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# Preparation of 2-Aminobenzophenones and Polysubstituted Quinolines through $SmI_2$ Promoted Reductive Cleavage of 3-Aryl-2,1-Benzisoxazoles

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ABSTRACT: *Promoted by $SmI_2$, 3-aryl-2,1-benzisoxazoles underwent reductive cleavage of the N—O bond leading to 2-aminobenzophenones in high yields upon protonation. Otherwise, if ketones with active methylene group were added to the reaction mixture prior to protonation, the desired polysubstituted quinolines could be obtained under mild conditions in a one-pot manner.* © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:637–643, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20164

## *INTRODUCTION*

2-Aminobenzophenones have drawn much attention due to the fact that they are among the important starting materials for the synthesis of a wide variety of heterocyclic systems [1]. In particular, it has been reported that 2-aminobenzophenones can be used as intermediates for the preparation of numerous CNS drugs of the 1,4-benzodiazepine class [1a,2a]. Moreover, some 2-aminobenzophenone derivatives themselves have demonstrated to be potent antiproliferative agents, inhibitors of tubulin polymerization, and inhibitor of colchicines binding to tubulin [2b]. On the other hand, significant attention has also been focused on the synthesis of quinolines and their derivatives, as many naturally occurring quinolines are known for their biological activities, and specially designed quinolines have found many applications in the pharmaceutical field. In addition, they have been used as agrochemicals as well as general synthetic-building blocks [3]. Accordingly, it is not surprising that many synthetic methods have been developed for 2-aminobenzophenones [2b,4] and quinolines [5], respectively. Moreover, pursuance of more convenient and practical synthetic methods still remains an active research area [6,7].

It is well known that Kagan's reagent, samarium(II) iodide [8], is an exceptional reagent for promoting reductive reactions, and the chemistry of this reagent has been well documented in several reviews [9]. It has been demonstrated that $SmI_2$ can efficiently promote the selective reduction of isoxazoles to give enamino ketones [10]. In a recent communication, we have reported an efficient reductive cleavage of the N—O bond in 3-aryl-2,1-benzisoxazoles to give 2-aminobenzophenones or 2,4-diaryl substituted quinoline derivatives, respectively, depending

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on different manipulations [11]. Herein, we would like to report further expansion of these methodologies together with the experimental details of our earlier results.

## *RESULTS AND DISCUSSION*

First, 3-Aryl-2,1-benzisoxazole (**1**, Scheme 1) was treated with a solution of 2 equiv. of $SmI_2$ in THF at room temperature under a nitrogen atmosphere. It turned out that the deep blue color of $SmI_2$ changed into deep brown red immediately after treatment. TLC analysis indicated that the reductive cleavage process completed within a few minutes and afforded 2-aminobenzophenones (**2**, Scheme 1) smoothly upon subsequent protonation. The results are summarized in Table 1.

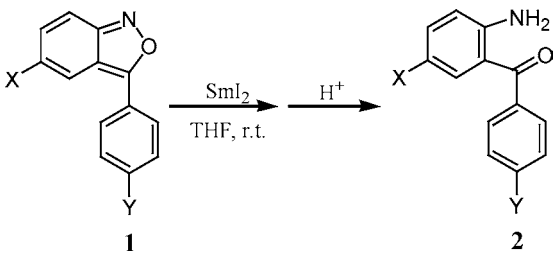
With regard to the preparation of 2-aminobenzophenones, several methods have already been reported. Of which classical preparation method requires appropriately substituted aniline substrates and high temperature reaction conditions [12], previously reported catalytic reduction of 2,1-benzisoxazoles to give 2-aminobenzophenones necessitates the use of expensive palladium as a catalyst [13]. In addition, aluminum tri-iodide has also been used to promote the cleavage of 2,1-benzisoxazoles to give 2-aminobenzophenones under reflux conditions [6a]. Compared with the methods mentioned above, our process has the advantage of milder reaction conditions, a shorter reaction time, and a cheap reagent.

**TABLE 1** $SmI_2$-Mediated Conversion of 2,1-Benzisoxazoles into 2-Aminobenzophenones

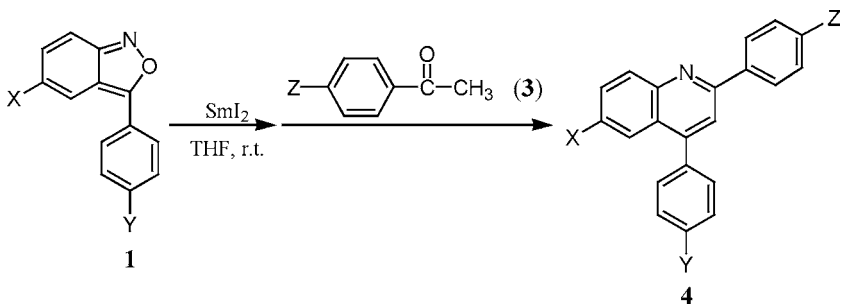
| *Entry* | *X* | *Y* | *Reaction Time (min)* | *Product* | *Yield (%)* |
|---|---|---|---|---|---|
| 1 | Cl | H | 5 | **2a** | 90 |
| 2 | Cl | Br | 5 | **2b** | 84 |
| 3 | Cl | Cl | 5 | **2c** | 82 |
| 4 | Cl | $OCH_3$ | 5 | **2d** | 85 |
| 5 | Br | H | 5 | **2e** | 86 |

With the success of the preparation of **2** from **1** and bearing in mind that **2** have been frequently used in the preparation of a variety of heterocyclic compounds by reacting with various carbonyl compounds, we then investigated the possibility of one-pot preparation of 2,4-diarylquinolines (**4**, Scheme 2) directly from **1** and acetophenones (**3**, Scheme 2). It turned out that when acetophenone (**3a**, 0.6 mmol) was added to the deep brown red colored reaction mixture resulting from 3-phenyl-5-chloro-2,1-benzisoxazole (**1a**, 0.5 mmol) on treatment with a solution of $SmI_2$(1 mmol) in THF, the color of the reaction mixture faded gradually and eventually changed into light yellow within 1 h. Subsequent separation of the reaction mixture afforded 6-chloro-2,4-diphenylquinoline **4a** in moderate yield. Several other substrates bearing different functional groups have also been investigated and all gave **4** in moderate yields (Shown in Table 2).

There have been reports on the preparation of 2,4-disubstituted quinolines in the literature. For example, it has been accomplished through the reaction between *N*-arylideneanilines and alkynes in the presence of 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) [14] or di-isopropyl peroxydicarbonate (DPDC) [15]. 2,4-Disubstituted quinolines can




SCHEME 1




SCHEME 2

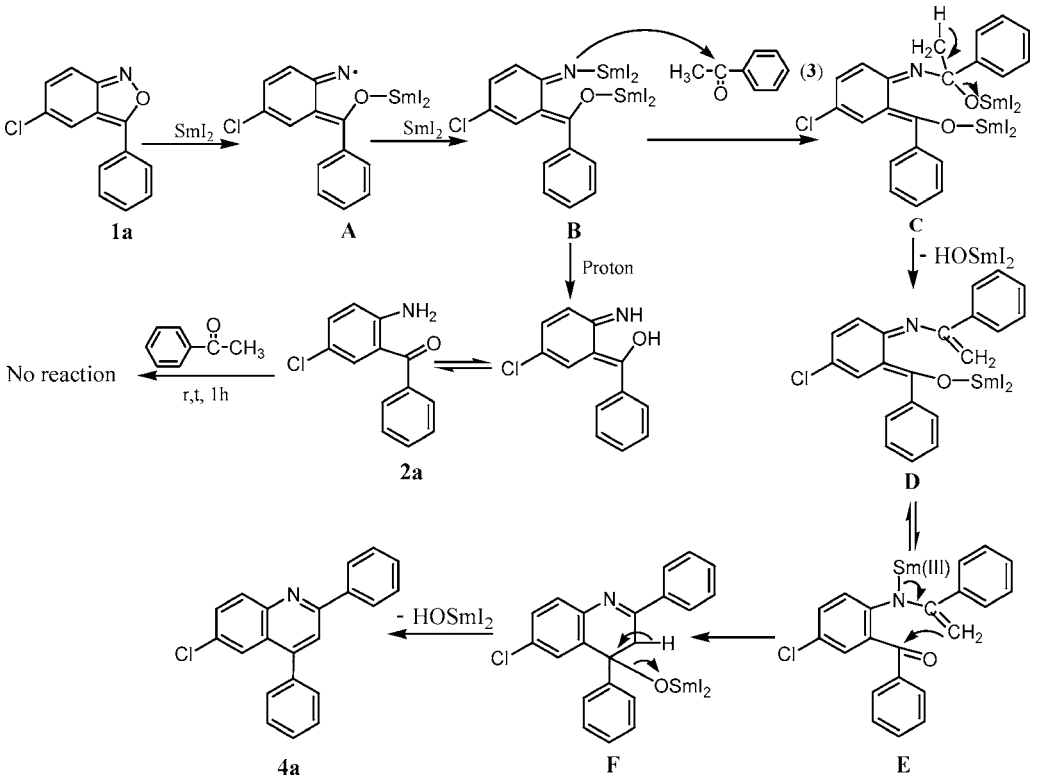
**TABLE 2** $SmI_2$-Mediated Preparation of 2,4-Diarylquinolines from **1** and Ary1 Methy1 Ketones

| *Entry* | *X* | *Y* | *Z* | *Product* | *Yield (%)*[a] |
|---|---|---|---|---|---|
| 1 | Cl | H | H | **4a** | 62 |
| 2 | Cl | H | $CH_3$ | **4b** | 70 |
| 3 | Cl | H | Cl | **4c** | 72 |
| 4 | Cl | H | Br | **4d** | 70 |
| 5 | Cl | Cl | Br | **4e** | 62 |
| 6 | Cl | $OCH_3$ | H | **4f** | 65 |
| 7 | Cl | $OCH_3$ | $CH_3$ | **4g** | 68 |
| 8 | Cl | $OCH_3$ | Cl | **4h** | 66 |
| 9 | Cl | $OCH_3$ | Br | **4i** | 56 |
| 10 | Cl | Br | Br | **4j** | 52 |

[a]Isolated yields based on **1**.

also be prepared through the condensation of 2-aminobenzophenone with ketones, but this process requires harsh conditions such as an acid or base as a catalyst and moderate to high thermal conditions [1d]. We can obtain 2,4-diarylquinolines directly from 3-aryl-2,1-benzisoxazoles and acetophenones without acid or base promoters, and the whole process is completed within 1–2 h at room temperature. Thus, our method for the preparation of 2,4-diarylquinolines has advantages such as being a one-pot process from easily accessible and inexpensive starting materials and much milder reaction conditions. Considering the differences in terms of the reaction conditions used in our method and in the literature **1d**, it may be reasonable to say that in our process the substance involved in the reaction toward ketones (**3**) could not be 2-aminobenzophenone (**2**) itself. It may be an intermediate (**B**, Scheme 3) formed in situ through $SmI_2$-induced reductive cleavage of the N—O bond in 3-aryl-2,1-benzisoxazoles [10]. Much higher reactivity of this active intermediate makes the condensation process in our method accomplished under much milder conditions when compared with 2-aminobenzophenone as the substrates [1e].

While trying to justify our proposal for the reaction pathway, a different manipulation of the condensation process has been tried. Thus, after substrate **1a** was treated with $SmI_2$ in THF for several minutes, instead of adding acetophenone directly to the reaction system, drops of methanol as a proton source was added to protonate the proposed intermediate **B** and then acetophenone was added as usual and the mixture was stirred at room temperature for 1 h. Unfortunately, subsequent separation of the reaction mixture only gave **2a** together with the intact acetophenone. Quinoline product **4a** was not formed at all. To further confirm the proposed mechanism, 1 mmol $SmI_3$ was prepared in situ by stirring the mixture of powdered samarium and iodine in dry



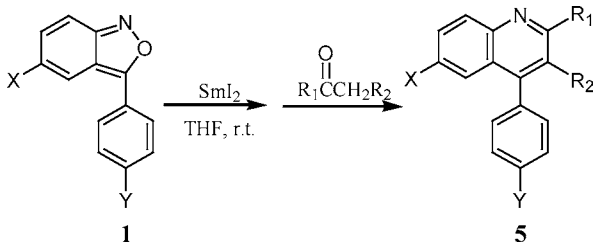

SCHEME 3

THF under nitrogen ($N_2$) atmosphere at room temperature until samarium disappeared. The resulted pale yellow suspension of $SmI_3$, **2a** (1 mmol) and acetophenone (1 mmol) were added, and the mixture was then stirred at room temperature for 1 h. Subsequent analysis of the reaction mixture showed again that no reaction took place under such conditions. This result may serve as another support for the proposed reaction mechanism shown in Scheme 3.

In order to broaden the application of the above method, we then investigated the possibility of preparation of 2,3,4-trisubstituted quinoline derivatives from **1** and aliphatic ketones possessing one or two α-methyl or methylene group. To our delight, this method succeeded equally well in various kinds of aliphatic ketones including acetone, 3-pentanone, methyl ethyl ketone, and cyclohexanone (shown in Scheme 4, Table 3). It is worth to note that with unsymmetrical ketone substrate of the type $CH_3COCH_2R$, from which two different modes of cyclization process are theoretically expected, condensation occurred predominantly at the more substituted α position and thus only one product was obtained (Table 3, entry 3).

## CONCLUSION

In conclusion, with high yields, mild and neutral conditions, as well as easily accessible starting materials, this paper may provide useful and novel methods for the preparation of 2-aminobenzophenones and polysubstituted quinoline derivatives. Further studies to develop other new uses of 3-aryl-2,1-benzisoxazoles as intermediate and $SmI_2$ as an efficient promoter in organic synthesis are now in progress in our laboratory.




**1** **5**

**SCHEME 4**

**TABLE 3** Preparation of 2,3,4-Trisubstituted Quinolines from **1** and Aliphatic Ketones

| *Entry* | *X* | *Y* | $R^1$ | $R^2$ | *Products* | *Isolated Yield (%)*[a] |
|---|---|---|---|---|---|---|
| 1 | Cl | H | $CH_3$ | H | **5a** | 68 |
| 2 | Cl | H | $CH_3$ | $CH_3$ | **5b** | 65 |
| 3 | Cl | H | $C_2H_5$ | $CH_3$ | **5c** | 70 |
| 4 | Cl | H | $-(CH_2)_4-$ | | **5d** | 71 |

[a]Isolated yields based on **1**.

## EXPERIMENTAL

Tetrahydrofuran was distilled from sodium-benzophenone immediately prior to use. All reactions were conducted under a nitrogen atmosphere. Melting points are uncorrected. $^1$H NMR spectra were recorded on a Bruker AC-400 instrument as $CDCl_3$ solutions using TMS as an internal standard. $^{13}$C NMR spectra were recorded on a Bruker AC-100 instrument as $CDCl_3$ solutions using TMS as an internal standard. Chemical shifts (δ) are reported in ppm, and coupling constants *J* are given in hertz. IR spectra were taken as KBr disks or thin films with a Bruker Vector-22 infrared spectrometer. Elemental analyses were performed on an EA-1110 instrument. Metallic samarium and all solvents were purchased from commercial sources and were used without further purification. The starting material 3-aryl-2,1-benzisoxazoles **1** were prepared according to the literature [16].

### *General Procedure for the Preparation of 2-Aminobenzophenones (**2a–2e**)*

Under anhydrous conditions, a mixture of powdered samarium (0.15 g, 1 mmol) and iodine (0.25 g, 1 mmol) in dry THF (20 mL) was stirred at room temperature until the samarium disappeared. To the resulting dark blue suspension of $SmI_2$, 3-aryl-2,1-benzisoxazole (0.5 mmol) was added. The mixture was stirred at room temperature for 5 min. On completion, the reaction mixture was poured into $H_2O$ (10 mL) and extracted with ethyl acetate (3 × 15 mL). The combined extracts were washed subsequently with a saturated solution of $Na_2S_2O_3$ (15 mL) and a saturated solution of NaCl (15 mL) and dried over anhydrous $Na_2SO_4$. After evaporating the solvent under reduced pressure, the crude product was purified by preparative TLC on silica gel using ethyl acetate-cyclohexane (1:4) as eluent to yield the corresponding 2-aminobenzophenones.

*2-Amino-5-chlorobenzophenone* **2a**. Light yellow crystal, mp 98–99°C (lit. [4] 99°C); IR $\nu$ 3419, 3315, 1617 cm$^{-1}$; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.42–7.66 (m, 6H), 7.24–7.29 (m, 1H), 6.70 (d, 1H, $J$ = 8 Hz), 6.08 (br s, 2H); MS *m/z* (%): 233 ($M^+$ + 2), 231 ($M^+$), 77 (100).

*2-Amino-4′-chloro-5-chlorobenzophenone* **2b**. Light yellow crystal, mp 116–117°C (lit. [4] 118–119°C); IR $\nu$ 3426, 3321, 1623 cm$^{-1}$; $^1$H NMR (400

MHz, $CDCl_3$) δ 7.59 (d, 2H, $J$ = 8.0 Hz), 7.47 (d, 2H, $J$ = 8 Hz), 7.37 (d, 1H, $J$ = 2.4 Hz), 7.27–7.24 (m, 1H), 6.70 (d, 1H, $J$ = 8.0 Hz), 6.07 (br s, 2H).

*2-Amino-4′-methyl-5-chlorobenzophenone* **2c**. Light yellow crystal, mp 104–106°C (lit. [4] 105.5–108°C); IR $\nu$ 3434, 3332, 1613 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 2H, $J$ = 8.0 Hz), 7.26 (s, 1H), 7.15–7.12 (m, 1H), 6.75 (d, 2H, $J$ = 8.0 Hz), 6.65–6.62 (m, 1H), 6.08 (br s, 2H), 2.27 (s, 3H).

*2-Amino-4′-methoxy-5-chlorobenzophenone* **2d**. Light yellow crystal, mp 99–100°C (lit. [4] 101–102°C); IR $\nu$ 3484, 3010, 1623 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.68 (d, 2H, $J$ = 8.0 Hz), 7.43 (s, 1H), 7.24–7.21 (m, 1H), 6.98 (d, 2H, $J$ = 8.0 Hz), 6.70–6.68 (m, 1H), 5.83 (br s, 2H), 3.90 (s, 3H).

*2-Amino-5-bromobenzophenone* **2e**. Light yellow crystal, mp 108–109°C (lit. [4] 110°C); IR $\nu$ 3420, 3310, 1625 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.78–7.58 (m, 6H), 7.38–7.35 (m, 1H), 6.83–6.81 (m, 1H), 6.15 (br s, 2H).

### *General Procedure for the Preparation of 2,4-Diarylquinolines (**4a–4j**)*

To a dark blue suspension of $SmI_2$(1 mmol) in THF was added 3-aryl-2,1-benzisoxazole (0.5 mmol). The mixture was stirred at room temperature for 5 min. Then, to the reaction mixture was added acetophenone (0.6 mmol). Stirring was continued for 1 h. On completion, the reaction mixture was poured into $H_2O$ (15 mL) and extracted with diethyl ether (3 × 15 mL). The combined extract was washed with a saturated solution of $Na_2S_2O_3$ (15 mL) and a saturated solution of NaCl (15 mL) and dried over anhydrous $Na_2SO_4$. After evaporating the solvent under reduced pressure, the crude product was purified by preparative TLC on silica gel using ethyl acetate-cyclohexane (1:8) as eluent.

*6-Chloro-2,4-diphenylquinoline* **4a**. mp 127–129°C; IR $\nu$ 3059, 1600, 1591 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.20–8.16 (m, 3H), 7.90 (d, 1H, $J$ = 2.4 Hz), 7.82 (s, 1H), 7.65–7.63 (m, 2H), 7.55–7.50 (m, 7H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 119.7, 124.5, 126.7, 128.9, 129.1, 129.4, 130.7, 131.7, 132.5, 135.9, 137.4, 137.6, 147.0, 148.8, 155.7; MS *m/z* (%): 317 ($M^+$+ 2), 315 ($M^+$, 100). Anal. calcd for $C_{21}H_{14}ClN$: C 79.87, H 4.47, N 4.44; found: C 79.90, H 4.40, N 4.38.

*6-Chloro-2-(4-methylphenyl)-4-phenylquinoline* **4b**. mp 131–2°C; IR $\nu$ 3025, 1590, 1578 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.22 (d, 1H, $J$= 8.4 Hz), 8.15 (d, 2H, $J$ = 8.0 Hz), 7.88 (d, 1H, $J$ = 4.4 Hz), 7.82 (s, 1H), 7.70–7.65 (m, 1H), 7.60–7.55 (m, 5H), 7.38 (d, 2H, $J$ = 8.0 Hz), 2.48 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 21.4, 119.9, 124.5 126.5, 127.4 128.7, 128.8 129.5, 129.6, 130.4, 131.7, 131.9, 136.4, 137.9, 139.8, 147.3, 148.3, 157.1; MS *m/z* (%): 331 ($M^+$+ 2), 329 ($M^+$, 100). Anal. calcd for $C_{22}H_{16}ClN$: C 80.11, H 4.89, N 4.25; found: C 80.19, H 4.76, N 4.32.

*6-Chloro-2-(4-chlorophenyl)-4-phenylquinoline* **4c**. mp 161–162°C; IR $\nu$ 3050, 1605, 1590 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.30 (d, 1H, $J$ = 8.4 Hz), 8.19 (d, 2H, $J$ = 8.4 Hz), 7.90 (d, 1H, $J$ = 2.4 Hz), 7.84 (s, 1H), 7.70–7.67 (m, 1H), 7.61–7.50 (m, 7H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 119.2, 124.2, 124.7, 128.8, 129.0, 129.2, 129.4, 130.8, 131.5, 132.1, 132.6, 137.9, 138.5, 147.5, 148.8, 156.6; MS *m/z* (%): 353 ($M^+$+ 4), 351 ($M^+$+ 2), 349 ($M^+$, 100). Anal. calcd for $C_{21}H_{13}Cl_2N$: C 72.02, H 3.74, N 4.00; found: C 72.00, H 3.69, N 4.11.

*6-Chloro-2-(4-bromophenyl)-4-phenylquinoline* **4d**. mp 172–173°C; IR $\nu$ 3050, 1600, 1588 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.20 (d, 1H, $J$ = 8.8 Hz), 8.11 (d, 2H, $J$ = 8.8 Hz), 7.98 (d, 1H, $J$ = 2.4 Hz), 7.85 (s, 1H), 7.72–7.68 (m, 3H), 7.66–7.59 (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 119.5, 124.3, 124.6, 128.8, 128.9, 129.1, 129.4, 130.7, 131.7, 132.1, 132.6, 137.6, 138.1, 147.2, 148.8, 155.8; MS *m/z* (%): 397 ($M^+$+ 4), 395 ($M^+$+ 2, 100), 393 ($M^+$). Anal. calcd for $C_{21}H_{13}BrClN$: C 63.90, H 3.32, N 3.55; found: C 63.88, H 3.26, N 3.58.

*6-Chloro-2-(4-bromophenyl)-4-chlorophenylquinoline* **4e**. mp 178–180°C; IR $\nu$ 3052, 1610, 1588 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.23 (d, 1H, $J$= 8.4 Hz), 8.18 (d, 2H, $J$ = 8.4 Hz), 7.90–7.84 (m, 2H), 7.64 (d, 2H, $J$ = 8.4 Hz), 7.58–7.50 (m, 5H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 123.4, 126.3, 126.7, 129.9, 131.8, 131.9, 132.4, 132.8, 133.2, 134.3, 134.7, 139.8, 140.2, 149.6, 150.9, 159.8; MS *m/z* (%): 433 ($M^+$+ 6), 431 ($M^+$+ 4), 429 ($M^+$+ 2, 100), 427 ($M^+$). Anal. calcd for $C_{21}H_{12}BrCl_2N$: C 58.78, H 2.82, N 3.26; found: C 58.83, H 2.81, N 3.23.

*6-Chloro-2-phenyl-4-(4-methoxyphenyl)-quinoline* **4f**. mp 136–138°C; IR $\nu$ 3059, 1600, 1590 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.15 ~8.18 (m, 3H), 7.90 (d, 1H, $J$ = 2.4 Hz), 7.81 (s, 1H), 7.67–7.64 (m, 1H), 7.52–7.48 (m, 5H), 7.10 (d, 2H, $J$ = 8.4 Hz), 3.92 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 55.5, 114.4, 119.9, 124.6, 126.7, 127.5, 128.9, 129.6, 130.3, 130.7, 131.8, 132.1, 139.4, 147.4, 148.2, 157.1,

160.1; MS *m/z*(%): 347 ($M^+$+ 2), 345 ($M^+$, 100). Anal. calcd for $C_{22}H_{16}ClNO$: C 76.41, H 4.66, N 4.05; found: C 76.43, H 4.68, N 4.03.

*6-Chloro-2-(4-methylphenyl)-4-(4-methoxyphenyl)-quinoline* **4g**. mp 132–134°C; IR $\nu$ 3060, 1612, 1588 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.13 (d, 1H, $J$ = 8.8 Hz), 8.10 (d, 2H, $J$ = 8.0 Hz), 7.89 (d, 1H, $J$= 2.4 Hz), 7.79 (s, 1H), 7.66–7.62 (m, 1H), 7.48 (d, 2H, $J$ = 8.8 Hz), 7.32 (d, 2H, $J$ = 8.0 Hz), 7.09 (d, 2H, $J$ = 8.8 Hz), 3.92 (s, 3H), 2.43 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 21.4, 55.5, 114.3, 119.8, 124.6, 126.7, 127.4, 129.6, 130.2, 130.3, 130.7, 131.7, 131.9, 136.6, 139.7, 147.4, 148.1, 155.2; MS *m/z* (%): 361 ($M^+$+ 2), 359 ($M^+$, 100). Anal. calcd for $C_{23}H_{18}ClNO$: C 76.77, H 5.04, N 3.89; found: C 76.74, H 4.99, N 3.83.

*6-Chloro-2-(4-chlorophenyl)-4-(4-methoxyphenyl)-quinoline* **4h**. mp 164–166°C; IR $\nu$ 3049, 1601, 1588 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.13 (d, 2H, $J$ = 8.4 Hz), 7.90 (d, 1H, $J$ = 2.4 Hz), 7.77 (s, 1H), 7.67–7.65 (m, 1H), 7.51–7.47 (m, 5H), 7.10 (d, 2H, $J$= 8.8 Hz), 3.93 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 55.5, 114.4, 119.5, 124.7, 126.8, 128.8, 129.0, 130.6, 131.7, 132.4, 136.8, 137.7, 147.3, 148.5, 155.8, 160.2; MS *m/z* (%): 383 ($M^+$+ 4), 381 ($M^+$+ 2), 379 ($M^+$, 100). Anal. calcd for $C_{22}H_{15}Cl_2NO$: C 69.49, H 3.98, N 3.68; found: C 69.47, H 3.99, N 3.63.

*6-Chloro-2-(4-bromophenyl)-4-(4-methoxyphenyl)-quinoline* **4i**. mp 175–177°C; IR $\nu$ 3038, 1600, 1578 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.14 (d, 1H, $J$ = 8.4 Hz), 8.10 (d, 2H, $J$ = 8.4 Hz), 7.90 (d, 1H, $J$ = 2.2 Hz), 7.77 (s, 1H), 7.68–7.65 (m, 3H), 7.47 (d, 2H, $J$ = 8.4 Hz), 7.10 (d, 2H, $J$ = 8.4 Hz), 3.93 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 55.5, 114.4, 119.4, 124.2, 124.6, 126.8, 129.0, 129.8, 130.5, 130.7, 131.7, 132.0, 138.1, 147.8, 148.4, 155.8, 160.2; MS *m/z* (%): 427 ($M^+$+ 4), 425 ($M^+$+ 2, 100), 423 ($M^+$). Anal. calcd for $C_{22}H_{15}BrClNO$: C 62.21, H 3.56, N 3.30; found: C 62.24, H 3.59, N 3.33.

*6-Chloro-2-(4-bromophenyl)-4-(4-bromophenyl)-quinoline* **4j**. mp 190–192°C; IR $\nu$ 3055, 1610, 1590 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.15 (d, 1H, $J$ = 8.8 Hz), 8.06 (d, 2H, $J$ = 8.4 Hz), 7.79–7.64 (m, 7H), 7.41 (d, 2H, $J$ = 8.4 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 119.6, 125.3, 125.7, 129.6, 129.9, 131.3, 131.8, 133.6, 134.8, 135.1, 135.7, 139.6, 140.6, 150.2, 152.8, 161.6; MS *m/z* (%): 477 ($M^+$+ 6), 475 ($M^+$+ 4), 473 ($M^+$+ 2, 100), 471 ($M^+$). Anal. calcd for $C_{21}H_{12}Br_2ClN$: C 53.26, H 2.55, N 2.96; found: C 53.24, H 2.58, N 2.94.

## *General Procedure for the Preparation of 2,3,4-Trisubstituted Quinolines (***5a–5d***)*

The preparative procedure of 2,3,4-trisubstituted quinolines was very similar to what has been previously described for the preparation of 2,4-diarylquinolines. The following is the physical and spectra data of the corresponding products.

*6-Chloro-2-methyl-4-phenylquinoline* **5a**. mp 86–88°C; IR $\nu$ 3060, 3005, 1600 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.21 (d, 1H, $J$ = 8.8 Hz), 7.91 (d, 1H, $J$ = 2.4 Hz), 7.88 (dd, 1H, $J_1$ = 8.8 Hz, $J_2$ = 2.4 Hz), 7.66–7.58 (m, 5H), 7.38 (s, 1H), 2.75 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 20.8, 118.6, 121.1, 124.5, 124.8, 125.4, 125.8, 127.4, 135.2, 136.6, 146.3, 148.2, 158.4; MS *m/z* (%): 255 ($M^+$+ 2), 253 ($M^+$, 100). Anal. calcd for $C_{16}H_{12}ClN$: C 75.74, H 4.77, N 5.52; found: C 75.78, H 4.69, N 5.55.

*6-Chloro-2,3-dimethyl-4-phenylquinoline* **5b**. mp 123–125°C; IR $\nu$ 3050, 2982, 1610 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.12 (d, 1H, $J$ = 8.4 Hz), 7.62–7.55 (m, 4H), 7.38 (d, 1H, $J$= 2.4 Hz), 7.28–7.25 (m, 2H), 2.82 (s, 3H), 2.16 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 16.1, 19.9, 120.9, 125.1, 126.5, 126.8, 127.4, 128.8, 129.1, 130.3, 133.4, 138.6, 145.3, 148.1, 160.2; MS *m/z* (%): 269 ($M^+$+ 2), 267 ($M^+$, 100). Anal. calcd for $C_{17}H_{14}ClN$: C 76.26, H 5.27, N 5.23; found: C 76.32, H 5.31, N 5.22.

*6-Chloro-2-ethyl-3-methyl-4-phenylquinoline* **5c**. mp 136–138°C; IR $\nu$ 3038, 2935, 1610 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.02 (d, 1H, $J$ = 8.4 Hz), 7.56–7.47 (m, 4H), 7.22–7.27 (m, 3H), 3.06 (q, 2H, $J$ = 7.2 Hz), 2.22 (s, 3H), 1.40 (t, 3H $J$ = 7.2 Hz);$^{13}C$ NMR (100 MHz, $CDCl_3$) δ 14.5, 19.2, 21.9, 120.6, 121.8, 124.9, 126.5, 126.8, 126.9, 127.8, 129.2, 129.4, 133.5, 139.2; 145.5, 147.2, 159.4; MS *m/z* (%): 283 ($M^+$+ 2), 281 ($M^+$, 100). Anal. calcd for $C_{18}H_{16}ClN$: C 76.72, H 5.72, N 4.97; found: C 76.77, H 5.75, N 4.91.

*6-Chloro-2,3-tetramethylene-4-phenylquinoline* **5d** . mp 166–168°C; IR $\nu$ 3050, 3000, 1621 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$) δ 8.11 (1H, d, $J$ = 8.4 Hz), 7.60–7.53 (m, 4H), 7.30 (1H, d, $J$ = 2.4 Hz), 7.25–7.22 (m, 2H), 3.20 (t, 2H, $J$ = 7.2 Hz), 2.61 (t, 2H, $J$ = 7.2 Hz), 2.03–1.97 (m, 2H), 1.85–1.80 (m, 2H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 24.8, 28.5, 32.6, 34.9, 121.6, 124.9, 125.6, 126.7, 126.8, 126.9, 127.9, 129.1, 129.2, 130.5, 133.9; 145.6, 148.2, 163.4; MS *m/z* (%): 295 ($M^+$+ 2), 293 ($M^+$, 100). Anal. calcd for $C_{19}H_{16}ClN$: C 77.68, H 5.49, N 4.77; found: C 77.59, H 5.41, N 4.65.

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