Chinese Chemical Letters xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

A novel and facile synthesis of 4-arylquinolin-2(1*H*)-ones under metal-free conditions

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ARTICLE INFO

Article history:
Received 4 March 2015
Received in revised form 13 April 2015
Accepted 20 April 2015
Available online xxx

Keywords:
4-Arylquinolin-2(1*H*)-one
Metal-free
Selectfluor
Synthesis

ABSTRACT

A novel and facile synthesis of 4-arylquinolin-2(1*H*)-ones without metal catalysis has been developed. This reaction involved cyclization/elimination steps and was performed under metal-free conditions using inexpensive reagents such as NaI, selectfluor and KOH.

1. Introduction

The scaffold of quinolin-2(1*H*)-one is an outstanding structural motif found in many natural products and pharmaceutically active compounds [1]. In particular, the derivatives of 4-arylquinolinones have attracted considerable attention in organic chemistry due to their anticancer, antiviral, antibiotic and other activities [2]. Many analogs of this type of heterocyclic compounds have been developed as the lead compounds or clinical candidates [3]. Thus, the synthesis of these valuable compounds has attracted a great deal of interest (Fig. 1).

Many strategies have been used in the synthesis of quinolin-2(1*H*)-one derivatives including classic base-catalyzed Friedländer condensation or acid-catalyzed Knorr and Baylis–Hillman reactions [4], palladium-catalyzed carbonylative annulation of alkynes with 2-iodoanilines and CO [5], metal-catalyzed carbonylative annulation of internal alkynes [6], palladium-catalyzed tandem cyclization of 2-bromocinnamami-des and aryl iodides [7], Ir-catalyzed annulation of *N*-arylcarba-moyl chlorides with internal alkynes [8]. However, some of these procedures needed strong acids and the others were carried out in the presence of noble metals. Nonmetal-catalyzed syntheses of 4-aryl-2-quinolinones remain rare. During our previous work for the synthesis of 2-quinolin-2(1*H*)-one [9], we focused on silver-catalyzed radical tandem cyclization reactions. Herein, we wish to report a semi-one-pot synthesis of 4-arylquinolinones (Scheme 1).

2. Experimental

All reagents were used directly as obtained commercially or after purification. Column chromatography was performed using silica gel (300–400 mesh) and analytical TLC used silica 60-F24. ^{1}H NMR and ^{13}C NMR spectra were collected in $CDCl_3$ on a Bruker Fourier 400 MHz spectrometer and chemical shifts (δ) were reported relative to the internal TMS. The substrate **1** was prepared through a short sequence (Scheme 1). A 50 mL anhydrous flask was charged with magnetic stir bar, cinnamic acid (5 mmol) and $SOCl_2$ (5 mL). After stirring at 60 °C for 3 h, the redundant $SOCl_2$ was evaporated under reduced pressure and then the liquid was dropwise added into another flask containing *N*-methylaniline (10 mmol) in anhydrous CH_2Cl_2 (20 mL). The mixture was stirred for 1 h at room temperature. The organic phase was then washed by aqueous HCl and aqueous K_2CO_3, then dried over anhydrous Na_2SO_4. After evaporating the CH_2Cl_2, the *N*-methyl-*N*-phenylcinnamamide was obtained as a pale yellow solid in 97% yield. The yield is almost quantitative and we used it without further purifications.

Substrate **1**: Pale yellow solid, ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (d, 1H, J = 16.0 Hz), 7.45 (dt, 2H, J = 6.4, 1.2 Hz), 7.36–7.38 (m, 1H), 7.22–7.32 (m, 7H, overlapping $CDCl_3$), 6.39 (d, 1H, J = 16.0 Hz), 3.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.17, 143.66, 141.70,

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http://dx.doi.org/10.1016/j.cclet.2015.05.008
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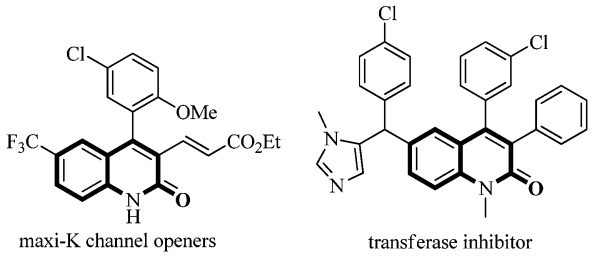
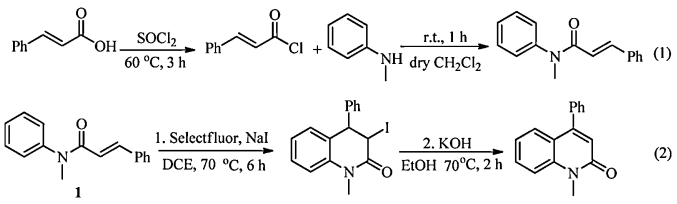


Fig. 1. Some representative compounds containing the 4-arylquinolinone.



Scheme 1. Semi-one-pot synthesis of 4-arylquinolinones.

135.22, 129.63, 129.49, 128.68, 127.85, 127.59, 127.35, 118.76, 37.58.

3. Results and discussion

N-Methyl-*N*-phenylcinnamamide **1** was selected for screening the optimal reaction conditions (Scheme 1, Eq. 2).

The substrate **1** and 1.0 equiv. of NaI were added to a flask, then 2.0 equiv. of selectfluor and 5 mL of CH_3CN were added, the reaction proceeded at 70 °C for 6 h, after that, the solvent was evaporated and 1.0 equiv. of KOH, 3 mL of EtOH were added to the residue, the mixture was subsequently stirred at 70 °C for 2 h, the desired product was obtained in 35% yield (Table 1, entry 1). Changing the solvent to dichloroethane (DCE), the desired product could be obtained in 55% yield after two steps (Table 1, entry 5). However, other solvents such as dioxane, acetone and CH_2Cl_2 were not favorable for this transformation (Table 1, entries 2–4). Different oxidants such as DTBP, $K_2S_2O_8$ and $PhI(OAc)_2$ were also examined under the same conditions (Table 1, entries 9–11), only $PhI(OAc)_2$ showed measurable catalytic effect (Table 1, entry 11). The reaction was also performed at 100 °C, but the results did not improve (Table 1, entry 12). For the step 2, the reaction did not occur using DCE as a solvent (Table 1, entry 13).

Table 1
Optimization of the reaction.

Entry	Step 1		Step 2		Total yield (%)[a]
	Solvent	Temp (°C)	Oxidant	Solvent	
1	CH_3CN	70	Selectfluor	EtOH	35
2	Dioxane	70	Selectfluor	EtOH	0
3	Acetone	70	Selectfluor	EtOH	Trace[b]
4	CH_2Cl_2	70	Selectfluor	EtOH	Trace[b]
5	DCE	70	Selectfluor	EtOH	55
6	Toluene	70	Selectfluor	EtOH	0
7	DMF	70	Selectfluor	EtOH	Trace[b]
8	DMSO	70	Selectfluor	EtOH	0
9	DCE	70	DTBP	EtOH	Trace[b]
10	DCE	70	$K_2S_2O_8$	EtOH	0
11	DCE	70	$PhI(OAc)_2/I_2$	EtOH	<10[b]
12	DCE	100	Selectfluor	EtOH	50
13	DCE	70	Selectfluor	DCE	Trace[b]

[a] Isolated yield after two steps.
[b] The yield of step 2.

After screening the reaction conditions, the substrates testing were carried out subsequently. As shown in Fig. 2, the *N*-alkyl-*N*-arylcinnamamides bearing electron-donating or electron-withdrawing groups on the phenyl ring A at the *ortho*, *meta*, and *para* positions are all reactive in the reaction, the corresponding products were obtained in moderate yields (Fig. 2, **2**–**4**, **12**–**13**). Different substituents such as OMe, Br, Cl, F and Me could be tolerated in the catalytic processes. It is worth noting that halogen atoms (F, Cl, and Br) were well tolerated under the conditions, enabling further functionalization of the corresponding quinolin-2(1*H*)-ones at the halogenated positions using palladium-catalyzed cross-coupling reactions.

In addition, switching the *N*-protecting group of the substrate to Et or *n*-Bu, the reaction still proceeded well (Fig. 2, **5** and **11**). Unfortunately, substituents such as F and Cl at the *ortho* or *para* position of aniline (phenyl ring **B**) affect the efficiency of the reaction dramatically and only a trace amount of products was observed. The NO_2 group at the *para* position of aniline completely shut down the reaction. However, the reaction could proceed when a methyl group is at the *para* position of the aniline and 38% product was obtained (Fig. 2, **8**).

Based on the previous work which described the oxidation of iodide to iodine cation [10], a mechanism for the cyclization/elimination processes has been proposed (Scheme 2). At first, the iodine anion was oxidized to iodine cation by selectfluor. Then I^+ is attacked by the electron-rich double bond of *N*-methyl-*N*-phenyl-cinnamamide (**1**) to form intermediate **2**. After that, the iodinium ion undergoes nucleophilic attack by phenyl ring to form the six-membered ring. Finally, compound **3** eliminate hydroiodic acid under basic condition to produce compound **4**.

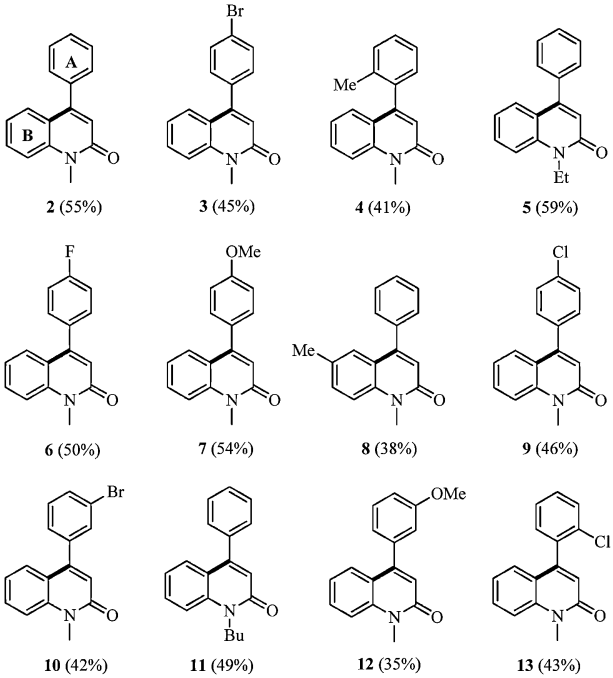


Fig. 2. Structures of synthesized 4-arylquinoline-2(1*H*)-ones with isolated yield after two steps.

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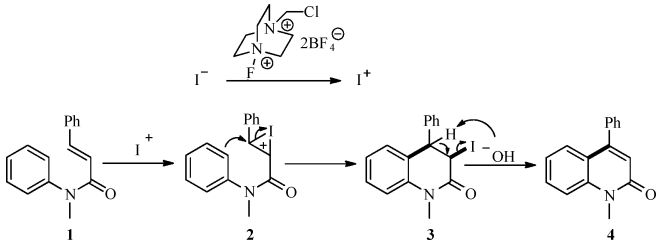

Scheme 2. Proposed mechanism for the reaction.

4. Conclusion

In conclusion, we have developed a novel approach for the convenient synthesis of 4-arylquinolin-2(1*H*)-ones under metal-free conditions. This transformation represents a novel and facile method for the construction of quinolin-2(1*H*)-one motif without metal catalysis. A mechanism has also been proposed for this transformation.

Acknowledgments

This work was financially supported by the National Natural Science Foundation of China (Nos. 21302042 and 21172055), the Program for Innovative Research Team from Zhengzhou (No. 131P-CXTD605), and the Plan for Scientific Innovation Talent of Henan University of Technology (No. 171147)

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2015.05.008.

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