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Synthesis of 4-quinolones via triflic anhydride-mediated intramolecular Houben-Hoesch reaction of β-arylamino acrylonitriles

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ABSTRACT

A facile and efficient synthesis of 4-quinolones was described via intramolecular Houben-Hoesch reaction of β-arylamino acrylonitriles mediated by triflic anhydride in *N*,*N*-dimethylformamide.

1. Introduction

The 4-quinolone ring makes up the core structure of numerous natural products and synthetic compounds along with diverse biological properties, such as antibacterial,[1] antitumor,[2] antimalarial,[3] *anti*-inflammatory,[4] calpain inhibitory,[5] *anti*-HIV-1 integrase,[6] and cannabinoid CB_2 receptor agonist activities.[7] In addition, functionalized 4-quinolones are used as molecular fluorescent probes,[8] ligands in coordination chemistry,[9] and building blocks for the synthesis of other heterocyclic systems.[10] The biological and synthetic importance of 4-quinolone derivatives have directed great research activity towards the construction of the skeleton of this kind of heterocycle. Conventional synthesis of 4-quinolones include the intramolecular Friedel–Crafts acylation of β-arylamino acrylates,[11] cyclocondensation of *N*-(2-acylaryl)amides,[12] and intramolecular nucleophilic aromatic substitution of 3-amino-1-(2-haloaryl)prop-2-en-1-one derivatives.[13] Other methods are reported by means of acid-promoted cyclization of phenacyl anthranilamides or anthranilates,[14] palladium-catalyzed inter-/intramolecular amination of alkenyl or alkynyl aryl ketones,[15] nickel-catalyzed decarboxylative carboamination of isatoic anhydrides with alkynes,[16] reductive cyclization of 2-nitroaryl vinyl ketones,[17] metal-free oxidative Mannich reaction of *N*-arylmethyl-2-aminophenylketones,[18] or the transformations of other functionalized heterocycles such as oxazolines, isoxazoles, and β-lactams.[19] However, some of these reported methods suffer from harsh reaction conditions, prolonged reaction times, tedious workup, and/or generation of acidic/metallic wastes. Therefore, to match the increasing scientific and practical demands, it is still of continued interest and great importance to explore simple and efficient synthetic approaches for the construction of 4-quinolones, especially those with wide applicability to achieve more elaborate and flexible substitution patterns.

On the other hand, the electrophilic substitution reaction of aromatic C–H bonds with intramolecular nitriles, known as Houben-Hoesch reaction,[20] represents a classical organic transformation for the synthesis of benzene-fused cyclic ketones, such as 1-tetralone,[21] thiochromone,[22] 9-acridinone.[23] However, this reaction is usually restricted to a narrow scope of substrates and generally requires strong acidic conditions. Therefore, the development of mild and efficient processes to overcome such drawbacks and extend the scope of Houben-Hoesch reaction is highly desirable. Recently, Kobayashi and co-workers reported a triflic anhydride (Tf_2O)-mediated intramolecular Houben-Hoesch cyclization of cyanoacetanilides to 3-formyl-4-hydroxyquinolin-2(1*H*)-ones under mild conditions.[24] As part of our on-going research directed to the development of methods for the synthesis of heterocycles,[25] we envisaged that an intramolecular Houben-

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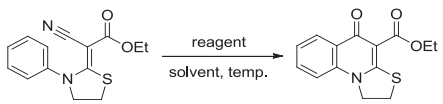
Hoesch reaction of β-arylamino acrylonitriles might be possible under appropriate conditions. Thus, the reactions of various β-arylamino acrylonitriles with Tf_2O were investigated. As a result of these studies, we developed a facile synthesis of 4-quinolones. Herein, we wish to report our experimental results and a proposed mechanism involved in the 4-quinolone synthesis.

2. Results and discussion

The substrates, α-cyano *N*-aryl ketene-*N*,*S*-acetals **1**, were prepared from commercially available methylene nitriles, aryl isothiocyanates, and alkyl bromides (1,2-dibromoethane, 1,3-dibromopropane, or ethyl bromide) in *N*,*N*-dimethylformamide (DMF) in the presence of K_2CO_3 in excellent yields according to the reported procedure.[26] We selected ethyl 2-cyano-2-(3-phenylthiazolidin-2-ylidene)acetate (**1a**) as the model compound to examine its behavior under different conditions (Table 1). Upon treatment of **1a** with 3.0 equiv of Tf_2O in DMF at room temperature for 24 h, the reaction could proceed and furnished a product, which was characterized as 4-quinolone **2a** along with recovery of some substrate **1a** (Table 1, entry 1). Increase of the reaction temperature, the reaction was accelerated, as could be seen by the shortened reaction time and higher yields of **2a** (Table 1, entries 2 and 3). Further increase of the reaction temperature to 100 °C would result in slightly lower yield of **2a** (Table 1, entry 4). The loaded amount of Tf_2O also had a significant influence on the reaction (Table 1, entries 5 and 6). It should be noted that no reaction was observed when dichloroethane (DCE), acetonitrile, or toluene was employed, which suggested that the nature of the solvents played a crucial role during the cyclization process. (Table 1, entries 7–9). Other anhydrides, such as trifluoroacetic anhydride (TFAA), thionyl chloride, and acetic anhydride were less effective than Tf_2O for the cyclization (Table 1, entries 10–12). The reaction could not take place as indicated by TLC analysis when **1a** was subjected to trifluoromethanesulfonic acid (TfOH), indicating that the cyclization reaction was not promoted by Brönsted acid (Table 1, entry 13).[27]

Under the conditions as for **2a** in entry 3 (Table 1), a series of reactions of α-cyano *N*-aryl ketene-*N*,*S*-acetals **1** with Tf_2O were carried out, and some of the results are summarized in Table 2. It was observed that the reactions of electron-rich *N*-aryl ketene-*N*,*S*-acetals **1b** and **1c** proceeded smoothly to afford the corresponding

Table 1
Optimization of the reaction conditions for the synthesis of 4-quinolones[a]

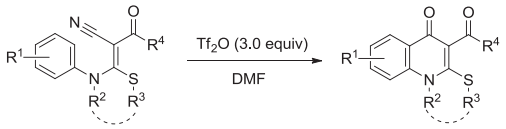


1a 2a

Entry	Reagent (equiv)	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	Tf_2O (3.0)	DMF	rt	24	28 (60)[c]
2	Tf_2O (3.0)	DMF	60	0.7	75
3	Tf_2O (3.0)	DMF	80	0.5	82
4	Tf_2O (3.0)	DMF	100	0.2	78
5	Tf_2O (3.5)	DMF	80	0.3	80
6	Tf_2O (2.5)	DMF	80	0.8	74
7	Tf_2O (3.0)	DCE	80	8	0 (92)[c]
8	Tf_2O (3.0)	CH_3CN	80	8	0 (91)[c]
9	Tf_2O (3.0)	Toluene	80	8	0 (94)[c]
10	TFAA (3.0)	DMF	80	8	57 (26)[c]
11	$SOCl_2$(3.0)	DMF	80	8	12 (76)[c]
12	Ac_2O (3.0)	DMF	80	8	8 (83)[c]
13	TfOH (6.0)	DMF	80	8	0 (90)[c]

[a] Reagents and conditions: **1a** (1.0 mmol), anhydrous solvent (2.0 mL).
[b] Isolated yields.
[c] Recovery of **1a** in parentheses.

Table 2
Synthesis of 4-quinolones **2** from *N*-aryl ketene-N,*S*-acetals **1**[a]



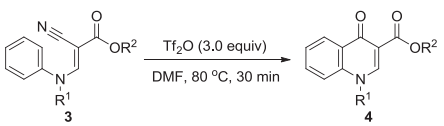
1 2

Entry	1	R^1	R^2–R^3	R^4	2	Yield (%)[b]
1	**1a**	H	$(CH_2)_2$	OEt	**2a**	82
2	**1b**	4-MeO	$(CH_2)_2$	OEt	**2b**	84
3	**1c**	4-Me	$(CH_2)_2$	OEt	**2c**	81
4[c]	**1d**	4-Cl	$(CH_2)_2$	OEt	**2d**	75
5[c]	**1e**	2-Cl	$(CH_2)_2$	OEt	**2e**	70
6[c]	**1f**	4-EtOCO	$(CH_2)_2$	OEt	**2f**	0 (90)[d]
7[c]	**1g**	4-CF_3	$(CH_2)_2$	OEt	**2g**	0 (93)[d]
8	**1h**	3-Me	$(CH_2)_2$	OEt	**2h/2h′**	76[e]
9	**1i**	H	H, Et	OEt	**2i**	0 (92)[d]
10	**1j**	H	$(CH_2)_3$	OEt	**2j**	68
11	**1k**	H	$(CH_2)_2$	OMe	**2k**	80
12	**1l**	H	$(CH_2)_2$	O^{i}Pr	**2l**	59
13	**1m**	H	$(CH_2)_2$	NEt_2	**2m**	56
14	**1n**	H	$(CH_2)_2$	Ph	**2n**	68

[a] Reagents and conditions: **1** (1.0 mmol), Tf_2O (3.0 mmol), DMF (anhydrous, 2 mL), 80 °C, 20–30 min.
[b] Isolated yields.
[c] The reaction was run at 100 °C.
[d] Recovery of the corresponding substrate in parentheses.
[e] The ratio of **2h** (8-Me) and **2h′** (6-Me) is 3:1.

4-quinolones **2b** and **2c** in good yields, respectively (Table 2, entries 2 and 3). For the electron-deficient substrates **1d** and **1e**, the cyclization required higher temperature (Table 2, entries 4 and 5). However, substrates **1f** and **1g** were proven to be inert under identical conditions, which may be due to the strong electron-withdrawing nature of the ester and trifluoromethyl groups (Table 2, entries 6 and 7). In the case of *N*-*m*-tolyl ketene-*N*,*S*-acetal **1h**, a pair of inseparable regioisomers of 4-quinolones **2h** and **2h′** with a ratio of 3:1 were formed, with the cyclization occurred preferentially at the less hindered position, as indicated by their NMR spectra (Table 2, entry 8). It should be noted that ketene-*N*,*S*-acetal **1i** could not undergo the cyclization under identical conditions, which might be attributed to the electronic and steric effects (Table 2, entry 9).[24] In the same fashion, the substrates **1j**–**n** bearing varied ester, amide or ketone substituents R^4 could be converted to the corresponding 4-quinolones **2j**–**n** in moderate to good yields (Table 2, entries 10–14).

The versatility of the 4-quinolone synthesis was next evaluated by subjecting β-phenylamino acrylonitriles **3**, prepared from cyanoacetic esters, triethyl orthoformate, and aniline according to the reported procedure,[28] to the optimal conditions. It was found that substrates **3a** and **3b** bearing a methyl substituent on the nitrogen atom were smoothly converted to the corresponding 4-quinolones **4a** and **4b** in 75% and 80% yields, respectively (Scheme 1). However, for acrylonitrile **3c** that bears no substitution on the nitrogen atom, the reaction afforded a complex mixture. These results further demonstrated the protection of the nitrogen atom is crucial to the cyclization reaction.



Scheme 1. Synthesis of 4-quinolones **4** from β-phenylamino acrylonitriles **3**.