Acta Chemica Scandinavica B 38 (1984) 505–508

# Synthesis of Some 5-Trifluoromethylpyrimidines

TORE BENNECHE and KJELL UNDHEIM

Department of Chemistry, University of Oslo, Oslo 3, Norway

5-Trifluoromethyl-2-pyrimidinones have been prepared by selective substitution reactions from 2-chloro-5-methylpyrimidine.

A number of aromatic trifluoromethyl derivatives show useful biological activity.[1] The trifluoromethyl group may often replace a halogen in a biologically active molecule with retention of biological activity. For our continued studies of 5-halopyrimidines as cytostatic agents,[2,3] we needed ready access to 5-trifluoromethyl derivatives; a method for their synthesis is described in this report.

The trifluoromethyl group can be introduced into aromatic and heteroaromatic molecules either by direct carbon-carbon bond formation between a trifluoromethyl group and the aromatic molecule,[4] or by transforming a substituent into a trifluoromethyl group.[5] Thus 5-trifluoromethylpyrimidines without substituents in the 4- and 6-position have been prepared from 2-amino-5-carboxypyrimidine using sulfur tetrafluoride, and from 2-chloro-5-trichloromethylpyrimidine with a mixture of antimony trifluoride and antimony pentachloride.[6] The latter approach requires that 2-chloro-5-trichloromethylpyrimidine *2* is easily available. Photochlorination using chlorine at elevated temperatures over several hours has been reported for the synthesis of *2* from 2-chloro-5-methylpyrimidine.[6] We have found the reaction to proceed readily using *N*-chlorosuccinimide (NCS) or sulfuryl chloride; sulfuryl chloride is the superior reagent. The hydrochloride of *2* should be used since the main component (*ca.* 85 %) in the crude product from the chlorination of the free base, was the 5-dichloromethyl analogue according to spectroscopy and GLC.

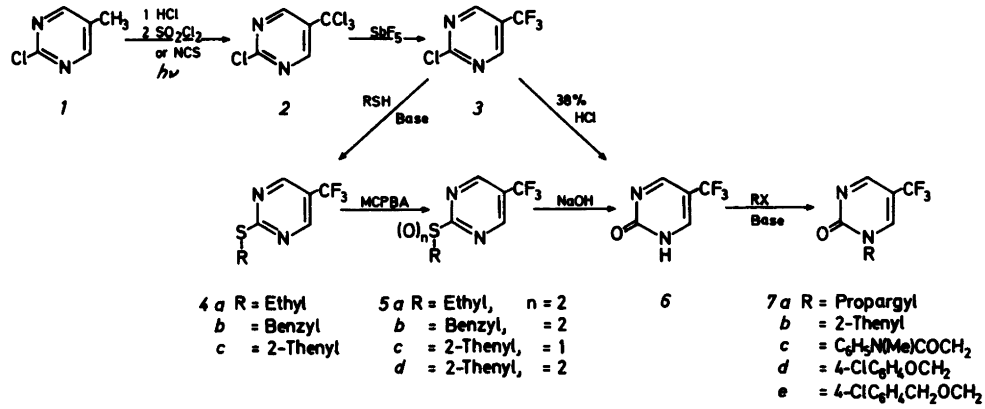
Since antimony pentafluoride is a stronger fluorinating agent than the mixture of antimony trifluoride and antimony pentachloride,[7] the latter reagent was replaced by the former which significantly improved the yield of the 5-trifluoromethyl derivative *3*.

The electron attracting properties of the trifluoromethyl group activates further the chlorine in the active pyrimidine 2-position towards nucleophilic substitution. On the other hand the trifluoromethyl group itself, which is coupled to an electron deficient system, will readily undergo hydrolytic conversion to a carboxylic acid; thus *3* was rapidly decomposed by dilute sodium hydroxide (TLC). For comparison it is pointed out that 5-trifluoromethyluracil is completely hydrolyzed to the 5-carboxy derivative in 0.1 M sodium bicarbonate after 24 h or in 1.0 M sodium hydroxide after 20 min.[8] The selective hydrolysis of the 2-chloro substituent was therefore carried out in acid solution; optimum conditions for the conversion of *3* to the pyrimidinone *6* were found in the use of 38 % hydrochloric acid at 50 °C for 40 min. When the 5-trichloromethyl precursor *2*, however, was subjected to the same hydrolytic conditions, complete hydrolysis of the trichloromethyl group took place with the formation of 5-carboxy-2-pyrimidinone.[9]

Selective substitution of the 2-chloro substituent in *3* can also be effected by sulfur nucleophiles; with potassium ethyl, benzyl or thenyl thiolates in dimethylformamide or dimethoxyethane the corresponding 2-sulfides are formed. Under the same reaction conditions the 5-trichloromethyl derivative gave products which were also partially substituted in the trichloromethyl group.

The leaving properties of a sulfide substituent

0302-4369/84 $2.50




*Scheme 1.*

in an activated azine position are improved after oxidation. The sulfides *4* were readily oxidized to sulfones *5*; in one case the intermediate sulfoxide *5c* was isolated by using one equivalent of peracid. Selective hydrolysis of the sulfonyl group to the lactam *6* could be achieved by running the reaction in 1 M sodium hydroxide at room temperature for 10 min.

The trifluoromethyl group is more strongly electron attracting than a halogen in the 5-position in pyrimidine and hence *N*-alkylation is made more difficult in 5-trifluoromethyl-2-pyrimidinones. *O*-Alkylation may be a competing reaction especially when the relatively hard chloromethyl ether electrophiles are used; this is also the case in the reaction with 5-halo-2-pyrimidinones.[10]

## EXPERIMENTAL

GLC was carried out on an 3 % SP-2100 column in all cases except for *3* where a 3 % SP-2250 column was used; percentage compositions of mixtures quoted refer to relative signal intensities of the components. The mass spectrometry data are reported as MS 70 eV; *m/z* (% rel. int.).

*2-Chloro-5-trichloromethylpyrimidine*[6] 2. *Method A:* 2-Chloro-5-methylpyrimidine[11] (1.00 g, 7.8 mmol) in dry tetrachloromethane (125 ml) was treated with dry hydrogen chloride to precipitate the hydrogen chloride salt. *N*-Chlorosuccinimide (5.21 g, 39.0 mmol) was added and the mixture irradiated with a 250 W high-pressure mercury lamp at reflux temperature for 3 h before another portion of *N*-chlorosuccinimide (1.00 g, 7.5 mmol) was added. The mixture was heated for 1 h, cooled, filtered and evaporated. The crude product was purified on a silica gel column (chloroform); yield 0.73 (40 %), m.p. 60 °C (light petroleum). Anal. $C_5H_2Cl_4N_2$: C,H. $^1$H NMR($CHCl_3$): $\delta$ 9.05 (H-4, H-6).

*Method B.* The hydrogen chloride salt of 2-chloro-5-methylpyrimidine (7.8 mmol) was prepared as above. Sulfuryl chloride (10 ml, 124 mol) was added and the mixture irradiated with a 250 W high-pressure mercury lamp at reflux temperature for 3 h before the cooled solution was filtered and evaporated. The residue was dissolved in ether, filtered and evaporated to give the title compound; yield 1.17 g (65 %) more than 90 % pure (GLC).

*2-Chloro-5-trifluoromethylpyrimidine*[6] 3. Antimony pentafluoride (2.0 ml, 28 mmol) was carefully added to 2-chloro-5-trichloromethylpyrimidine (3.50 g, 15 mmol) at 50 °C under $N_2$ and the mixture heated to 150 °C during 35 min, and then stirred at 150° for 15 min. The mixture was poured into ice/water (50 ml) and tartaric acid added (30 g in 75 ml of water). The product was extracted into ether (3×50 ml), washed with an aqueous solution of tartaric acid (20 g in 50 ml of water), water (2×50 ml) and a saturated solution of sodium bicarbonate (50 ml). The solution was dried ($MgSO_4$) and the ether removed at atmospheric pressure before the residue was distilled under vacuum; yield 1.40 g (51 %), b.p. 76–78 °C/45 mmHg [lit.[6], 145 °C/760 mmHg]. Anal. $C_5H_2ClF_3N_2$: C,H. $^1$H NMR ($CDCl_3$): $\delta$ 8.90 (H-4, H-6). MS 184/182 (30/100, M), 155(15), 154(10), 147(25), 86(28), 75(26), 69(36).

*2-Ethylthio-5-trifluoromethylpyrimidine* 4a. Potassium *tert*-butoxide (1.00 g, 8.9 mmol) was added to a solution of ethanethiol (0.66 ml, 8.9

mmol) in 1,2-dimethoxyethane (40 ml) at 5 °C. The mixture was stirred for 10 min before 2-chloro-5-trifluoromethylpyrimidine (1.60 g, 8.9 mmol) in 1,2-dimethoxyethane (10 ml) was added dropwise over 3 min. The mixture was stirred at room temperature for 2 h and at 85 °C for 30 min, before water (125 ml) was added and the product extracted into chloroform. The solution was dried ($MgSO_4$), evaporated and the residue distilled under reduced pressure; yield 1.40 g (76 %), b.p. 110–112 °C/40 mmHg. $^1H$ NMR ($CDCl_3$): $\delta$ 1.41 (Et, $J$ 7 $H_Z$), 3.21 (Et, $J$ 7 $H_Z$), 8.65 (H-4, H-6). IR (film): 1540 $cm^{-1}$ (pyrimidine). MS: 208 (100, M), 193 (39), 189 (17), 180 (41), 175 (84), 174 (25), 148 (34), 136 (16), 121 (19), 75 (33).

*2-Benzylthio-5-trifluoromethylpyrimidine* 4b. 2-Chloro-5-trifluoromethylpyrimidine (0.91 g, 5 mmol) in DMF (5 ml) was added to a mixture of benzyl mercaptan (0.59 ml, 3 mmol) and potassium *tert*-butoxide (0.56 g, 5 mmol) in DMF (15 ml) at 5 °C under $N_2$. The mixture was stirred for 10 min at 5 °C and for 1 h at room temperature before the solvent was distilled off and the residue triturated with water. The product was extracted into ether and washed with water (5 x). The dried solution ($MgSO_4$) was evaporated and the residue recrystallized from pentane; yield 1.10 g (81 %), m.p. 65 °C. Anal. $C_{12}H_9F_3N_2S$: C,H. $^1H$ NMR ($CDCl_3$): $\delta$ 4.40 ($CH_2$), 7.1–7.4 (Ph), 8.64 (H-4, H-6). IR (KBr): 1540 $cm^{-1}$ (pyrimidine). MS: 270 (30, M), 237 (30), 121 (8), 91 (100), 65 (18).

*2-(2-Thenylthio)-5-trifluoromethylpyrimidine* 4c was prepared as (*4b*) above. Yield 60 %, m.p. 73 °C (pentane). Anal. $C_{10}H_7F_3N_2S_2$: C,H. $^1H$ NMR ($CDCl_3$): $\delta$ 4.60 ($CH_2$), 6.7–7.2 (thiophene), 8.60 (H-4, H-6), IR (KBr): 1600 $cm^{-1}$. MS: 276 (13, M), 243 (14), 97 (100), 53 (7), 45 (12).

*2-Ethylsulfonyl-5-trifluoromethylpyrimidine* 5a. 90 % *m*-Chloroperbenzoic acid (2.30 g, 12.1 mmol) in dichloromethane (5 ml) was added to a solution of 2-ethylthio-5-trifluoromethylpyrimidine (1.15 g, 5.5 mmol) in dichloromethane (25 ml). The mixture was stirred for 24 h at room temperature before washing with aqueous sodium bicarbonate. The organic layer was separated, dried ($MgSO_4$) and evaporated. The product was recrystallized from ether/light petroleum; yield 1.00 g (76 %), m.p. 98 °C. Anal. $C_7H_7F_3N_2SO_2$: C,H. $^1H$ NMR ($CDCl_3$): $\delta$ 1.44 (Et, $J$ 7 Hz), 3.61 (Et, $J$ 7 Hz), 9.15 (H-4, H-6). IR (KBr): 1320 and 1150 $cm^{-1}$ (sulfone). MS: 241 (1, M+1), 212(1), 176(8), 175(7), 149(9), 148(100), 121(15), 111(3).

*2-Benzylsulfonyl-5-trifluoromethylpyrimidine* 5b was prepared as *5a* above. Yield 88 %, m.p. 148 °C. Anal. $C_{12}H_9F_3N_2O_2S$: C,H. $^1H$ NMR ($CDCl_3$): $\delta$ 4.78 ($CH_2$), 7.30 (Ph), 9.11 (H-4, H-6). IR (KBr): 1150 $cm^{-1}$ (sulfone). MS: 302 (1, M), 238 (26), 237 (13), 91 (100), 65 (12).

*2-(2-Thenylsulfinyl)-5-trifluoromethylpyrimidine* 5c. 90 % *m*-Chloroperbenzoic acid (0.23 g, 1.2 mmol) was added to a solution of 2-(2-thenylthio)-5-trifluoromethylpyrimidine (0.28 g, 1.0 mmol) in dichloromethane (10 ml) at −10 °C. The mixture was allowed to reach room temperature and stirred overnight before dichloromethane (10 ml) was added and the solution washed with aqueous sodium bicarbonate. The dried ($MgSO_4$) solution was evaporated and the product purified on a silica gel column (chloroform); yield 0.17 g (58 %), m.p. 102 °C (chloroform/light petroleum). Anal. $C_{10}H_7F_3N_2OS_2$: C,H. $^1H$ NMR ($CDCl_3$): $\delta$ 4.45 and 4.57 ($CH_2SO$, $J$ *gem* 13 $H_Z$), 6.8–7.3 (thiophene), 9.00 (H-4, H-6). IR (KBr): 1050 $cm^{-1}$ (sulfoxide). MS: 196 (1), 148 (1), 147 (1), 99 (3), 97 (100), 69 (3), 53 (8).

*2-(2-Thenylsulfonyl)-5-trifluoromethylpyrimidine* 5d 90 % *m*-Chloroperbenzoic acid (0.43 g, 2.2 mmol) was added to a solution of 2-(2-thenylthio)-5-trifluoromethylpyrimidine (0.28 g, 1.0 mmol) in dichloromethane (15 ml). The mixture was stirred at room temperature for 2 d before dichloromethane (10 ml) was added and the solution washed with aqueous sodium bicarbonate. The dried ($MgSO_4$) solution was evaporated and the product purified on a silica gel column (chloroform); yield 0.13 g (42 %), m.p. 134 °C. Anal. $C_{10}H_7F_3N_2O_2S_2$: C,H. $^1H$ NMR ($CDCl_3$): $\delta$ 5.08 ($CH_2$), 6.9–7.4 (thiophene), 9.2 (H-4, H-6). IR (KBr): 1160 $cm^{-1}$ (sulfone). MS: 308 (0.2, M), 275 (1), 244 (4), 243 (2), 199 (1), 97 (100), 53 (10).

*5-Trifluoromethyl-2-pyrimidinone* 6. *Method A*. 2-Chloro-5-trifluoromethylpyrimidine (1.25 g, 6.8 mmol) in 38 % hydrogen chloride (5 ml) was stirred at 50 °C for 40 min before the mixture was cooled and the pH adjusted to *ca* 2. The solvent was removed and the residue dried, extracted with boiling ethyl acetate (3×50 ml) and evaporated to give the title compound; yield 0.92 g (83 %). The product can be purified by sublimation (110–120 °C/0.01 mmHg) or by recrystallization (EtOAc); m.p. 200 °C (decomp). Anal. $C_5H_3N_2F_3O$: C,H. $^1H$ NMR (acetone-$d_6$): $\delta$ 8.50 (H-4, H-6). IR (KBr): 1720, 1670 and 1650 $cm^{-1}$ (lactam). MS: 164 (100, M), 145 (16), 136 (80), 117 (15), 116 (11), 90 (19), 89 (23), 75 (20), 69 (18), 68 (11).

*Method B*. 2-Ethylsulfonyl-5-trifluoromethylpyrimidine (0.27 g, 1.1 mmol) in 1 M sodium hydroxide (5 ml) was stirred at room temperature for 10 min. The mixture was acidified (pH *ca* 2)

and filtered. The filtrate was evaporated, dried and extracted with boiling ethyl acetate. The solvent was distilled off to give 5-trifluoromethyl-2-pyrimidinone; yield 0.12 g (67 %).

*1-Propargyl-5-trifluoromethyl-2-pyrimidinone* 7a. Potassium *tert*-butoxide (0.11 g, 1.0 mmol) was added to a solution of 5-trifluoromethyl-2-pyrimidinone (0.16 g, 1.0 mmol) in DMF (5 ml) and the mixture stirred for 5 min before propargyl bromide (0.13 g, 1.1 mmol) was added. The mixture was stirred at room temperature overnight before the solvent was distilled off at reduced pressure and the residue triturated with water. The product was extracted into chloroform, dried ($MgSO_4$) and evaporated. The residue was washed with ether and dried; yield 0.13 g (64 %), m.p. 106 °C (sublimed at 90–100 °C/0.01 mmHg). Anal. $C_8H_5F_3N_2O$: C,H. $^1H$ NMR ($CDCl_3$): $\delta$ 2.72 (t, $J$ 3 Hz), 4.75 (d, $J$ 3 Hz), 8.39 (H-6, $J$ 3 Hz), 8.67 (H-4, $J$ 4 Hz). IR (KBr): 3225 $cm^{-1}$ (≡CH), 1680 (CO). MS: 202 (46, M), 183 (6), 174 (4), 173 (69), 148 (21), 147 (18), 127 (5), 52 (10), 39 (100).

*1-(2-Thenyl)-5-trifluoromethyl-2-pyrimidinone* 7b was prepared as (*7a*) above. Yield (80 %), m.p. 153 °C (sublimed at 110–120 °C/0.01 mmHg). Anal. $C_{10}H_7F_3N_2OS$: C,H. $^1H$ NMR ($CDCl_3$): $\delta$ 5.22 ($CH_2$), 6.8–7.3 (thiophene), 7.85 (H-6, $J$ 3 Hz). 8.55 (H-4, $J$ 3 Hz). IR (KBr): 1675 $cm^{-1}$ (CO). MS: 260 (32, M), 231 (2), 199 (2), 148 (59), 98 (5), 97 (100), 69 (5).

*1-(N-Methyl-N-phenylcarbamoyl)methyl-5-trifluoromethyl-2-pyrimidinone* 7c was prepared as *7a* above, using α-chloro-*N*-methylacetanilide;[12] yield 96 %, m.p. 195 °C. Anal. $C_{14}H_{12}F_3N_3O_2$: C,H. $^1H$ NMR (MeCN-$d_3$): $\delta$ 3,25 (Me), 4.43 ($CH_2$), 7.26 (Ph), 8.26 (H-6, $J$ 3 Hz), 8.70 (H-4, $J$ 3 Hz). MS: 311 (1, M), 205 (21), 177 (49), 148 (12), 147 (28), 134 (18), 107 (100), 106 (25).

*1-(4-Chlorophenoxy)methyl-5-trifluoromethyl-2-pyrimidinone* 7d. Triethylamine (0.14 ml, 1 mmol) was added to a mixture of 5-trifluoromethyl-2-pyrimidinone (0.16 g, 1 mmol) in dichloromethane (10 ml) and the solution stirred for 5 min before 4-chloro-1-chloromethoxybenzene (0.18 g, 1 mmol) in dichloromethane (2 ml) was added. The mixture was stirred at room temperature overnight and at 40 °C for 3 h before the solvent was distilled off and the residue triturated with water. The product was extracted into chloroform, dried ($MgSO_4$) and evaporated. The residue was washed with ether and dried; yield 0.29 g (95 %), m.p. 98 °C. Anal. $C_{12}H_8ClF_3N_2O_2$: C,H. $^1H$ NMR ($CDCl_3$): $\delta$ 5.82 ($CH_2$), 6.8–7.4 (Ph), 8.15 (H-6, $J$ 3 Hz), 8.77 (H-4, $J$ 3 Hz). IR (KBr): 1690 $cm^{-1}$ (CO). MS: 285 (1), 178 (7), 177 (100), 150 (10), 75 (5).

*1-(4-Chlorobenzyloxy)methyl-5-trifluoromethyl-2-pyrimidinone* 7e was prepared as for *7d* above using 4-chlorobenzyl chloromethyl ether; yield 91 %, m.p. 120 °C. Anal. $C_{13}H_{10}ClF_3N_2O_2$: C,H. $^1H$ NMR ($CDCl_3$): $\delta$ 4.64 ($CH_2$Ph), 5.38 ($NCH_2$), 7.24 (Ph), 8.11 (H-6, $J$ 3 Hz), 8.74 (H-4, $J$ 3 Hz). IR (KBr): 1680 $cm^{-1}$ (CO). MS: 269 (1), 178 (100), 150 (12), 149 (13), 127 (25), 125 (77), 119 (14), 89 (17).

## REFERENCES


1. a. Heidelberger, C. *Cancer Res. 30* (1970) 1549; b. Knunyants, I. L. and Polishchuk, V. R. *Russ. Chem. Rev. 44* (1975) 339; c. Heidelberger, C., Parsons, D. G. and Remy, D. C. *J. Med. Chem. 7* (1964) 1; d. Smith, F. A. *Chemtech* (1973) 422; e. Filler, R. *Chemtech* (1974) 752.
2. Benneche, T., Gacek, M. and Undheim, K. *Eur. Pat. Appl.* 33195 (1981).
3. Gacek, M., Undheim, K., Oftebro, R. and Laland, S. G. *FEBS Lett. 98* (1979) 355.
4. a. Kondratenko, N. V., Vechirko, E. P. and Yagupolskii, L. M. *Synthesis* (1980) 932; b. Cech, D. and Schwarz, B. *Nucleic Acids Res. 9* (1981) 29; c. Umemoto, T. and Miyano, O. *Tetrahedron Lett. 23* (1982) 3929; d. Matsui, K., Tobita, E., Ando, M. and Kondo, K. *Chem. Lett.* (1981) 1719; e. Kobayashi, Y., Yamamoto, K., Asai, T., Nakano, M. and Kumadaki, I. *J. Chem. Soc. Perkin Trans 1* (1980) 2755; f. Hein, L. and Cech, D. *Z. Chem. 17* (1977) 415.
5. a. Yagupolskii, L. M., Shein, S. M., Krasnoselskaya, M. I. and Solodushenkov, S. N. *Zh. Obshch. Khim. 35* (1965) 1261; b. Jones, R. G. *J. Am. Chem. Soc. 69* (1947) 2346; c. Weaver, L. C. and Jones, W. R. *J. Pharm. Sci. 52* (1963) 508; d. Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, 2nd. Ed., Wiley, New York 1976, p. 36 ff.
6. Serban, A., Warner, R. B. and Watson, K. G. *Ger. Offen.* 2,820.032 (1978); *Chem. Abstr. 90* (1979) 72231 g.
7. Sheppard, W. A. and Sharts, C. M. *Organic Fluorine Chemistry*, Benjamin, New York 1969, p. 76.
8. Heidelberger, C., Parsons, D. and Remy, D. C. *J. Am. Chem. Soc. 84* (1962) 3597.
9. Dyer, E. and Johnson, T. B. *J. Am. Chem. Soc. 56* (1934) 222.
10. Benneche, T. and Undheim, K. *Acta Chem. Scand. B 37* (1983) 345.
11. Brown, D. J. and Waring, P. *Aust. J. Chem. 26* (1973) 443.
12. Heinisch, L. *J. Prakt. Chem. 317* (1975) 435.


Received August 10, 1983.