

## PAPER

View Article Online  
View Journal | View IssueCite this: *RSC Adv.*, 2018, 8, 4584Catalyst- and solvent-free approach to 2-arylated quinolines *via* [5 + 1] annulation of 2-methylquinolines with diynones†Hai-Yuan Zhao,<sup>‡ab</sup> Fu-Song Wu,<sup>‡b</sup> Li Yang,<sup>c</sup> Ying Liang,<sup>\*a</sup> Xiao-Lin Cao,<sup>b</sup>  
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A novel route for the synthesis of 2-arylated quinolines through a [5 + 1] annulation directly from 2-methylquinolines and diynones under catalyst-free and solvent-free conditions was disclosed. This synthetic process was atom-economic, with good tolerance of a broad range of functional groups, and with great practical worth.

Nitrogen-containing heterocyclic compounds are ubiquitous in natural molecules and exhibit a wide array of biological activities.<sup>1</sup> Among various N-heterocycles, quinoline nuclei are privileged scaffolds that occupy an important role in many medicinally relevant compounds.<sup>2</sup> 2-Arylated quinolines are found in many medicinal compounds including etoricoxib,<sup>3</sup> rosuvastatin,<sup>4</sup> and gleevec,<sup>5</sup> as well as molecules designed for other purposes including P, N ligands, such as QUINAP.<sup>6</sup> Because of their unique biological activity and wide application, the functionalized 2-arylated quinoline elicited considerable synthetic interest, and a variety of synthetic routes have been established.<sup>7</sup> In addition, some classical synthetic methods such as Kumada,<sup>8</sup> Suzuki,<sup>9</sup> Negishi,<sup>10</sup> or Stille<sup>9b</sup> are usually used to efficiently prepare these compounds, but these methods require the preparation of cross-coupling reagents such as Grignard reagents, boronic acids, organozinc, and organostannanes in advance and these cross-coupling reagents are unstable or toxic or can't be isolated as solids.<sup>11</sup> More recently, much research has been directed toward the synthesis of 2-arylated quinolones and their derivatives *via* transition-metal-catalyzed C–H arylation<sup>12</sup> and many other methods also have been developed by transitional-metal-catalyzed cross-

couplings.<sup>13</sup> These transition metals included Co, Cu or Pd. Moreover, 2-arylated quinolines synthesis *via* direct C–H arylation of quinolones with various aryl bromides, arylboronic acid, or arylzinc reagents catalyzed by transition metal catalyst, such as Rh, Fe, or Ni, have been investigated by Bergman,<sup>14</sup> Maiti,<sup>15</sup> and Tobisu.<sup>16</sup> Ru<sup>17</sup> or Mn<sup>18</sup> also was used to catalyze indirect Friedländer synthesis to obtain 2-arylated quinolines that involved oxidative cyclization of 2-aminobenzyl alcohol with either ketones or alcohols. Although these processes were highly efficient and significance, none of these procedures could directly provide the final products with a low content of the heavy metal impurities which are strict restrictions in drugs and pharmaceuticals.<sup>19</sup> Thus, an alternative, general, solvent-free, and environmentally sustainable procedure is urgently required for the quick synthesis of 2-arylated quinolines.

Recently, as our continuous study on the C(sp<sup>3</sup>)–H activation of 2-methylquinolines, which provided a facile synthetic approach to access substituted pyrrolo[1,2-*a*]quinolones (Scheme 1),<sup>20</sup> we had found that the methyl of 2-

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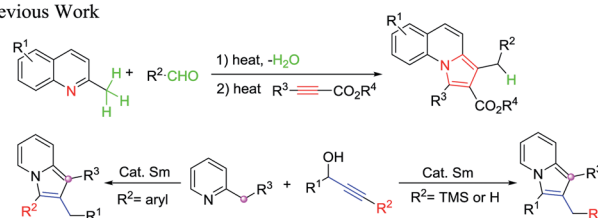
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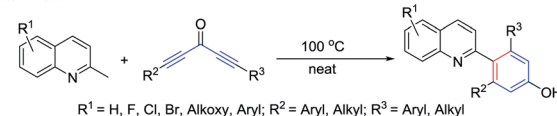
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data and spectra data. CCDC 1534893. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ra12716b

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## Previous Work



## This Work



Scheme 1 C–H bond activation of 2-methylquinolines and 2-methylpyridine.

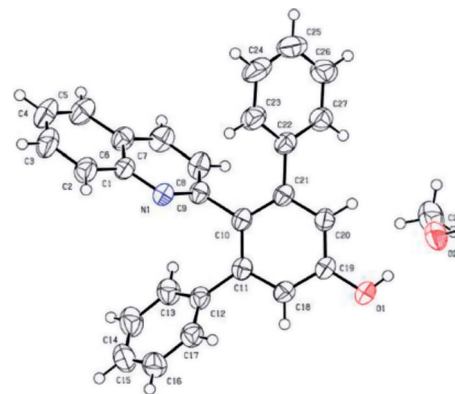
Table 1 Optimization of reaction conditions<sup>a</sup>

Entry	Cat.	Solvent	Temp. (°C)	Yield <sup>b</sup> (%)
1	—	PhCl	120	65
2	Sm(OTf) <sub>3</sub>	PhCl	120	55
3 <sup>c</sup>	Sm(OTf) <sub>3</sub>	PhCl	120	0
4	Cs <sub>2</sub> CO <sub>3</sub>	PhCl	120	0
5	Et <sub>3</sub> N	PhCl	120	0
6	AcOH	PhCl	120	0
7	—	Toluene	120	35
8	—	DMF	120	63
9	—	DMSO	120	45
10	—	1,4-Dioxane	120	Trace
11 <sup>d</sup>	—	—	120	73
12 <sup>d</sup>	—	—	110	75
13 <sup>d</sup>	—	—	100	85
14 <sup>d</sup>	—	—	90	60
15 <sup>d,e</sup>	—	—	100	86

<sup>a</sup> Reactions conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), catalyst (10 mol% to **2a**), solvent (1 mL), sealed tube, 10 h. <sup>b</sup> Isolated yield of pure product based on **2a**. <sup>c</sup> Cs<sub>2</sub>CO<sub>3</sub> as base was added to the reaction. <sup>d</sup> **1a** (1.5 mmol), **2a** (0.5 mmol), sealed tube, 10 h. <sup>e</sup> Reaction time was 15 h.

methylquinolines has very high reactivity. Based on this, herein we reported the catalyst-free and solvent-free [5 + 1] annulation of 2-methylquinolines and diynones to access 4-(quinolin-2-yl)-phenols. To the best of our knowledge, there were none of the group that reported direct construction of six-member aromatic-ring at the methyl of 2-methylquinolines with diynones to give 4-(quinolin-2-yl)-phenols. The present novel construction protocol for 4-(quinolin-2-yl)-phenols had several significant advantages: (1) this chemistry provided a novel and simple strategy for the synthesis of highly valuable 4-(quinolin-2-yl)-phenols under very simple conditions; (2) according to the atom economy concept, this protocol was carried out under catalyst-free and solvent-free conditions, without the addition of any acid, base, or other reagents, which provided the final products without heavy metal impurities and improved its potential utility; (3) the method featured high functional group tolerance, high yields, and broad substrate scopes. Particularly, this route could directly introduce two different substituent groups on the newly formed of six-member aromatic-ring (see Table 2).

To examine the feasibility of our proposed protocol, 2-methylquinoline (**1a**) and 1,5-diphenylpenta-1,4-diyn-3-one (**2a**) were chosen as the model substrates and diverse reaction conditions were screened as shown in Table 1. Initially, treatment of **1a** (0.6 mmol) with **2a** (0.5 mmol) in chlorobenzene (PhCl) at 120 °C for 10 hours led to the arylation product 2'-(quinolin-2-yl)-[1,1':3',1''-terphenyl]-5'-ol (**3a**) in 65% yield (Table 1, entry 1). The structure of **3a** was confirmed by its <sup>1</sup>H

Fig. 1 X-ray crystal structure of **3a** (CCDC 1534893†).

and <sup>13</sup>C NMR spectra, mass spectra, and single-crystal X-ray diffraction analysis (Fig. 1).<sup>21</sup> To improve the efficiency, we used Sm(OTf)<sub>3</sub> as catalyst, but the result provided **3a** in less than 60% (Table 1, entry 2). And then, when we used base (Cs<sub>2</sub>CO<sub>3</sub>, Et<sub>3</sub>N) or acid (AcOH) as additives, no desired products was isolated (Table 1, entries 4–6) because of **2a** degradation in the presence of acid or base. Subsequently, we used other solvents such as toluene, DMF, DMSO, and 1,4-dioxane in place of PhCl and these reactions were completed in the absence of additives, providing the yields of **3a** in less than 65% (Table 1, entries 7–10). Gratifyingly, when the reaction was carried out in the

Table 2 Synthesis of 4-(quinolin-2-yl)phenol derivatives<sup>a,b,c</sup>

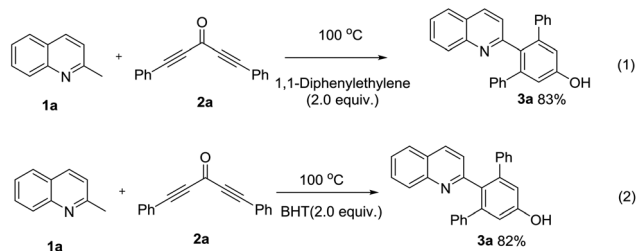
<p> <b>3a</b>: R<sup>1</sup> = H (85%, 10 h)  <b>3b</b>: R<sup>1</sup> = 5-Cl (58%, 6 h)  <b>3c</b>: R<sup>1</sup> = 6-F (55%, 6 h)  <b>3d</b>: R<sup>1</sup> = 6-Br (77%, 10 h)  <b>3e</b>: R<sup>1</sup> = 7-Cl (60%, 7 h)  <b>3f</b>: R<sup>1</sup> = 6-EtO (58%, 6 h)  <b>3g</b>: R<sup>1</sup> = 6-Cl-7-Cl (73%, 10 h)  <b>3h</b>: R<sup>1</sup> = 6-Br, R<sup>2</sup> = 4-Me (70%, 10 h)  <b>3i</b>: R<sup>1</sup> = 7-F, R<sup>2</sup> = 3-Me (62%, 7 h)  <b>3j</b>: R<sup>2</sup> = 4-FC<sub>6</sub>H<sub>4</sub> (76%, 8 h)  <b>3k</b>: R<sup>2</sup> = 4-ClC<sub>6</sub>H<sub>4</sub> (74%, 8 h)  <b>3l</b>: R<sup>2</sup> = 3-Me-5-MeC<sub>6</sub>H<sub>3</sub> (68%, 9 h)  <b>3m</b>: R<sup>2</sup> = <i>n</i>-C<sub>3</sub>H<sub>7</sub> (70%, 10 h)  <b>3n</b>: R<sup>2</sup> = 2-Cl (82%, 8 h)  <b>3o</b>: R<sup>2</sup> = 3-Me (75%, 9 h)  <b>3p</b>: R<sup>2</sup> = 3-MeO (65%, 10 h)  <b>3q</b>: R<sup>2</sup> = 4-Me (73%, 9 h)  <b>3r</b>: R<sup>2</sup> = 4-Et (70%, 9 h)  <b>3s</b>: R<sup>2</sup> = 4-F (79%, 7 h)  <b>3t</b>: R<sup>2</sup> = 4-FC<sub>6</sub>H<sub>4</sub> (76%, 8 h)  <b>3u</b>: R<sup>2</sup> = 4-ClC<sub>6</sub>H<sub>4</sub> (74%, 8 h)  <b>3v</b>: R<sup>2</sup> = 3-Me-5-MeC<sub>6</sub>H<sub>3</sub> (68%, 9 h)  <b>3w</b>: R<sup>2</sup> = <i>n</i>-C<sub>3</sub>H<sub>7</sub> (70%, 10 h)  <b>3x</b>: 87%, 7 h  <b>3y</b>: 67%, 9 h  <b>3z</b>: 63%, 8 h         </p>	

<sup>a</sup> Yield of the isolated product, calculated from **2**. <sup>b</sup> The reaction completed under solvent-free (see ESI). <sup>c</sup> **3d**, **3g**, **3h**, **3j** completed in PhCl (see ESI).

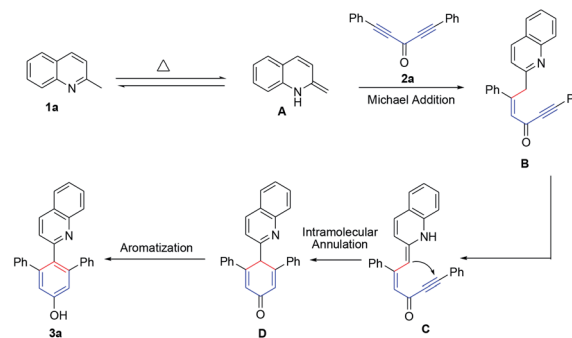


absence of solvent, the yield of corresponding product **3a** was increased to 73% (Table 1, entry 11). Subsequently, we carefully adjusted the reaction temperature (Table 1, entries 12–14) and the desired product **3a** was obtained in the best yield (85%) when the reaction was performed at 100 °C. The reaction time extended to 15 hours, but the yield of **3a** was not increased (Table 1, entry 15).

With the optimized conditions in hand, a series of diynones and 2-methylquinolines were subjected to the reaction to investigate the scope and the results were shown in Table 2. The 2-methylquinoline ring has been substituted with electron-rich or electron-deficient groups  $R^1$  whereas  $R^2$ ,  $R^3$  in the diynones included alkyl and aryl moieties. All reactions proceeded smoothly to afford the corresponding 4-(quinolin-2-yl)phenols/4-(pyridin-2-yl)phenols in moderate to high yields (55–89%). Desired products **3b–3f** were obtained in moderate to good yields (55–77%) with an electron-rich group (–EtO) or electron-deficient substituent (–F, –Cl, –Br) at C-5, C-6, or C-7 of 2-methylquinolines. The reaction of 6,7-dichloro-2-methylquinoline and diynones provided the corresponding product **3g** in 73% yield with the PhCl as solvent. Symmetric diynones bearing electron-donating substituents such as Me, MeO, and Et or electron-withdrawing groups such as F and Cl on the benzene ring were found to be good substrates for this reaction and provided the desired products (**3l–3q**) in moderate to high yields, which showed that the position of the substituents on the benzene ring did not affect the transformation significantly. In addition, the diynones reacted with 2-methylquinoline which has an electron-deficient substituent at C-6 or C-7, furnishing the corresponding 4-(quinolin-2-yl)-phenols products in good yields (**3h**, **3i**). It was found that the reaction of the 3-methylbenzo[*l*]quinoline and 2,6-dimethylpyridine also proceeded smoothly and afforded the desired product **3j** and **3k** in 82% and 68% yields, respectively. Unfortunately, the reaction of 2-methylpyridine and 1,5-diphenylpenta-1,4-diyne-3-one (**2a**) under the standard conditions only give a trace amount of the desired product. Then, we investigated the reaction with heterocycle substituted diynones, and found the thiophene substrates furnishing the desired product in higher yield (**3v**). Subsequently, other asymmetrical diynones which have two different substituents were also tested for the present reaction and the corresponding products were isolated in good to excellent yields (**3r–3u**, **3x–3z**). We found that strained cyclopropyl was tolerated for this transformation and provided the corresponding products **3w** and **3y** in moderate yields.



Scheme 2 Control experiments.



Scheme 3 Plausible mechanism.

To support the proposed reaction pathway, additional control experiments were carried out and the results were presented in Scheme 2. It was observed that the presence of 2 equiv. of 1,1-diphenylethyne or BHT (2,6-di-*tert*-butyl-4-methylphenol) didn't suppress the synthesis of **3a**. These results suggested that a radical mechanism wasn't likely involved.

A possible mechanism is proposed in Scheme 3. At first, the enamine intermediate **A** was formed from **1a** via tautomerization,<sup>22</sup> followed by, Michael addition to diynones, giving the intermediate **B**. And then, the enamine intermediate **C** was generated from **B** via the requisite disruption of aromaticity. Subsequently, intermediate **C** was transformed into intermediate **D** by intramolecular annulation reaction and the intermediate **D** was rapidly aromatized to form the stable product **3a**.

In summary, we have developed a rapid, simple, efficient, catalyst-free, and solvent-free reaction to access 4-(quinolin-2-yl)-phenols through a [5 + 1] annulation directly from 2-methylquinolines and diynones. The synthetic process was atom-economic, applicable to wide range of substrates, and has functional group tolerance, and these features would render this method attractive for academic and industrial use.

## Conflicts of interest

There are no conflicts to declare.

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