Cyclization of *o*-Functionalized α-Trifluoromethylstyrenes: Synthesis of Isoquinoline Derivatives Bearing Fluorinated One-Carbon Units

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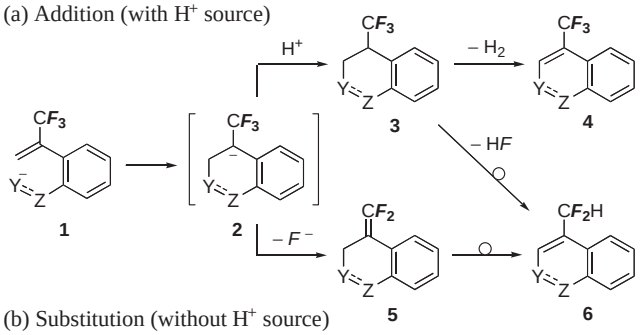
(Received March 7, 2005; CL-050304)

α-Trifluoromethylstyrenes with a formimidoyl, an *N*-hydroxyformimidoyl, or a tosylamidomethyl group at the ortho position undergo intramolecular addition or S_N2'-type substitution at the trifluoromethylvinyl moiety, leading to a variety of isoquinoline derivatives bearing 4-trifluoromethyl, 4-difluoromethyl, and 4-difluoromethylene groups.

Isoquinoline and its derivatives are widespread in the alkaloid family and constitute an important class of compounds in pharmaceuticals, agrochemicals, and materials.[1] In the field of these sciences, especially in medicinal and agricultural chemistry, introduction of fluoroalkyl groups into heterocycles has come into wide use as one of the most efficient methods for modification of their biological activities and physical properties.[2] Among fluorocarbon substituents, fluorinated one-carbon units are attractive:[3] (i) The incorporation of a trifluoromethyl (CF_3) group into organic molecules increases lipophilicity and affects electron density.[4] (ii) A difluoromethyl (CF_2H) group has hydrogen-bond-donor ability without nucleophilicity and with high lipophilicity,[5] which makes it a special mimic of a hydroxy group.[6] (iii) A difluoromethylene (CF_2=) group acts as a reactive site toward nucleophiles[7] and a potential isostere of carbonyl groups.[8] Despite such immense potential, there are few methods especially for the introduction of CF_2H and CF_2= groups. Thus, a general access to fluorocarbon-substituted isoquinolines poses a significant challenge.

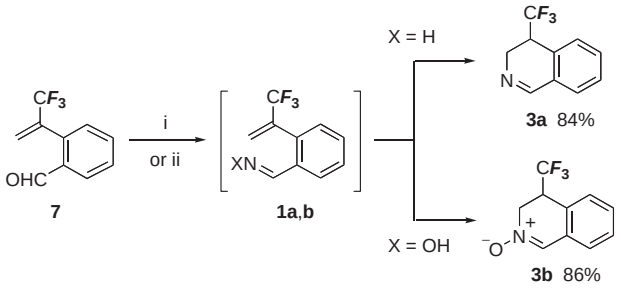


Scheme 1. A synthetic strategy for heterocycles bearing fluorinated one-carbon units.

This fact prompted us to devise a synthetic strategy for heterocycles bearing fluorinated one-carbon units, as depicted in Scheme 1. Recently, we have reported a synthesis of 4-difluoromethylated quinolines **6** (Y = C, Z = N) from *o*-substituted α-trifluoromethylstyrenes **1** via intramolecular S_N2'-type substitution of *carbon* nucleophiles (Scheme 1b).[9] In order to construct a series of fluorocarbon-bearing isoquinoline rings **3**–**6** (Y = N, Z = C), we investigated addition (Scheme 1a) as well as substitution of *nitrogen* nucleophiles. Cyclized intermediates **2** were expected to undergo either of these two reactions, depending on the reaction conditions with or without a proton source. Carbanions **2** stabilized by the CF_3 group could be trapped by the proton source before elimination of a fluoride ion, leading to trifluoromethylated products **3**, which would provide **4** and **6** via dehydrogenation and dehydrofluorination. Herein, we report the synthesis of isoquinoline derivatives bearing CF_3, CF_2H, and CF_2= groups from styrenes **1** bearing imine, oxime, and amidomethyl moieties at the ortho position.

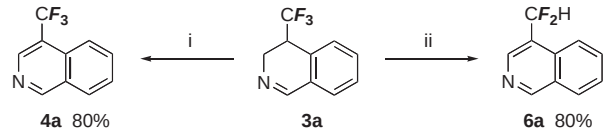
As a common precursor for imine **1a** (X = H), and oxime **1b** (X = OH), *o*-formyl-substituted α-trifluoromethylstyrene **7** was prepared by the coupling reaction of 2-bromo-3,3,3-trifluoropropene with *o*-iodobenzaldehyde via 1-(trifluoromethyl)vinylboronic acid according to a modified literature procedure.[9,10] *o*-Tosylamidomethyl-substituted styrene **1c** was prepared via (i) a similar coupling reaction of 1-(trifluoromethyl)vinylboronic acid with *o*-iodobenzyl alcohol and (ii) the Mitsunobu reaction of the resulting alcohol with BocNHTs,[11] followed by (iii) deprotection of the Boc group.

Imine **1a**, prepared in situ from aldehyde **7** and ammonium acetate (NH_4OAc) in DMF–H_2O (10:1), readily underwent intramolecular addition without elimination to give 4-trifluoromethyl-3,4-dihydroisoquinoline (**3a**) in 84% yield from **7**.[12] Similarly, treatment of **7** with 1.2 molar amounts of hydroxylamine hydrochloride (NH_2OH·HCl) promoted an oxime-formation–intramolecular-addition sequence to afford 4-trifluoromethyl-3,4-dihydroisoquinoline *N*-oxide (**3b**) in 86% yield from **7** through **1b** (Scheme 2).[12,13] Thus obtained **3b** is a cyclic nitrone, which is a highly valuable synthetic intermediate.[14]



Scheme 2. Reagents and conditions: i, NH_4OAc (5 ma), rt, 5 h, DMF–H_2O (10:1). ii, NH_2OH·HCl (1.2 ma), 70 °C, 3 h, DMF–H_2O (10:1). ma: molar amount.

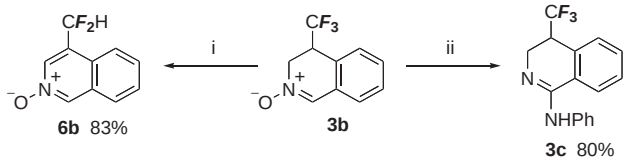
Aromatization of dihydroisoquinolines **3a** and **3b** leading to isoquinoline synthesis was examined. Dehydrogenation of **3a** was effected by palladium on charcoal to give 4-trifluoromethylisoquinoline (**4a**) in 80% yield.[15] Furthermore, on treatment of **3a** with a small excess amount of DBU, the desirable HF-elimination–isomerization occurred to give 4-difluoromethyliso-



Scheme 3. Reagents and conditions: i, Pd/C, reflux, 4 days, xylene. ii, DBU (1.2 ma), LiBr (1 ma), 100 °C, 3 h, DMSO.

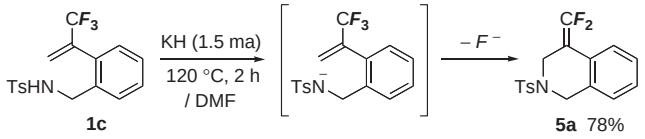
quinoline (**6a**) in 66% yield. Addition of an equimolar amount of LiBr in this reaction raised the yield of **6a** up to 80% (Scheme 3).[16]

Nitrone **3b** readily underwent a similar dehydrofluorination on treatment with 1.4 molar amounts of DBU and 2 molar amounts of LiBr, leading to 4-difluoromethylisoquinoline *N*-oxide (**6b**) in 83% yield.[16] The reactivity of **3b** was also examined in 1,3-dipolar cycloaddition with phenylisocyanate (PhNCO).[17] Treatment of **3b** with 1.2 molar amounts of PhNCO in DMF promoted the expected cycloaddition followed by elimination of carbon dioxide to give 1-anilino-4-trifluoromethyl-3,4-dihydroisoquinoline (**3c**) in 80% yield (Scheme 4).



Scheme 4. Reagents and conditions: i, DBU (1.4 ma), LiBr (2 ma), 80 °C, 40 min, DMSO. ii, PhNCO (1.2 ma), rt, 15 min, DMF.

In addition, the S_N2'-type cyclization was carried out under anhydrous conditions to provide isoquinoline derivatives bearing a difluoromethylene group. Treatment of sulfonamide **1c** with 1.5 molar amounts of KH in DMF successfully promoted intramolecular substitution to afford 4-difluoromethylene-1,2,3,4-tetrahydroisoquinoline (**5a**) in 78% yield (Scheme 5).[18]



Scheme 5.

Thus, we have accomplished the construction of isoquinoline frameworks via intramolecular addition or substitution of *o*-functionalized α-trifluoromethylstyrenes. This methodology provides a variety of isoquinoline derivatives bearing fluorinated one-carbon units (CF_3, CF_2H, and CF_2=), starting from 2-bromo-3,3,3-trifluoropropene and *o*-iodobenzaldehyde or *o*-iodobenzyl alcohol.

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

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12 The possibility of 6π-electrocyclization in the formation of **3a** and **3b** cannot be ruled out.
13 4-Trifluoromethyl-3,4-dihydroisoquinoline *N*-oxide (**3b**): $NH_2OH \cdot HCl$ (33 mg, 0.47 mmol) was added to 2-(3,3,3-trifluoroprop-1-en-2-yl)benzaldehyde **7** (78 mg, 0.39 mmol) in DMF (3 mL)–H_2O (0.3 mL) at room temperature under air. After the reaction mixture was heated at 70 °C for 3 h, phosphate buffer (pH 7) was added to quench the reaction. Organic materials were extracted with $CHCl_3$ three times. 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 (AcOEt–MeOH, 10:1) to give **3b** (72 mg, 86%) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.74–3.82 (1H, m), 4.34 (1H, dd, J = 17.1, 2.0 Hz), 4.42 (1H, ddd, J = 17.1, 7.1, 2.0 Hz), 7.22 (1H, d, J = 7.5 Hz), 7.38–7.40 (2H, m), 7.42–7.46 (1H, m), 7.77 (1H, d, J = 2.0 Hz). ^{13}C NMR (125 MHz, $CDCl_3$) δ 42.4 (q, J_{CF} = 29 Hz), 56.2 (q, J_{CF} = 2 Hz), 122.1, 125.1 (q, J_{CF} = 282 Hz), 125.9, 128.9, 129.6, 129.7, 130.0, 133.0. ^{19}F NMR (471 MHz, $CDCl_3/C_6F_6$) δ_F 89.5 (d, J_{FH} = 9 Hz). IR (ZnSe) 3392, 1599, 1568, 1267, 1238, 1209, 1171, 1120, 912 cm^{-1}. HRMS Calcd for $C_{10}H_8NF_3O$ 216.0636 (M^+); found 216.0625.
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Published on the web (Advance View) May 7, 2005; DOI 10.1246/cl.2005.778