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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

Chuanmei Qi, Qingwei Zheng, Ruimao Hua *

Department of Chemistry, Tsinghua University, Innovative Catalysis Program, Key Laboratory of Organic Optoelectronics & Molecular Engineering of Ministry of Education, Beijing 100084, China

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ABSTRACT

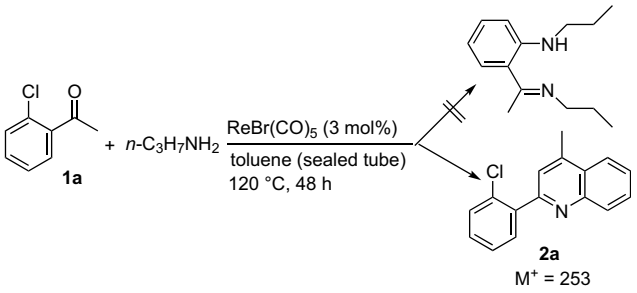
Halogen-substituted quinolines have been synthesized in good yields by the condensation and cyclization of two molecules of *ortho*-haloacetophenones with urea or primary amines. The formation of halogen-substituted quinolines takes place through the unexpected catalyst-free cleavage of C(sp^2)–X (X=Cl, 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**.

* Corresponding author. Fax: +86 10 62771149.
E-mail address: ruimao@mail.tsinghua.edu.cn (R. Hua).

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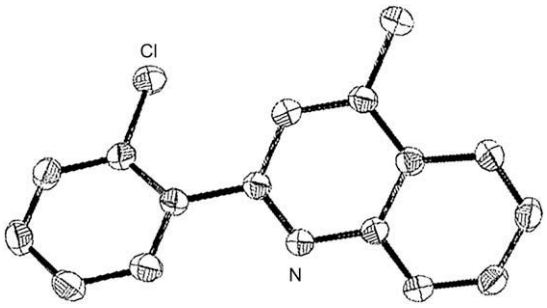


Figure 1. Molecular structure of **2a**. All hydrogen atoms are omitted for clarity.

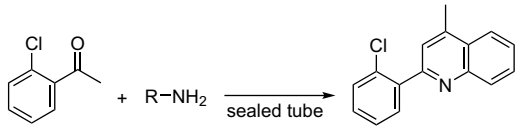
n-propylamine, in which the C–Cl, C–H bonds of **1a** and C–N bond of *n*-propylamine were cleaved and the new C–C, C–N bonds were created to form an quinoline ring, and *n*-propylamine was the only source of nitrogen. Surprisingly, our further studies disclosed that **2a** could be also obtained in 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]

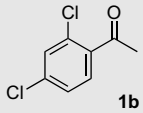
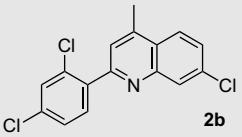
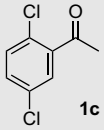
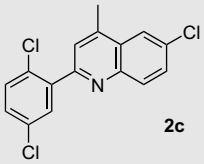
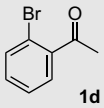
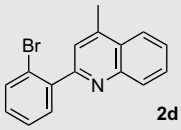
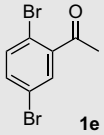
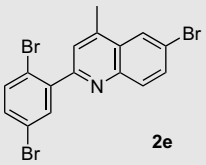


1a **2a**

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.