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Preparation of Novel β-Trifluoromethyl Vinamidinium Salt and Its Synthetic Application to Trifluoromethylated Heterocycles

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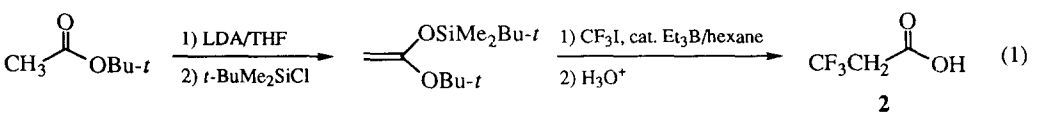
Abstract: β -Trifluoromethylated vinamidinium salt (**1**) was prepared in high yield by the reaction between 3,3,3-trifluoropropanoic acid and phosphorus oxychloride in *N,N*-dimethylformamide at 70 °C for 1 h. This salt **1** reacted readily with bifunctional nitrogen nucleophiles, such as amidine and hydrazine derivatives, in acetonitrile or dimethyl sulfoxide to furnish the corresponding trifluoromethylated azaheterocycles in good yields.

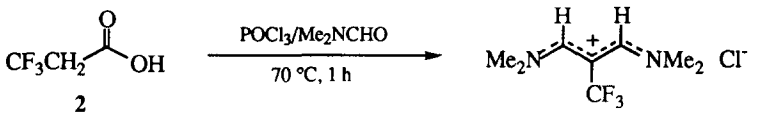
Recently, much attention has been paid to the development of efficient methods for the synthesis of heterocycles bearing the trifluoromethyl (CF_3) substituent, since these compounds have biological potential.[1] A number of trifluoromethylating reagents have been applied to the preparation of such compounds. For instance, iodo- or bromotrifluoromethane, dibromodifluoromethane, trifluoroacetic acid, and trifluoromethanesulfonic acid are widely used for trifluoromethylation through a CF_3 radical or CF_3-metal species.[2] On the other hand, many types of CF_3-containing building blocks have hitherto been developed and occupied an important position in organic synthesis as well as organofluorine chemistry.[3] We have focused our attention to vinamidinium (1,5-diazapentadienium) salts which are unique and versatile compounds serving as three-carbon building blocks.[4] Although many types of the vinamidinium salts have appeared in the literature,[5] there are few or no reports on fluorinated vinamidinium salts,[4,6] particularly on trifluoromethylated salts which will be a valuable building block for synthesizing regioselectively trifluoromethylated compounds. Herein we wish to report the first example for the preparation of β-trifluoromethyl vinamidinium salt, 1,1,5,5-tetramethyl-1,5-diaza-3-(trifluoromethyl)-1,3-pentadienium chloride (**1**), by the Vilsmeier-Haack reaction of 3,3,3-trifluoropropanoic acid (**2**) with phosphorus oxychloride in *N,N*-dimethylformamide and its reactions with bifunctional nitrogen nucleophiles leading to trifluoromethylated azaheterocycles.



(1)

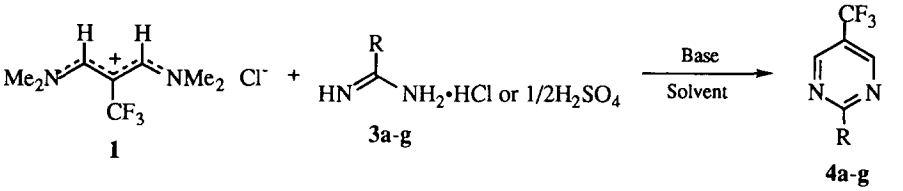
3,3,3-Trifluoropropanoic acid (**2**) employed in this study was prepared in 69% overall yield through the radical addition of trifluoromethyl iodide[7] to *t*-butyldimethylsilyl enol ether[8] of *t*-butyl acetate (r.t., 2 h) follwed by acidic hydrolysis (r.t., 15 h) (Eq 1). Thus obtained acid **2** (10.0 mmol) was allowed to react with

phosphorus oxychloride (30.0 mmol) in *N,N*-dimethylformamide (DMF) (10 mL) at 70 °C for 1 h. After cooling to room temperature, the reaction mixture was subjected directly to flash column chromatography on silica gel using ethyl acetate, THF, ethyl acetate-ethanol (1:1), and then ethanol as eluents to give pure β-trifluoromethyl vinamidinium salt (**1**)[9] in 91% yield (Eq 2). It should be noted that aqueous workup of the reaction mixture caused the hydrolysis of **1** to result in a substantial decrease of the yield of **1**. In fact, exposure of the isolated salt **1** to acidic (1*M* HCl aqueous solution) or basic (0.5*M* K_2CO_3 aqueous solution) hydrolysis conditions led to the formation of 3,3,3-trifluoropropanal[10] or the decomposition to fluoride ion, respectively. High susceptibility for the hydrolysis of **1** is in sharp contrast to that observed previously for β-fluoro vinamidinium salt under similar conditions.[4b]



2 **1** (2)

The reactions between **1** and bifunctional nitrogen nucleophiles, such as amidine hydrochlorides (**3a-c**) and guanidine hydrochlorides (**3d-g**), were carried out under various reaction conditions (Eq 3). The results are summarized in Table 1, together with ^{19}F NMR data of the products. The treatment of **1** with acetamidine hydrochloride (**3a**) (1.2 equiv.) at room temperature for 3 h in acetonitrile (MeCN) did not afford any desired product, the starting salt **1** being recovered unchanged (Entry 1). However, the addition of a base to the reaction mixture was found to allow the reaction to proceed smoothly. Thus, when the salt **1** was allowed to react with **3a** (1.2 equiv.) in the presence of triethylamine (1.2 equiv.) at room temperature for 3 h in MeCN, 2-methyl-5-(trifluoromethyl)pyrimidine (**4a**)[11] was given in 65% yield (Entry 3). The reaction time, temperature, and molar ratio of **1** to **3a** did not affect the yield of **4a** (Entries 2 and 4-6). Sodium methylate was also effective as the base for the reaction (Entry 7). Other aprotic or protic solvents than MeCN, such as dimethyl sulfoxide (DMSO), DMF, carbon tetrachloride, and ethanol, were equally employable, the product **4a** being obtained in good yields (Entries 8-11).



1 **3a-g** **4a-g** (3)

a: R = Me, **b**: R = Ph, **c**: R = H
d: R = NH_2, **e**: R = NHMe, **f**: R = OMe, **g**: R = SMe

Similarly, on treating **1** with benzamidine hydrochloride (**3b**), formamidine hydrochloride (**3c**), or guanidine hydrochloride (**3d**) in MeCN or DMSO under the same reaction conditions, the corresponding 5-(trifluoromethyl)pyrimidines[11] **4b**, **4c**, and **4d** were obtained in fairly good to excellent yields (Entries 12-15). The reaction of **1** with **3e** in MeCN at room temperature for 3 h gave only a moderate yield (54%) of 2-(methylamino)-5-(trifluoromethyl)pyrimidine (**4e**)[11] (Entry 16) , but the reaction at higher temperature (70 °C, 1 h) provided an 82% yield of **4e** (Entry 17). *O*-Methylisourea (**3f**) and *S*-methylisothiourea (**3g**) also reacted

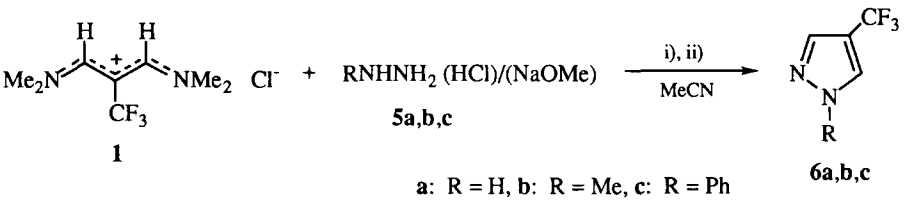
Table 1. Synthesis of 5-Trifluoromethylated Pyrimidine Compounds **4**

Entry	R	**3** (equiv.)	Base (equiv.)	Solvent	Temp./°C	Time/h	Yield[a]/% of **4**		^{19}F NMR[b]
1	Me	**3a** (1.2)	–	MeCN	r.t.	3		0[c]	
2	Me	**3a** (1.2)	Et_3N (1.2)	MeCN	r.t.	1	**4a**	61	15.7
3	Me	**3a** (1.2)	Et_3N (1.2)	MeCN	r.t.	3	**4a**	65	
4	Me	**3a** (1.2)	Et_3N (1.2)	MeCN	r.t.	24	**4a**	67	
5	Me	**3a** (1.2)	Et_3N (1.2)	MeCN	70	1	**4a**	67	
6	Me	**3a** (2.2)	Et_3N (2.2)	MeCN	r.t.	3	**4a**	66	
7	Me	**3a** (1.2)	NaOMe[d] (1.5)	MeCN	r.t.	3	**4a**	69 (41)[e]	
8	Me	**3a** (1.2)	NaOMe[d] (1.5)	DMSO	r.t.	3	**4a**	68	
9	Me	**3a** (1.2)	NaOMe[d] (1.5)	DMF	r.t.	3	**4a**	69	
10	Me	**3a** (1.2)	NaOMe[d] (1.5)	CCl_4	r.t.	3	**4a**	66	
11	Me	**3a** (1.2)	NaOMe[d] (1.5)	EtOH	r.t.	3	**4a**	69	
12	Ph	**3b** (1.2)	NaOMe[d] (1.5)	MeCN	r.t.	3	**4b**	85 (85)	16.0
13	H	**3c** (1.2)	NaOMe[d] (1.5)	MeCN	r.t.	3	**4c**	60 (40)[e]	15.7
14	NH_2	**3d** (1.2)	NaOMe[d] (1.5)	MeCN	r.t.	3	**4d**	(69)	17.5
15	NH_2	**3d** (1.2)	NaOMe[d] (1.5)	DMSO	r.t.	3	**4d**	80 (70)	
16	NHMe	**3e** (1.2)	NaOMe[d] (1.5)	MeCN	r.t.	3	**4e**	54 (43)	17.0
17	NHMe	**3e** (1.2)	NaOMe[d] (1.5)	MeCN	70	1	**4e**	82 (70)	
18	OMe[f]	**3f** (1.2)	NaOMe[d] (1.5)	MeCN	r.t.	3	**4f**	80 (69)	16.7
19	SMe[f]	**3g** (1.2)	NaOMe[d] (1.5)	MeCN	r.t.	3	**4g**	(71)	16.3
20	SMe[f]	**3g** (1.2)	NaOMe[d] (1.5)	DMSO	r.t.	3	**4g**	76 (73)	

[a] Determined by ^{19}F NMR. Figures in parentheses are of the yields of isolated products. [b] The chemical shifts are shown in ppm downfield from external trifluoroacetic acid (TFA). [c] The starting salt **1** remained unreacted. [d] A methanol solution (28 wt%) was used. [e] Lowered due to high volatility of the product. [f] The sulfate was employed.

with **1** to afford the corresponding pyrimidines **4f** and **4g**,[11] respectively, in good yields (Entries 18-20).

Hydrazine derivatives also participated nicely in the present reaction. For example, the reaction of **1** with hydrazine hydrochloride (**5a**), methylhydrazine (**5b**), or phenylhydrazine (**5c**) (1.2 equiv.) in MeCN took



(4)

a: R = H, **b**: R = Me, **c**: R = Ph

6a: i) r.t., 1 h; ii) AcOH or TFA (3 equiv.), 70 °C, 1 h (74-78%)
6b: i) r.t., 1 h; ii) AcOH (3 equiv.), r.t., 1 h (77%)
6c: i) r.t., 1 h; ii) TFA (3 equiv.), 70 °C, 1 h (81%)

place cleanly under the conditions cited in Eq 4 to give 4-(trifluoromethyl)pyrazole (**6a**),[11] 1-methyl- (**6b**)[11] or 1-phenyl-4-(trifluoromethyl)pyrazole (**6c**)[11] in 78%, 77%, and 81% yield, respectively.

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9. Pale yellow solid; IR (KBr) 2905, 1600, 1371, 1292 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.33 (q, J = 2.0 Hz, 6H), 3.62 (s, 6H), 9.03 (s, 2H); ^{19}F NMR ($CDCl_3$, TFA, 56.47 MHz) δ 30.3 (bs); ^{13}C NMR ($CDCl_3$, 75.61 MHz) δ 42.68 (q, J = 5.1 Hz), 49.29 (s), 91.33 (q, J = 37.1 Hz), 122.42 (q, J = 270.0 Hz), 164.81 (s); SIMS m/z 425 ($2M^+$-Cl), 195 (M^+-Cl).
10. ^1H NMR ($CDCl_3$, 200 MHz) δ 3.22 (dq, J = 2.0, 10.7 Hz, 2H), 9.74 (tq, J = 2.0, 1.9 Hz, 1H); ^{19}F NMR ($CDCl_3$, TFA, 56.47 MHz) δ 16.0 (dt, J = 1.9, 10.7 Hz). Melting point (149.5-150.5 °C) of 2,4-dinitrophenylhydrazone of this propanal was consistent with the literature value (lit.[12] m.p. 150.2-150.8 °C).
11. All isolated compounds **4** and **6** exhibited spectroscopic (IR, MS, HRMS, ^1H and ^{19}F NMR) and analytical data which are in good accord with the assigned structures.
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