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Catalyst-free concise synthesis of multi-functional 3-cyano-4-quinolinone derivatives from cyanoacetylenaminones and DMF-DMA

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ABSTRACT

An efficient one-pot synthesis of 3-cyano-4-quinolinone derivatives has been developed via the intramolecular cyclization of cyanoacetylenaminones **1** with *N,N*-dimethylformamide dimethyl acetal (DMF-DMA) **2** under catalyst-free conditions in CH_3CN. The reaction offers several advantages, including operational simpleness, easily available starting materials, target molecular diversity, and facile purification. Additionally, the 3-cyano substituted quinolinones may undergo further functionalization and assist in the discovery of novel drugs.

1. Introduction

Quinolinone is a structural motif often found in pharmaceutically relevant compounds and natural products.[1] One of the most biologically significant subfamilies of quinolinones is 4-quinolinone, whose derivatives show promise in anti-HIV,[2] antitumor,[3] antimicrobial,[4] antiviral,[5] and antimalarial research,[6] and also as cannabinoid type 2 receptor[7] and $S1P_1$ agonists.[8] As such, 4-quinolinone derivatives are promising drug candidates; Avelox, levofloxacin (Cravit), Norfloxacin, and ciprofloxacin (Ciproxan), for example, are used as antibacterial drugs (Fig. 1).[9] Due to the importance of quinolinone scaffolds in recent drug development, the synthesis and screening of 4-quinolinone based compounds for drug discovery has been of interest in medicinal chemistry.

Several methods have been developed for the synthesis of 4-quinolinones, including the Gould-Jacobs reaction,[10] Grohe-Heitzer reaction,[11] Gerster-Hayakawa syntheses,[12] 9-azajulolidine-catalyzed cyclization of *N,N*-diacyl-o-alkynoylaniline,[13] alumina-supported solid phase reaction,[14] and metal-catalyzed heterocycle formation.[15] However, harsh conditions are required for many of these procedures and they often result in moderate to low yields and poor functional group tolerance. Therefore, it is of great interest to develop alternative methods for the synthesis of such compounds.

Enaminones, which are versatile synthons for the construction of heterocyclic systems, have recently received great attentions.[16] Many heterocycles synthesized from enaminones have demonstrated promising biological activity.[17] Cyanoacetylenaminones, for example, which are enaminones with four reactive sites, can be synthesized by the regio-selective cyanoacylation reaction of β-enaminones with cyanoacetic acid. Cyanoacetylenaminones exhibit unique structural features with an active methylene and CN electrophilic center, and can be used in the creation of novel heterocycles.

Our work focuses on the development of new reactions for the development of diverse and highly substituted fused heterocycles from enaminones.[18] We recently reported a concise and efficient protocol for the synthesis of novel 2-amino-4-quinolinone derivatives from the intramolecular cyclization of

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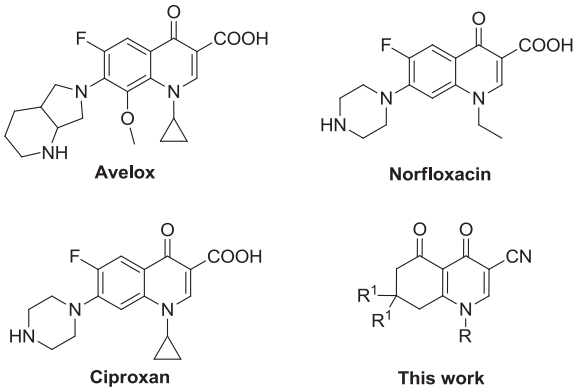


Fig. 1. Antimicrobial drugs with a 4-quinolinone skeleton.

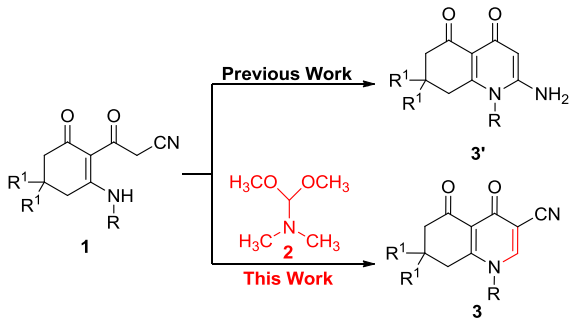
cyanoacetylenaminones. To further investigate the chemistry of cyanoacetylenaminones, herein we report an efficient protocol for the synthesis of 3-cyano-4-quinolinones via intramolecular cyclization of cyanoacetylenaminones with *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) under catalyst-free conditions (Scheme 1).

2. Result and discussion

Initial efforts were focused on reaction condition optimization by using cyanoacetylenaminones **1g** and DMF-DMA **2** as model substrates (Table 1). The screening began by evaluating the reaction without a catalyst in CH_3CN under room temperature or reflux conditions. The desired product **3g** was obtained in 71% and 65% yield, respectively (Table 1, entries 1–2). To further improve the yield, different catalysts (basic and acidic), *i.e.*, piperidine, Et_3N, HOAc, *p*-TSA, and *L*-Proline were employed. However, lower yields were obtained (Table 1, entries 3–7). Subsequently, this transformation was performed in several other solvents (Table 1, entries 8–12), and CH_3CN proved to be the most compatible. Additional screening studies to determine a more suitable alkylating agent revealed that triethoxymethane did not yield the expected product **3g** (Table 1, entries 13–14). Therefore, the optimal reaction conditions for the preparation of **3** are the following: catalyst-free, CH_3CN as the medium at room temperature, and DMF-DMA as the alkylating agent.

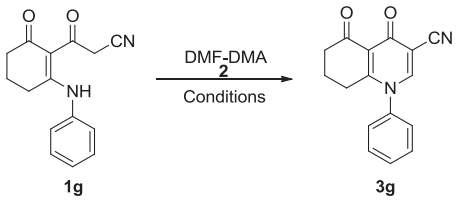
After establishing the optimal reaction conditions, the reaction was investigated using different starting materials. It was discovered that all reactions with various cyanoacetylenaminones proceeded well and yielded the corresponding compound **3** (Table 2).

First, cyanoacetylenaminones **1a**-**1k** were investigated. The results indicate that substituted cyanoacetylenaminones, both with electron with drawing (F, Cl, and Br) or electron-donating (Me, OMe) groups on the aromatic ring, generated the corresponding products in good to excellent yields. Additionally, it was observed that aromatic groups on substrates **1** with diverse substitution patterns (*para*, *ortho*, and *meta*) formed the target products **3** in good yields (Table 2, entries 1–11). The scope of the reaction was then extended by using 4,4-dimethyl cyanoacetylenaminones **1l**-**1y**, in which all reactions successfully gave the corresponding 4-quinolinone derivatives **3l**-**3y** (Table 2, entries 12–25). It is worthwhile noting that the 4,4-dimethyl cyanoacetylenaminones afforded higher yields than those without a substituent. Finally, *N*-alkyl cyanoacetylenaminone **1a′**-**1c′** were also employed. This reaction proceeded well, yielding the corresponding 4-quinolinone **3a′**-**3c′** (Table 2, entries 26–28).



Scheme 1. Comparison of previous and current protocols.

Table 1
Optimization of the reaction conditions.[a]



Entry	Solvent	Catalyst	*T* (°C)	*t* (h)	Yield (%)[b]
1	CH_3CN	–	r.t	1	71
2	CH_3CN	–	reflux	1	65
3	CH_3CN	Piperidine	r.t	1	43
4	CH_3CN	Et_3N	r.t	1	70
5	CH_3CN	HOAc	r.t	1	43
6	CH_3CN	*p*-TSA	r.t	3	38
7	CH_3CN	*L*-Proline	r.t	1	67
8	CH_3OH	–	r.t	1	67
9	CH_2Cl_2	–	r.t	1	61
10	1,4-Dioxane	–	r.t	1	Trace
11	EtOH	–	r.t	1	10
12	H_2O	–	r.t	3	N.R
13[c]	CH_3CN	–	r.t	1	N.R
14[c]	CH_3CN	–	reflux	1	N.R

[a] Reactions were carried out using **1g** (1.0 mmol), **2** (2.0 mmol), catalyst (0.2 mmol), and solvent (15 mL).
[b] Isolated yield based on cyanoacetylenaminone **1g**.
[c] DMF-DMA **2** was replaced by triethoxymethane.

For purification, all the precipitated products **3** required only washing and recrystallization rather than column chromatography. The chemical structures of the 4-quinolinones **3** were fully characterized by ^1H NMR, ^{13}C NMR, ^{19}F NMR, HRMS, and IR spectroscopy.

Scheme 2 depicts a proposed mechanism for this domino reaction based on our previous work and related literatures.[18] Cyanoacetylenaminone **1** reacts with *N*,*N*-dimethylformamide dimethyl acetal **2** to form intermediate **5**. Then, intermediate **5** undergoes an intramolecular Michael addition and loses a molecule of dimethylamine, leading to the 4-quinolinone derivatives **3**.

3. Conclusion

An efficient and convenient procedure for the synthesis of 3-cyano-4-quinolinone with different substitution patterns via the intramolecular cyclization of cyanoacetylenaminone with *N*,*N*-dimethylformamide dimethyl acetal under catalyst-free conditions was developed. The reaction offers several advantages, ranging from its environmental-friendliness, excellent target molecular diversity, and readily available starting materials. We therefore anticipate that this protocol will draw wide interest in the organic