METALATION OF DIAZINES

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Abstract - The metalation of diazines has been recently developed, below are reported the main results in this area of research.

CONTENTS

INTRODUCTION

The high reactivity of diazines towards nucleophiles makes the metalation of these compounds more difficult than most aromatic compounds which are less sensitive to nucleophilic addition. This type of addition is clearly a consequence of the strong electron withdrawing effect of the two sp^2 nitrogen atoms that lowers the energy level of their LUMO (Table 1).

benzene	pyridine	pyrazine	pyridazine	pyrimidine
+ 0.55	+ 0.14	- 0.32	- 0.29	- 0.23

Table 1 : Energy level of LUMO (eV) as calculated by the AM1 method.

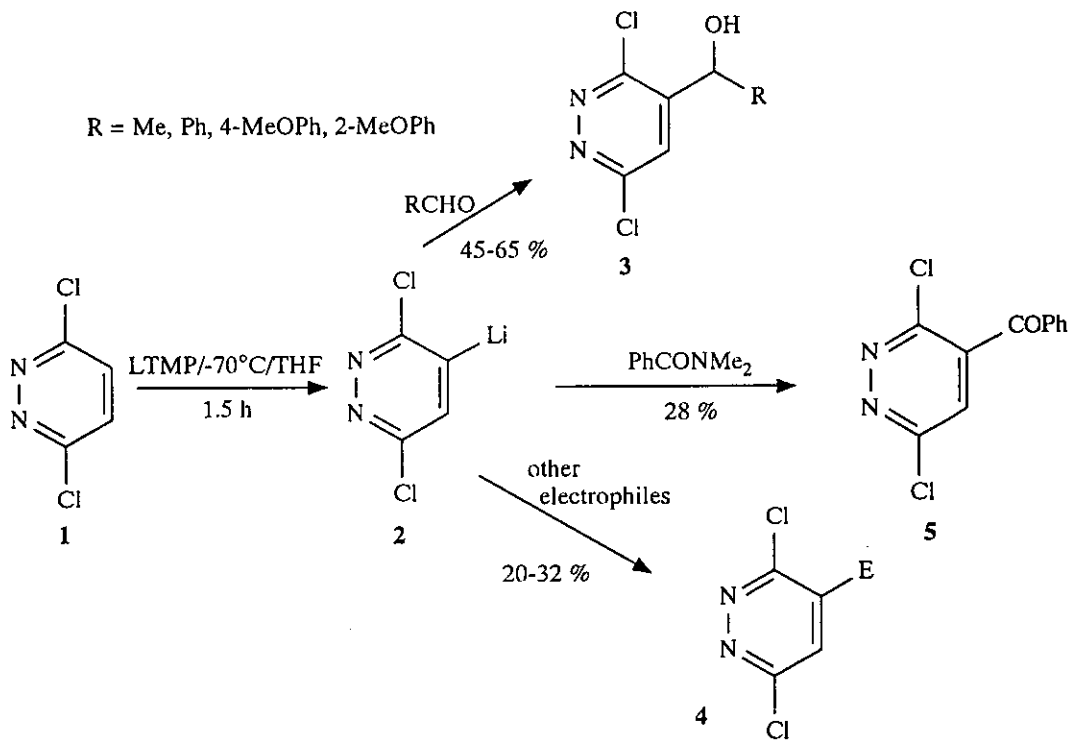
Therefore the metalation of diazines has only been investigated recently with the current use of lithium alkylamides such as LDA or LTMP (lithium diisopropylamide or lithium 2,2,6,6- tetramethylpiperidylamide) which are less prone to nucleophilic addition than alkyl- or aryllithium. A careful study of the metalation reactions have allowed the developement of the metalation of diazines in recent years.[1,2] Before 1990 there was no publication dealing with the metalation of pyridazine. Since then a few studies have been published on the metalation of pyrazine[3,4] and little research has been done on pyrimidines.[5-11]

A classical methodology consisting in the introduction of substituents on the diazine rings would be worthless as these compounds are difficult or impossible to functionalize by classical methods like halogenation, nitration and the action of Grignard reagents. So, most of the syntheses of substituted diazines call for use a final cyclisation reaction with the appropriate groups in the right places. Moreover there was no practical reaction to prepare organometallics in the diazine series.

In this review we will only be taking into account the reaction of ortho directed metalation excluding metal halogen exchange, addition of organometallics and side chain metalation.

2. METALATION OF PYRIDAZINES

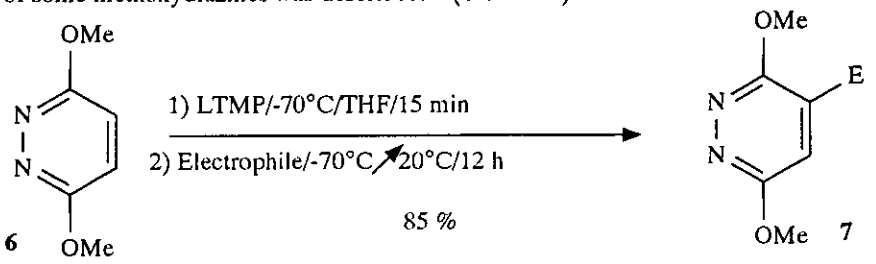
The first publication[12] described the metalation of 3,6-dichloropyridazine, this compound was easy to prepare from the industrial used maleic hydrazide (Scheme 1).



Scheme 1

Oxidation of secondary alcohols (**3**) with manganese IV oxide afforded dichloropyridazinyl ketones in moderate yields (68-84 %). A more straightforward access to ketone (**5**) was the reaction of the lithio derivative (**2**) with *N,N*-dimethylbenzamide, yield remained however poor in this case (Scheme 1).

Metalation of some methoxydiazines was described.[13] (Scheme 2) :

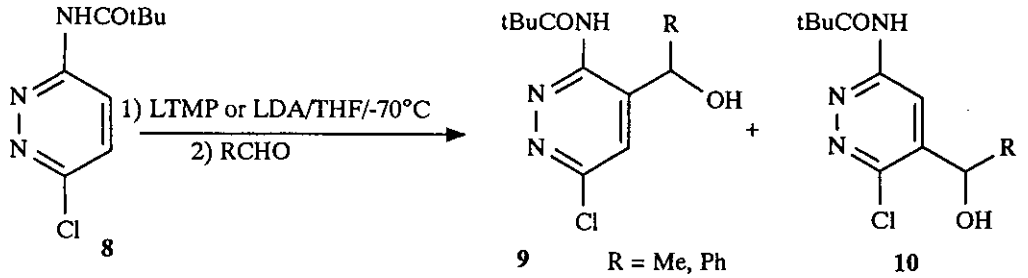


Scheme 2

The methodology employed here was closer to the equilibrium shift technique. The electrophiles which were used successfully reacted slowly with LTMP and allowed the metalation to take place even after the introduction of the electrophiles. After 15 minutes of metalation a test with DCl as electrophile revealed that there was only 15 % of the deuterated product.[14]

Recently, the metalation of various 3-substituted and 3,6-disubstituted pyridazines was published.[15]

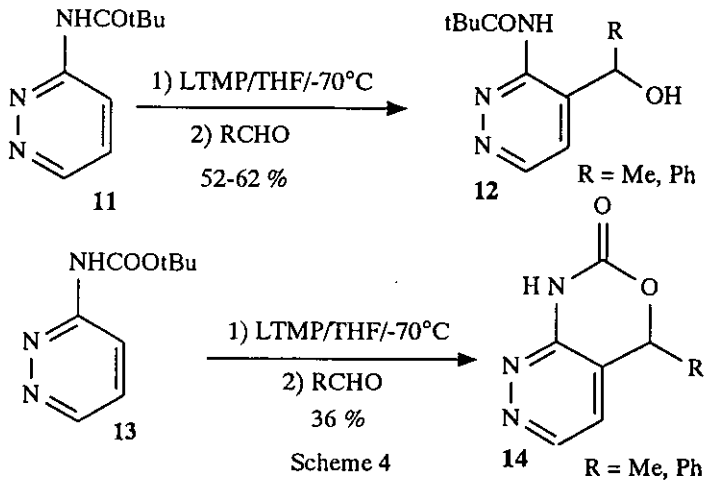
The metalation of *N*-(6-chloro-3-pyridazinyl)pivalamide (**8**) is illustrated on Scheme 3:



Scheme 3

The regioselectivity of the metalation was studied. With LTMP as metalating agent a mixture of the two isomers (**9**,**10**) was obtained whereas with LDA there was metalation in ortho to the chlorine atom affording only the isomer (**10**). The yields however were found to be lower with LDA (82-68 %) than with LTMP (100-83 %). Authors report it was necessary to use 4 equivalents of metalating agent to obtain these good yields.

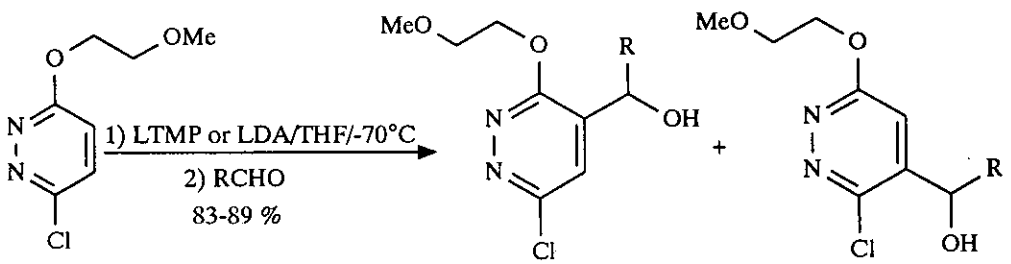
The metalation of *N*-(3-pyridazinyl)pivalamide (**11**) and *tert*-butyl *N*-(3-pyridazinyl)carbamate (**13**) is illustrated on Scheme 4 :



Scheme 4

In the case of carbamate (**13**), the initially formed alcohols cyclized during work up directly leading to compound (**14**) (Scheme 4).

The metalation of 3-chloro-6-(2-methoxyethoxy)pyridazine (**15**) is illustrated on Scheme 5 :

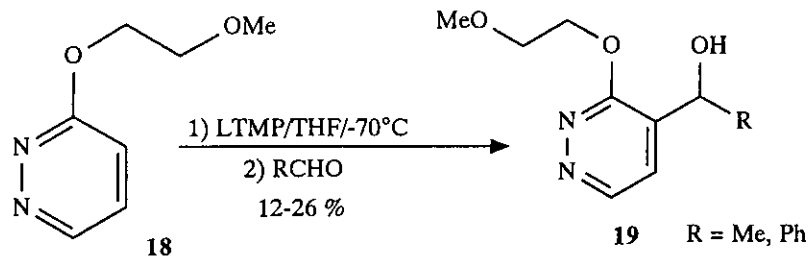


15 **16** R = Me, Ph **17**

Scheme 5

As for compound (**8**) one equivalent of LTMP did not lead to the expected metalation and 2,2 equivalents were necessary to obtain products in good yields. The regioselectivity was less contrasted than for (**8**): with LTMP the main reaction took place ortho to the methoxyethoxy group leading to (**16**) whereas with LDA it was ortho to the chlorine atom leading to (**17**).

This metalation becomes perfectly regioselective in case of 3-(2-methoxyethoxy)pyridazine (**18**) (Scheme 6) :



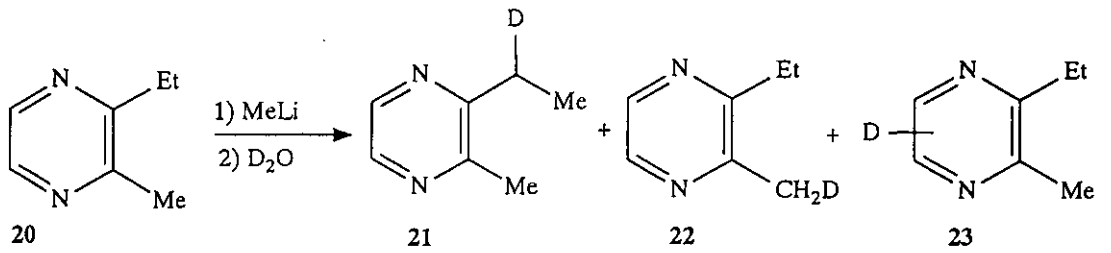
18 **19** R = Me, Ph

Scheme 6

3. METALATION OF PYRAZINES AND PYRAZINE 1-OXIDES

Metalation of pyrazines was first mentionned in 1971.[3] The authors investigated the reaction of alkylpyrazines with some alkyllithiums and when reacting 2,5-dimethylpyrazine with ethyllithium they isolated in low yield (< 5 %) a compound which could come from a ring metalation followed by oxidation. More importantly in

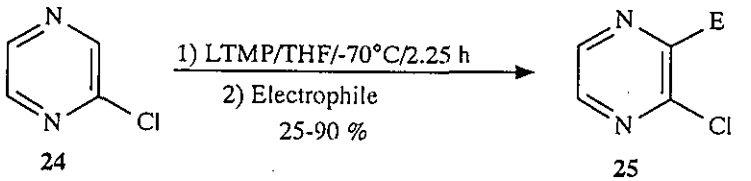
1974[4] the reaction of 2-ethyl-3-methylpyrazine (**20**) with methyllithium followed by quenching with D_2O highlighted up to 15 % of ring metalation. Ring metalation product (**23**) was obtained beside products (**21**) and (**22**) coming from a metalation reaction on the side chains. (Scheme 7) :



Scheme 7

3.1 Chloropyrazines

Metalation of 2-chloropyrazine (**24**) with LTMP has been subjected to several studies[16-18] and some electrophiles were reacted. (Scheme 8) :

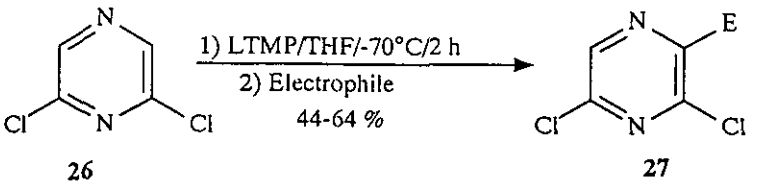


E = D, R_2COH, CHO, COOH, PhCO, SnR_3, I.

Scheme 8

Except for CO_2 and I_2 the yields were greater than 50 %.

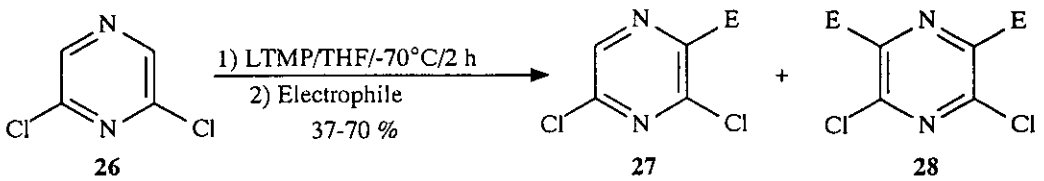
Metalation of 2,6-dichloropyrazine (**26**) was then studied (Scheme 9) and it was demonstrated that it was possible to achieve a dimetalation under the proper conditions[17,19] (Scheme 10) :



Scheme 9

E : PhCO, CHO, RCHOH

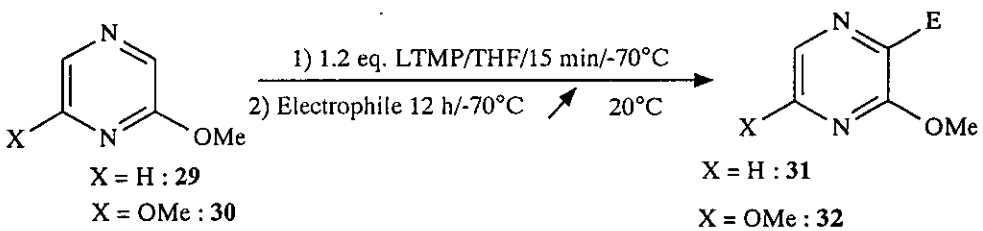
With an excess of metalating agent some compounds resulting from a dimetalation such as (**28**) were isolated (Scheme 10) :



Scheme 10

3.2 Methoxy and thiomethylpyrazines

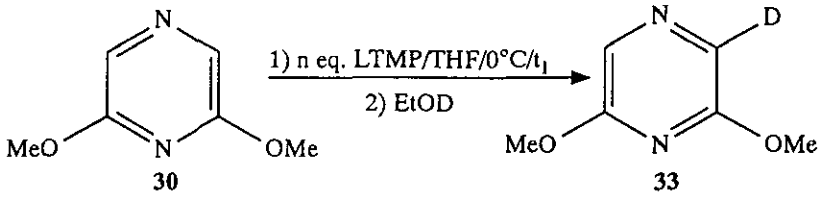
These were metalated in two different ways. Firstly by using a short metalation time and a long reaction time for the electrophile[13] (Scheme 11) :



X	E	Yields
H, OMe	$SiMe_3$, Me, PhCHOH	57-95 %

Scheme 11

In another publication[19] a study of the metalation conditions for (**30**) was performed with deuterated ethanol as electrophile to afford compound (**33**) (Scheme 12). The deuteriation percentage was assessed from the nmr spectrum (Table 2).



30 33

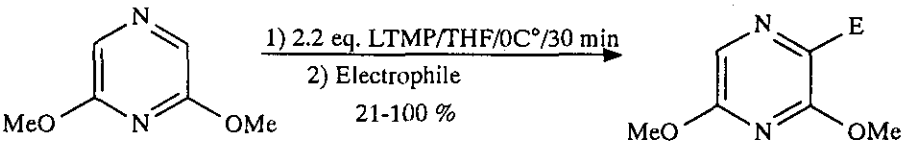
Scheme 12

n eq. LTMP	1.2	1.2	1.2	2.2	2.2
t_1 min	15	30	60	15	30
yields of **33**	32%	44%	48%	83%	100%

Table 2

It can be seen that the yield of the reaction was dramatically affected by the ratio of LTMP and (**30**). Furthermore this is a rare example of a metalation of a diazine that has not been performed at a very low temperature.

Various electrophiles were tested under these experimental conditions (Scheme 13) :



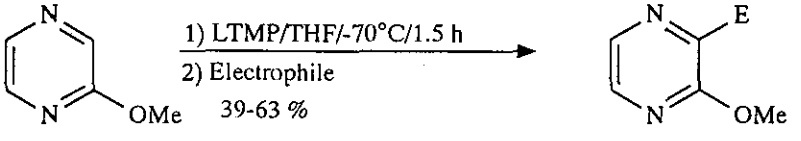
30 **32**

E = D, R-CHOH , CHO, COPh, I, CONHtBu, COOMe

Scheme 13

The phenylketone was also obtained at -70°C with *N*-methoxy-*N*-methylbenzamide as the electrophile[17] but with a lower yield.

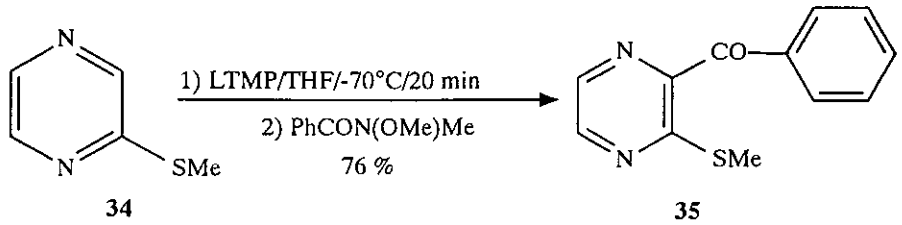
For 2-methoxypyrazine (**29**) the best results were obtained at a temperature of -70°C[17,20] (Scheme 14) :



29 **31**

Scheme 14 E : RCHOH , COPh, I, CONHtBu

Compound (**34**) : 2-(thiomethyl)pyrazine was metalated at -70°C with a high yield[17] (Scheme 15) :

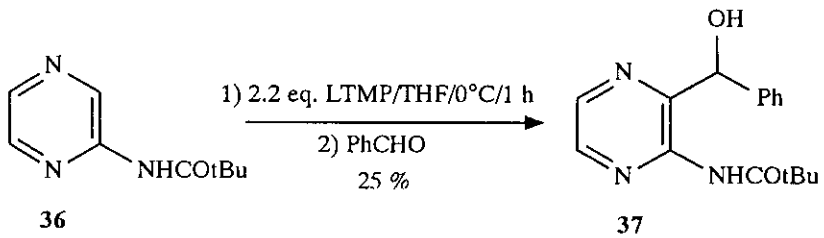


34 35

Scheme 15

3.3. Aminopyrazines

Metalation of pivalamidopyrazine (**36**)[21] was thoroughly investigated however poor results were obtained (Scheme 16) :



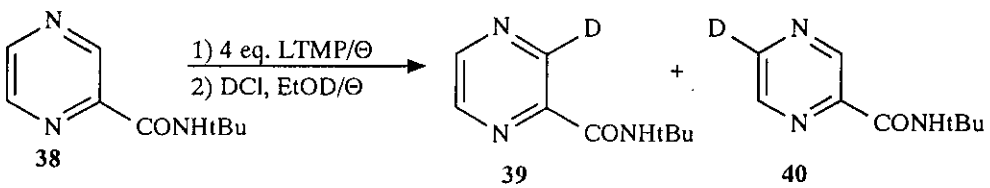
36 37

Scheme 16

More powerful metalating agents, such as n-butyllithium and mesithyllitium, were tested and found to lead to intense nucleophilic addition.

3.4. Pyrazinamides

Metalation of *N*-t-butylpyrazinamide (**38**)[21] with LTMP followed by deuteriolysis was first tested at -70°C and an unexpected regioselectivity was observed. A temperature variation effect has been performed (Scheme 17), (Table 3) :



38 39 40

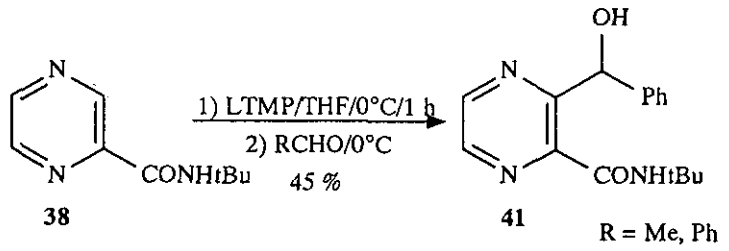
Scheme 17

Θ	Yields of **39** Ortho isomer	Yields of **40** Para isomer
0°C	75 %	0 %
-30°C	70 %	0 %
-70°C	25 %	40 %
-80°C	25 %	45 %

Table 3

It was further demonstrated by metalation using the "equilibrium shift" technique with $ClSiMe_3$ as the electrophile that the para isomer was the kinetic isomer.

Acetaldehyde and benzaldehyde were also used as electrophiles at 0°C and selectively afforded the corresponding carbinols (**41**) (Scheme 18).

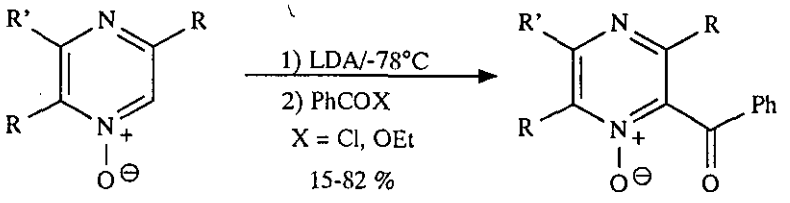


38 **41** R = Me, Ph

Scheme 18

3.5. Pyrazine 1-oxides :

Substituted pyrazines 1-oxides were metalated early with LDA,[22] and the lithio derivative reacted with benzoyl chloride and methyl benzoate (Scheme 19).



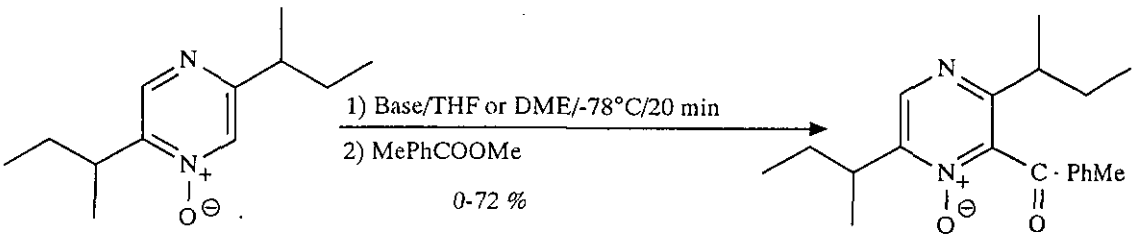
42 **43**

R = alkyl

R' = H,Cl

Scheme 19

More recently[44] polyalkylpyrazines 1-oxides were metalated. The metalation conditions were tested with various metalating agents on 2,5-di-*sec*-butylpyrazine 1-oxide (**44**) and with methyl *p*-toluate as the electrophile (Scheme 20) :



44 **45**

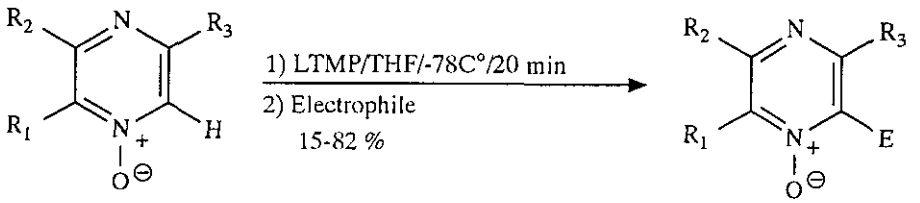
Scheme 20

The best results were obtained with LTMP as the metalating agent, the addition of a chelating agent (HMPA or TMEDA) enhancing only slightly the final yield.

A test with D_2O as the electrophile in the optimale conditions, afforded the 6-deuterioderivative with a 95 % yield.

The site of deuteration was determined by X-Ray analysis and found to be at the 6 position as was done with the other electrophiles.

Some other electrophiles were tested on polysubtituted pyrazines 1-oxides (**46**) (Scheme 21) :



46 **47**

R_1, R_2, R_3 : alkyl, phenyl, H E : *p*MePhCO, EtCHOH, PhCHOH, CHO

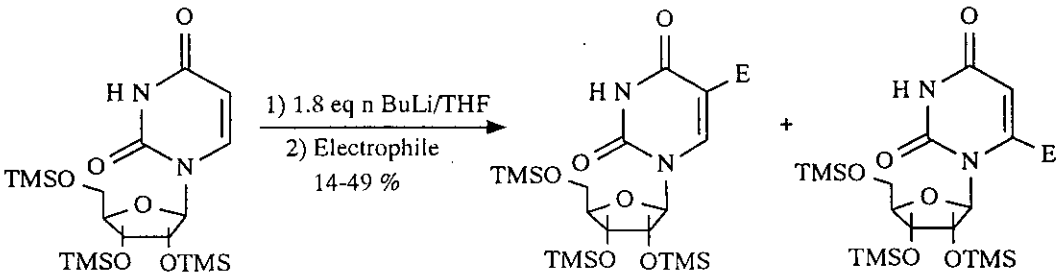
Scheme 21

The *N*-oxide group in the pyrazine series is a good directing group as was also demonstrated with pyridines.[1] Pyrazines 1-oxides are easy to obtain in good yields if alkyl groups or chlorine atoms are present on the ring.

4. METALATION OF PYRIMIDINES

4.1. Nucleosides

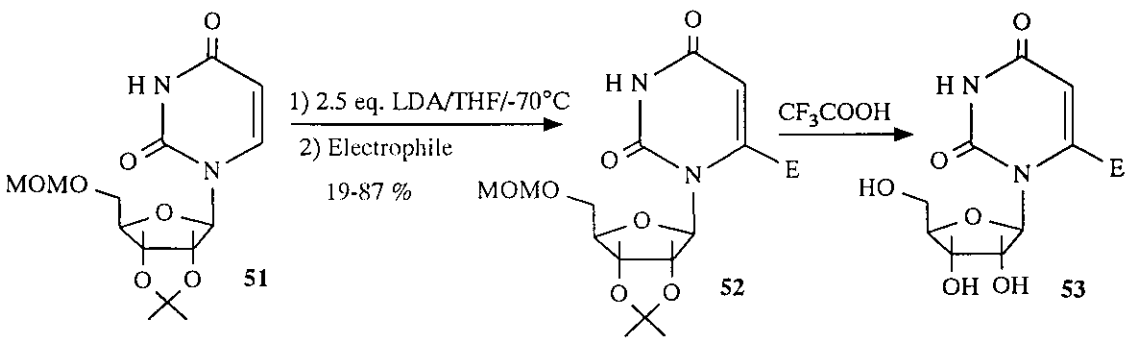
The first mention of pyrimidine nuclei metalations was described (Scheme 22) for uridine, thymidine derivatives[23] and cytidine derivatives.[24]



48 **49** **50**

Scheme 22

With n-butyllithium as metalating agent no regioselectivity was observed with uridine derivatives (**48**) (Scheme 22), and cytidine derivatives.[24] Later[25] it was found that the metalation of 2',3'-*O*-isopropylidene-5'-*O*-methoxymethyluridine (**51**) with LDA took place mainly at the C_6 position and various types of 6-substituted uridines (**53**) were obtained (Scheme 23) after a deprotection reaction with trifluoroacetic acid.

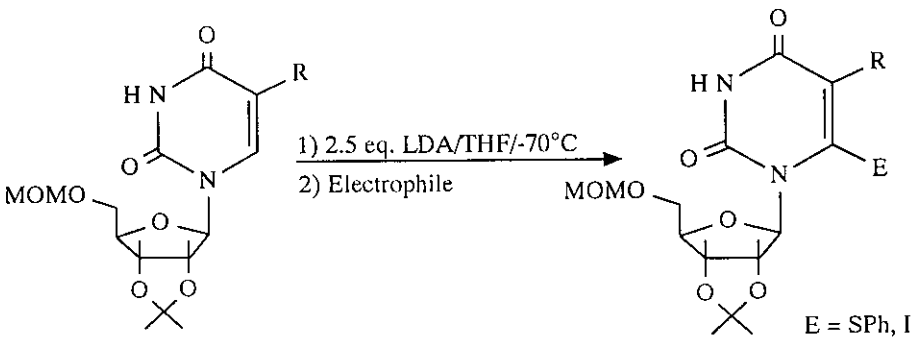


51 **52** **53**

E = PhS, RCO, RCH(OH), CHO, COOEt, CH_2CH_2OH, $R_2C(OH)$

Scheme 23

A new class of antileukemic nucleosides was prepared by lithiation under the same experimental conditions from 5-substituted uridines and subsequent electrophilic reactions[26] (Scheme 24).

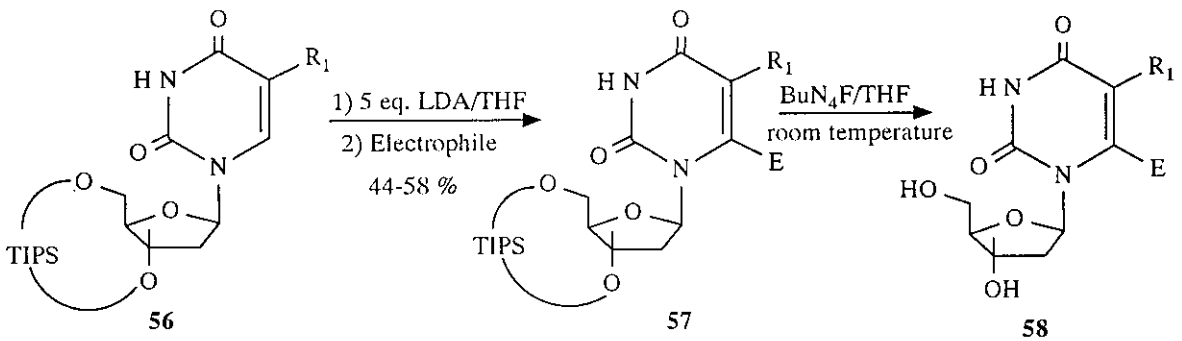


54 55

Scheme 24

The research of new biologically active nucleosides led to a synthesis of 6-substituted 2'-deoxyuridines (**58**) *via* lithiation of (**56**) with LDA.[27]

This technique provides a general, regiospecific route to various types of 6-substituted 2'-deoxyuridines which have been known to be difficult to prepare (Scheme 25).



56 57 58

TIPS : 1,1,3,3-tetraisopropyl disiloxane-1,3-diyl

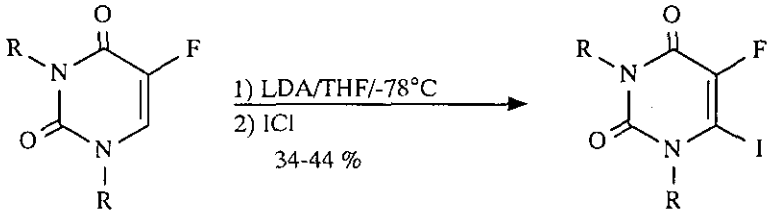
R_1 = H, E = SPh, COOMe, CH(OH)Ph, CH_2OH, I

R_1 = F, E = SPh

Scheme 25

After the clinical efficiency of 3'-azido-3'-deoxythymidine (AZT) in the treatment of AIDS (acquired immunodeficiency syndrome) was highlighted, a growing interest towards the metalation of uracils derivatives has been developped.

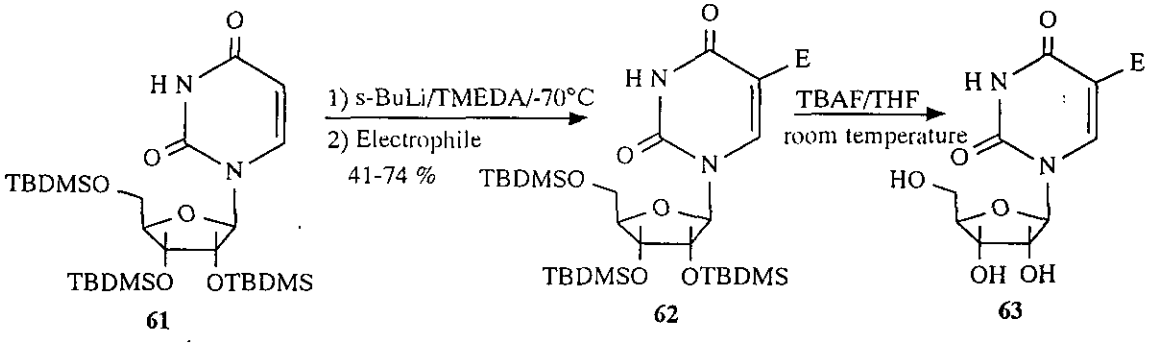
Metalation of 1,3-dialkyl-5-fluorouracil (**59**) was performed with LDA and the reaction of the lithio derivative with the iodine monochloride led to the 6-iodo derivative (**60**)[28] (Scheme 26).



59 **60**

Scheme 26

The 5-substituted uridines constitute a class of biologically molecules important for their chemotherapeutic activities. A general entry to these uridine derivatives was based on the regioselective lithiation at C-5, controlled by the protecting group in the sugar moiety.[29] Lithiation of (**61**) with *sec*-BuLi/TMEDA occurred at C-5 with a high regioselectivity (Scheme 27).



61 **62** **63**

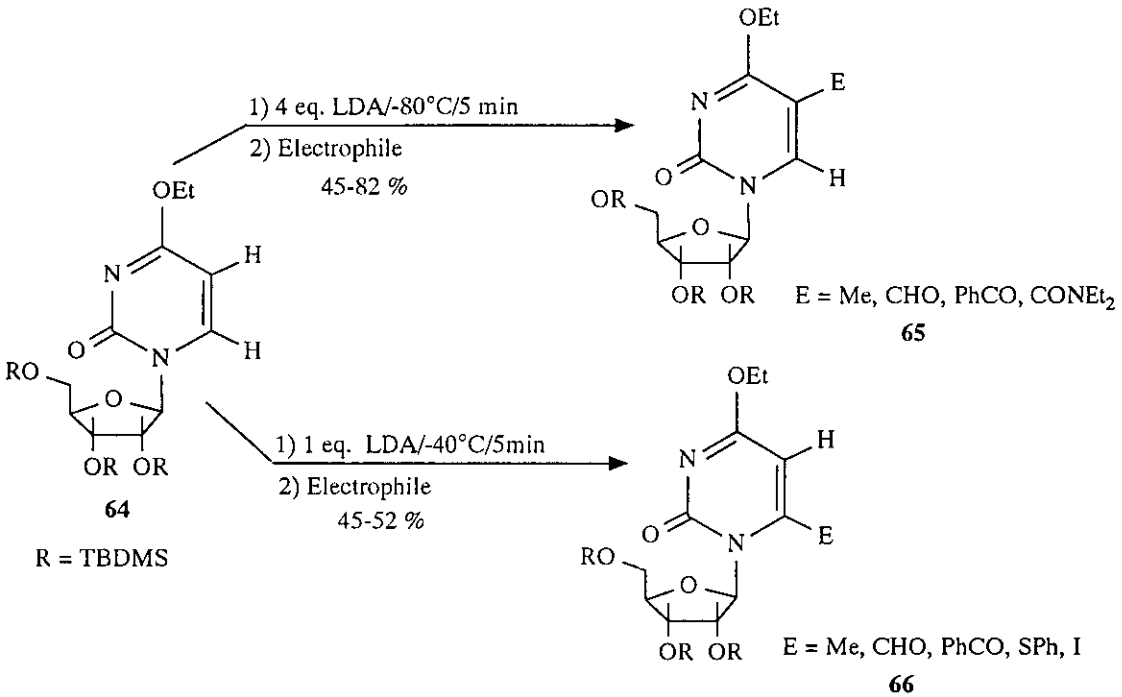
E = SPh, Me, CH_2Ph, t-BuCO, PhCO, $SiMe_3$

Scheme 27

After the study of competitive C_5/C_6 metalation of uridines[29-31] it was found that this ratio was governed by the protecting group on the sugar moiety. The regioselectivity of 2'-deoxyuridine derivatives was also studied[32] and it was found that metalation with s-BuLi/TMEDA led to a high regioselective lithiation at C_5.

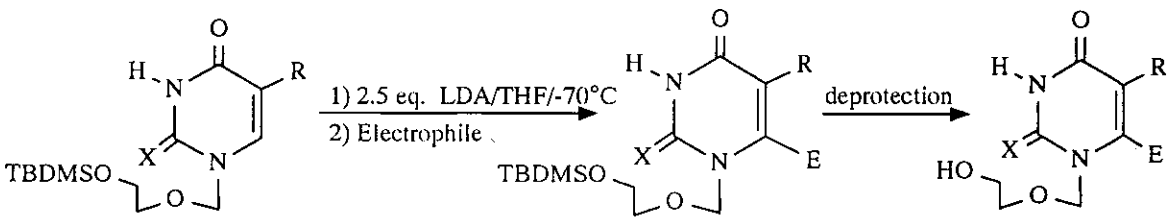
Another interesting problem of regioselectivity was studied with the LDA lithiation of an arabinofuranosyl derivative of 4-ethoxy-2-pyrimidone (**64**).[45]

It was observed that regioselectivity (C_5 vs C_6) in the LDA lithiation of (64) could be controlled by changing the reaction conditions (temperature and amount of LDA), providing an alternative route to 5 or 6-substituted derivatives (Scheme 28).



Scheme 28

A number of 6-substituted uracil acylnucleosides have been synthetized to evaluate their anti-HIV virus activity.[33-37] In all the experiments, LDA was used as metalating agent with 5-substituted uracil or thymine acylnucleosides (Scheme 29), (Table 4).



Scheme 29

References	X	R	E	overall yield
33	O	H, F, Cl, Br, Me	SPh, I	26-94 %
34	O	Me	SR'	39-79 %
		Me	COPh, I, Br, Cl	32-83 %
35	S	Me, H	SPh	64-79 %
36	O,S	H, Me, F, Cl, Br	SePh	65-85 %
37	O,S	Me	R'-Ph-S	16-87 %

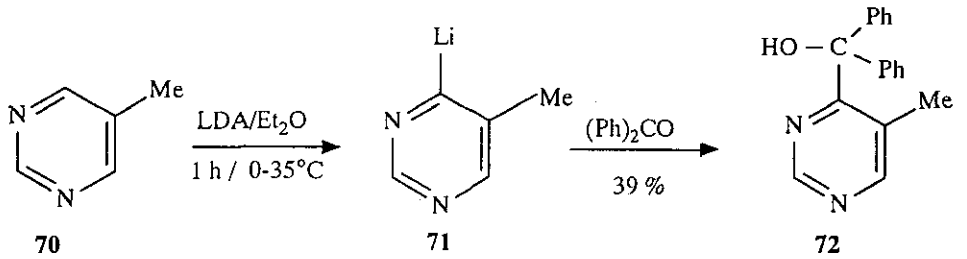
Table 4

These compounds were tested for antiviral activity and compared to AZT, which is still one of the most effective drugs for AIDS.

The metalation of the pyrimidine moiety of nucleosides was developped at the same time and therefore the direct metalation of pyrimidine was also studied.

4.2. Pyrimidines

The first report of a pyrimidine metalation[6] was in 1974. The authors of this report studied a side-chain metalation which showed also a ring metalation of 5-methylpyrimidine (Scheme 30) :



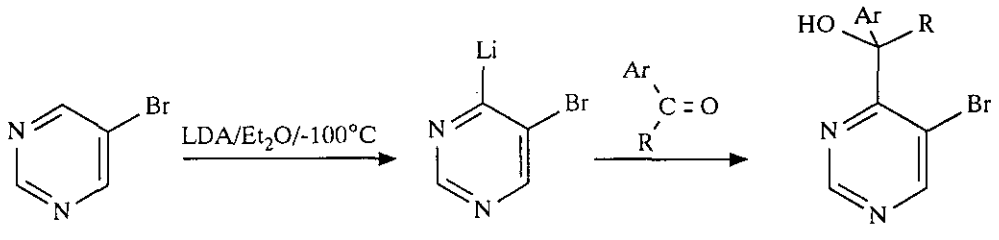
70 **71** **72**

Scheme 30

Bipyrimidine compounds have been synthesized[5,7,9] resulting from a metalation side reaction during a bromine-lithium exchange reaction with n-butyllithium.

4.2.1. Chloropyrimidines

In 1979 T. J. Kress[8] reported the metalation of 5-bromopyrimidine (**73**) with LDA, leading to the 4-lithio derivative (**74**) which was reacted with arylcarbonyl compounds (Scheme 31).

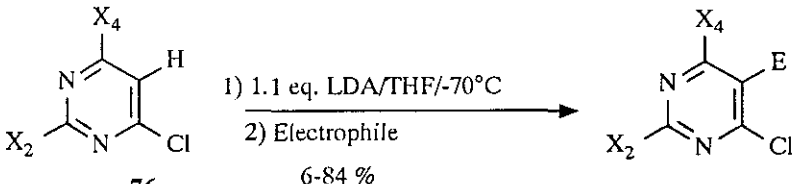


73 **74** **75**

Ar	R	overall yield
p-ClPh	o-ClPh	25 %
p-ClPh	iPr	40 %
Ph	H	41 %

Scheme 31

More recently the metalation of polychloropyrimidines (**76**) was studied.[10,12,38] When the LDA was used as the metalating agent a regioselective metalation of polychloropyrimidines occurred at the C-5 position[38] (Scheme 32).



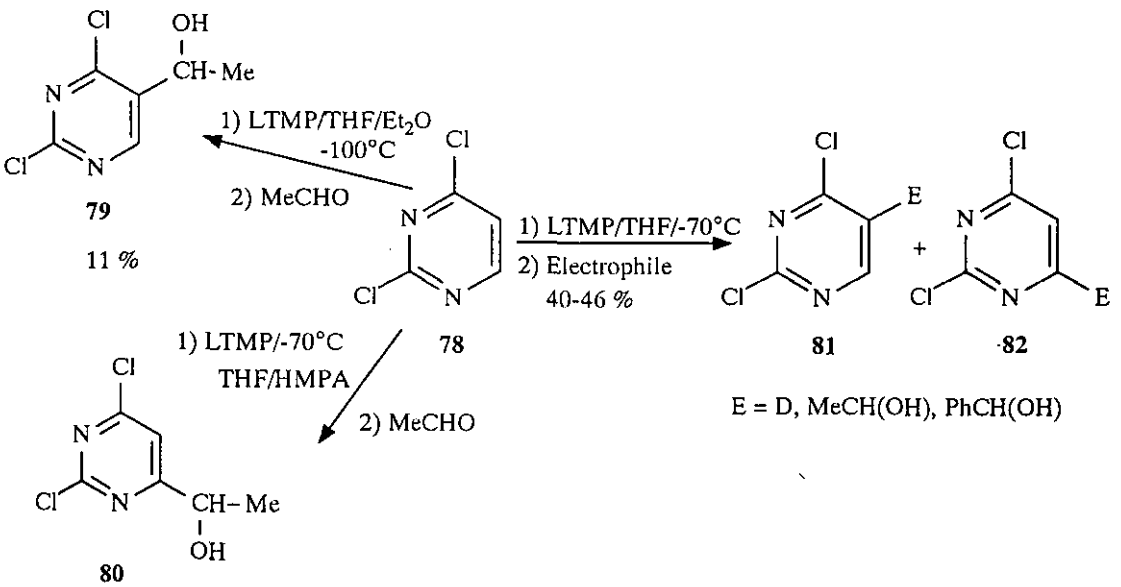
76 **77**

X_2, X_4 \ E	SiMe	PhCH(OH)
H, Cl	44 %	60 %
Cl, H	6 %	38 %
Cl, Cl	67 %	84 %

Scheme 32

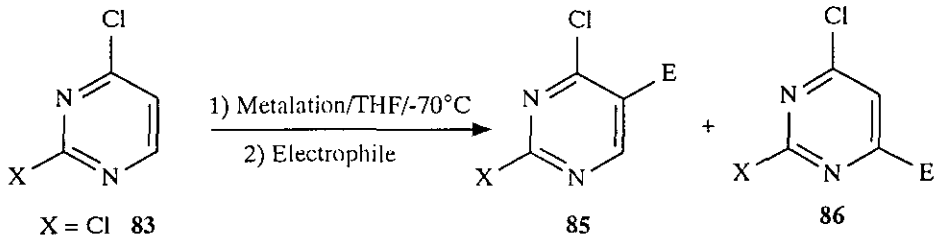
Metalation of 4,6-dichloro and 2,4,6-trichloropyrimidine has also been achieved with n-BuLi. Quenching with benzaldehyde, yields to the corresponding carbinols in 27% and 90 % respectively.

A problem of regioselectivity was highlighted in the LTMP metalation of 2,4-dichloropyrimidine (**78**).[12] Quenching at -70°C in THF with electrophiles (DCl, CH_3CHO or PhCHO) led to a 50:50 mixture of 5 and 6-substituted pyrimidines. The regioselectivity was shown to be dependent on both temperature and solvent. In THF/Et_2O at -100°C metalation followed by acetaldehyde quenching afforded the 5-substituted product, whereas in THF/HMPA mixture at -70°C, a reaction with the same electrophile afforded the corresponding 6-substituted derivative, but the yields were low (Scheme 33) :



Scheme 33

More recently an interesting problem of regioselectivity with 4-chloropyrimidines[39] was reported. Metalation of 2,4-dichloropyrimidine (**83**) and 2-thiomethyl-4-chloropyrimidine (**84**) was performed in THF at -78°C with LTMP or LDA as metalating agent. When lithiation of both **83** or **84** was performed with LDA the metalation was highly regioselective at C-5 ortho to the chlorine atom and the expected 5-substituted compounds were obtained as major products. By contrast metalation of **84** performed with LTMP followed by the reaction with various electrophiles led, beside the 5-derivatives, to the unexpected 6-substituted compounds which resulted from a lithiation at the C-6 position ortho to the pyrimidine nitrogen (Scheme 34) :



X = Cl **83**
X = SMe **84**

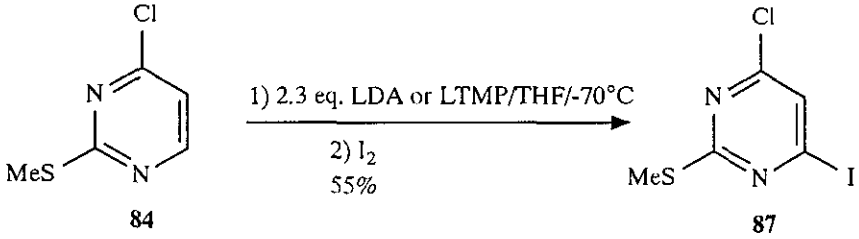
85 **86**

E = D, CH(OH)R, CH(OH)Ar

X	Metalating agent	Ratio **85** : **86**	Yield (**85** + **86**)
Cl	LTMP	1 : 1	40-45 %
83	LDA	9 : 1	38-40 %
SMe	LTMP	1 : 2	50-60 %
84	LDA	19 : 1	38-45 %

Scheme 34

It can be seen that a complete and surprising regioselectivity at the C_6 position was also observed with iodine as the electrophile : the unexpected 2-thiomethyl-4-chloro-6-iodopyrimidine (**87**) was obtained with either LDA or LTMP as metalating agent (Scheme 35) :



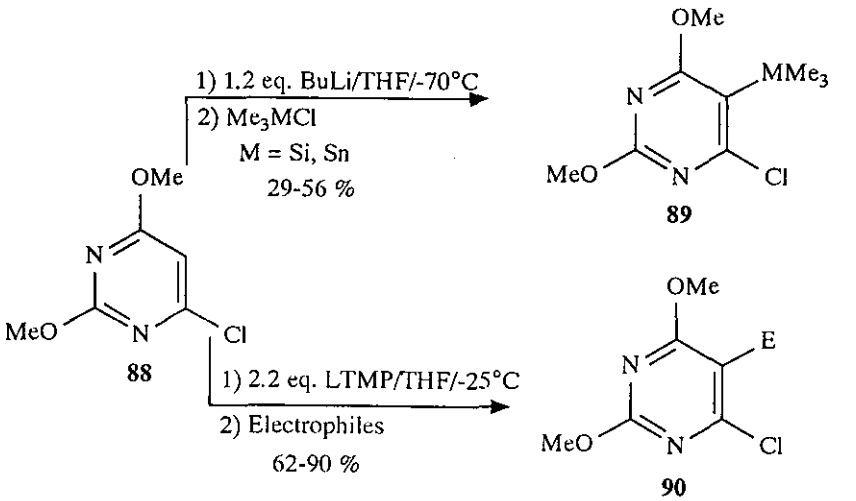
84 **87**

Scheme 35

4.2.2. Chloromethoxypyrimidines

Metalation of 2,6-dimethoxy-4-chloropyrimidine (**88**) was performed firstly with n-BuLi in THF and the reaction of the corresponding lithio derivative with trimethylsilyl chloride or trimethylstannyl chloride afforded compound (**89**).[40]

Metalation of the same product (**88**) was performed with LTMP affording compounds (**90**) in higher yields[41] (Scheme 36) :

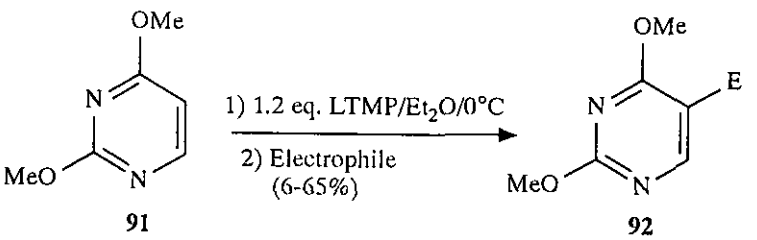


E = D, RCH(OH), I, CHO, $SnMe_3$

Scheme 36

4.3.2. Methoxypyrimidines

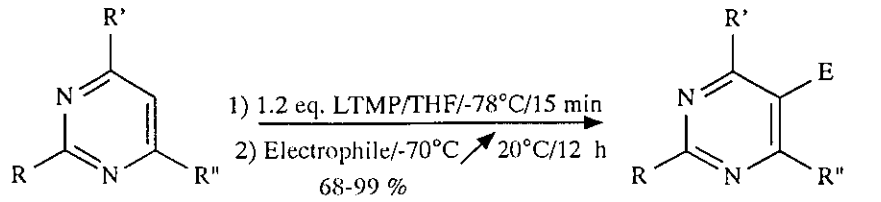
Metalation of 2,4-dimethoxypyrimidine (**91**) could be performed using LTMP affording the expected 5-substituted pyrimidines (**92**) in moderate yields. Very low yields were obtained using LDA, with recovery of the starting material[41,42] (Scheme 37) :



E = RCH(OH), COOH, CHO, COOEt, $SiMe_3$

Scheme 37

Some polymethoxypyrimidines were lithiated with LTMP[13] (Scheme 38) :



93 **94**

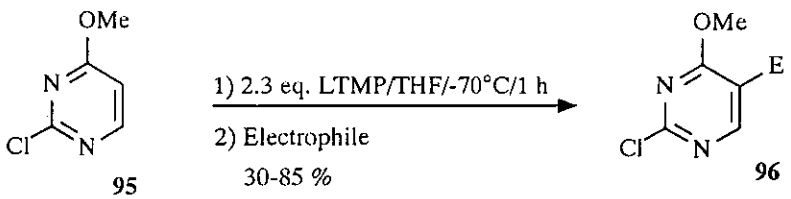
R, R', R" : OMe, OMe, H
H, OMe, OMe
OMe, OMe, OMe

E = TMS, Me, PhCH(OH), Ph_2CO

Scheme 38

As was previously seen for pyridazines and pyrazines the metalation conditions used are closer to the "equilibrium shift" technique.

Later the direct lithiation and functionalization of 2-chloro- 4-methoxypirimidine (**95**) was studied.[43] The authors indicated that use of 2.3 equivalents of LTMP was necessary to achieve this reaction in high yields (Scheme 39) :

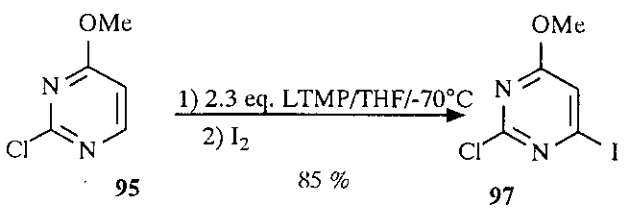


95 **96**

E = D, $SiMe_3$, RCH(OH), CHO

Scheme 39

A high yield of the unexpected 6-iodo derivative (**97**) was obtained with iodine as the electrophile (Scheme 40):

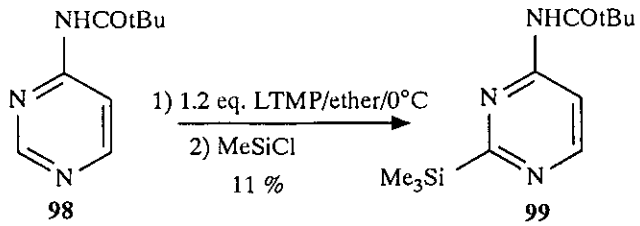


95 **97**

Scheme 40

4.2.4. Pivaloylaminopyrimidine

When 4-pivaloylaminopyrimidine (**98**) was lithiated with LTMP, and TMSCl was used as the electrophile, the ortho-substituted product was not detectable and a low yield of the 2-substituted product (**99**) was obtained[42] (Scheme 41) :



98 **99**

Scheme 41

REFERENCES

1. G. Quéguiner, F. Marsais, V. Snieckus, and J. Epsztajn, 'Advances in Heterocyclic Chemistry :Directed metalation of pi-deficient azaaromatics,' Vol 52, ed. by A. R. Katritzky, Academic Press, Inc, London, 1991, pp. 187-304.
2. A. Godard, A. Turck, N. Plé, F. Marsais, and G. Quéguiner, *Trends in Heterocyclic Chemistry*, 1993, **3**, 19.
3. W. Schwaiger and J. P. Ward, *Recl. Trav. Chim. Pays-bas*, 1971, **90**, 513.
4. G. P. Rizzi, *J. Org. Chem.*, 1974, **39**, 3598.
5. L. Strekowski, *Roczniki Chemii*, 1974, **48**, 2157.
6. A. J. Clarke, S. Mc Namara, and O. Meth-Cohn, *Tetrahedron Lett.*, 1974, **15**, 2373.
7. T. Kauffmann, B. Greving, J. König, A. Mitschker, and A. Woltermann, *Angew. Chem., Int. Ed. Engl.*, 1975, **14**, 713.
8. T. J. Kress, *J. Org. Chem.*, 1979, **44**, 2081.
9. A. Kowalewski, L. Strekowski, M. Szajda, K. Walenciak, and D. J. Brown, *Aust. J. Chem.*, 1981, **34**, 2629.
10. R. Radinov, M. Haimova, and E. Simova, *Synthesis*, 1986, 886.
11. A. Wada, J. Yamamoto, and S. Kanatomo, *Heterocycles*, 1987, **26**, 585.
12. A. Turck, N. Plé, L. Mojovic, and G. Quéguiner, J. Heterocycl. Chem., 1990, **27**, 1377.

13. R. J. Mattson and C. P. Sloan, *J. Org. Chem.*, 1990, **55**, 3410.

14. B. Ndzi, A. Turck, N. Plé, and G. Quéguiner, unpublished results, France (1990).

15. A. Turck, N. Plé, B. Ndzi, G. Quéguiner, N. Haider, H. Schuller, and G. Heinisch, *Tetrahedron*, 1993, **49**, 599.

16. A. Turck, L. Mojovic, and G. Quéguiner, *Synthesis*, 1988, **11**, 881.

17. J. S. Ward and L. Merritt, *J. Heterocycl. Chem.*, 1991, **28**, 765.

18. L. Mojovic, Thesis, university of Rouen, France, 1990.

19. A. Turck, D. Trohay, L. Mojovic, N. Plé, and G. Quéguiner, *J. Organomet. Chem.*, 1991, **412**, 301.

20. D. Trohay, Thesis, University of Rouen, France, 1990.

21 A. Turck, N. Plé, D. Trohay, B. Ndzi, and G. Quéguiner, *J. Heterocycl. Chem.*, 1992, **29**, 699.

22. A. Ohta, Y. Akita, and M. Inoue, *Heterocycles*, 1983, **20**, 154.

23. L. Pichat, J. Godbillon, and M. Herbert, Bull. Soc. Chim. Fr., 1973, **9-10**, 2715.

24. L. Pichat and J. P. Guilbert, *C. R. Hebd. Seances Acad. Sci., Ser. C,* 1973, **277**, 1157.

25. H. Tanaka, H. Hayakawa, and T. Miyasaka, *Tetrahedron*, 1982, **38**, 2635.

26. H. Tanaka, Y. Uchida, M. Shinozaki, H. Hayakawa, A. Matsuda, and T. Miyasaka, *Chem. Pharm. Bull.*, 1983, **31**, 2164.

27. H. Tanaka, H. Hayakawa, S. Iijma, K. Haraguchi, and T. Miyasaka, *Tetrahedron*, 1985, **41**, 861.

28. H. Urata, M. Tanaka, and T. Fuchikami, *Chem. Lett.*, 1987, 751.

29. H.Hayakawa, H.Tanaka, K.Obi, M.Itoh, and T.Miyasaka, *Tetrahedron Lett.*, 1987, **28**, 87.

30. H. Tanaka, H. Hayakawa, K. Obi, and T. Miyasaka, *Tetrahedron*, 1986, **42**, 4187.

31. H. Hayakawa, H. Tanaka, Y. Maruyama, and T. Miyasaka, *Chem. Lett.*, 1985, 1401.

32. R. W. Amstrong, S. Gupta, and F. Whelihan, *Tetrahedron Lett.*, 1989, **30**, 2057.

33. T. Miyasaka, H. Tanaka, M. Baba, M. Hayakawa, R. T. Watker, J. Balzarini, and E. D. Clercq, *J. Med. Chem.*, 1989, **32**, 2507.

34. H. Tanaka, M. Baba, H. Hayakama, T. Sakamaki, T. Miyasaka, M. Ubasawa, H. Takashima, I Nitta, K. Sekiya, S. Shigeta, R. T. Walker, J. Balzarini, and E. D. Clercq, *J. Med. Chem.*, 1991, **34**, 349.

35. H. Tanaka, M. Baba, M. Ubasawa, H. Takashima, K. Sekiya, I. Nitta, S. Shigeta, R. T. Walker, E. D. Clercq, and T. Miyasaka, *J. Med. Chem.*, 1991, **34**, 1394.

36. N. M. Goudgaon and R. F. Schinazi, J. Med. Chem., 1991, **34**, 3305.

37. H. Tanaka, H. Takashima, M. Ubasawa, K. Sekiya, I. Nitta, M. Baba, S. Shigata, R. T. Walker, E. D. Clercq, and T. Miyasaka, *J. Med. Chem.*, 1992, **35**, 337.

38. R. Radinov, C. Chanev, and M. Haimova, *J. Org. Chem.*, 1991, **56**, 4793.

39. N. Plé, A. Turck, P. Martin, S. Barbey, and G. Quéguiner, *Tetrahedron Lett.*, 1993, **34**, 1605.

40. C. Parkanyi, N. S. Cho, and G. S. Yoo, J. Organomet. Chem., 1988, **1**, 342.

41. N. Plé, A. Turck, E. Fiquet, and G. Quéguiner, *J. Heterocycl. Chem.*, 1991, **28**, 283.

42. A. Wada, J. Yamamoto, Y. Hamaoka, K. Ohki, S. Nagai, and S. Kanatomo, *J. Heterocycl. Chem.*, 1990, **27**, 1831.

43. N. Plé, A. Turck, F. Bardin, and G. Quéguiner, *J. Heterocycl. Chem.*, 1992, **29**, 467.

44. Y. Aoyagi, A. Maeda, M.Inoue, M. Shiraishi, Y. Sakakibara, Y. Fukui, A. Ohta, K. Kajii, and Y. Kodama, *Heterocycles*, 1991, **32**, 735.

45. M. Shimizu, H. Tanaka, H. Hayakawa, and T. Miyasaka, *Tetrahedron Lett.*, 1990, **31**, 1295.

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