KCN-Catalyzed C–C Bond Formation between Imine and *gem*-Difluoroalkene Moieties: A Facile Synthesis of 2,4-Disubstituted 3-Fluoroquinolines

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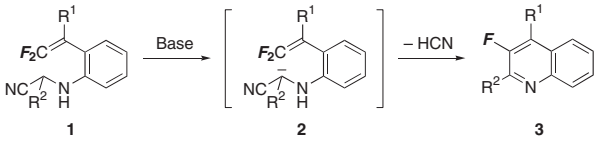
Intramolecular cyclization of β,β-difluoro-*o*-methyleneaminostyrenes leading to 3-fluoroquinolines is efficiently promoted by a catalytic amount of KCN and a small excess of K_2CO_3. The reaction proceeds via (i) the generation of intramolecular carbon nucleophiles from imine moieties and (ii) the cyclization by their substitution for the vinylic fluorine.

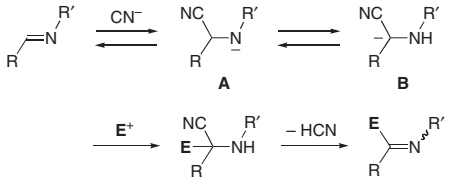
Recently, we have reported a synthetic method for 3-fluoroquinolines based on the unique reactivity of *gem*-difluoroalkenes toward nucleophilic substitution of their vinylic fluorine via addition–elimination processes (Scheme 1).[1,2] *o*-Cyanomethylamino-β,β-difluorostyrenes **1** are treated with a base (LiTMP or NaH) to generate the corresponding carbanions **2**, which in turn readily undergo intramolecular replacement of the fluorine to afford 2,4-disubstituted 3-fluoroquinolines **3**.



Scheme 1. 3-Fluoroquinoline synthesis from *o*-cyanomethylamino-β,β-difluorostyrenes **1**.

This reaction required (i) a strong base such as LiTMP or NaH for the generation of carbanions **2** and (ii) a stoichiometric amount of KCN for the preparation of the starting materials **1** from the corresponding *o*-aminostyrenes and aldehydes via the Strecker reaction. In order to overcome these drawbacks, we considered a benzoin-type condensation of imines where the carbanions like **2** would be generated by a catalytic amount of cyanide ion without using a strong base. As shown in Scheme 2, addition of CN^- to imines generates nitrogen anions **A**, followed by proton transfer to provide carbon nucleophiles **B**. The reaction of thus generated carbanions **B** with electrophiles accompanying elimination of HCN allows the imino carbon to act as a nucleophile, which is in a sharp contrast to the usual role of imine as an electrophile. Although this sequence has potential use for carbon–carbon bond formation, self-condensation has limited its further applications.[3] On the basis of these considerations, β,β-difluorostyrenes **4** bearing an imine moiety were designed as starting materials. We sought to trap the in situ generated carbanions effectively with the intramolecular *gem*-difluoroalkene moiety and therefore avoid self-condensation.

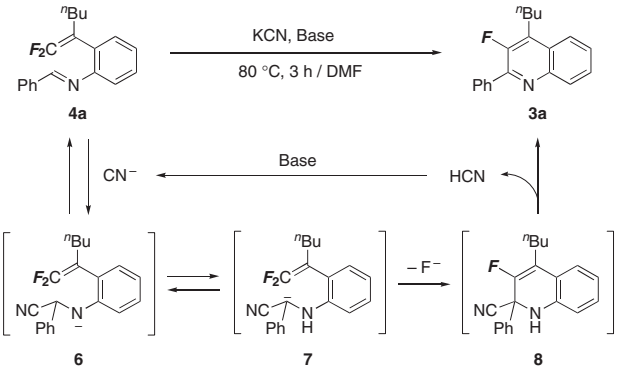
Herein, we wish to report 3-fluoroquinoline synthesis via cyanide-ion catalyzed intramolecular substitution of **4**.[4–6] 3-Fluoroquinolines have been reported to exhibit notable biological activities with potential medicinal and agricultural use.[7] Moreover, their significant potential as intermediates has also been disclosed.[8] In spite of their great utility, only a limited number of methods have been reported for fluoroquinoline synthesis.[4,9] Thus, new synthetic methods for 3-fluoroquinolines are desired to open an entry into the various applications.



Scheme 2. Benzoin-type condensation of imines.

The starting materials, *o*-methyleneamino-substituted β,β-difluorostyrenes **4** were easily prepared via the one-pot synthesis of β,β-difluorostyrene derivatives that we have previously reported,[10] followed by imine formation. *o*-Amino-β,β-difluorostyrenes **5**[4b] were reacted with aldehydes to give the desired compounds **4**.

Table 1. Synthesis of 2,4-disubstituted 3-fluoroquinoline **3a**



Entry	KCN/mol %	Base/110 mol %	Yield of **3a**/%
1[a]	110	—	86
2[b]	20	DBU	32
3[b]	20	NaH	20
4	20	K_2CO_3	85

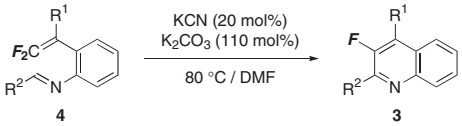
[a] 18-Crown-6 (30 mol %) was added.
[b] Substrate **4a** was recovered in 33% (Entry 2) or 11% (Entry 3) yield.

We first attempted the generation of intramolecular carbon nucleophiles in difluorostyrenes **4** by using an equimolar amount of CN^-. When **4a** was treated with 110 mol % of KCN and 30 mol % of 18-crown-6 in DMF, the expected 3-fluoroisoquinoline **3a** was obtained in 86% yield (Table 1, Entry 1). This reaction proceeded via (i) the generation of carbanion **7** by the attack of CN^- on the imino carbon and a prototropic shift, (ii) the subsequent cyclization to intermediate **8**, and (iii) aromatization involving elimination of HCN leading to 3-fluoroquinoline **3a**. We expected that CN^- could be regenerated from HCN by adding a

base to complete a catalytic cycle. The cyclization of **4a** with a catalytic amount (20 mol %) of KCN was examined in the presence of several bases (110 mol %). While DBU or NaH gave 3-fluoroquinoline **3a** only in 32% or 20% yield (Entries 2 and 3), K_2CO_3 successfully promoted the desired catalytic cycle to afford **3a** in 85% yield (Entry 4).[11]

Under the reaction conditions obtained above, we examined the cyclization of several other substrates. 2,4-Disubstituted 3-fluoroquinolines **3a–3j** were successfully synthesized on treatment of difluorostyrenes **4a–4j** with 20 mol % of KCN and 110 mol % of K_2CO_3 (Table 2). The scope of this reaction was extended to substrates **4c–4h** bearing aryl groups with electron-donating groups (Entries 3–6) and electron-withdrawing groups (Entries 7 and 8). In addition, substrates **4i** and **4j** bearing carbonyl groups at the imino carbon were also applicable to this KCN-catalyzed cyclization (Entries 9 and 10).

Table 2. Synthesis of 2,4-disubstituted 3-fluoroquinolines **3**



4 **3**

Entry	R^1	R^2	**4**	Time/h	Yield/%
1	*n*-Bu	Ph	**4a**	3	85 (**3a**)
2	*sec*-Bu	Ph	**4b**	2	64 (**3b**)
3	*n*-Bu	*p*-$MeOC_6H_4$	**4c**	1.5	79 (**3c**)
4	*n*-Bu	*m*-$MeOC_6H_4$	**4d**	5	69 (**3d**)
5	*n*-Bu	*p*-MeC_6H_4	**4e**	2	79 (**3e**)
6	*n*-Bu	*o*-MeC_6H_4	**4f**	14	58 (**3f**)
7	*n*-Bu	*p*-$CF_3C_6H_4$	**4g**	2.5	77 (**3g**)
8	*n*-Bu	*p*-BrC_6H_4	**4h**	4	81 (**3h**)
9	*n*-Bu	PhCO	**4i**[a]	2	46 (**3i**)[b]
10	*n*-Bu	EtO_2C	**4j**[a]	2	44 (**3j**)[b]

[a]Substrates **4i** and **4j** were prepared from the corresponding aniline **5** and phenylglyoxal hydrate (130 mol %) or ethyl glyoxylate (150 mol %) in refluxing benzene (2 h, 80% or 85% ^{19}F NMR yield), respectively, and used without purification. [b]Yield based on aniline **5**.

In conclusion, we have accomplished the efficient construction of ring-fluorinated quinoline frameworks via intramolecular cyclization of *o*-methyleneamino-substituted β,β-difluorostyrenes. The reaction sequence includes (i) the generation of the intramolecular carbon nucleophiles from imine moieties and (ii) the cyclization by their substitution for the vinylic fluorine. Moreover, this process is effected under KCN catalysis in the presence of K_2CO_3, which represents a quite rare example of benzoin-type condensation of imines, carbon–carbon bond formation at the imino carbon with electrophiles.[3,12]

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11 4-Butyl-3-fluoro-2-phenylquinoline (**3a**): To a solution of *o*-benzylideneamino-α-butyl-β,β-difluorostyrene (**4a**) (93 mg, 0.31 mmol) in DMF (3 mL) was added KCN (4.0 mg, 0.062 mmol) and K_2CO_3 (47 mg, 0.34 mmol) under argon. After the reaction mixture was heated at 80 °C for 3 h, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted three times each with 30 mL of EtOAc. The combined extracts were washed with brine (40 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–EtOAc, 5:1) to give **3a** (74 mg, 85%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 0.98 (3H, t, $J = 7.6$ Hz), 1.49 (2H, tq, $J = 7.6$, 7.6 Hz), 1.67–1.76 (2H, m), 3.14 (2H, td $J = 7.6$ Hz, $J_{HF} = 1.9$ Hz), 7.49–7.57 (4H, m), 7.63–7.67 (1H, m), 7.96 (1H, d, $J = 8.2$ Hz), 8.02–8.06 (2H, m), 8.16 (1H, d, $J = 8.2$ Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 13.8, 22.8, 24.7 (d, $J_{CF} = 4$ Hz), 31.9, 123.3 (d, $J_{CF} = 5$ Hz), 126.8, 127.8 (d, $J_{CF} = 3$ Hz), 128.1, 128.4, 129.3, 129.4, 130.8, 132.6 (d, $J_{CF} = 15$ Hz), 136.2 (d, $J_{CF} = 5$ Hz), 145.2 (d, $J_{CF} = 3$ Hz), 148.6 (d, $J_{CF} = 17$ Hz), 152.9 (d, $J_{CF} = 256$ Hz). ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$) δ_F 32.4 (1F, s). IR (neat) 2958, 2929, 2871, 1603, 1458, 1406, 1381, 1362, 1192, 760 cm^{-1}. HRMS calcd for $C_{19}H_{18}NF$ 279.1423 (M^+); found 279.1385.
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