Journal of Fluorine Chemistry, 27 (1985) 379–384

Received: July 6, 1984; accepted: October 20, 1984

2-HYDRYL-2-(F-METHYL)-F-PROPANOYL FLUORIDE AS A USEFUL BUILDING BLOCK FOR THE SYNTHESIS OF TRIFLUOROMETHYLATED HETEROCYCLIC COMPOUNDS. SYNTHESIS OF 1,3-DIMETHYL-2,3-DIHYDRO-5-(F-METHYL)-6-FLUORO-2-THIOXO-4(1H)-PYRIMIDINONE AND 1,3-DIMETHYL-5-(F-METHYL)-6-FLUORO-2,4(1H,3H)-PYRIMIDINEDIONE

YOSHIO INOUYE*

Department of Resources and Environment Science,
Tokai University, 1117 Kita-Kaname, Hiratsuka-shi,
Kanagawa 259-12 (Japan)

TSUTOMU YOKOZAWA and NOBUO ISHIKAWA

Department of Chemical Technology,
Tokyo Institute of Technology, Ookayama, Meguro-ku,
Tokyo 152 (Japan)

SUMMARY

The usefulness of 2-hydryl-2-(F-methyl)-F-propanoyl fluoride as a building block for the synthesis of trifluoro methylated compounds has been shown in the synthesis of the title compounds by the reaction of the acid fluoride with 1,3-dimethylthiourea and 1,3-dimethylurea followed by intramolecular cyclization.

INTRODUCTION

Recently, much attention has been focussed on fluorine-containing organic compounds, because of their possible biological activities [1]. Among these interests, introduction of the trifluoromethyl group into organic molecules is one of the major topics in fluorine chemistry, since the trifluoromethyl group has been shown to increase lipophilicity [2]. Here we wish to report the synthesis of 1,3-dimethyl-2,3-dihydro-5-(F-methyl)-6-fluoro-2-thioxo-4(1H)-pyrimidinone (5) and

1,3-dimethyl-5-(F-methyl)-6-fluoro-2,4(1H,3H)-pyrimidinedione (7) from 2-hydryl-2-(F-methyl)-F-propanoyl fluoride (3), a useful building block for synthesis of trifluoromethylated compounds.

RESULTS AND EXPERIMENTAL

The fluorinated acid fluoride 3 was readily derived from methyl 2-(F-methyl)-2-hydryl-F-propyl ether (1), a stable methanol adduct of 2-(F-methyl)-F-propene. The methanol adduct 1 (4.64 g, 20 mmole) was reacted with triethylamine (4.25 g, 42 mmole) in dry diglyme (20 ml). Dehydrofluorination followed by nucleophilic substitution on the methyl group gave triethylmethylammonium 2-(F-methyl)-F-propenolate (2) [3] in solution. Formation of 2 was ensured by the ^{19}F NMR analysis of the reaction mixture after 7 h at room temperature.* The F-methyl group cis to vinyl fluorine atom appeared at δ -28.4 as a quartet of doublets ($J_{cis\text{-}F\text{-}C=C\text{-}CF_3}$=16.9 Hz, $J_{gem\text{-}CF_3\text{-}CF_3}$= 10.5 Hz). The other F-methyl group appeared at δ -26.9 as a quartet of doublets ($J_{trans\text{-}F\text{-}C=C\text{-}CF_3}$=11.5 Hz). A vinyl fluorine substituent appeared at δ -80.0 as a multiplet.

To the resultant reaction mixture was introduced hydrogen chloride, generated by the addition of concentrated hydrochloric acid (10 ml) to concentrated sulfuric acid (50 ml) The ^{19}F NMR analysis of this reaction mixture showed bands at δ -13.3 (6F) as a doublet of doublets ($J_{CF_3\text{-}H}$=7.0 Hz, $J_{CF_3\text{-}F}$=8.6 Hz) and -125.8 (1F) as a multiplet, indicating the formation of 3 and complete consumption of 2.

$$\underset{1}{(CF_3)_2CHCF_2OCH_3} \longrightarrow \underset{2}{[(CF_3)_2C{=}CF{-}O^-\ Et_3MeN^+]} \longrightarrow \underset{3}{(CF_3)_2CHCOF}$$

Attempts were made to isolate the acid fluoride 3 in vacuum. However, the best yield was only 46% based on 1, although 96% yield was obtained by the ^{19}F NMR assay of the

---

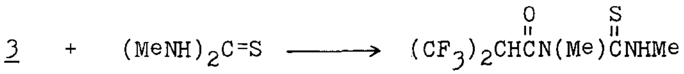
* All ^{19}F NMR chemical shifts throughout this article are given in δ ppm up-field from external F-acetic acid.

reaction mixture using an internal standard. Accordingly, the following reactions were carried out with 3 formed in diglyme solution.

When methyl 2-(F-methyl)-F-propenyl ether was used, quarternary ammonium salt formation was complete within 1 h in diglyme at room temperature. In DMF, formation of 2 was complete within 30 min at room temperature, even from 1 with two equivalents of triethylamine. However, subsequent HCl treatment gave complicated products.

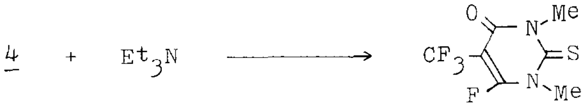
1,3-Dimethylthiourea (6.25 g, 60 mmole) was then added to the solution of 3 in diglyme, and the resultant mixture was stirred at room temperature overnight. After pouring into water, 4.92 g of 1-[2-(F-methyl)-2-hydryl-F-propanoyl]-1,3-dimethylthiourea (4) was collected as a white precipitate (87% yield based on 1 used). A pure sample of 4 was obtained by recrystallization from $CHCl_3$. Mp 119-120.5°C. Its ^{19}F NMR spectrum showed bands at δ -13.5 as a doublet split by the adjacent hydrogen (J_{CF_3-H}=7.6 Hz). The ^1H NMR spectrum of 4 showed bands at δ 3.21 (3-CH_3, d, J_{H-CF_3}=4.9 Hz), 3.37 (1-CH_3, s), 5.59 (2-H, sept, J_{H-CF_3}=7.6 Hz), and 9.91 (3-H, br). The elemental analysis of this sample gave a good accordance with the theoretical values (Calcd for $C_7H_8F_6N_2OS$; C, 29.79; H, 2.86; N, 9 93. Found; C, 29.21, H, 2.75; N, 9.68).

Cyclization via dehydrofluorination of the acylthiourea 4 followed by an intramolecular addition-elimination reaction gave 5. Acylthiourea 4 (2.82 g, 10 mmole) and triethylamine (2.23 g, 22 mmole) were dissolved in 20 ml of CH_2Cl_2. After 3 h at room temperature, the reaction mixture was washed with water twice, and dried over $MgSO_4$. Evaporation of CH_2Cl_2 gave 2.44 g of 5 (99% yield). A pure sample was prepared by column chromatography on silica-gel using hexane-ether mixed eluent. Mp 48-49°C.



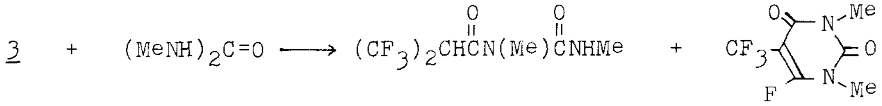
$$\underline{3} + (MeNH)_2C{=}S \longrightarrow (CF_3)_2CH\overset{O}{\overset{\|}{C}}N(Me)\overset{S}{\overset{\|}{C}}NHMe$$

4



5

Reaction of 3 with 1,3-dimethylurea was carried out similarly. In this case, products were 1-[2-(F-methyl)-2-hydryl-F-propanoyl]-1,3-dimethylurea (6) and 7 in a ratio of 45 : 55 respectively. Compounds 6 and 7 were separated by column chromatography on silica-gel using hexane-ether eluent. The fluorinated uracil 7 was formed by dehydrofluorination of 6 with unreacted 1,3-dimethylurea and subsequent cyclization. Acylurea 6 was similarly converted to 7 by triethylamine. The combined yield of 7 was 42% based on 1. A pure sample of 7 was obtained by distillation. Bp 112°C/0.3 mmHg.

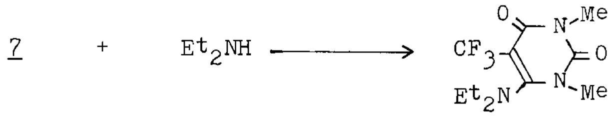


6 7

The structure of the fluorinated uracil (7) and thiouracil (5) were established unequivocally by various spectral data, elemental analysis and chemical derivatization. The ^{19}F NMR spectrum of 5 showed a doublet and a quartet of quartets at δ -20.2 and 6.8 with 3 : 1 integrated ratio respectively. The former was assigned to a trifluoromethyl group and the latter to a fluorine atom. The magnitude of the coupling constant (J_{CF_3-F}=23.5 Hz) supported the presence of cis-CF_3-C=C-F. On the other hand, the ^1H NMR spectrum showed two kinds of methyl group. One appeared at δ 3.52 as a doublet (J_{CH_3-F}=3.6 Hz) split by the adjacent fluorine atom. This was assigned to the 3-methyl group, and the other (δ 3.37), a singlet, to the 1-methyl group. The mass spectrum of 5 showed a molecular ion peak at m/e=226, which also supported the proposed structure. Finally, the elemental analysis of this sample showed a good accordance with the theoretical values. (Calcd for $C_7H_6F_4N_2OS$; C, 34.71; H, 2.50; N, 11.57. Found; C, 34.45; H, 2.42; N, 11.51)

Similarly, the ^{19}F NMR spectrum of 7 showed a doublet and a quartet (J_{CF_3-F}=28.0 Hz) at δ -20.7 and -4.5, which were assigned to a trifluoromethyl group and a fluorine atom respectively. The methyl signals for 7 appeared at δ 3.26 and 3.46 in the ^{1}H NMR spectrum. By contrast with the result obtained on thiouracil 5, the 3-methyl protons did not show a coupling with the 4-fluorine substituent. The mass spectrum of 7 displayed a molecular ion peak at m/e=242. Again, the elemental analysis of this compound showed a good accordance with the theoretical values. (Calcd for $C_7H_6F_4N_2O_2$; C, 37.18; H, 2.67; N, 12.39. Found; C, 37.11; H, 2.86, N, 12.04)

The structure of 7 was further supported by a chemical reaction, since a β-fluorine substituent bonded to the conjugated enone system should be very susceptible towards nucleophilic displacement. Thus, diethylamine (0.45 g, 6.2 mmole) was added to 7 (0.68 g, 3 mmole) in DMF at 0°C. After 1 h at room temperature, 0.52 g of 1,3-dimethyl-5-(F-methyl)-6-diethylamino-2,4(1H,3H)-pyrimidinedione (8) was obtained (62% yield). A pure sample was obtained by



8

recrystallization from CCl_4. Mp 125-126.5°C. Its ^{19}F NMR spectrum showed a singlet at δ -20.5. The ^{1}H NMR spectrum showed bands at δ 3.35, 3.38 (1-CH_3, 3-CH_3, s), 1.17 (CH_3, t, J=7.5 Hz), and 3.26 (CH_2, q, J=7.5 Hz). The mass spectrum of 8 showed a molecular ion peak at m/e=279. Again, the elemental analysis of this sample showed a good accordance with the theoretical values. (Calcd for $C_{11}H_{16}F_3N_3O_2$; C, 47.31; H, 5.78; N, 15.05. Found; C, 47.49; H, 5.89; N, 15.09)

REFERENCES

1 K. L. Kirk and L. A. Cohen in 'Biochemistry Involving Carbon-Fluorine Bonds,' ed. by R. Filler, Am. Chem. Soc., Washington, 1976, p.23.

2 R. Filler in 'Organofluorine Chemicals and Their Industrial Applications,' ed. by R. E. Banks, Ellis Horwood, London, 1979, p.123.

3 S. T. Kocharyan, E. M. Rokhlin, I. D. Rubin, P. V. Petrovsk E. I. Fedin and I. L. Knunyants, Izv. Akad. Nauk SSSR, Ser. Khim., (1967) 2366, Chem. Abst. 68 (1968) 77432d.