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SYNTHETIC UTILIZATION OF METHYL 2-(F-METHYL)-2-HYDRYL-F-PROPYL ETHER. PART III [1]. A SIMPLE ONE-POT PREPARATION AND DERIVATIZATION OF 2-ALKYLTHIO-5-(F-METHYL)-6-FLUORO-3,4-DIHYDRO-4(3H)-PYRIMIDINONES

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SUMMARY

The title compounds were readily synthesized in one pot by the reaction of methyltriethylammonium 2-(F-methyl)-F-propenolate, formed directly by the reaction of methyl 2-(F-methyl)-2-hydryl-F-propyl ether with two equivalents of triethylamine in DMF, and S-alkylisothiourea hydrogen halide, followed by the reaction with triethylamine again. Derivatizations via nucleophilic substitution of the fluorine atom at the 6-position were performed after alkylation of the title compounds leading to the preparation of various trifluoromethyl substituted pyrimidines.

INTRODUCTION

In recent years, considerable attention has been paid to heterocyclic compounds having the trifluoromethyl group,

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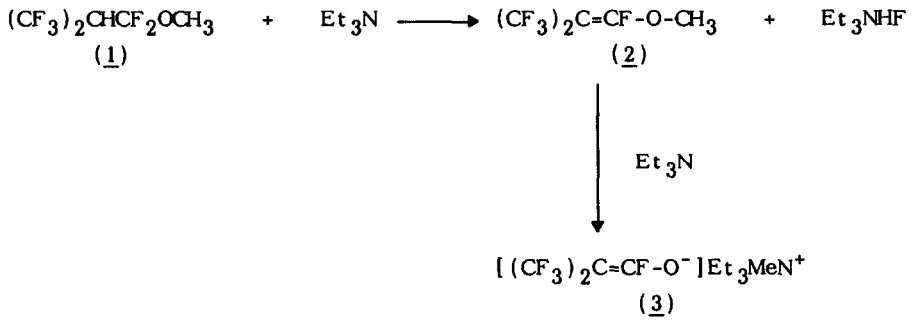
because their possible biological activities may be enhanced by its strong antioxidation ability and increasing lipophilicity [2]. 2-(F-methyl)-F-propene is a major by-product in the manufacturing of F-propene, but has not been utilized much as a raw material, due to its extreme toxicity and high volatility; it is readily converted [3] to a less harmful methanol adduct, methyl 2-hydryl-2-(F-methyl)-F-propyl ether (1). We have investigated the synthetic utilization of 1 as a useful starting material for the synthesis of trifluoromethylated compounds, and have already reported the synthesis of trifluoromethyl pyrimidines [4] and uracils [1]. In the latter case, the key step was the generation of 2-(F-methyl)-2-hydryl-F-propanoyl fluoride (4) by the tedious treatment of methyltriethylammonium 2-(F-methyl)-F-propenolate (3) with hydrogen chloride. Also compound 4 was reported to be prepared by the reaction of 1 with sulfur trioxide [5] or antimony pentafluoride[6]. However, the procedure seemed to us not to be suitable for ordinary laboratory equipment and limited availability of the reagent. Herein, we wish to report a simple preparation of 2-alkylthio-5-(F-methyl)-6-fluoro-3,4-dihydro-4(3H)-pyrimidinones (9) in one pot from 1 using inexpensive and ordinary reagents.

RESULTS AND DISCUSSION

Quantitative formation of the ammonium enolate 3 [7] was achieved within 1 h in DMF, when 1 was treated with two equivalents of triethylamine. This was measured by the internal standard method in the ^{19}F NMR analysis of the reaction mixture*. The reaction apparently proceeded via dehydrofluorination of 1 with one equivalent of

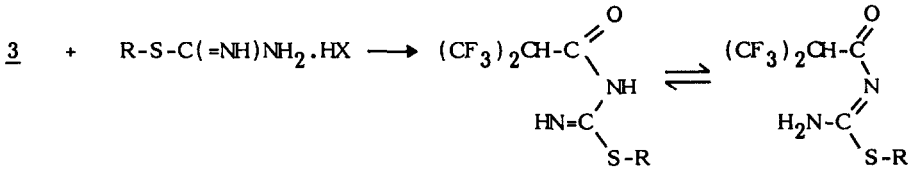
* Chemical shifts of the ^{19}F NMR spectrum throughout this article are given in δ ppm upfield from external trifluoroacetic acid.

triethylamine.Quarternary ammonium salt formation from the first-formed methyl 2-(F-methyl)-F-propenyl ether (2) then occurred, using the rest of triethylamine. When 1 was treated with an equimolar amount of triethylamine in DMF, none of 2 was detected either by GLC or ^{19}F NMR analysis, and the formation of 3 was quantitative based on the consumption of 1.



This result indicated that the second step was faster than the first one.

To the solution of 3 was added S-alkylisothiourea hydrogen halide, prepared by the addition of an alkyl halide to thiourea in DMF. Since the reaction was exothermic, the reaction mixture was cooled in an ice-bath, and the temperature was controlled below 20°C. After the addition was completed, the reaction mixture was stirred at room temperature, and then it was poured into water. The precipitate was collected by suction filtration.

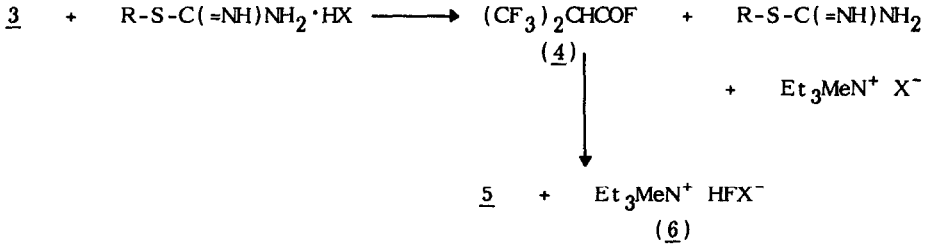


(5)

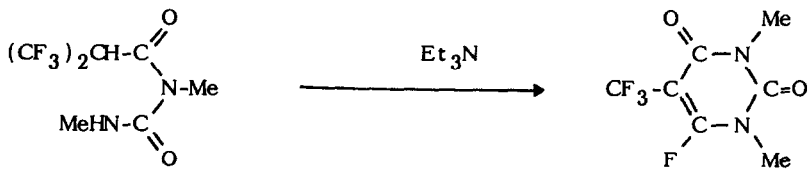
The structure of the product was elucidated by the ^{19}F and ^{1}H NMR, IR and mass spectra as N-[2-(F-methyl)-2-hydryl-F-

propanoyl]-S-alkylisothiourea (5). The results are shown in Table 1. The presence of the hexafluoroisopropyl group was confirmed by both the ^{19}F and ^{1}H NMR spectra, where a doublet and a septet were measured respectively. Alkyl groups were also detected with ease. Although hydrogens bonded to nitrogen were sometimes elusive, the mass spectra showed the molecular ion peak definitively.

The reaction sequence can be explained as follows. The pre-formed enolate abstracts hydrogen from S-alkylisothiourea hydrogen halide to yield 4 and S-alkylisothiourea, which, in turn, react to give 5 and hydrogen fluoride, and the latter then forms 6. Since 3 can not abstract hydrogen from a tetraalkylammonium fluoride, hydrogen abstraction occurs only from the isothiuronium salt, not from 6.



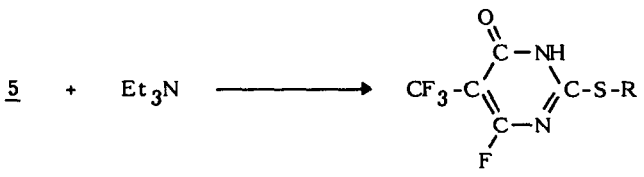
Intramolecular cyclization of 5 was expected by the reaction with triethylamine, since a similar cyclization had been achieved previously by the reaction of 1-[2-(F-methyl)-2-hydryl-F-propanoyl]-1,3-dimethylurea (7) with triethylamine, which yielded 1,3-dimethyl-5-(F-methyl)-6-fluoro-2,4(1H,3H)-pyrimidinedione (8) [1].



(7) (8)

Thus, 5 was reacted with triethylamine in DMF. Exothermic reaction started at about 45°C, and the temperature was controlled below 70°C by adjusting the rate of the addition. Reaction was followed by TLC analysis, and it was observed that the reaction finished within 1 h. Solid product was collected by suction filtration from aqueous mixture of the reaction mass, and recrystallized.

The structure of the product was established by various spectral measurements including the ^{19}F and ^{1}H NMR, IR and mass spectra as 9. The ^{19}F NMR spectrum of 9a showed a doublet and a quartet in a relative intensity ratio of 3 : 1 respectively, whose coupling constant was 22.6 Hz. This result indicated the presence of cis-CF_3-C=C-F. Similar results were also obtained for 9b-d. Results are summarized in Table 2. The chemical shifts for CF_3 groups appeared around -20 ppm, but those for fluorine varied from -17 to -23 ppm. The ^{1}H NMR spectrum of 9a showed a methyl group at δ 2.57 ppm, and a broad peak at δ 12.47 ppm indicating the presence of acidic hydrogen bonded either to nitrogen or oxygen.



(9)

The formation of 9 could be carried out in one pot starting from 1. Yields obtained by this method are also given in parentheses in Table 2.

Next, the introduction of various groups through displacement of the fluorine atom in 9a and 9b was attempted, but only salt formation was observed between 9 and nucleophiles, and none of the displaced products were formed. Also, quantitative recovery of 9 was obtained when the reaction mixture was acidified.

In order to block the acidic hydrogen, alkylation was carried out in acetonitrile with iodomethane or bromoethane in the presence of potassium fluoride supported on alumina [8].

TABLE 1

Preparation of 5

Compound	R	Yield (%)	Mp (°C)	^{19}F NMR	
				δ ppm	J(Hz)
5a	Me	92	117.5-118.5	-14.3	7.9
5b	Et	83	96-97	-14.2	7.9
5c	Pr	72	68.5-69.5	-14.3	7.5
5d	Bu	65	49-50	-14.0	8.1

TABLE 2

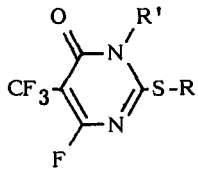
Preparation of 9

Compound	R	Yield (%)[a]	Mp (°C)	^{19}F NMR		
				CF_3	F	J(Hz)
9a	Me	70 (83)	190-191	-20.5	-17.6	22.6
9b	Et	79 (79)	163-164	-20.3	-17.9	22.6
9c	Pr	72 (75)	117-117.5	-19.9	-22.9	22.6
9d	Bu	74	59.5-61	-19.8	-22.4	22.8

[a] Isolated yields based on 5 are given. Also, isolated yields of products prepared in one pot are given in parentheses.

TABLE 3

Results on the alkylation of 9



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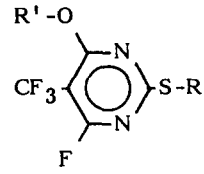
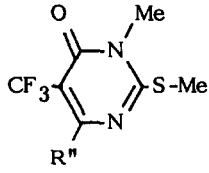


(11)

R	R'	Yield (%)	Conditions	Product Ratio 10 : 11 (Physical Property)
Me	Me	88	RT/48 h	90 : 10 (Mp 90-91) (Bp 79-80/5)
Me	Et	82	80°C/6 h	39 : 61 (Mp 54-56) (Bp 77-80/2)
Et	Me	85	RT/48 h	92 : 8 (Mp 50-51)

TABLE 4

Derivatization of 10 and 11



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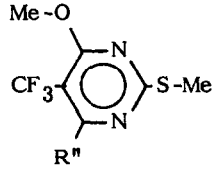
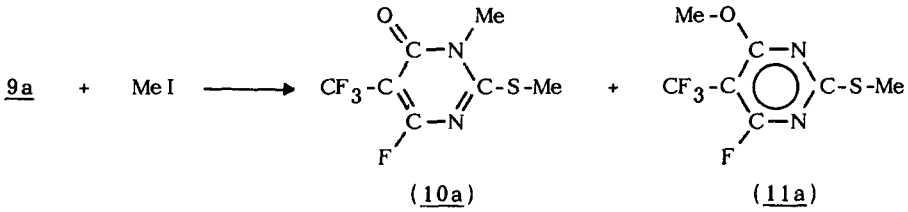


(13)

	R"	Yield (%)	Mp (Bp/mmHg)
12	NH_2	81	197-197.5
	NHMe	75	193-194
	NHEt	55	164-165
	NEt_2	83	120-121.5
	OMe	44	112-113.5
	OPh	77	132.5-134

13	NH_2	84	140-143
	NHPh	41	(68-69/1.2)

Both N- and O-alkylated products were obtained. Regioselective alkylation was observed when the reaction was carried out at room temperature, but this selectivity was destroyed at elevated temperature as shown in Table 3.



(10a) (11a)

O-Methylated product, 2-methylthio-4-fluoro-5-(F-methyl)-6-methoxypyrimidine (11a), was alternatively synthesized by the reaction of 2 and S-methylisothiourea in benzene in the presence of aqueous sodium hydroxide. This method was similar to, but modified slightly from that reported previously [4].

Derivatization of 10a and of 11a via nucleophilic substitution of the fluorine atom could be achieved, and gave a variety of trifluoromethyl substituted pyrimidinones and pyrimidines. Some of these results are shown in Table 4.

EXPERIMENTAL

Synthesis of 9a from 1 in one pot

Triethylamine and DMF were dried by distillation over calcium hydride.

To a 1-liter three necked flask equipped with magnetic stirring bar, condenser capped by calcium chloride tube, thermometer, and pressure-equalized addition funnel was added thiourea (151 g, 1.98 moles) dissolved in 300 ml of DMF, and cooled in an ice-bath below 10°C. Iodomethane (282 g, 1.98 moles) was added at such a rate that the temperature was kept

below 30°C for the preparation of S-methylisothiourea hydrogen iodide. Also, to a 3-liter flask equipped with mechanical stirring rod, thermometer, condenser capped with calcium chloride tube, and addition funnel was added 1 (450 g, 1.94 moles) dissolved in 1 liter of DMF, and cooled in an ice-bath. Triethylamine (392 g, 3.88 moles) was added below 20°C to the DMF solution of 1. After completion of the addition, the enolate solution was stirred in an ice-bath for 1 h. Then, the S-methylisothiourea solution was added to the enolate solution below 25°C. All the procedures described above were carried out in an ice-bath. Now, the bath was removed, and the reaction mixture was stirred at room temperature for 1 h. It was then heated to 45°C, and the heating was disconnected. Triethylamine (392 g, 3.88 moles) was added at such a rate that the temperature was kept below 70°C. After the addition was finished, the reaction mixture was heated at 70°C for 1 h. Then, the reaction mixture was poured into water and the precipitate formed was collected by suction filtration. Since it was difficult to dry this product, it was treated in vacuum rotary evaporator to dryness. Thus, 364 g of 9a was obtained in 83% yield. Mp 186-188°C. Recrystallization from benzene gave a pure sample having mp 190-191°C.

Methylation of 9a

To a flask with a large magnetic stirring bar and condenser were added 100 g (439 mmoles) of 9a dissolved in 1.4 liters of acetonitrile, 84 g (592 mmoles) of iodomethane, and 132 g of 10% potassium fluoride supported on alumina. The TLC analysis of the reaction mixture showed that the reaction was completed within 2 days. After the removal of the solid material by suction filtration, the filtrate was concentrated on a rotary evaporator, and the residue was extracted with benzene. Again, the benzene extract was evaporated on an evaporator to give 93.3 g (88% yield) of the products mixture, whose ratio was 9 : 1 relative to 10a and 11a checked by GLC analysis. Recrystallization from hexane gave pure 10a (80 g, 75% yield). Mp 90-91°C.

Alternative synthesis of 11a

A heterogeneous mixture containing 64.3 g (303 mmoles) of 2 dissolved in 400 ml of benzene, 99.7 g (457 mmoles) of S-methylisothiuronium iodide dissolved in 300 ml of water, 74.4 g (1.86 moles) of sodium hydroxide dissolved in 150 ml of water, and 0.5 g of benzyltriethylammonium chloride was heated to reflux with vigorous stirring for 3 h. The benzene layer was separated, and the aqueous phase was extracted with ether (300 ml each, twice). The combined mixture was dried over $MgSO_4$, and concentrated on a rotary evaporator. The residual oil was distilled in vacuum to give 48.7 g (67% yield) of 11a at 67-69°C under 4 mmHg. Chromatographic properties as well as spectral results of this sample were consistent with the ones obtained by the alkylation of 9a.

Nucleophilic substitution on 10a

The reaction of 10a with ammonia is given as a typical example.

To a flask equipped with magnetic stirring bar, condenser capped with calcium chloride tube, and thermometer was added 10.0 g (41 mmoles) of 10a dissolved in 50 ml of DMF and cooled in an ice-bath. Aqueous ammonia (25%, 21 ml) was then added. Spontaneous reaction occurred. After stirring for 30 min in the bath, the reaction mixture was poured into water, and precipitated product was collected by suction filtration to afford 8.9 g (90% yield, mp 188-190°C) of 2-methylthio-3-methyl-5-(F-methyl)-6-amino-3,4-dihydro-4(3H)-pyrimidinone. Recrystallization from benzene gave 8.0 g (81% yield) of a pure sample having mp 197-197.5°C.

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