ELSEVIER

Journal of Fluorine Chemistry 77 (1996) 93–95

JOURNAL OF FLUORINE CHEMISTRY

A new synthesis of 5-trifluoromethyluracil

Peter Andres *, Albrecht Marhold

Central Research Department, Bayer AG, D-51368 Leverkusen, Germany

Received 28 September 1995; accepted 15 December 1995

Abstract

5-Trifluoromethyluracil, an important intermediate for the preparation of the antiviral trifluridine, is obtained by chlorinating thymine to give the new 2,4-dichloro-5-trichloromethylpyrimidine. Reacting the latter with hydrogen fluoride yields the new 2,4-difluoro-5-trifluoromethylpyrimidine, and hydrolysis with water gives 5-trifluoromethyluracil in high purity and good yield.

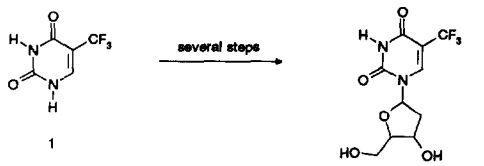
Keywords: Synthesis; 5-Trifluoromethyluracil; NMR spectroscopy; Mass spectrometry

1. Introduction

5-Trifluoromethyluracil (**1**) is an important intermediate for the preparation of trifluridine [1–3] (**2**) (5′-trifluoromethyl-2′-deoxyuridine; α,α,α-trifluorothymidine; TFT), a known antiviral active ingredient (Scheme 1).

It is known that 5-trifluoromethyluracil can be synthesized by (a) reacting uracil-5-carboxylic acid with a large excess of sulphur tetrafluoride [4], (b) direct trifluoromethylation [5] of uracil with bis(trifluoromethyl)mercury in an aqueous medium in the presence of azoisobutyronitrile (AIBN), (c) a Kolbe electrolysis of a trifluoroacetic acid solution of uracil with an iron cathode and a nickel anode [6], (d) reacting 5-trifluoromethyl-5,6-dihydrouracil (prepared by heating 2-bromo-3,3,3-trifluoropropene, bis(triphenylphosphine)-palladium(II) chloride, urea, triethylamine and dimethylformamide together at 100 °C for 10 h under 40 atm of carbon monoxide) [7] with bromine in acetic acid followed by heating in dimethylformamide (DMF) solution [8] or (e) heating trifluormethylacrylic acid (prepared by the reaction of carbon monoxide with 2-bromo-3,3,3-trifluoropropene catalyzed by bis(triphenylphosphine)palladium(II) chloride) with urea in the presence of acetic anhydride [9].

All these preparations have some important disadvantages in common: either they make use of highly toxic or expensive reagents, or the yields are low.



1 2

Scheme 1.

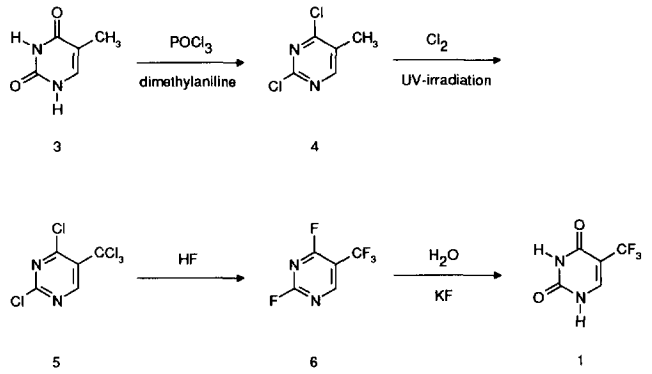
2. Results and discussion

Scheme 2 illustrates our new synthesis of 5-trifluoromethyluracil (**1**). Thus commercially available thymine (**3**) is chlorinated under mild conditions with phosphorus oxychloride in the presence of *N,N*-dimethylaniline. The starting materials are mixed at room temperature and then heated to reflux for 20 h. After separation of the excess phosphorus oxychloride, 2,4-dichloro-5-methylpyrimidine (**4**) can be isolated by distillation in yields up to 95%.

The chlorination of 2,4-dichloro-5-methylpyrimidine (**4**) can be carried out with elemental chlorine under UV irradiation at temperatures of 180–220 °C to give the new compound 2,4-dichloro-5-trichloromethylpyrimidine (**5**) in yields over 90%. Initiation of chlorination is also possible by adding radical-forming agents, for example azoisobutyronitrile or dibenzoylperoxide, instead of UV irradiation. It is surprising that the chlorination in this step produces the tri-

* Corresponding author.

SSDI 0022-1139(95)03386-6



Scheme 2.

chloromethyl compound in good yield under these drastic conditions, and that practically no dichloromethyl and chloromethyl derivatives and practically no decomposition reactions are observed.

The fluorination of pyrimidine **5** with an excess of anhydrous hydrogen fluoride at about 140 °C under a pressure of 10 bar of nitrogen yields the novel 2,4-difluoro-5-trifluoromethylpyrimidine (**6**). The work-up can be carried out by cooling, relieving the pressure, removing excess hydrogen fluoride and distilling the remaining residue. It is remarkable that five fluorine atoms can be introduced in a single reaction step, the said fluorine atoms then being found both on the aromatic ring and in the methyl side-chain. The isolated yield in this step is 90%.

In the last reaction step, 2,4-difluoro-5-trifluoromethylpyrimidine (**6**) is hydrolyzed with excess water in the presence of potassium fluoride at 50 °C to give 5-trifluoromethyluracil (**1**) in a yield of over 85%. Purification is possible by recrystallization from water to yield the pure product (purity > 99% by HPLC) with b.p. 251–252 °C. It is amazing that only the ring fluorine atoms are saponified under the aforementioned conditions, bearing in mind the known lability of the trifluoromethyl function in **1** to hydrolysis [1a,b].

Our new synthesis of 5-trifluoromethyluracil has a number of advantages in comparison with the known ones. It can be carried out with readily available starting materials and simple reagents (e.g. $POCl_3$, Cl_2, HF and H_2O); it affords 5-trifluoromethyluracil in high purity, good yields and with little waste; and it can be carried out satisfactorily on an industrial scale [10].

3. Experimental details

The NMR spectra were obtained on a Varian VXR 200 nuclear magnetic resonance spectrometer with a $^1H/^{19}F$ dual sample holder. ^1H NMR spectra were recorded in ppm downfield from tetramethylsilane and ^{19}F NMR spectra were recorded in ppm downfield from tichlorofluoromethane. All measurements were carried out in $CDCl_3$. The MS spectra were recorded on a Hewlett Packard MSD 5970B mass spectrometer. Thymine was purchased from Hüls AG.

3.1. Preparation of 2,4-dichloro-5-methylpyrimidine (4)

Dimethyklaniline (48 g) was slowly added dropwise to 3067 g of phosphorus oxychloride with cooling, and the mixture was subsequently stirred for 5 min at 25 °C. Thymine (5-methyluracil) (252 g) was then slowly added at 25 °C and the mixture subsequently stirred under reflux for 20 h. After cooling, excess phosphorus oxychloride was distilled off at 30–35 °C under a water-jet vacuum to give 301 g (92% of theory) of 2,4-dichloro-5-methylpyrimidine with b.p. 110 °C/16 mbar.

3.2. Preparation of 2,4-dichloro-5-trichloromethylpyrimidine (5)

2,4-Dichloro-5-methylpyrimidine (257 g) was placed in a three-necked flask equipped with a reflux condenser, and chlorine was then introduced under irradiation with a UV lamp with the temperature increasing gradually up to 230 °C, until gas chromatographic analysis showed that the CCl_3 product had been formed (approx. 35 h). The 2,4-dichloro-5-trichloromethylpyrimidine obtained in this way was isolated by distillation (b.p. 80–82 °C/0.08 mbar; n_D^{20} 1.5903) in a yield of 387 g (92% of theory). ^1H NMR spectra (200 MHz, $CDCl_3$) δ: 9.3 ppm. MS spectra (EI, 70 eV) *m/z*: 266 (6%); 231 (100%); 195 (10%); 161 (4%); 141 (26%); 107 (18%).

3.3. Preparation of 2,4-difluoro-5-trifluoromethylpyrimidine (6)

2,4-Dichloro-5-trichloromethylpyrimidine (500 g) and 600 ml of anhydrous hydrogen fluoride acid were placed in a stainless steel stirred autoclave at 0 °C. The apparatus was sealed, a pressure of 10 bar of nitrogen applied and the mixture heated to 142 °C. The pressure of the hydrogen chloride formed was relieved continuously via a condenser. The reaction time was 4 h. The mixture was then cooled, the pressure relieved and firstly the excess hydrogen fluoride and then the product separated off by distillation to give 311 g (90% of theory) of 2,4-difluoro-5-trifluoromethylpyrimidine with b.p. 105 °C/1013 mbar. ^1H NMR spectra (200 MHz, $CDCl_3$)/δ: 9.0 ppm. ^{19}F NMR spectra (188 MHz, $CDCl_3$) δ: −36.65; −52.85; −62.02 ppm. MS spectra (EI, 70 eV) *m/z*: 184 (85%); 165 (80%); 138 (15%); 119 (15%); 93 (55%); 69 (70%); 31 (100%).

3.4. Preparation of 5-trifluoromethyluracil (1)

Potassium fluoride (510 g) was placed in 4900 ml of water and 1620 g of 2,4-difluoro-5-trifluoromethylpyrimidine added. The mixture was then stirred for 5 h at 50 °C. The product which had crystallized out after cooling the reaction mixture to room temperature was then filtered off under suction to give 1442 g (91% of theory) of 5-trifluoromethyluracil with m.p. 251–252 °C.

References

[1] (a) C. Heidelberger *et al., J. Am. Chem. Soc., 84* (1962) 3567; (b) C. Heidelberger *et al., J. Med. Chem., 7* (1964) 1; (c) K.J. Ryan *et al., J. Org. Chem., 31* (1966) 1181; (d) Y. Kobayashi *et al., J. Chem. Soc., Perkin Trans. 1,* (1980) 2755; (e) H. Kawakami, T. Ebata, K. Koseki, H. Matsushita, Y. Naoi, K. Itoh and N. Mizutani, *Heterocycles, 31* (1990) 569; (f) T. Sugimoto, Y. Sunaga, Y. Hayashi, T. Shiba, A. Katsuyama and Y. Mikami (to Yuki Gosei Kogyo Co./Jpn. Tobacco Inc.), Eur. Pat. 0 351 853, 1990 [*Chem. Abs., 113* (1990) 22 225]; (g) K. Itoh, Y. Naoi, H. Matsushita, T. Ebata and H. Kawakami (to Yuki Gosei Kogyo Co./Jpn. Tobacco Inc.), Eur. Pat. 0 389 110, 1990; [*Chem. Abs., 114* (1990) 185 943]; (h) N. Kawauchi, N. Fukazawa, H. Ishibashi and K. Otsuka (to Mitsui Toatsu Chemicals Inc.), Eur. Pat. 0 635 517, 1995; [*Chem. Abs., 122* (1995) 291 455].

[2] C. Heidelberger, *Ann. N.Y. Acad. Sci., 255* (1975) 317.

[3] (a) C. Heidelberger *et al., Pharmacol. Ther., 6* (1979) 427; (b) A.A. Carmine *et al., Drugs, 23* (1982) 329; (c) J. Yamashita, S. Tekeda, H. Matsumoto, N. Unemi and M. Yasumoto, *Chem. Pharm. Bull., 35* (1987) 2090; (d) J. Yamashita, S. Tekeda, H. Matsumoto, N. Unemi and M. Yasumoto, *Chem. Pharm. Bull., 35* (1987) 2373; (e) J. Yamashita, S. Tekeda, H. Matsumoto, N. Unemi and M. Yasumoto, *J. Med. Chem., 32* (1989) 136.

[4] M.P. Mertes and S.E. Saheb, *J. Pharm. Sci., 52* (1963) 508.

[5] B. Schwarz, D. Cech and J. Reefschlager, *J. Prakt. Chem., 326* (1984) 985.

[6] L. Hein and D. Cech, *Z. Chem., 11* (1977) 415.

[7] T. Fuchikami and I. Ojima, *Tetrahedron Lett., 23* (1982) 4099.

[8] T. Fuchikami and A. Yamanouchi, *Chem. Lett.,* (1984) 1595.

[9] T. Fuchikami, A. Yamanouchi and I. Ojima, *Synthesis,* (1984) 766.

[10] P. Andres and A. Marhold (to Bayer AG), Ger. Pat. 4 222 518, 1994; [*Chem. Abs., 120* (1994) 191 733].