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# α-Dimethylaminomethylenation-induced Houben–Hoesch-type cyclization of cyanoacetanilides: a practical synthesis of 3-formyl-4-hydroxyquinolin-2(1*H*)-ones

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ABSTRACT

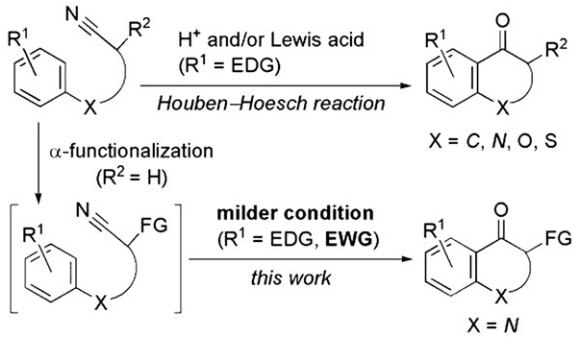
The tandem reaction of cyanoacetanilides with triflic anhydride in DMF proceeded at room temperature to afford 3-formyl-4-hydroxyquinolin-2(1*H*)-ones in good to high yields. A detailed mechanistic study revealed that the tandem reaction proceeded via α-dimethylaminomethylenation, which promoted the subsequent Houben–Hoesch-type cyclization. Both α-functionalization and the cyclization steps were optimized, and a multi-gram scale synthesis of 3-formyl-4-hydroxyquinolin-2(1*H*)-one was achieved.



## 1. Introduction

The intramolecular Houben–Hoesch reaction (electrophilic aromatic substitution reactions with nitriles[1]) provides benzene-fused cyclic ketones, such as 1-tetralone,[2] (thio)chromone,[3] and 4-quinolone[4] derivatives, which are key structural features of numerous pharmaceuticals and biologically active natural products (Scheme 1). However, aromatic C–H bond functionalization with nitriles[5] has attracted less attention because of the poor reactivity of nitriles.[6] Such reactions generally require strong acidic conditions as well as electron-rich aromatic substrates to achieve high product yields.[1–4] Therefore, the development of mild and efficient methods for achieving electrophilic aromatic substitution with intramolecular CN groups is highly desirable. We envisioned that functionalization of the cyclization precursor at the α-position of the CN group would be useful not only for increasing the reactivity of the CN groups but also for synthesizing functionalized cyclic ketones from simple precursors[4a,b] (Scheme 1).

In a preliminary communication[4b], we reported the reaction of cyanoacetanilide[7] (**1a**) under Vilsmeier conditions[8] (Eqs. 1–3). Although the reaction of **1a** with thionyl chloride or oxalyl chloride in DMF produced complex mixtures (Eq. 1), the combination of phosphoryl chloride with DMF gave the α-functionalized product **2a**,[9] albeit in low yields (Eq. 2). Interestingly, treatment of **1a** with triflic anhydride ($Tf_2O$) in DMF afforded the 3-formyl-4-hydroxyquinolin-2(1*H*)-ones **3a** in 84% yield (Eq. 3), where α-formylation and cyclization of **1a** occurred even at room temperature. These results prompted us to investigate the details of the tandem reaction of cyanoacetanilides **1**. In this article, we revealed that the α-dimethylaminomethylene substituent of the reaction intermediates **2**




**Scheme 1.** Synthetic Strategy for α-functionalized benzene-fused cyclic ketones.

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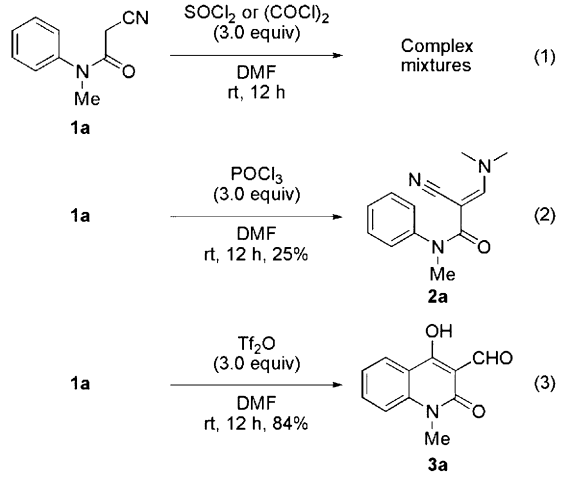
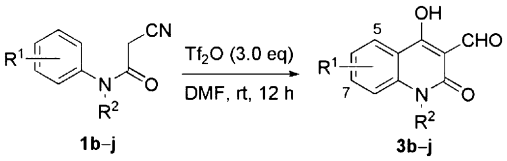
increased the reactivity of the CN groups, facilitating the subsequent intramolecular Houben–Hoesch-type reactions.

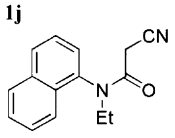
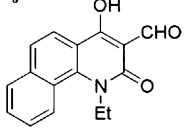



## 2. Results and discussion

We first examined the scope and limitations of the substrates available for the triflic anhydride-mediated tandem reaction (Table 1). The tandem reaction of cyanoacetanilides **1b** and **1c**, substituted at the *para* position with an electron-donating methyl or methoxy groups, occurred smoothly to afford the desired quinolinones **3b** and **3c** in 79% and 69% yields, respectively (entries 1 and 2). It was noteworthy that the tandem reactions successfully proceeded with arenes bearing electron-withdrawing substituents **1d**–**f** (entries 3–5). The halogenated products **3d** and **3e** could in principle be further functionalized by way of transition metal-catalyzed coupling reactions. Interestingly, the cyanoacetanilide **1g** afforded the regioisomers **3g** and **3g′** in a 79% combined yield upon cyclization primarily at the *ortho* position to the methyl group (35:65 ratio of *para* to *ortho*) (entry 6). The *ortho*-substituted cyanoacetanilides **1h** and **1i** were also effective in the tandem reactions (entries 7 and 8). Moreover, when this methodology was followed using cyanoacetanilide **1j**, a tricyclic compound (**3j**) was obtained in high yield (entry 9). Notably, the isolation of all products **3a**–**j** was easily accomplished by precipitation and filtration.

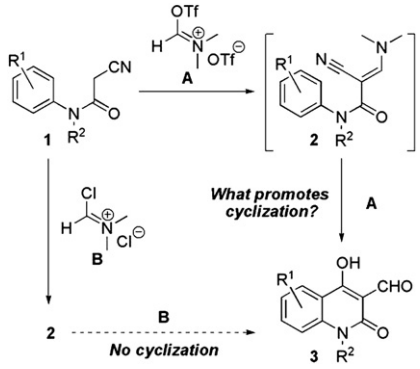
**Table 1**
$Tf_2O$-mediated tandem formylation/cyclization of cyanoacetanilides **1b**–**j**[a,b]




| Entry | **1** ($R^1$, $R^2$) | Products | Yield[c] (%) |
|---|---|---|---|
| 1 | **1b** (*p*-Me, Me) | **3b** | 79 |
| 2 | **1c** (*p*-OMe, Me) | **3c** | 69 |
| 3 | **1d** (*p*-Cl, Me) | **3d** | 80 |
| 4 | **1e** (*p*-Br, Me) | **3e** | 68 |
| 5 | **1f** (*p*-$CF_3$, Me) | **3f** | 61 |
| 6 | **1g** (*m*-Me, Me) | **3g** (5-Me)+**3g′** (7-Me) | 78[d] |
| 7 | **1h** (*o*-Me, Me) | **3h** | 80 |
| 8 | **1i** (*o*-OMe, Me) | **3i** | 69 |
| 9 | **1j**  | **3j**  | 82 |

[a] Unless otherwise stated, the reactions were carried out with 3.0 mmol of substrates in *N*,*N*-dimethylformamide (3.0 mL, 13 equiv).
[b] Tf=trifluoromethanesulfonyl.
[c] Isolated yields.
[d] The ratio between **3g** and **3g′** determined by $^1$H NMR experiment was 35:65.

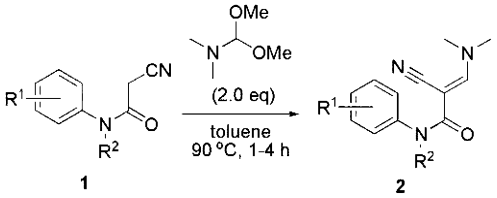
We next focused on the elucidation of the mechanism of the $Tf_2O$-mediated tandem reaction of **1**. The results shown in Eqs. 1–3 indicate that the tandem reaction proceeded via the acrylanilide **2** formed by the reaction of **1** with the Vilsmeier-type reagent **A** (Scheme 2). Although the Vilsmeier reagent **B** derived from $POCl_3$ also reacted with **1** to afford **2**, the cyclization product **3** was not observed at all. These differences intrigued us to explore the reactivity of **2** and to identify the factors that promote cyclization of **2**.




**Scheme 2.** Working hypothesis for the tandem reaction of **1**.

Using the cyanoacetanilides **1** with 2.0 equiv of *N*,*N*-dimethylformamide dimethylacetal (DMFDMA) in toluene, several acrylanilides **2** were synthesized in 62–93% yields (Table 2).

**Table 2**
Synthesis of 2-cyano-3-dimethylaminoacrylanilides **2**[a]



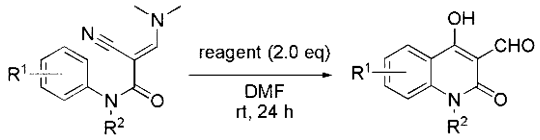

| Entry | **1** ($R^1$, $R^2$) | Products | Yield[b] (%) |
|---|---|---|---|
| 1 | **1a** (H, Me) | **2a** | 91 |
| 2[c] | **1a** | **2a** | 99 |
| 3 | **1b** (*p*-Me, Me) | **2b** | 85 |
| 4 | **1g** (*m*-Me, Me) | **2g** | 61 |
| 5 | **1h** (*o*-Me, Me) | **2h** | 76 |
| 6 | **1i** (*o*-OMe, Me) | **2i** | 93 |
| 7 | **1k** (H, PMB) | **2k** | 62 |
| 8 | **1l** (H, H) | **2l** | 83 |

[a] All reactions were carried out with 3.0 mmol of substrates in toluene.
[b] Isolated yields.
[c] Compound **1a** (80 mmol) was used.

We then investigated the reactivity of **2** toward various reagents (Table 3). Importantly, treatment of **2a** with $Tf_2O$ in DMF cleanly afforded **3a** in 88% yield (entry 1). This result strongly suggests that the tandem reaction of **1** proceeded via the acrylamide **2a** (Scheme 2). We found DMF was essential for the cyclization of **2a**[10] (entry 1 vs entry 2). As expected, the treatment of **2a** with $POCl_3$ did not afford **3a** at all[11] (entry 3). In addition, the Brönsted-acid-mediated Houben–Hoesch reaction was not included in the tandem reaction because **2a** did not react with TfOH, which was expected to be

formed in situ (entry 4). It is worth noting that trifluoroacetic anhydride (TFAA) facilitated the cyclization of **2a** to furnish the quinolone **3a** in 89% yield (entry 5), indicating that $Tf_2O$ was not necessarily required for the cyclization of **2a**. The TFAA-mediated Houben–Hoesch cyclization of **2** may provide a practical method for synthesizing **3** because TFAA is a much cheaper and safer regent than $Tf_2O$.[12] Thus, a large-scale reaction can be conducted easily and inexpensively (entry 6). We then applied TFAA-mediated reactions to several acrylanilides **2** (entries 7–12). To our delight, the TFAA-mediated Houben–Hoesch reactions of *para*- (entry 7), *meta*- (entry 8), and *ortho*-substituted acrylanilides (entries 9 and 10), as well as *N*-(4-methoxybenzyl)-acrylanilide (entry 11), proceeded smoothly to afford the corresponding quinolinones **3** in 70–95% yields. The annulation of the secondary acrylanilide **2l** did not occur (entry 12), most likely due to conformational constraints.[13]

**Table 3**
Investigation of the reactivity of **2**[a]




**2** **3**

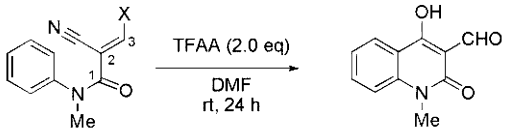
| Entry | **2** ($R^1$, $R^2$) | Reagent | Products | Yield[b] (%) |
|---|---|---|---|---|
| 1 | **2a** (H, Me) | $Tf_2O$ | **3a** | 88 |
| 2[c] | **2a** | $Tf_2O$ | **3a** | 0[d] |
| 3 | **2a** | $POCl_3$ | **3a** | 0[d] |
| 4 | **2a** | TfOH | **3a** | 0[d] |
| 5 | **2a** | TFAA | **3a** | 89 |
| 6[e] | **2a** | TFAA | **3a** | 88 |
| 7 | **2b** (*p*-Me, Me) | TFAA | **3b** | 91 |
| 8 | **2g** (*m*-Me, Me) | TFAA | **3g**+**3g′** | 86[f] |
| 9 | **2h** (*o*-Me, Me) | TFAA | **3h** | 83 |
| 10 | **2i** (*o*-OMe, Me) | TFAA | **3i** | 70 |
| 11 | **2k** (H, PMB) | TFAA | **3k** | 95 |
| 12 | **2l** (H, H) | TFAA | **3l** | 0[d] |

[a] Unless otherwise noted, all reactions were carried out with 1.0 mmol of substrates in DMF.
[b] Isolated yields.
[c] Dichloromethane was used as solvent instead of DMF.
[d] No reaction occurred.
[e] Compound **2a** (80 mmol) was used.
[f] The ratio between **3g** and **3g′** determined by $^1H$ NMR experiment was 35:65.

We finally investigated the factors that promoted the TFAA-mediated cyclization of **2**. We hypothesized that the α-dimethylaminomethylene substituents should play an important role in the cyclization of **2**, and we compared the reactivity of the 2-cyanoacrylanilides **2m**–**s** bearing different substituents (X) at the C3 position (Table 4). When the substituents (X) were *N*,*N*-dialkylamino groups, the TFAA-mediated reaction of **2m**–**p** proceeded smoothly to furnish **3a** in 55–84% yields (entries 1–4). In the case of **2q**, the nitrogen lone pair on the substituent (X) was delocalized into the aromatic ring, and **3a** was obtained in a relatively low yield (entry 5). Furthermore, the reactions of **2r** and **2s**, with weaker electron-donating groups,[14] did not produce the desired quinolone **3a** (entries 6 and 7). These results suggest that the electron-donating effects of the α-substituents facilitated the Houben–Hoesch-type cyclization of **2**.

Taking these results into consideration, a plausible mechanism for the reactions of **1** (and **2**) under the Vilsmeier conditions is shown in Scheme 3. Initially, the active methylene of **1** reacted with the Vilsmeier-type reagent **A** (or **B**) at the iminium carbon to generate the acrylanilides **2**. The mesomeric electron-donating effect[14] (+M) of the α-dimethylaminomethylene substituent of **2**

**Table 4**
The influence of α-substituents on Houben–Hoesch-type cyclization of **2**

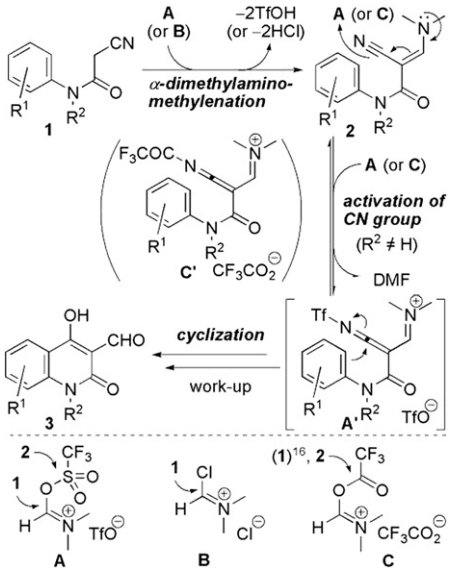



**2m–s** **3a**

| Entry | Substrates (X) | Yield[a] (%) |
|---|---|---|
| 1 | **2m** | 55 |
| 2[c] | **2n** | 84 |
| 3 | **2o** | 62 |
| 4 | **2p** | 64 |
| 5 | **2q** | 42 |
| 6 | **2r** | 0[b] |
| 7 | **2s** (–OEt) | 0[c] |

[a] Isolated yields.
[b] The reaction led to a complex mixture.
[c] Compound **2s** (56%) was recovered.

accelerated the reaction of the CN group with the electrophile **A** (or **C**[15,16]), activating the CN group by triflation (or trifluoroacetylation[16]). The Vilsmeier reagent **B**, however, could not activate the CN group in such a manner.[9,11] The activated CN groups of the intermediates **A′** (or **C′**[17]) would be subject to the subsequent electrophilic aromatic substitution to furnish the quinolinones **3** after aqueous work-up.




**Scheme 3.** A plausible mechanism.

## 3. Conclusions

We have identified the detailed mechanism of the $Tf_2O$-mediated tandem formylation/cyclization of the cyanoacetanilides **1**. The $Tf_2O$-derived reagent **A** played two different roles in the tandem reaction: (1) introduction of dimethylaminomethylene substituents into the active methylene of **1** and (2) electrophilic activation of the CN groups of **2**. The ability to activate the CN groups is a significantly different between the reagents **A** and **B**. We also revealed that the introduction of dimethylaminomethylene substituents into the α-position with respect to the CN groups greatly increased the reactivity of the CN groups. Moreover, we found that the relatively inexpensive and safe reagent **C** was effective for achieving the Houben–Hoesch-type cyclization of **2**. These findings have great potential to widen the scope of the chemistry of electrophilic aromatic substitution reactions with nitriles.

## 4. Experimental section

### 4.1. General information

TLC analysis of the reaction mixtures was performed using Merck silica gel 60 $F_{254}$ TLC plates. For column chromatography, Kanto silica gel 60 N (spherical, neutral, 100–210 μm) was used. The melting points were reported without correction. Unless otherwise noted, NMR spectra were recorded in $CDCl_3$ at the ambient temperature (27–35 °C). $^1H$ NMR (400 or 500 MHz) spectra were recorded using Bruker AV-400, JEOL JNM-ECP400, or JEOL JNM-ECP500 spectrometers, and chemical shifts were expressed in δ (ppm) relative to TMS (in $CDCl_3$) as the internal standard. $^{13}C$ NMR (100 or 125 MHz) spectra were referenced with respect to the residual $CHCl_3$ signals. $^1H$ NMR multiplicities were reported as follows: br=broad; m=multiplet; s=singlet; d=doublet; t=triplet; and q=quartet. IR spectra were recorded by using a Perkin–Elmer FT-IR system 2000 spectrophotometer and expressed by wavenumber ($cm^{-1}$). Mass spectra (MS) were obtained using JEOL JMS-700 instruments or a Bruker MicroTOF spectrometer fitted with an ESI.

### 4.2. Materials

Unless otherwise noted, all commercial materials were used without further purification. Solvents were purchased from Wako and Kanto Chemical Co., Inc. Trifluoromethanesulfonic anhydride ($Tf_2O$, in an ampoule) was purchased from Wako Chemical Co., Inc. The use of $Tf_2O$ from other suppliers (in glass bottles) gave poor results.

### 4.3. General procedure for the triflic anhydride-mediated reaction of cyanoacetanilides 1

To a solution of cyanoacetanilide **1** (3.0 mmol) in DMF (3.0 mL) was carefully added $Tf_2O$ (1.5 mL, 9.0 mmol) at 0 °C. The mixture was stirred at room temperature for 12 h, at which point TLC analysis indicated that the reaction was completed. The reaction mixture was then poured into ice-cold water (100 mL). The precipitate was collected by filtration and washed with water, EtOH, and ether. Recrystallization from EtOH gave pure **3**.

The mother and washing liquors were acidic. They were treated with solid $NaHCO_3$ prior to disposal.

*4.3.1. 4-Hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (**3a**).* Pale yellow needles; mp 176–178 °C (EtOH); $^1H$ NMR: δ 14.62 (br, 1H), 10.24 (s, 1H), 8.16 (dd, 1H, *J*=8.0, 1.6 Hz), 7.72 (ddd, 1H, *J*=8.8, 7.6, 1.6 Hz), 7.32 (d, 1H, *J*=8.8 Hz), 7.29 (dd, 1H, *J*=7.6, 8.0 Hz), 3.64 (s, 3H); $^{13}C$ NMR: δ 196.3, 171.7, 162.0, 142.7, 135.2, 125.9, 122.4, 114.7, 114.6, 106.1, 28.8; IR (KBr) 3428 (O–H), 1657 (C=O) $cm^{-1}$; HRMS (ESI-TOF) calcd for $C_{11}H_9NNaO_3$ ($[M+Na]^+$): 226.0475; found: 226.0474.

*4.3.2. 4-Hydroxy-1,6-dimethyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (**3b**).* Pale yellow solid; mp 167–169 °C (EtOH); $^1H$ NMR: δ 14.58 (br, 1H), 10.20 (s, 1H), 7.89 (s, 1H), 7.51 (d, 1H, *J*=8.4 Hz), 7.18 (d, 1H, *J*=8.4 Hz), 3.59 (s, 3H), 2.42 (s, 3H); $^{13}C$ NMR: δ 196.2, 171.4, 161.8, 140.7, 136.5, 132.2, 125.2, 114.52, 114.45, 106.1, 28.7, 20.5; IR (KBr) 3436 (O–H), 1641 (C=O) $cm^{-1}$; HRMS (ESI-TOF) calcd for $C_{12}H_{11}NNaO_3$ ($[M+Na]^+$): 240.0631; found: 240.0632.

*4.3.3. 4-Hydroxy-6-methoxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (**3c**).* Yellow needles; mp 183–185 °C (EtOH); $^1H$ NMR: δ 14.62 (br, 1H), 10.21 (s, 1H), 7.48 (d, 1H, *J*=2.8 Hz), 7.31 (dd, 1H, *J*=9.2, 2.8 Hz), 7.23 (d, 1H, *J*=9.2 Hz), 3.89 (s, 3H), 3.60 (s, 3H); $^{13}C$ NMR: δ 196.4, 170.9, 161.5, 154.9, 137.4, 124.8, 116.1, 115.1, 106.2, 106.0, 55.7, 28.8; IR (KBr) 3437 (O–H), 1645 (C=O) $cm^{-1}$; HRMS (ESI-TOF) calcd for $C_{12}H_{11}NNaO_4$ ($[M+Na]^+$): 256.0580; found: 256.0588.

*4.3.4. 6-Chloro-4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (**3d**).* Pale yellow solid; mp 177–179 °C (EtOH); $^1H$ NMR: δ 14.59 (br, 1H), 10.23 (s, 1H), 8.09 (d, 1H, *J*=2.8 Hz), 7.65 (dd, 1H, *J*=8.8, 2.4 Hz), 7.27 (d, 1H, *J*=8.8 Hz), 3.63 (s, 3H); $^{13}C$ NMR: δ 196.3, 170.4, 161.6, 141.0, 135.1, 128.3, 125.1, 116.2, 115.8, 106.4, 29.0; IR (KBr) 3435 (O–H), 1637 (C=O) $cm^{-1}$; HRMS (ESI-TOF) calcd for $C_{11}H_8ClNNaO_3$ ($[M+Na]^+$): 260.0085; found: 260.0087.

*4.3.5. 6-Bromo-4-hydroxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (**3e**).* Pale yellow solid; mp 194–197 °C (EtOH); $^1H$ NMR: δ 14.58 (br, 1H), 10.22 (s, 1H), 8.22 (d, 1H, *J*=2.0 Hz), 7.76 (dd, 1H, *J*=8.8, 2.4 Hz), 7.20 (d, 1H, *J*=9.2 Hz), 3.61 (s, 3H); $^{13}C$ NMR: δ 196.3, 170.3, 161.5, 141.4, 137.8, 128.1, 116.4, 116.1, 115.5, 106.4, 28.9; IR (KBr) 3447 (O–H), 1655 (C=O) $cm^{-1}$; HRMS (ESI-TOF) calcd for $C_{11}H_8BrNNaO_3$ ($[M+Na]^+$): 303.9580; found: 303.9586.

*4.3.6. 4-Hydroxy-1-methyl-2-oxo-6-(trifluoromethyl)-1,2-dihydroquinoline-3-carbaldehyde (**3f**).* Pale yellow solid; mp 125–128 °C (EtOH); $^1H$ NMR: δ 14.65 (br, 1H), 10.24 (s, 1H), 8.42 (s, 1H), 7.92 (dd, 1H, *J*=8.8, 2.0 Hz), 7.44 (d, 1H, *J*=8.8 Hz), 3.68 (s, 3H); $^{13}C$ NMR: δ 196.2, 170.9, 161.7, 144.4, 131.2 (q, *J*=3.0 Hz), 124.8 (q, *J*=33 Hz), 123.5 (q, *J*=4.0 Hz), 123.4 (q, *J*=270 Hz); 115.3, 114.5, 106.5, 29.1; IR (KBr) 3437 (O–H), 1660 (C=O) $cm^{-1}$; HRMS (ESI-TOF) calcd for $C_{12}H_7F_3NNa_2O_3$ ($[M-H+2Na]^+$): 316.0168; found: 316.0172.

*4.3.7. 4-Hydroxy-1,5-dimethyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (**3g′**).* From 3.00 mmol (565 mg) of **1g**, an inseparable mixture of **3g** and **3g′** (510 mg, 78%, **3g**/**3g′**=35/65) was obtained. $^1H$ NMR: δ 15.62 (br, 1H), 10.17 (s, 1H), 7.53 (dd, 1H, *J*=8.4, 7.6 Hz), 7.16 (d, 1H, *J*=8.8 Hz), 7.02 (d, 1H, *J*=7.6 Hz), 3.60 (s, 3H), 2.78 (s, 3H).

*4.3.8. 4-Hydroxy-1,7-dimethyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (**3g**).* $^1H$ NMR: δ 14.59 (br, 1H), 10.17 (s, 1H), 7.99 (d, 1H, *J*=8.4 Hz), 7.09–7.07 (m, 2H), 3.60 (s, 3H), 2.51 (s, 3H).

*4.3.9. 4-Hydroxy-1,8-dimethyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (**3h**).* Yellow needles; mp 137–140 °C (EtOH); $^1H$ NMR: δ 14.55 (br, 1H), 10.22 (s, 1H), 8.02 (dd, 1H, *J*=8.0, 1.2 Hz), 7.49 (dd, 1H, *J*=7.6, 0.8 Hz), 7.17 (dd, 1H, *J*=7.6, 7.6 Hz), 3.74 (s, 3H), 2.68 (s, 3H); $^{13}C$ NMR: δ 196.0, 171.9, 163.9, 144.1, 139.6, 125.7, 123.9, 122.8, 116.7, 105.7, 36.2, 23.7; IR (KBr) 3436 (O–H), 1645 (C=O) $cm^{-1}$; HRMS (ESI-TOF) calcd for $C_{12}H_{11}NNaO_3$ ($[M+Na]^+$): 240.0631; found: 240.0640.

*4.3.10. 4-Hydroxy-8-methoxy-1-methyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (**3i**).* Yellow solid; mp 155–157 °C (EtOH); $^1H$ NMR: δ14.50 (br, 1H), 10.24 (s, 1H), 7.76 (dd, 1H, *J*=4.8, 4.4 Hz), 7.19

(d, 2H, *J*=4.8 Hz), 3.91 (s, 3H), 3.86 (s, 3H); $^{13}$C NMR: $\delta$ 196.5, 171.2, 163.1, 148.6, 134.3, 123.0, 117.79, 117.78, 116.9, 106.1, 56.6, 34.7; IR (KBr) 3447 (O–H), 1650 (C=O) cm$^{-1}$; HRMS (ESI-TOF) calcd for $C_{12}H_{11}NNaO_4$ ([M+Na]$^+$): 256.0580; found: 256.0589.

*4.3.11. 1-Ethyl-4-hydroxy-2-oxo-1,2-dihydrobenzo[h]quinoline-3-carbaldehyde (**3j**).* Yellow needles; mp 137–139 °C (EtOH); $^1$H NMR: $\delta$ 14.42 (br, 1H), 10.24 (s, 1H), 8.36 (d, 1H, *J*=8.8 Hz), 7.97 (d, 1H, *J*=8.4 Hz), 7.87 (dd, 1H, *J*=8.4, 0.8 Hz), 7.65 (ddd, 1H, *J*=7.6, 7.2, 0.8 Hz), 7.58–7.54 (m, 2H), 4.45 (q, 2H, *J*=6.8 Hz), 1.72 (t, 3H, *J*=6.8 Hz); $^{13}$C NMR: $\delta$ 195.9, 171.2, 164.6, 144.2, 137.7, 129.2, 129.0, 125.79, 125.76, 124.0, 123.3, 119.8, 112.6, 106.0, 46.1, 15.3; IR (KBr) 3436 (O–H), 1649 (C=O) cm$^{-1}$; HRMS (ESI-TOF) calcd for $C_{16}H_{13}NNaO_3$ ([M+Na]$^+$): 290.0788; found: 290.0790.

### 4.4. General procedure for the synthesis of 2a–l

To a solution of cyanoacetanilide **1** (5.0 mmol) in toluene (15 mL) was added *N*,*N*-dimethylformamide dimethylacetal (1.32 mL, 10 mmol) at room temperature. The mixture was stirred at 90 °C for 1–4 h, when TLC indicated the reaction was completed. The reaction mixture was then concentrated in vacuo. The residue was collected by filtration and washed with ether (three times) to give pure **2**, which was used in the subsequent reaction without further purification.

*4.4.1. 2-Cyano-3-(dimethylamino)-N-methyl-N-phenylacrylamide (**2a**).* Colorless solid; mp 142–143 °C; $^1$H NMR: $\delta$ 7.74 (s, 1H), 7.39 (dd, 2H, *J*=7.6, 6.0 Hz), 7.29 (dd, 1H, *J*=7.6, 6.0 Hz), 7.22 (d, 2H, *J*=7.2 Hz), 3.35 (s, 3H), 3.17 (br, 6H); $^{13}$C NMR: $\delta$ 167.3, 158.2, 144.6, 129.3, 126.9, 126.8, 117.8, 73.1, 47.5, 39.3, 38.2; IR (thin film) 2189 (C≡N), 1652 (C=O) cm$^{-1}$; HRMS (ESI-TOF) calcd for $C_{13}H_{15}N_3NaO$ ([M+Na]$^+$): 252.1107; found: 252.1095.

*4.4.2. 2-Cyano-3-(dimethylamino)-N-methyl-N-p-tolylacrylamide (**2b**).* White solid; mp 158–160 °C; $^1$H NMR: $\delta$ 7.71 (s, 1H), 7.17 (d, 2H, *J*=6.6 Hz), 7.09 (d, 2H, *J*=6.6 Hz), 3.29 (s, 3H), 3.14 (br, 6H), 2.35 (s, 3H); $^{13}$C NMR: $\delta$ 167.3, 158.2, 142.1, 136.5, 130.0, 126.7, 117.9, 73.3, 47.5, 39.4, 38.2, 21.1; IR (thin film) 2187 (C≡N), 1652 (C=O) cm$^{-1}$; MS (EI$^+$) *m*/*z* (relative intensity) 243 (M$^+$, 25), 123 (100); HRMS (EI$^+$) calcd for $C_{14}H_{17}N_3O$ ([M]$^+$): 243.1372; found: 243.1373.

*4.4.3. 2-Cyano-3-(dimethylamino)-N-methyl-N-m-tolylacrylamide (**2g**).* Pale yellow solid; mp 99–101 °C; $^1$H NMR: $\delta$ 7.72 (s, 1H), 7.25 (dd, 1H, *J*=7.7, 7.7 Hz), 7.08 (d, 1H, *J*=7.3 Hz), 7.03–7.00 (m, 2H), 3.32 (s, 3H), 3.15 (br, 6H), 2.36 (s, 3H); $^{13}$C NMR: $\delta$ 167.3, 158.2, 144.6, 139.2, 129.1, 127.64, 127.61, 124.1, 117.9, 73.4, 47.5, 39.4, 38.2, 21.3; IR (thin film) 2194 (C≡N), 1652 (C=O) cm$^{-1}$; MS (EI$^+$) *m*/*z* (relative intensity) 243 (M$^+$, 31), 123 (100); HRMS (EI$^+$) calcd for $C_{14}H_{17}N_3O$ ([M]$^+$): 243.1372; found: 243.1371.

*4.4.4. 2-Cyano-3-(dimethylamino)-N-methyl-N-o-tolylacrylamide (**2h**).* Pale yellow solid; mp 135–138 °C; $^1$H NMR: $\delta$ 7.77 (s, 1H), 7.24–7.18 (m, 3H), 7.07 (d, 1H, *J*=6.2 Hz), 3.20 (s, 3H), 3.13 (br, 6H), 2.28 (s, 3H); $^{13}$C NMR: $\delta$ 167.3, 158.5, 143.0, 136.1, 131.1, 128.5, 128.1, 126.9, 117.3, 72.7, 47.6 (2C), 38.3, 17.8; IR (thin film) 2190 (C≡N), 1645 (C=O) cm$^{-1}$; MS (EI$^+$) *m*/*z* (relative intensity) 259 (M$^+$, 32), 123 (100); HRMS (EI$^+$) calcd for $C_{14}H_{17}N_3O_2$ ([M]$^+$): 259.1321; found: 259.1323.

*4.4.5. 2-Cyano-3-(dimethylamino)-N-(2-methoxyphenyl)-N-methylacrylamide (**2i**).* Pale yellow solid; mp 143–144 °C; $^1$H NMR: $\delta$ 7.72 (s, 1H), 7.32 (ddd, 1H, *J*=1.2, 7.3, 6.2 Hz), 7.11 (dd, 1H, *J*=1.5, 6.2 Hz), 6.96–6.94 (m, 2H), 3.87 (s, 3H), 3.22 (s, 3H), 3.14 (br, 6H); $^{13}$C NMR: $\delta$ 167.6, 158.3, 155.6, 132.9, 129.5, 129.2, 120.9, 117.7, 112.4, 73.1, 55.7, 47.4, 38.1, 37.8; IR (thin film) 2186 (C≡N), 1652 (C=O) cm$^{-1}$; MS (EI$^+$) *m*/*z* (relative intensity) 243 (M$^+$, 28), 123 (100); HRMS (EI$^+$) calcd for $C_{14}H_{17}N_3O$ ([M]$^+$): 243.1372; found: 243.1369.

*4.4.6. N-(4-Methoxybenzyl)-2-cyano-3-(dimethylamino)-N-phenylacrylamide (**2k**).* White powder; mp 104–105 °C; $^1$H NMR: $\delta$ 7.79 (br, 1H), 7.31 (dd, 2H, *J*=7.3, 7.3 Hz), 7.25 (dd, 1H, *J*=7.3, 6.9 Hz), 7.14 (d, 2H, *J*=8.3 Hz), 7.09 (d, 2H, *J*=7.3 Hz), 6.77 (d, 2H, *J*=7.8 Hz), 4.90 (s, 2H), 3.75 (s, 3H), 3.15 (br, 6H); $^{13}$C NMR: $\delta$ 167.8, 158.8, 158.7, 143.1, 130.1, 129.8, 129.2, 128.1, 127.1, 117.8, 113.7, 73.9, 55.2, 54.4, 47.7, 38.3; IR (thin film) 2191 (C≡N), 1645 (C=O) cm$^{-1}$; MS (EI$^+$) *m*/*z* (relative intensity) 335 (M$^+$, 43), 121 (100); HRMS (EI$^+$) calcd for $C_{20}H_{21}N_3O_2$ ([M]$^+$): 335.1634; found: 335.1634.

*4.4.7. Cyano-3-(dimethylamino)-N-phenylacrylamide (**2l**).* All spectral data agreed with the corresponding data in the literature; see Ref. 9a.

*4.4.8. 2-Cyano-N-methyl-N-phenyl-3-(pyrrolidin-1-yl)acrylamide (**2m**).* A mixture of acrylamide **2a** (687 mg, 3.0 mmol) and pyrrolidine (0.81 mL, 15 mmol) was stirred at room temperature for 2 h. The reaction mixture was then poured into ice-cold water (20 mL). The precipitate was collected by filtration, washed with water (three times), and *n*-hexane (three times), and dried under vacuum to give the title compound (470 mg, 61%), which was used in the subsequent reaction without further purification. White solid; mp 109–111 °C; $^1$H NMR: $\delta$ 7.94 (s, 1H), 7.39 (ddd, 2H, *J*=1.9, 8.3, 6.0 Hz), 7.29 (ddd, 1H, *J*=1.4, 7.3, 7.4 Hz), 7.23 (dd, 2H, *J*=8.7, 2.3 Hz), 3.69 (t, 2H, *J*=6.4 Hz), 3.57 (t, 2H, *J*=6.4 Hz), 3.34 (s, 3H), 1.96 (m, 2H), 1.86 (m, 2H); $^{13}$C NMR: $\delta$ 167.2, 154.9, 144.8, 129.3, 127.0, 126.8, 118.3, 73.7, 55.0, 47.7, 39.3, 25.8, 24.3; IR (thin film) 2190 (C≡N), 1652 (C=O) cm$^{-1}$; MS (EI$^+$) *m*/*z* (relative intensity) 255 (M$^+$, 22), 149 (100); HRMS (EI$^+$) calcd for $C_{15}H_{17}N_3O$ ([M]$^+$): 255.1372; found: 255.1370.

*4.4.9. 2-Cyano-N-methyl-N-phenyl-3-(piperidin-1-yl)acrylamide (**2n**).* A mixture of acrylamide **2a** (229 mg, 1.0 mmol) and piperidine (1.0 mL, 10 mmol) in DMF (2.0 mL) was stirred at 80 °C for 2 h. The reaction mixture was then poured into ice-cold water (50 mL). The precipitate was collected by filtration, washed with water (three times), and dried under vacuum to give the title compound (181 mg, 67%), which was used in the subsequent reaction without further purification. White solid; mp 106–108 °C; $^1$H NMR: $\delta$ 7.74 (s, 1H), 7.38 (dd, 2H, *J*=7.4, 8.3 Hz), 7.27 (dd, 1H, *J*=7.3, 7.4 Hz), 7.21 (d, 2H, *J*=8.3 Hz), 3.71 (br, 2H), 3.45 (br, 2H), 3.34 (s, 3H), 1.64 (br, 6H); $^{13}$C NMR: $\delta$ 167.7, 156.5, 144.8, 129.4, 127.1, 126.8, 118.0, 72.0, 57.6, 47.1, 39.4, 26.1, 23.7; IR (thin film) 2189 (C≡N), 1640 (C=O) cm$^{-1}$; MS (EI$^+$) *m*/*z* (relative intensity) 269 (M$^+$, 19), 163 (100); HRMS (EI$^+$) calcd for $C_{16}H_{19}N_3O$ ([M]$^+$): 269.1528; found: 269.1528.

*4.4.10. 2-Cyano-N-methyl-3-morpholino-N-phenylacrylamide (**2o**).* A mixture of acrylamide **2a** (459 mg, 2.0 mmol) and morpholine (1.75 mL, 20 mmol) in DMF (4.0 mL) was stirred at 80 °C for 2.5 h. The reaction mixture was then poured into ice-cold water (50 mL). The precipitate was collected by filtration, washed with water (three times), and dried under vacuum to give the title compound (228 mg, 42%), which was used in the subsequent reaction without further purification. White solid; mp 140–144 °C; $^1$H NMR: $\delta$ 7.74 (s, 1H), 7.39 (dd, 2H, *J*=7.8, 7.8 Hz), 7.29 (ddd, 1H, *J*=1.4, 7.3, 7.4 Hz), 7.21 (dd, 2H, *J*=8.7, 1.1 Hz), 3.69 (br, 7H), 3.34 (s, 3H), 3.16 (br, 1H); $^{13}$C NMR: $\delta$ 166.9, 156.7, 144.5, 129.5, 127.08, 127.05, 117.5, 73.6, 66.4, 47.5, 39.5, 38.3; IR (thin film) 2191 (C≡N), 1645 (C=O) cm$^{-1}$; MS (EI$^+$) *m*/*z* (relative intensity) 271 (M$^+$, 31), 165 (100); HRMS (EI$^+$) calcd for $C_{15}H_{17}N_3O_2$ ([M]$^+$): 271.1321; found: 271.1324.

*4.4.11. 3-(N-Benzyl-N-methylamino)-2-cyano-N-methyl-N-phenylacrylamide (**2p**).* A mixture of acrylamide **2a** (687 mg, 3.0 mmol) and benzylamine (1.64 mL, 15 mmol) was stirred at room temperature for

3 h. The reaction mixture was then poured into ice-cold water (20 mL). The precipitate was collected by filtration, washed with water (three times) and EtOH (three times), and dried under vacuum to give 3-(benzylamino)-2-cyano-*N*-methyl-*N*-phenylacrylamide **S-1** (699 mg, 80%), which was used in the subsequent reaction without further purification. To a stirred solution of the above-prepared **S-1** (291 mg, 1.0 mmol) in THF (5.0 mL) was added NaH (48.0 mg, 1.2 mmol, ca. 60% in mineral oil) at 0 °C and the reaction mixture was stirred at room temperature for 1 h. To this clear pale yellow solution was added MeI (0.13 mL, 2.0 mmol), and the reaction mixture was stirred for 2 h before being quenched with satd $NH_4Cl$. The product was extracted with EtOAc three times and the combined extracts were washed with water and brine, dried over $Na_2SO_4$, and evaporated to afford a crude oil, which was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/1) to give the title compound **2p** as a white solid (266 mg, 87%). Mp 118–121 °C; $^1$H NMR: $\delta$ 7.96 (br, 1H), 7.41–7.17 (m, 10H), 4.43 (br, 2H), 3.37 (s, 3H), 3.09 (s, 3H); $^{13}$C NMR: $\delta$ 167.2, 158.0, 144.7, 134.7, 129.3, 129.0, 128.4, 127.6, 126.9, 126.8, 117.6, 73.8, 64.0, 39.3, 36.3; IR (thin film) 2190 (C≡N), 1645 (C=O) cm$^{-1}$; MS (EI$^+$) *m*/*z* (relative intensity) 305 (M$^+$, 32), 91 (100); HRMS (EI$^+$) calcd for $C_{19}H_{19}N_3O$ ([M]$^+$): 305.1528; found: 305.1526.

*4.4.12. 3-[N-(4-Methoxyphenyl)-N-methylamino]-2-cyano-N-methyl-N-phenylacrylamide (**2q**).* A solution containing acrylamide **2a** (687 mg, 3.0 mmol) and *p*-anisidine (123 mg, 1.0 mmol) in toluene (3.0 mL) was stirred under reflux (oil bath temp 120 °C) for 6 days. The reaction mixture was directly purified by silica gel column chromatography (EtOAc/*n*-hexane=1/1) to give 3-(4-methoxyphenylamino)-2-cyano-*N*-methyl-*N*-phenylacrylamide **S-2** (210 mg, 68% based on *p*-anisidine). To a stirred solution of the above-prepared **S-2** (200 mg, 0.65 mmol) in THF (2.0 mL) was added NaH (39.0 mg, 1.2 mmol, ca. 60% in mineral oil) at 0 °C and the reaction mixture was stirred at room temperature for 1 h. To this clear pale yellow solution was added MeI (0.08 mL, 1.3 mmol), and the reaction mixture was stirred overnight before being quenched with satd $NH_4Cl$. The product was extracted with EtOAc three times and the combined extracts were washed with water and brine, dried over $Na_2SO_4$, and evaporated to afford a crude oil, which was purified by silica gel column chromatography (EtOAc/*n*-hexane=1/1) to give the title compound **2q** as a white solid (141 mg, 68%). Mp 102–104 °C; $^1$H NMR: $\delta$ 7.97 (s, 1H), 7.40 (dd, 2H, *J*=7.3, 7.8 Hz), 7.29 (dd, 1H, *J*=7.3, 7.4 Hz), 7.24 (d, 2H, *J*=7.3 Hz), 7.06 (d, 2H, *J*=8.7 Hz), 6.86 (d, 2H, *J*=9.2 Hz), 3.78 (s, 3H), 3.56 (s, 3H), 3.36 (s, 3H); $^{13}$C NMR: $\delta$ 166.8, 158.4, 156.4, 144.6, 140.2, 129.4, 127.0, 123.5, 116.9, 114.7, 77.0, 55.5, 39.4 (two carbon peaks were missing due to overlapping); IR (thin film) 2197 (C≡N), 1645 (C=O) cm$^{-1}$; MS (EI$^+$) *m*/*z* (relative intensity) 321 (M$^+$, 40), 215 (100); HRMS (EI$^+$) calcd for $C_{19}H_{19}N_3O_2$ ([M]$^+$): 321.1477; found: 321.1477.

*4.4.13. 2-Cyano-3-(1H-imidazol-1-yl)-N-methyl-N-phenylacrylamide (**2r**).* A mixture of acrylanilide **2s** (112 mg, 0.48 mmol) and imidazole (98.9 mg, 1.45 mmol) in toluene (3.0 mL) was stirred under reflux (oil bath temp 120 °C) for 6 h, and the mixture was directly purified by silica gel column chromatography (EtOAc/*n*-hexane=2/1) to obtain **2r** as a white solid (12.6 mg, 10%). Mp 170–175 °C (decomp.); $^1$H NMR: $\delta$ 8.31 (s, 1H), 7.93 (s, 1H), 7.79 (m, 1H), 7.48–7.40 (m, 3H), 7.26–7.23 (m, 2H), 7.16 (d, 1H, *J*=0.9 Hz), 3.45 (s, 3H); $^{13}$C NMR: $\delta$ 161.4, 143.9, 142.4, 139.6, 132.6, 130.1, 128.7, 127.3, 117.1, 113.2, 95.1, 39.5; IR (thin film) 2217 (C≡N), 1662 (C=O) cm$^{-1}$; MS (EI$^+$) *m*/*z* (relative intensity) 252 (M$^+$, 100); HRMS (EI$^+$) calcd for $C_{14}H_{12}N_4O$ ([M]$^+$): 252.1011; found: 252.1014.

*4.4.14. 2-Cyano-3-ethoxy-N-methyl-N-phenylacrylamide (**2s**).* A mixture of cyanoacetanilide **1a** (2.61 g, 15 mmol) and zinc chloride (204 mg, 1.5 mmol) in triethyl orthoformate (7.5 mL, 45 mmol) was heated at 130 °C for 10 h, and the mixture was directly purified by silica gel column chromatography (EtOAc/*n*-hexane=1/1) to obtain **2s** as a colorless solid (1.13 g, 33%). Mp 118–121 °C; $^1$H NMR: $\delta$ 7.98 (s, 1H), 7.42 (dd, 2H, *J*=6.9, 7.8 Hz), 7.36 (dd, 1H, *J*=7.4, 7.4 Hz), 7.21 (d, 2H, *J*=7.8 Hz), 4.23 (q, 2H, *J*=7.3 Hz), 3.36 (s, 3H), 1.36 (t, 3H, *J*=7.4 Hz); $^{13}$C NMR: $\delta$ 172.2, 162.5, 143.0, 129.8, 128.2, 127.4, 112.0, 89.1, 73.0, 38.9, 15.2; IR (thin film) 2210 (C≡N), 1645 (C=O) cm$^{-1}$; MS (EI$^+$) *m*/*z* (relative intensity) 230 (M$^+$, 100); HRMS (EI$^+$) calcd for $C_{13}H_{14}N_2O_2$ ([M]$^+$): 230.1055; found: 230.1058.

### 4.5. General procedure for the reaction of 2 with TFAA

To a solution of 2-cyano-3-(*N*,*N*-dimethylamino)acetanilide **2** (1.0 mmol) in DMF (3.0 mL) was added TFAA (0.28 mL, 2.0 mmol) at room temperature. The mixture was stirred at room temperature for 24 h, when TLC indicated the reaction was completed. The reaction mixture was then poured into ice-cold water (30 mL). The precipitate was collected by filtration and washed with water (three times). Recrystallization from $CHCl_3$/*n*-hexane gave pure **3**.

The mother and washing liquors were acidic. They were treated with solid $NaHCO_3$ prior to disposal.

*4.5.1. 1-(4-Methoxybenzyl)-1,2-dihydro-4-hydroxy-2-oxoquinoline-3-carbaldehyde (**3k**).* Pale orange solid; mp 203–209 °C ($CHCl_3$/*n*-hexane); $^1$H NMR: $\delta$ 14.73 (br, 1H), 10.31 (s, 1H), 8.17 (d, 1H, *J*=6.6 Hz), 7.57 (dd, 1H, *J*=8.2, 7.7 Hz), 7.27 (d, 1H, *J*=8.7 Hz), 7.22 (dd, 1H, *J*=7.7, 7.7 Hz), 7.18 (d, 2H, *J*=8.7 Hz), 6.84(d, 2H, *J*=8.7 Hz), 5.41 (s, 2H), 3.75 (s, 3H); $^{13}$C NMR: $\delta$ 196.4, 172.0, 162.3, 159.0, 142.3, 135.2, 128.1, 127.9, 126.0, 122.5, 115.6, 115.2, 114.4, 106.2, 55.3, 44.9; IR (KBr) 3437 (O–H), 1650 (C=O) cm$^{-1}$; MS (EI$^+$) *m*/*z* (relative intensity) 309 (M$^+$, 26), 121 (100); HRMS (EI$^+$) calcd for $C_{18}H_{15}NO_4$ ([M]$^+$): 309.1001; found: 309.1003.

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## Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2011.03.040. These data include MOL files and InChIKeys of the most important compounds described in this article.

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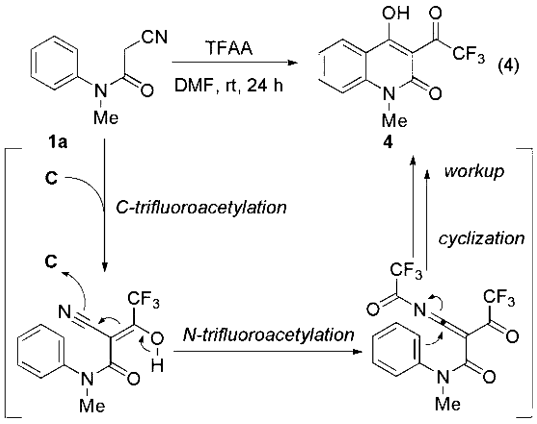
8. For reviews, see: (a) Jones, G.; Stanforth, S. P. The Vilsmeier Reaction of Fully Conjugated Carbocycles and Heterocycles In. *Organic Reactions*; Paquette, L. A., Ed.; John Wiley: New York, NY, 1997; Vol. 49, p 1; (b) Marson, C. M.; Giles, P. R. *Synthesis Using Vilsmeier Reagents*; CRC: Boca Raton, 1994; p 1; (c) Marson, C. M. *Tetrahedron* **1992**, *48*, 3659; (d) Jutz, C. Iminium Salts in Organic Chemistry In. *Advances in Organic Chemistry*; Taylor, E. C., Ed.; John Wiley: New York, NY, 1976; Vol. 9; Part I, p 225.
9. (a) Selvi, S.; Perumal, P. T. *Org. Prep. Proced. Int.* **2001**, *33*, 194; (b) Meth-Cohn, O.; Rhouati, S.; Tarnowski, B.; Robinson, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 1537.
10. This result suggests that the Vilsmeier-type reagent A would be a stronger electrophile than $Tf_2O$, see Scheme 3. However, in the presence of DMAP (13 equiv), $Tf_2O$-mediated reaction of **2** surprisingly did not proceed at all in $CH_2Cl_2$ (or even in pyridine).
11. It was reported that treatment of 2 (R1=EDG, R2=H) with POCl3 caused Meth–Cohn cyclization [18] to give 2-chloro-3-cyanoquinolines, see: Adams, D. R.; Adams, C. *Synth. Commun.* **1990**, *20*, 469 However, Houben–Hoesch-type cyclization of **2** has not been reported.
12. TFAA is ca. 9600 JPY/mol whereas $Tf_2O$ is ca. 57000 JPY/mol (Aldrich, 2010).
13. (a) Itai, A.; Toriumi, Y.; Tomioka, N.; Kagechika, H.; Azumaya, I.; Shudo, K. *Tetrahedron Lett.* **1989**, *30*, 6177; (b) Nanjan, M. J.; Kannappan, V.; Ganesan, R. *Indian J. Chem.* **1979**, *18B*, 461; (c) Pederson, B. F.; Pederson, B. *Tetrahedron Lett.* **1965**, *6*, 2995.
14. The electron-donating effects of the substituents (X) can be estimated by the comparison among the chemical shifts of the C2 (and CN carbon) atoms in the $^{13}C$ NMR spectra; the C2 atoms of **2a**–**q**, having stronger electron-donating substituents (X), were shielded (71.3–77.0 ppm) relative to those of **2r** and **2s** (95.0 and 89.1 ppm, respectively). The CN carbon atoms of **2a**–**q** were deshielded (116.9–119.7 ppm) than those of **2r** and **2s** (113.2 and 112.0 ppm, respectively)
15. Mekhalfia, A.; Mutter, R.; Heal, W.; Chen, B. *Tetrahedron* **2006**, *62*, 5617.
16. In contrast to the reaction of **1a** with $Tf_2O$ in DMF, the reaction of **1a** with TFAA in DMF afforded 4-hydroxy-3-trifluoroacetylquinolin-2(1*H*)-one **4** where the Vilsmeier-type reagent **C** not only trifluoroacetylated the active methylene of **1a** (*C*-trifluoroacetylation) but also activated the CN group by *N*-trifluoroacetylation[4a] (Eq. 4).




17. To detect the intermediate, such as, C′, we carried out the NMR experiments using piperidine-derived acrylamide with TFAA and DMF. However, we could not observe the cation species, such as C′ on the NMR time scale, see the Supplementary data.
18. (a) Meth-Cohn, O.; Narine, B.; Tarnowski, B. *Tetrahedron Lett.* **1979**, *20*, 3111; (b) Meth-Cohn, O.; Narine, B. *Tetrahedron Lett.* **1978**, *19*, 2045.