A Facile Synthesis of 2,4-Disubstituted 3-Fluoroquinolines via Intramolecular Cyclization of *o*-Cyanomethylamino-β,β-difluorostyrenes

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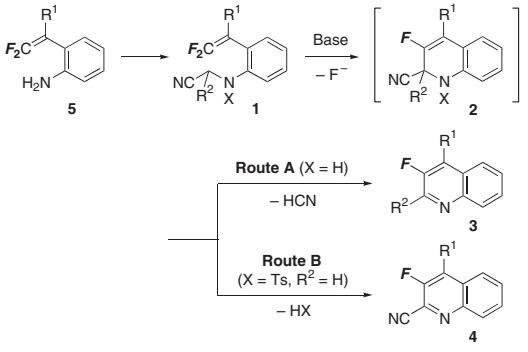
o-Cyanomethylamino-β,β-difluorostyrenes are treated with base (LiTMP, NaH, or K_2CO_3) to generate the corresponding carbanions, which in turn readily undergo intramolecular replacement of the vinylic fluorine and subsequent elimination to afford 2,4-disubstituted 3-fluoroquinolines in good yield.

Quinolines are widespread in the alkaloid family and constitute an important class of compounds in medicinal and agricultural chemistry, and also in material science.[1] Since the incorporation of fluorine into organic molecules has come into wide use as a means of modifying their biological activities and physical properties, fluorine-containing quinoline derivatives have been attracting considerable attention.[2,3] 3-Fluorinated quinolines have been reported to exhibit notable biological activities, and especially to be noted is their apparent lack of genotoxicity that is often observed in quinolines, which would allow their medicinal and agricultural use.[4] In spite of the significant potential of ring-fluorinated quinoline frameworks both as components and intermediates,[5] so far their synthetic methods have been quite limited.[6,7]

In our recent publications, we have reported the construction of six-membered ring-fluorinated heterocyclic compounds, such as isochromenes, isothiochromenes, isoquinolines, and quinolines.[8] β,β-Difluorostyrene derivatives bearing sp^3-*O*, sp^3-*S*, sp^2-*N*, and sp^2-*C* nucleophiles undergo intramolecular substitution of the fluorine in a 6-*endo-trig* fashion, leading to heterocycle formation.[9] The reactions are promoted by the unique reactivity of *gem*-difluoroalkenes toward nucleophilic vinylic substitution (S_NV) via addition–elimination processes.[10]



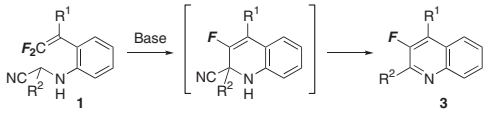
Scheme 1. Synthetic strategy for 3-fluoroquinolines.

In order to synthesize 3-fluoroquinolines bearing substituents and functional groups, the "intramolecular substitution" concept was applied to *o*-cyanomethylamino-β,β-difluorostyrenes **1**, where CN would function as a leaving group as well as a transformable group. Herein we wish to report a facile synthesis of 3-fluoroquinolines by cyclization of **1** via carbanions generated by deprotonation of the cyanomethyl groups[11] and subsequent aromatization of intermediates **2** that can be conducted in two ways (Scheme 1); (i) elimination of HCN leading to 3-fluoroquinolines **3** (Route A; X = H), or (ii) elimination of HX leading to 2-cyano-3-fluoroquinolines **4** (Route B; X = Ts, R^2 = H).[12]

The starting materials were easily prepared via the one-pot synthesis of *o*-amino-β,β-difluorostyrenes **5** (**5a**: R^1= *n*-Bu, **5b**: R^1 = *s*-Bu)[9] starting from 2,2,2-trifluoroethyl *p*-toluenesulfonate and *o*-iodoaniline,[13] followed by known transformations. The Strecker reaction of **5** with aldehydes gave the substrates **1a–e** suitable for Route A. Substrates **1f**, **g** for Route B bearing a *p*-toluenesulfonyl group (Ts) on the nitrogen were obtained by tosylation of **5** and subsequent cyanomethylation with bromoacetonitrile.

We then attempted the cyclization of difluorostyrenes **1** obtained above under basic conditions. The reaction of **1a** with NaH (6 molar amounts), LDA (3 molar amounts), or lithium hexamethyldisilazide (LiHMDS, 6 molar amounts) in THF was unsuccessful and gave **5a** instead, probably through the loss of HCN and successive hydrolysis of the resulting imine (vide infra). After many trials, we found that treatment with 6 molar amounts of lithium tetramethylpiperidide (LiTMP) in THF surprisingly promoted the expected intramolecular substitution even at −78 °C to afford 3-fluoroquinoline **3a** in 64% yield (Table 1, Entry 1).[14]

Table 1. Synthesis of 2,4-disubsutituted 3-fluoroquinolines **3a–e**



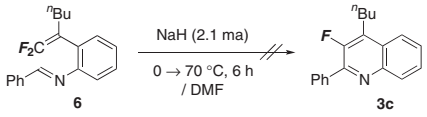
Entry	R^1	R^2	**1**	Base (ma)[a]	Solv.	Conditions	Yield%[b]
1	*n*-Bu	H	**1a**	LiTMP (6.0)	THF	−78 °C, 1 h	64 (**3a**)
2	*s*-Bu	H	**1b**	LiTMP (6.0)	THF	−78 °C, 1 h	56 (**3b**)
3	*n*-Bu	Ph	**1c**	NaH (2.1)	DMF	0 °C, 1.5 h	81 (**3c**)
4	*n*-Bu	2-Furyl	**1d**	NaH (2.1)	DMF	r.t., 1.5 h	81 (**3d**)
5	*n*-Bu	1-*c*-C_6H_9	**1e**	NaH (2.1)	DMF	70 °C, 0.5 h	27 (**3e**)

[a]ma: molar amount. [b]Isolated yields.

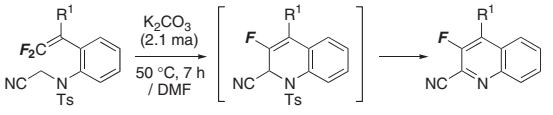
As further examples of the reaction, difluorostyrenes **1b**, **c** were subjected to similar conditions. On their treatment with 6 molar amounts of LiTMP, **1b** afforded the expected product **3b** (Table 1, Entry 2), whereas **1c** gave a complex mixture of products. Screening of base and reaction conditions was conducted again for **1c** to reveal the following fact. When **1c** was treated with 2.1 molar amounts of NaH in DMF, the intramolecular replacement by the in situ generated carbon nucleophile suc-

cessfully proceeded to give **3c** in 81% yield (Entry 3). Substrates **1d**, **e** bearing a heteroaryl or an alkenyl group as R^2 also underwent the cyclization under the latter conditions (Entries 4 and 5).

There was one more plausible reaction pathway other than substitution–elimination process (path I depicted in Table 1), namely an HCN-elimination–6π-electrocyclization–HF-elimination process (path II). In order to elucidate the reaction mechanism, we prepared imine **6** from aminostyrene **5a** and benzaldehyde and then subjected **6** to the conditions employed above. The corresponding 3-fluoroquinoline **3c** was not observed in this reaction, which ruled out the possibility of path II, a 6π-electrocyclization process. Consequently, the cyclization of **1** proceeds through vinylic substitution of fluorine, followed by elimination of HCN (path I, Table 1).



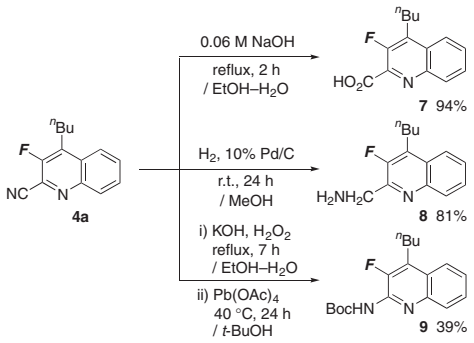
We next attempted the cyclization of difluorostyrene **1f** to provide 3-fluoroquinoline **4a** bearing a cyano group, which is a versatile substituent that can be readily converted into other functional groups. We tried to keep the cyano group during the cyclization and aromatization to allow the synthesis of functionalized 3-fluoroquinolines. A tosyl group in **1f** was introduced on the nitrogen atom to function as a leaving group instead of the cyano group.[12] Treatment of **1f** under similar conditions for **1c**–**e** promoted intramolecular cyclization and successive elimination of *p*-toluenesulfinic acid to give the desired cyanoquinoline **4a**. When **1f**, **g** were treated with 2.1 molar amounts of K_2CO_3 in DMF at 50 °C, the two processes proceeded smoothly to afford **4a**, **b** in better yield.



1f R^1 = *n*-Bu
1g R^1 = *s*-Bu
(ma: molar amount)
4a R^1 = *n*-Bu: 85%
4b R^1 = *s*-Bu: 79%

After having obtained **4**, we examined their transformation into 2-functionalized 3-fluoroquinolines **7**–**9** having a carboxy, an aminomethyl, or an amino group. On treatment of **4a** with aqueous NaOH, hydrolysis of the cyano group selectively occurred without the loss of fluorine to afford 2-quinolinecarboxylic acid **7** in excellent yield. Hydrogenation of **4a** in methanol over palladium on activated carbon successfully reduced the cyano group to give fluoroquinoline **8** bearing an aminomethyl group at the 2-position in 81% yield. Moreover, hydrolysis of the cyano group followed by the Hofmann rearrangement of the corresponding amide led to Boc-protected 2-amino-3-fluoroquinoline **9** in 39% yield. Functionalized 3-fluoroquinolines **7**–**9** are attractive compounds as building blocks because their carboxy and amino groups allow to introduce the fluoroquinoline moiety into organic molecules.

In conclusion, we have accomplished the construction of quinoline frameworks via intramolecular cyclization of *o*-cyanomethylamino-β,β-difluorostyrenes. Thus obtained 3-fluorinated quinolines with sp^2-*C* substituents and functional groups at the 2-position are complementary to the products of our former fluoroquinoline synthesis.[8b]



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