

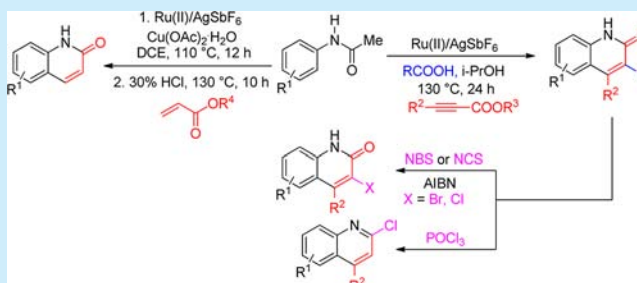
Ruthenium-Catalyzed Cyclization of Anilides with Substituted Propiolates or Acrylates: An Efficient Route to 2-Quinolinones

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S Supporting Information

ABSTRACT: A Ru-catalyzed cyclization of anilides with propiolates or acrylates affording 2-quinolinones having diverse functional groups in good to excellent yields is described. Later, 2-quinolinones were converted into 3-halo-2-quinolinones and 2-chloroquinolines. The proposed mechanism was strongly supported by experimental evidence and deuterium labeling studies.



2-Quinolinones are a naturally occurring heterocyclic moiety. It shows a broad range of biological activities including antibiotic, anticancer, antiviral, and antihypersensitivity.¹ This core is also present in various natural products (Figure 1).² 2-Quinolinones

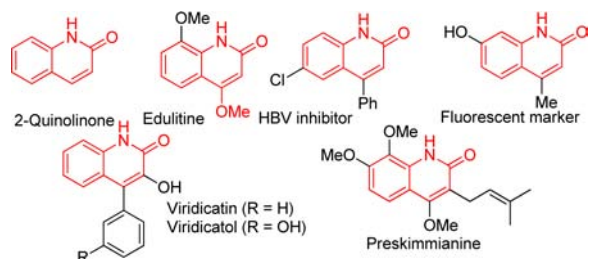
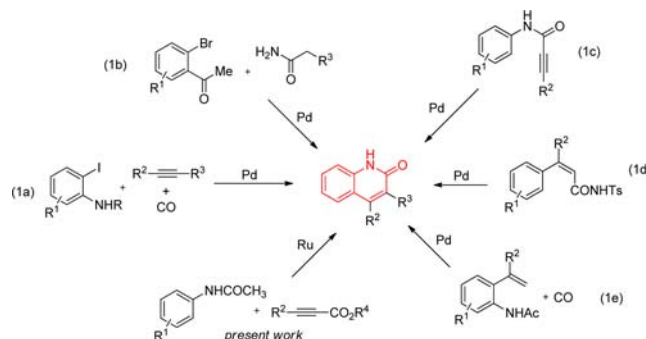


Figure 1. Selected biologically active 2-quinolinones.

are also efficient fluorescent markers for amino acids, peptides, amino carbohydrates, and amino polysaccharides (Figure 1).³ Also, 2-quinolinones are key synthetic intermediates for synthesizing 2-halo, 2-alkoxy, and 2-amino substituted quinolines.⁴

As a result, various synthetic methods are reported in the literature for the synthesis of 2-quinolinone derivatives.^{5–7} Traditionally, 2-quinolinone derivatives are prepared by the acid-mediated intramolecular cyclization of β -keto anilides (Knorr synthesis) and a base-mediated intramolecular aldol condensation of 2-aminophenyl substituted carbonyl compounds (Friedlander synthesis).⁵ Recently, 2-quinolinones were efficiently prepared via Pd catalysis.⁶ Larock reported the synthesis of 3,4-disubstituted quinolinones by a Pd-catalyzed carbonylative annulation of 2-iodoanilides with alkynes and CO (eq 1a).^{6a} Manley reported a Pd-catalyzed amidation of *ortho*-halo acetophenone with alkyl amides leading to 4-substituted quinolinones (eq 1b).^{6b} Fujiwara reported the synthesis of 4-substituted quinolinones via a Pd-catalyzed intramolecular

electrophilic cyclization of *ortho*-alkynyl anilides (eq 1c).^{6c} Doi reported the synthesis of 2-quinolinones through a Pd-catalyzed intramolecular amidation of phenyl substituted enamides (eq 1d).^{6d} Very recently, Alper reported the synthesis of 2-quinolinones via the oxidative cyclocarbonylation of 2-vinyl anilines with CO in the presence of a Pd catalyst (eq 1e).^{6e} In most of these methods, a preactivated species, such as C–X or C–M having starting material, is required to synthesize the key starting materials. In the meantime, the synthesis of 2-quinolinones are also achieved by the other protocols without a metal catalyst.⁷



Transition-metal-catalyzed cyclization of heteroatom substituted aromatics with a carbon–carbon π -component via chelation-assisted C–H bond activation is a powerful method to synthesize heterocyclic molecules in one pot.⁸ In this method, a preactivated species such as C–X or C–M having starting material is not required to activate the carbon of the aromatic moiety. By using this method, various heterocyclic compounds were synthesized efficiently in a highly atom economical and environmentally friendly manner.⁸ But, the synthesis of 2-

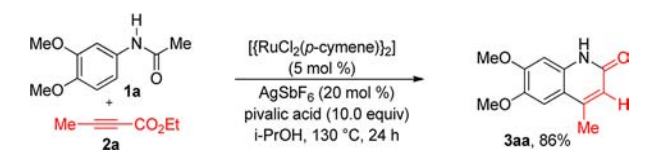
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quinolinone derivatives via a chelation-assisted C–H bond activation pathway is limited in the literature. Herein, we wish to report the synthesis of 4-substituted-2-quinolinone derivatives from easily available starting materials via a Ru-catalyzed cyclization of anilides with substituted propiolates. By using acrylates instead of propiolates, unsubstituted 2-quinolinone derivatives were prepared. Later, a halo group such as Cl or Br was introduced at the C-3 position of 4-substituted-2-quinolinones in the presence of NBS or NCS. Further, highly useful 2-chloroquinolines were prepared from 2-quinolinones in the presence of POCl₃. It is important to point out that the anilines or enamines reacted with alkynes in the presence of a rhodium or Ru catalyst furnishing indole and pyrrole derivatives.⁹

The cyclization of 3,4-dimethoxy acetanilide (**1a**) with ethyl-2-butynoate (**2a**) in the presence of [{RuCl₂(*p*-cymene)}₂] (5.0 mol %), AgSbF₆ (20 mol %), and pivalic acid (10.0 equiv) in *i*-PrOH at 130 °C for 24 h gave 4-methyl substituted-2-quinolinone **3aa** in 86% isolated yield (Scheme 1) (for the

Scheme 1. Cyclization of 3,4-Dimethoxy Acetanilide (**1a**) with Ethyl-2-butynoate (**2a**)



detailed optimization studies, see Supporting Information (SI) in Table S1). The *ortho* C–H bond activation of substrate **1a** is very selective, and the activation selectively takes place at a sterically less hindered side. The cyclization reaction was also tested with anilines having other removable directing groups at the nitrogen atom such as sulfonamide (NH–SO₂Me) and aryl urea (NHCONMe₂) instead of (NHCOMe). However, in the reaction, no cyclization product was observed.

The scope of the cyclization was examined with various substituted anilides **1b–p** with ethyl-2-butynoate (**2a**) (Table 1). In all these reactions, the expected 4-methyl substituted 2-quinolinone derivatives were observed in good to excellent yields. In addition, the reaction was compatible with various sensitive functional groups such as OMe, F, Cl, Br, NO₂, ester, keto, and OH substituted anilides. The reaction of electron-donating groups such as OMe, Me, and OH substituted anilides **1b–e** with **2a** gave the corresponding quinolinones **3ba–ea** in an excellent 81%, 79%, 76%, and 80% yield, respectively (entries 1–4). But, the conditions using *i*-PrOH/pivalic acid as the solvent was not superior for halogen and electron-withdrawing group substituted anilides **1f–k**. For these substrates, acetic acid as the solvent proved superior to pivalic acid/*i*-PrOH (for the detailed optimization studies, see SI in Table S2). Under these modified reaction conditions, F-, Cl-, and Br-substituted anilides **1f–h** provided products **3fa–ha** in 62%, 64%, and 69% yields, respectively (entries 5–7). A less reactive electron-withdrawing group such as keto, ester, and nitro substituted anilides **1i–k** also efficiently participated in the reaction using AcOH as the solvent, giving quinolinone derivatives **3ia–ka** in 66%, 71%, and 69% yields, respectively (entries 8–10). It is important to note that, in the substrates **1i–j**, the C–H bond activation selectively takes place at the *ortho* position to the NHCOMe group and the keto and ester groups remain intact. Sterically hindered *ortho*-methoxy acetanilide **1l** was also involved in the reaction, yielding product **3la** in 77% yield (entry 11). Very interestingly,

Table 1. Cyclization of Substituted Anilides **1b–m** with Ethyl-2-butynoate (**2a**)^a

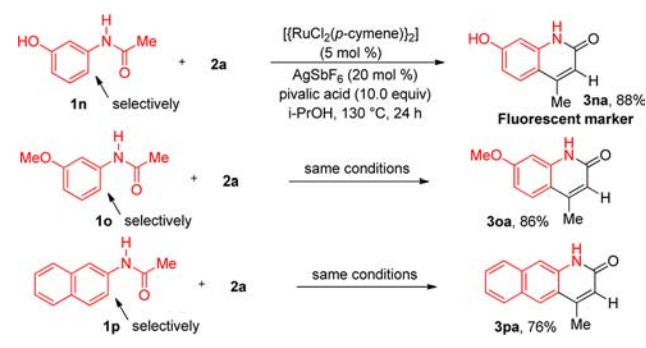
entry	1	product 3	yield (%) ^b
1	1b : R ¹ = OMe	3ba : R ¹ = OMe	81
2	1c : R ¹ = Me	3ca : R ¹ = Me	79
3	1d : R ¹ = OH	3da : R ¹ = OH	76
4	1e : R ¹ = H	3ea : R ¹ = H	80
5	1f : R ¹ = F	3fa : R ¹ = F	62
6	1g : R ¹ = Cl	3ga : R ¹ = Cl	64
7	1h : R ¹ = Br	3ha : R ¹ = Br	69
8	1i : R ¹ = COMe	3ia : R ¹ = COMe	66
9	1j : R ¹ = CO ₂ Me	3ja : R ¹ = CO ₂ Me	71
10	1k : R ¹ = NO ₂	3ka : R ¹ = NO ₂	69
11			77
12			83

^aMethod A: **1b–e**, **1l**, and **1m** (100 mg) were treated with ethyl-2-butynoate (**2a**) (1.5 equiv), [{RuCl₂(*p*-cymene)}₂] (0.05 equiv), AgSbF₆ (0.20 equiv), and pivalic acid (10.0 equiv) in *i*-PrOH (2.5 mL) at 130 °C for 24 h. Method B: **1f–k** (100 mg) were treated with ethyl-2-butynoate (**2a**) (1.5 equiv), [{RuCl₂(*p*-cymene)}₂] (0.05 equiv), and AgSbF₆ (0.20 equiv) in AcOH (3.0 mL) at 130 °C for 24 h. ^bIsolated yield.

heteroaromatic thiophene-2-acetamide (**1m**) also efficiently reacted with **2a**, affording the cyclization product **3ma** in an excellent 83% yield (entry 12).

The scope of the reaction was further tested with unsymmetrical acetanilides **1n–p** (Scheme 2). In all these reactions, a

Scheme 2. Regioselective Studies

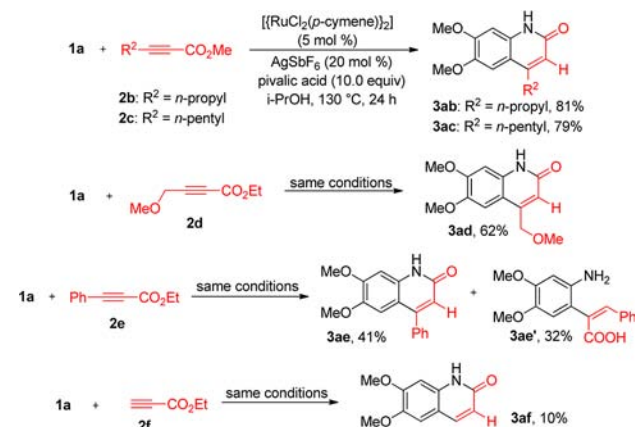


less hindered *ortho* C–H bond of anilide participated in the reaction in a highly regioselective manner. *Meta* hydroxy **1n** and methoxy **1o** acetanilides underwent cyclization with **2a**, giving the corresponding 2-quinolinone derivatives **3na** and **3oa** in excellent 88% and 86% yields, respectively. It is important to note that the compound **3na** is used as a reference material for study and analysis of carcinogenicity and quinolone metabolism

activity.¹¹ 2-Naphthyl acetamide (**1p**) also efficiently reacted with **2a**, providing quinolinone derivative **3pa** in 76% yield.

Next, the scope of the catalytic reaction was examined with substituted alkynes **2b–f** (Scheme 3). Thus, methyl-2-hexynoate

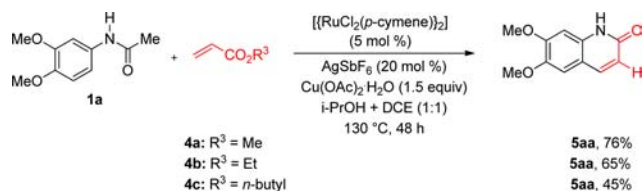
Scheme 3. Scope of Substituted Propiolates



(**2b**), methyl-2-octynoate (**2c**), and ethyl 4-methoxybut-2-ynoate (**2d**) nicely reacted with **1a** to give the corresponding quinolinone derivatives **3ab–3ad** in 81%, 79%, and 62% yields, respectively. The structure of compound **3ac** was confirmed by a single-crystal X-ray diffraction (see SI). Ethylphenyl propiolate (**2e**) also reacted with **1a** providing 4-aryl substituted quinolinone **3ae** in 41% yield. However, in the reaction, the other alkyne regioisomer product **3ae'** was observed in 32% yield. It is important to note that the 4-aryl-2-quinolinone unit was present in various natural products and medicinal compounds.¹² A terminal alkyne, ethyl propiolate (**2f**), was also compatible for the reaction. However, in the reaction, quinolinone derivative **3af** was observed only in 10% yield.

The alkyne cyclization reaction prompted us to explore the possibility of cyclization of anilides **1** with acrylates **4a–c**. Thus, we have tried the cyclization of **1a** with methyl acrylate (**4a**) under the optimized reaction conditions (Scheme 4). In the

Scheme 4. Cyclization of **1a** with Acrylates **4a–c**



reaction, the cyclization product **5aa** was observed only in 32% yield. To increase the yield, we have added 1.50 equiv of $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ to the reaction mixture instead of pivalic acid. It is important to note that $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ is an efficient oxidant for the alkenylation reaction of anilides with alkenes.¹³ However, using these conditions, product **5aa** was observed only in 32% yield. Then, the reaction was carried out with a 1:1 mixture of $\text{ClCH}_2\text{CH}_2\text{Cl}$ (DCE) and *i*-PrOH solvents. Interestingly, product **5aa** was observed in 76% yield. The cyclization reaction was also tested with other acrylates such as ethyl acrylate (**4b**) and *n*-butyl acrylate (**4c**). However, product **5aa** was observed in only 65% and 45% yields, respectively. But, the above reaction conditions such as $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ in a 1:1 mixture of solvents is not suitable for the cyclization of anilides **1b**, **1e–g**, **1i**, and **1k**

with **4a**. To increase the yield, the reaction of anilides **1** with **4a** was done in the presence of $[(\text{RuCl}_2(p\text{-cymene}))_2]$ (5.0 mol %), AgSbF_6 (20 mol %), and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1.5 equiv) in DCE at 110 °C. After that, 0.5 mL of 30% HCl was added into the reaction mixture directly and further allowed to stir at 130 °C. Under the reaction conditions, the cyclization products **5ba–5ka** were observed in 64%, 60%, 54%, 56%, 46%, and 48% yields, respectively (Table 2). In the substrate, 4-acetyl acetanilide (**1i**), the C–H bond activation takes place only *ortho* to NHCOMe .

Table 2. Cyclization of Substituted Anilides **1** with Methyl Acrylate (**4a**)^a

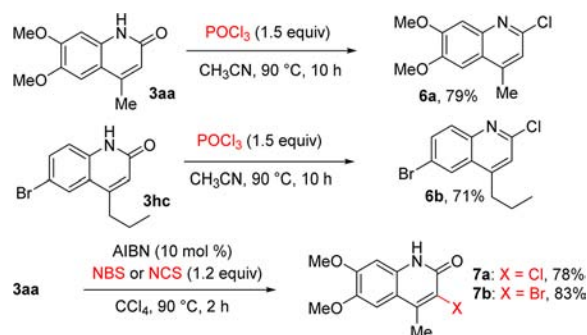
entry	1	product 5	yield (%) ^b
1	1b : R ¹ = OMe	5ba : R ¹ = OMe	64 ^c
2	1e : R ¹ = H	5ea : R ¹ = H	60 ^c
3	1f : R ¹ = F	5fa : R ¹ = F	54
4	1g : R ¹ = Cl	5ga : R ¹ = Cl	56
5	1i : R ¹ = COMe	5ia : R ¹ = COMe	46
6	1k : R ¹ = NO ₂	5ka : R ¹ = NO ₂	48

^aAll reactions were carried out using **1** (100 mg), **4a** (1.5 equiv), $[(\text{RuCl}_2(p\text{-cymene}))_2]$ (0.05 equiv), AgSbF_6 (0.20 equiv), and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ (1.5 equiv) in DCE (2.5 mL) at 110 °C for 12 h. After that, 30% of HCl was added and heated at 130 °C for 10 h.

^bIsolated yield. ^cThe first step was allowed for only 5 h. After that, 30% of HCl was added and heated at 130 °C for 5 h.

Quinolinone derivatives **3aa** and **3hc** were converted into useful 2-chloroquinolines **6a** and **6b** in 79% and 71% yields, respectively, in the presence of POCl_3 in CH_3CN at 90 °C for 10 h (Scheme 5). Further, **3aa** reacted with NCS or NBS in the

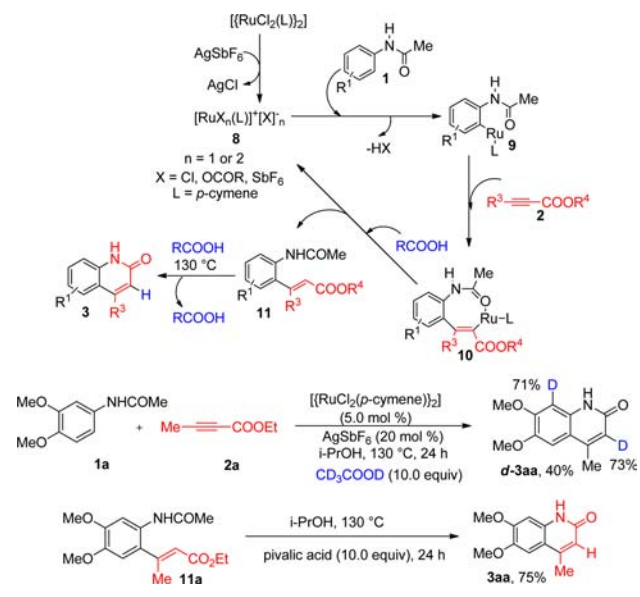
Scheme 5. Transformation of 2-Quinolinones



presence of AIBN (10 mol %) in CCl_4 at 90 °C for 2 h, yielding 3-Cl or Br substituted quinolinones **7a–b** in 78% and 83% yields, respectively. By using **7a–b**, various functionalizations can be undertaken at the 3-carbon of the quinolinone ring.

A possible reaction mechanism is proposed to account for the present cyclization reaction in Scheme 6. AgSbF_6 likely removes the Cl^- ligand from the $[(\text{RuCl}_2(p\text{-cymene}))_2]$ complex, providing a cationic Ru species **8**. Coordination of the carbonyl group of **1** to the Ru species **8** followed by *ortho*-metalation provides ruthenacycle **9**. Coordinative insertion of alkyne **2** into the Ru–C bond of intermediate **9** gives intermediate **10**.

Scheme 6. Proposed Mechanism



Protonation at the Ru–C bond of intermediate **10** by RCOOH affords *ortho*-alkenylated anilide **11** and regenerates the Ru species **8**. Later, it could be possible that the carboxylic acid or solvent *i*-PrOH accelerates *trans*–*cis* isomerization of the double bond of **11** via Michael addition followed by intramolecular nucleophilic addition of NHCOMe to the ester moiety followed by a loss of the acetyl group, leading to cyclic compound **3**.¹⁴ In the reaction, organic acid plays multiple roles such as acting as a proton source, accelerating *cis*–*trans* isomerization and decylation of anilide to aniline.

To support the multiple roles of organic acid, the reaction of **1a** with **2a** was carried out in the presence of CD_3COOD instead of pivalic acid under similar reaction conditions. In the reaction, product **d-3aa** was observed in 40% yield, in which 73% of deuterium incorporation was observed at the C-3 carbon of quinolinone. In the meantime, 71% deuterium incorporation was also observed at the C-8 carbon of **d-3aa**. This result clearly supports that the *ortho* C–H bond cleavage of anilide **1** is a reversible process. Further, to support the conversion of product **11** into **3**, product **11a** was prepared separately and treated with pivalic acid (10.0 equiv) in *i*-PrOH at $130^\circ C$ for 12 h without a catalyst. As expected, product **3aa** was observed in 75% yield. But, the same reaction did not produce product **3aa** without an acid source. This result clearly reveals the multiple role of organic acid in the cyclization reaction.

In conclusion, we demonstrated a Ru-catalyzed cyclization of anilides with substituted propiolates or acrylates in the presence of carboxylic acid, which provides 4-substituted-2-quinolinones and 2-quinolinones in good to excellent yields. 3-Halo-4-substituted-2-quinolinones and 2-chloroquinolines were prepared using the obtained 2-quinolinones.

■ ASSOCIATED CONTENT

Supporting Information

General experimental procedure, starting materials preparation, and characterization details. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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