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PAPER

A quick and efficient route to substituted quinolines by electrophilic cyclization of 1-(2-aminoaryl)-2-yn-1-ols†‡

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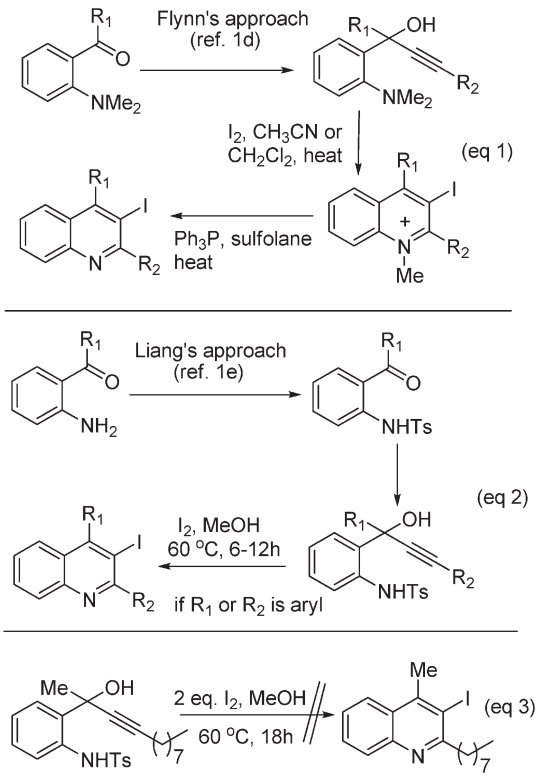
A practical method for the synthesis of substituted quinolines from 2-aminoarylketones (*via* 1-(2-aminoaryl)-2-yn-1-ols) using mild and simple reaction conditions is described. A study of several electrophiles in various reaction conditions is presented. Out of three electrophilic iodine sources (I_2, NIS and ICl) studied, I_2 was found to work efficiently for the synthesis of 3-iodoquinolines. Several Brønsted acids (*p*TSA, PPTS, AcOH, TFA, HCl) were able to catalyze the formation of 2,4-substituted quinolines from the same starting materials. Good to excellent overall yields were observed with both aromatic and aliphatic substitutions at the reaction center.

Introduction

The wide occurrence of quinolines and their derivatives in nature, and their interesting biological and pharmacological activities have been continuously attracting synthetic, biological and medicinal chemists over the years. Though a number of methods are available for the synthesis of the quinoline motifs,[1] due to their pharmaceutical importance,[2] the development of new synthetic approaches for novel substitution patterns remains an active research area. In particular, the synthesis of halogen-substituted quinolines[1b–e] has attracted attention in recent chemistry because the halogen gives an excellent lever for further convenient structural elaborations.

As part of a medicinal chemistry project in our laboratory, it was required to synthesize 3-iodoquinoline intermediates, and we were attracted by the recent publications of Larock,[1b–c] Flynn[1d] and Liang.[1e] Larock's method[1b–c] involves the electrophilic cyclization of aryl substituted propargylamines. This method works very well for 2,4-aryl substituted quinolines, however no reactions or unsatisfactory yields were observed for alkyl substitutions. On the other hand, Flynn *et al.*[1d] reported an elegant approach *via* electrophilic iodo cyclization of 1-(2-*N*,*N*-dimethylaminoaryl)-2-yn-ols (Scheme 1, eq 1). To improve its practicality and substrate scope, Liang *et al.*[1e] reported an improved method by substituting the dimethylamino group in Flynn's starting material with a tosylamino group (Scheme 1, eq 2). Although it works well for diaryl substituted substrates at *pro*-2C and *pro*-4C (numbering based on product), this method still suffers from multiple steps, long reaction times, elevated reaction temperatures, incompatible reaction conditions for acid sensitive substrates,[3] and lower overall yields if one of the aryl groups (at *pro*-2C or *pro*-4C) is substituted by an alkyl group in the starting substrates. Furthermore, it did not work for dialkyl (at *pro*-2C and *pro*-4C) substrates even after prolonged reaction times in the given conditions (Scheme 1, eq 3).[4] We were curious



Scheme 1 Analysis of previous approaches.

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† Electronic supplementary information (ESI) available: Copies of ^{1}H NMR, ^{13}C NMR and HRMS spectra of all compounds. See DOI: 10.1039/c2ra20213a
‡ CDRI communication number: 8201

to know why unsubstituted amino (–NH_2 instead of –NMe_2 or –NHTs) starting materials, which were recently disclosed by Gabriele,[1h] were not used in Flynn's and Liang's approach to get the target products directly. This might avoid multiple steps and, would increase the reactivity of substrates and reduce reaction temperatures and times because of the steric bulkiness around the nitrogen is reduced (compared to Flynn's substrate) and nucleophilicity of the amino group is increased (compared to Liang's substrate). This might also allow access to the 1,3-dialkyl counterparts in the ultimate dehydration step, which in this case could be easier compared to the dehydroxylation followed by detosylation in Liang's approach.

Results and discussion

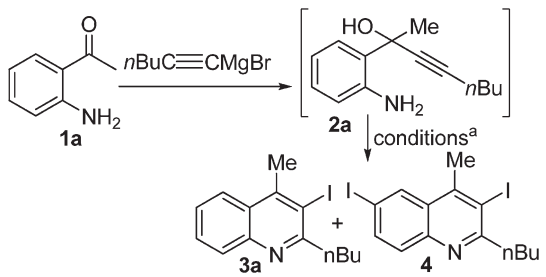
First we wanted to examine the reaction substrates with aliphatic groups at *pro*-2C and *pro*-4C which has been proved to be difficult in previous reports.[1b–e] Thus, we treated crude substrate **2a**,[1g,5] prepared from **1a** and 1-hexynylmagnesium bromide, with 2 equivalents of I_2 in MeOH. Within ten minutes at room temperature the starting material disappeared (TLC) and two products were found. The major product was identified as the expected product **3a** and the minor one as 3,6-diiodoquinoline **4** (see Table 1). The latter was formed through electrophilic substitution followed by electrophilic cyclization as the reverse is very difficult, and hence the ratio of the products remained constant even after extended reaction times. Reaction of **2a** with other electrophilic iodine sources such as *N*-iodosuccinimide (NIS) and ICl also led to the formation of a mixture of **3a** and **4** but in a different ratio. The use of $NaHCO_3$ along with I_2 in MeOH gave a slightly better result but **4** was still formed in 10% yield.

NIS and ICl, using the same base and solvent, also resulted in a mixture of products. However, a change of solvent from MeOH to CH_2Cl_2 cleanly produced **3a** as the sole product by using 2 eq. I_2 and no base. Even in CH_2Cl_2, NIS and ICl produced a mixture of products though in favour of the required iodoquinoline. Meanwhile, we also performed the optimization with substrate **2b** in parallel and the results are described in Table 2. Surprisingly, **2b**, on exposure to I_2 in MeOH at ambient temperature, gave quinoline **5b** as a byproduct.[6] By switching the solvent from MeOH to CH_2Cl_2, the byproduct **5b** was formed in negligible quantities (8%). In this case, we did not observe any aromatic electrophilic substitution product. We reasoned that the HI formed during the electrophilic iodo cyclization could be responsible for the formation of the non-iodinated product **5**.[6] We conclude that the activation energy of electrophilic cyclizations is considerably reduced with the aromatic substitution at *pro*-2C, resulting in no formation of the diiodoquinoline derivative like in the case of **1a**. On the other hand, in the case of *pro*-2C alkyl substrate **2a**, HI-induced electrophilic cyclization was not favored due to absence of conjugation and hence the non-iodinated quinoline derivative byproduct was not observed (Table 1).

With the optimal conditions (2 eq. of I_2 in CH_2Cl_2 at room temperature for 10–20 min) in hand, the scope of the approach was examined. Several 1-(2-aminoaryl)-2-yn-1-ols were prepared and tested for their reactivity, and the results are presented in Table 3. Dialkyl substrates **2c**–**2g** reacted well under the standard conditions to give 70–81% overall yields. Substrates **2h**–**2k** bearing aromatic substituents were more reactive and were smoothly converted into the corresponding products in 67–92% overall yields.

Notably, *pro*-4C-aryl substrates gave relatively higher yields compared to *pro*-2C-aryl substrates. It is worth mentioning that the presence of a withdrawing group on the aromatic ring, as in case of **2k**, did not have a negative impact on reactivity, with product **3k** being formed in 92% yield. Similarly, substrate **2l**, bearing the acid sensitive OTHP group, also provided the corresponding quinoline **5l**, though in a moderate overall yield of 63%. We also performed the reaction of **2d** to **3d** on a 50 mmol scale (6.7 g of **1a**) which produced the product in almost the same percentage yield as the experiment that was carried out at a smaller scale (11.7 g, 70% instead of 78%).

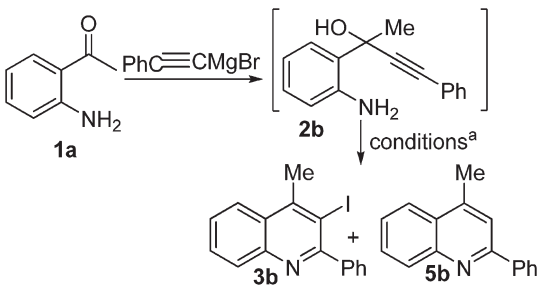
Table 1 Optimization of the reaction conditions[a]



Entry	I^+ source	Base	Solvent	Temp.	Time (min)	Yield[b]	
						3a	**4**
1	I_2	—	MeOH	rt	10	62	19
2	NIS	—	MeOH	rt	10	7	71
3	ICl	—	MeOH	rt	10	13	52
4	I_2	$NaHCO_3$	MeOH	rt	10	66	10
5	NIS	$NaHCO_3$	MeOH	rt	10	22	55
6	ICl	$NaHCO_3$	MeOH	rt	10	18	50
7	**I_2**	**—**	**CH_2Cl_2**	**rt**	**20**	**74**	**trace**
8	NIS	—	CH_2Cl_2	rt	20	48	28
9	ICl	—	CH_2Cl_2	rt	20	52	18

[a] The reactions were carried out with 5 mmol substrate using 2 eq. I_2 at 0.13 M concentration. [b] Isolated overall yields after two steps.

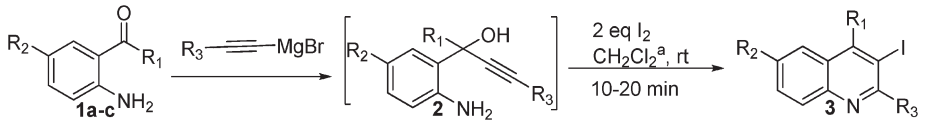
Table 2 Optimization studies[a]

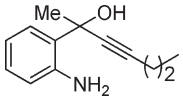
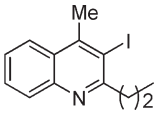
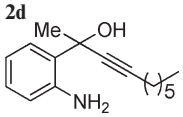
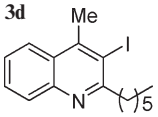
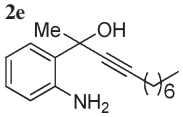
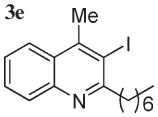
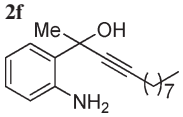
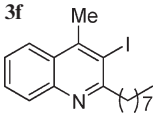
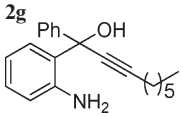
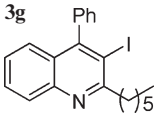
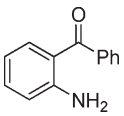
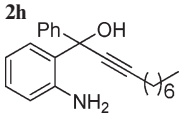
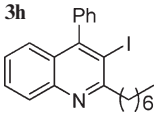
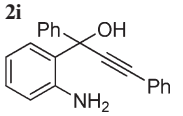
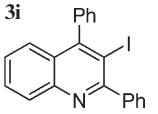
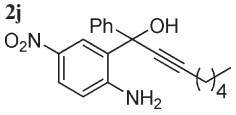
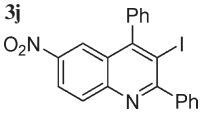
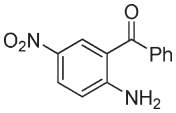
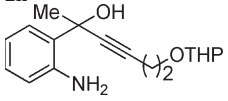
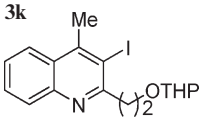


Entry	I^+ source	Base	Solvent	Temp.	Time (min)	Yield[b]	
						3b	**5b**
1	I_2	—	MeOH	rt	5	35	30
2	I_2	$NaHCO_3$	MeOH	rt	5	46	20
3	I_2	—	CH_2Cl_2	rt	10	67	8
4	I_2	$NaHCO_3$	CH_2Cl_2	rt	10	68	9

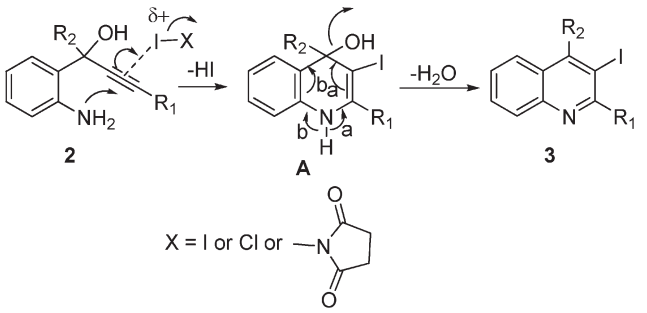
[a] The reactions were carried out with 5 mmol substrate using 2 eq. I_2 at 0.13 M concentration. [b] Isolated overall yields after two steps.

Table 3 Synthesis of 3-iodoquinolines *via* electrophilic iodocyclization of 1-(2-aminoaryl)-2-yn-ols[a]



Entry	1	2	Time (min)	Product	Yield[b]
1	**1a**	**2a**	20	**3a**	74%
2	**1a**	**2b**	10	**3b**	67%
3	**1a**	**2c** 	20		75%
4	**1a**	**2d** 	20	**3d** 	81%
5	**1a**	**2e** 	20	**3e** 	80%
6	**1a**	**2f** 	10	**3f** 	70%
7	**1a**	**2g** 	10	**3g** 	74%
8		**2h** 	10	**3h** 	81%
9	**1b**	**2i** 	10	**3i** 	69%
10	**1b**	**2j** 	10	**3j** 	92%
11		**2k** 	20	**3k** 	63%
12	**1c** **1a**	**2l**		**3l**	

[a] The reactions were carried out at 0.13 M concentration. [b] Isolated overall yields after two steps.



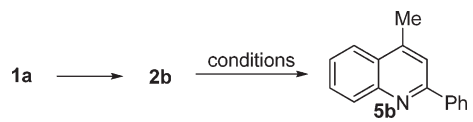
Scheme 2 A plausible mechanism for the formation of iodoquinolines.

A plausible mechanism for electrophilic iodocyclization is presented in Scheme 2. Electrophilic iodine initiated cyclization could lead to the intermediate **A** which on dehydration/aromatization forms the 3-iodoquinoline **3**.

As we have seen, the results obtained with substrate **2b** (Table 2) suggested that Brønsted acid might catalyze the formation of 2,3-substituted quinolines (*pro*-3H counterparts). We accordingly tested the reactivity of **2b** under acidic conditions. We began our study by treating **2b** with HCl, AcOH, TFA, TfOH, *p*TSA, and PPTS under various conditions; the results are summarized in Table 4. As can be seen from Table 4, almost all catalysts worked very well, with the exception of TfOH. AcOH and TFA were found to work at room temperature to give 62% and 55% overall yields respectively. PPTS produced a better yield (78%) though it needed a higher temperature (60 °C).

To explore the feasibility of the method, various substrates bearing alkyl and/or aryl substituents were subjected to the reaction and the results are reported in Table 5. As is apparent from Table 4, the method worked very well for both aliphatic and aromatic substituted substrates giving excellent overall yields (70–90%). The same conversion was reported earlier by Gabriele *et al.* using Cu and Pd metal catalysts.[1h] Although the method proposed here appears to be less general and less versatile with respect with the Gabriele's method, it nevertheless shows that acid catalysis is also possible for the conversion of substrates **2a–j** in to quinolines **5a–j**.

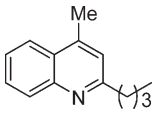
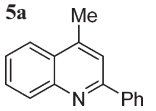
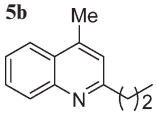
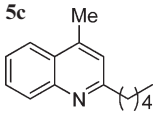
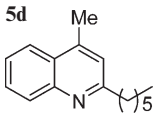
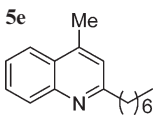
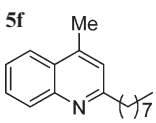
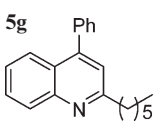
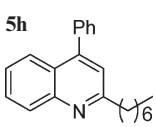
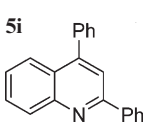
Table 4 Optimization studies[a]



Entry	2	Reagent (5 mmol%)	Temp. (°C)	Time (h)	5	Overall yield[b]
1	**2b**	HCl	50	2	**5b**	60%
2	**2b**	AcOH	rt	5	**5b**	62%
3	**2b**	TFA	rt	1	**5b**	55%
4	**2b**	TfOH	rt	1	**5b**	30%
5	**2b**	*p*TSA	50	5	**5b**	70%
6	**2b**	PPTS	50	1	**5b**	78%

[a] All reactions were carried out with 5 mmol substrate using 5 mol% catalyst in MeOH (0.13 M). [b] Isolated overall yields after two steps.

Table 5 Optimization and synthesis of quinolines *via* H^+ catalyzed electrophilic cyclization[a]

Entry	2	Time (h)	5	Overall yield[b]
1	**2a**	5		85%
2	**2b**	1	**5a** 	78%
3	**2c**	5	**5b** 	74%
4	**2d**	5	**5c** 	76%
5	**2e**	5	**5d** 	90%
6	**2f**	5	**5e** 	70%
7	**2g**	5	**5f** 	70%
8	**2h**	2	**5g** 	78%
9	**2i**	2	**5h** 	80%
10	**2j**	1	**5i**  **5j**	80%

[a] All reactions were carried out with 5 mmol substrate using 5 mol% catalyst in MeOH (0.13 M) at 50 °C. [b] Isolated overall yields after two steps.

Conclusion

In summary, an efficient and convergent approach has been described for the synthesis of conveniently substituted quinolines through an electrophilic cyclization of 1-(2-aminoaryl)-2-yn-1-ols.

The method features mild conditions and good overall yields in addition to benign substitution compatibility.

Experimental section

General information

All reagents were commercial and were used without further purification unless otherwise noted. Infrared spectra were recorded with FT-IR as a thin film and are expressed in cm^{-1}. ^1H NMR (at 200 or 300 MHz) and ^{13}C NMR (50 or 75 MHz) spectra were recorded using $CDCl_3$ as solvents and TMS as an internal standard. Mass spectra were obtained on a ESI mass spectrometer and HR/ESI mass spectra were obtained on a high resolution ESI mass spectrometer.

Representative procedure for the preparation of 3-iodoquinolines (3) from 2-aminoarylketones (1) *via* 1-(2-aminoaryl)-2-yn-1-ols (2). 1-(2-Aminoaryl)-2-yn-1-ols **2** were prepared from 2-aminoarylketones **1** as described by Gabriele *et al.*[1h] and were used directly in the electrophilic iodocyclization step without purification. The yields here were considered to be 100% to calculate the reagents in the following step (electrophilic cyclization), and the final yields are given as overall yield in two steps. To a mixture of crude substrate **2** (5 mmol, 1 eq.) in CH_2Cl_2 (40 mL, 0.13 M) was added I_2 (2.54 g, 10 mmol, 2 eq.) portion wise at room temperature and the contents were stirred at the same temperature. The reaction was followed by TLC and was observed to be completed in 10 to 20 min. The excess reagent was quenched by adding saturated aq. $Na_2S_2O_3$ (30 mL). The organic layer was separated and the remaining aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried on Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography (on silica gel, using EtOAc and Hexane) to obtain the pure 3-iodoquinolines **3**.

Representative procedure for the preparation of quinolines (5) from 2-aminoarylketones (1) *via* 1-(2-aminoaryl)-2-yn-1-ols (2). 1-(2-Aminoaryl)-2-yn-1-ols **2** were prepared from 2-aminoarylketones **1** as described by Gabriele *et al.*[1h] and were used directly in the electrophilic cyclization step without purification. The yields here were considered to be 100% to calculate the reagents in the following step (electrophilic cyclization), and the final yields are given as overall yield in two steps. A mixture of crude substrate **2** (5 mmol, 1 eq.) and PPTS (13 mg, 0.25 mmol, 0.05 eq.) in MeOH (40 mL, 0.13 M) was stirred at 60 °C. The reaction was followed by TLC and was completed in 1 to 5 h. The reaction mixture was quenched by adding saturated aq. $NaHCO_3$ (5 mL) after cooling to rt. Water (30 mL) was added to the resulting mixture and it was extracted with EtOAc (3 × 20 mL). The combined organic extracts were dried on Na_2SO_4, filtered and concentrated. The crude material was purified by column chromatography (on silica gel, using EtOAc and hexane) to obtain the pure 3-iodoquinolines **5**.

*2-Butyl-3-iodo-4-methylquinoline (**3a**).* 74% over all yield (in two steps); light yellow solid; m.p. 75–78 °C; R_f = 0.75 (EtOAc/hexane = 1/9); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.04-7.98 (m, 2H), 7.72-7.64 (m, 1H), 7.53–7.45 (m, 1H), 3.27–3.20 (m, 2H), 2.91 (s, 3H), 1.86–1.74 (m, 2H), 1.58–1.46 (m, 2H), 1.00 (t, 3H, J = 7.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 162.8, 148.3, 146.7, 129.6, 129.4, 126.8, 126.5, 124.3, 102.3, 43.3, 31.4, 25.7, 22.9, 14.1. ; IR (KBr) v: 3020, 2959, 2866, 1636, 1571, 1492, 1459, 1216, 955, 668, 559 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{17}IN$ $[M + H]^+$: 326.0406, found: 326.0739.

*3-Iodo-4-methyl-2-phenylquinoline (**3b**).* 67% over all yield (in two steps); known compound;[1e] light yellow solid, m.p. 105–108 °C; (lit.[1e] 105–110 °C); R_f= 0.65 (EtOAc/hexane = 1/9); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.15–8.08 (m, 2H), 7.78–7.70 (m, 2H), 7.62–7.45 (m, 6H), 3.00 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 162.1, 149.2, 146.6, 144.4, 130.2, 129.7, 129.2, 128.6, 128.1, 127.3, 124.4, 100.6, 26.0 ; IR (KBr) v: 2969, 2852, 1634, 1443, 1344, 1219, 771, 691, 547, 493 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{13}IN$ $[M + H]^+$: 346.0093, found: 346.0162.

*3-Iodo-4-methyl-2-propylquinoline (**3c**).* 75% over all yield (in two steps); light yellow solid; m.p. 85–88 °C; R_f = 0.73 (EtOAc/hexane = 1/9); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.04–7.98 (m, 2H), 7.72–7.65 (m, 1H), 7.54–7.46 (m, 1H), 3.25–3.17 (m, 2H), 2.91 (s, 3H), 1.92–1.79 (m, 2H), 1.08 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162. 6, 148.2, 146.7, 129.6, 129.5, 126.9, 126.5, 124.3, 102.4, 45.5, 25.68, 22.6, 14.2; IR (KBr) v: 2957, 2928, 2867, 1638, 1491, 1459, 1379, 966, 772, 747, 658, 558 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{15}IN$ $[M + H]^+$: 312.0249, found: 312.0378.

*3-Iodo-4-methyl-2-pentylquinoline (**3d**).* 78% over all yield (in two steps); light yellow solid; m.p. 72–75 °C; R_f = 0.70 (EtOAc/hexanes = 1/9); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.06–7.97 (m, 2H), 7.72–7.64 (m, 1H), 7.53–7.45 (m, 1H), 3.27–3.18 (m, 2H), 2.90 (s, 3H), 1.88–1.76 (m, 2H), 1.54–1.34 (m, 4H), 0.94 (t, 3H, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 162.8, 148.3, 146.7, 129.6, 129.5, 126.9, 126.5, 124.3, 102.4, 43.6, 32.0, 29.0, 25.7, 22.7, 14.3; IR (KBr) v: 3067, 2928, 2860, 1640, 1568, 1458, 1379, 962, 758, 657 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{18}IN$ $[M + H]^+$: 340.0562, found: 340.0563.

*2-Hexyl-3-iodo-4-methylquinoline (**3e**).* 81% over all yield (in two steps); orange oil; R_f = 0.67 (EtOAc/hexanes = 1/9); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.04–7.98 (m, 2H), 7.73–7.65 (m, 1H), 7.53–7.46 (m, 1H), 3.27–3.18 (m, 2H), 2.91 (s, 3H), 1.88–1.74 (m, 2H), 1.56–1.30 (m, 6H), 0.91 (t, 3H, J = 6.8 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 162.8, 148.2, 146.7, 129.5, 129.5, 126.8, 126.4, 124.3, 102, 7, 43.6, 31.8, 29.5, 29.2, 25.7, 22. 8, 14.2; IR (KBr) v: 2928, 2860, 2364, 1629, 1488, 1449, 1378, 1218, 966, 764, 672, 532 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{21}IN$ $[M + H]^+$: 354.0719, found: 354.0782.

*2-Heptyl-3-iodo-4-methylquinoline (**3f**).* 80% over all yield (in two steps); orange oil; R_f = 0.62 (EtOAc/hexane = 1/9); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.04–7.97 (m, 2H), 7.72–7.64 (m, 1H), 7.53–7.46 (m, 1H), 3.26–3.18 (m, 2H), 2.90 (s, 3H), 1.88–1.74 (m, 2H), 1.54–1.24 (m, 8H), 0.89 (t, 3H, J = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 162.8, 148.2, 146.7, 129.5, 129.4, 126.8, 126.4, 124.3, 102.3, 43.60, 32.0, 29.8, 29.3, 25.7, 22.8, 14.3; IR (KBr) v: 2926, 2856, 2363, 1637, 1460, 1379, 769, 668, 515 cm^{-1}; HRMS (ESI) m/z calcd for $C_{17}H_{23}IN$ $[M + H]^+$: 368.0875, found: 368.1523.

*3-Iodo-4-methyl-2-octylquinoline (**3g**).* 70% over all yield (in two steps); yellow oil; R_f = 0.60 (EtOAc/hexanes = 1/9); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.05–7.98 (m, 2H), 7.73–7.65(m, 1H), 7.54–7.46 (m, 1H), 3.27–3.18 (m, 2H), 2.91 (s, 3H), 1.87–1.75 (m, 2H), 1.54–1.20 (m, 10H), 0.88 (t, 3H, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.8, 148.3, 146.7, 129.6, 129.5, 126.9, 126.5, 124.4, 102.4, 43.6, 32.0, 29.8, 29.6, 29.4, 29.3, 25.7, 22.8, 14.3; IR (KBr) v: 2924, 2856, 1627, 1454, 1377, 1257, 960, 766, 658, 551 cm^{-1}; HRMS (ESI) m/z calcd for $C_{18}H_{25}IN$ $[M + H]^+$: 382.1032, found: 382.1395.

*3-Iodo-2-pentyl-4-phenylquinoline (**3h**).* 74% over all yield (in two steps); yellow solid; m.p. 85–90 °C; R_f = 0.9 (EtOAc/hexane 1/9); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.07 (d, 1H, J = 8.25 Hz), 7.72–7.64 (m, 1H), 7.60–7.50 (m, 3H), 7.37–7.19 (m, 4H), 3.28 (t, 2H, J = 7.7 Hz), 1.95–1.80 (m, 2H), 1.58–1.38 (m, 4H), 0.95 (t, 3H, J = 6.9 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 162.9, 154.0, 147.0, 142.3, 129.8, 129.2, 128.8, 128.7, 128.4, 127.1, 126.9, 126.5, 100.4, 43.3, 32.0, 29.0, 22.7, 14.2; IR (KBr) v: 3063, 2951, 2860, 1623, 1572, 1449, 1379, 1218, 699, 610, 519 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{21}IN$ $[M + H]^+$: 402.0719, found: 402.0730.

*2-Hexyl-3-iodo-4-phenylquinoline (**3i**).* 81% over all yield (in two steps); yellow solid; m.p. 80–85 °C; R_f = 0.85 (EtOAc/hexane = 1/9); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.06 (d, 1H, J = 8.4 Hz), 7.72–7.64 (m, 1H), 7.60–7.50 (m, 3H), 7.37–7.19 (m, 4H), 3.34–3.22 (m, 2H), 1.94–1.80 9m, 2H), 1.60–1.28 (m, 6H), 0.91 (t, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.9, 154.0, 147.0, 142.4, 129.8, 129.20, 128.8, 128.7, 128.4, 127.1, 126.9, 126.5, 100.4, 43.4, 31.8, 29.5, 29.3, 22.8, 14.2; IR (KBr) v: 2926, 2722, 1633, 1467, 1218, 1111, 1030, 769, 700, 612 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{23}IN$ $[M + H]^+$: 416.0875, found: 416.0884.

*3-Iodo-2,4-diphenylquinoline (**3j**).* 69% over all yield (in two steps); known compound;[1e] yellow solid; m.p. 115–118 °C; (lit.[1e] 118–122 °C); R_f= 0.55 (EtOAc/hexanes = 1/9); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.19–8.13 (d, 1H, J = 8.3 Hz), 7.77–7.38 (m, 11H), 7.34–7.24 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.0, 154.8, 147.0, 143.9, 142.3, 130.2, 129.5, 129.4, 129.2, 128.7, 128.7, 128.6, 128.1, 127.5, 127.4, 127.0, 98.6; IR (KBr) v: 1636, 1480, 1442, 1340, 1220, 771, 697, 625, 583 cm^{-1}; HRMS (ESI) m/z calcd for C21H_{15}IN $[M + H]^+$ 408.0249, found: 408.0519.

*3-Iodo-6-nitro-2-pentyl-4-phenylquinoline (**3k**).* 92% over all yield (in two steps); yellow solid; m.p. 100–105 °C; R_f = 0.7 (EtOAc/hexane 1/9); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.44 (dd, 1H, J = 9.2, 2.4 Hz), 8.27 (d, 1H, J = 2.4 Hz), 8.17 (d, 1H, J = 9.2 Hz), 7.65–7.55 (m, 3H), 7.28–7.20 (m, 2H), 3.31 (t, 2H, J = 7.8 Hz), 1.98–1.84 (m, 2H), 1.60–1.20 (m, 6H), 0.97 (t, 3H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 155.8, 149.0, 145.5, 140.8, 130.7, 129.3, 129.1, 129.0, 125.8, 123.7, 123.2, 102.9, 43.7, 31.9, 28.6, 22.6, 14.2; IR (KBr) v: 3015, 2926, 2857, 1622, 1528, 1343, 1219, 840, 768, 697, 611 cm^{-1}; HRMS (ESI) m/z calcd for $C_{20}H_{20}IN_2O_2$ $[M + H]^+$ 447.0569, found: 447.0605.

*3-Iodo-4-methyl-2-(2-(tetrahydro-2H-pyran-2-yloxy)ethyl)quinoline (**3l**).* 63% over all yield (in two steps); yellow oil; R_f = 0.4 (EtOAc/hexane = 1/9); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04–7.97 (m, 2H), 7.72–7.64 (m, 1H), 7.52–7.46 (m, 1H), 4.77–4.73 (m, 1H), 4.32-4.31 (m, 1H), 4.03–3.84 (m, 2H), 3.62–3.47 (m, 3H), 2.90 (s, 3H), 1.90–1.44 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.5, 148.2, 146.6, 129.6, 129.6, 127.0, 126.7, 124.3, 102.7, 99.0, 66.5, 62.3, 43.2, 30.8, 29.8, 25.6, 19.6 ; IR (KBr) v: 2940.6, 1636, 1448, 1378, 1125, 1026, 758, 635, 578 cm^{-1}; ESI-MS m/z :M^+ 397.9.

*2-Butyl-3,6-diiodo-4-methylquinoline (**4**).* yellow solid; m.p. 78–81 °C; R_f = 0.8 (EtOAc/hexane = 1/9); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.34 (s, 1H), 7.88 (d, 1H, J = 8.8 Hz), 7.70 (d, 1H, J = 8.8 Hz), 3.19 (t, 2H, J = 7.7 Hz), 2.82 (s, 3H), 1.82–1.72 (m, 2H), 1.57–1.42 (m, 2H), 0.99 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 163.5, 147.1, 145.7, 138.3, 133.4, 131.2, 128.4, 103.2, 92.1, 43.3, 31.18, 25.7, 22.9, 14.1; ESI-MS m/z: M^+ 452.1.

*2-Butyl-4-methylquinoline (**5a**).* 78% over all yield (in two steps); known compound;[1h] yellow oil; R_f = 0.8 (EtOAc/hexane = 2/8); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04 (d, 1H, J = 8.2 Hz), 7.95 (d, 1H, J = 7.8 Hz), 7.70–7.63 (m, 1H), 7.54–7.46 (m, 1H), 7.14 (s, 1H), 2.93 (t, 2H, J = 7.7 Hz), 2.68 (s, 3H), 1.86–1.73 (m, 2H), 1.52–1.38 (m, 2H), 0.96 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.8, 147.8, 144.1, 129.4, 129.0, 126.8, 125.4, 123.6, 122.1, 39.0, 32.2, 22.8, 18.7, 14.0; IR (KBr) v: 2956, 2929, 2865, 1606, 1563, 1507, 1448, 1350, 863, 758, 663, 537, 500 cm^{-1}; HRMS (ESI) m/z calcd for $C_{14}H_{18}N$ $[M + H]^+$: 200.1439, found: 200.1474.

*4-Methyl-2-phenylquinoline (**5b**).* 85% over all yield (in two steps); known compound;[11] yellow oil ; R_f = 0.72 (EtOAc/hexane = 2/8); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.22–8.12 (m, 3H), 8.01 (d, 1H, J = 7.8 Hz), 7.77–7.68 (m, 2H), 7.60–7.42 (m, 4H), 2.78 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 157.1, 148.2, 144.8, 139.8, 130.3, 129.4, 129.2, 128.8, 127.6, 127.3, 126.0, 123.6, 119.8, 19.0; IR (KBr) v: 3066, 2926, 1602, 1552, 1449, 1348, 1219, 865, 766, 694, 573, 538 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{14}N$ $[M + H]^+$: 220.1126, found: 220.1161.

*4-Methyl-2-propylquinoline (**5c**).* 74% over all yield (in two steps); known compound;[7] clear liquid; R_f = 0.83 (EtOAc/hexane = 2/8); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.05 (d, 1H, J = 8.3 Hz), 7.94 (d, 1H, J = 7.8 Hz), 7.70–7.63 (m, 1H), 7.56–7.45 (m, 1H), 7.14 (s, 1H), 2.91 (t, 2H, J = 7.6 Hz), 2.68 (s, 3H), 1.90–1.77 (m, 2H), 1.02 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.5, 147.7, 144.1, 129.3, 129.0, 126.8, 125.4, 123.5, 122.1, 41.2, 23.3, 18.6, 14.1; IR (KBr) v: 3066, 2959, 2931, 2870, 1605, 1562, 1509, 1448, 1411, 1218, 861, 758, 664, 524 cm^{-1}; HRMS (ESI) m/z calcd for $C_{13}H_{16}N$ $[M + H]^+$: 186.1283, found: 186.1314.

*4-Methyl-2-pentylquinoline (**5d**).* 74% over all yield (in two steps); known compound;[7] clear liquid; R_f = 0.8 (EtOAc/hexane = 2/8); ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.05 (d, 1H, J = 8.3 Hz), 7.94 (d, 1H, J = 8.1 Hz), 7.70–7.63 (m, 1H), 7.52–7.45 (m, 1H), 7.14 (s, 1H), 2.91 (t, 2H, J = 7.7 Hz), 2.67 (s, 3H), 1.87–1.70 (m, 2H), 1.48–1.32 (m, 4H), 0.90 (t, 3H, J = 6.73 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 162.8, 147.8, 144.2, 129.4, 129.0, 126.8, 125.4, 123.6, 122.1, 39.3, 31.9, 29.5, 22.7, 18.7, 14.1; IR (KBr) v: 3014, 2930, 2861, 1606, 1509, 1452, 1412, 1216, 763, 667, 610,

479 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{20}N$ $[M + H]^+$: 214.1596, found: 214.1808.

*2-Hexyl-4-methylquinoline (**5e**)*. 90% over all yield (in two steps); known compound;[8] yellow oil; R_f = 0.76 (EtOAc/hexane = 2/8); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.02 (d, 1H, J = 8.1 Hz), 7.95 (d, 1H, J = 8.2 Hz), 7.70–7.63 (m, 1H), 7.53–7.46 (m, 1H, 7.14 (s, 1H), 2.92 (t, 2H, J = 7.8 Hz), 2.68 (s, 3H), 1.86–1.72 (m, 2H), 1.48–1.22 (m, 6H), 0.88 (t, 3H, J = 6.6 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 162.8, 147.8, 144.1, 129.4, 129.0, 126.8, 125.4, 123.6, 122.1, 39.3, 31.8, 30.1, 29.3, 22.6, 18.7, 14.1; IR (KBr) ν: 2927, 2857, 1605, 1562, 1509, 1449, 1411, 1349, 1218, 863, 761, 666, 594, 512 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{16}H_{22}N$ $[M + H]^+$: 228.1752, found: 228.1882.

*2-Heptyl-4-methylquinoline (**5f**)*. 70% over all yield (in two steps); known compound;[9] yellow oil; R_f = 0.73 (EtOAc/hexane = 2/8); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.04 (d, 1H, J = 8.1 Hz), 7.95 (d, 1H, J = 7.8 Hz), 7.70–7.63 (m, 1H), 7.53–7.46 (m, 1H), 7.14 (s, 1H), 2.92 (t, 2H, J = 7.8 Hz), 2.68 (s, 3H), 1.90–1.70 (m, 2H), 1.50–1.20 (m, 8H), 0.87 (t, 3H, J = 6.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.9, 147.8, 144.2, 129.4, 129.1, 126.9, 125.5, 123.7, 122.2, 39.4, 31.9, 30.2, 29.7, 29.3, 22.8, 18.8, 14.2; IR (KBr) ν: 2929, 2858, 1608, 1562, 1509, 1454, 1354, 1218, 868, 761, 667, 531 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{17}H_{24}N$ $[M + H]^+$: 242.1909, found: 242.2139.

*4-Methyl-2-octylquinoline (**5g**)*. 70% over all yield (in two steps); yellow oil; R_f = 0.7 (EtOAc/hexane = 2/8); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.04 (d, 1H, J = 8.3 Hz), 7.95 (d, 1H, J = 8.1 Hz), 7.70–7.63 (m, 1H), 7.54–7.46 (m, 1H), 7.14 (s, 1H), 2.92 (t, 2H, J = 7.7 Hz), 2.68 (s, 3H), 1.86–1.64 (m, 2H), 1.50–1.20 (m, 10H), 0.87 (t, 3H, J = 6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 162.9, 147.9, 144.3, 129.5, 129.1, 126.9, 125.5, 123.7, 122.2, 39.4, 32.0, 30.2, 29.8, 29.6, 29.3, 22.8, 18.8, 14.2; IR (KBr) ν: 2926, 2856, 1635, 1561, 1508, 1452, 1373, 1218, 860, 767, 689, 658, 507 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{26}N$ $[M + H]^+$: 256.2065, found: 256.2148.

*2-Pentyl-4-phenylquinoline (**5h**)*. 78% over all yield (in two steps); known compound;[10] liquid; R_f = 0.7 (EtOAc/hexane = 2/8); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.12 (d, 1H, J = 8.17 Hz), 7.86 (d, 1H, J = 7.7 Hz), 7.72–7.65 (m, 1H), 7.57–7.40 (m, 6H), 7.25 (s, 1H), 3.00 (t, 2H, J = 7.7 Hz), 1.90–1.78 (m, 2H), 1.50–1.32 (m, 4H), 0.91 (t, 3H, J = 6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 162.7, 148.6, 148.5, 138.3, 129.6, 129.2, 128.5, 128.3, 125.7, 125.7, 125.3, 121.6, 39.4, 31.9, 29.8, 22.6, 14.1; IR (KBr) ν: 3060, 2933, 2860, 1595, 1489, 1449, 1409, 1218, 884, 769, 701, 664, 577, 539 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{20}H_{22}N$ $[M + H]^+$: 276.1752, found: 276.1864.

*2-Hexyl-4-phenylquinoline (**5i**)*. 80% over all yield (in two steps); yellow oil; R_f = 0.7 (EtOAc/hexane = 2/8); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.12 (d, 1H, J = 8.3 Hz), 7.87 (d, 1H, J = 7.9 Hz), 7.73–7.64 (m, 1H), 7.57–7.40 (m, 6H), 7.25 (s, 1H), 3.00 (t, 2H, J = 7.7 Hz), 1.90–1.78 (m, 2H), 1.50–1.24 (m, 6H), 0.88 (t, 3H, J = 6.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 162.7, 148.5, 138.4, 129.6, 129.3, 128.5, 128.3, 125.7, 125.6, 125.3, 121.6, 39.4, 31.8, 30.1, 29.8, 29.4, 22.6, 14.1; IR (KBr) ν: 3063, 2928, 2857, 1594, 1557, 1490, 1409, 1218, 881, 767, 701, 659, 615, 576 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{24}N$ $[M + H]^+$: 290.1909, found: 290.2009.

*2,4-Diphenylquinoline (**5j**)*. 80% over all yield (in two steps); known compound;[1h] yellow solid m.p. 105–108 °C; (lit.[1] 107–108 °C); white solid; R_f = 0.62 (EtOAc/hexane = 2/8); ^1H NMR (300 MHz, $CDCl_3$) δ: 8.30–8.17 (m, 3H), 7.92 (d, 1H, J = 7.8 Hz), 7.83 (s, 1H), 7.78–7.70 (m, 1H), 7.63–7.44 (m, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 156.9, 149.2, 148.9, 139.7, 138.4, 130.2, 129.6, 129.4, 128.9, 128.6, 128.5, 127.6, 126.4, 125.8, 125.7, 119.4; IR (KBr) ν: 3061, 2966, 1590, 1546, 1489, 1407, 1357, 1075, 1027, 883, 769, 697, 616, 590, 544 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{21}H_{16}N$ $[M + H]^+$ 282.1283, found: 282.1464.

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References

1 Some recent examples: (*a*) A. K. Verma, T. Kesharwani, J. Singh, V. Tandon and R. C. Larock, *Angew. Chem., Int. Ed.*, 2009, **48**, 1138; (*b*) X. Zhang, M. A. Campo, T. Yao and R. C. Larock, *Org. Lett.*, 2005, **7**, 763–766; (*c*) X. Zhang, T. Yao, M. A. Campo and R. C. Larock, *Tetrahedron*, 2005, **66**, 1177–1187; (*d*) K. O. Hessian and B. L. Flynn, *Org. Lett.*, 2006, **8**, 243–246; (*e*) S. Ali, H.-T. Zhu, X.-F. Xia, K.-G. Ji, Y.-F. Yang, X.-R. Song and Y.-M. Liang, *Org. Lett.*, 2011, **13**, 2598–2601; (*f*) M. J. Sandelier and P. DeShong, *Org. Lett.*, 2007, **9**, 3209–3212; (*g*) Z. Huo, I. D. Gridnev and Y. Yamamoto, *J. Org. Chem.*, 2010, **75**, 1266–1270; (*h*) B. Gabriele, R. Mancuso, G. Salerno, G. Ruffolo and P. Plastina, *J. Org. Chem.*, 2007, **72**, 6873–6877; (*i*) B. Jiang and Y.-G. Si, *J. Org. Chem.*, 2002, **67**, 9449–9451; (*j*) B. Gabriele, R. Mancuso, G. Salerno, E. Lupinacci, G. Ruffolo and M. Costa, *J. Org. Chem.*, 2008, **73**, 4971–4977. And the references therein.

2 Some recent examples for pharmaceutical importance: (*a*) O. Billker, V. Lindo, M. Panico, A. E. Etienne, T. Paxton, A. Dell, M. Rogers, R. E. Sinden and H. R. Morris, *Nature*, 1998, **392**, 289–292; (*b*) S. W. Elmore, M. J. Coghlan, D. D. Anderson, J. K. Pratt, B. E. Green, A. X. Wang, M. A. Stashko, C. W. Lin, C. M. Tyree, J. N. Miner, P. B. Jacobson, D. M. Wilcox and B. C. Lane, *J. Med. Chem.*, 2001, **44**, 4481–4491; (*c*) W. Peczynskaczoch, F. Pognan, L. Kaczmarek and J. Boratynski, *J. Med. Chem.*, 1994, **37**, 3503–3510; (*d*) A. A. Joshi and C. L. Vishwanathan, *Bioorg. Med. Chem. Lett.*, 2006, **16**, 2613–2617; (*e*) C. Portela, C. M. M. Afonso, M. M. Pinta and M. J. Ramos, *Bioorg. Med. Chem.*, 2004, **12**, 3313–3321. And the references therein.

3 We observed that acid sensitive groups like OTHP and OTBS could not withstand Liang's electrophilic cyclization conditions.

4 The starting material has disappeared and a mixture of unknown products' spots were observed by TLC.

5 ^1H NMR of crude **2a** showed a single product. In subsequent investigations, we found that purification of **2** did not show any considerable change in product yields. Also, **2** was observed to be sensitive to silica gel.

6 In later observations, we found that **2b** was slowly converted to quinoline **5b** upon prolonged standing at room temperature.

7 B. K. Mehta, K. Yanagisawa, M. Shiro and H. Kotsuki, *Org. Lett.*, 2003, **5**, 1605–1608.

8 F. Minisci, F. Fontana, G. Pianese and Y. M. Yan, *J. Org. Chem.*, 1993, **58**, 4207–4211.

9 G. I. Nikishin, L. L. Sokova, V. M. Makhaev and N. I. Kapustina, *Russ. Chem. Bull., Int. Ed.*, 2007, **54**, 1599–1605.

10 R. Martínez, D. J. Ramón and M. Yus, *J. Org. Chem.*, 2008, **73**, 9778–9780.

11 R. Martínez, D. J. Ramón and M. Yus, *Eur. J. Org. Chem.*, 2007, 1599–1605.

