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A domino three-component condensation of *ortho*-haloacetophenones with urea or amines: a novel one-pot synthesis of halogen-substituted quinolines

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ABSTRACT

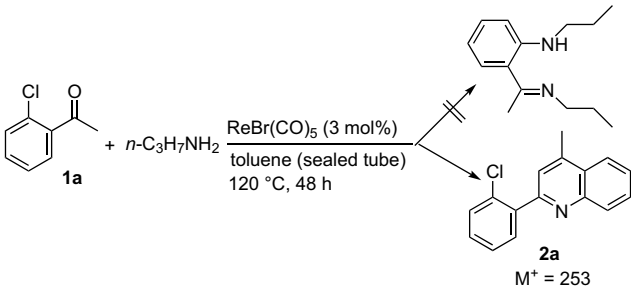
Halogen-substituted quinolines have been synthesized in good yields by the condensation and cyclization of two molecules of *ortho*-haloacetophenones with urea or primary amines. The formation of halogen-substituted quinolines takes place through the unexpected catalyst-free cleavage of C(sp^2)–X (X=Cl, Br), α-C(sp^3)–H bonds and formation of C–C, C–N bonds in a selective manner. The attractive features of the present synthetic method for halogen-substituted quinolines include catalyst-free, one-pot process, easy availability of starting materials, and introduction of halogen on the quinoline ring for further transformation.

1. Introduction

Development of the efficient methods for the synthesis of nitrogen heterocycles is one of the most important research topics in synthetic chemistry.[1] Quinoline derivatives have attracted considerable attention owing to their biological properties,[2] occurrence in many natural products,[3] and applications in the synthesis of pharmaceuticals and biological active molecules.[4] Therefore, designing the synthetic method for constructing quinoline ring has become interesting topic to many organic and medicinal chemists.[5] In this paper, we report an one-pot synthesis of quinoline derivatives from the condensation of two molecules of *o*-haloacetophenones with urea or primary amines via the domino non-catalytic cleavage of C(sp^2)–X (X=Cl, Br), α-C(sp^3)–H bonds and formation of C–C, C–N bonds.

2. Results and discussion

The purpose of our initial work was to examine the catalytic activity of low-valent rhenium complexes in the N-arylation of electron-deficient aryl chlorides with primary amines, since rhenium complexes have been recently employed as both transition metal and Lewis acid catalysts in diverse organic transformations.[6] Thus we investigated the reaction of *o*-chloroacetophenone (**1a**) with *n*-propylamine in the presence of $ReBr(CO)_5$. However, heating a solution of **1a**, *n*-propylamine (2 equiv), and $ReBr(CO)_5$ (3 mol %) in toluene in a sealed tube at 120 °C for 48 h did not produce the desired *N*-arylated product. Instead, the formation of the corresponding ketimine and a new compound with the molecular weight of 253 was observed by GC–MS analysis of the reaction mixture (Scheme 1). The structure of the new compound was assigned as 2-(2′-chlorophenyl)-4-methylquinoline (**2a**), which was isolated in 21% yield and characterized by its ^1H, ^{13}C NMR, GC–MS, elemental analysis, and further unambiguously confirmed by X-ray crystallography (Fig. 1).[7] It is apparent that the formation of **2a** was resulted from the domino three-component condensation of two molecules of **1a** and one molecule of



Scheme 1. Reaction of *o*-chloroacetophenone (**1a**) with *n*-propylamine affording quinoline derivative **2a**.

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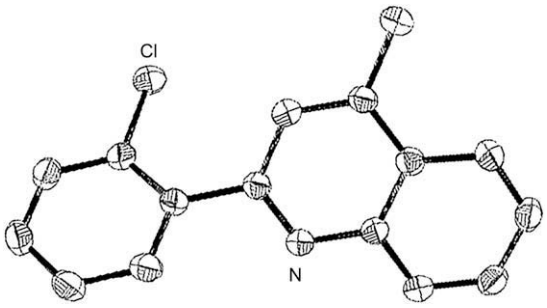


Figure 1. Molecular structure of **2a**. All hydrogen atoms are omitted for clarity.

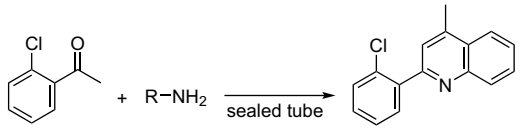
n-propylamine, in which the C–Cl, C–H bonds of **1a** and C–N bond of *n*-propylamine were cleaved and the new C–C, C–N bonds were created to form an quinoline ring, and *n*-propylamine was the only source of nitrogen. Surprisingly, our further studies disclosed that **2a** could be also obtained in a comparable yield without $ReBr(CO)_5$. Therefore, we investigated the effects of temperature, solvent, and the source of nitrogen for the formation of **2a** to optimize the reaction conditions to develop a practical one-pot process for the synthesis of quinolines as summarized in Table 1.

To improve the yield of **2a**, we first repeated the reaction of **1a** with *n*-propylamine (2.0 equiv) at an elevated temperature (150 °C), and the yield of **2a** was slightly increased to 35% (entry 1). The use of much more excess amount of *n*-propylamine (4 equiv) led to the unexpected decrease of the yield to 16% (entry 2), indicating that the use of the excess amount of *n*-propylamine was unfavorable for **2a** formation. Indeed, when 1.0 equiv of *n*-propylamine was employed, the yield of **2a** was similar to that in the case of 2.0 equiv of *n*-propylamine used (entry 3 vs entry 1), and a good yield of **2a** was achieved when 0.5 equiv of *n*-propylamine was used under the similar reaction conditions (entry 4). It was also found that the yield of **2a** depended on the reaction temperature and the nature of amines. For example, repeating the reaction in entry 4 at 120 °C resulted in the significant decrease of the yield (entry 5 vs entry 4), and when benzyl and cyclohexylamines (0.5 equiv) were used as sources of nitrogen, **2a** was formed in fair yields only (entries 6 and 7).

Urea is a cheap chemical reagent, and its thermal decomposition in the presence of water to eliminate ammonia was a known process.[8] We believed that under this reaction conditions, even if the additional water was not added, ammonia should be produced by the thermal decomposition of urea because of the presence of trace amount of water in organic starting materials, which were used without further purification. Once the reaction is initiated, the reaction should proceed smoothly due to in situ generation of water (vide infra). Therefore we examined the reaction of **1a** with urea. As shown in Table 1, the amount of urea used greatly affected the yield of **2a** (entries 8–12). When 3.5 equiv of urea was used, the yield of **2a** reached 74% (NMR yield, entry 12). However, more excess amount of urea did not improve the yield further. In addition, we used DMSO and DMF instead of toluene as solvents, the isolated yields of **2a** were comparable (entries 13 and 14). Decreasing the reaction temperature to 130 °C resulted in a significant decrease of the yield (entry 15). Fortunately, a prolonged reaction time (from 48 h to 60 h) improved the yields considerably, giving the desired product in 81% NMR yield (entry 16 vs entry 12).

We applied similar conditions of entry 16 in Table 1 for the condensation of other *o*-halogen-substituted acetophenones with urea. As summarized in Table 2,[9] the reactions of 2,4-dichloroacetophenone (**1b**) and 2,5-dichloroacetophenone (**1c**) with urea afforded the corresponding quinoline derivatives **2b** and **2c** in 69% and 68% isolated yields, respectively (entries 1 and 2). These results indicated that the introduction of one more chloro group on the aromatic ring had little effect for the formation of quinoline derivatives. When the analogue of chloro-substituted acetophenones such as *o*-bromoacetophenone (**1d**) and 2,5-dibromoacetophene (**1e**) were employed, as expected, the corresponding quinoline derivatives were isolated in good yields (entries 3 and 4).

Table 1
Synthesis of 2-(2′-chlorophenyl)-4-methylquinoline[a]

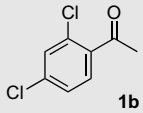
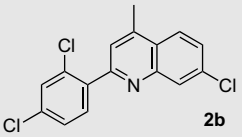
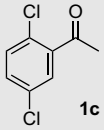
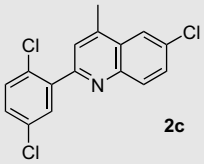
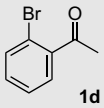
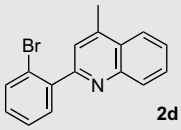
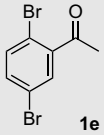
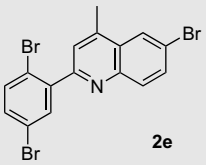


1a **2a**

Entry	RNH_2 (equiv to **1a**)	Solvent	Temp (°C)/time (h)	Yield[b] (%)
1	$C_3H_7NH_2$ (2)	Toluene	150/48	(35)[c]
2	$C_3H_7NH_2$ (4)	Toluene	150/48	(16)[c]
3	$C_3H_7NH_2$ (1)	Toluene	150/48	(36)[c]
4	$C_3H_7NH_2$ (0.5)	Toluene	150/48	(69)[c]
5	$C_3H_7NH_2$ (0.5)	Toluene	120/48	(7)[c]
6	$C_6H_5CH_2NH_2$ (0.5)	Toluene	150/48	(39)[c]
7	*c*-$C_6H_{11}NH_2$ (0.5)	Toluene	150/48	(21)[c]
8	H_2NCONH_2 (0.25)	Toluene	150/48	(<10)[c]
9	H_2NCONH_2 (0.5)	Toluene	150/48	(22)[c]
10	H_2NCONH_2 (1)	Toluene	150/48	(45)[c]
11	H_2NCONH_2 (2)	Toluene	150/48	(62)[d]
12	H_2NCONH_2 (3.5)	Toluene	150/48	62 (74)[d]
13	H_2NCONH_2 (3.5)	DMSO	150/48	60.0
14	H_2NCONH_2 (3.5)	DMF	150/48	62.0
15	H_2NCONH_2 (3.5)	Toluene	130/48	(25)[d]
16	H_2NCONH_2 (3.5)	Toluene	150/60	75 (81)[d]

[a] Reaction were carried out using 0.5–1.0 mmol of **1a** in 0.5–1.0 mL of solvent in sealed tube.
[b] Isolated yield based on **1a** used.
[c] GC yield based on the less amount of substrate used with $C_{16}H_{34}$ as internal standard material.
[d] ^1H NMR yield based on **1a** used with ferrocene as internal material.

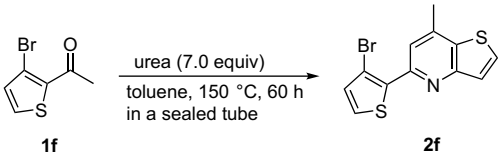
Table 2
Reactions of *o*-haloacetophenones with urea[a]

Entry	Haloacetophenone	Product	Yield[b] (%)
1	 **1b**	 **2b**	69
2	 **1c**	 **2c**	68
3	 **1d**	 **2d**	75 (83)
4	 **1e**	 **2e**	63

[a] Reactions were carried out using 2.0 mmol of **1** and 14.0 mmol of urea in 0.5 mL of toluene at 150 °C for 60 h in a sealed tube.
[b] Isolated yield, number in parenthesis is ^1H NMR yield.

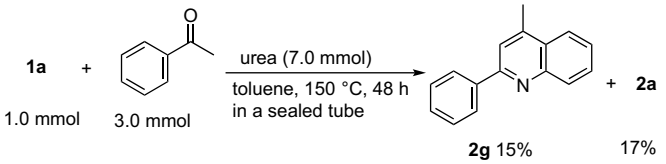
In order to further extend the present reaction in synthesis of the heterocycle containing two different heteroatoms, the reaction of 2-acetyl-3-bromothiophene (**1f**) with urea was also examined. As shown in Eq. 1, **2f** was obtained in 32% isolated yield. In this case, **1f** was recovered in 59% (Eq. 1).

In addition, the condensation of three different substrates of **1a**, acetophenone (3 equiv), and urea (7.0 equiv) was also briefly examined (Eq. 2). Heating the mixture at 150 °C for 48 h resulted in a complex mixture of products, and the *real* three-component condensation products **2g**, as well as **2a** were isolated in 15% and 17% yields, respectively.



(1)

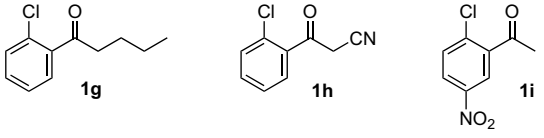
32% yield of **2f** and recovered 59% of **1f**



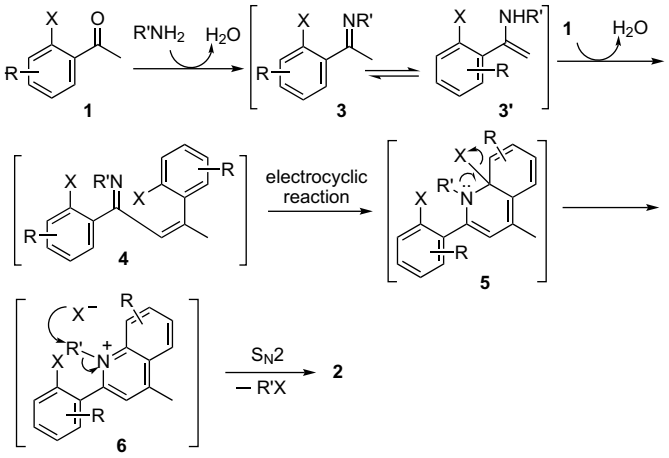
(2)

It should be noted that when 1-(2-chlorophenyl)-pentanone (**1g**) and 2-chlorobenzoylacetonitrile (**1h**) were subjected to thermal reaction under the same conditions, the formation of the corresponding quinolines was not observed, indicating that instead of acetyl, the sterically hindered acyl groups were unfavorable to this cyclic coupling reaction.

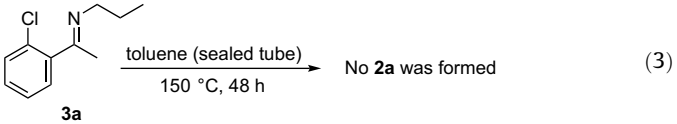
Furthermore, 2-chloro-5-nitroacetophenone (**1i**), which is a much more electron-deficient substrate, did not give the corresponding quinoline derivative either. The reaction solution became black immediately as soon as urea was added, and therefore the reaction was not further examined. In the case of *n*-propylamine used, the determinable product was 2-propylamino-5-nitroacetophenone, indicating that the nucleophilic substitution reaction of C–Cl with *n*-propylamine occurred predominately.



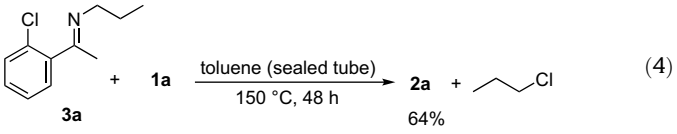
The reaction mechanism is proposed based on the following results: (1) when ketimine **3a** was subjected to the thermal reaction conditions, the formation of **2a** was not observed (Eq. 3); (2) heating a mixture of **3a** with 1 equiv of **1a** under the same conditions resulted in the formation of **2a** in the comparable yield as shown in entry 4 of Table 1, accompanied with the formation of *n*-propyl chloride confirmed by GC–MS (Eq. 4); (3) the formation of *n*-propyl, benzyl, and cyclohexyl chloride were observed in the reactions of entries 4, 6, and 7 in Table 1 by careful GC and GC–MS analyses of the reaction mixtures. Therefore, the proposed route may involve: (1) first the formation of ketimine **3** by dehydration of **1** with amine or NH_3; (2) intermolecular nucleophilic attack of **1** by enamine carbon of **3′** followed by dehydration to give α,β-unsaturated imine **4**; (3) electrocyclic reaction of **4** to form the intermediate **5**; (4) elimination of X^- and subsequent S_N2 reaction of **5** to produce **2** (Scheme 2).



Scheme 2. Possible route for the formation of isoquinolines **2**.



(3)



(4)

Based on this proposed route, it is reasonable to explain why the best result was achieved in the reaction of **1a** with 0.5 equiv of *n*-propylamine (Table 1, entry 4), since the formation of **2a** is resulted from the condensation of ketimine **3** with **1a** in a 1:1 ratio. Therefore, the use of excess amount of amine would only transfer **1a** into **3a** in an excess amount, leading to a decrease of the yield of **2a**. In case of urea employed, it might require an excess amount of urea to generate **3** to promote the condensation reaction.

3. Conclusions

We have established a novel and straightforward domino catalyst-free process for the synthesis of halogen-substituted quinolines from the condensation of *o*-haloacetophenones with urea or primary amines. This method has the advantages of simplicity and readily accessible starting materials, without employing a catalyst and good yields. To the best of our knowledge, the present report is the first example on the catalyst-free cleavage of $C(sp^2)$–X bond and the formation of C–C bond. In addition, the obtained halogen-substituted quinolines may potentially be applied to construct the highly conjugated π system with *N*-heteroaromatics, which have attracted much attention as promising organic materials for electronic devices.

4. Experimental section

4.1. General methods

All organic starting materials are analytically pure and used without further purification. ^1H and ^{13}C NMR spectra were recorded on JOEL JNM-ECA300 spectrometers at 300 MHz and 75 MHz, respectively. ^1H chemical shifts (δ) were referenced to TMS and ^{13}C NMR chemical shifts (δ) were referenced to internal solvent resonance. GC analyses of organic compounds were performed on an

Agilent Technologies 1790 GC (with a TC-WAX capillary 25 m column) instrument. Mass spectra were obtained on a HEWLETT 5890 PACKARD SERIES II GC/MS spectrometer with a PEG-25M column. Element analyses were obtained with a Flash EA 1112 Element Analyzer in the Institute of Chemistry, Chinese Academy of Sciences.

4.2. Typical experimental procedure for the formation of quinoline 2a (Table 1, entry 16)

In a thick-walled Pyrex screw-cap tube (10 mL) equipped with a magnetic stirring bar were placed *o*-chloroacetophenone (309.0 mg, 2.0 mmol), urea (420.0 mg, 7.0 mmol), and toluene (0.5 mL). The tube was capped and the mixture was stirred at 150 °C for 60 h. After the reaction mixture was cooled to room temperature, CH_2Cl_2 (10 mL) was added, and the insoluble materials were filtrated off. The filtrate was then subjected to GC and GC–MS analyses. Removal of solvent and volatiles under reduced pressure afforded a viscous residue, which was dissolved in $CDCl_3$ (2.0 mL), and ferrocene (22.9 mg) was added as internal material for ^{1}H NMR. Compound **2a** was isolated in 189.2 mg (0.748 mmol, 75%) as colorless solid by column chromatography (silica gel, eluted with petroleum ether/ethyl acetate=100:0–100:20). Recrystallization of **2a** in CH_2Cl_2 and *n*-hexane gave the suitable crystals for X-ray diffraction analysis. ^{1}H NMR analysis of the reaction mixture disclosed that **2a** was formed in 81% yield.

4.3. Characterization data for all products

4.3.1. 2-(2′-Chlorophenyl)-4-methylquinoline (**2a**)

Colorless solid, mp 87.0–87.5 °C (recrystallization from *n*-hexane and CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18–7.35 (m, 9H), 2.75 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.2, 147.9, 143.7, 139.8, 132.3, 131.6, 130.3, 130.0, 129.7, 129.3, 127.2, 127.1, 126.5, 123.7, 123.3, 18.9. GC–MS *m*/*z* (% relative intensity): 255 (M^+, 19), 253 (M^+, 62), 238 (19), 218 (100), 203 (7), 189 (7), 109 (22). IR (KBr): 3058, 2947, 2918, 1602, 1569, 1550, 1507, 1349, 1044, 754 cm^{-1}. TLC R_f=0.50 (silica, CH_2Cl_2). Anal. Calcd for $C_{16}H_{12}ClN$: C, 75.74; H, 4.77; N, 5.52. Found: C, 75.37; H, 4.85; N, 5.57.

4.3.2. 7-Chloro-2-(2′,4′-dichlorophenyl)-4-methylquinoline (**2b**)

White solid, mp 181.0–183.0 °C (recrystallization from a mixture of solvents of *n*-hexane, CH_2Cl_2, and THF). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16–7.37 (m, 7H), 2.74 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 148.6, 144.5, 137.8, 135.6, 135.4, 133.2, 132.6, 130.0, 129.1, 127.8, 127.6, 125.8, 125.2, 123.4, 18.9. GC–MS *m*/*z* (% relative intensity): 327 (M^+, 3), 325 (M^+, 22), 323 (M^+, 68), 321 (M^+, 67), 286 (100), 251 (40), 216 (31), 189 (10), 108 (30). IR (KBr): 3062, 2961, 2926, 1601, 1557, 1542, 1500, 1097, 912, 824 cm^{-1}. TLC R_f=0.35 (silica, CH_2Cl_2). Anal. Calcd for $C_{16}H_{10}Cl_3N$: C, 59.57; H, 3.12; N, 4.34. Found: C, 59.31; H, 3.18; N, 4.25.

4.3.3. 6-Chloro-2-(2′,5′-dichlorophenyl)-4-methylquinoline (**2c**)

White solid, mp 188.0–188.5 °C (recrystallization from a mixture of solvents of *n*-hexane, CH_2Cl_2, and THF). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11–7.32 (m, 7H), 2.73 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 146.3, 143.7, 140.7, 133.2, 132.8, 131.9, 131.6, 131.3, 130.7, 130.6, 130.0, 128.1, 123.8, 122.9, 18.9. GC–MS *m*/*z* (% relative intensity): 327 (M^+, 4), 325 (M^+, 23), 323 (M^+, 73), 321 (M^+, 67), 286 (100), 251 (36), 216 (33), 189 (9), 107 (25). IR (KBr): 3074, 2957, 2923, 1598, 1542, 1490, 1096, 1041, 803 cm^{-1}. TLC R_f=0.36 (silica, CH_2Cl_2). Anal. Calcd for $C_{16}H_{10}Cl_3N$: C, 59.57; H, 3.12; N, 4.34. Found: C, 59.53; H, 3.18; N, 4.23.

4.3.4. 2-(2′-Bromophenyl)-4-methylquinoline (**2d**)

Pale yellow solid, mp 85.0–86.0 °C (recrystallization from *n*-hexane and CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.20–7.24 (m, 9H), 2.75 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 147.7, 144.1, 141.8, 133.3, 131.6, 130.3, 130.0, 129.5, 127.7, 127.3, 126.7, 123.8, 123.4, 122.0, 19.0. GC–MS *m*/*z* (% relative intensity): 299 (M^+, 21), 297 (M^+, 23), 218 (100), 203 (9), 189 (7), 109 (23). IR (KBr): 3062, 2961, 2926, 1601, 1589, 1557, 1500, 1097, 1042, 824 cm^{-1}. TLC R_f=0.35 (silica, CH_2Cl_2). Anal. Calcd for $C_{16}H_{12}BrN$: C, 64.45; H, 4.06; N, 4.70. Found: C, 64.64; H, 4.15; N, 4.68.

4.3.5. 6-Bromo-2-(2′,5′-dibromophenyl)-4-methylquinoline (**2e**)

Yellow solid, mp 162.0–162.5 °C (recrystallization from a mixture of solvents of *n*-hexane, CH_2Cl_2, and THF). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34–7.46 (m, 7H), 2.74 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.4, 148.5, 144.6, 140.2, 135.7, 132.6, 132.4, 131.0, 130.3, 126.0, 125.3, 123.8, 123.4, 123.3, 122.5, 18.9. GC–MS *m*/*z* (% relative intensity): 459 (M^+, 11), 457 (M^+, 36), 455 (M^+, 34), 453 (M^+, 12), 376 (100), 297 (27), 216 (44), 189 (54), 108 (37). IR (KBr): 2954, 2922, 1600, 1578, 1552, 1493, 1092, 1031, 878 cm^{-1}. TLC R_f=0.23 (silica, CH_2Cl_2). Anal. Calcd for $C_{16}H_{10}Br_3N$: C, 42.15; H, 2.21; N, 3.07. Found: C, 42.27; H, 2.34; N, 2.99.

4.3.6. 5-(3-Bromo-thiophen-2-yl)-7-methyl-thieno[3,2-b]-pyridine (**2f**)

Orange solid, mp 82.0–83.5 °C (recrystallization from *n*-hexane and CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.74 (d, 1H, *J*=5.5 Hz), 7.60 (d, 1H, *J*=5.5 Hz), 7.36 (d, 1H, *J*=5.5 Hz), 7.08 (d, 1H, *J*=5.5 Hz), 2.66 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.0, 149.6, 141.8 (2C), 139.2, 132.4, 130.5, 127.2, 125.8, 117.6, 107.8, 20.5. GC–MS *m*/*z* (% relative intensity): 311 (M^+, 100), 309 (M^+, 92), 308 (99), 230 (85), 215 (21), 186 (31), 115 (40). IR (KBr): 3048, 2977, 2910, 1564, 1518, 1443, 1365, 708 cm^{-1}. TLC R_f=0.40 (silica, CH_2Cl_2). Anal. Calcd for $C_{12}H_8BrNS_2$: C, 46.60; H, 2.59; N, 4.53. Found: C, 46.37; H, 2.83; N, 4.57.

4.3.7. 4-Methyl-2-phenylquinoline (**2g**)[10]

Colorless solid (recrystallization with *n*-hexane and CH_2Cl_2). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18–7.42 (m, 10H), 2.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.1, 148.3, 144.9, 139.9, 130.4, 129.4, 129.3, 128.9, 127.6, 127.4, 126.1, 123.7, 119.9, 19.1. GC–MS *m*/*z* (% relative intensity): 219 (M^+, 100), 204 (70), 189 (6), 174 (24), 132 (22), 108 (19).

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Supplementary data

Copies of ^{1}H, ^{13}C NMR and MS charts for all products and the full X-ray structural details for **2a** are concluded in Supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.12.039.

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