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# Catalyst- and solvent-free approach to 2-arylated quinolines *via* [5 + 1] annulation of 2-methylquinolines with diynones†

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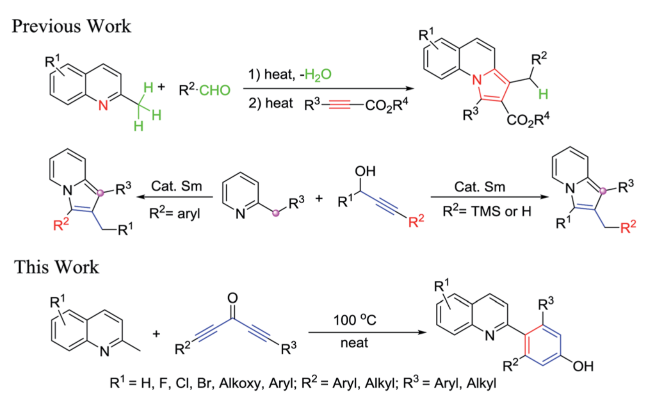
A novel route for the synthesis of 2-arylated quinolines through a [5 + 1] annulation directly from 2-methylquinolines and diynones under catalyst-free and solvent-free conditions was disclosed. This synthetic process was atom-economic, with good tolerance of a broad range of functional groups, and with great practical worth.

Nitrogen-containing heterocyclic compounds are ubiquitous in natural molecules and exhibit a wide array of biological activities.[1] Among various N-heterocycles, quinoline nuclei are privileged scaffolds that occupy an important role in many medicinally relevant compounds.[2] 2-Arylated quinolines are found in many medicinal compounds including etoricoxib,[3] rosuvastatin,[4] and gleevec,[5] as well as molecules designed for other purposes including P, N ligands, such as QUINAP.[6] 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.[7] In addition, some classical synthetic methods such as Kumada,[8] Suzuki,[9] Negishi,[10] or Stille[9b] are usually used to efficiently prepare these compounds, but these methods require the preparation of cross-coupling reagents such as Grignard reagents, boronic acids, organozincs, and organostannanes in advance and these cross-coupling reagents are unstable or toxic or can't be isolated as solids.[11] More recently, much research has been directed toward the synthesis of 2-arylated quinolones and their derivatives *via* transition-metal-catalyzed C–H arylation[12] and many other methods also have been developed by transitional-metal-catalyzed cross-couplings.[13] 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,[14] Maiti,[15] and Tobisu.[16] Ru[17] or Mn[18] 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.[19] 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($sp^3$)–H activation of 2-methylquinolines, which provided a facile synthetic approach to access substituted pyrrolo[1,2-*a*]quinolones (Scheme 1),[20] we had found that the methyl of 2-




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

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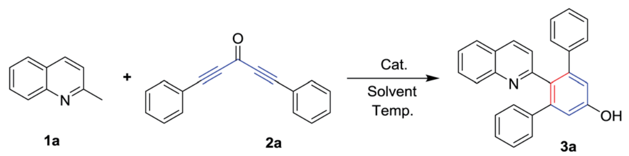
Table 1 Optimization of reaction conditions[a]




| Entry | Cat. | Solvent | Temp. (°C) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | — | PhCl | 120 | 65 |
| 2 | $Sm(OTf)_3$ | PhCl | 120 | 55 |
| 3[c] | $Sm(OTf)_3$ | PhCl | 120 | 0 |
| 4 | $Cs_2CO_3$ | PhCl | 120 | 0 |
| 5 | $Et_3N$ | 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[d] | — | — | 120 | 73 |
| 12[d] | — | — | 110 | 75 |
| **13**[d] | — | — | **100** | **85** |
| 14[d] | — | — | 90 | 60 |
| 15[d,e] | — | — | 100 | 86 |

[a] Reactions conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), catalyst (10 mol% to **2a**), solvent (1 mL), sealed tube, 10 h. [b] Isolated yield of pure product based on **2a**. [c] $Cs_2CO_3$ as base was added to the reaction. [d] **1a** (1.5 mmol), **2a** (0.5 mmol), sealed tube, 10 h. [e] 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 $^1$H

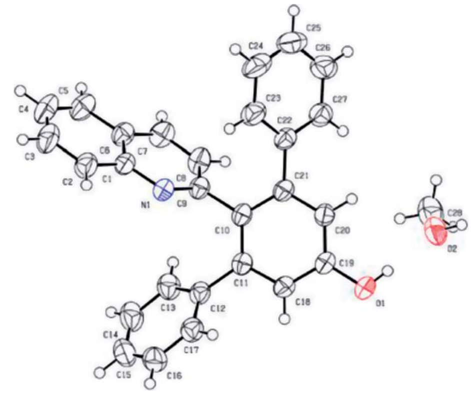
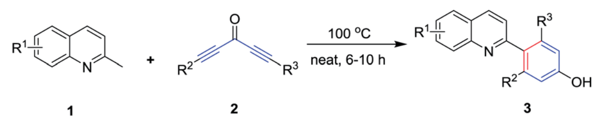
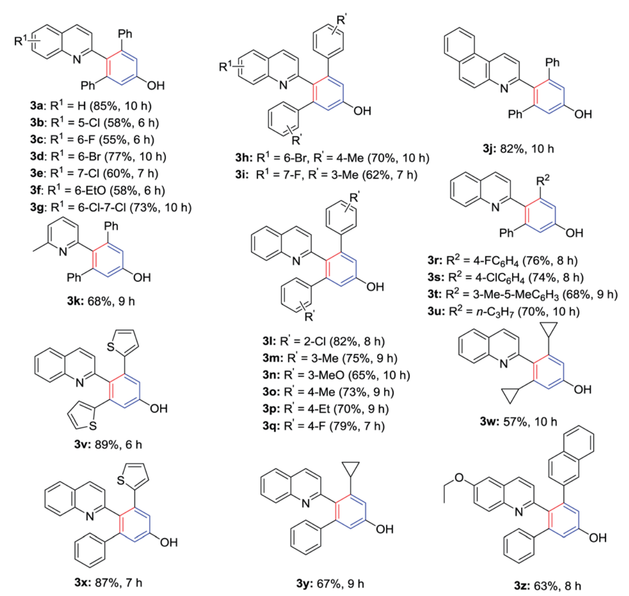


Fig. 1 X-ray crystal structure of **3a** (CCDC 1534893†).

and $^{13}$C NMR spectra, mass spectra, and single-crystal X-ray diffraction analysis (Fig. 1).[21] To improve the efficiency, we used $Sm(OTf)_3$ as catalyst, but the result provided **3a** in less than 60% (Table 1, entry 2). And then, when we used base ($Cs_2CO_3$, $Et_3N$) 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[a,b,c]

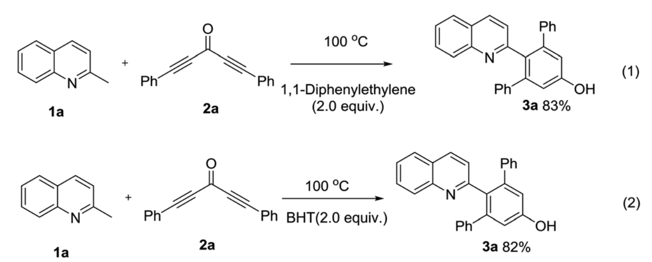


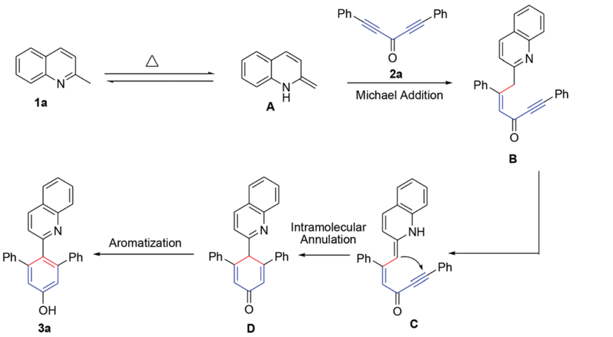

[a] Yield of the isolated product, calculated from **2**. [b] The reaction completed under solvent-free (see ESI). [c] **3d**, **3g**, **3h**, **3j** completed in PhCl (see ESI).

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[*f*]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-diyn-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-diphenylethylene 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,[22] 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.

## Acknowledgements

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21 CCDC 1534893 (**3a**) contains the supplementary crystallographic data for this paper.†

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