Synthesis of 1-Methyl-7-(trifluoromethyl)-1*H*-pyrido[2,3-*c*][1,2]thiazin-4(3*H*)-one 2,2-Dioxide

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The reaction of methyl 2-bromo-6-(trifluoromethyl)-3-pyridinecarboxylate (**1**) with methanesulfonamide gave methyl 2-[(methylsulfonyl)amino]-6-(trifluoromethyl)-3-pyridine-carboxylate (**2**). Alkylation of compound **2** with methyl iodide followed by cyclization of the resulting methyl 2-[methyl(methylsulfonyl)amino]-6-(trifluoromethyl)-3-pyridinecarboxylate (**3**) yielded 1-methyl-7-(trifluoromethyl)-1*H*-pyrido[2,3-*c*][1,2]thiazin-4(3*H*)-one 2,2-dioxide (**4**). The reaction of compound **4** with α,2,4-trichlorotoluene, methyl bromopropionate, methyl iodide, 3-trifluoromethylphenyl isocyanate, phenyl isocyanate and 2,4-dichloro-5-(2-propynyloxy)phenyl isothiocyanate gave, respectively, 4-[(2,4-dichlorophenyl)methoxy]-1-methyl-7-(trifluoromethyl)-1*H*-pyrido[2,3-*c*][1,2]thiazine 2,2-dioxide (**5**), methyl 2-[[1-methyl-2,2-dioxido-7-(trifluoromethyl)-1*H*-pyrido[2,3-*c*][1,2]thiazin-4-yl]oxy]propanoate (**6**), 1,3,3-trimethyl-7-(trifluoromethyl)-*1H*-pyrido[2,3-*c*][1,2]thiazin-4(3*H*)-one 2,2-dioxide (**7**), 4-hydroxy-1-methyl-7-(trifluoromethyl)-*N*-[3-(trifluoromethyl)phenyl]-1*H*-pyrido[2,3-*c*][1,2]thiazine-3-carboxamide 2,2-dioxide (**8**), 4-hydroxy-1-methyl-7-(trifluoromethyl)-*N*-phenyl-1*H*-pyrido[2,3-*c*][1,2]thiazine-3-carboxamide 2,2-dioxide (**9**) and *N*-[2,4-dichloro-5-(2-propynyloxy)phenyl]-4-hydroxy-1-methyl-7-(trifluoromethyl)-1*H*-pyrido[2,3-*c*][1,2]thiazine-3-carboxamide 2,2-dioxide (**10**).

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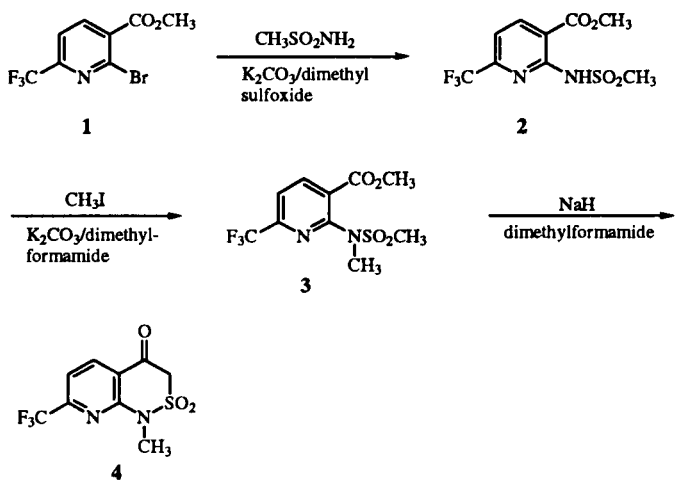
Our interest in the synthesis of compounds for biological evaluation and the presence of a trifluoromethyl moiety in many different types of chemicals that are used to control weeds (diflufenican, haloxyfop, thiazafluron, oxyflurofen and trifluralin), fungi (triflumizole, flurolanil and fluotrimazole) and insects (tefluthrin, hydramethylnon and cyhalothrin), and the knowledge that pyrido [2,3-*c*][1,2]thiazines that carry substituents on the pyridine ring other than hydrogen [1] or methyl groups [2] are unknown prompted us to prepare the title compound and use it as an intermediate.

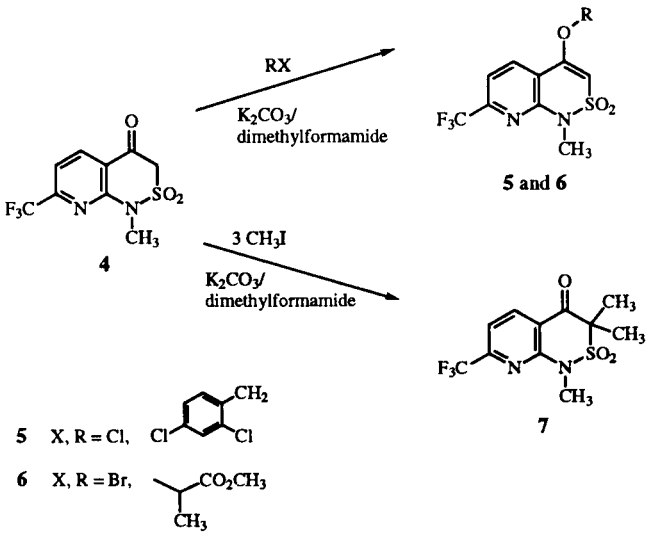
The 1-methyl-7-(trifluoromethyl)-1*H*-pyrido[2,3-*c*][1,2]thiazin-4(3*H*)-one 2,2-dioxide (**4**) was prepared by the reaction of methyl 2-bromo-6-(trifluoromethyl)-3-pyridinecarboxylate (**1**) with methanesulfonamide in the presence of potassium carbonate to give methyl 2-[(methylsulfonyl)amino]-6-(trifluoromethyl)-3-pyridinecarboxylate (**2**). Alkylation of compound **2** with methyl iodide gave methyl 2-[methyl(methylsulfonyl)amino]-6-(trifluoromethyl)-3-pyridinecarboxylate (**3**). Treatment of compound **3** with sodium hydride in dimethylformamide led to the formation of 1-methyl-7-(trifluoromethyl)-1*H*-pyrido[2,3-*c*][1,2]thiazin-4(3*H*)-one 2,2-dioxide (**4**). The synthetic method is outlined in Scheme 1. The reaction of compound **4** with 1.0 equivalent of α,2,4-trichlorotoluene or methyl 2-bromopropionate in the presence of potassium carbonate in dimethylformamide gave the *O*-alkylated products, 4-[(2,4-dichlorophenyl)methoxy]-1-methyl-7-(trifluoromethyl)-1*H*-pyrido[2,3-*c*][1,2]thiazine 2,2-dioxide (**5**) and methyl 2-[[1-methyl-2,2-dioxido-7-(trifluoromethyl)-1*H*-pyrido[2,3-*c*][1,2]thiazin-4-yl]oxy]propanoate (**6**). On the other hand, the reaction with 3.0 equivalents of methyl iodide gave the *C*-alkylated compound, 1,3,3-trimethyl-7-(trifluoromethyl)-1*H*-pyrido[2,3-*c*][1,2]thiazin-4(3*H*)-one 2,2-dioxide (**7**) (Scheme 2).

Scheme 1



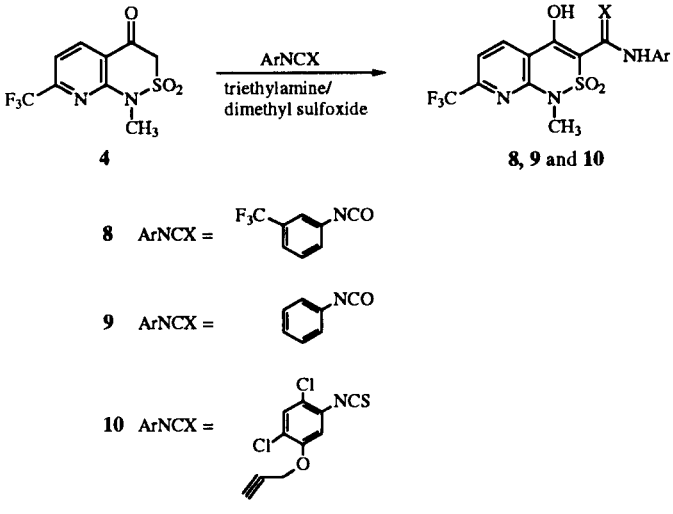
The addition of 3-trifluoromethylphenyl isocyanate, phenyl isocyanate and 2,4-dichloro-5-(propynyloxy)-phenyl isothiocyanate to a solution of compound **4** in dimethyl sulfoxide in the presence of triethylamine gave 4-hydroxy-1-methyl-7-(trifluoromethyl)-*N*-[3-(trifluoromethyl)phenyl]-1*H*-pyrido[2,3-*c*][1,2]thiazine-3-carboxamide 2,2-dioxide (**8**), 4-hydroxy-1-methyl-7-(trifluoro-

Scheme 2



methyl)-*N*-phenyl-1*H*-pyrido[2,3-*c*][1,2]thiazine-3-carboxamide 2,2-dioxide (**9**) and *N*-[2,4-dichloro-5-(2-propynyloxy)phenyl]-4-hydroxy-1-methyl-7-(trifluoromethyl)-1*H*-pyrido-[2,3-*c*][1,2]thiazine-3-carboxamide 2,2-dioxide (**10**).

Scheme 3



EXPERIMENTAL

Melting points were determined with a Thomas Hoover capillary melting point apparatus and are reported uncorrected. The ^{1}H nmr spectra were recorded using a Varian Unity Plus 300 or Varian VXRS 400. Chemical shift values are reported in parts per million on the δ scale. The nmr spin multiplicities are indicated by the symbols: s (singlet), d (doublet), t (triplet), q (quartet) and m (multiplet). Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, New Jersey, U.S.A.

The methyl 2-bromo-6-(trifluoromethyl)-3-pyridinecarboxylate used in this project was obtained from Hickson and Welch Ltd., Castleford, England. We used a dispersion of sodium hydride in mineral oil (60%).

Methyl 2-[(Methylsulfonyl)amino]-6-(trifluoromethyl)-3-pyridinecarboxylate (**2**).

Under a nitrogen atmosphere, methyl 2-bromo-6-(trifluoromethyl)-3-pyridinecarboxylate (**1**) (14.2 g, 0.05 mole) was added to a suspension of potassium carbonate (7.0 g, 0.05 mole) and methanesulfonamide (7.0 g, 0.07 mole) in 25 ml of dimethyl sulfoxide. The reaction mixture was stirred and heated at 95-100° for 6 hours. The reaction mixture was cooled to ambient temperature, acidified with 1*N* hydrochloric acid and the precipitated solid was removed by filtration. The crude product was washed with water, dried and crystallized from acetonitrile, yield 7.2 g (48%), mp 173-174°; ^{1}H nmr (deuteriochloroform): 3.52 (s, 3H), 3.99 (s, 3H), 7.40 (d, J = 8.1 Hz, 1H), 8.48 (d, J = 8.1 Hz, 1H), 10.41 (br s, 1H).

Anal. Calcd. for $C_9H_9F_3N_2O_4S$: C, 36.24; H, 3.04; N, 9.40. Found: C, 36.27; H, 2.96; N, 9.16.

Methyl 2-[(Methylsulfonyl)amino]-6-(trifluoromethyl)-3-pyridinecarboxylate (**3**).

Under a nitrogen atmosphere, methyl iodide (2.8 g, 0.019 mole) was added dropwise to a stirred suspension of potassium carbonate (4.0 g, 0.029 mole) and methyl 2-[(methylsulfonyl)amino]-6-(trifluoromethyl)-3-pyridinecarboxylate (**2**) (4.5 g, 0.015 mole) in 20 ml of dimethylformamide. The reaction mixture was stirred at ambient temperature overnight, diluted with water (100 ml) and extracted with ethyl acetate (2 x 100 ml). The ethyl acetate extracts were combined, washed with water and dried over magnesium sulfate. Removal of the magnesium sulfate by filtration and concentration of the filtrate gave the crude product. The product was purified by column chromatography (silica gel, eluting with 1/2 ethyl acetate:hexane), yield 3.6 g (77%) as a yellow oil; ^{1}H nmr (deuteriochloroform): 3.03 (s, 3H), 3.43 (s, 3H), 3.97 (s, 3H), 7.69 (d, J = 7.9 Hz, 1H), 8.35 (d, J = 7.9 Hz, 1H).

Anal. Calcd. for $C_{11}H_{11}F_3N_2O_4S$: C, 38.46; H, 3.55; N, 8.97. Found: C, 38.72; H, 3.44; N, 8.80

1-Methyl-7-(trifluoromethyl)-1*H*-pyrido[2,3-*c*][1,2]thiazin-4(3*H*)-one 2,2-Dioxide (**4**).

Under a nitrogen atmosphere, sodium hydride (0.8 g, 0.02 mole) was added in one portion to a stirred solution of methyl 2-[methyl(methylsulfonyl)amino]-6-(trifluoromethyl)-3-pyridinecarboxylate (**3**) (2.8 g, 0.009 mole) in 10 ml of dimethylformamide. The reaction mixture was stirred at ambient temperature for 5 hours. A few milliliters of methanol were added to quench the excess sodium hydride used and then the reaction mixture was acidified with 1*N* hydrochloric acid. The solid product was removed by filtration, washed with water, dried and crystallized from 1-chlorobutane, yield 2.0 g (79%), mp 87-88°; ^{1}H nmr (deuteriochloroform): 3.60 (s, 3H), 4.44 (s, 2H), 7.53 (d, J = 7.9 Hz, 1H), 8.56 (d, J = 7.9 Hz, 1H).

Anal. Calcd. for $C_9H_7F_3N_2O_3S$: C, 38.57; H, 2.52; N, 9.99. Found: C, 38.80; H, 2.59; N, 9.84.

4-[(2,4-Dichlorophenyl)methoxy]-1-methyl-7-(trifluoromethyl)-1*H*-pyrido[2,3-*c*][1,2]thiazine 2,2-Dioxide (**5**).

Under a nitrogen atmosphere α,2,4-trichlorotoluene (0.58 g, 0.0021 mole) was added to 1-methyl-7-(trifluoromethyl)-1*H*-

pyrido[2,3-*c*][1,2]thiazin-4(3*H*)-one 2,2-dioxide (**4**) (0.58 g, 0.0021 mole) and potassium carbonate (0.60 g, 0.0043 mole) in dimethylformamide (3 ml). The reaction mixture was stirred at room temperature for 16 hours, diluted with water (75 ml) and extracted with ethyl acetate (2 x 50 ml). The ethyl acetate extracts were combined, washed with water and dried over magnesium sulfate. Removal of the magnesium sulfate by filtration and concentration of the filtrate under vacuum gave the crude product which solidified and was crystallized from acetonitrile, yield 0.23 g (25%), mp 239-240°; ^{1}H nmr (deuteriochloroform): 3.64 (s, 3H), 5.16 (s, 2H), 6.31 (s, 1H), 7.35 (dd, J = 1.9, 8.3 Hz, 1H), 7.42 (d, J = 8.3 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.51 (d, J = 1.9 Hz, 1H), 8.29 (d, J = 8.0 Hz, 1H).

Anal. Calcd. for $C_{16}H_{11}Cl_2F_3N_2O_3S$: C, 43.75; H, 2.52; N, 6.38. Found: C, 43.63; H, 2.63; N, 6.22.

The following compounds were prepared by the above method from the appropriate reactants.

Methyl 2-[[1-Methyl-2,2-dioxido-7-(trifluoromethyl)-1*H*-pyrido[2,3-*c*][1,2]thiazin-4-yl]oxy]propanoate (**6**).

This compound was prepared from 1-methyl-7-(trifluoromethyl)-1*H*-pyrido[2,3-*c*][1,2]thiazin-4(3*H*)-one 2,2-dioxide **4** and methyl 2-bromopropionate. The crude product was purified by column chromatography (silica gel, eluting with 2/1 hexane: ethyl acetate), followed by crystallization from 1-chlorobutane, yield 43%, mp 147-148°; ^{1}H nmr (deuteriochloroform): 1.74 (d, J = 6.8 Hz, 3H), 3.60 (s, 3H), 3.83 (s, 3H), 4.79 (q, J = 6.8 Hz, 1H), 6.07 (s, 1H), 7.47 (d, J = 7.9 Hz, 1H), 8.39 (d, J = 7.9 Hz, 1H).

Anal. Calcd. for $C_{13}H_{13}F_3N_2O_5S$: C, 42.62; H, 3.58; N, 7.65. Found: C, 43.02; H, 3.76; N, 7.27.

1,3,3-Trimethyl-7-(trifluoromethyl)-1*H*-pyrido[2,3-*c*][1,2]thiazin-4(3*H*)-one 2,2-Dioxide (**7**).

This compound was prepared from 1-methyl-7-(trifluoromethyl)-1*H*-pyrido[2,3-*c*][1,2]thiazin-4(3*H*)-one 2,2-dioxide (**4**) and methyl iodide, yield 26% and crystallized from 1-chlorobutane, mp 89-90°; ^{1}H nmr (deuteriochloroform): 1.69 (s, 6H), 3.62 (s, 3H), 7.50 d, J = 8.0 Hz, 1H), 8.56 (d, J = 8.0 Hz, 1H).

Anal. Calcd. for $C_{11}H_{11}F_3N_2O_3S$: C, 42.85; H, 3.60; N, 9.09. Found: C, 42.86; H, 3.44; N, 8.96.

4-Hydroxy-1-methyl-7-(trifluoromethyl)-*N*-[3-(trifluoromethyl)phenyl]-1*H*-pyrido[2,3-*c*][1,2]-thiazine-3-carboxamide 2,2-Dioxide (**8**).

Under a nitrogen atmosphere, 3-trifluoromethylphenyl isocyanate (0.18 g, 0. 00095 mole) was added to a solution of 1-methyl-7-(trifluoromethyl)-1*H*-pyrido[2,3-*c*][1,2]thiazin-4(3*H*)-one 2,2-dioxide (**4**) (0.27 g, 0.00094 mole) and triethylamine (0. 14 ml/1 equivalent) in dimethyl sulfoxide (3 ml). The reaction mixture was stirred at ambient temperature for 48 hours, diluted with 0.5 *N* hydrochloric acid and extracted with ethyl acetate (2 x 25 ml). The ethyl acetate extracts were combined, washed with water and dried over magnesium sulfate. Removal of the magnesium sulfate by filtration and concentration of the filtrate under vacuum gave the crude product which was crystallized from 1-chlorobutane, yield 34%, mp 152-153°; ^{1}H nmr (deuteriochloroform): 3.72 (s, 3H), 7.49-7.54 (m, 2H), 7.62 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 7.8 Hz, 1H), 7.95 (s, 1H), 8.62 (d, J = 8. 0 Hz, 1H), 9.57 (br s, 1H), 15.44 (s, 1H).

Anal. Calcd. for $C_{17}H_{11}F_6N_3O_4S$: C, 43.69; H, 2.37; N, 8.99. Found: C, 43.57; H, 2.39; N, 8.86.

The following compounds were prepared by the above method from the appropriate reactants.

4-Hydroxy-1-methyl-7-(trifluoromethyl)-*N*-phenyl-1*H*-pyrido[2,3-*c*][1,2]thiazine-3-carboxamide 2,2-Dioxide (**9**).

This compound was prepared from 1-methyl-7-(trifluoromethyl)-1*H*-pyrido[2,3-*c*][1,2]thiazin-4(3*H*)-one 2,2-dioxide (**4**) and phenyl isocyanate. The product precipitated when the reaction mixture was diluted with hydrochloric acid. The crude product was crystallized from acetonitrile yield 47%, mp 189-191°; ^{1}H nmr (acetone-d_6): 3.69 (s, 3H), 7.26-7.71 (m, 5H), 7.89 (d, J = 8.1 Hz, 1H), 8.79 (d, J = 8.1 Hz, 1H), 9.54 (s, 1H), 15.85 (s, 1H).

Anal. Calcd. for $C_{16}H_{12}F_3N_3O_4S$: C, 48.12; H, 3.03; N, 10.52. Found: C, 48.0,H, 3.20; N, 10.47.

N-[2,4-Dichloro-5-(2-propynyloxy)phenyl]-4-hydroxy-1-methyl-7-(trifluoromethyl)-1*H*-pyrido[2,3-*c*][1,2]thiazine-3-carbothioamide 2,2-Dioxide (**10**).

This compound was prepared from 1-methyl-7-(trifluoromethyl)-1*H*-pyrido[2,3-*c*][1,2]thiazin-4(3*H*)-one 2,2-dioxide (**4**) and 2,4-dichloro-5-(2-propynyloxy)phenyl isothiocyanate [3], yield 87% and crystallized from 1-chlorobutane/hexane, mp 152-153°; ^{1}H nmr (deuteriochloroform): 2.61 (t, J = 2.4 Hz, 1H), 3.75 (s, 3H), 4.81 (d, J = 2.4 Hz, 2H), 7.55 (s, 1H), 7.56 (s, 1H), 7.62 (d, J = 8. 1 Hz, 1H), 8.68 (d, J = 8. 1 Hz, 1H), 11.02 (s, 1H), 16.33 (s, 1H).

Anal. Calcd. for $C_{19}H_{12}Cl_2F_3N_3O_4S_2$: C, 42.39; H, 2.25; N, 7.81. Found: C, 42.49; H, 2.34; N, 7.72.

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[2a] T. Zawisza, A. Milian and T. Jakobiec, *Pol. J. Chem.*, **54**, 1267 (1980); [b] T. Zawisza, A. Milian and T. Jakobiec, *Acta Pol. Pharm.*, **37**, 25 (1980).

[3] 2,4-Dichloro-5-(2-propynyloxy)phenylisothiocyanate was prepared by the dropwise addition over 30 minutes of a solution of 2,4-dichloro-5-(2-propynyloxy)aniline (21.6 g, 0.1 mole) in dichloromethane (100 ml) to a cold (0-5°) mechanically stirred two phase system of thiophosgene (13.6 g, 0.117 mole), dichloromethane (100 ml) and water (350 ml). The reaction mixture was stirred at 10° for 1 hour, the layers were separated, the dichloromethane layer was washed with water and dried over magnesium sulfate. Removal of the magnesium sulfate by filtration and concentration of the filtrate gave the crude product. Crystallized from 1-chlorobutane/hexane, mp 78-80°, yield 20.5 g (79%); ^{1}H nmr (deuteriochloroform): 2.60 (t, J = 2. 0 Hz, 1H), 4.76 (d, J = 2. 0 Hz, 2H), 6.93 (s, 1H), 7.44 (s, 1H).

Anal. Calcd. for $C_{10}H_5Cl_2NOS$: C, 46.53; H, 1.95; N, 5.43. Found: C, 46.75; H, 1.88; N, 5.31.