Synthesis and Metalation of Trifluoromethylpyrimidines. Metalation of Diazines. XVI

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A new route to trifluoromethylpyrimidines is described. Lithiation of trifluoromethylpyrimidines was successfully achieved and was used to synthesize new pyrimidine derivatives. A new synthetic route to a biologically active molecule with antimycotic activities is reported.

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Introduction.

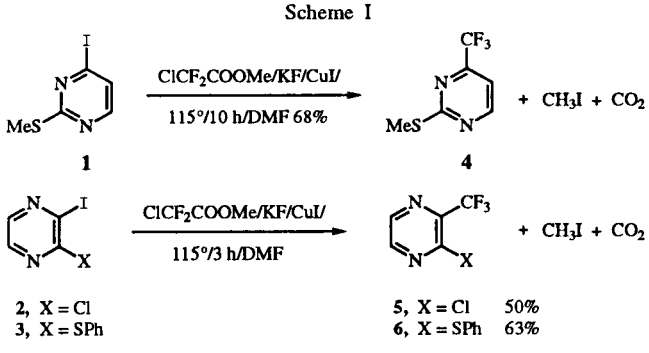
During the last decade, considerable attention has been devoted to find novel methods for introducing the trifluoromethyl group into organic compounds because of its interesting effects on physicochemical properties and biological activities [1]. Some trifluoromethylpyrimidine derivatives exhibit antimycotic, trichomonazide and anti-HIV properties [2]. The reported preparations of these pyrimidines have been based on classical condensation reactions which involve the pyrimidine ring construction. As a continuation of our investigation on fluorinated pyrimidines [3] and metalation reactions [4], we report here a new route to trifluoromethylpyrimidines starting from iodopyrimidines and their functionalization by direct lithiation. As an application a new synthesis of the 2-[(2-hydroxyethyl)methylamino]-6-phenylpyrimidine (**21**) which exhibits significant antimycotic activities [2] is described.

Recently, various trifluoromethylating agents were proposed [1,5,6] to trifluoromethylate aryl, alkenyl and alkyl halides. We have chosen the methylchlorodifluoroacetate [1], which is readily available and has never been used with halodiazines to obtain the expected trifluoromethyl compounds.

Results.

Heating methyl chlorodifluoroacetate with 2-methylthio-4-iodopyrimidine (**1**) or 2-iodopyrazines **2**, **3** in the presence of anhydrous potassium fluoride and copper(I) iodide in dimethylformamide gave the corresponding trifluoromethyl compounds **4-6** in good yields with simultaneous elimination of carbon dioxide and methyl iodide (Scheme 1). During the synthesis of **1**, small amounts of 2-thiomethyl-4-chloropyrimidine were observed (5%).

Scheme I



According to its electron withdrawing effect, the trifluoromethyl group had been previously used to induce the metalation reaction. Trifluoromethylbenzene was metalated by *n*-butyllithium less readily than anisole but more readily than benzene to give *ortho*- and *meta*-trifluoromethylbenzoic acids in a ratio of about 5:1 with moderate yield [7a], whereas the use of stronger bases such as the super basic mixture of *n*-butyllithium and potassium *tert*-butoxide led only to the *ortho*-derivative in better yield [8]. The metalation of 1,3-bis(trifluoromethyl)benzene had also been studied with various metalating agents and dry ice; when *n*-butyllithium was used, a mixture of 2,6- and 2,4-bis(trifluoromethyl)benzoic acids was obtained [9]. The metalation occurred essentially at C_2 (*ortho* to two trimethylfluoro groups) with the complex *n*-butyllithium/*N,N,N',N'*-tetramethyldiaminoethane [10].

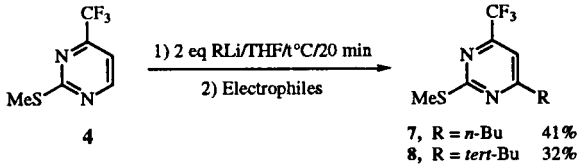
In spite of the electron withdrawing effect of trifluoromethyl group which favours the *ortho*-lithiation, the steric hindrance [12] of the trifluoromethyl group can alter this orientation. So, with more bulky metalating agents such as *tert*-butyllithium the metalation of 1,3-bis(trifluoromethyl)benzene occurred at C_4 (*ortho* position) and C_5 (*meta* position) in a 1:1 ratio.

More recently, the lithiation of 3-trifluoromethylsubstituted pyridines with *n*-buthyllithium was examined [11] and a regioselective lithiation at the 2-position has been observed.

In our attempts to lithiate the 2-thiomethyl-4-trifluoromethylpyrimidine (**4**) various metalating agents were tested (Scheme II). When **4** was reacted with alkyllithiums (*n*-buthyllithium, *tert*-butyllithium) in tetrahydrofuran (THF) at -100°, only 6-alkyl derivatives resulting from a nucleophilic addition at C_6 were observed and identified by their nmr spectra.

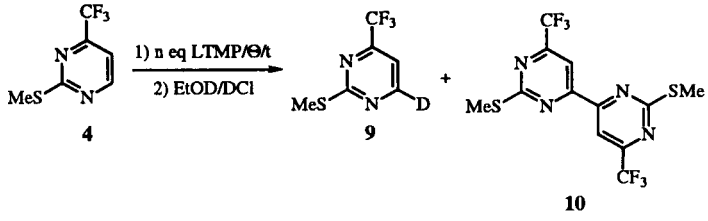
To avoid these nucleophilic addition, lithium alkylamides which are less nucleophilic than alkyllithiums were used. To determine the most efficient conditions for

Scheme II



metalation, preliminary tests were performed with a mixture of deuterium chloride and deuterioethanol as electrophile and with various parameters (amounts of metalating agent, temperature, reaction time, concentration) (Scheme III).

Scheme III



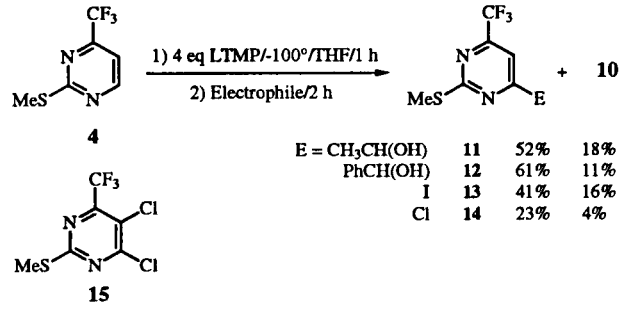
Entry	n eq LTMP	Θ (°C)	t (min)	4	9	10
1	1.1	-78	30	24%	—	17%
2	2.2	-78	30	26%	—	19%
3	4	-78	15	—	33%	10%
4	4	-78	60	—	42%	12%
5	4	-100	60	—	22%	30%
6a	4	-100	105	—	46%	11%

[a] Concentration of **4** in THF was 4 times lower, introduction time 45 minutes, reaction time 60 minutes.

With lithium 2,2,6,6-tetramethylpiperidide (LTMP) in excess in tetrahydrofuran at -100° metalation occured at the C_6 position, whereas with lithium diisopropylamide, weaker base than lithium 2,2,6,6-tetramethylpiperidide, only starting material was recovered at low temperature (-100 to -70°), and tarry products were observed with higher temperatures than -30°.

It must be noticed that with 1.1 or 2.2 equivalents of lithium 2,2,6,6-tetramethylpiperidide the starting material was recovered beside dimeric product **10** and no deuteriated compound was identified. It could be assumed that under these experimental conditions the metalation was slow or incomplete and **4** underwent a nucleophilic attack from the lithioderivative to give **10**. To prevent this competitive reaction we used a large excess of lithium 2,2,6,6-tetramethylpiperidide (4 equivalents), so the deuteriated compound **9** was obtained without starting material, but small amounts of dimer **10** were always present. At a lower temperature (-100°), the metalation reaction became slower and the amounts of dimer were higher. At last, we used 4 equivalents of lithium 2,2,6,6-tetramethylpiperidide at -100° with a slow introduction (45 minutes) of a diluted solution of 4 in tetrahydrofuran to allow the formation of the lithioderivative without the presence of a large excess of starting material. Under these conditions the result was slightly better than for entry 4 and these experimental conditions were chosen for the further reaction of **4** with other electrophiles, however small amounts of dimer were still present (Scheme IV).

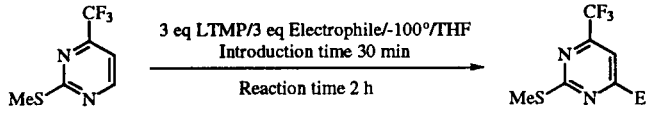
Scheme IV



It can be noticed that with hexachloroethane as an electrophile 5,6-dichloro-2-thiomethyl-4-trifluoromethylpyrimidine (**15**) was obtained in 13% yield beside the monochloro derivative **14**.

To avoid nucleophilic addition, a metalation by the *in situ* trapping method was tested with various electrophiles which are compatible with the metalating agent. The simultaneous introduction of the electrophile and the compound **4** would prevent the formation of dimer **10** (Scheme V).

Scheme V

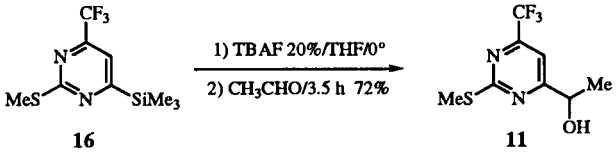


12	E = PhCH(OH)	69%	16	E = $SiMe_3$	96%
13	E = I	26%	17	E = $Ph_2C(OH)$	77%
14	E = Cl	19%	18	E = SPh	98%

Reaction of the lithio derivative with iodine or hexachloroethane as electrophiles gave the 6-halogenopyrimidines in low yields, whereas very good yields were observed for **16** and **18** with trimethysilyl chloride and diphenyl sulfide.

The reaction of silicon compounds under nucleophilic catalytic conditions has been widely used in synthesis [13a]. Some reactions have been published in the pyridine series [13b-d] and more recently with a pyridazine derivative [14]. The desilylation performed in THF with tetra-*n*-butylammonium fluoride (TBAF) in presence of aromatic or aliphatic aldehydes led to secondary alcohols. This methodology applied for the first time to the pyrimidine derivative **16** allowed to obtain the secondary alcohol **11** in still better yield than with the direct metalation (Scheme VI).

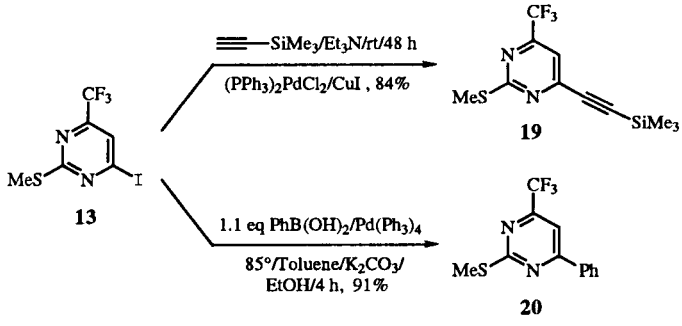
Scheme VI



16 11

Iodo derivatives are of interest because they can be used to create a carbon-carbon bond by cross-coupling reactions catalyzed by transition metals. The palladium catalyzed coupling reactions of 2-thiomethyl-4-trifluoromethyl-6-iodopyrimidine **13** with trimethylsilylacetylene and with phenylboronic acid were performed and good yields were obtained (Scheme VII).

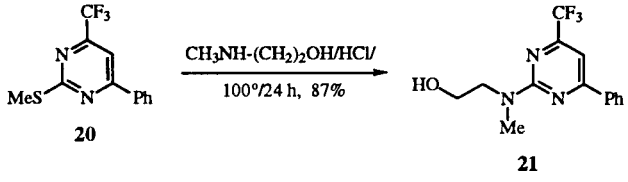
Scheme VII



13 19 20

Nucleophilic substitution of the thiomethyl group of **20** by 2-(*N*-methylamino)ethanol was easily performed at 100°C for 24 hours to give the biologically active molecule **21** in good yield, **21** was known to exhibit significant antimycotic activities [2] (Scheme VIII).

Scheme VIII



20 21

The synthesis of **21** previously described involved the pyrimidine ring construction by condensation of *N*-(2-hydroxyethyl)-*N*-methylguanidine sulfate with 4,4,4,-trifluoro-1-phenyl-1,3-butanedione to give **21** in low yield (11%).

Conclusion.

A new route to trifluoromethylpyrimidines has been described and for the first time, the 2-thiomethyl-4-trifluoromethylpyrimidine was successfully lithiated by lithium 2,2,6,6-tetramethylpiperidide. The regioselectivity of the metalation was observed at C_6 in *meta* to the trifluoromethyl group. This result could be explained by the steric hindrance of the metalating agent. The resulting lithio derivatives were reacted with various electrophiles for the synthesis of new pyrimidines. A new synthetic route to a biologically active molecule with antimycotic activities was reported by use of cross-coupling reaction with an iodotrifluoromethylpyrimidine.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage. The ^1H nmr spectra were recorded in deuteriochloroform with tetramethylsilan as internal standard or in deuterated dimethylsulfoxide with hexamethyldisiloxan as internal standard on a Varian EM 360 L, Bruker AC 200 instrument. Microanalyses were performed on a Carlo Erba CHNOS 1106 apparatus. Tetrahydrofuran was distilled from benzophenone sodium and used immediately. Water content of the solvent was estimated by the modified Karl-Fischer method (THF less than 50 ppm water). Metallations were performed under an argon atmosphere whose water content was regularly checked. Reagents were handled with syringues through septa.

Typical Procedure for Trifluoromethylation of Iododiazines.

Copper(I) iodide (5.7 g, 30 mmoles), anhydrous potassium fluoride (2.3 g, 40 mmoles), iododiazine (20 mmoles) and methyl chlorodifluoroacetate (5.8 g 40 mmoles) in dimethylformamide (45 ml) were heated with stirring to 115° under an atmosphere of dry argon, and kept at this temperature for a time t. After addition of 200 ml of water, made acidic with aquous hydrochloric acid (*p*H = 1), the mixture was extracted with ether (4 x 150 ml). The organic extract was washed with water (2 x 50 ml), then with a saturated solution of sodium bicarbonate and at last with a saturated solution of sodium thiosulfate (2 x 10 ml). After a new washing with water, the organic extracts were dried (magnesium sulfate) and evaporated. The crude product was purified by column chromatography on silical gel or distillation.

2-Methylthio-4-trifluoromethylpyrimidine **4**.

Reaction of **1** (5.0 g 30 mmoles) according to the typical procedure (t = 10 hours), gave after purification by column chromatography on silica gel with a mixture of dichloromethane/cyclohexane (3:1) as an eluent and a further distillation (91°/15 mm Hg) 2.49 g (68%) of a yellow oil of **4**; ^1H nmr (deuteriochloroform): δ 2.57 (s, 3H, SCH_3), 7.23 (d, 1H, J = 4.9 Hz, H_5), 8.71 (d, 1H, H_6).

Anal. Calcd. for $C_6H_5F_3N_2S$: C, 37.11; H, 2.59; N, 14.43. Found: C, 37.1; H, 2.2; N, 14.7.

2 -Chloro-4-trifluoromethylpyrazine **5**.

Reaction of **2** (0.585 g, 2.43 mmoles) according to the typical procedure (t = 3 hours), gave after purification by column chromatography on silical gel with a mixture of ether/cyclohexane (1:2) as eluent and a further distillation (65°C/15 mm Hg) 0.22 g (50%) as a colorless liquid of **5**; ^1H nmr (deuteriochloroform): δ 8.53 (s); ^{13}C nmr (deuteriochloroform): δ 120.3 (CF_3), 148.3, 147.1, 143.2, 139.2; ^{19}F nmr (deuteriochloroform) (ref fluorotrichloromethane): δ -68.24.

Anal. Calcd. for $C_5H_2ClF_3N_2$: C; 32.87; H, 1.09; N, 15.35. Found: C, 32.8; H, 1.1; N, 15.3.

2-Phenylthio-3-trifluoromethylpyrazine **6**.

Reaction of **3** (1 g, 3.2 mmoles) according to the typical procedure (t = 3 hours) gave after purification by column chromatography on silica gel with a mixture of ethyl acetate/light petroleum 1:9) as eluent then distillation (110°/5 mm Hg), 0.52 g (63%) of **6**, mp 61-63°; ^1H nmr (deuteriochloroform): δ 7.5 (m, 2H, phenyl), 7.4 m (3H, phenyl), 8.28 (d, 1H, J = 2.3 Hz), 8.37 (d, 1H, J = 2.3 Hz), ^{13}C nmr (deuteriochloroform): δ 121.3 (CF_3), 127.4, 129.4, 129.8, 135.9, 138.3, 146.2, 156.3.

Anal. Calcd. for $C_{11}H_7F_3N_2S$: C, 51.56; H, 2.75; N, 10.93. Found: C, 51.4; H, 2.5; N, 10.8.

2-Methylthio-4-trifluoromethyl-6-*n*-butylpyrimidine **7**.

A solution of **4** (0.100 g, 0.51 mmole) in anhydrous tetrahydrofuran (10 ml) was slowly added to a cold solution (-70°) of 2.5 *M* *n*-butyllithium in hexane (0.43 ml, 1.08 mmoles) in tetrahydrofuran (20 ml). The resulting solution was stirred for 2 hours at -78° before addition of deuterium oxide. The solution was stirred for 2 hours at -78°, then warmed slowly to room temperature. Then a saturated solution of sodium bicarbonate was added (until *p*H = 8). The mixture was extracted with dichloromethane (3 x 20 ml). The organic extract was dried (magnesium sulfate) and evaporated. The crude product was purified by flash chromatography on silica gel with a mixture of dichloromethane/hexane (1:1) as an eluent 0.052 g (41%) of **7**; ^1H nmr (deuterichloroform): δ 0.92 (t, 3H, CH_3), 1.53 (m, 2H, CH_2), 1.69 (m, 2H, CH_2), 2.56 (s, 3H, SCH_3), 2.74 (t, 2H, CH_2), 7.05 (s, 1H, H_5).

Anal. Calcd. for $C_{10}H_{13}F_3N_2S$: C, 47.99; H, 5.23; N, 11.19. Found: C, 48.0; H, 5.2; N, 11.2.

2-Methylthio-4-trifluoromethyl-6-*tert*-butylpyrimidine **8**.

A solution of **4** (0.100 g, 0.51 mmole) in anhydrous tetrahydrofuran (10 ml) was slowly added to a cold solution (-70°) of 1.5 *M* *tert*-butyllithium in hexane (0.79 ml, 1.08 mmoles) in tetrahydrofuran (20 ml). The resulting solution was stirred for 20 minutes at -100° before the addition of a solution of 0.15 g (0.6 mmole) of iodine in 5 ml of tetrahydrofuran. The solution was stirred for 2 hours at -100° then warmed slowly to room temperature. Then a saturated solution of sodium bicarbonate was added (until *p*H = 8). The mixture was extracted with dichloromethane (3 x 20 ml). The organic extract was dried with magnesium sulfate and evaporated. The crude product was purified by flash chromatography on silica gel with a mixture of dichloromethane/cyclohexane as an eluent, 0.40 g (32%) of a yellow oil of **8**; ^1H nmr (deuteriochloroform): δ 1.32 (s, 9H, CH_3), 2.56 (s, 3H, SCH_3), 7.21 (s, 1H, H_5).

Anal. Calcd. for $C_{10}H_{13}F_3N_2S$: C, 47.99; H, 5.23; N, 11.19. Found: C, 47.9; H, 5.2; N, 11.2.

General Procedure A. Synthesis of Substitued Pyrimidines by Metalation.

A solution of *n*-butyllithium (1.6 *M* in hexane, 1 ml, 2.04 mmoles) was added to cold (-30°) stirred, anhydrous tetrahydroluran (20 ml) under an atmosphere of dry argon. Then 2,2,6,6-tetramethylpiperidine (0.36 ml, 2.11 mmoles) was added and the mixture was allowed to stand at 0° for 20 minutes, after which it was cooled at -78°. A solution of **4** (0.100 g, 0.51 mmole) in 5 ml of tetrahydrofuran was slowly added in 45 minutes and the mixture stirred at -78° for 1 hour. The electrophile was added and stirring was continued for 2 hours at -78°. Hydrolysis was then carried out at this temperature using a mixture of 35% aqueous hydrochloric acid (1 ml), ethanol (2 ml) and tetrahydrofuran (2 ml). The solution was gently warmed to room temperature, made slightly basic with a saturated sodium hydrogenocarbonate solution and evaporated under vacuum nearly to dryness. The residue was extracted with dichloromethane (3 x 20 ml). The organic extract was dried (magnesium sulfate) and evaporated. The crude product was purified by column chromatography on silica gel.

General Procedure B. Synthesis of Substituted Pyrimidines by the *in situ* Trapping Technique.

A mixture of **4** (0.100 g, 0.51 mmole) in tetrahydrofuran (5 ml) and the required electrophile (1.5 mmoles) in tetrahydrofuran (15 ml) were added simultaneously to a cold (-100°) solution of lithium 2,2,6,6-tetramethylpiperidide (1.5 mmoles) in dry tetrahydrofuran (20 ml) in 30 minutes. The mixture was stirred for 1 hour at -100°, then 1 hour at -75° before hydrolysis by a mixture of 35% aqueous hydrochloric acid (1 ml), ethanol (2 ml) and tetrahydrofuran (2 ml). The solution was gently warmed to room temperature, treated with a saturated sodium bicarbonate solution (5 ml) and evaporated under vacuum nearly to dryness. The residue was extracted with dichloromethane (3 x 20 ml). The organic extract was dried (magnesium sulfate) and evaporated. The crude product was purified by column chromatography on silica gel.

2-Methylthio-4-trifluoromethyl-6-deuteropyrimidine **9**.

Metalation of **4** according to the general procedure A and reaction with 1 ml of mixture deuteriomethanol, deuterium chloride 1:1 gave **9** (46%); ^1H nmr (deuteriochloroform): δ 2.60 (s, 3H, SCH_3), 7.26 (s, H_5).

2,2'-Dimethylthio-4,4'-trifluoromethyl-6,6'-bipyrimidine **10**.

Metalation of **4** according to general procedure A and reaction with various electrophiles gave **10** (4-30%). The crude product was purified by column chromatography on silica gel with a mixture of dichloromethane/cyclohexane 3:1 as an eluent, mp 160-162° dec; ^1H nmr (deuteriochloroform): δ 2.70 (s, 3H, SCH_3), 8.31 (s, 1H, H_5).

Anal. Calcd. for $C_{12}H_8F_6N_4S_2$: C, 37.27; H, 2.07; N, 14.49. Found: C, 37.5; H, 2.0; N, 14.4.

2-Methylthio-4-trifluoromethyl-6-pyrimidinyl)ethanol **11**.

Procedure 1.

Metalation of **4** (0.100 g, 0.51 mmole) according to general procedure and reaction with acetaldehyde (1 ml, 18 mmoles) gave after purification by column chromatography on silica gel with a mixture of ethyl acetate/cyclohexane/ethanol (5:15:0.5) as an eluent, 0.064 g (52%) of a yellow liquid of **11**.

Procedure 2.

To a cold solution of 2-methylthio-4-trifluoromethyl-6-trimethylsilylpyrimidine (**16**) (0.106 g, 0.39 mmole) in tetrahydrofuran (5 ml) was added at 0° acetaldehyde (0.56 ml, 10 mmoles) and tetrabutylammonium fluoride (1*M* in tetrahydrofuran, 0.8 ml, 20% molar). The solution was stirred and kept at 0° for 3.5 hour, then filtered on silica gel. The solvent was removed under reduced pressure and the crude product was purified by column chromatography on silica gel as described above,

0.69 g (72%) of **11**; ^{1}H nmr (deuteriochloroform): δ 1.49 (d, 3H, C*H*$_3$, J = 7 Hz), 2.55 (s, 3H, SC*H*$_3$), 3.4 (s, 1H, O*H*), 4.83 (q, 1H, C*H*(OH), J = 7 Hz), 7.32 (s, 1H, H$_5$).

Anal. Calcd. for $C_8H_9F_3N_2OS$: C, 40.33; H, 3.81; N, 11.76. Found: C, 40.2; H, 4.1; N, 11.5.

(2-Methylthio-4-trifluoromethyl-6-pyrimidinyl)phenylmethanol **12**.

Metalation of **4** (0.100 g, 0.51 mmole) according to general procedure A and the reaction with benzaldehyde (0.06 ml, 0.6 mmole) gave, after purlfication by column chromatography on silica gel with a mixture of dichloromethane/cyclohexane (3:1) as an eluent, 0.095 g (62%) of a colorless liquid of **12**; ^{1}H nmr (deuteriochloroform): δ 2.60 (s, 3H, SC*H*$_3$), 4.21 (s, 1H, O*H*) 5.73 (s, 1H, C*H*(OH)), 7.23 (s, 1H, H$_5$), 7.37 (m, 5H, phenyl).

Anal. Calcd. for $C_{13}H_{11}F_3N_2OS$: C, 51.99; H, 3.69; N, 9.33. Found: C, 51.9; H, 3.6; N, 9.4.

2-Methylthio-4-trifluoromethyl-6-iodopyrimidine **13**.

Metalation of **4** (0.100 g, 0.51 mmole) according to general procedure A or B and reaction with a solution of 0.38 g (1.5 mmoles) of iodine in 5 ml of tetrahydrofuran gave, after purification by column chromatography on silica gel with a mixture of cyclohexane/dichloromethane (40:1) as an eluent, 0.068 g (41%) method A, 0.043 g (26%) method B of **13**, mp 90-92°; ^{1}H nmr (deuteriochloroform): δ 2.53 (s, 3H, SC*H*$_3$), 7.63 (s, 1H, H$_5$).

Anal. Calcd. for $C_6H_4F_3IN_2S$: C, 22.51; H, 1.26; N, 8.75. Found: C, 22.5; H, 1.0; N, 8.8.

2-Methylthio-4-trifluoromethyl-6-chloropyrimidine **14**.

Metalation of **4** (0.100 g, 0.51 mmole) according to general procedure A or B and reaction with a solution of 0.35 g (1.5 mmoles) of hexachloroethane in 5 ml of tetrahydrofuran gave, after purification by column chromatography on silica gel with a mixture of dichloromethane/cyclohexane (1:3) as an eluent, 0.028 g (25%) method A, 0.023 g (19%) method B of a colorless oil of **14**; ^{1}H nmr (deuteriochloroform): δ 2.57 (s, 3H, SC*H*$_3$), 7.25 (s, 1H, H$_5$).

Anal. Calcd. for $C_6H_4ClF_3N_2S$: C, 31.52; H, 1.76; N, 12.25. Found: C, 31.6; H, 1.7; N, 12.3.

5,6-Dichloro-2-methylthio-4-trifluoromethylpyrimidine **15**.

Obtained beside compound **14** by metalation of **4** according to general procedure A, 0.018 g (13%) of a colorless oil of **15**; ^{1}H nmr (deuteriochloroform): δ 2.57 (s, 3H, SC*H*$_3$).

Anal. Calcd. for $C_6H_3Cl_2F_3N_2S$: C, 27.39; H, 1.15; N, 10.65. Found: C, 27.4; H, 1.4; N, 10.6.

2-Methylthio-4-trifluoromethyl-6-trimethylsilylpyrimidine **16**.

Metalation of **4** (0.100 g, 0.51 mmole) according to general procedure B and reaction with a solution of trimethylchlorosilane (0.4 ml, 1.5 mmole) in 5 ml of tetrahydrofuran gave, after purification by column chromatography on silica gel with a mixture of dichloromethane/cyclohexane (1:1) as an eluent, 0.128 g (96%) of a yellow oil of **16**; ^{1}H nmr (deuteriochloroform): δ 0.31 (s, 9H, Si (C*H*$_3$)$_3$), 2.56 (s, 3H, SC*H*$_3$), 7.34 (s, 1H, H$_5$).

Anal. Calcd. for $C_9H_{13}F_3N_2SSi$: C, 40.58; H, 4.92; N, 10.52. Found: C, 40.5; H, 5.1; N, 10.3.

(2-Methylthio-4-trifluoromethyl-5-pyrimidinyl)-diphenylmethanol **17**.

Metalation of **4** (0.100 g, 0.51 mmole) according to general procedure B and reaction with a solution of benzophenone (0.27 g, 1.5 mmoles) in 15 ml of the tetrahydrofuran gave after purification by column chromatography on silica gel with a mixture of cyclohexane/ethylacetate (40:1) as an eluent, 0.145 g (77%) of a yellow oil of **17**; ^{1}H nmr (deuteriochloroform): δ 2.59 (s, 3H, SC*H*$_3$), 5.04 (s, 1H, OH), 7.17 (s, 1H, H$_5$), 7.27-7.38 (m, 10H, phenyl).

Anal. Calcd. for $C_{19}H_{15}F_3N_2OS$: C, 60.63; H, 4.01; N, 7.44. Found: C, 60.3; H, 4.0; N, 7.8.

2-Methylthio-6-phenylthio-4-trifluoromethylpyrimidine **18**.

Metalation of **4** (0.100 g, 0.51 mmole) according to general procedure B and reaction with a solution of diphenyl disulphide (0.33 g, 1.6 mmoles) in 15 ml of tetrahydrofuran gave, after purification by column chromatography on silica gel with a mixture of dichloromethane/cyclohexane (1:3) as an eluent, 0.151 g (98%) of a yellow oil of **18**; ^{1}H nmr (deuteriochloroform): δ 2.37 (s, 3H, SC*H*$_3$), 6.74 (s, 1H, H$_5$), 7.4-7.6 (m, 5H, phenyl).

Anal. Calcd. for $C_{12}H_9F_3N_2S_2$: C, 47.67; H, 3.00; N, 9.26. Found: C, 47.9; H, 3.1; N, 9.2.

2-Methylthio-4-trifluoromethyl-6[2-(trimethylsilyl)ethinyl]-pyrimidine **19**.

Through triethylamine (5 ml) argon was bubbled for 30 minutes with stirring. Copper(I) iodide (1.8 mg, 9.5 x 10^{-6} mole) was added, then 10 minutes later (trimethylsilyl)acetylene (0.04 ml, 0.30 mmole) was added. Then 10 minutes later bis(triphenylphosphane)palladium(II) dichloride (5 mg, 7.1 x 10^{-6} mole) was added. After 60 minutes **13** (0.050 g, 0.16 mmole) was added. The mixture was stirred for 48 hours at room temperature. The reaction was monitored by tlc. After completion of the reaction, the mixture was filtered, the residue washed with diethyl ether (3 x 10 ml), and the combined filtrates were dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel with a mixture of dichloromethane/cyclohexane (1:5) as an eluent to provide 0.039 g (84%) of a yellow oil of **19**; ^{1}H nmr (deuteriochloroform): δ 0.25 (s, 9H, (C*H*$_3$)$_3$Si), 2.55 (s, 3H, SC*H*$_3$), 7.26 (s, 1H, H$_5$).

Anal. Calcd. for $C_{11}H_{13}F_3N_2SSi$: C, 45.45; H, 4.51; N, 9.65. Found: C, 45.7; H, 4.3; N, 9.6.

2-Methylthio-6-phenyl-4-trifluoromethylpyrimidine **20**.

To a solution of potassium carbonate (2*M*, 0.507 ml) and ethanol (0.2 ml) in deoxygenated toluene (4 ml) were added 13 (0.100 g, 0.31 mmole) and phenylboronic acid (0.049 g, 0.4 mmole). Dry argon was bubbled through the resulting mixture for 30 minutes. Tetrakis(triphenylphosphine)palladium(0) (0.0018 g, 0.016 mmole) was added and the reaction mixture was warmed at 85° for 4 hours. After cooling, filtration and extraction with toluene (2 x 10 ml), the organic extracts were dried over magnesium sulfate, and solvent removal afforded a crude product which was purified by column chromatography on silica gel with a mixture of dichloromethane/cyclohexane (1:5) as an eluent. A second purification by column chromatography on neutral aluminium oxide with the same mixture as an eluent as performed providing 0.083 g (91%) of **20** mp 73-75°; ^{1}H nmr (deuteriochloroform): δ 2.64 (s, 3H, SC*H*$_3$), 7.52 (m, 3H, phenyl), 7.59 (s, 1H, H$_5$), 8.08 (m, 2H, phenyl).

Anal. Calcd. for $C_{12}H_9F_3N_2S$: C, 53.33; H, 3.35; N, 10.36. Found: C, 53.3; H, 3.0; N, 10.3.

2-[(2-Hydroxyethyl)-methylamino]-4-trifluoromethyl-6-phenylpyrimidine **21**.

A mixture of **20** (0.050 g, 0.18 mmole), 2-(methylamino)-ethanol (0.5 ml, 6.2 mmoles), and 10*N* hydrochloric acid (0.05 ml) was warmed at 100° for 24 hours. After cooling, water was added 15 ml, and the *p*H was adjusted to 3-4 with hydrochloric acid. The aqueous solution was extracted with dichloromethane (3 x 10 ml) and the combined organic extracts were dried over magnesium sulfate and evaporated. The crude product was purified by column chromatography on silica gel with a mixture of dichloromethane/ethyl acetate (5:1) as an eluent giving 0.046 g (87%) of **21** mp 51-53°; ^{1}H nmr (deuteriochloroform): δ 3.31 (s, 4H, N-CH_3, OH), 3.67 (s, 4H, $(CH_2)_2$), 7.18 (s, 1H, H_5), 7.45 (m, 3H, phenyl), 8.01 (m, 2H, phenyl).

Anal. Calcd. for $C_{14}H_{14}F_3N_3O$: C, 56.51; H, 4.74; N, 14.13. Found: C, 56.2; H, 4.8; N, 14.4.

REFERENCES AND NOTES

[1] D. B. Su, J. X. Duan, and Q. Y. Chen, *Tetrahedron Letters*, **32**, 7689 (1991).

[2a] A. Kreutzberger and J. Gillessen, *J. Heterocyclic Chem.*, **22**, 101 (1985); [b] A. Kreutzberger and A. Burger, *Arch. Pharm.*, **326**, 473 (1993); [c] A. Kreutzberger and A. Burger, *J. Fluorine Chem.*, **60**, 257 (1993).

[3] N. Plé, A. Turck, A. Heynderickx, and G. Quéguiner, *J. Heterocyclic Chem.*, **31**, 1311 (1994).

[4] A. Turck, N. Plé, and G. Quéguiner, *Heterocycles*, **37**, 2149 (1994).

[5a] D. J. Burton and D. M. Wiemers, *J. Am. Chem. Soc.*, **107**, 5014 (1985); [b] D. J. Burton and D. M. Wiemers, *J. Am. Chem. Soc.*, **108**, 832 (1986).

[6a] Q. Y. Chen and S. W. Wu, *J. Chem Soc., Perkin Trans I*, 2385 (1989); [b] Q. Y. Chen and S. W. Wu, *J. Chem Soc., Chem. Commun.*, 705 (1989).

[7a] J. D. Robert and D. Y. Curtin, *J. Am. Chem. Soc.*, **68**, 1658 (1946); [b] D. A. Shirley, J. R. Johnson, and J. P. Hendrix, *J. Organomet. Chem.*, **11**, 209 (1968).

[8a] M. Schlosser, G. Katsoulos, and S. Tagagishi, *Synlett*, 747 (1990); [b] G. Katsoulos, S. Tagagishi, and M. Schlosser, *Synlett*, 731 (1991); [c] S. Tagagishi, G. Katsoulos, and M. Schlosser, *Synlett*, 360 (1992); [d] G. Katsoulos, Thesis, (Lausanne), 1993.

[9a] P. Aeberli and W. J. Houlihan, *J. Organomet. Chem.*, **67**, 321 (1974); [b] K. D. Bartle, G. Hallas, and J. D. Hepworth, *Org. Magn. Reson.*, **5**, 479 (1973).

[10] D. E. Grocock, T. K. Jones, G. Hallas, and J. D. Hepworth, *J. Chem. Soc., Perkin Trans. C*, 3305 (1971).

[11] J. Porwisiak and W. Dmowski, *Tetrahedron*, **50**, 12259 (1994).

[12] H. C. Clark, *Adv. Fluorine Chem.*, **3**, 21 (1963).

[13a] O. A. Vyazankiu, B. A. Gostevsky, N. S. Vyazankiu, and G. G. Furin, *Tetrahedron*, **44**, 2675 (1988); [b] F. J. Pinkeston and S. F. Thames, *J. Organomet. Chem.*, **24**, 623 (1970); [c] M. Tsukazaki and V. Snieckus, *Heterocycles*, **33**, 533 (1992); [d] M. Tsukazaki and V. Snieckus, *Heterocycles*, **33**, 689 (1992).

[14] F. Trécourt, A. Turck, N. Plé, A. Paris, and G. Quéguiner, *J. Heterocyclic Chem.*, **32**, 1057 (1995).