An Effective and Convenient Route to 5-Trifluoromethyl-5,6-dihydrouracils and their Thio Derivatives

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Fluorine-containing nucleic acids such as 5-fluoro- and 5-trifluoromethyluridines have attracted much attention because of their unique and strong antitumor and/or antiherpes acitivities[1]. In the course of our study on the syntheses of organofluorine compounds having biological or chemical properties based on the functionalization of fluorine-containing olefins, we found and reported a facile one-step synthesis of 5-trifluoromethyl-5,6-dihydrouracils **(4)** by a novel ureidocarbonylation of 2-bromo-3,3,3-trifluoropropene[2]. The dihydrouracils **(4)** thus obtained were converted to the corresponding uracils in almost quantitative yields by treatment with bromine[2]. Although the ureidocarbonylation gave mono- or dimethyl derivatives in good yields, the reaction afforded 5-trifluoromethyl-5,6-dihydrouracil itself only in 26% yield. We now describe more convenient and general routes to these dihydrouracils, including 2-thio derivatives **(7)**, starting from 2-trifluoromethylacrylic acid **(1)** which is obtained in good yield by the palladium complex catalyzed carbonylation of 2-bromo-3,3,3-trifluoropropene.

The dihydrouracils **(4)** and thiouracils **(7)** are obtained by the following three methods. The simplest method is heating a mixture of **1** and a 1,3-disubstituted urea in dimethylformamide at 90°C (Method A). However, this method is only applicable to 1,3-dimethylurea **(2a)** and 1,3-dimethylthiourea **(5a)**, which are thus converted into the dihydrouracils

Table 1. Synthesis of 2-Trifluoromethyl-3-ureidopropanoic Acids **(3)**, 5-Trifluoromethyl-5,6-dihydrouracils **(4)**, and their Thio Derivatives (**7** and **8**)

Ureas or Thioureas	Method	Temperature [°C]	Time [h]	Products and Yields [%]
Dimethylurea	A	90	28	**4a** [82]
(2a)	C	100	1	**4a** [84]
Urea	A	90	6	**3b** [54]
(2b)	B	90	6	**4b** [42]
	C	100	1	**4b** [67]
Benzylurea	A	90	7	**3c** [76]
(2c)	B	90	7	**4c** [86]
	C	100	1	**4c** [72]
Phenylurea	A	90	10	**3d** [79]
(2d)	B	90	10	**4d** [28]
	C	100	1	**4d** [67]
Methylurea	A	90	4	**3e** [66], **4e** [2], **4f** [12]
(2e)	B	80	4	**4e** [43], **4f** [18]
	C	100	1	**4e** [48], **4f** [32]
Dimethylthiourea **(5a)**	A	90	28	**7a** [24]
Thiourea	B	90	5	**7b** [55]
(5b)	C	100	1	**8** [71]
Phenylthiourea **(5d)**	B	90	8	**7d** [50]
Methylthiourea **(5e)**	B	80	4	**7e** [54]

4a and **7a** in 82% and 24% yields, respectively. When a monosubstituted urea (**2c–f**) or urea itself (**2b**) is used, the reaction gives the corresponding 2-trifluoromethyl-3-ureidopropanoic acid (**3**) as the main product via a Michael-type addition of the urea to **1**, the cyclization to give **4** being sluggish in this case. However, the compound **3** thus formed is easily cyclized to give the dihydrouracil **4** by treatment with dicyclohexylcarbodiimide. In order to obtain **4** (or **7**) it is not necessary to isolate **3** (or **6**). Thus, Method B consists of heating a mixture of **1** and **2** (or **5**) at 80–90 °C for 6–10 h followed by the addition of dicyclohexylcarbodiimide at 0 °C. It has turned out that acetic anhydride is an excellent reagent to promote the cyclization. Thus, Method C consists of heating a mixture of **1** and **2** in the presence of acetic anhydride at 80–100 °C, thus affording **4** directly in good yield.

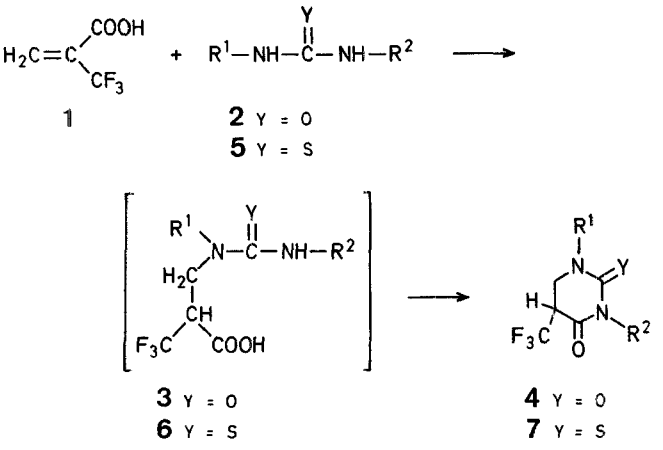
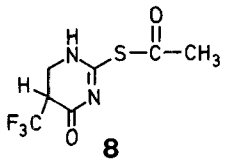


Table 2. Characterization of Products **3**, **4**, **7**, and **8**

Product	X	R^1	R^2	m.p. [°C]	Molecular Formula[a] or Lit. m.p. [°C]	I.R. (KBr) $\nu_{C=O}$ [cm^{-1}]	^{1}H-N.M.R. (acetone-d_6/TMS_{int}) δ [ppm]	^{19}F-N.M.R. (acetone-d_6/$CFCl_3$) δ [ppm]
3b	O	H	H	149–149.5°	$C_5H_7F_3N_2O_3$ (200.1)	1730, 1640	3.3–4.0 (m, 3H); 5.3–7.0 (m, 3H); 8.4 (br. s, 1H)	−66.8 (m)
3c	O	H	$-CH_2-C_6H_5$	183–183.5°	$C_{12}H_{13}F_3N_2O_3$ (290.2)	1740, 1600	3.4–3.9 (m, 3H); 4.3 (m, 2H); 6.15 (br. s, 2H); 7.27 (m, 6H)	−66.8 (m)
3d	O	H	C_6H_5	180.5–181°	$C_{11}H_{11}F_3N_2O_3$ (276.2)	1735, 1600	3.3–4.0 (m, 3H); 6.1 (br. s, 1H); 6.7–7.6 (m, 5H); 7.8 (br. s, 1H); 8.1 (br. s, 1H)	−66.6 (m)
3e	O	H	CH_3	149.5–150.5°	$C_6H_9F_3N_2O_3$ (214.2)	1740, 1725, 1610	2.70 (s, 3H); 3.3–3.8 (m, 3H); 5.9 (br. s, 1H); 6.1 (br. s, 1H); 10.7 (br. s, 1H)	−66.1 (m)
4a	O	CH_3	CH_3	44.8–46°	$C_7H_9F_3N_2O_2$ (210.2)	1725, 1685	3.09 (s, 3H); 3.20 (s, 3H); 3.2–3.7 (m, 3H)[b]	−67.9 (m)[b]
4b	O	H	H	203–205° (dec)	203–205° (dec)[3]	1750, 1710	3.4–4.2 (m, 3H); 7.0 (br. s, 1H); 9.5 (br. s, 1H)	−66.6 (m)
4c	O	H	$-CH_2-C_6H_5$	129.2–129.7°	$C_{12}H_{11}F_3N_2O_2$ (272.2)	1735, 1690	3.1–3.7 (m, 3H); 4.94 (br. s, 2H); 6.83 (br. s, 1H); 7.29 (m, 5H)[b]	−67.5 (m)[b]
4d	O	H	C_6H_5	215–216°	$C_{11}H_9F_3N_2O_2$ (258.2)	1740, 1690	3.6–4.2 (m, 3H); 7.0–7.5 (m, 6H)	−66.5 (d, J = 8 Hz)
4e	O	H	CH_3	162–163°	$C_6H_7F_3N_2O_2$ (196.1)	1730, 1705, 1690	3.03 (s, 3H); 3.4–4.0 (m, 3H); 7.0 (br. s, 1H)	−67.0 (m)
4f	O	CH_3	H	142–143°	$C_6H_7F_3N_2O_2$ (196.1)	1735, 1720, 1700	2.96 (s, 3H); 3.4–4.0 (m, 3H); 9.4 (br. s, 1H)	−67.0 (m)
7a	S	CH_3	CH_3	oil	$C_7H_9F_3N_2OS$ (226.5)	1710[c]	3.51 (s, 3H); 3.56 (s, 3H); 3.4–3.7 (m, 1H); 3.82 (br. s, 2H)[b]	−67.9 (d, J = 8 Hz)[b]
7b	S	H	H	188.5–190° (dec)	$C_5H_5F_3N_2OS$ (198.4)	1720	3.4–3.8 (m, 3H); 3.96 (br. s, 2H)[d]	−67.8 (m)[d]
7d	S	H	C_6H_5	185–186.5°	$C_{11}H_9F_3N_2OS$ (274.5)	1720	3.5–4.0 (m, 1H); 3.98 (br. s, 1H); 4.0–4.3 (m, 2H); 6.8–7.7 (m, 5H)[d]	−67.3 (d, J = 8 Hz)[d]
7e	S	H	CH_3	137.5–138°	$C_6H_7F_3N_2OS$ (212.5)	1715, 1690	3.44 (s, 3H); 3.7–4.3 (m, 3H); 10.1 (br. s, 1H)	−67.1 (m)
8				213–214°	$C_7H_7F_3N_2O_2S$ (240.5)	1720, 1675	2.14 (s, 3H); 3.0–3.5 (m, 3H); 11.8 (br. s, 1H)[e]	−66.0 (d, J = 8 Hz)[e]

[a] All compounds gave satisfactory microanalyses: C, ±0.31; H, ±0.36; N, ±0.36.
[b] In $CDCl_3$.
[c] Neat.
[d] In $CDCl_3/CD_3OD$.
[e] In DMSO-d_6.

However, the attempted synthesis of 5-trifluoromethyl-2-thio-5,6-dihydrouracil (**7b**) resulted in the formation of the acetylated product **8** in 71% yield.



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The reaction with acetylurea does not give *N*-acetyl-5-trifluoromethyl-5,6-dihydrouracil and that with methylthiourea gives a complex mixture under the conditions of Method C.

As regards the regioselectivity of the reaction, the exclusive formation of 3-substituted isomers was observed using Method B and C with phenyl- and benzylureas while with methylurea a mixture of the 1-methyl and 3-methyl isomers was obtained.

It is worthy of note that the dihydrouracils **4a**, **4e** and **4f**, exhibit considerable antitumor activity toward the tumor cells of ascitic mastocarcinoma MM2 of inbred mice.

2-Trifluoromethylacrylic Acid (1):
A mixture of dichlorobis[triphenylphosphine]-palladium (5.5 g, 7.85 mmol), 2-bromo-3,3,3-trifluoropropene (139 g, 0.794 mol), water (20 g, 1.11 mol), and triethylamine (109 g, 1.08 mol) in tetrahydrofuran (500 ml) is put in a one-liter stainless-steel autoclave and heated at 75–80 °C for 2 h with stirring under 35 atm of carbon monoxide. Then, the autoclave is cooled to 0 °C and depressurized. 2 Normal hydrochloric acid (300 ml) is added to the reaction mixture and the mixture is extracted with ether (4 × 300 ml) and dried with sodium sulfate. The solvent is evaporated and the residue distilled under reduced pressure to give **1**; yield: 74.1 g (67%); b.p. 90 °C/28 torr; m.p. 52.5–53 °C (Ref.[4], m.p. 50–51 °C; Ref.[5], 50–51 °C).

1,3-Dimethyl-5-trifluoromethyl-5,6-dihydrouracil (4a); Typical Procedure for Method A:
In a Pyrex ampoule, a mixture of 2-trifluoromethylacrylic acid (**1**; 700 mg, 5.0 mmol) and 1,3-dimethylurea (**2a**; 441 mg, 5.0 mmol) in dimethylformamide (3 ml) is heated at 90 °C for 28 h with stirring. Then, the solvent is removed under reduced pressure and the residue is submitted to a column chromatography on silica gel (eluent: chloroform); yield of **4a**: 861 mg (82%), m.p. 44.8–46 °C.

3-Methyl- and 1-Methyl-5-trifluoromethyl-5,6-dihydrouracils (4e and 4f); Typical Procedure for Method B:
In a Pyrex ampoule, a solution of 2-trifluoromethylacrylic acid (**1**; 700 mg, 5.0 mmol) and methylurea (**2e**; 370 mg, 5.0 mmol) in dimethylformamide (5 ml) is heated at 80 °C for 4 h with stirring. The mixture is then cooled to 0 °C, a solution of dicyclohexylcarbodiimide (1.05 g, 5.1 mmol) in dimethylformamide (3 ml) is added, and stirring is continued at room temperature for 1 h. Then, ethyl acetate is added, the precipitated dicyclohexylurea is filtered off, and the filtrate is concentrated under reduced pressure. The residue is column-chromatographed on silica gel (eluent: ethyl acetate/chloroform 1/3); yield of **4e** (eluted first): 424 mg (43%) [m.p. 162–163 °C]; yield of **4f**: 174 mg (18%) [m.p. 142–143 °C].

5-Trifluoromethyl-5,6-dihydrouracil (4b); Typical Procedure for Method C:
In a Pyrex ampoule, a mixture of 2-trifluoromethylacrylic acid (**1**; 4.20 g, 30.0 mmol), urea (**2b**; 1.89 g, 31.5 mmol), and acetic anhydride (24 ml) is heated at 100 °C for 1 h with stirring. The acetic anhydride is then removed under reduced presure and the residual solid recrystallized from ethanol; yield of **4b**: 3.64 g (67%); m.p. 203–205 °C (dec).

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