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Synthesis of Trifluoromethylamino-Substituted Pyridines and Pyrimidines by Oxidative Desulfurization-Fluorination

Manabu Kuroboshi,* Katsuya Mizuno, Kiyoshi Kanie, and Tamejiro Hiyama*

Tokyo Institute of Technology, Research Laboratory of Resources Utilization
4259 Nagatsuta, Midori-ku, Yokohama, Kanagawa 227, Japan

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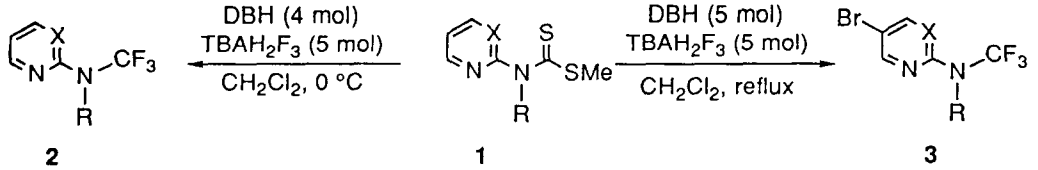
Abstract: Oxidative desulfurization-fluorination of methyl *N*-pyridyl(or *N*-pyrimidyl)-*N*-alkyldithiocarbamates gave the corresponding trifluoromethylamino-substituted pyridines (or pyrimidines), which underwent cross-coupling reaction to give a new type of liquid crystalline compounds having trifluoromethylamino group.

Nucleophilicity and basicity of amines are expected to be reduced when trifluoromethyl group is introduced to nitrogen atom. Thus, physical, chemical, and/or biological properties of trifluoromethylamines will be modified enormously as compared with those of the corresponding methylamines. Dialkyl(trifluoromethyl)amines are susceptible to hydrolysis and, in some cases, used for fluorination of alcohols and carboxylic acids.[1]

Trifluoromethylamines have been so far prepared[2-5] by use of a highly toxic reagent like SF_4 or anhydrous hydrogen fluoride in low yields. Thus, these harsh conditions have hampered the wide applications of trifluoromethylamines.

Oxidative desulfurization-fluorination[6] is an efficient method to synthesize organofluorine compounds under mild reaction conditions. For example, trifluoromethylamines (R^1R^2N-CF_3) were readily prepared from methyl dithiocarbamates (R^1R^2N-C(S)SMe).[6d] We report herein that this methodology can be extended to the synthesis of trifluoromethylamino-substituted pyridines and pyrimidines. We also describe the reactivity of these heteroaromatics as well as the first synthesis of liquid crystalline compounds containing trifluoromethylamino group.



2 **1** **3**

Table 1. Synthesis of Trifluoromethylaminopyridines and -pyrimidines

Yield/%[a]		R	X	Yield/%[b]	
2a	72	CH_3	CH	**3a**	74
2b	80	CH_2Ph	CH	**3b**	78
		nC_6H_{13}	CH	**3c**	89
2d	76[b]	nC_8H_{17}	CH	**3d**	89
2e	86[b]	$nC_{12}H_{25}$	CH	**3e**	90
2f	82	CH_3	N	**3f**	84
		nC_3H_7	N	**3g**	81
2h	58	nC_6H_{13}	N	**3h**	61
2i	80	nC_8H_{17}	N	**3i**	24
2j	63	$nC_{12}H_{25}$	N	**3j**	15

a) Isolated yields are given. b) Carried out at -20 °C.

A typical procedure follows. To a CH_2Cl_2 (1.5 mL) suspension of tetrabutylammonium dihydrogentrifluoride ($TBAH_2F_3$, 2.5 mmol) and 1,3-dibromo-5,5-dimethylhydantoin (DBH, 2 mmol) was added *Het*(R)N-C(S)SMe (**1**, 0.5 mmol) at 0 °C, and the resulting mixture was stirred for 30 min at 0 °C. Workup and purification by silica-gel column chromatography afforded *Het*(R)N-CF_3 (**2**) in good yields as shown in Table 1.

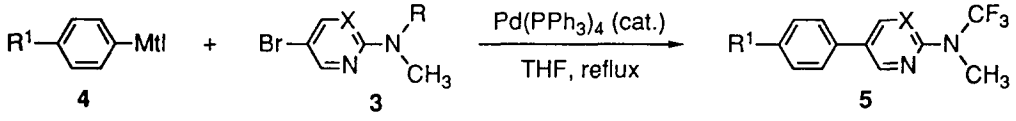
At higher temperatures, ring bromination accompanied. To avoid the side reaction, the reaction should be carried out below 0 °C, especially at -20 °C in the case of **1d** and **1e**. When the fluorination was effected at room temperature, the ring bromination became obvious; in refluxing CH_2Cl_2 brominated trifluoromethylamines **3** predominated (Table 1). Hereby selective monobromination at C-4 resulted due to the electron-withdrawing trifluoromethylamino group. By treatment with DBH-$TBAH_2F_3$, **2b** was converted into **3b** in 49% yield. These results contrast sharply to bromination of 2-dimethylaminopyridine which underwent dibromination under the same conditions. The products **2** and **3** tolerated hydrolysis like trifluoromethylaminobenzene derivatives.[6d]

Fluorination of methyl *N*-benzyl-*N*-(3-pyridyl)dithiocarbamate also successfully took place in refluxing CH_2Cl_2 to give benzyl(3-pyridyl)(trifluoromethyl)amine in 82% yield without any extent of bromination.

Trifluoromethylamines are highly resistant to oxidation as compared with ordinary methylamines: oxidation potential of **3f** was found by cyclic voltammetry to be 2.32 V vs SCE, 0.97 V higher than that of 2-dimethylamino-4-bromopyrimidine which showed 1.45 V. Similarly, oxidation potential of trifluoromethyl(diphenyl)amine was 1.90 V vs SCE, 0.94 V higher than that of diphenylmethylamine (0.96 V), and close to that of diphenyl ether (1.87 V).

We next studied the synthesis of liquid crystalline compounds derived from bromopyridines and -pyrimidines **3** through cross-coupling reaction. Reaction of **3** with arylzinc reagents and/or

aryl(ethyl)(difluoro)silane[7] in the presence of catalytic amount of $Pd(PPh_3)_4$ gave rise to heterobiaryl compounds **5**. The yields and phase transition temperatures of **5** are shown in Table 2.



4 **3** **5**

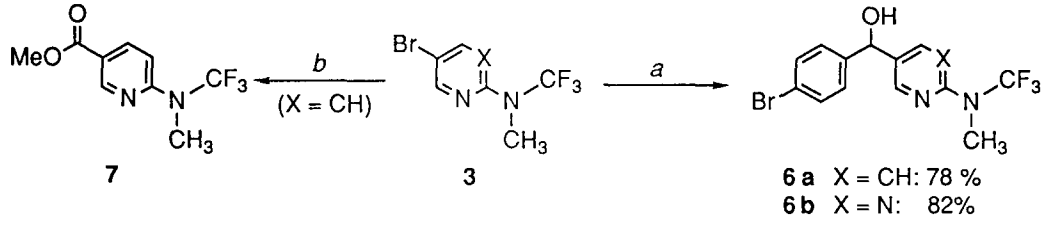
Table 2. Synthesis and Phase Transition Temperature of Heterobiaryls

Run	R^1	MtI	X	R	Yield/%[a]		Phase transition temp.[b]
1	*n*-C_3H_7	ZnCl	CH	CF_3	**5a**	62	Cr 54 S_A 65 I
2	*n*-C_3H_7O	ZnCl	CH	CF_3	**5b**	58	Cr 68 S_A 95 I
3	*n*-$C_6H_{13}O$	ZnCl	CH	CF_3	**5c**	67	Cr 48 S_A 72 I
4	*n*-$C_6H_{13}O$	ZnCl	CH	CH_3	**5d**	35	Cr 113 I
5	*n*-$C_8H_{17}O$	ZnCl	CH	CF_3	**5e**	20	Cr 38 S_A 65 I
6	CH_3O	$SiEtCl_2$[c]	N	CF_3	**5f**	45	Cr 87 I
7	*n*-C_3H_7O	ZnCl	N	CF_3	**5g**	45	Cr 103 I
8	*n*-C_3H_7O	ZnCl	N	CH_3	**5h**	48	Cr 115 I
9	*n*-$C_6H_{13}O$	ZnCl	N	CF_3	**5i**	38	Cr 90 I

a) Isolated yields. b) Phase transition temperatures were measured on a polarizing microscope equipped with a hot stage. c) Two chlorines were replaced by two fluorines with excess KF.

Trifluoromethyl(methyl)amino-substituted phenylpyridines **5a**, **5b**, **5c** and **5e** were found to exhibit smectic A phase, whereas 2-dimethylamino-5-(4-hexyloxyphenyl)pyridine (**5d**) and phenylpyrimidines **5f**, **5g**, **5h** and **5i** did not show any liquid crystal phase. Thus, the trifluoromethyl group on amine nitrogen appears to render liquid crystallinity. This is the first example of the liquid crystalline compounds containing trifluoromethylamino moiety. In addition, melting points of pyridines and pyrimidines were lowered by changing CH_3 into CF_3 (compare **5c** and **5g** with **5d** and **5h**, respectively).

Lithium-bromine exchange of **3** was readily effected by means of *n*-BuLi at -78 °C, and the resulting pyridyl- and pyrimidyllithium reacted with 4-bromobenzaldehyde to give the corresponding adducts **6a** and **6b**, respectively, in good yields. Methyl 6-[trifluoromethyl(methyl)amino]nicotinate (**7**) was obtained in 42% yield by lithiation of **3a** followed by treatment with CO_2 and CH_2N_2. During these transformations, both trifluoromethylamino group and heteroaromatic rings remained intact.



7 3

a: 1) *n*-BuLi (1.1 mol), THF, -78 °C, 0.5 h. 2) *p*-BrC_6H_4CHO (1.2 mol), -78 °C ~ rt, 12h.
b: 1) *n*-BuLi (1.1 mol), THF, -78 °C, 0.5 h. 2) CO_2 (excess), -78 °C ~ rt, 3) CH_2N_2 (excess), rt.

The present method allows us to prepare trifluoromethylaminopyridines and -pyrimidines under extremely mild conditions, starting from readily accessible dithiocarbamates. We have demonstrated that these trifluoromethylamines are tolerant of oxidation as compared with the corresponding methylamines and that phenylpyridines containing trifluoromethylamino group show liquid crystalline phase. We are studying further the synthesis and properties of trifluoromethylamino-substituted liquid crystals.

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