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Metalation of Diazines VIII
Metalation of 4-Chloropyrimidine Derivatives
New Synthesis of Trimethoprim

N. Plé, A. Turck, P. Martin, S. Barbey, G. Quéguiner*

Laboratoire de Chimie Organique Fine et Hétérocyclique URA CNRS 1429.
IRCOF-INSA, B.P. 08, 76131 Mont-Saint-Aignan. France

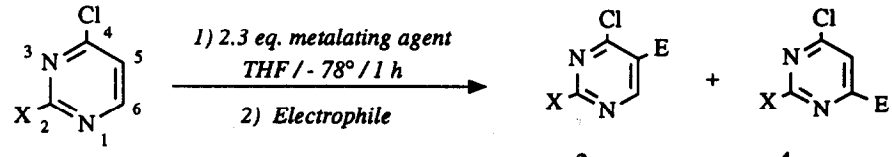
Key Words : Trimethoprim; Synthesis; Pyrimidine; Metalation; Regioselectivity.

Abstract: A new synthesis of trimethoprim is described; metalation of a pyrimidine has been used in the key step. An exceptional regioselectivity in the metalation of pyrimidine derivatives has been highlighted.

We report here an exceptional problem of regioselectivity which has been highlighted with 4-chloropyrimidines : the metalation was not induced by the "ortho-directing group" but by a cyclic nitrogen. A new synthesis of trimethoprim, one of the most potent antibacterial agents known, is described.

The metalation of 2,4-dichloropyrimidine **1** and of 2-thiomethyl-4-chloropyrimidine **2** was studied as follows : **1** and **2**[8,9] were treated in anhydrous tetrahydrofuran (THF) with 2.3 equivalents of metalating agent, lithium tetramethylpiperidide (LTMP) or lithium diisopropylamide (LDA) at -78°C for 1.5 hours. Subsequent quenching with electrophiles afforded a mixture of compounds **3** and **4**. The relative amounts of compounds **3** and **4** were monitored by ^{1}H NMR spectra of the crude reaction products. The major products were obtained by purification via column chromatography.

When lithiation of **1** or **2** was performed with LDA in THF, the metalation was highly regioselective at C-5, ortho to chlorine, and the expected compounds **3** were observed as major products. The lithiation of 2,4-dichloropyrimidine **1**, with LDA as a metalating agent and benzaldehyde as electrophile, led to the expected compound **3c** and to 10% of an unexpected compound **4c**. The metalation of **1** was recently reported[1] with LDA as a metalating agent and benzaldehyde as the sole electrophile and was described with exclusive lithiation at C-5.



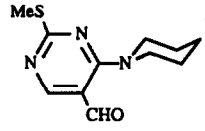
X = Cl 1

X = SMe 2

3 4

X	Entry	E	Metalating agent	(relative yield) 3	4	Overall yield %
Cl	1	D	LDA	**3a** (*94*)	**4a** (*6*)	58
	2	MeCH(OH)	"	**3b** (*100*)	-	57
	3	PhCH(OH)	"	**3c** (*90*)	**4c** (*10*)	45
	4	2(OMe)PhCH(OH)	"	**3d** (*91*)	**4d** (*9*)	53
	5	3,4,5(OMe)$_3$PhCH(OH)	"	**3e** (*90*)	**4e** (*10*)	58
SMe	6	D	LTMP	**3f** (*38*)	**4f** (*62*)	61
	7	MeCH(OH)	"	**3g** (*35*)	**4g** (*65*)	54
	8	EtCH(OH)	"	**3h** (*29*)	**4h** (*71*)	54
	9	I	"	-	**4i** (*100*)	55
	10	D	LDA	**3f** (*100*)	-	38
	11	MeCH(OH)	"	**3g** (*95*)	**4g** (*5*)	39
	12	EtCH(OH)	"	**3h** (*100*)	-	54
	13	I	"	-	**4i** (*100*)	55
	14	3,4,5(OMe)$_3$PhCH(OH)	"	**3j** (*98*)	**4j** (*2*)	35
	15	CHO	"	**3k** (*100*)	-	32
	16	CHO	"	**3l** (*100*)	-	35

3l :



Formylation of **2**, performed with N-formylpiperidine as an electrophile on the lithioderivative obtained with LDA, led to compound **3l**. In this case, a subsequent nucleophilic substitution of the chlorine atom by the piperidine moiety was observed.

With LTMP as a metalating agent the results are quite different. The major products obtained after lithiation of **2** with LTMP and subsequent reaction with electrophiles, are the unexpected compounds **4**, which result from a lithiation at the C-6 position, ortho to the pyrimidine nitrogen.

In a previous paper[3], concerning the directed metalation of diazines[2-7], we reported the lithiation of 2,4-dichloropyrimidine **1** with LTMP as metalating agent and DCl or acetaldehyde as electrophiles. This reaction was not regioselective at -70°C in THF; compounds **3** and **4** were obtained in equal amounts. However, when metalation was performed at a lower temperature, -100°C, the metalation became regioselective and occured exclusively at the C-5 position (ortho to the chlorine atom).

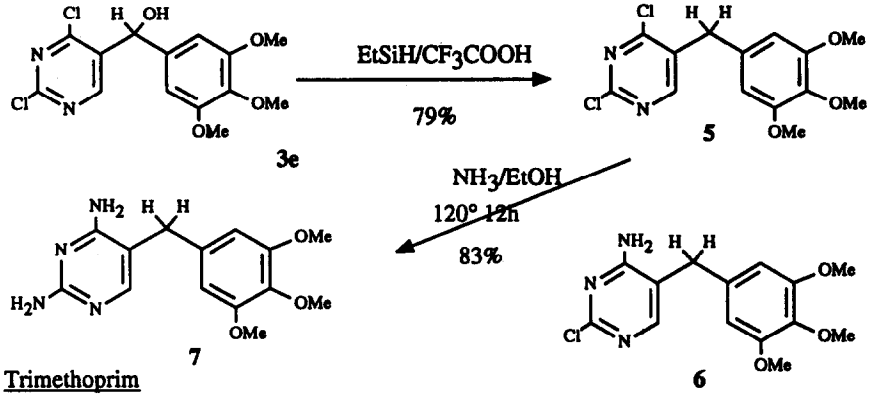
A complete and surprising regioselectivity at the C-6 position was also observed with iodine as an electrophile, to give the unexpected compound **4i** after lithiation of **2**, with LDA or with LTMP.

Finally it should be mentioned that the overall yield was generally lower with LDA than with LTMP and that the starting material was recovered, when LDA was used as a metalating agent.

This novel control of the regioselectivity of metalation of 4-chloropyrimidines allowed us to conceive a new synthesis of trimethoprim on a few steps.

Trimethoprim, a benzyldiaminopyrimidine derivative, is one of the most powerful antibacterial agents known. It is used to treat a wide range of bacterial infections in humans.
Used in combination with sulfamethoxyazole this gives one of the best selling antibacterial agents, Bactrim®

Lithiation of **1** with LTMP led to a C-5 lithioderivative which reacted with 3,4,5-trimethoxybenzaldehyde to give the secondary alcohol **3e**. Hydrogenolysis of **3e** by triethylsilane in trifluoroacetic acid at room temperature[10] gave 3,4,5-trimethoxyphenyl -2,4-dichloropyrimidine **5** in high yield (79%). A further nucleophilic substitution of chlorines by amino groups with ammonia can be used to give trimethoprim **7**. 22% of 4-amino-2-chloropyrimidine **6** resulting from a substitution of one chlorine and 55% of Trimethoprim **7** were observed when compound **5** was heated with ammonia in ethanol at 120° for 8 hours. Longer heating of **5** with ammonia in ethanol at 120° for 12h gave an overall yield of trimethoprim of 83%.



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8. Typical procedure : A solution of pyrimidine derivative (2.0 mmol.) in 5 ml of THF was added to 4.6 mmol. of TMPLi or LDA in THF at - 78° and kept at - 78° for 1 hour. The electrophile was then added at - 78°. Hydrolysis was carried at - 78° after 1 hour. The solution was gently warmed to room temperature, made basic and evaporated nearly to dryness. The residue was extracted with CH_2Cl_2. The crude product was purified by flash chromatography or sublimation.

9. Selected data (mp, ^{1}H NMR, 200 Mz, $CDCl_3$) : **3a**^{2}, **3**^{2}**b**, **4a**^{2}, **3c**, mp 120-122; ^{1}H NMR : δ = 4.6 (s, 1H, OH), 5.9 (s, 1H, CH), 7.3 (s, 5H, Ph), 8.8 (s, 1H, H6); **3d**, ^{1}H NMR : δ = 3.77 (s, 3H, OCH_3), 4.23 (s, 1H, OH), 6.17 (s, 1H, CH), 7.03 (m, 4H, Ph), 8.63 (s, 1H, H6); **3e**, mp 125-123; ^{1}H NMR : δ = 2.93 (s, 1H, OH),3.80 (s, 9H, OCH_3), 5.98 (s, 1H, CH), 6.55 (m, 2H, Ph), 8.63 (s, 1H, H6); **3f**, ^{1}H NMR : δ = 2.43 (s, 3H, SCH_3), 8.27 (s, 1H, H6); **4f**, ^{1}H NMR : δ = 2.43 (s, 3H, SCH_3), 6.89 (s, 1H, H5); **3g**, ^{1}H NMR : δ = 1.4O (d, 3H, CH_3, J = 7 Hz), 2.47 (s, 3H, SCH_3), 4.00 (s, 1H, OH), 5.05 (q, 1H, CH), 8.56 (s, 1H, H6); **4g**, ^{1}H NMR : δ = 1.4O (d, 3H,C H_3, J = 7 Hz), 2.47 (s, 3H, SCH_3), 4.00 (s, 1H, OH), 4.72 (q, 1H, CH), 7.14 (s, 1H, H5); **3h**, ^{1}H NMR : δ = 0.94 (t, 3H, CH_3, J = 7 Hz), 1.75 (m, 2H, CH_2), 2.50 (s, 3H, SCH_3), 3.58(s, 1H, OH), 4.86 (t, 1H, CH), 8.53 (s, 1H, H6); **4h**, ^{1}H NMR : δ = 0.93 (t, 3H, CH_3, J = 7 Hz), 1.75 (m, 2H, CH_2), 2.52 (s, 3H, SCH_3), 3.60(s, 1H, OH), 4.55 (t, 1H, CH), 7.04 (s, 1H, H5); **4i**, mp 109-110; H NMR : δ = 2.53 (s, 3H, SCH_3), 7.47 (s, 1H, H6); **3j**, mp 125-126; ^{1}H NMR : δ = 2.56 (s, 3H, SCH_3), 2.94 (d, 1H, OH, J = 3 Hz), 3.82(s, 9H, OCH_3), 5.97 (d, 1H, CH), 6.58 (s, 2H, Ph), 8.63 (s, 1H, H6); **3k**, ^{1}H NMR : δ = 2.65 (s, 3H, SCH_3), 8.83 (s, 1H, H6), 10.27 (s, 1H, CHO); **3l**, ^{1}H NMR : δ = 1.8 (m, 6H, CH_2), 2.5 (s, 3H, SCH_3), 3.75 (s, 4H, CH_2-N), 8.35 (s, 1H, H6), 9.66 (s, 1H, CHO); **5**, mp 130-132; ^{1}H NMR : δ = 3.84 (s, 9H, OCH_3), 3.99 (s, 2H, CH_2), 6.39 (m, 2H, Ph), 8.30 (s, 1H, H6); **6**, mp 170-171; ^{1}H NMR : δ = 3.70 (s, 2H, CH_2),3.98 (s, 9H, OCH_3), 5.52 (s, 2H, NH_2), 6.34 (m, 2H, Ph), 7.92 (s, 1H, H6); **7**, mp 200-201; ^{1}H NMR : δ = 3.65 (s, 2H, CH_2),3.81 (s, 9H, OCH_3), 4.67 (s, 2H, NH_2), 4.89 (s, 2H, NH_2), 6.38 (m, 2H, Ph), 7.77 (s, 1H, H6).

10. The structures of all compounds were confirmed by IR, ^{1}H NMR, MS spectra and by CHN analysis.

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