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PRELIMINARY NOTE

A Facile One-pot Preparation of 2-Methyl- and 2-Phenyl-4-fluoro-5-trifluoromethyl-6-methoxypyrimidine from Methyl 2-hydryl-2-(F-methyl)-F-propyl Ether

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SUMMARY

The title compounds were readily prepared in one-pot by phase-transfer reaction of a methanol adduct of 2-(F-methyl)-F-propene with acetamidine or benzamidine in the presence of aqueous sodium hydroxide in CH_2Cl_2. Various 5-trifluoromethylpyrimidines were also synthesized via nucleophilic substitution of the 4-fluorine of the title compounds.

There is increasing interest in organic compounds bearing the trifluoromethyl group, because of their possible physiological activities as well as increasing lipophilicities [1]. As far as the methodologies are concerned, there are two possible ways to synthesize trifluoromethylated compounds; 1) to build molecules having the trifluoromethyl group starting from fluorinated compounds, and 2) to modify established molecules with trifluoromethylating reagents or to fluorinate suitable functional groups to trifluoromethyl groups. Here we wish to report our results showing the potentiality of methyl

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2-(F-methyl)-F-propenyl ether (2) as a building block for the synthesis of trifluoromethylated heterocyclic compounds in the preparation of 4-fluoro-5-trifluoromethylpyrimidines, and eventually 5-trifluoromethylpyrimidines via nucleophilic substitution of 4-fluorine. This reaction is featured by its rapidity, simple procedure, and inexpensive reagents used.

The reaction of 2 with acetamidine hydrochloride was first examined in the presence of bases, such as sodium hydride and sodium carbonate, in various solvents (DMF, MeCN, THF, Et_2O, CH_2Cl_2). Even in the presence of excess amount of bases, the major product was methyl 2-hydryl-2-(F-methyl)-F-propyl ether (1), a starting material of 2, and the expected product, 2-methyl-4-fluoro-5-trifluoromethyl-6-methoxypyrimidine (3), was formed only in a very poor yield (3-8% isolated). Since four equivalents of HF should be liberated from the formation of 3, the liberated HF was trapped by 2 faster than the heterogeneous neutralization with bases in the reaction mixture. However, the formation of 1 was totally suppressed, and the yield of 3 was improved when the reaction was carried out in CH_2Cl_2 in the presence of aqueous sodium hydroxide solution. Reaction proceeded smoothly even in the absence of phase transfer catalyst. The presence of phase transfer catalyst neither helped to improve the yield of 3 nor shorten the reaction time. Various reaction

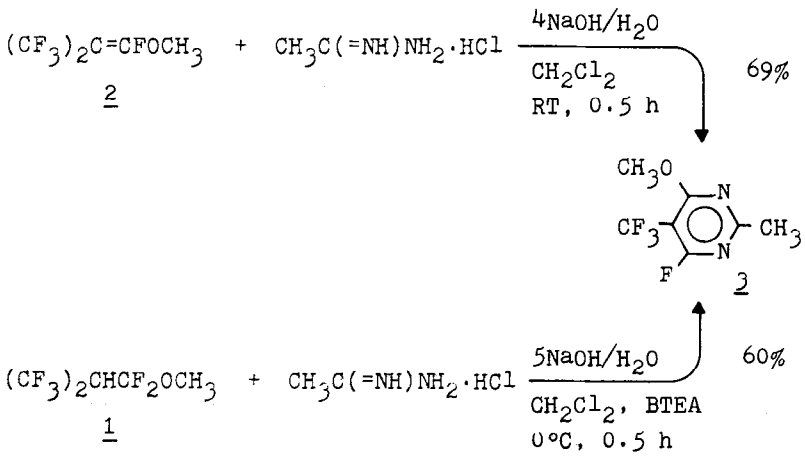


TABLE 1

Formation of 3 from 2

Run	Molar ratio 2 : acetamidine : NaOH			Temp	Period	Yield (%)[a]
1	1 :	1.5	: 3	RT	2 h	52[b]
2	1 :	1.5	: 4	RT	30 min	69
3	1 :	1.5	: 4	reflux	20 min	62
4	1 :	1.5	: 4.7	reflux	30 min	61
5	1 :	1.2	: 4	RT	2 h	42
6	1 :	1.1	: 4	RT	6 h	53
7	1 :	1.5	: 4[c]	0°C	30 min	65

[a] Isolated yield is given.

[b] Small amount of 2 was remained unreacted.

[c] Catalytic amount of BTEA was used.

TABLE 2

Formation of 3 from 1

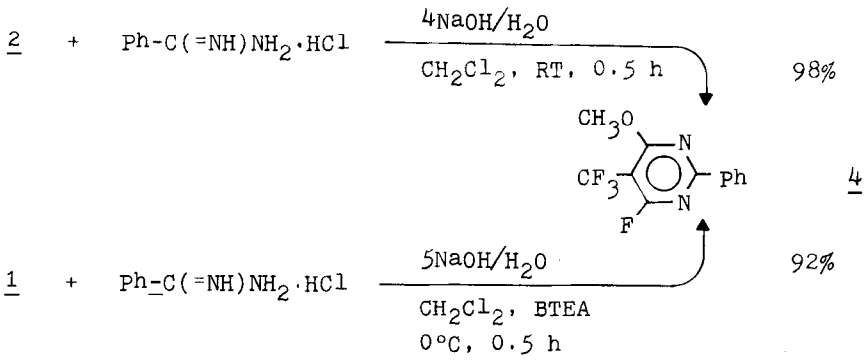
Run	Molar ratio 1 : acetamidine : NaOH			Temp	Period	Catalyst (BTEA)	Yield[a] (%)
1	1	: 1.5	: 5	RT	2 h	no	45
2	1	: 1.5	: 5	0°C	3 h	no	50
3	1	: 1.5	: 5	RT	30 min	yes	48
4	1	: 1.5	: 5	0°C	30 min	yes	60

[a] Isolated yield is given.

conditions were examined, and the results are summarized in Table 1. These results suggested to us to use 1 instead of 2 for the preparation of 3, since 2 was prepared from 1 under similar reaction conditions*. In this case, the use of a catalytic amount of benzyltriethylammonium chloride (BTEA) helped to increase the yield and to shorten the reaction period. Results are shown in Table 2.

*Compound 2 was prepared in 72% yield by dehydrofluorination of 1 with calcium hydroxide in water in the presence of a catalytic amount of BTEA.

Similarly, benzamidine gave 2-phenyl-4-fluoro-5-trifluoromethyl-6-methoxypyrimidine (4). When 2 was used as a starting material, 4 was obtained in 98% yield after stirring at room temperature for 30 min in the absence of phase transfer catalyst. Compound 1 also could be used directly for the synthesis of 4, in which a mixture of 1 in CH_2Cl_2, and benzamidine hydrochloride and sodium hydroxide in water was agitated at 0°C for 30 min in the presence of a catalytic amount of BTEA. The yield of 4 was reached to 92%.

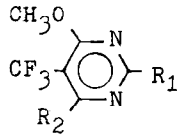


Structures of these products were established unequivocally by various spectral data. The ^{19}F NMR spectrum* of 3 gave two different kinds of absorption at δ -20.3 (d) and -16.3 (q), which were assigned to a trifluoromethyl group and a fluorine atom, respectively (J_{CF_3-F}=22.6 Hz). A similar spectrum was also obtained for compound 4; δ -20.7 (d) for a trifluoromethyl group and -17.6 (q) for a fluorine atom, J_{CF_3-F}=22.6 Hz. The ^1H NMR spectrum of 3 showed a 2-methyl group at δ 2.63 and a methoxyl group at δ 4.15. Similarly, the ^1H NMR spectrum of 4 exhibited a methoxyl group at δ 4.20, and a phenyl group at δ 7.40-8.52. The mass spectrum of 3 and 4 gave their molecular ion peaks at m/e=210 and 272, respectively.

*Chemical shifts of the ^{19}F NMR spectrum throughout this article are given in δ ppm up-field from external trifluoroacetic acid.

TABLE 3

Synthesis and physical properties of 5-trifluoromethyl-6-methoxypyrimidines



Run	R_1	R_2	Yield (%)	bp/mmHg (mp)	^{19}F NMR
1	Me	NEt_2	83	118-120/16	-21.6
2	Me	NHPr	72	115-117/15	-22.5[a]
3	Me	NHPh	45	(93-94)	-24.3[b]
4	Me	NH_2	35	(122-123.5)	-23.8
5	Me	OMe	32	(94-95.5)	-22.1
6	Me	OEt	48	(30.5-31)	-21.7
7	Me	OPh	57	110-112/2	-21.8
8	Ph	NEt_2	86	(30-34)	-22.2
9	Ph	NHPr	80	(53-53.5)	-23.5[c]
10	Ph	OMe	85	(59-62)	-22.7
11	Ph	OPh	64	(128-129)	-22.8

[a] d, J_{CF_3-NH}=4.2 Hz. [b] d, J_{CF_3-NH}=2.8 Hz. [c] d, J_{CF_3-NH}=4.5 Hz.

A fluorine atom at 4-position of compound 3 and 4 should be susceptible towards nucleophilic substitution, since it is activated by ring nitrogens and an adjacent trifluoromethyl group. Thus, various nucleophiles were successfully introduced, and some of the results are summarized in Table 3.

Synthesis of 3 and 4

To a flask containing 1 (2.32 g, 10 mmole), acetamidine hydrochloride (1.42 g, 15 mmole) and BTEA (10 mg) in 10 ml each of CH_2Cl_2 and water, cooled in an ice-bath, was added aqueous solution of sodium hydroxide (2.0 g, 50 mmole in 10 ml of water) dropwise. After stirring vigorously by a magnetic stirrer for 30 min, CH_2Cl_2 layer was separated, washed with 10% HCl, and

water, and dried over $MgSO_4$. Methylene chloride was recovered on rotary evaporator, and the residual oil was subjected to distillation under reduced pressure to give 1.25 g of 3 (60% yield) at 66-67°C/18 mmHg. In the case of benzamidine, crude product 4 was obtained after evaporation of CH_2Cl_2. Recrystallization from petroleum ether gave a pure sample having mp 59.5-62°C.

Derivation of 3 and 4

A typical experimental procedure is given in the reaction of 3 with propylamine.

To an ethereal solution (30 ml) of 3 (2.10 g, 10 mmole) cooled in an ice-bath, was added n-propylamine (1.80 g, 30 mmole). After stirring at 0°C for 30 min, precipitates were filtered, and the filtrate was concentrated. Distillation under reduced pressure gave 1.60 g (64% yield) of 2-methyl-4-propylamino-5-trifluoromethyl-6-methoxypyrimidine at 115-117°C/15 mmHg.

1 a) K. L. Kirk and L. A. Cohen in 'Biochemistry Involving Carbon-Fluorine Bonds,' (ed. by R. Filler) Am. Chem. Soc., Washington, 1976, p.23; b) R. Filler in 'Organofluorine Chemicals and Their Industrial Applications,' (ed. by R. E. Banks), Ellis Horwood, London, 1979, p.123; c) W. G. M. Jones in 'Preparation, Properties, and Industrial Applications of Organofluorine Compounds,' (ed. by R. E. Banks), Ellis Horwood, London, 1982, p.157.