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Fluoride Ion-Promoted Reaction of Polyfluoro-1-propenyl *p*-Toluenesulfonate with Amines. Highly Efficient and General Access to (*Z*)-α-Fluoro-β-amino Acrylaldehydes

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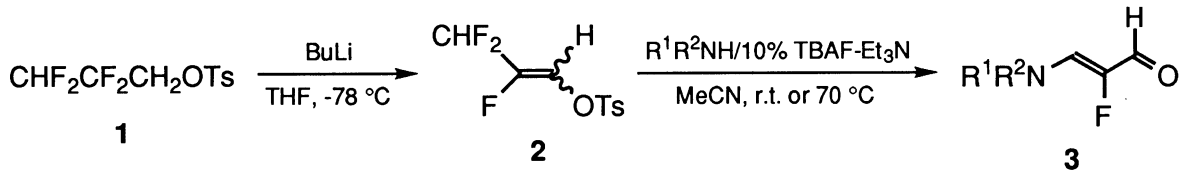
2,3,3-Trifluoro-1-propenyl *p*-toluenesulfonate, readily available by dehydrofluorination of 2,2,3,3-tetrafluoropropyl *p*-toluenesulfonate, reacted smoothly with various primary or secondary amines in the presence of triethylamine and a catalytic amount of fluoride ion at ambient temperature for 3 h or at 70 °C for 1-2 h to afford the corresponding (*Z*)-α-fluoro-β-(alkylamino- or -dialkylamino)acrylaldehydes in good to excellent yields, together with the formation of *p*-toluenesulfonyl fluoride.

Vinyl fluorides and related compounds are one of the most useful and pervasive building blocks for constructing a variety of monofluorinated substances. Recently, vinyl fluorides carrying a specific functionality such as the carbonyl and hydroxyl groups have received increasing attention in organic and bioorganic syntheses, in close connection with the suggestion that fluoroolefinic units are prominent substitutes mimicking both steric and electronic features of the peptide bond.[1] For instance, α-fluoroacrylaldehydes are nicely incorporated in the preparation of fluorine-containing dipeptide isosterers,[1-3] and also employed as key intermediates for preparing fluorinated analogs of insect sex pheromones[4] and fluorinated precursors of enzyme inhibitors.[5]

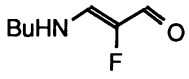
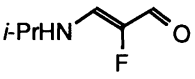
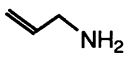
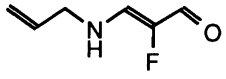
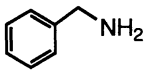
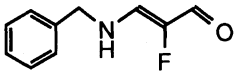
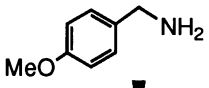
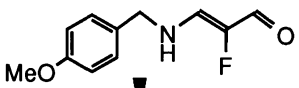
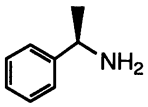
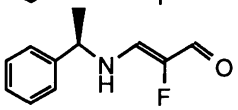
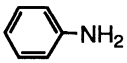
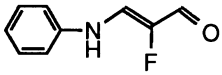
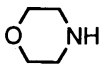
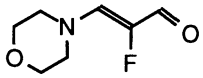
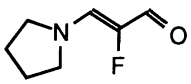
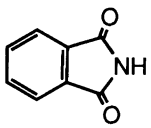
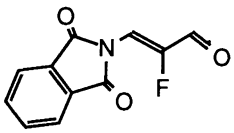
Although a number of methods for the synthesis of functionalized vinyl fluorides have appeared in the literature,[6,7] there is still much demand for the synthetic methods for such compounds. In our continuing studies on the synthesis and applications of polyfluorinated olefinic and acetylenic compounds,[8] polyfluorovinyl tosylates were found to undergo facile cleavage of the enol oxygen-sulfur bond with fluoride ion leading to α-fluoro-β-substituted acrylaldehydes. This communication discloses a new fluoride ion-promoted reaction of 2,3,3-trifluoro-1-propenyl *p*-toluenesulfonate (**2**) with various primary and secondary amines, offering a simple and efficient method which is widely applicable for synthesizing (*Z*)-α-fluoro-β-amino acrylaldehydes (**3**) in good yields.[9]



1 **2** **3**

2,3,3-Trifluoro-1-propenyl *p*-toluenesulfonate (**2**) was readily obtained as a mixture of stereoisomers (*E*/*Z* = 14 : 86) in 70% yield by the treatment of 2,2,3,3-tetrafluoropropyl *p*-toluenesulfonate (**1**) with 2.2 equiv. of butyllithium in tetrahydrofuran (THF) at -78 °C for 10 min.[10] Both the ratio of butyllithium to **1** and the short reaction time were crucial to this reaction; the use of a stoichiometric amount (1.0 equiv.) of butyllithium resulted

Table 1. Preparation of (*Z*)-α-fluoro-β-amino Acrylaldehydes (**3**)

Entry	Amine	Product		Yield[a]/% of **3**	^{19}F NMR[b] δ (*J*, Hz)
1	$BuNH_2$		**3a**	85	-87.7 (22.4, 22.2)
2	*i*-$PrNH_2$		**3b**	86 (80)[c]	-87.3 (23.4, 22.6)
3			**3c**	78	-86.7 (23.0, 22.0)
4			**3d**	89	-87.8 (26.0, 23.0)
5			**3e**	84	-86.5 (22.0, 21.0)
6			**3f**	94	-85.5 (22.2, 22.0)
7	EtO_2C $NH_2 \cdot HCl$	EtO_2C	**3g**	81[d]	-87.0 (22.4, 22.0)
8			**3h**	89	-80.6 (24.8, 22.0)
9	Et_2NH	Et_2N	**3i**	99	-90.3 (28.0, 20.4)
10	*i*-Pr_2NH	*i*-Pr_2N	**3j**	73	-83.7 (28.2, 20.0)
11			**3k**	74	-85.2 (26.8, 20.4)
12			**3l**	78	-90.7 (26.8, 20.4)
13	EtO_2C $NHMe \cdot HCl$	EtO_2C	**3m**	82[d]	-88.9 (25.8, 20.4)
14			**3n**	52[e]	-49.2[f] (30.0, 19.8)

a) Yields refer to pure isolated products. b) Measured in chloroform-*d* with external trifluoroacetic acid (TFA). c) Dichloromethane was employed as the solvent. d) Carried out at 70 °C for 2 h by using 2.0 equiv. of triethylamine. e) Conducted at 70 °C for 1 h. f) Measured in DMSO-d_6.

in decrease of the yield (36%) of **2** and in remaining (38%) of the tosylate **1**. Longer reaction time (30 min) also reduced the yield (32%) of **2**.[11] Among the bases examined, such as butyllithium, lithium diisopropylamide (LDA), potassium *t*-butoxide (*t*-BuOK), and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), butyllithium gave the best results and LDA was less effective for the reaction. Neither *t*-BuOK nor DBU caused the reaction at all, irrespective of the reaction period and temperature being varied.

When enol tosylate **2** was treated with a primary or secondary amine in the presence of a catalytic amount of tetrabutylammonium fluoride (TBAF) and an equimolar amount of triethylamine, (*Z*)-α-fluoro-β-(alkylamino- or -dialkylamino)acrylaldehydes (**3**)[12] were produced in good to excellent yields. The results of the reaction are summarized in Table 1, together with the fluorine chemical shifts and coupling constants of the products **3**. Acetonitrile and dichloromethane were suitable solvents, whereas ethereal solvents such as THF and 1,2-dimethoxyethane rendered the reaction insufficient to leave the enol tosylate. Out of triethylamine, ethyldiisopropylamine, and pyridine employed as base, triethylamine was the most efficient for the reaction. The reaction performed in the absence of TBAF was extremely sluggish to give a low yield (37%) of **3**. Using potassium fluoride in place of TBAF was not effective in this reaction. A variety of aliphatic and aromatic amines reacted smoothly with **2** at room temperature to afford the corresponding acrylaldehyde derivatives **3** in high yields (Entries 1-6 and 8-12). It is very valuable that glycine ethyl ester and sarcosine ethyl ester hydrochlorides participated nicely in the reaction to give the corresponding **3** in 81% and 82% yields, respectively, though the reactions necessitated not only an elevated temperature (70 °C) but also the use of two equimolar amounts of triethylamine (Entries 7 and 13). The reaction of phthalimide at ambient temperature provided the product only in low yield (35%), which could be improved by raising the reaction temperature (70 °C) (Entry 14).

Of much significance is that the present reaction exclusively afforded the (*Z*)-isomers of α-fluoro-β-amino acrylaldehydes (**3**), which are assumed to have an *s*-trans conformation. The stereochemical assignment was made directly by ^{1}H and ^{19}F NMR, based upon the magnitudes of couplings between the fluorine and vinylic hydrogen as well as those between the fluorine and aldehydic hydrogen atoms (Table 1).

The fact that *p*-toluenesulfonyl fluoride was formed quantitatively in the reaction will allow us to draw the following mechanism. Thus, the enol tosylate **2** may undergo cleavage of the enol oxygen-sulfur bond with fluoride ion followed by the loss of an allylic fluorine atom to generate α,β-difluoroacrylaldehyde, which reacts with amine in an addition-elmination sequence to furnish the product **3**.

The reaction with isopropylamine (Entry 2) is described as a typical procedure. To a solution of isopropylamine (1.1 mmol), triethylamine (1.0 mmol), and a catalytic amount of TBAF (10 mol%, 0.1 mL of a 1.0 mol dm^{-3} THF solution) in acetonitrile (1 mL) was added a solution of **2** (1.0 mmol) in acetonitrile (2 mL) at 0 °C. The mixture was stirred at ambient temperature for 3 h and was then quenched with brine, followed by extraction with dichloromethane, drying over Na_2SO_4, and concentration *in vacuo*. The resultant residue was chromatographed on a silica-gel column using ethyl acetate as eluent to give analytically pure (*Z*)-α-fluoro-β-(isopropylamino)acrylaldehyde (**3b**)[12] in 86% yield, along with 87% of *p*-toluenesulfonyl fluoride.[12]

Further studies on the application of this enol tosylate **2** to the synthesis of fluorinated biologically active compounds are now under way in our laboratory.

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8) H. Yamanaka, S. Yamashita, and T. Ishihara, *Tetrahedron Lett.*, **33**, 357 (1992); H. Yamanaka, K. Tamura, K. Funabiki, K. Fukunishi, and T. Ishihara, *J. Fluorine Chem.*, **57**, 177 (1992); K. Tamura, T. Ishihara, and H. Yamanaka, *ibid.*, in press.
9) Only two contributions to the synthesis of α-fluoro-β-amino acrylaldehydes have hitherto been made: C. Reichart and K. Halbritter, *Justus Liebigs Ann. Chem.*, **737**, 99 (1970); H. Yamanaka, S. Yamashita, and T. Ishihara, *Synlett*, **1993**, 353. These methods suffer serious disadvantages, such as toxicity or availability of the starting materials, poor yields of the products, and low applicability of the reaction.
10) To a THF solution of **1** (3.0 mmol) was added dropwise butyllithium (4.1 mL of a 1.6 mol dm^{-3} hexane solution, 6.6 mmol) at -78 °C over 20 min under argon. After 10 min at -78 °C, the reaction was quenched with a cold 10% HCl solution. Extraction, drying, concentration, and column chromatography (benzene) gave **2** as a pale yellow solid: 70% (*E*/*Z* = 14 : 86); IR (KBr) 1720, 1350, 1172 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 2.44 (s, 3H), 6.16 (dt, *J* = 51.2, 15.8 Hz, 1H), 6.85 (d, *J* = 4.4 Hz, 1H), and 7.1-8.0 (m, 4H) for the (*E*)-isomer, 2.46 (s, 3H), 5.96 (dt, *J* = 52.6, 7.0 Hz, 1H), 6.63 (dt, *J* = 18.0, 2.0 Hz, 1H), and 7.1-8.0 (m, 4H) for the (*Z*)-isomer; ^{19}F NMR ($CDCl_3$, TFA) δ = -48.3 (dd, *J* = 51.2, 16.9 Hz, 2F) and -87.0 (ddt, *J* = 16.9, 15.8, 4.4 Hz, 1F) for the (*E*)-isomer, -45.4 (ddd, *J* = 52.6, 17.6, 2.0 Hz, 2F) and -68.3 (ddt, *J* = 18.0, 17.6, 7.0 Hz, 1F) for the (*Z*)-isomer; HRMS (CI) Found: *m*/*z* 267.0246. Calcd for $C_{10}H_{10}F_3O_3S$: M, 267.0303. This procedure can also be applied to a large-scale (15 mmol) preparation.
11) These results are strongly suggestive of the intermediacy of vinyllithium, $CHF_2CF=C(Li)OTs$. In fact, the treatment of **1** with butyllithium (2.2 equiv.) at -78 °C for 10 min followed by quenching with deuterium oxide gave rise to 1-deuterio-2,3,3-trifluoro-1-propenyl *p*-toluenesulfonate[12] in 65% yield. Detailed results on the reaction of the vinyllithium intermediate with other electrophiles will be reported elsewhere.
12) All isolated products exhibited satisfactory spectral and analytical data.

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