Reactions of 1-Substituted-polyfluoro-1-propenyl *p*-Toluenesulfonates with Bifunctional Nitrogen Nucleophiles. A New Expedient Access to Monofluorinated Nitrogen Heterocycles[1]

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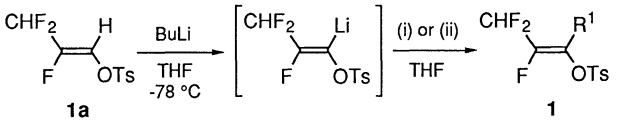
1-Substituted-2,3,3-trifluoro-1-propenyl *p*-toluenesulfonates, readily available by the alkylation or arylation of 2,3,3-trifluoro-1-tosyloxy-1-propenyllithium or -zinc reagent, reacted smoothly with amidine or hydrazine derivatives at 70 °C for 1 h to give the corresponding 5-fluoropyrimidine or 4-fluoropyrazole compounds, respectively, in moderate to excellent yields.

Much attention has been given to the chemistry of heterocyclic compounds bearing a fluorine atom and/or polyfluoroalkyl groups,[2] because they often have unique biological and physiological activities.[3] In particular, nitrogen-containing heterocyclic compounds play an important part in medicinal and agrochemical fields,[4] for example, where 5-fluorouracil and its derivatives have shown great promise as anticancer agents.[5] Therefore, it is still of great significance to develop simple and effective methods for the synthesis of fluorine-containing azaheterocyclic compounds.

In our continuing studies on the synthesis and applications of fluorinated acetylenic and olefinic compounds,[6] we have found that polyfluorovinyl tosylates **1** undergo cleavage of the enol oxygen-sulfur bond with either fluoride ion[6b] or nitrogen nucleophiles. In this communication is described the reaction between 1-substituted-2,3,3-trifluoro-1-propenyl *p*-toluenesulfonates **1** and amidines or hydrazines, which provides a new convenient and efficient approach to 5-fluoropyrimidine and 4-fluoropyrazole derivatives in good yields.

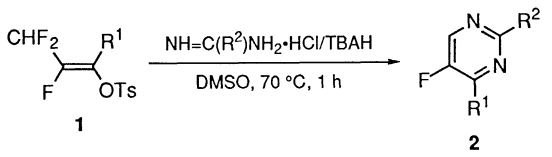
(*Z*)-2,3,3-Trifluoro-1-propenyl *p*-toluenesulfonate (**1a**) was prepared according to the method reported by us.[6b] (*Z*)-2,3,3-Trifluoro-1-methyl-1-propenyl *p*-toluenesulfonate (**1b**)[7] was obtained in 81% yield through the methylation of vinyllithium[8] generated from **1a** with methyl trifluoromethanesulfonate (MeOTf). The use of methyl iodide in place of MeOTf decreased the yield (17%) of **1b**, the starting tosylate **1a** being recovered in 31% yield. 1-Aryl-substituted enol tosylates **1c-e**[7]



b: R^1 = Me (81%)
c: R^1 = Ph (68%)
d: R^1 = *p*-$MeOC_6H_4$ (68%)
e: R^1 = *p*-$EtOCOC_6H_4$ (61%)

(i) MeOTf, -78 °C, 0.5 h
(ii) 1) $ZnBr_2$, -78 °C→ r.t.; 2) 5 mol% Pd(0), ArI, refl., 24 h

were prepared in 61-68% yields by the palladium-catalyzed coupling reaction between the corresponding vinylzinc reagent and aryl iodides.[9] Among the catalysts examined, such as tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$), dichlorobis(triphenylphosphine)palladium(II), and palladium(II) chloride, $Pd(PPh_3)_4$ was the most effective for the reaction. The coupling reaction with aryl bromide was unsuccessful.[10]



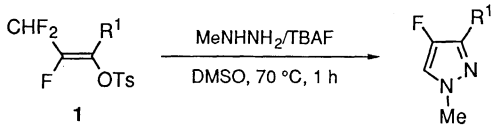
When enol tosylate **1a** was treated with benzamidine, which had been generated from 2.2 equimolar amounts each of benzamidine hydrochloride and tatrabutylammonium hydroxide (TBAH), in dimethyl sulfoxide (DMSO) at 70 °C for 1 h, 5-fluoro-2-phenylpyrimidine (**2a**)[7] was given in 86% yield. The presence of a base was essential for allowing the reaction to proceed smoothly. Sodium hydride and potassium hydroxide were not suitable for the reaction. The use of DMSO as the solvent afforded the most satisfactory results. Other solvents, such as acetonitrile, tetrahydrofuran, and dichloromethane (CH_2Cl_2), were much less sufficient than DMSO. The reaction at ambient temperature resulted in a slightly lower yield (70%) of the product **2a** than that at 70 °C (Entry 1).

Similarly, 1-substituted enol tosylates **1b-e** reacted readily with benzamidine under the same reaction conditions to afford the corresponding 4-substituted 5-fluoro-2-phenylpyrimidines (**2d**, **e**, **i**, and **j**)[7] in excellent yields (Entries 5, 6, 10, and 11). Other amidine salts, such as acetamidine hydrochloride (Entry 3), formamidine hydrochloride (Entry 7), guanidine hydrochloride (Entries 4 and 8), and *O*-methylisourea sulfate (Entry 9), could also participate in the reaction to lead to the corresponding 5-fluoropyrimidine compounds **2**. The reactions with formamidine or guanidine hydrochloride gave **2** in fair yields, which were not improved at all in spite of the reaction time, temperature, and molar ratios being varied. The results of the reactions are summarized in Table 1.

A typical procedure for the preparation of **2** (Entry 2) is as follows. A suspension of benzamidine hydrochloride (2.2 mmol) and TBAH (a 10% solution in methanol) (2.2 mmol) was stirred at room temperature for 0.5 h and then the solvent was removed. To this residue were added sequentially DMSO (1 mL) and a DMSO solution of **1a** (1 mmol) at 0 °C. The whole mixture was stirred at 70 °C for 1 h. The reaction was quenched with cold brine and the resulting mixture was extracted with CH_2Cl_2. The extracts were dried over Na_2SO_4 and concentrated *in vacuo* to leave a residue, which was chromatographed on silica gel with CH_2Cl_2 to afford 5-fluoro-2-phenylpyrimidine (**2a**)[7] in 86% yield.

Enol tosylates **1** were found to react with another bifunctional nitrogen nucleophile. On treating **1** with methylhydrazine (1.2 equiv.) in the presence of tetrabutylammonium

fluoride (TBAF)[11] (1 equiv.) at 70 °C for 1 h, the corresponding 1-methyl-4-fluoropyrazole derivatives (**3**)[7] were produced in high yields, as shown below.

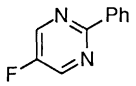
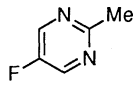
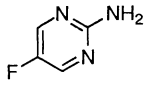
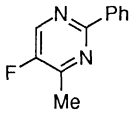
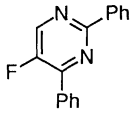
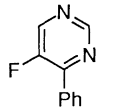
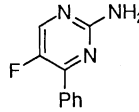
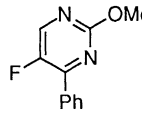
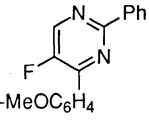
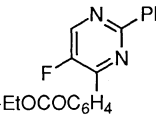


1 → **3**

a: R^1 = H (71%)
c: R^1 = Ph (88%)
d: R^1 = *p*-$MeOC_6H_4$ (83%)
e: R^1 = *p*-$EtOCOC_6H_4$ (86%)

Thus, the above described reactions can serve as a facile and effective route to the synthesis of various sorts of monofluoropyrimidines and pyrazoles in good yields.

Table 1. Synthesis of 5-Fluoropyrimidines **2**

Entry	Tosylate **1**	Amidine R^2	Product **2**		Yield[a]/% of **2**
1	**1a**	Ph		**2a**	70[b]
2	**1a**	Ph		**2a**	86
3	**1a**	Me		**2b**	60 (71)[c]
4	**1a**	NH_2		**2c**	40 (56)[c]
5	**1b**	Ph		**2d**	86
6	**1c**	Ph		**2e**	87
7	**1c**	H		**2f**	40
8	**1c**	NH_2		**2g**	47
9	**1c**	OMe[d]		**2h**	57
10	**1d**	Ph		**2i**	88
11	**1e**	Ph		**2j**	85

[a] Yields refer to isolated products. [b] Conducted at room temperature for 3 h. [c] Determined by ^{19}F NMR. [d] A sulfate salt was used.

References and Notes

1 Presented partly at the 14th International Symposium on Fluorine Chemistry, Yokohama, Japan, July 31-August 5 1994, Abstr. No. 1P-43.

2 For recent examples on the preparation of fluorine-containing pyrimidines or pyrazoles, see: T. Ishihara, Y. Okada, M. Kuroboshi, T. Shinozaki, and T. Ando, *Chem. Lett.*, **1988**, 819; H. Molines and C. Wakselman, *J. Org. Chem.*, **54**, 5618 (1989); G. de Nanteuil, *Tetrahedron Lett.*, **32**, 2467 (1991); B. C. Hamper, M. L. Kurtzweil, and J. P. Beck, *J. Org. Chem.*, **57**, 5680 (1992); J. -P. Bouillon, C. Ates, Z. Janousek, and H. G. Viehe, *Tetrahedron Lett.*, **34**, 5075 (1993); M. Soufyane, C. Mirand, and J. Lévy, *Tetrahedron Lett.*, **34**, 7737 (1993); P. Bravo, D. Diliddo, and G. Resnati, *Tetrahedron*, **50**, 8827 (1994); B. Dondy, P. Doussot, and C. Portella, *Tetrahedron Lett.*, **35**, 409 (1994).

3 J. T. Welch, *Tetrahedron*, **43**, 3123 (1987); R. Filler and Y. Kobayashi, *Biomedicinal Aspects of Fluorine Chemistry*, Kodansha and Elsevier Biomedical, Tokyo and New York, 1982.

4 For a recent review, see; B. Roth and C. C. Cheng, *Prog. Med. Chem.*, **19**, 270 (1982).

5 M. Inaba, J. Mitsuhashi, and S. Ozawa, *Jpn. J. Cancer Res.*, **81**, 1039 (1990), and references cited therein.

6 a) H. Yamanaka, K. Tamura, K. Funabiki, K. Fukunishi, and T. Ishihara, *J. Fluorine Chem.*, **57**, 177 (1992); b) K. Funabiki, T. Ohtsuki, T. Ishihara, and H. Yamanaka, *Chem. Lett.*, **1994**, 1075; c) K. Funabiki, K. Tamura, T. Ishihara, and H. Yamanaka, *Bull. Chem. Soc. Jpn.*, **67**, 3021 (1994).

7 All products gave satisfactory spectral and analytical data.

8 For recent reports on fluorinated vinyllithiums, see: J. -F. Normant, *J. Organomet. Chem.*, **400**, 19 (1990); D. J. Burton, Z. -Y. Yang, and P. A. Morken, *Tetrahedron*, **50**, 2993 (1994). It is reported that the alkylation reaction of 2,2-difluoro-1-[(diethylcarbamoyl)oxy]ethenyllithium with alkyl halides is unsuccessful, see: A. J. Bennett, J. M. Percy, and M. H. Rock, *Synlett*, **1992**, 483.

9 For a recent review on transition metal catalyzed reactions of organozinc reagents, see: E. Erdik, *Tetrahedron*, **44**, 9577 (1992). For the coupling reaction of fluorinated vinylzinc reagents, see: ref. 8.

10 Burton and Heinze reported that perfluorovinylzinc reagent failed to couple with aryl bromides in the presence of a palladium catalyst. See: P. L. Heinze and D. J. Burton, *J. Org. Chem.*, **53**, 2714 (1988).

11 The absence of TBAF led to appreciably low yields (40-50%) of **3**. Potassium fluoride was much less effective than TBAF.