Synthetic Protocols Mutually Applicable to 4-Oxoquinolines and 4-Oxo-1,8-naphthyridines: Synthesis of 1-Aryl-2-substituted and 1-Aryl-3-fluoro-4-oxoquinolines and 4-Oxo-1,8-naphthyridines

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Received 5 October 2011

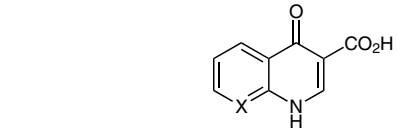
Abstract: We have achieved the synthesis of 1-aryl-2-substituted 4-oxoquinoline and 4-oxo-1,8-naphthyridine derivatives, which cannot be synthesized by known methods, via two useful synthons, 2-formyl-4-oxoquinoline and 2-methylsulfonyl-4-oxo-1,8-naphthyridine. We also succeeded in the synthesis of 1-aryl-3-fluoro-4-oxoquinoline by fluorocyclization of *N*-arylenaminone with Selectfluor® and potassium carbonate in DMF in a one-pot procedure. To the best of our knowledge, this is the first synthesis of 3-fluoro-4-oxoquinoline derivatives. We confirmed that these protocols were mutually applicable to the synthesis of 4-oxoquinoline and 4-oxo-1,8-naphthyridine derivatives.

Key words: antiviral agents, heterocycles, HIV, 4-oxoquinoline, 4-oxo-1,8-naphthyridine, fluorocyclization

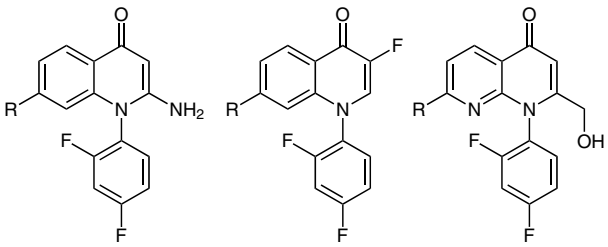
4-Oxoquinoline-3-carboxylic acid and 4-oxo-1,8-naphthyridine-3-carboxylic acid derivatives possess antimicrobial activities that reflect their ability to inhibit bacterial DNA-gyrase.[1] Furthermore, their decarboxylic acid compounds such as 4-oxoquinoline and 4-oxo-1,8-naphthyridine derivatives are abundant in many biologically active compounds that contain anticancer [2] or antiviral agents.[3] Recently, we have also found that 4-oxoquinoline and 4-oxo-1,8-naphthyridine derivatives possessed strong anti-HIV activity (Figure 1).[4]

Owing to their interesting pharmacological activities, many synthetic methods for 4-oxoquinoline and 4-oxo-1,8-naphthyridine derivatives have been documented.[1,5] Among these methods, a classical and commonly used approach is the condensation of an aniline with Meldrum's acid and trimethylorthoformate to afford the corresponding enamine, followed by cyclization under harsh reaction conditions.[6] Alternatively, Camps-type cyclization has been widely used because of its mild reaction conditions.[7] To date, many other synthetic methods for 4-oxoquinoline and 4-oxo-1,8-naphthyridine derivatives have been developed. Despite this variety, little is known about the synthesis of 1-aryl-2-substituted 4-oxoquinoline and 4-oxo-1,8-naphthyridine derivatives.[8] Several efforts have been made to introduce a polyfluoroalkyl group (e.g., a trifluoromethyl, difluoromethyl, or pentafluoroethyl group) on the C-2 position of 4-oxoquinolines.[9] Recently, Bernini and co-workers have reported a synthesis of 1,2-disubstituted 4-oxoquinolines via copper-catalyzed heterocyclization of 1-(2-bromophenyl)- or 1-(2-chlorophenyl)-2-en-3-amin-1-ones.[10] Zhao and Xu have also reported a palladium-catalyzed tandem amination reaction for the synthesis of 1,2-disubstituted 4-oxoquinolines.[11] Although these methods are effective, the reactions cannot be applied to a synthesis of 1-aryl-2-carboxyl-, amino-, hydroxyl-, hydroxymethyl-, aminomethyl-, cyano-, azido-, or methoxy-4-oxoquinoline and 4-oxo-1,8-naphthyridine derivatives. Here we report a synthesis of 1-aryl-2-substituted 4-oxoquinoline and 4-oxo-1,8-naphthyridine derivatives via two synthetically useful intermediates, 1-aryl-2-formyl-4-oxoquinoline **3**, which is produced by oxidizing 1-aryl-2-methyl-4-oxoquinoline **2** with selenium dioxide, and 1-aryl-2-methylsulfonyl-4-oxo-1,8-naphthyridine **10b**. We also report a synthesis of a novel 1-aryl-3-fluoro-4-oxoquinoline **15** via a fluorocyclization reaction.

Our strategy of synthesizing 1-aryl-2-substituted 4-oxoquinolines is shown in Scheme 1. We envisioned that 1-aryl-2-formyl-4-oxoquinoline **3**, which is useful for transformations into other substituents, would be prepared by oxidizing a methyl group of 1-aryl-2-methyl-4-oxoquinoline **2**. Quinolone **2** would readily be synthesized from 4-bromo-2-fluoroacetophenone (**1**).



4-oxoquinoline-3-carboxylic acid (X = CH)
4-oxo-1,8-naphthyridine-3-carboxylic acid (X = N)

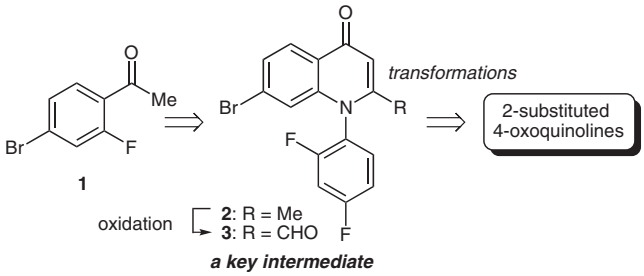


R = 3,5-dimethylisoxazol-4-yl

these 4-oxoquinoline and 4-oxo-1,8-naphthryidine derivatives show strong anti-HIV activity

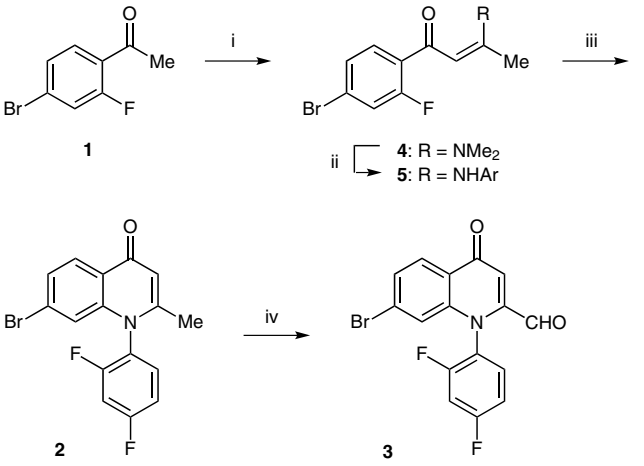
Figure 1 4-Oxoquinoline and 1,8-naphthyridin-4-one derivatives

SYNLETT 2012, 23, 448–452
Advanced online publication: 03.01.2012
DOI: 10.1055/s-0031-1290079; Art ID: U51611ST



Scheme 1 Synthetic strategy of 1-aryl-2-substituted 4-oxoquinolines via 1-aryl-2-formyl-4-oxoquinoline

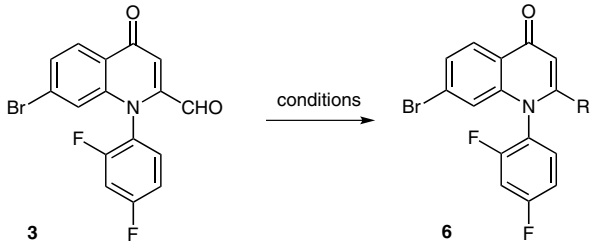
The synthesis of the key intermediate **3** is shown in Scheme 2. Our synthetic procedure commenced with treatment of acetophenone **1** with *N*,*N*-dimethylacetamide dimethylacetal (DMADA) under reflux to afford the *N*,*N*-dimethylenaminone **4** in 52% yield.[12] The enaminone **4** underwent substitution with 2,4-difluoroaniline in acetic acid at 50 °C to give *N*-arylenaminone **5** in 92% yield. Although the ^{1}H NMR spectrum of **5** in $CDCl_3$ indicated a single isomer, the geometry of the trisubstituted olefin could not be determined.[13] Cyclization of the *N*-arylenaminone **5** in the presence of potassium carbonate in dimethylsulfoxide (DMSO) at 90 °C afforded 1-aryl-2-methyl-4-oxoquinoline **2** in 98% yield. We examined the oxidation of a C-2 methyl group of **2** with a variety of oxidizing agents. We found that oxidation of the C-2 methyl group of **2** with selenium dioxide in 1,4-dioxane under reflux gave the best result of obtaining 1-aryl-2-formyl-4-oxoquinoline **3** in 60% yield.



Scheme 2 *Reagents and conditions*: (i) DMADA, reflux, 8 h, 52%; (ii) 2,4-difluoroaniline, AcOH, 50 °C, 3 h, 92%; (iii) K_2CO_3, DMSO, 90 °C, 1 h, 98%; (iv) SeO_2, 1,4-dioxane, reflux, 4 h, 60%.

With the requisite aldehyde **3** in hand, we then focused on further transformation of **3** into other functional groups (Table 1). Reduction of the aldehyde group in **3** with sodium triacetoxyborohydride in dichloromethane at room temperature afforded methylol **6a** in 90% yield (entry 1). Azidation of **6a** in the presence of diphenylphosphoryl azide (DPPA) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in 1,4-dioxane at room temperature, followed by reduction of the resulting azide group with Ph_3P in tetrahydrofuran (THF) and water at room temperature afforded 2-aminomethyl-4-oxoquinoline **6b** in 30% yield via two steps (entry 2). Reductive amination of the aldehyde **3** and dimethylamine with sodium triacetoxyborohydride in dichloromethane at room temperature gave 2-dimethylaminomethyl-4-oxoquinoline **6c** in 51% yield (entry 3). Horner–Wadsworth–Emmons reaction of **3** in the presence of ethyl diethylphosphonoacetate and sodium hydride in THF at 5 °C to room temperature provided the α,β-unsaturated ester **6d** in 58% yield (entry 4). Pinnick oxidation of **3** in the presence of sodium chlorite, sodium phosphate, and 2-methyl-2-butene in *tert*-butanol, THF and water afforded carboxylic acid **6e** in 87% yield (entry 5). Curtius rearrangement of the resulting **6e** with DPPA and triethylamine in *tert*-butanol at 85 °C provided carbamate, which was treated with trifluoroacetic acid (TFA) and ethanol at room temperature to afford 2-amino-4-oxoquinoline **6f** in 38% yield via two steps (entry 6). Although not explicitly shown in the scheme, a series of 1-aryl-2-substituted 4-oxo-1,8-naphthyridine derivatives could be prepared from 3-acetyl-2,6-dichloropyridine via the same synthetic protocol.

Table 1 Transformation of 2-Formyl-4-oxoquinoline **3**



Entry	Conditions[a]	R	Product	Yield (%)
1	i	CH_2OH	**6a**	90
2[b]	ii	CH_2NH_2	**6b**	30
3	iii	CH_2NMe_2	**6c**	51[c]
4	iv	$CH{=}CHCO_2Et$	**6d**	58
5	v	CO_2H	**6e**	87
6[b]	vi	NH_2	**6f**	38

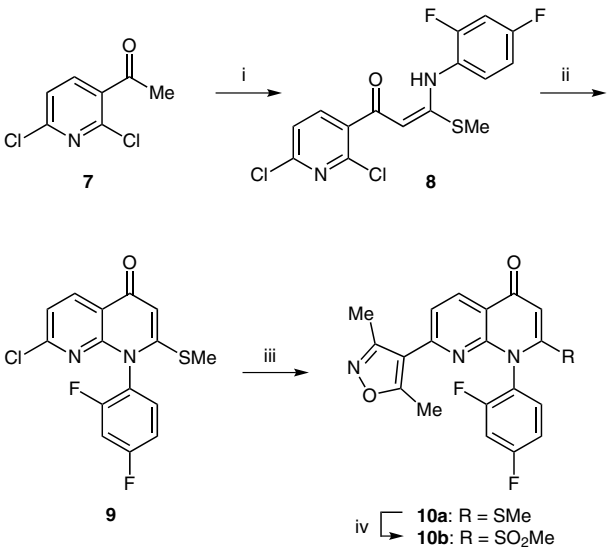
[a] *Reagents and conditions*: (i) **3**, $NaBH(OAc)_3$, CH_2Cl_2, r.t., 4 h; (ii) **6a**, DPPA, DBU, 1,4-dioxane, r.t., 6 h, then Ph_3P, THF–H_2O, r.t., 60.5 h; (iii) **3**, $NHMe_2$·HCl, Et_3N, $NaBH(OAc)_3$, CH_2Cl_2, r.t., 3 h; (iv) **3**, $(EtO)_2P(O)CH_2CO_2Et$, NaH, THF, 5 °C to r.t., 2 h; (v) **3**, $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, THF, H_2O, r.t., 3 h; (vi) **6e**, DPPA, Et_3N, *t*-BuOH, 85 °C, 5 h, then TFA, EtOH, r.t., 17.5 h.

[b] In entries 2 and 6, the product **6a** and **6e** were used as starting materials, respectively.

[c] Compound **6a** was obtained as a by-product in 35% yield.

As shown in Table 1, however, this synthetic method could not be applied to 1-aryl-4-oxoquinoline and 4-oxo-1,8-naphthyridine derivatives with a hydroxy, alkoxy, cyano, azido or alkyl group at the C-2 position. Therefore, we proposed an alternative synthetic route to these 2-sub-

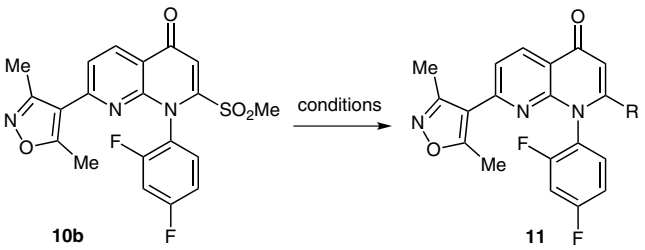
stituted compounds. Rudorf and co-workers have reported the synthesis of 1-phenyl-2-methylthio-4-oxoquinoline via ketene-*S*,*N*-acetal derived from phenylisothiocyanate and *o*-chloroacetophenone.[14] Although 1-aryl-2-methylthio-4-oxoquinoline derivatives could be synthesized by this method in moderate yield,[15] this method could be inapplicable to a synthesis of 1-aryl-2-methylthio-4-oxo-1,8-naphthyridine derivatives. We then attempted to improve their reaction conditions for a synthesis of 4-oxo-1,8-naphthyridine derivatives by changing the solvent, base, and reaction temperature. When 3-acetyl-2,6-dichloropyridine (**7**) was used as the starting material, the enolate formation was conducted with lithium diisopropylamide (LDA) as a base in THF at –40 °C. The enolate was reacted with a corresponding phenyl isothiocyanate at the same temperature and then the reaction was quenched with iodomethane at 5 °C to give ketene-*S*,*N*-acetal **8** in 35% yield. Cyclization of **8** with potassium phosphate in DMSO at 100 °C afforded 2-methylthio-4-oxo-1,8-naphthyridine **9** in 94% yield. Suzuki–Miyaura cross-coupling reaction of **9** and 3,5-dimethylisoxazole-4-boronic acid in the presence of palladium diacetate, 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl (S-Phos)[16] and triethylamine in 1,4-dioxane under reflux provided **10a** in 95% yield. The methylthio group in **10a** was readily oxidized to a methylsulfonyl group with *m*-chloroperbenzoic acid (MCPBA) in dichloromethane at room temperature in 59% yield (Scheme 3).



Scheme 3 *Reagents and conditions*: (i) LDA, THF, –40 °C, 30 min, then 2,4-difluorophenyl isothiocyanate, –40 °C to r.t., 1.5 h and MeI, 5 °C to r.t., 20 min, 35%; (ii) K_3PO_4, DMSO, 100 °C, 30 min, 94%; (iii) 3,5-dimethylisoxazole-4-boronic acid, Et_3N, S-Phos, $Pd(OAc)_2$, 1,4-dioxane, reflux, 5 h, 95%; (iv) MCPBA, CH_2Cl_2, r.t., 21 h, 59%.

Treatment of methylsulfonyl compound **10b** with various nucleophiles afforded 1-aryl-2-substituted 4-oxo-1,8-naphthyridine derivatives **11a–e** in moderate to high yields (Table 2).

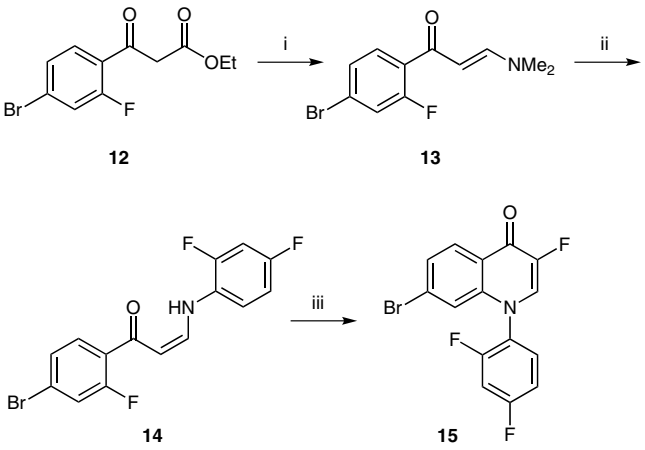
Table 2 Transformation of 2-Methylsulfonyl Compound **10b**



Entry	Conditions[a]	R	Product	Yield (%)
1	i	OMe	**11a**	98
2	ii	N_3	**11b**	87
3	iii	CN	**11c**	90
4	iv	OH	**11d**	96
5	v	Et	**11e**	64

[a] *Reagents and conditions*: (i) NaOMe, MeOH, r.t., 15 min; (ii) NaN_3, DMSO, THF, r.t., 4 h; (iii) KCN, DMSO, THF, r.t., 4 h; (iv) NaOH, H_2O, 1,4-dioxane, 50 °C, 30 min; (v) EtMgBr, THF, -60 °C to r.t., 2 h.

Additionally, we also have developed an efficient synthetic method for the preparation of novel 1-aryl-3-fluoro-4-oxoquinolines by fluorocyclization (Scheme 4). Treatment of β-keto ester **12** with hydrochloric acid in 1,4-dioxane under reflux, followed by reaction with *N*,*N*-dimethylformamide dimethylacetal (DMFDA) under reflux afforded *N*,*N*-dimethylenaminone **13** in 68% yield in two steps. Amine exchange reaction of the enaminone **13** with a corresponding aniline in acetic acid at 50 °C gave *N*-arylenaminone **14** in 92% yield, followed by fluorocyclization, a reaction in which both fluorination and cyclization occur in a one-pot procedure, of the resulting *N*-arylenaminone **14**. Fluorination of **14** in the presence of Selectfluor®[17] in *N*,*N*-dimethylformamide (DMF) at room temperature, followed by cyclization with potassium carbonate at 80 °C afforded 1-aryl-3-fluoro-4-oxoquinoline **15** in 38% yield in two steps.



Scheme 4 *Reagents and conditions*: (i) HCl, 1,4-dioxane, reflux, 3.5 h, then DMFDA, reflux, 2.5 h, 68%; (ii) 2,4-difluoroaniline, AcOH, 50 °C, 2 h, 92%; (iii) Selectfluor®, DMF, r.t., 1.5 h, then K_2CO_3, 80 °C, 30 min, 38%.

In summary, we have developed new synthetic methods for the preparation of 1-aryl-2-substituted 4-oxoquinoline and 4-oxo-1,8-naphthyridine derivatives via two key intermediates, 1-aryl-2-formyl-4-oxoquinoline prepared by oxidation of the C-2 methyl group in 1-aryl-2-methyl-4-oxoquinoline with selenium dioxide and 1-aryl-2-methylsulfonyl-4-oxo-1,8-naphthyridine prepared by improving Rudorf's method.[18,19] These intermediates were useful synthons for the modification at the C-2 functional group of 4-oxoquinolines and 4-oxo-1,8-naphthyridines. We transformed these useful synthons (**3** and **10b**) into other 1-aryl-2-substituted 4-oxoquinoline and 4-oxo-1,8-naphthyridine derivatives. We have also developed a method of synthesizing novel 1-aryl-3-fluoro-4-oxoquinoline derivatives by fluorocyclization of *N*-arylenaminone **14** with Selectfluor® and potassium carbonate in DMF in a one-pot procedure.[20] These synthetic methods could be applied to both 4-oxoquinoline and 4-oxo-1,8-naphthyridine derivatives.

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(4) (a) These three compounds having a substituent on the C-2 or C-3 position in Figure 1 exhibited potent anti-HIV activity in the nanomolar range (IC_{50} = 0.23–9.2 nM). (b) An anti-HIV activity was evaluated using MaRBLE cells obtained by transfection of HPB-Ma derived from human T-lymphocytes with a luciferase gene and a CCR5 gene etc. of which expressions were regulated by HIV-1 LTR. (c) For more details, see: Oonishi, Y.; Awasaguchi, K.; Nomura, N.; Todo, K.; Kawai, H.; Wakatsuki, T. Int. Patent Appl., WO2011090095, **2011**. (d) Chiba-Mizutani, T.; Miura, H.; Matsuda, M.; Matsuda, Z.; Yokomaku, Y.; Miyauchi, K.; Nishizawa, M.; Yamamoto, N.; Sugiura, W. *J. Clin. Microbiol.* **2007**, *45*, 447.

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(13) **Analytical and Spectral Data of *N*-Arylenaminone 5**: pink solid; mp 112–113 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (dd, *J* = 8.3, 8.0 Hz, 1 H), 7.36 (dd, *J* = 8.3, 1.7 Hz, 1 H), 7.29 (dd, *J* = 10.4, 1.7 Hz, 1 H), 7.22 (ddd, *J* = 8.8, 8.5, 5.8 Hz, 1 H), 6.88–6.98 (m, 2 H), 5.89 (d, *J* = 2.2 Hz, 1 H), 2.02 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 184.6 (d, *J* = 4.1 Hz), 163.8, 161.1 (dd, *J* = 249.6, 10.8 Hz), 160.1 (d, *J* = 256.2 Hz), 157.0 (dd, *J* = 250.4, 12.4 Hz), 131.7 (d, *J* = 3.3 Hz), 128.5 (d, *J* = 9.1 Hz), 127.7 (d, *J* = 3.3 Hz), 127.2 (d, *J* = 13.2 Hz), 125.1 (d, *J* = 9.9 Hz), 122.6 (dd, *J* = 13.2, 4.1 Hz), 119.8 (d, *J* = 27.2 Hz), 111.6 (dd, *J* = 22.3, 4.1 Hz), 104.9 (dd, *J* = 26.0, 24.4 Hz), 98.6 (d, *J* = 10.7 Hz), 19.8 (d, *J* = 2.5 Hz). IR (neat): 1590, 1568, 1541, 1433, 1395, 1318, 1304, 1283, 1094, 882, 857, 778 cm^{-1}. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{16}H_{12}BrF_3NO$: 370.00544; found: 370.00546.

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(18) **General Procedure for the Synthesis of Aldehyde 3**: To a solution of 1-aryl-2-methyl-4-oxoquinoline **2** (1.58 g, 4.51 mmol) in 1,4-dioxane (18 mL) was added selenium dioxide (0.53 g, 4.51 mmol) at r.t. The mixture was heated under reflux for 4 h. The solvent was concentrated in vacuo, then the residue was diluted with EtOAc and the suspension was filtered. The filtrate was washed with sodium thiosulfate solution and brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was subjected to silica gel column chromatography (hexane–EtOAc, 2:1 → 1:1, gradient) to afford aldehyde **3** (0.99 g, 60% yield) as a pale yellow solid. **Analytical and Spectral Data of Aldehyde 3**: pale yellow solid; mp 195–196 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 9.64 (s, 1 H), 8.16 (d, *J* = 8.5 Hz, 1 H), 7.75 (ddd, *J* = 8.9, 8.9, 6.0 Hz, 1 H), 7.68 (dd, *J* = 8.5, 1.7 Hz, 1 H), 7.64–7.72 (m, 1 H), 7.36–7.42 (m, 1 H), 7.01 (br s, 1 H), 6.97 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.4, 177.3, 163.0 (dd, *J* = 250.0, 12.0 Hz), 158.3 (dd, *J* = 250.9, 13.6 Hz), 143.9, 142.7, 132.2 (d, *J* = 10.7 Hz), 128.2, 127.9, 127.8, 125.2, 121.1 (dd, *J* = 13.2, 4.1 Hz), 119.4, 118.5, 113.3 (dd, *J* = 22.3, 3.3 Hz), 105.7 (dd, *J* = 26.9, 23.6 Hz).

IR (neat): 1702, 1631, 1595, 1512, 1448, 1271, 1149, 1008, 972, 947, 856, 830 cm^{-1}. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{16}H_9BrF_2NO_2$: 363.97847; found: 363.97898.

(19) **General Procedure for the Synthesis of Ketene-*S*,*N*-acetal 8**: To a solution of 3-acetyl-2,6-dichloropyridine (**7**) in THF (26 mL) was added lithium diisopropylamide (2.0 M, 3.0 mL, 6.05 mmol) dropwise at –40 °C under nitrogen atmosphere. After stirring at –40 °C for 30 min, to the mixture was added a solution of 2,6-difluorophenyl isothiocyanate (2.08 g, 12.1 mmol) in THF (11 mL). The mixture was gradually warmed up to r.t. while stirring for 1.5 h. After stirring, the mixture was cooled in an ice bath. To the mixture was added iodomethane (0.75 mL, 12.1 mmol) at 5 °C and the mixture was warmed up to r.t. while stirring for 20 min. The reaction was quenched with sat. NH_4Cl solution at 5 °C and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was subjected to silica gel column chromatography (hexane–EtOAc, 20:1 → 10:1, gradient) to afford ketene-*S*,*N*-acetal **8** (0.66 g, 35% yield) as a pale yellow solid. **Analytical and Spectral Data of Ketene-*S*,*N*-acetal 8**: pale yellow solid; mp 164–165 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.78 (br s, 1 H), 7.91 (d, *J* = 8.1 Hz, 1 H), 7.41 (ddd, *J* = 8.7, 8.7, 5.9 Hz, 1 H), 7.35 (d, *J* = 8.1 Hz, 1 H), 6.90–7.00 (m, 2 H), 5.70 (s, 1 H), 2.41 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 183.6, 170.5, 161.7 (dd, *J* = 250.4, 10.8 Hz), 157.3 (dd, *J* = 252.5, 12.8 Hz), 150.5, 146.7, 141.0, 135.6, 129.4 (d, *J* = 10.7 Hz), 123.1, 121.8 (dd, *J* = 12.4, 4.1 Hz), 111.5 (dd, *J* = 22.3, 4.1 Hz), 105.0 (dd, *J* = 26.5, 24.0 Hz), 92.9, 14.7. IR (neat): 1575, 1512, 1468, 1411, 1260, 1143, 1045, 966, 846, 730 cm^{-1}. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{15}H_{11}Cl_2F_2N_2OS$: 374.99372; found: 374.99405.

(20) **General Procedure for the Synthesis of 1-Aryl-3-fluoro-4-oxoquinoline 15**: To a solution of *N*-arylenaminone **14** (100 mg, 0.28 mmol) in DMF (2.8 mL) was added Selectfluor® (149 mg, 0.42 mmol) at r.t. The mixture was stirred for 30 min at the same temperature. To the mixture was added K_2CO_3 (116 mg, 0.84 mmol) and the mixture was heated to 80 °C. After stirring for 30 min at 80 °C, the mixture was cooled and diluted with EtOAc and H_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated in vacuo. The residue was subjected to silica gel column chromatography (hexane–EtOAc, 3:1) to afford 1-aryl-3-fluoro-4-oxoquinoline **15** (38 mg, 38% yield) as a pale yellow solid. **Analytical and Spectral Data of 1-Aryl-3-fluoro-4-oxoquinoline 15**: pale yellow solid; mp 197–198 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.66 (d, *J* = 8.3 Hz, 1 H), 8.24 (d, *J* = 8.6 Hz, 1 H), 7.89 (ddd, *J* = 8.8, 8.8, 5.9 Hz, 1 H), 7.69–7.76 (m, 1 H), 7.64 (dd, *J* = 8.6, 1.6 Hz, 1 H), 7.40–7.46 (m, 1 H), 7.17 (s, 1 H). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.8 (d, *J* = 14.9 Hz), 162.9 (dd, *J* = 249.6, 11.6 Hz), 157.7 (dd, *J* = 252.5, 13.6 Hz), 146.6 (d, *J* = 238.0 Hz), 140.6, 132.0 (d, *J* = 28.9 Hz), 131.7 (d, *J* = 3.3 Hz), 127.8 (d, *J* = 4.1 Hz), 127.2, 126.6, 125.4 (d, *J* = 9.9 Hz), 123.5 (dd, *J* = 12.8, 3.7 Hz), 119.1, 113.4 (dd, *J* = 22.7, 3.7 Hz), 106.0 (dd, *J* = 27.3, 23.1 Hz). IR (neat): 1624, 1587, 1509, 1328, 1217, 1193, 1143, 1101, 968, 926, 853, 834, 772 cm^{-1}. HRMS (DART): *m/z* $[M + H]^+$ calcd for $C_{15}H_8BrF_3NO$: 353.97414; found: 353.97405.

