4-Difluoromethylated Quinoline Synthesis via Intramolecular S_N2' Reaction of α-Trifluoromethylstyrenes Bearing Imine Moieties

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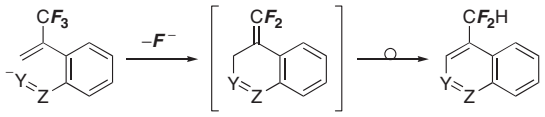
Intramolecular cyclization of *o*-methyleneamino-substituted α-trifluoromethylstyrenes is promoted by DBU and a catalytic amount of KCN to provide 4-(difluoromethyl)quinolines. The reaction proceeds via (i) the generation of carbon nucleophiles from the imine moieties, (ii) their intramolecular S_N2' reaction with loss of a fluoride ion, and (iii) subsequent aromatization by alkene isomerization.

The difluoromethyl (CF_2H) group is of considerable interest in the design of bioactive molecules.[1] Such attention to the CF_2H group is mainly due to its remarkable property, hydrogen bond donor ability without nucleophilicity and with high lipophilicity,[2] which individuates CF_2H from typical hydrogen donors such as OH and NH groups and makes it a special mimic of the hydroxy function.[3] In spite of its characteristic properties and potential, only a few methods have been reported for the construction of the CF_2H moiety:[4] (1) difluorination of a formyl group or its equivalents,[5] (2) hydrogenation of the difluorovinylidene (CF_2=C) group,[3] and (3) alkylation with difluoromethyl halides.[3a,6] Among these, the methods applicable to the synthesis of CF_2H-containing heteroaromatic compounds are further limited. Thus, the development of an efficient method for constructing difluoromethylated heteroaromatic systems is a highly desirable goal.

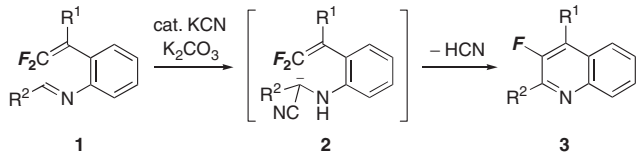
α-Trifluoromethylstyrenes tend to react with nucleophiles accompanying loss of a fluoride ion in an S_N2' fashion, leading to *gem*-difluoroalkenes.[7] This fact prompted us to investigate an intramolecular version of this nucleophilic substitution to construct CF_2H-substituted heteroaromatics. As shown in Scheme 1, the generation of an sp^2 nucleophile (Y^-) or its equivalent on the position δ to the 1-(trifluoromethyl)vinyl group would promote an intramolecular S_N2' reaction to give exo-difluoromethylene compounds, which would readily undergo alkene isomerization to aromatize them, leading to the desired CF_2H-substituted heteroarenes.



Scheme 1. A synthetic strategy for the construction of CF_2H-substituted heteroaromatics.

Recently, we have reported a synthetic method for 3-fluoroquinolines.[8] The reaction is based on (i) the generation of carbanions **2** via a benzoin-type process of imine moieties and (ii) the cyclization via their substitution for the vinylic fluorine of *gem*-difluoroalkene moieties. This sequence allows the imine moieties to act as an imidoyl (sp^2) anion equivalent (Scheme 2).

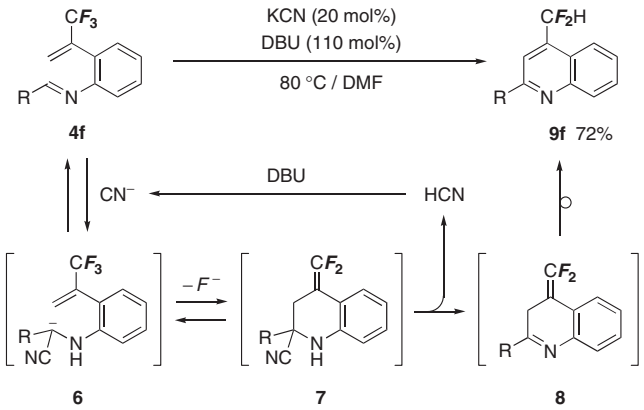
On the basis of these considerations, we attempted the intramolecular S_N2' reaction by the carbon nucleophiles generated from imine moieties on treatment with a catalytic amount of KCN and a small excess of a base. Herein, we wish to report the synthesis of 4-(difluoromethyl)quinolines via cyanide-ion-catalyzed intramolecular cyclization of *o*-methyleneamino-substituted α-trifluoromethylstyrenes **4**.



Scheme 2. Synthesis of 3-fluoroquinolines **3** from β,β-difluorostyrene derivatives **1**.

The starting materials **4** were easily prepared by the coupling reaction of 2-bromo-3,3,3-trifluoro-1-propene with *o*-iodoanilines via 1-(trifluoromethyl)vinylboronic acid according to a modified literature procedure,[9,10] followed by imine formation. The coupling products, *o*-amino-α-trifluoromethylstyrenes **5** were reacted with aldehydes to give the desired substrates **4**.

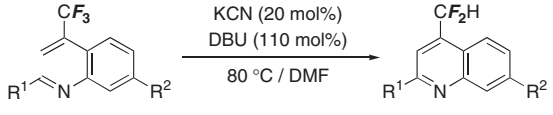
When the substrate **4f** was treated with 20 mol % of KCN and 110 mol % of K_2CO_3 at 80 °C in DMF, 4-(difluoromethyl)-quinoline **9f** was directly obtained as expected in 60% yield. Screening of bases other than K_2CO_3 revealed that DBU promoted the catalytic transformation of **4f** most effectively to give **9f** in 72% yield.[11] This reaction proceeds via (i) the generation of carbanion **6** by the attack of CN^- on the imino carbon and a prototropic shift, (ii) the subsequent cyclization to intermediate **7**, and (iii) its aromatization involving elimination of HCN and alkene isomerization, which sequence leads to the desired product **9f**. The base, DBU regenerates CN^- from HCN to complete a catalytic cycle (Scheme 3).



Scheme 3. Synthesis of 4-difluoromethylquinoline **9f** from α-trifluoromethylstyrene derivative **4f** (R = *p*-$CF_3C_6H_4$).

Under the reaction conditions obtained above, we conducted the reaction of several other substrates. Consequently, 2-substituted 4-(difluoromethyl)quinolines **9a**, **9d**–**9f**, **9i**, **9j** and 2,7-disubstituted 4-(difluoromethyl)quinolines **9b**, **9c**, **9g**, **9h** were synthesized on treatment of trifluoromethylstyrenes **4a**–**4j** with 20 mol % of KCN and 110 mol % of DBU (Table 1).[12] The scope of this reaction was found to be extended to substrates **4d**–**4h** bearing aryl groups with electron-donating groups (Entry 4) and electron-withdrawing groups (Entries 5–8). In addition, substrates **4i**, **4j** bearing carbonyl groups at the imino carbon were also applicable to this KCN-catalyzed cyclization (Entries 9 and 10).

Table 1. Synthesis of 2-substituted 4-(difluoromethyl)quinolines **9**



4 **9**

Entry	R^1	R^2	**4**	Time/h	Yield/%
1	Ph	H	**4a**	12	76 (**9a**)
2	Ph	Cl	**4b**	9	56 (**9b**)
3	Ph	OMe	**4c**[a]	14	61 (**9c**)[b]
4	*p*-MeC_6H_4	H	**4d**	12	51 (**9d**)
5	*p*-BrC_6H_4	H	**4e**	1	70 (**9e**)
6	*p*-$CF_3C_6H_4$	H	**4f**	3	72 (**9f**)
7	*p*-$CF_3C_6H_4$	Cl	**4g**	2	44 (**9g**)
8	*p*-$CF_3C_6H_4$	OMe	**4h**[a]	3	73 (**9h**)[b]
9	PhCO	H	**4i**[a]	1	30 (**9i**)[b]
10	EtO_2C	H	**4j**[a]	1	27 (**9j**)[b]

[a]Substrates **4c**, **4h**–**4j** were prepared by the reaction of the corresponding anilines **5** with benzaldehyde (120 mol %), 4-(trifluoromethyl)benzaldehyde (120 mol %), phenylglyoxal hydrate (130 mol %), or ethyl glyoxylate (150 mol %) in refluxing benzene (12, 12, 3, or 2 h), respectively, and used without purification.

[b]Yield based on *o*-amino-α-trifluoromethylstyrene **5**.

In conclusion, we have accomplished an efficient construction of CF_2H-substituted quinoline frameworks via intramolecular S_N2' reaction of *o*-methyleneamino-substituted α-trifluoromethylstyrenes. Furthermore, this process is effected under KCN catalysis to allow carbon–carbon bond formation at the imino carbon with electrophiles, which provides another rare example of benzoin-type condensation of imines.[8,13]

We are grateful to TOSOH F-TECH, INC. for a generous gift of 2-bromo-3,3,3-trifluoropropene.

References and Notes

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10 1-(Trifluoromethyl)vinylboronic acid: To a suspension of magnesium turnings (1.41 g, 58 mmol) and trimethoxyborane (16.2 mL, 145 mmol) in THF (100 mL) was added 2-bromo-3,3,3-trifluoropropene (5.00 mL, 48.3 mmol) in THF (5 mL) over 1 h at 0 °C under argon. The reaction mixture was stirred at 0 °C for 3 h. The reaction was quenched with aq HCl (6 M), and organic materials were extracted three times each with 100 mL of Et_2O. The combined extracts were washed with brine and then dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was immediately used without purification in the following palladium-catalyzed coupling reaction with *o*-iodoanilines.[9]

11 4-(Difluoromethyl)-2-(4-trifluoromethylphenyl)quinoline (**9f**): To a solution of **4f** (112 mg, 0.33 mmol) in DMF (3 mL) was added KCN (4.2 mg, 0.065 mmol) and DBU (0.053 mL , 0.36 mmol). 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 and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by PTLC on silica gel (hexane–EtOAc, 10:1) to give **9f** (75 mg, 72%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.19 (1H, t, $J_{HF} = 54.7$ Hz), 7.63 (1H, ddd, $J = 8.3$, 8.3, 1.2 Hz), 7.76 (2H, d, $J = 8.1$ Hz), 7.79 (1H, ddd, $J = 8.3$, 8.3, 1.2 Hz), 8.03 (1H, s), 8.05 (1H, dd, $J = 8.3$, 1.2 Hz), 8.23 (1H, dd, $J = 8.3$, 1.2 Hz), 8.27 (2H, d, $J = 8.1$ Hz). ^{13}C NMR (126 MHz, $CDCl_3$) δ 113.2 (t, $J_{CF} = 241$ Hz), 115.5 (t, $J_{CF} = 8$ Hz), 123.0, 123.3 (t, $J_{CF} = 3$ Hz), 124.1 (q, $J_{CF} = 272$ Hz), 125.8 (q, $J_{CF} = 4$ Hz), 127.7, 128.0, 130.4, 130.7, 131.5 (q, $J_{CF} = 33$ Hz), 138.8 (t, $J_{CF} = 22$ Hz), 141.9, 148.7, 155.2. ^{19}F NMR (470 MHz, $CDCl_3/C_6F_6$) δ_F 46.4 (2F, d, $J_{HF} = 55$ Hz), 99.1 (3F, s). IR (neat) 3070, 2974, 2252, 1716, 1610, 1323, 1169, 1113, 904 cm^{-1}. Anal. Found: C, 63.20; H, 3.30; N, 4.15%. Calcd for $C_{17}H_{10}NF_5$: C, 63.16; H, 3.12; N, 4.33%.

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