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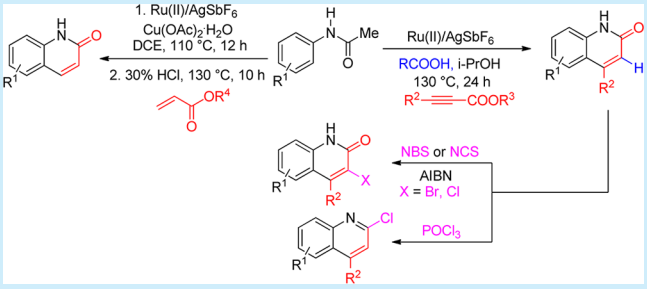
Ruthenium-Catalyzed Cyclization of Anilides with Substituted Propiolates or Acrylates: An Efficient Route to 2-Quinolinones

Rajendran Manikandan and Masilamani Jeganmohan*

Department of Chemistry, Indian Institute of Science Education and Research, Pune 411021, India

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

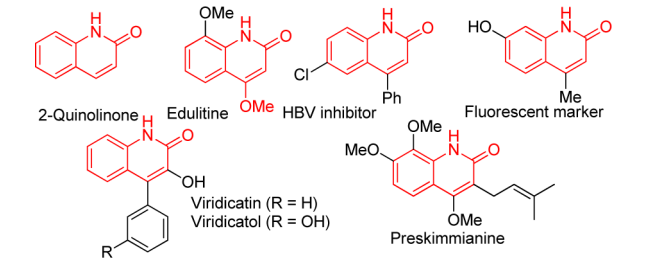
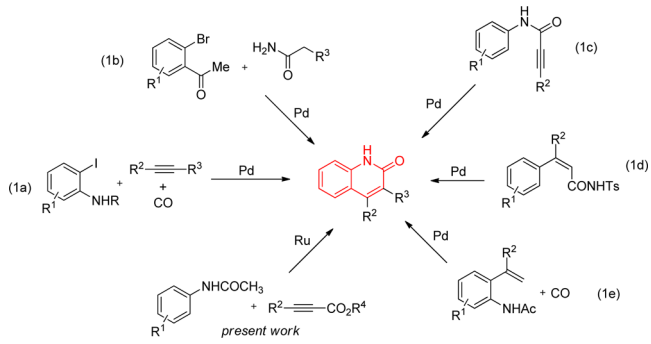


Figure 1. Selected biologically active 2-quinolinones.

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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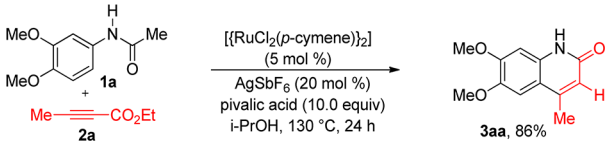
quinolinone derivatives via a chelation-assisted C−H bond activation pathway is limited in the literature. Herein, we wish to report the synthesis of 4-substituted-2-quinolinone derivatives from easily available starting materials via a Ru-catalyzed cyclization of anilides with substituted propiolates. 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 $POCl_3$. 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 [{$RuCl_2$(*p*-cymene)}$_2$] (5.0 mol %), $AgSbF_6$ (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

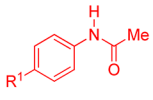
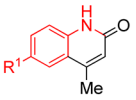
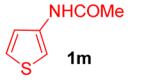
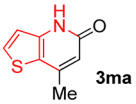
Scheme 1. Cyclization of 3,4-Dimethoxy Acetanilide (1a) with Ethyl-2-butynoate (2a)



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−SO_2Me) and aryl urea (NHCONMe_2) 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, NO_2, 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]

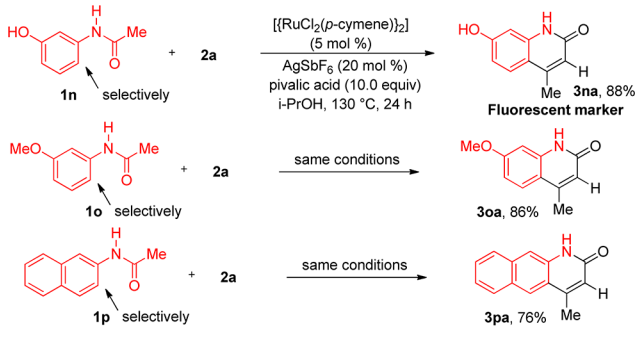
entry	1	product 3	yield (%)[b]
			
1	**1b**: R^1 = OMe	**3ba**: R^1 = OMe	81
2	**1c**: R^1 = Me	**3ca**: R^1 = Me	79
3	**1d**: R^1 = OH	**3da**: R^1 = OH	76
4	**1e**: R^1 = H	**3ea**: R^1 = H	80
5	**1f**: R^1 = F	**3fa**: R^1 = F	62
6	**1g**: R^1 = Cl	**3ga**: R^1 = Cl	64
7	**1h**: R^1 = Br	**3ha**: R^1 = Br	69
8	**1i**: R^1 = COMe	**3ia**: R^1 = COMe	66
9	**1j**: R^1 = CO_2Me	**3ja**: R^1 = CO_2Me	71
10	**1k**: R^1 = NO_2	**3ka**: R^1 = NO_2	69
11			77
12			83

[a]Method A: **1b−e**, **1l**, and **1m** (100 mg) were treated with ethyl-2-butynoate (**2a**) (1.5 equiv), [{$RuCl_2$(*p*-cymene)}$_2$] (0.05 equiv), $AgSbF_6$ (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), [{$RuCl_2$(*p*-cymene)}$_2$] (0.05 equiv), and $AgSbF_6$ (0.20 equiv) in AcOH (3.0 mL) at 130 °C for 24 h. [b]Isolated yield.

heteroaromatic thiophene-2-acetamine (**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

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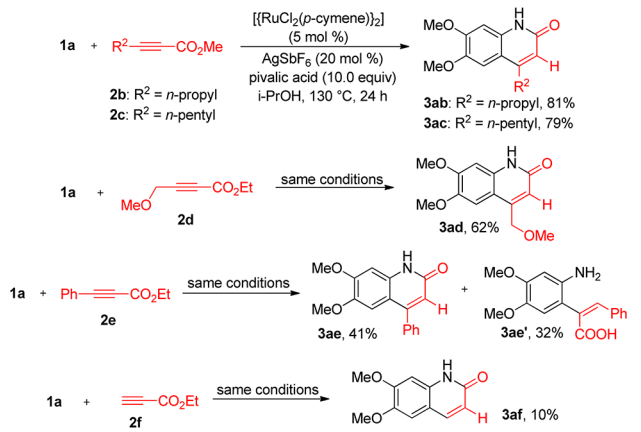
activity.[11] 2-Naphthyl acetamide (**1p**) also efficiently reacted with **2a**, providing quinolinone derivative **3pa** in 76% yield.

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

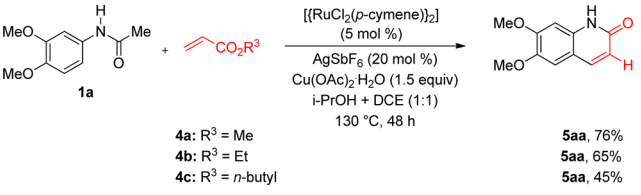
Scheme 3. Scope of Substituted Propiolates



(**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.

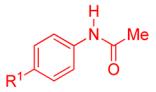
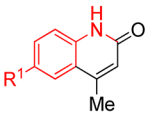
The alkyne cyclization reaction prompted us to explore the possibility of cyclization of anilides **1** with acrylates **4a–c**. Thus, we have tried the cyclization of **1a** with methyl acrylate (**4a**) under the optimized reaction conditions (Scheme 4). In the

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 $Cu(OAc)_2·H_2O$ to the reaction mixture instead of pivalic acid. It is important to note that $Cu(OAc)_2·H_2O$ 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 $ClCH_2CH_2Cl$ (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 $Cu(OAc)_2·H_2O$ 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 $[\{RuCl_2(p\text{-cymene})\}_2]$ (5.0 mol %), $AgSbF_6$ (20 mol %), and $Cu(OAc)_2·H_2O$ (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.

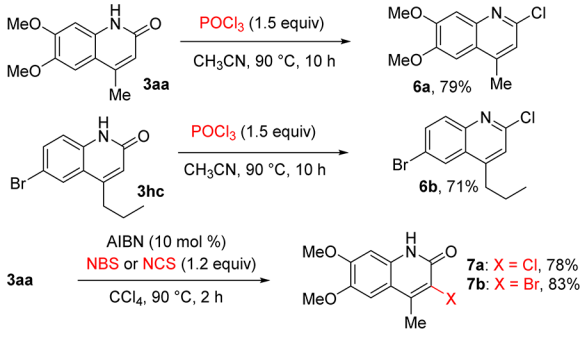
Table 2. Cyclization of Substituted Anilides 1 with Methyl Acrylate (4a)[a]

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

[a]All reactions were carried out using **1** (100 mg), **4a** (1.5 equiv), $[\{RuCl_2(p\text{-cymene})\}_2]$ (0.05 equiv), $AgSbF_6$ (0.20 equiv), and $Cu(OAc)_2·H_2O$ (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. [b]Isolated yield. [c]The 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 $[\{RuCl_2(p\text{-cymene})\}_2]$ 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**.

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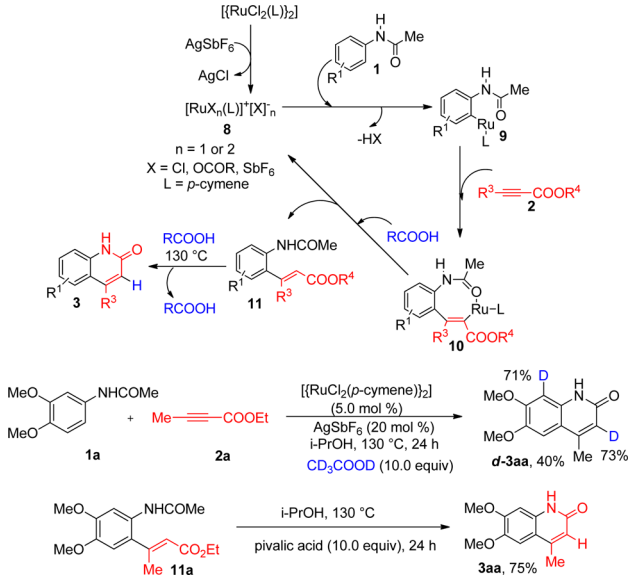
Scheme 6. Proposed Mechanism



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 deacylation 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 °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.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: mjeganmohan@iiserpune.ac.in.

Notes

The authors declare no competing financial interest.

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