil. ^{1}H NMR ($CDCl_3$) δ = 0.98 (s, 9H, Me), 1.86-1.97 (m, 4H, CH_2), 2.94 (dd, 2H, *J* = 6.0 Hz and 6.2 Hz, CH_2), 3.09-3.16 (m, 4H, CH_2), 7.39 (dd, 1H, *J* = 7.2 Hz and 8.0 Hz, Ar), 7.55 (dd, 1H, *J* = 7.2 Hz and 8.0 Hz, Ar), 7.95 (d, 1H, *J* = 8.0 Hz, Ar), 8.02 (d, 1H, *J* = 8.0 Hz, Ar). ^{13}C NMR ($CDCl_3$) δ = 22.67, 23.16, 28.09 (CH_2), 31.22 (Me), 34.42, 34.82 (CH_2), 38.71 ($C(Me)_3$), 124.70, 125.49, 127.98, 128.02, 129.09, 130.92, 143.22, 146.51, 159.27 (Ar). HRMS: Calcd for $C_{18}H_{23}N$; 253.1830. Found; (M^+) 253.1826.

One-pot synthesis of quinoline 3a from 2-iodonitrobenzene.

To a suspension of 2-iodonitrobenzene (0.124 g, 0.5 mmol), $PdCl_2(PPh_3)_2$ (0.004 g, 0.005 mmol), and CuI (0.005 g, 0.025 mmol) in diethylamine (8 mL) was added phenylacetylene (0.066 mL, 0.6 mmol) in one portion. After refluxing for 6 h, the suspension was evaporated and added Sn (0.118 gm 1.0 mmol), $Na_2S{\cdot}9H_2O$ (0.060 g, 0.25 mmol), acetylacetone (0.062 mL, 0.6 mmol), EtOH (6 mL), H_2O (1 mL), and HCl (0.42 mL, 5 mmol). After refluxing for 16 h, 5% aq. Na_2CO_3 was added and extracted with EtOAc (5mL x 3). The combined extract was dried over magnesium sulfate, filtered, and evaporated to give brown solid, which was chromatographed over silica gel by elution with hexane: EtOAc (5:1) to afford quinoline **3a** (0.088 g, 0.33 mmol, 65%). Other reactions were carried out in a similar manner.

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