Microwave-assisted, palladium-catalyzed carbonylative cyclization — Rapid synthesis of 2-quinolones from unprotected 2-iodoanilines and terminal alkynes

Jia-Rong Chen, Jie Liao, and Wen-Jing Xiao

Abstract: Palladium-catalyzed cyclocarbonylations of 2-iodoanilines with various terminal alkynes have been carried out by the use of commercially available molybdenum hexacarbonyl as a convenient and solid carbon monoxide source. The reactions were conducted at 160 °C for 30 min under microwave irradiation and in the presence of Et_3N in THF, affording the corresponding 2-quinolone derivatives in good regioselectivities and yields.

Key words: microwave, palladium, carbonylation, 2-iodoaniline, 2-quinolone.

Résumé : Faisant appel à des catalyseurs de palladium et de l'hexacarbonyle de molybdène disponible commercialement comme source commode et solide de monoxyde de carbone, on a effectué des cyclocarbonylations de 2-iodoanilines avec divers alcynes en position terminale. Les réactions ont été effectuées à 160 °C, pendant 30 minutes, sous irradiations de micro-ondes et en présence de Et_3N dans le THF et elles conduisent à la formation des 2-quinoléones correspondantes avec de bons rendements et de bonnes régiosélectivités.

Mots-clés : micro-onde, palladium, carbonylation, 2-iodoaniline, 2-quinoléone.

[Traduit par la Rédaction]

Introduction

Undoubtedly, the transition-metal-catalyzed carbonylation has become one of the most important carbonyl-formation reactions in organic synthesis.[1] Particularly, palladium-catalyzed cyclocarbonylation of unsaturated substrates provides a unique, concise, and efficient approach toward carbo- and hetero-cycles bearing a carbonyl moiety.[2] For example, the insertion of CO into aryl–palladium bond leading to the formation of acylpalladium complex, which could react with various nucleophiles, is a ubiquitous process for the synthesis of aryl carbonyl compounds.[3] Representative examples include palladium-catalyzed carbonylative cyclizations of 2-iodophenols or 2-iodoanilines with unsaturated substrates, such as terminal alkynes, 1,2- and 1,3- dienes, and allenes by the use of gaseous CO.[4]

2-Quinolones are widely distributed in nature and in many biologically important alkaloids, which showed remarkable activities, such as anticancer,[5] antitumor, and antihypertensive properties.[6] In addition, they are useful intermediates in organic synthesis.[7] Conventional methods for the synthesis of 2-quinolones are usually based on the Friedländer synthesis via Schiff base condensation[8] and the Knorr synthesis through acid-catalyzed cyclization of β-ketoanilides.[9] Recently, Kadnikov and Larock reported an elegant approach to 2-quinolones, which was based on palladium-catalyzed carbonylative annulation of terminal or internal alkynes with 2-iodoanilines.[10] However, relatively long reaction time and an additive (e.g., *n*-Bu_4NCl) are usually required. Moreover, the amino group of 2-iodoanilines has to be protected in the reaction process. Therefore, the development of more rapid and flexible strategy for the synthesis of 2-quinolones is still highly desirable.

Microwave activation as a potential energy source has proven to be a very popular and useful technology in synthetic organic chemistry, especially in the synthesis of heterocyclic compounds.[11] Compared to the traditional heating, the microwave-accelerated reaction has the major advantages of shorter reaction times, cleaner product profiles, and minimal quantities of solvent. As part of our ongoing endeavors on carbo- and hetero-cycle-oriented organometallic catalysis,[12] we recently reported a rapid synthesis of chromen-2-one by microwave-accelerated, palladium-catalyzed carbonylative cyclization of 2-iodophenol with alkynes.[13] This method features the use of commercially available molybdenum hexacarbonyl as a convenient and solid carbon monoxide source.[14] Herein, we extend this carbonylative cyclization strategy as a practical and convenient synthesis

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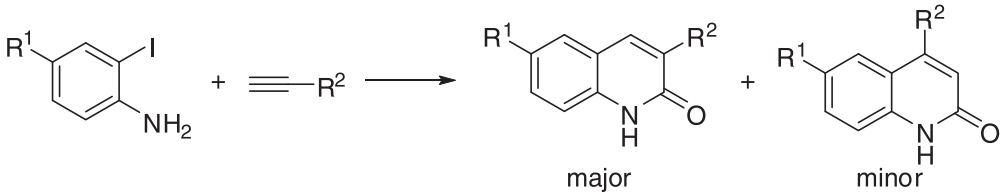
Scheme 1.



of 3- and 4-substituted 2-quinolones from 2-iodoanilines and terminal alkynes (Scheme 1).

Results and discussion

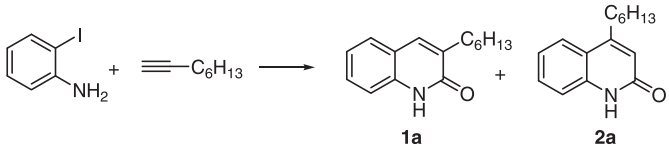
The reaction conditions previously used for the carbonylative cyclization reactions of 2-iodophenol with alkynes[13a] were initially applied to the reaction of 2-iodoaniline with 1-octyne (Table 1, entry 1). To our delight, the desired 2-quinolone was obtained in a 59% yield as a mixture of two regioisomers. The structure of 2-quinolone (**1a**) was proposed by NMR and unambiguously confirmed by X-ray crystallographic analysis (Figure 1) (see Supplementary data). Fortunately, these two isomers can easily be separated by flash column chromatography. To optimize the reaction conditions, the effects of the bases, catalysts, ligands, and solvents on the model reaction were further examined.

As can be seen from the results summarized in Table 1, both organic and inorganic bases were effective in this reaction. Among the organic bases screened, trialkylamine gave better results than secondary alkyl amines did (Table 1, entries 2 and 4 vs. entry 3). The use of unhindered pyridines or DMAP as the base resulted in decreased yields but with better regioselectivity (Table 1, entries 5 and 7). A similar effect was also observed in the case of DBU (Table 1, entry 6). The employment of inorganic bases led to low yields and moderate regioselectivity for this reaction. As a result, Et_3N proved to be the best base, and the desired products were obtained in overall 60% yield with 3.5:1 regioselective ratio. Thereafter, different palladium catalysts, ligands, and solvents were also carefully examined to further improve the yields and regioselectivity with Et_3N as the base.

Among the three palladium–PPh_3 systems examined, $Pd(OAc)_2$ exhibited good catalytic activity (Table 2, entry 2). Thus, other common phosphine ligands, such as DPPB, DPPP, DPPE, and DPPF were then examined. It was found that DPPE was the best choice in terms of regioselectivity and yield (**1a**:**2a** = 4:1, 60%) (Table 2, entry 6). The profile of solvent via reaction efficiency revealed that the reaction in THF gave higher yield and regioselectivity than in other solvents (Table 2, entries 8–12). Thus, the optimized reaction conditions for the microwave-accelerated carbonylative cyclization of 2-iodoaniline and alkynes with $Mo(CO)_6$ as the CO source have been determined to be 1 mmol of 2-iodoaniline, 2 equiv. of alkyne, 0.5 equiv. of $Mo(CO)_6$, 5 mol% $Pd(OAc)_2$, and 20 mol% DPPE in the presence of 2 equiv. of Et_3N in 1 mL of THF under microwave irradiation at 160 °C for 30 min (**1a**:**2a** = 3.9:1, 62% yield) (Table 2, entry 8).

With the standard conditions in hand, we next investigated the scope and limitation of this process. A series of alkyl/aryl alkynes and differently substituted 2-iodoanilines were subjected to the optimized conditions. Generally, the carbonylative cyclization proceeded smoothly with good yields. For example, 1-octyne, 1-heptyne, and 1-hexyne were suitable for this protocol (Table 2, entries 16 and 17), affording the 2-quinolones **1** and **2** in 60%, 69%, and 70% overall yields, respectively (Table 3, entries 1–3). Aryl-substituted alkynes can also be employed in this transformation. Importantly, only one regioisomer was isolated in these cases, although the yield was moderate (Table 3, entries 4, 6, 8, and 10–12). Structural variation in the iodoanilines component is also possible. For example, methyl, Cl, and Br can be introduced on the benzene ring at the C(4) position without significant loss in reaction yield or efficiency (Table 3, entries 5–12). As shown in Table 3 (entries 5, 6, and 9–15), we have successfully utilized halogenated 2-iodoaniline substrates in this reaction. Moreover, these products should be valuable for further chemical transformations.[15] Note that the reaction has some limitations. Neither internal alkynes or N-protected 2-iodoanilines can be used in this carbonylative annulation.

Table 1. Effects of the base on the carbonylative annulations of 2-iodoaniline with 1-octyne.



Entry	Base	Yield (%)[a]	Ratio of **1a**:**2a**[b]
1[c]	DMAP–DIPEA	59	1.2:1
2	Et_3N	60	3.5:1
3	Et_2NH	38	3:1
4	DIPEA	62	1.5:1
5	Pyridine	39	3:1
6	DBU	23	3.5:1
7	DMAP	28	>10:1
8	Imidazole	35	4:1
9	K_2CO_3	44	4.6:1
10	Cs_2CO_3	29	1.5:1

Note: Representative experimental procedure: 2-iodoaniline (1 mmol), 1-octyne (2 mmol), base (2 mmol), $Pd(OAc)_2$ (5 mol%, 0.05 mmol), PPh_3 (20 mol%, 0.2 mmol), and $Mo(CO)_6$ (0.5 mmol); carried in THF (1 mL) under microwave irradiation at 60 °C for 10 min and then at 160 °C for 30 min.

[a]Isolated yield.

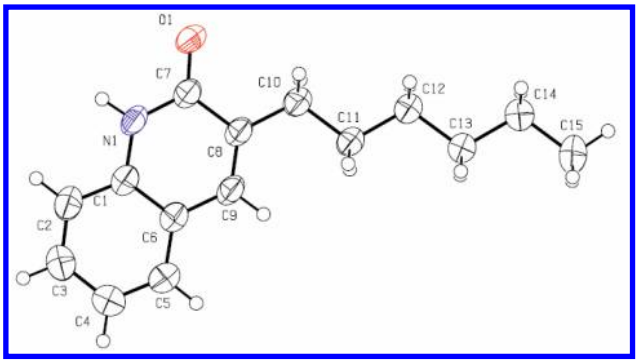
[b]The ratios were determined by GC.

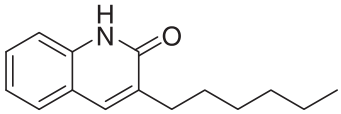
[c]DMAP (1 mmol) and DIPEA (1 mmol) were used.

Conclusions

In summary, we have established a rapid and efficient synthesis of 3- or 4-substituted 2-quinolones starting from readily available unprotected 2-iodoanilines and alkynes

Fig. 1. Crystal structure of **1a**.





1a

Table 2. Optimization of reaction conditions for the carbonylative annulations.

Entry	Catalyst	Ligand	Solvent	Yield (%)[a]	Ratio of **1a**:**2a**[b]
1	$PdCl_2$	PPh_3	Dioxane	58	2.5:1
2	$Pd(OAc)_2$	PPh_3	Dioxane	60	3.5:1
3	$Pd(PPh_3)_4$	PPh_3	Dioxane	54	2.2:1
4	$Pd(OAc)_2$	DPPB	Dioxane	59	2.4:1
5	$Pd(OAc)_2$	DPPP	Dioxane	49	3.0:1
6	$Pd(OAc)_2$	DPPE	Dioxane	60	4.0:1
7	$Pd(OAc)_2$	DPPF	Dioxane	17	1.1:1
8	$Pd(OAc)_2$	DPPE	THF	62	3.9:1
9	$Pd(OAc)_2$	DPPE	DMF	25	>10:1
10	$Pd(OAc)_2$	DPPE	CH_3CN	15	>10:1
11	$Pd(OAc)_2$	DPPE	CH_2Cl_2	28	2.4:1
12	$Pd(OAc)_2$	DPPE	$ClCH_2CH_2Cl$	ND[c]	ND[c]

Note: Representative experimental procedure: iodoaniline (1 mmol), alkyne (2 mmol), Et_3N (2 mmol), palladium catalyst (5 mol%, 0.05 mmol), ligand (20 mol%, 0.2 mmol), and $Mo(CO)_6$ (0.5 mmol); carried out in solvent (1 mL) under microwave irradiation at 60 °C for 10 min and then at 160 °C for 30 min.

[a]Isolated yield.

[b]The ratios were determined by GC.

[c]ND: no products were detected.

under microwave-irradiation conditions. The current methodology is attractive because of the short reaction time, the operational simplicity, and the absence of toxic gaseous carbon monoxide.

Experimental section

General methods

Unless otherwise noted, materials were purchased from commercial suppliers and used without further purification. Solvents and liquid organic bases were freshly distilled according to the known procedures.[16] Column chromatography was performed using 200–300 mesh silica gel. All melting points are uncorrected. ^{1}H NMR spectra were recorded on Varian Mercury 400 (400 MHz) spectrometers. Chemical shifts are reported in ppm from TMS with the solvent resonance as the internal standard ($CDCl_3$: δ 7.24, DMSO: δ 2.50). Data are reported as follows: chemical shift, multiplicity (singlet (s), doublet (d), triplet (t), quartet (q), broad (br), or multiplet (m)), coupling constants (Hz). ^{13}C NMR spectra were recorded on Varian Mercury 400 (100 MHz) with complete proton decoupling spectrophotometers ($CDCl_3$: δ 77.7, DMSO: δ 39.5). Elemental analysis was performed on a Vario EL III elemental analysis instrument. Compounds **1b**, **1c**, **1d**, **1f**, **1j**, **2a**, **2b**, and **2c** are known compounds; and the data of these compounds have been found to be identical with those reported.[10a,17]

All experiments were performed in a Smith Synthesizer producing controlled irradiation at 2450 MHz with a power of 0–300 W.

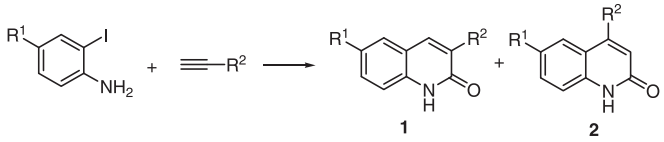
Representative procedure for the synthesis of 2-quinolones from unprotected 2-iodoanilines and terminal alkynes

To a 2.0–5.0 mL process vial were added 2-iodoaniline (1 mmol) and $Pd(OAc)_2$ (0.05 mmol), DPPE (0.2 mmol), Et_3N (2 mmol), alkyne (2 mmol), $Mo(CO)_6$ (0.5 mmol), and anhydrous THF (1 mL). The vial was immediately capped with a Teflon septum under N_2 and irradiated with microwave at 60 °C for 10 min, then at 160 °C for another 30 min. After cooling to room temperature, the contents of the vessel were filtered through a short Celite pad, washed with acetone, and then concentrated under reduced pressure. The residue was purified by silica-gel chromatography to afford the desired products.

3-*n*-Hexyl-2-1*H*-quinoline (1a)

White solid (recrystallized from petroleum ether/acetone).

Table 3. Scope of the carbonylative annulations.



Entry	R^1	R^2	Product(s)		Yield (%)[a]	Ratio of **1**:**2**[b]
1	H	*n*-Hex	**1a**	**2a**	60	3.9:1
2	H	*n*-Pen	**1b**	**2b**	69	4.0:1
3	H	*n*-Bu	**1c**	**2c**	70	6.7:1
4[c]	H	Ph	**1d**		39	
5	Cl	*n*-Bu	**1e**	**2e**	67	4.3:1
6[c]	Cl	Ph	**1f**		29	
7	Me	*n*-Bu	**1g**	**2g**	68	7.2:1
8[c]	Me	Ph	**1h**		73	
9	Br	*n*-Bu	**1i**	**2i**	66	10.7:1
10[c]	Br	Ph	**1j**		29	
11[c]	Br	4-MeC_6H_4	**1k**		46	
12[c]	Br	3-FC_6H_4	**1l**		47	

Note: Representative experimental procedure: iodoaniline (1 mmol), alkyne (2 mmol), Et_3N (2 mmol), $Pd(OAc)_2$ (5 mol%, 0.05 mmol), DPPE (10 mol%, 0.10 mmol), and $Mo(CO)_6$ (0.5 mmol); carried out in THF (1 mL) under microwave irradiation at 60 °C for 10 min and then at 160 °C for 30 min.

[a]Isolated yield.

[b]The ratios were determined by GC.

[c]Only the major isomers were detected.

Mp 113–116 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 11.04 (s, 1H), 7.60 (s, 1H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.29 (t, *J* = 10.6 Hz, 1H), 7.19 (t, *J* = 7.6 Hz, 1H), 2.67 (t, *J* = 7.6 Hz, 2H), 1.69 (t, *J* = 7.6 Hz, 1H), 1.64 (s, 2H), 1.43 (s, 2H), 1.35 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.5, 137.4, 136.5, 134.3, 129.2, 127.0, 122.3, 120.3, 115.6, 31.7, 30.2, 29.1, 28.3, 22.6, 14.1. MS *m*/*z*: 229 [M^+]. Anal. calcd. for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.60; H, 8.30; N, 6.14.

4-*n*-Hexyl-2-1*H*-quinoline (2a)

White solid (recrystallized from petroleum ether/acetone). Mp 155–157 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 12.33 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.52–7.46 (m, 2H), 7.27–7.22 (m, 1H), 76.60 (s, 1H), 2.86 (t, *J* = 7.8 Hz, 2H), 1.83–1.69 (2H, m), 1.45 (t, *J* = 10.4 Hz, 2H), 1.83–1.69 (m, 2H), 1.36–1.33 (m, 4H), 0.95–0.88 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.7, 153.3, 138.7,130.2, 124.0, 122.3, 119.8, 119.2, 116.9, 32.2, 31.5, 29.1, 28.7, 22.5, 14.0. MS *m*/*z*: 229 [M^+]. Anal. calcd. for $C_{15}H_{19}NO$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.59; H, 8.34; N, 6.14.

3-*n*-Pentyl-2-1*H*-quinoline (1b)

Brown solid (recrystallized from petroleum ether/acetone). Mp 133–136 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 11.83 (s, 1H), 7.62 (s, 1H), 7.53–7.18 (m, 4H), 2.69 (t, *J* = 7.6 Hz, 2H), 1.71 (t, *J* = 1.6 Hz, 2H), 1.43–1.40 (m, 4H), 0.93 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.6, 137.4, 136.4, 134.2, 129.2, 126.9, 122.2, 120.3, 115.7, 31.6, 30.2, 28.0, 22.6, 14.0. MS *m*/*z*: 215 [M^+]. Anal. calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.14; H, 7.92; N, 6.53.

4-*n*-Pentyl-2-1*H*-quinoline (2b)

White solid (recrystallized from petroleum ether/acetone). Mp 142–145 °C. ^{1}H NMR ($CDCl_3$, 600 MHz) δ: 12.75 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 13.2 Hz, 2H), 7.25–7.21 (m, 1H), 6.59 (s, 1H), 2.84 (t, *J* = 7.6 Hz, 2H), 1.74–1.68 (2H, m), 1.50–1.44 (2H, m), 0.98 (t, *J* = 4.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.6, 153.4, 138.5, 130.3, 124.1, 122.4, 119.8, 119.2, 116.8, 32.2, 31.6, 28.0, 22.5, 14.0. MS *m*/*z*: 215 [M^+]. Anal. calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.13; H, 7.98; N, 6.50.

3-*n*-Butyl-2-1*H*-quinoline (1c)

Brown solid (recrystallized from petroleum ether/acetone). Mp 151–154 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 12.20 (s, 1H), 7.62 (s, 1H), 7.53–7.40 (m, 2H), 7.21–7.17 (m, 1H), 2.70 (t, *J* = 7.4 Hz, 2H), 1.74–1.66 (m, 2H), 1.49–1.44 (m, 2H), 0.99 (t, 7.4 Hz, 3H). ^{13}C NMR($CDCl_3$, 100 MHz) δ: 164.6, 137.5, 136.4, 134.2, 126.9, 122.2, 120.3, 115.7, 30.5, 29.9, 22.5, 14.0. MS *m*/*z*: 201 [M^+]. Anal. calcd. for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96. Found: C, 77.60; H, 7.49; N, 6.99.

4-*n*-Butyl-2-1*H*-quinoline (2c)

Brown solid (recrystallized from petroleum ether/acetone). Mp 112–115 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 12.77 (s, 1H), 7.72 (d, *J* = 5.2 Hz, 1H), 7.48 (d, *J* = 2.4 Hz, 2H), 7.24–7.21 (m, 1H), 6.60 (s, 1H), 2.85 (t, *J* = 5.2 Hz, 2H), 1.73–1.68 (m, 1H), 1.50–1.44 (m, 2H), 0.98 (t, *J* = 4.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.6, 153.4, 138.5, 130.3, 124.1, 122.4, 119.8, 119.2, 116.9, 31.9, 30.9, 22.6, 14.0. MS *m*/*z*: 201 [M^+]. Anal. calcd. for $C_{13}H_{15}NO$:

C, 77.58; H, 7.51; N, 6.96. Found: C, 77.56; H, 7.53; N, 6.94.

3-*n*-Phenyl-2-1*H*-quinoline (1d)

White solid (recrystallized from petroleum ether/acetone). Mp 229–232 °C. ^{1}H NMR (DMSO, 400 MHz) δ: 11.98 (s, 1H), 8.11 (s, 1H), 7.78–7.73 (m, 3H), 7.51–7.20 (m, 6H). ^{13}C NMR (DMSO, 100 MHz) δ: 161.1, 138.4, 136.3, 131.6, 130.2, 128.7, 128.1, 128.0, 121.9, 119.6, 114.7. MS *m*/*z*: 221 [M$^+$]. Anal. calcd. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33. Found: C, 81.46; H, 5.04; N, 6.30.

3-*n*-Butyl-6-chloro-2-1*H*-quinoline (1e)

White solid (recrystallized from petroleum ether/acetone). Mp 169–172 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 12.76 (s, 1H), 7.48 (d, *J* = 12.8 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 2.67 (t, *J* = 3.6 Hz, 2H), 1.69–1.63 (m, 2H), 1.50–1.40 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.4, 135.9, 135.5, 135.2, 129.4, 127.5, 126.0, 121.2, 117.2, 30.4, 29.9, 22.5, 14.0. MS *m*/*z*: 238 [M$^+$]. Anal. calcd. for $C_{13}H_{14}ClNO$: C, 66.24; H, 5.99; N, 5.94. Found: C, 66.26; H, 5.96; N, 5.92.

4-*n*-Butyl-6-chloro-2-1*H*-quinoline (2e)

White solid (recrystallized from petroleum ether/acetone). Mp 163–165 °C. ^{1}H NMR (DMSO, 400 MHz) δ: 11.75 (s, 1H), 7.76 (d, *J* = 2.0 Hz, 1H), 7.53 (1H, dd, *J* = 2.0, 2.0 Hz), 7.33 (d, *J* = 8.8 Hz, 1H), 6.60 (s, 1H), 2.79 (t, *J* = 7.6 Hz, 2H), 1.58 (t, *J* = 7.6 Hz, 2H), 1.42–1.37 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (DMSO, 100 MHz) δ: 161.4, 150.8, 137.6, 130.0, 125.8, 123.6, 120.9, 120.0, 117.5, 30.7, 30.4, 21.9, 13.7. MS *m*/*z*: 238 [M$^+$]. Anal. calcd. for $C_{13}H_{14}ClNO$: C, 66.24; H, 5.99; N, 5.94. Found: C, 66.27; H, 5.97; N, 5.95.

3-Phenyl-6-chloro-2-2*H*-quinoline (1f)

Brown solid (recrystallized from petroleum ether/acetone). Mp 244–247 °C. ^{1}H NMR (DMSO, 400 MHz) δ: 12.11 (s, 1H), 8.09 (s, 1H), 7.84 (d, *J* = 2.4 Hz, 1H), 7.76 (t, *J* = 4.2 Hz, 1H), 7.56–7.34 (m, 5H). ^{13}C NMR (DMSO, 100 MHz) δ: 162.8, 137.3, 136.3, 135.6, 133.7, 130.5, 128.9, 128.4, 127.9, 127.0, 121.2, 116.9. MS *m*/*z*: 256 [M$^+$]. Anal. calcd. for $C_{15}H_{10}ClNO$: C, 70.46; H, 3.94; N, 5.48. Found: C, 70.48; H, 3.96; N, 5.45.

3-Butyl-6-methyl-2-2*H*-quinoline (1g)

White solid (recrystallized from petroleum ether/acetone). Mp 144–147 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 11.67 (brs,1H), 7.54 (s, 1H), 7.27 (m, 3H), 2.68 (t, *J* = 7.8 Hz, 2H), 2.43–2.38 (m, 3H), 1.72–1.65 (m, 2H), 1.50–1.41 (m, 2H), 1.02–0.96 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.4, 136.2, 135.4, 134.0, 131.7, 130.5, 126.5, 120.2, 115.6, 30.5, 29.9, 22.5, 20.9, 14.0. MS *m*/*z*: 215 [M$^+$]. Anal. calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.14; H, 7.97; N, 6.49.

4-Butyl-6-methyl-2-1*H*-quinoline (2g)

Yellow solid (recrystallized from petroleum ether/acetone). Mp 171–174 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 12.52 (s, 1H), 7.56–7.49 (m, 1H), 7.38–7.26 (m, 2H), 7.24–7.21 (m, 1H), 6.59 (d, *J* = 9.6 Hz, 1H), 2.85 (t, *J* = 7.6 Hz, 2H), 2.47–2.42 (t, *J* = 10.0 Hz, 3H), 1.77–1.70 (m, 2H), 1.68–1.43 (m, 2H), 1.03–0.94 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 164.5, 153.0, 136.5, 131.8, 131.6, 123.6, 119.7, 119.1, 116.8, 31.8, 30.8, 22.5, 21.2, 13.9. MS *m*/*z*: 215 [M$^+$]. Anal. calcd. for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.14; H, 7.97; N, 6.48.

3-Phenyl-6-methyl-2-1*H*-quinoline (1h)

White solid (recrystallized from petroleum ether/acetone). Mp 220–223 °C. ^{1}H NMR (DMSO, 400 MHz) δ: 11.90 (s, 1H), 8.02 (t, *J* = 10.0 Hz, 1H), 7.78–7.72 (m, 2H), 7.53 (d, *J* = 10.0 Hz, 1H), 7.46–7.22 (m, 5H), 2.36 (t, *J* = 9.8 Hz, 3H). ^{13}C NMR (DMSO, 100 MHz) δ: 161.0, 137.4, 136.4, 131.5, 130.9, 128.8, 128.0, 127.8, 127.6, 119.6, 114.7, 20.5. MS *m*/*z*: 235 [M$^+$]. Anal. calcd. for $C_{16}H_{13}NO$: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.70; H, 5.60; N, 5.92.

3-Butyl-6-bromo-2-1*H*-quinoline (1i)

White solid (recrystallized from petroleum ether/acetone). Mp 172–174 °C. ^{1}H NMR (DMSO, 400 MHz) δ: 12.36 (s, 1H), 7.65 (d, *J* = 2.4 Hz, 1H), 7.53 (d, *J* = 4.6 Hz, 2H), 7.28 (t, *J* = 8.2 Hz, 1H), 2.68 (t, *J* = 7.8 Hz, 2H), 1.71–1.63 (m, 2H), 1.48–1.42 (m, 2H), 0.98 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (DMSO, 100 MHz) δ: 164.3, 136.2, 135.6, 135.2, 132.0, 129.2, 121.7, 117.4, 114.9, 30.4, 29.9, 22.5, 14.0. MS *m*/*z*: 281 [M$^+$]. Anal. calcd. for $C_{13}H_{14}BrNO$: C, 55.73; H, 5.04; N, 5.00. Found: C, 55.70; H, 5.08; N, 5.02.

4-Butyl-6-bromo-2-1*H*-quinoline (2i)

White solid (recrystallized from petroleum ether/acetone). Mp181–184 °C. ^{1}H NMR (DMSO, 400 MHz) δ: 11.78 (1s, H), 7.89 (s, 1H), 7.66 (t, *J* = 4.4 Hz,1H), 7.28 (d, *J* = 8.8 Hz, 1H), 6.4 (s, 1H), 2.79 (t, *J* = 7.4 Hz, 2H), 1.61–1.54(m, 2H), 1.43–1.36 (m, 2H), 0.93 (t, *J* = 7.4 Hz). ^{13}C NMR (DMSO, 100 MHz) δ: 164.3, 136.2, 135.6, 135.2, 132.0, 129.2, 121.7, 117.4, 114.9, 30.4, 29.9, 22.5, 14.0. MS *m*/*z*: 281 [M$^+$]. Anal. calcd. for $C_{13}H_{14}BrNO$: C, 55.73; H, 5.04; N, 5.00. Found: C, 55.70; H, 5.06; N, 5.01.

3-Phenyl-6-bromo-2-1*H*-quinoline (1j)

White solid (recrystallized from petroleum ether/acetone). Mp 256–259 °C. ^{1}H NMR (DMSO, 400 MHz) δ: 12.10 (s, 1H), 7.98 (d, *J* = 2.0 Hz, 1H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.66 (dd, *J* = 2.0, 1.6 Hz, 1H), 7.47–7.40 (m, 3H), 7.28 (d, *J* = 8.8 Hz, 1H). ^{13}C NMR (DMSO, 100 MHz) δ: 160.8, 137.4, 136.4, 135.9, 132.7, 130.0, 128.7, 128.1, 128.0, 121.3, 116.8, 113.4. MS *m*/*z*: 300 [M$^+$]. Anal. calcd. for $C_{15}H_{10}BrNO$: C, 60.02; H, 3.36; N, 4.67. Found: C, 60.04; H, 3.38; N, 4.65.

3-(*p*-Tolyl)-6-bromo-2-1*H*-quinoline (1k)

Yellow solid (recrystallized from petroleum ether/acetone). Mp 255–257 °C. ^{1}H NMR (DMSO, 400 MHz) δ: 12.07 (s, 1H), 8.06 (s, 1H), 7.96 (d, *J* = 2.4 Hz, 1H), 7.64 (dd, *J* = 8.0, 1.6 Hz, 3H), 7.29–7.24(m, 3H), 2.23 (m, 3H). ^{13}C NMR (DMSO, 100 MHz) δ: 160.9, 137.5, 137.2, 135.8, 133.0, 132.3, 129.9, 128.7, 128.5, 121.4, 116.9, 116.7, 113.4, 21.0. MS *m*/*z*: 314 [M$^+$]. Anal. calcd. for $C_{16}H_{12}BrNO$: C, 61.17; H, 3.85; N, 4.46. Found: C, 61.20; H, 3.83; N, 4.49.

3-(3-Fluorophenyl)-6-bromo-2-1*H*-quinoline (1l)

White solid (recrystallized from petroleum ether/acetone). Mp 279–282 °C. ^{1}H NMR (DMSO, 400 MHz) δ: 12.16 (s, 1H), 8.19 (s, 1H), 7. 98 (d, J = 1.6 Hz, 1H), 7.69–7.59 (m, 3H), 7.52–7.47 (m, 1H), 7.30–7.22 (m, 1H). ^{13}C NMR (DMSO, 100 MHz) δ: 163.0, 160.6, 138.1, 137.5, 133.0, 131.0, 130.0, 124.7, 121.1, 117.0, 115.6, 115.0, 113.5. MS *m/z*: 318 [M$^+$]. Anal. calcd. for $C_{15}H_9BrFNO$: C, 56.63; H, 2.85; N, 4.40. Found: C, 56.67; H, 2.83; N, 4.43.

Supplementary data

Supplementary data for this article are available on the journal Web site (canjchem.nrc.ca) or may be purchased from the Depository of Unpublished Data, Document Delivery, CISTI, National Research Council Canada, Ottawa, ON K1A 0R6, Canada. DUD 5355. For more information on obtaining material, refer to cisti-icist.nrc-cnrc.gc.ca/cms/unpub_e.shtml.

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