Metalation of Diazines. XI. Directed *Ortho*-Lithiation of Fluoropyrimidines and Application to Synthesis of an Azacarboline

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For the first time fluoropyrimidines were successfully lithiated. The resulting lithio derivatives were reacted with various electrophiles for the synthesis of new pyrimidines. The synthesis of an azacarboline derivative is reported.

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Introduction.

The pyrimidine skeleton is commonly found in pharmaceutical drugs, fungicides and herbicides. Some fluorine containing pyrimidines like 5-fluorouracil and 5-fluoromethyluridine derivatives were shown to have great biological activity. The reported preparations of such fluoropyrimidines have been based on classical condensation reactions which involve the pyrimidine ring construction. Some years ago synthesis of some fluoropyrimidines have been performed by substitution of chlorine by a fluorine atom [1,2,3].

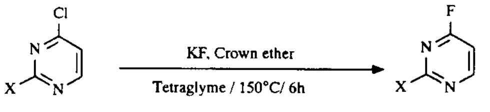
The metalation of diazines has been recently developed and shown to be a powerful tool to access to new compounds. As a continuation of our studies on diazines [4], we report the direct lithiation and functionalization of 4-fluoropyrimidines, using fluorine as *ortho*-directing group.

If the fluorine atom has been previously used as an *ortho*-directing group with pyridine [5] and quinoline derivatives [6], only one example of metalation of 1,3-dialkyl-5-fluorouracils was mentioned in the literature [7] using ICl as sole electrophile.

Results.

Treatment of 2,4-dichloropyrimidine **1** and 4-chloro-2-thiomethylpyrimidine **2** with anhydrous potassium fluoride in tetraglyme and catalytic amounts of dicyclohexano-18-crown-6 at 150-160° for 6 hours gave in high yields the corresponding fluorinated compounds: 2,4-difluoropyrimidine **3** [1] and the unknown 4-fluoro-2-thiomethylpyrimidine **4** as shown in Scheme I.

Scheme I



1 X = Cl

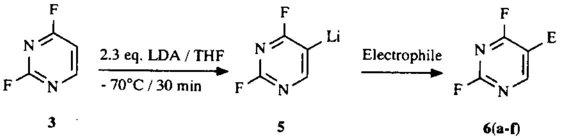
2 X = SMe

3 X = F 84%

4 X = SMe 67%

Reaction of 2,4-difluoropyrimidine **3** in anhydrous tetrahydrofuran (THF) with 2.3 equivalents of lithium diisopropylamide (LDA) as metalating agent at −70° for 30 minutes gave the *ortho*-lithio derivative **5** which was reacted with various electrophiles (Scheme II).

Scheme II



3

5

6(a-f)

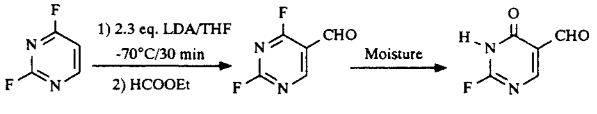
6a	E = $CH_3CH(OH)$	61%	**6d**	E = $2,4(Cl)_2PhCH(OH)$	20%
6b	E = PhCH(OH)	59%	**6e**	E = $3,4,5(OMe)_3PHCH(OH)$	47%
6c	E = 2(OMe)PhCH(OH)	25%	**6f**	E = I	27%

The most efficient conditions for metalation of **3** have been determined with LDA as the metalating agent rather with lithium-2,2,6,6-tetramethylpiperidide (LTMP) which was often advocated with diazines.

When LTMP was used as the metalating agent and under the same experimental conditions **6a** and **6b** were obtained respectively with only 32% and 12% yields. Moreover we observed a loss of regioselectivity in the *ortho* position of the fluorine atom: besides **6a** and **6b**, small amounts (7-8%) of metalation at the C-6 position (*ortho* to the cyclic nitrogen) were highlighted by the ^1H nmr spectrum of crude products. Such a problem of regioselectivity has been already described with 4-chloropyrimidines and LTMP as a metalating agent [4h].

Great difficulties were encountered in isolating the 2,6-difluoro-5-formylpyrimidine **6g** due to its instability on exposure to air and moisture. Compound **6g** which has been characterized by the ^1H nmr spectrum of the crude product underwent rapid hydrolysis to give 2-fluoro-5-formyl-4(3*H*)-pyrimidone **7** in 37% yield based on **3** (Scheme III).

Scheme III



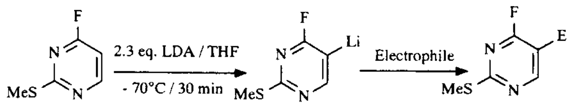
3

6g

7 (37%)

The metalation of 4-fluoro-2-thiomethylpyrimidine **4** was performed under the same experimental conditions as for **3** and the lithio derivative **8** was trapped with various electrophiles (Scheme IV).

Scheme IV



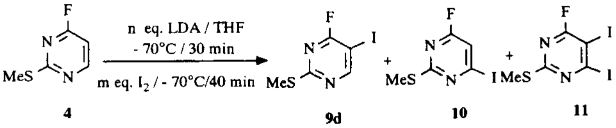
4 8 9(a-f)

9a	E = $CH_3CH(OH)$	87%	9d	E = I	87%
9b	E = PhCH(OH)	80%	9e	E = COOH	48%
9c	E = 2(OMe)PhCH(OH)	70%	9f	E = CHO	55%

Better yields were observed with 4-fluoro-2-thiomethylpyrimidine **4** than for the difluoro compound **3**. As previously the formyl derivative **9f** was sensitive to moisture and was identified by its ^{1}H nmr spectrum.

With iodine as an electrophile the results were quite dependent on the experimental conditions (amounts of metalating agent and iodine) (Scheme V).

Scheme V



4 9d 10 11

Entry	n eq. LDA	m eq. I_2	9d	10	11
1	1.1	3	87%	-	6%
2	2.3	3	10%	-	70%
3	2.3	1	-	77%	3%

Metalation of **4** with 1.1 equivalents of LDA followed by reaction with iodine in excess led to the expected C-5 iodo derivative **9d** (entry 1), the diiodo derivative **11** was the major product when the metalating agent and iodine were in excess (entry 2).

It can be assumed that reaction of **4** with 1.1 equivalents of LDA led to the C-5 lithio derivative **8** which reacted with iodine to give **9d**. In the presence of an excess of metalating agent, compound **9d** underwent a further lithiation at the C-6 position and after the reaction with an other equivalent of iodine afforded the diiodio derivative **11** (entry 2).

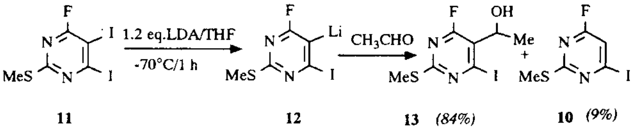
The unexpected C-6 iodo derivative **10** was observed when LDA was in excess (2.3 equivalents) and when iodine was in stoichiometric amounts (entry 3). Such an unusual regioselectivity with iodine as an electrophile has been observed during the metalation of 2-chloro-4-methoxypyrimidine [4i]. A study of the reaction pathway has been performed with this compound, the formation of a diiodo derivative as an intermediate and an halogen-migration reaction have been highlighted. It can be assumed that such an halogen migration can also explain the exclusive formation of the C-6 iodo derivative **10** (entry 3). A reaction of the diiodo derivative **11** with the lithiated species present in the mixture reaction (**8** or LDA) could lead to a C-5 lithio derivative **12** which can after hydrolysis give the mono iodo derivative **10**.

The formation of the lithio derivative **12** at the C-5 position resulting from the reaction of **11** with LDA, could be highlighted by a further reaction with an electrophile leading to a C-5 substituted compound.

This experimental result could appear as an halogen-lithium exchange leading to **12**. This kind of exchange was known with *n*-butyllithium as the metalating agent and halogeno aromatics and has been widely used in many syntheses. This unusual reaction has been mentioned for first time with iodopyrimidines and LTMP as the metalating agent [4i].

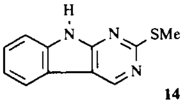
The reaction of **11** with 1.2 equivalents of LDA at −70° in THF for 1 hour followed by reaction with acetaldehyde in excess gave (2-thiomethyl-4-fluoro-6-iodo-5-pyrimidinyl)-ethanol **13** (84%) and small amounts of the C-5 iodo derivative **10** (9%) (Scheme VI).

Scheme VI



11 12 13 (84%) 10 (9%)

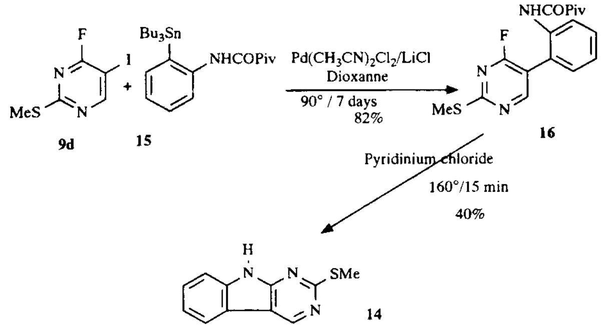
The 4-fluoro-5-iodo derivative **9d** was used as key intermediate to synthesize an azacarboline derivative: 3-thiomethyl-9*H*-pyrimido[4,5-*b*]indole **14**.



14

Only few compounds of this skeleton have been described in the literature and they were obtained either by photocyclization of anilinuracils [8-12] or from substituted indoles [13]. Our synthesis starts from a pyrimidine derivative and uses *ortho*-directed metalation and cross coupling reactions (Scheme VII).

Scheme VII



After metalation of **4** and subsequent reaction with iodine as shown previously, a reaction between the iodo derivative **9d** and (2-(pivaloylamino)phenyl)tributyl stannate **15** using bis(acetonitrile)palladiumII chloride $Pd(CH_3CN)_2Cl_2$ as catalyst under Stille [14] conditions resulted in heteroring cross-coupling leading to compound **16**. A subsequent cyclization with pyridinium chloride at 160° for 15 minutes led to the new azacarboline derivative **14**.

Conclusion.

Lithiation in the pyrimidine series with a fluorine as the *ortho*-directing group at the C-4 position afforded various substituted pyrimidines. This methodology is a powerful synthetic tool to obtain to *ortho*-functionalized 5-substituted pyrimidines which can easily by hydrolysed into uracils. A new synthetic route to pyrimidoindoles was highlighted by the use of cross coupling reaction with *ortho*-iodofluoropyrimidines.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. The ^{1}H nmr spectra were recorded in deuteriochloroform with tetramethylsilane as the internal standard or in deuterated dimethyl sulfoxide with hexamethyldisiloxan as the internal standard on a Varian EM 360 L, Bruker AC 200 instrument. Microanalyses were performed on a Carlo Erba CHNOS 1106 apparatus. The ir spectra were obtained as potassium bromide pellets with a Perkin Elmer R12 spectrophotometer.

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).

Metalations were performed under an argon atmosphere whose water content was regularly checked. Reagents were handled with syringes through septa.

2,4-Difluoropyrimidine **3**.

To a stirred solution of 2,4-dichloropyrimidine (7.45 g, 50 mmoles) in 30 ml of tetraglyme was added 0.3 g of dicyclohexano-18-crown-6 and 18 g (0.3 mole) of finely ground anhydrous potassium fluoride. The slurry was heated at 150° for 12 hours. A distillation under reduced pressure gave 4.8 g (82%) of **3** as a colorless liquid; ^{1}H nmr (deuteriochloroform): δ 7.1 (ddd, 1H, $J_{5,2F}$ = $J_{5,4F}$ = 2 Hz, $J_{5,6}$ = 6 Hz, H_5), 8.7 (ddd, 1H, $J_{6,2F}$ = 2 Hz, $J_{6,4F}$ = 12 Hz, $J_{5,6}$ = 6 Hz, H_6); ^{13}C nmr (deuteriochloroform): δ 171.8 (C_2), 164.1 (C_4), 164.0 (C_6), 105.2 (C_5); ^{19}F nmr (deuteriochloroform, reference fluorotrichloromethane): δ -43.27 (F_2), -55.77 (F_4).

2-Thiomethyl-4-fluoropyrimidine **4**.

The same experimental procedure was used for preparation of 2-thiomethyl-4-fluoropyrimidine **4** starting from commercial 2-thiomethyl-4-chloropyrimidine (Aldrich Chemical Co.). A distillation under reduced pressure gave 4.8 g (67%) of **4** as a colorless liquid; ^{1}H nmr (deuteriochloroform): δ 2.53 (s, 3H, SCH_3), 6.6 (dd, 1H, $J_{5,4F}$ = 2 Hz, $J_{5,6}$ = 6 Hz, H_5), 8.5 (dd, 1H, $J_{6,4F}$ = 12 Hz, $J_{5,6}$ = 6 Hz, H_6).

Anal. Calcd. for $C_5H_5FN_2S$: C, 41.65; N, 19.43; H, 3.49. Found: C, 41.4; N, 19.3; H, 3.3.

General Procedure for Metalation.

A solution of butyllithium (1.6 *M* in hexane, 2.9 ml, 4.6 mmoles) is added to cold ($-30°$), stirred, anhydrous tetrahydrofuran (40 ml) under an atmosphere of dry argon. The mixture is warmed to 0° and diisopropylamine (0.88 ml, 5.2 mmoles) is added, the solution is kept at 0° for 45 minutes, it is then cooled to $-70°$. A solution of 2,4-difluoro- or 2-thiomethyl-4-fluoropyrimidine (2.0 mmoles) in 5 ml of tetrahydrofuran is added and the mixture is stirred for 1 hour at $-70°$. The electrophile is added and stirring is continued for 1 hour at $-70°$. Hydrolysis is then carried out at $-70°$ using a mixture of 35% aqueous hydrochloric acid (2 ml), ethanol (2 ml) and tetrahydrofuran (8 ml). The solution is gently warmed to room temperature, made slightly basic with a saturated sodium hydrogenocarbonate solution (10 ml) and evaporated under vacuum nearly to dryness. The residue is extracted with dichloromethane (4 x 40 ml). The organic extract is dried (magnesium sulphate) and evaporated. The crude product is purified by column chromatography on silica gel or by sublimation.

(2,4-Difluoro-5-pyrimidinyl)ethanol **6a**.

Metalation of **3** (0.23 g, 2.0 mmoles) according to the general procedure and reaction with acetaldehyde (1 ml, 18 mmoles) gave after purification by column chromatography on silica gel with a mixture of ether, cyclohexane (5:1) as an eluent 0.195 g (61%) of a colorless liquid of **6a**; ^{1}H nmr (deuteriochloroform): δ 1.66 (d, 3H, CH_3, J = 7 Hz), 3.8 (s, 1H, OH), 5.1 (q, 1H, $CH(OH)$, J = 7 Hz), 8.73 (dd, 1H, J = 2 Hz, J = 12 Hz, H_6); ir: ν 3230, 1669, 1451 cm^{-1}.

Anal. Calcd. for $C_6H_6F_2N_2O$: C, 45.00; N, 17.49; H, 3.77. Found: C, 45.2; N, 17.8; H, 3.9.

(2,4-Difluoro-5-pyrimidinyl)phenylmethanol **6b**.

Metalation of **3** (0.23 g, 2.0 mmoles) according to the general procedure and reaction with benzaldehyde (0.25 ml, 2.4 mmoles) gave after purification by column chromatogaphy on silica gel with a mixture of dichloromethane, ether (4:1) as an eluent 0.26 g (59%) of a colorless liquid of **6b**; ^{1}H nmr (deuteriochloroform): δ 2.9 (s, 1H, OH), 6.0 (s, H, $CH(OH)$, 7.4 (m, 5H, phenyl), 8.8 (dd, 1H, J = 2 Hz, J = 12 Hz, H_6); ir: ν 3372, 3064, 1580, 1437 cm^{-1}.

Anal. Calcd. for $C_{11}H_8F_2N_2O$: C, 59.46; N, 12.61; H, 3.63. Found: C, 59.8; N, 12.5; H, 3.9.

(2,4-Difluoro-5-pyrimidinyl)-2-methoxyphenylmethanol **6c**.

Metalation of **3** (0.23 g, 2.0 mmoles) according to the general procedure and reaction with 2-methoxybenzaldehyde (0.29 ml, 2.4 mmoles) gave after purification by column chromatography on silica gel with a mixture of dichloromethane, ether (4:1) as an eluent 0.126 g (25%) of a yellow oil of **6c**; ^{1}H nmr (deuteriochloroform): δ 3.76 (s, 3H, OCH_3), 6.05 (s, 1H, $CH(OH)$), 7 (m, 4H, phenyl), 8.5 (dd, 1H, J = 2 Hz, J = 12 Hz, H_6); ir: ν 3395, 3073, 1599, 1492, 1438 cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}F_2N_2O_2$: C, 57.11; N, 11.10; H, 3.96. Found: C, 56.7; N, 10.82; H, 3.9.

(2,4-Difluoro-5-pyrimidinyl)-2,4-dichlorophenylmethanol **6d**.

Metalation of **3** (0.23 g, 2.0 mmoles) according to the general procedure and reaction with 2,4-dichlorobenzaldehyde (0.3 ml, 2.4 mmoles) gave after purification by column chromatography on silica gel with a mixture of dichloromethane, ether, cyclohexane (20:3:6) as an eluent 0.116 g (20%) of **6d**, mp 51-53°; ^{1}H nmr (deuteriochloroform): δ 4.26 (s, 1H, OH), 6.2 (s, 1H, $CH(OH)$), 7.26 (m, 3H, phenyl), 8.46 (dd, 1H, J = 2 Hz, J = 12 Hz, H_6); ir: ν 3309, 1593, 1561, 1469, 1438 cm^{-1}.

Anal. Calcd. for $C_{11}H_6Cl_2F_2N_2O$: C, 45.39; N, 9.62; H, 2.07. Found: C, 45.1; N, 9.4; H, 2.4.

(2,4-Difluoro-5-pyrimidinyl)-3,4,5-trimethoxyphenylmethanol **6e**.

Metalation of **3** (0.23 g, 2.0 mmoles) according to the general procedure and reaction with 3,4,5-trimethoxybenzaldehyde (0.45 g, 2.3 mmoles) gave after purification by column chromatography on silica gel with a mixture of dichloromethane, ether (4:1) as an eluent 0.293 g (47%) of **6e**, mp 96-98°; ^{1}H nmr (deuteriochloroform): δ 3.8 (s, 9H, OCH$_3$), 5.26 (s, 1H, C*H*(OH)), 5.9 (s, 1H, C*H*(OH)), 6.6 (s, 2H, phenyl), 8.76 (dd, 1H, J = 2 Hz, J = 12 Hz, H$_6$); ir: ν 3420, 3070, 1598, 1508, 1436 cm^{-1}.

Anal. Calcd. for $C_{14}H_{14}F_2N_2O_4$: C, 53.81; N, 8.97; H, 4.48. Found: C, 54.1; N, 8.5; H, 4.2.

2,4-Difluoro-5-iodopyrimidine **6f**.

Metalation of **3** (0.23 g, 2.0 mmoles) according to the general procedure and reaction with a solution of 0.56 g (2.2 mmoles) of iodine in 5 ml of tetrahydrofuran gave after purification by column chromatography on silica gel with a mixture of dichloromethane, cyclohexane (4:5) as an eluent 0.13 g (27%) of **6f**, sublimes 49-50°; ^{1}H nmr (deuteriochloroform): δ 8.88 (dd, 1H, J = 2 Hz, J = 10 Hz, H$_6$); ir: ν 3421, 1560, 1420 cm^{-1}.

Anal. Calcd. for $C_4H_1F_2N_2I$: C, 19.84; N, 11.57; H, 0.49. Found: C, 19.9; N, 11.1; H, 0.5.

2,4-Difluoro-5-formylpyrimidine **6g**.

This compound had ^{1}H nmr (deuteriochloroform): δ 8.88 (dd, 1H, J = 2 Hz, J = 12 Hz, H$_6$), 10.2 (s, 1H, CHO).

2-Fluoro-5-formyl-4(3*H*)-pyrimidinone **7**.

Metalation of **3** (0.23 g, 2.0 mmoles) according to the general procedure and reaction with ethyl formate (0.19 ml, 2.3 mmoles) gave after purification by column chromatography on silica gel with dichloromethane as an eluent 0.105 g (37%) of **7**, mp 178-180°; ^{1}H nmr (deuteriochloroform): δ 8.76 (d, 1H, J = 2 Hz, H$_6$), 10.2 (s, 1H, CHO).

Anal. Calcd. for $C_5H_3FN_2O_2$: C, 42.26; N, 19.71; H, 2.13. Found: C, 42.5; N, 19.6; H, 2.3.

(2-Thiomethyl-4-fluoro-5-pyrimidinyl)ethanol **9a**.

Metalation of **4** (0.29 g, 2.0 mmoles) according to the general procedure and reaction with acetaldehyde (1 ml, 18 mmoles) gave after purification by column chromatography on silica gel with a mixture of ether, cyclohexane (9:4) as an eluent 0.33 g (87%) of a colorless liquid of **9a**; ^{1}H nmr (deuteriochloroform): δ 1.5 (d, 3H, C*H*$_3$, J = 7 Hz), 2.57 (s, 3H, SCH$_3$), 3.4 (s, 1H, O*H*), 5.05 (q, 1H, C*H*(OH)), J = 7 Hz), 8.65 (d, 1H, J = 12 Hz, H$_6$).

Anal. Calcd. for $C_7H_9FN_2OS$: C, 44.67; N, 14.88; H, 4.82. Found: C, 44.7; N, 14.8; H, 4.9.

(2-Thiomethyl-4-fluoro-5-pyrimidinyl)phenylmethanol **9b**.

Metalation of **4** (0.29 g, 2.0 mmoles) according to the general procedure and reaction with benzaldehyde (0.25 ml, 2.4 mmoles) gave after purification by column chromatography on silica gel with a mixture of dichloromethane, ether (30:1) as an eluent 0.40 g (80%) of **9b**, mp 55-57°; ^{1}H nmr (deuteriochloroform): δ 2.54 (s, 3H, SCH$_3$), 3.66 (s, 1H, O*H*), 5.9 (s, H, C*H*(OH)), 7.3 (m, 5H, phenyl), 8.56 (d, 1H, J = 12 Hz, H$_6$).

Anal. Calcd. for $C_{12}H_{11}FN_2OS$: C, 57.58; N, 11.09; H, 4.43. Found: C, 58.0; N, 10.7; H, 4.5.

(2-Thiomethyl-4-fluoro-5-pyrimidinyl)-2-methoxyphenylmethanol **9c**.

Metalation of **4** (0.29 g, 2.0 mmoles) according to the general procedure and reaction with 2-methoxybenzaldehyde (0.29 ml, 2.4 mmoles) gave after purification by column chromatography on silica gel with a mixture of dichloromethane, ether (40:1) as an eluent 0.39 g (70%) of **9c**, mp 138-140°; ^{1}H nmr (deuteriochloroform): δ 2.6 (s, 3H, SCH$_3$), 3.3 (d, 1H, J = 6 Hz, O*H*), 3.85 (s, 3H, OCH$_3$), 6.1 (d, 1H, J = 6 Hz, C*H*(OH)), 7.1 (m, 4H, phenyl), 8.5 (d, 1H, J = 12 Hz, H$_6$).

Anal. Calcd. for $C_{13}H_{13}FN_2O_2S$: C, 55.70; N, 9.99; H, 4.67. Found: C, 56.2; N, 9.6; H, 4.6.

2-Thiomethyl-4-fluoro-5-iodopyrimidine **9d**.

Metalation of **4** (0.29 g, 2.0 mmoles) according to the general procedure with 1.1 equivalents of LDA and reaction with a solution of 1.52 g (6 mmoles) of iodine in 10 ml of tetrahydrofuran gave after purification by column chromatography on silica gel with a mixture of cyclohexane, dichloromethane (5:4) as an eluent 0.47 g (87%) of **9d**, mp 55-57°; ^{1}H nmr (deuteriochloroform): δ 2.57 (s, 3H, SCH$_3$), 8.67 (d, 1H, J = 12 Hz, H$_6$); ir: ν 1566, 1519, 1409 cm^{-1}.

Anal. Calcd. for $C_5H_4FIN_2S$: C, 22.24; N, 10.37; H, 1.49. Found: C, 22.1; N, 10.4; H, 1.3.

2-Thiomethyl-4-fluoro-6-iodopyrimidine **10**.

Metalation of **4** (0.29 g, 2.0 mmoles) according to the general procedure with 2.3 equivalents of LDA and reaction with a solution of 0.48 g (2.0 mmoles) of iodine in 5 ml of tetrahydrofuran gave after purification by column chromatography on silica gel with a mixture of cyclohexane, dichloromethane (5:4) as an eluent 0.43 g (80%) of **10**, mp 61-63°; ^{1}H nmr (deuteriochloroform): δ 2.5 (s, 3H, SCH$_3$), 7.1 (d, 1H, J = 4 Hz, H$_5$); ir: ν 1558, 1523, 1406 cm^{-1}.

Anal. Calcd. for $C_5H_4FIN_2S$: C, 22.24; N, 10.37; H, 1.49. Found: C, 22.2; N, 10.4; H, 1.3.

2-Thiomethyl-4-fluoro-5,6-diiodopyrimidine **11**.

Metallation of **4** (0.29 g, 2.0 mmoles) according to the general procedure with 2.3 equivalents of LDA and reaction with a solution of 1.52 g (6.0 mmoles) of iodine in 10 ml of tetrahydrofuran gave after purification by column chromatography on silica gel with a mixture of cyclohexane, dichloromethane (5:4) as an eluent 0.55 g (70%) of **11**, mp 99-101°; ^{1}H nmr (deuteriochloroform): δ 2.5 (s, 3H, SCH$_3$); ir: ν 1534, 1475, 1431 cm^{-1}.

Anal. Calcd. for $C_5H_3FI_2N_2S$: C, 15.17; N, 7.07; H, 0.76. Found: C, 15.3; N, 7.0; H, 0.5.

2-Thiomethyl-4-fluoropyrimidine-5-carboxylique Acid **9e**.

Metalation of **4** (0.29 g, 2.0 mmoles) according to the general procedure. A stream of carbon dioxide (supplied by evaporation of 5 g of solid carbon dioxide) is passed through the solution for 30 minutes. After purification by recrystallization from toluene 0.18 g (48%) of **9e** were obtained, mp 135-137°; ^{1}H nmr (deuteriochloroform): δ 2.5 (s, 3H, SCH$_3$), 9.0 (d, 1H, J = 12 Hz, H$_6$).

Anal. Calcd. for $C_6H_5FN_2O_2S$: C, 38.29; N, 14.89; H, 2.68. Found: C, 38.3; N, 14.9; H, 2.5.

2-Thiomethyl-4-fluoro-5-formylpyrimidine **9f**.

This compound had ^{1}H nmr (deuteriochloroform): δ 2.5 (s, 3H, SCH$_3$), 8.93 (d, 1H, J = 2 Hz, J = 12 Hz, H$_6$), 10.2 (s, 1H, CHO).

(2-Thiomethyl-4-fluoro-6-iodo-5-pyrimidinyl)ethanol **13**.

Metalation of **11** (0.79 g, 2.0 mmoles) according to the general procedure with 1.2 equivalents of LDA and reaction with acetaldehyde (1 ml, 18 mmoles) gave after purification by column chromatography on silica gel with a mixture of ether, cyclohexane (1:1) as an eluent 0.53 g (85%) of **13**, mp 103-105°; ^{1}H nmr (deuteriochloroform): δ 1.57 (d, 3H, CH_3, J = 7 Hz), 2.27 (d, 1H, J = 6 Hz, OH), 2.6 (s, 3H, SCH_3), 5.0 (m, 1H, CH(OH), J = 7 Hz).

Anal. Calcd. for $C_7H_8FIN_2OS$: C, 26.76; N, 8.92; H, 2.57. Found: C, 26.9; N, 8.9; H, 2.5.

2-Thiomethyl-4-fluoro-5-(2-pivaloylaminophenyl)pyrimidine **16**.

Argon was bubbled for 1 hour into a solution of 2-thiomethyl-4-fluoro-5-iodopyrimidine **9d** (0.20 g, 0.74 mmole), (2-(pivaloylamino)phenyl)tributyl stannate (0.52 g, 1.1 mmoles), and lithium chloride (0.155 g, 3.5 mmoles) in dioxane (6 ml). Bis(acetonitrile)palladiumII chloride (0.046 g, 0.18 mmole) was added and the mixture warmed at 90° for 7 days. After cooling 1 g of potassium fluoride was added and the mixture stirred for 3 hours at room temperature. The mixture was extracted with 20 ml of ether. The organic extract was dried (magnesium sulphate) and evaporated. The crude product was purified by column chromatography on silica gel with a mixture of ether, cyclohexane (1:1) as an eluent to give 0.193 g (82%) of **16**, mp 48-50°; ^{1}H nmr (deuteriochloroform): δ 1.2 (s, 9H, C(CH_3)$_3$), 2.6 (s, 3H, SCH_3), 7.05-7.8 (m, 5H, phenyl, NH), 8.04 (d, 1H, J = 12 Hz, H_6); ms: m/z 319 (M^+).

3-Thiomethyl-9*H*-pyrimido[4,5-*b*]indole **14**.

A solution of 2-thiomethyl-4-fluoro-5-(2-pivaloylaminophenyl)pyrimidine **16** (0.13 g, 0.4 mmole) in anhydrous pyridinium chloride (10 g) was heated at 160° for 15 minutes. The hot solution is poured onto a commercial ammonia solution and ice. The yellow precipitate was separated by filtration and purified by sublimation, yield 40%, mp >260°; ^{1}H nmr (deuteriochloroform): δ 7.2 (m, 1H, H_6), 7.4 (m, 2H, H_7, H_8), 7.95 (d, 1H, J = 8 Hz, H_5), 8.0 (s, 1H, H_4); ms: m/z 125 (M^+).

Anal. Calcd. for $C_{11}H_9N_3S$: C, 61.37; N, 19.52; H, 4.21. Found: C, 61.5; N, 19.9; H, 3.7.

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