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METALATION OF DIAZINES X
First Halogen Migration during Metalation of Pyrimidines Unusual Halogen-Lithium Exchange with LTMP New Synthesis of Leshmaniacides

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Abstract: An halogen migration of iodine during the metalation of pyrimidines has been highlighted and a mechanism is proposed. An unusual halogen-lithium exchange with LTMP has been observed. A new synthetic route to Leshmaniacides using metalation and cross coupling reactions is described.

INTRODUCTION

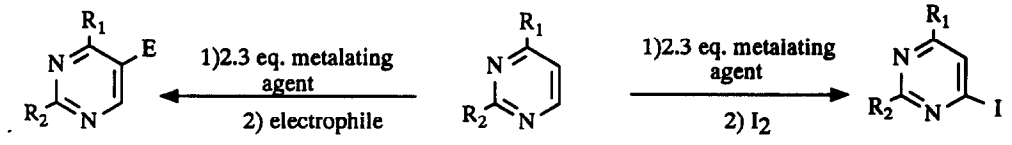
Directed ortho-lithiation of diazines has been recently reported, this methodology is currently defined to functionalize these heteroaromatic systems. In previous papers dealing with the direct metalation of pyrimidines with a chlorine atom or a methoxy group as directing groups, a surprising regioselectivity with iodine as the electrophile, has been reported for 2-chloro-4-methoxypyrimidine **1**[1] and 4-chloro-2-thiomethylpyrimidine **2**.[2] In both cases a complete regioselectivity at C-6 far from the directing group, was observed with LTMP or LDA as the metalating agent.

Some unexpected halogeno derivatives have been previously reported to be formed from metalation of halogenoimidazoles and isothiazoles.[3] Metalation of bromo-quinolines[4] and benzenes[5-7] has been carried out, and a "halogen-dance" phenomenon has been discovered with these bromoaromatic compounds; more recently an halogen migration has been established, with bromopyridines[8] and iodopyridines,[9] during metalation of halogenopyridines.

RESULTS

Reaction of **1** with 2.3 equivalents of LTMP at - 70°C for 1 hour followed by trapping with various electrophiles afforded 2-chloro-4-methoxy-5-substituted pyrimidines, whereas 2-chloro-4-methoxy-6-iodopyrimidine **3** was exclusively obtained using iodine as the electrophile[1]. Similarly when **2** was reacted with 2.3 equivalents of LDA, at - 70°, and then with various electrophiles 4-chloro-2-thiomethyl-5-substituted pyrimidines were obtained with excellent regioselectivity higher than 95%. Under the same conditions, with iodine as the electrophile 4-chloro-2-thiomethyl-6-iodopyrimidine **4** was obtained as the sole product[2] (Scheme 1).

Scheme 1



R_1= OMe, R_2= Cl **1** R_1= OMe, R_2= Cl **3**

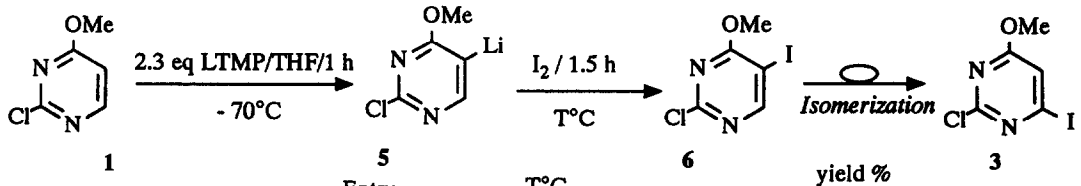
R_1= Cl, R_2= SMe **2** R_1= Cl, R_2= SMe **4**

We report the study of the mechanism of the reaction of metalated **1** with iodine which we undertook to explain this exceptional reactivity.

In view of the high C-5 regioselectivity observed from the LTMP metalation-electrophile quench of **1** led to the assumption that the C-5 lithio derivative **5** was the predominant species at low temperatures. In this case it can be assumed that the 5-iododerivative **6** was obtained initially and then underwent a further isomerization.

The C-5 lithio derivative **5**, resulting from treatment of **1** with 2.3 equivalents of LTMP, at - 70°, in THF for 1 hour was submitted to a subsequent reaction with iodine (1.3 eq.) performed at various temperatures T°C for 1.5 hour before hydrolysis (Scheme 2).

Scheme 2



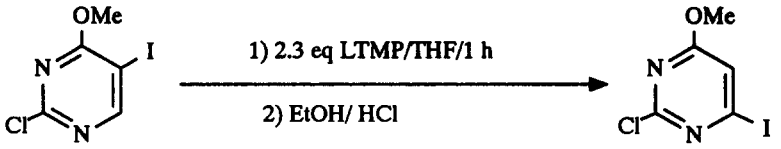
1 **5** **6** **3**

Entry	T°C	yield % 6	3
1	- 70°	5	65
2	- 100°	42	18
3	- 100° -65° - 100°	10	60

When the reaction with iodine was performed at - 70°C the 6-iododerivative **3** was found to predominate (entry 1); on lowering the temperature to -100°C (entry 2) the 5-iododerivative **6** was observed as the major compound. When the temperature was kept constant at - 100°C for 1 hour, then increased to - 65°C for 20 minutes and then decreased again to - 100°C for 10 minutes, before hydrolysis, (entry 3) **3** was found to be the major compound.

To confirm the isomerization with the migration of iodine from the C-5 to the C-6 position, the reaction of **6** with 2.3 equivalents of LTMP for 1 hour was performed, at - 70°C, followed by hydrolysis. In this case **3** was obtained quantitatively (Scheme 3) and complete isomerization was observed.

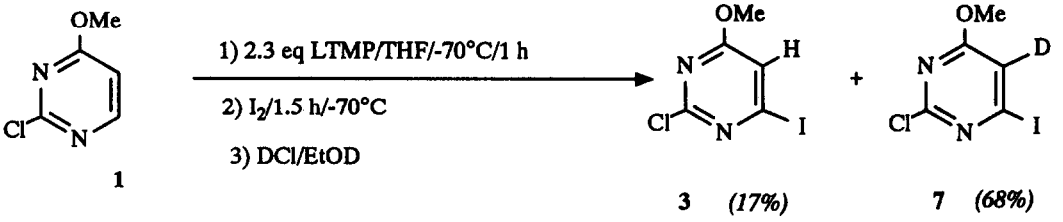
Scheme 3



6 **3**

When **1** was treated at - 70°C with 2.3 equivalents of LTMP and reacted with iodine at this temperature followed by deuteriolysis, a mixture of 2-chloro-4-methoxy-6-iodo-5-deuteriopyrimidine **7** (68%) and 2-chloro-4-methoxy-6-iodopyrimidine **3** (17%)was obtained (Scheme 4).

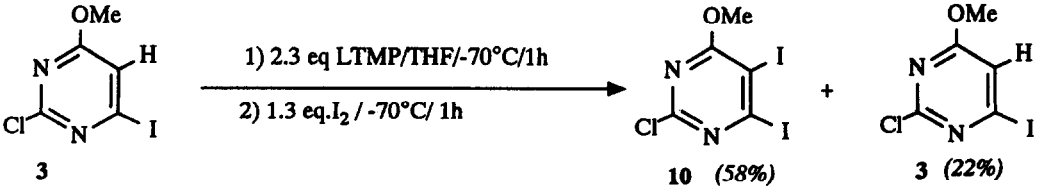
Scheme 4



1 **3** *(17%)* **7** *(68%)*

When metalation of **3** was performed, according to the general procedure at, - 70°C, followed by a subsequent reaction with iodine (1.3 eq.) as the electrophile the diiododerivative **10** was obtained with an overall yield of 58% and the starting material (22%) was recovered (Scheme 5).

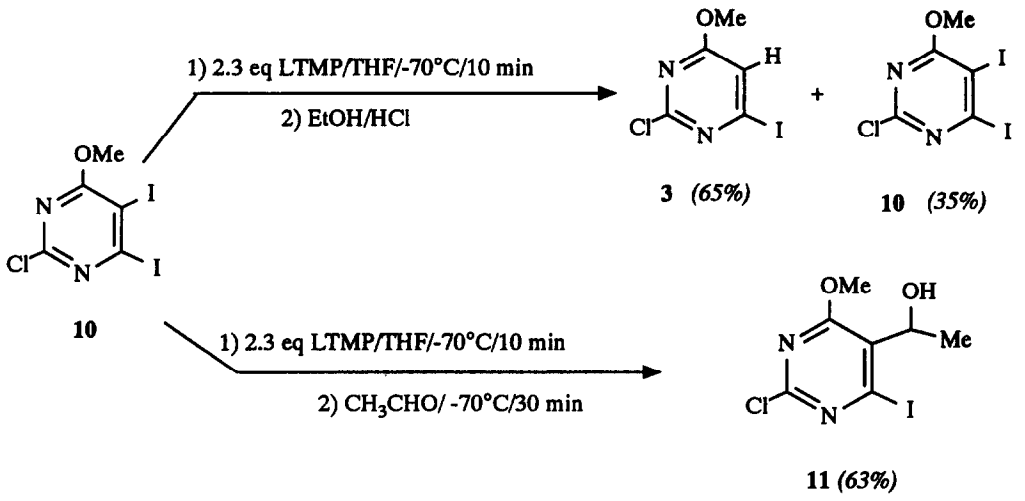
Scheme 5



3 **10** *(58%)* **3** *(22%)*

The presence of 22% of the starting material urged us to verify the completion of the reaction, or to see if a reaction between LTMP and the diiodo derivative **10** could occur. So the diiodo derivative **10** was treated with 2.3 equivalents of LTMP at -70°C for 10 minutes and a subsequent reaction with an electrophile was performed (Scheme 6).

Scheme 6



Using hydrochloric acid as the electrophile, the formation of the 6-iodo derivative **3** was observed in 65% yield, as well as the starting material 35%, whereas using acetaldehyde as the electrophile compound **11** was obtained with 63% overall yield without any recovery of the starting material.

DISCUSSION

The high C-5 regioselectivity observed from the LTMP metalation- electrophile quench of **1** led to the assumption that the C-5 lithioderivative was the predominant species at - 70°C. In this case it can be assumed that the 5-iodo derivative **6** was obtained initially and then underwent a further isomerization which was dramatically dependent on the temperature, to give the 6-iodo derivative **3** (Schemes 2 and 3).

Obtaining the 5-deuterio derivative **7** (Scheme 4) , from the metalation of **1**, according to the general procedure, at - 70°C,using iodine as the electrophile, followed by deuteriolysis, implied that the intermediate 2-chloro-4-methoxy-5-lithio-6-iodopyrimidine **8** was formed.

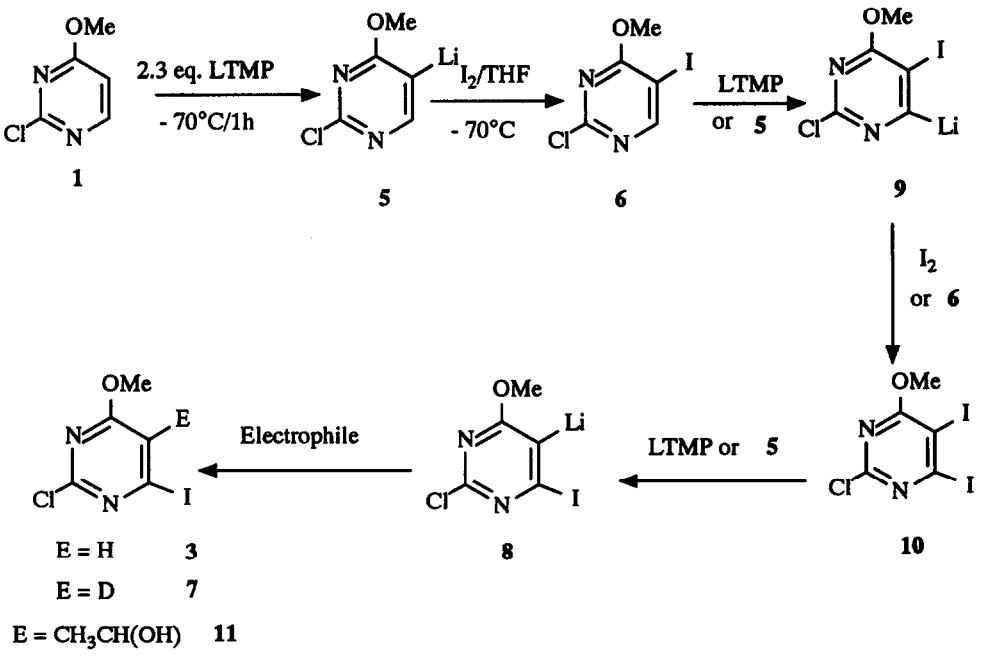
No isomerization occurred when the 6-iodo derivative **3** was treated with LTMP then iodine. Under these experimental conditions the formation of the diiodo derivative **10** (58%) was the sole product to be observed, along with the starting material (22%) (Scheme 5). The presence of the starting material **3** could result, either from an incomplete reaction, or from a reaction between **10** and a metalating agent (LTMP or lithio derivative) leading to the lithio intermediate **8** which would react with either of the electrophiles hydrochloric acid or acetaldehyde (Scheme 6). This experimental result could appear as a halogen-lithium

exchange leading to the lithio derivative **8**. This kind of exchange has been seen with n-butyllithium as the metalating agent and halogenoaromatics and has been widely used in many syntheses, in particular with pyridines, however, to our knowledge, it has never been observed with alkylamides like for example LTMP as the metalating agent.

It has been proposed, in various bromoaromatic series, that this "halogen-dance" was due to the reaction between bromolithio intermediaries and catalytic amounts of dibromoderivatives.[4,8e,15]

Such a reaction pathway could be proposed to explain the formation of **8** from the dilithio derivative **10** (Scheme 7).

Scheme 7



This reaction of halogen migration can be rationalized as follows : At - 70°, reaction of **1** with LTMP led to the C-5 lithio derivative **5** which reacted with iodine to give the 5-iododerivative **6** . A further metalation of **6**, either by unreacted LTMP, or C-5 lithioderivative **5**, obtained in the previous step led to the lithioderivative **9** . The lithio intermediate **9** either entered into an equilibrium with the C-5 iododerivative **6**, or reacted with iodine to afford the C-5 lithioderivative **5** and the diiododerivative **10** . A further reaction of unreacted LTMP or lithio derivative **5** with **10** gave the more stable C-5 lithio intermediate **8** and regenerated the **5** iododerivative **6** which was then recycled. Reaction of **8** with electrophiles HCl, EtOD or acetaldehyde led respectively to the 6-iododerivative **3** and 5-substituted derivatives **7** and **11**.

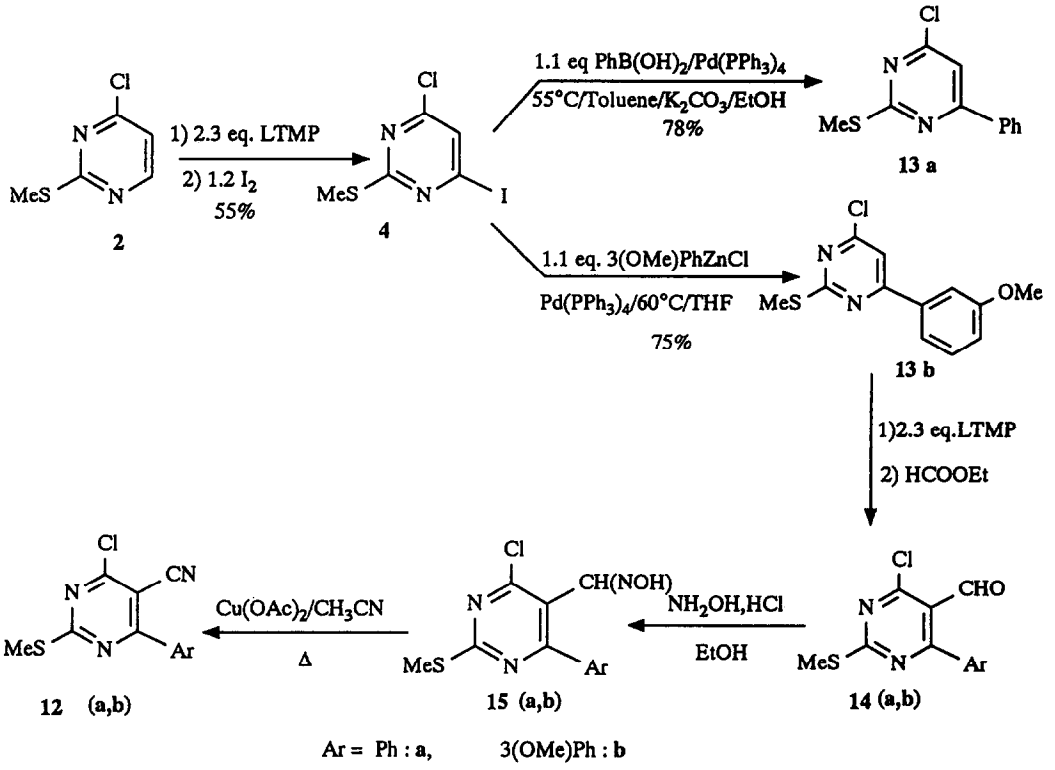
This kind of mechanism can also be used to explain the exclusive formation of 2-thiomethyl-4-chloro-6-iodopyrimidine **4**, obtained by metalation of 2-thioethyl-4-chlropyrimidine **2**, followed by a reaction with iodine.

An application to this halogen migration has been found with the synthesis of biologically active molecules.

Some thiopyrimidines are known to present antileshmanial and immunoadjuvant activities, among them 4-chloro-6-aryl-2-thiomethylpyrimidine-5-carbonitriles **12** and more especially 4-chloro-6-(3-methoxyphenyl)-2-thiomethylpyrimidine-5-carbonitrile **12b** show a high order of immunoadjuvant activity against *L. donovani in vivo*[10,11].

The synthetic route to these compounds has been performed using the metalation of 2-thiomethyl-4-chloropyrimidine **2** and the cross coupling reactions (Scheme 8).

Scheme 8



The 6-iododerivative **4** underwent a Suzuki cross-coupling reaction[12] with phenylboronic acid to give **13a**. The difficulties encountered trying to obtain 3-methoxyphenylboronic acid, prompted us to perform a cross-coupling reaction with the m-anisylzinc chloride[13] which was generated, in situ, by treating m-iodoanisole with n-Buli followed by transmetalation with $ZnCl_2$. A further lithiation of compounds **13**, with ethylformiate as the electrophile led to aldehydes **14**, which after a reaction with hydroxylamine gave quantitatively oximes **15**. A further dehydration, in acetonitrile,[14] with copper acetate, in an acidic medium, of compounds **15**, afforded quantitatively to the biologically active molecules **12**.

CONCLUSION

An interesting problem of isomerization has been highlighted with iodine as the electrophile during the metalation of 4-substituted pyrimidines. It was demonstrated that this isomerization involved a "halogen-dance" mechanism. This kind of mechanism has been studied before, with halogenopyridines, and is described here, for the first time, with pyrimidine derivatives.

The particular regioselectivity observed with iodine during metalation of 2-thiomethyl-4-choropyrimidine was used for the synthesis of leshmaniacides and biologically actives molecules.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. 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. 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). Metallations were performed under an argon atmosphere whose water content was regularly checked. Reagents were handled with syringues through septa.

General procedure for metalation

A solution of n-butyllithium (1.98 M in hexane, 0.92 ml, 1.83 mmole) was added to cold (-30°C), stirred, anhydrous tetrahydrofuran (20 ml) under an atmosphere of dry argon. Then 2,2,6,6-tetramethylpiperidine (0.32 ml, 1.9 mmole) was added, the solution was then cooled to -70°C and kept at this temperature for 15 minutes. A solution of the pyrimidine derivative (0.83 mmole) in 5 ml of tetrahydrofuran was added and the mixture stirred for a time t_1 at a temperature T_1. The electrophile was added and stirring was continued for a time t_2 at the temperature T_2. Hydrolysis was then carried out at T_2 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 (5 ml) and evaporated under vacuum nearly to dryness. The residue was extracted with dichloromethane (3x20 ml). The organic extract was dried (magnesium sulphate) and evaporated. The crude product was purified by column chromatography on silica gel or by sublimation.

2-Chloro-6-iodo-4-methoxypyrimidine 3

Metalation of 1 according to the general procedure (T_1 = - 70°C, t_1 = 1 h) and reaction with a solution of 0.26 g (1.0 mmoles) of iodine in 5 ml of tetrahydrofuran (T_2= - 70°C, t_2 = 1.5 h), gave after purification by column chromatography on silica gel (eluent dichloromethane/cyclohexane (8:2)), yield: 65% of 3, mp 110°;^1H NMR ($CDCl_3$): δ 3.99 (s, 3H, OCH_3), 7.17 (s, 1H, H_5). Anal. Calcd. for $C_5H_4ClIN_2O$: C, 22.19; H, 1.48; N, 10.35. Found: C, 22.4; H, 1.3; N, 10.1.

2-Chloro-5-iodo-4-methoxypyrimidine 6

Metalation of 1 according to the general procedure (T_1 = - 70°C, t_1 = 1 h) and reaction with a solution of 0.26 g (1.0 mmoles) of iodine in 5 ml of tetrahydrofuran (T_2= - 100°C, t_2 = 1.5 h) gave after purification by column chromatography on silica gel(eluent: dichloromethane/cyclohexane (8:2)), yield: 42% of 6, mp 86°;^1H NMR ($CDCl_3$): δ 4.05 (s, 3H, OCH_3), 8.55 (s, 1H, H_6). Anal. Calcd. for $C_5H_4ClIN_2O$: C, 22.19; H, 1.48; N, 10.35. Found: C, 22.6; H, 1.3; N, 10.2.

2-Chloro-5,6-diiodo-4-methoxypyrimidine 10.

Metalation of 3 (0.12 g, 0.83 mmole) according to the general procedure (T_1 = - 70°C, t_1 = 1 h) and reaction with a solution of 0.26 g (1.0 mmoles) of iodine in 5 ml of tetrahydrofuran (T_2= - 70°C, t_2 = 1 h) gave after purification by column chromatography on silica gel (eluent :dichloromethane/cyclohexane (8:2)), yield 58% of **10**, mp 132°;^{1}H NMR ($CDCl_3$): δ 4.05 (s, 3H, OCH_3) .Anal. Calcd. for $C_5H_3ClI_2N_2O$: C, 15.14; H, 0.76; N, 7.04. Found: C, 15.3; H, .8; N, 6.8.

2-Chloro-4-methoxy-5-(1-hydroxyethyl)-6-iodopyrimidine 11

Reaction of **10** with LTMP according to the general procedure of metalation (T_1 = - 70°C, t_1 = 10 min) and reaction with acetaldehyde in excess (T_2= - 70°C, t_2 = 30 min) gave after purification by column chromatography on silica gel (eluent: dichloromethane), yield 63% of **11** (oil), ^{1}H NMR ($CDCl_3$): δ 1.53 (s, 3H, CH_3); 3.00 (m, 1H, OH); 4.12 (s, 3H, OCH_3); 5.00 (m, 1H, CH).Anal. Calcd. for $C_7H_8ClIN_2O_2$: C, 26.72; H, 2.54; N, 8.91. Found: C, 26.6; H, 2.3; N, 8.8.

4-Chloro-2-thiomethyl-6-iodopyrimidine 4.

Metalation of **2** (0.133 g, 0.83 mmol) according to the general procedure (T_1 = - 70°C, t_1 = 1.5 h) and reaction with a solution of 0.21 g (0.83 mmol) of iodine in 5 ml of tetrahydrofuran (T_2= - 70°C, t_2 = 10 min) gave after purification by column chromatography on silica gel (eluent: dichloromethane/cyclohexane (6:4)), yield 55%, mp 116°;^{1}H NMR ($CDCl_3$): δ 2.56 (s, 3H, SCH_3); 7.46 (s, 1H, H_5). Anal. Calcd. for $C_5H_4ClIN_2S$: C, 20.95; H, 1.40; N, 9.78. Found: C, 21.1; H, 1.4; N, 9.8.

2-Thiomethyl-4-chloro-6-phenylpyrimidine 13a.

2-Thiomethyl-4-chloro-6-iodopyrimidine **4** (0.375 g, 1.31mmol) and phenylboronic acid (0.18g, 1.44 mmol) were added to a solution of potassium carbonate (2M, 1.31 ml) and ethanol (0.66ml) in deoxygenated toluene (13 ml). The resulting mixture was stirred under an argon atmosphere. Tetrakis(triphenylphosphine)palladium(0) (0.05g, 0.043 mmol) was added and the reaction mixture was warmed at 55°C for 7 days. After this time 0.08g of phenylboronic acid and 0.02g of catalyst were added to the reaction mixture. The reaction was continued during a further 7 days. Cooling, filtration, extraction with toluene, drying over $MgSO_4$, and solvent removal afforded a crude product which was purified by flash chromatography on silica gel with hexane/dichloromethane (8:2) as an eluent; yield (78%); mp 58°C; ^{1}H NMR ($CDCl_3$) δ 2.65 (s, 3H, SCH_3); 7.37 (s, 1H, H_5); 7.52 (m, 3H, $H_{3'}$, $H_{4'}$); 8.03 (s, 2H, $H_{2'}$). Anal. Calcd. for $C_{11}H_9ClN_2S$: C, 55.81; H, 11.84; N, 3.85. Found: C, 56.2; H, 11.9; N, 3.8.

2-Thiomethyl -4-chloro-6-(3-methoxyphenyl)pyrimidine 13b

n-Butyllithium (2.5 M, 0.93 ml, 2.33 mmol) was added to a solution of m-iodoanisole (0.54g, 2.33 mmol) in THF (20 ml) at - 75°C under an argon atmosphere. After 2h, a solution of zinc chloride (2.33 ml, 1 M, 2.33 mmol) was added dropwise to the mixture which was left stirring for a further hour, at - 75°C. The reaction mixture was gently warmed to room temperature. The iododerivative **4** (0.78g, 2.33 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.062g, 2 mol%), both dissolved in dry THF (10 ml), were added and the resulting solution was heated at 60°C for 4 days. The mixture reaction was cooled, hydrolysed with saturated aquous NH_4Cl (10 ml) then extracted with ethylacetate (5x 20 ml). After filtration on silica gel, the solvent was removed and the crude product was purified by flash chromatography on silica gel with cyclohexane/dichoromethane (8:2) as an eluent, yield 75%, mp 85°C; ^{1}H NMR ($CDCl_3$) δ 2.61 (s, 3H, SCH_3); 3.58 (s, 3H, OCH_3);7.00-7.58 (m, 5H). Anal. Calcd. for $C_{12}H_{11}ClN_2OS$: C, 54.01; H, 4.13; N, 10.50. Found: C, 54.8; H, 4.1; N, 10.3.

2-Thiomethyl-4-chloro-5-formyl-6-phenylpyrimidine 14a.

Metalation of **13a** according to the general procedure (T_1 = - 75°C, t_1 = 2 h) and reaction with ethylformiate (4 equiv.)(T_2= - 70°C, t_2 = 2 h), gave after purification by column chromatography on silica gel (eluent dichloromethane/hexane (8:2)), yield: 46% of **14a**, mp 134°;^{1}H NMR ($CDCl_3$): δ 2.65 (s, 3H, SCH_3), 7.53 (m, 5H, Ph), 10.0 (s, 1H, CHO). Anal. Calcd. for $C_{12}H_9ClN_2OS$: C, 54.44; H, 3.40; N, 10.59. Found: C, 54.7; H, 3.4; N, 10.4.

2-Thiomethyl -4-chloro-5-formyl-6-(3-methoxyphenyl)pyrimidine 14b

Metalation of **13b** with 3 equivalents of LTMP according to the general procedure (T_1 = - 75°C, t_1 = 2 h) and reaction with ethylformiate (4 equiv.)(T_2= - 70°C, t_2 = 2 h), gave after purification by column chromatography on silica gel (eluent dichloromethane), yield: 25% of **14b**, mp 162°;^{1}H NMR ($CDCl_3$): δ 2.67 (s, 3H, OCH_3), 3.85 (s, 3H,SCH_3),6.95-7.63 (m, 4H, Ph), 10.0 (s 1H, CHO). Anal. Calcd. for $C_{13}H_{11}ClN_2O_2S$: C, 52.95; H, 3.73; N, 9.50. Found: C, 53.0; H, 3.81; N, 9.56.

General procedure to formation of oximes.

A mixture of 0.15ml of pyridine (1.89 mmol) and 0.132g of hydroxylamine hydrochloride was added to a solution of 0.25 equivalent of aldehyde in ethanol (7 ml). The reaction mixture was heated under reflux, for 1 hour, cooled and hydrolysed with 7 ml of water. Extraction with CH_2Cl_2, drying over $MgSO_4$ and solvent removal afforded a crude product which was washed with Et_2O.

4-Chloro-6-phenyl-2-thiomethylpyrimidine-5-carboxime 15a

Yield: 100% of **15a**, mp 106°;^{1}H NMR ($CDCl_3$): δ 2.62 (s, 3H, SCH_3), 7.47 (m, 5H, Ph), 8.10 (s 1H, CH=N). Anal. Calcd. for $C_{12}H_{10}ClN_3OS$: C, 51.52; H, 3.58; N, 15.03. Found: C, 54.4;H, 3.6;N, 15.0.

2-Chloro-6-(3-methoxyphenyl)-2-thiomethylpyrimidine-5-carboxime 15b

Yield: 100% of **15b**, mp 138°;^{1}H NMR ($CDCl_3$): δ 2.63 (s, 3H, SCH_3),3.85 (s, 3H, OCH_3), 7.01-7.38 (m, 4H, Ph), 8.09 (s ,1H, CH=N),8.33 (s, 1H, OH). Anal. Calcd. for $C_{13}H_{12}ClN_3O_2S$: C, 50.38; H, 3.88; N, 13.57. Found: C, 50.2; H, 3.7; N, 13.9.

General procedure to formation of nitriles.

A mixture of 0.15g oxime, 0.40g of copper (II) acetate monohydrate in 20 ml of acetonitrile was gently warmed refluxed for 1 hour, cooled and hydrolysed with 10 ml a solution of H_2SO_4 (5%). Extraction with CH_2Cl_2, drying over $MgSO_4$ and solvent removal afforded a crude product which was purified by column chromatography on silica gel with CH_2Cl_2 as eluent.

4-Chloro-6-phenyl-2-thiomethylpyrimidine-5-carbonitrile 12a

Yield: 100% of **12a**, mp 139°;^{1}H NMR ($CDCl_3$): δ 2.67 (s, 3H, SCH_3), 7.57 (m, 3H, Ph), 8.06 (dd, 2H, Ph). Anal. Calcd. for $C_{12}H_8ClN_3S$: C, 55.07; H, 3.06; N, 16.06. Found: C, 55.0; H, 2.9; N, 16.0.

4-Chloro-6-(3-methoxyphenyl)-2-thiomethylpyrimidine-5-carbonitrile 12b

Yield: 100% of **12b**, mp 128°;^{1}H NMR ($CDCl_3$): δ 2.66 (s, 3H, SCH_3),3.89 (s, 3H, OCH_3), 7.01-7.38 (m, 4H, Ph). Anal. Calcd. for $C_{13}H_{10}ClN_3OS$: C, 53.49; H, 3.43; N, 14.40. Found: C, 53.7; H, 3.4; N, 13.7.

REFERENCES

1. Plé, N.; Turck, A.; Bardin, F.; Queguiner, G. J. *Heterocyclic Chem.* **1992**, *29*, 467-470.
2. Plé, N.; Turck, A.; Martin, P.; Barbey S.; Queguiner, G. *Tetrahedron Lett.* **1993**, *34*, 1605-1608.
3. a) De Bie, D. A.; Van der Plas, H. C. *Tetrahedron Lett.* **1968**, 3905-3908.
   b) De Bie, D. A.; Van der Plas, H. C. *Rec. Trav. Chim. Pays-Bas*, **1969**, *88*, 1246-1248.
4. Den Hertog, H. J.; Buurman, D. J.; *Rec. Trav. Chim. Pays-Bas*, **1973**, *92*, 304-310.
5. a) Bunnett, J. F.; Moyer, E. *J. Am. Chem. Soc.* **1971**, *93*, 1183-1190.

b) Bunnett, J. F.; Scorrano, G. *J. Am. Chem. Soc.* **1971**, *93*, 1190-1198.
c) Mc Lennan, D. J.; Bunnett, J. F. *J. Am. Chem. Soc.* **1971**, *93*, 1198-1201.
d) Bunnett, J. F.; Feit I. N. *J. Am. Chem. Soc.* **1971**, *93*, 1201-1205.

6. Bunnett, J. F.; Victor R. R. *J. Am. Chem. Soc.* **1968**, *88*, 810.
7. Bunnett, J. F. *Accounts Chem. Res.* **1972**, *5*, 139.
8. a) Marsais, F.; Pineau, Ph.; Nivolliers F.; Mallet, M.; Turck, A.; Godard, A.; Queguiner G. *J. Org. Chem.* **1992**, *57*, 565-573.
   b) Marsais, F.; Queguiner, G.; Snieckus, V.; Epsztajn, *J. Adv. Heterocycl. Chem.* **1991**,*52*,187-304.
9. Rocca P.; Cochennec C.; Marsais, F.; Thomas -dit-Dumont, L.; Mallet, M.; Godard, A.; Queguiner, G. *J. Org. Chem.* **1993**, *58*, 7832-7838.
10. Ram, V. F. J. Prakt. Chem. **1989**, *331*, 957-963.
11. Ram, V. F.; Kapil, A.; Guru, P. Y. Indian J. Chem. Sect. B, **1990**, *29*, 1129-1133.
12. a) Miyaura, N.; Yanagi, T.; Suzuki, A. Synth. Comm. **1981**, *11*, 513.
    b) Martin, A. R.; Yang Y. H.; *Acta Chem. Scand.* **1993**, *47*, 221.
13. Sandosham, J.; Undheim, K.; Rise, F. Heterocycles, **1993**, *35*, 235-244.
14. Attanasi, O.; Palina, P.; Serrezanetti, F. *Synthesis*, **1983**, 741.
15. Guilforo, A. J.; Tometski, M. A.; Turner, M. W.; *Synthesis*, **1983**, 987.

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