Pergamon

Tetrahedron, Vol. 52, No. 31, pp. 10417-10426, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00568-6

Metalation of diazines XVII

Very hindered bases as new metalating agents, Improvement of regioselectivity for the metalation of 3-chloro-6-methoxypyridazine

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Abstract : The different factors governing the regioselectivity of the metalation of 3-chloro-6-methoxypyridazine with alkylamides were studied. Very hindered bases were used as new metalating agents and a very good regioselectivity was obtained. Copyright © 1996 Elsevier Science Ltd

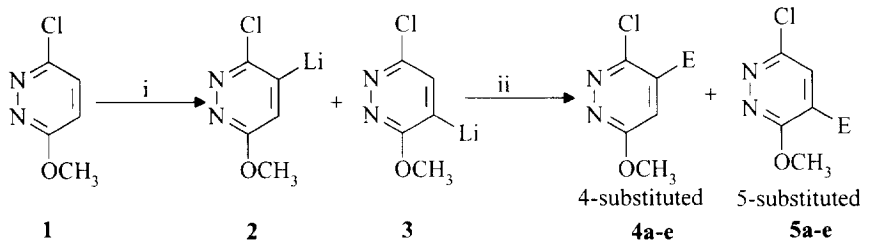
INTRODUCTION

In the course of the metalation of diazines with lithium alkyls or alkylamides, it was observed that the regioselectivity could be modified with the metalating agent and/or the experimental conditions.[1-7] The different regioselectivities found for the metalation reaction between butyllithium and alkylamides are easy to explain because the course of the reaction is very different. With butyllithium the main effect is the coordination with the ortho directing group whereas with alkylamides this coordination is much less important. However a difference in regioselectivity has been found even between two alkylamides: lithium diisopropylamide (LDA) and lithium-2,2,6,6-tetramethylpiperidide (LTMP). In order to highlight the main factors governing this regioselectivity we have planned to study the metalation of 3-chloro-6-methoxy pyridazine **1** with alkylamides. This compound was easy to obtain and the two o-directing group are in direct competition without vicinal participation of the ring nitrogens, furthermore a regioselective subtitution of this product would be interesting for the synthesis of pyridazine derivatives.[8]

RESULTS AND DISCUSSION

The complete reaction comprised two steps: a metalation step followed by reaction with the electrophiles.

Scheme 1



1 **2** **3** **4a-e** **5a-e**

i, metalation step ; ii, reaction with electrophile

It was first necessary to ensure that the first step governed the regioselectivity, so various electrophiles were reacted with the same metalation conditions (2.2 eq. LTMP/-70°C/2h), table 1.

Table 1: Action of Various Electrophiles.

electrophile	E	yield	products 4 and 5	regioselectivity ratio 4/5
DCl	-D	80 %	a	20/80
CH_3CHO	$-CH(OH)CH_3$	86 %	b	20/80
PhCHO	-CH(OH)Ph	94 %	c	15/85
ICH_3	$-CH_3$	74 %	d	20/80
I_2	-I	41 %	e	20/80

The percentage of the two isomers was determined by ^1H NMR. A variation of 5% of the regioselectivity was not considered as significant in view of the fact that small experimental variations may occur. From the results of table 1 it could be concluded that the second step of the reaction (action of electrophile) had few influence on the regioselectivity even when the yield was moderate (I_2) so we could concentrate on the metalation step. The main parameters of this reaction were studied: nature and amount of the metalating agent, temperature, reaction time, concentration, solvent. These metalation reactions were followed by the action of a large excess of acetaldehyde for 1.5h.

The nature and amount of metalating agent was first studied with LDA and LTMP at -70°C during 30 minutes (table 2).

Table 2: Nature and Amount of Alkylamide.

entry	metalating agent	eq. amount	yield	regioselectivity ratio 4/5
1	LTMP	1.2	70 %	20/80
2	LTMP	2.2	84 %	15/85
3	LDA	1.2	59 %	40/60
4	LDA	2.2	84 %	40/60

The nature of the base had a strong influence on regioselectivity. The yield was dependent on the amount of metalating agent and 2.2 equivalents amounts was necessary to achieve good yields as was previously found for methoxy derivatives of diazines.[9]

The reaction time was varied from 5 minutes to 2 h, with 2.2 equivalents amounts of alkylamides at -70°C (table 3).

Table 3: Variation of Time.

entry	metalating agent	metalation time	yield	regioselectivity ratio 4/5
1	LTMP	5 min	74 %	12/88
2	LTMP	15 min	86 %	20/80
3	LTMP	30 min	84 %	15/85
4	LTMP	120 min	71 %	25/75
5	LDA	5 min	85 %	40/60
6	LDA	90 min	85 %	40/60

When LDA was used as metalating agent no difference in yield or regioselectivity was found as the reaction time was modified (entries 5,6). With LTMP the yield increased when the time was increased from 5 to 15 minutes and then lowered for extended time. This could be due to a faster decomposition of the lithio derivatives in the presence of LTMP. Regioselectivity was not affected except for a very short metalation time (entry 1). In that case the isomer ortho to the methoxy group was favored.

The temperature was varied from 0°C to -100°C with 2.2 equivalents amounts of alkylamide (table 4).

Table 4: Variation of Temperature.

entries	metalating agent	Θ	metalation time	yield	regioselectivity ratio 4/5
1	LTMP	0°C	5 min	36 %	13/87
2	LTMP	-50°C	30 min	64 %	18/82
3	LTMP	-70°C	30 min	84 %	15/85
4	LTMP	-100°C	30 min	93 %	15/85
5	LDA	0°C	5 min	42 %	45/55
6	LDA	-50°C	30 min	84 %	38/62
7	LDA	-70°C	30 min	85 %	40/60
8	LDA	-100°C	30 min	88 %	50/50

At 0°C the time was reduced to 5 minutes (entries 1,5) because the decomposition of the lithio derivatives was very fast at this temperature. In all cases a lowering of the temperature increased the yield. The decomposition of the lithio derivatives was more marked with LTMP than with LDA at -50°C (entries 2,6), this confirms the result of table 3. At the temperature of -100°C (entries 4,8) the yields were very good but this temperature was not easy to use ; so the small lowering of the yield when working at -70°C was tolerated and this temperature was used for all the other experiments.

The regioselectivity was slightly affected by temperature. The results at 0°C were not significative as there was intense degradation of the lithio derivatives at this temperature. The regioselectivity at -100°C with LDA varied slightly towards the isomer in ortho to the chlorine atom.

The roles of the solvent and of the concentration were also tested at -70°C with 2.2 equivalents amounts of metalating agent in 30 minutes (table 5).

Table 5: Change of Solvent and Concentration.

entry	metal. agent	solvent	conc. mole/l	yield	regioselectivity ratio 4/5
1	LDA	THF	0.15	89 %	45/55
2	LDA	THF	0,04	85 %	40/60
3	LDA	ether	"	58 %	45/55
4	LTMP	THF	"	84 %	15/85
5	LTMP	ether	"	39 %	35/65

The yields were severely lowered when ether was used instead of THF (entries 3,5).

The regioselectivity change in the case of LTMP when ether was used as solvent (entry 5) could not be taken into account because the yield was too low (39%). The yields were close when using a fourfold concentration and the regioselectivity was not notably affected. The regioselectivity did not change with the solvent when LDA was used ; with LTMP and ether as solvent, the yield was so lowered that no serious comment on regioselectivity could be done.

The influence of the various factors is summarized below, table 6.

Table 6: Factors Governing the Yield and the Regioselectivity.

factor	electrophile	nature of alkylamide	amount of alkylamide	time	temp.	conc.	solvent
influence on yield	yes	very low	strong	low (LTMP) none (LDA)	strong	none	strong
influence on regioselectivity	none	yes	none	low (LTMP) none (LDA)	low with LDA	none	none with LDA

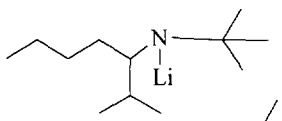
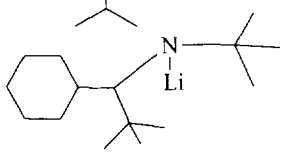
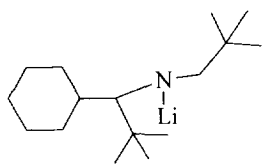
In summary, the regioselectivity was essentially dependent on the nature of the alkylamide, all other factors being secondary ones. In fact when the reaction conditions were not appropriate: too high temperature, too long metalation time or unsuitable solvent, the yield decreased much more by decomposition of the lithio derivatives. If one of the two isomeric lithio derivatives had a faster rate of decomposition then the resulting regioselectivity could be affected.

These results showing that the nature of the alkylamide was the main factor governing regioselectivity prompted us to test other alkylamides than LDA and LTMP for the metalation reaction. Some work had been done on the basic and nucleophilic properties of alkylamides [10-16] and in a 1984 publication[16] Mansour and Fraser listed several very hindered nitrogen bases with pKa higher than LDA and LTMP, so we tried three of them in order to test their efficiency as metalating agents.

Synthesis and reactivity of hindered bases

The pKa [16] of these bases are listed in table 7. It can be noticed that pKa of LDA and LTMP in tetrahydrofuran are respectively 35.7 and 37.3.

Table 7: pKa of lithiated hindered bases.

		pKa
6		38.3
7		39.5
8		40.0

The corresponding amines **6a**, **7a**, **8a**, have been prepared from the corresponding imines, which have been synthesized by a slightly modified Fraser's procedure,[16] (scheme 2, table 8).

Scheme 2

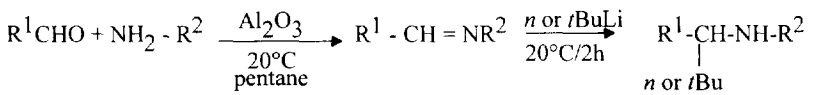
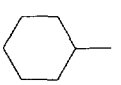
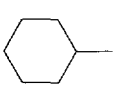


Table 8 : Syntheses of **6a**, **7a**, **8a.**

base	R^1	R^2	Buli	yield
6a		*t*Bu-	*n*Buli	47%
7a		*t*Bu-	*t*Buli	59%
8a		isopentyl	*t*Buli	30%

The workup of these syntheses were very easy and the starting materials for **6** and **7** easily available. These bases were lithiated with *n*-butyllithium and the corresponding alkylamides were tested on 3-chloro-6-methoxypyridazine with the best operating conditions (2.2 eq. Base/-70°C/30 minutes), and with various electrophiles (table 9).

The weak pKa difference between **7** and **8** and the much lower yield for its preparation made **8** less interesting to use, so we have tested **8** only with acetaldehyde as electrophile.

Table 9: Use of **6**, **7**, **8** as metalating agent.

Electrophile	metalating agent	yield	products 4 and 5	regioselectivity ratio 4/5
EtOD	**6**	78 %	a	6/94
EtOD	**7**	91 %	a	3/97
CH_3CHO	**6**	89 %	b	3/97
CH_3CHO	**7**	90 %	b	5/95
CH_3CHO	**8**	87 %	b	2/98
PhCHO	**6**	80 %	c	8/92
PhCHO	**7**	87 %	c	3/97
ICH_3	**6**	63 %	d	1/99
ICH_3	**7**	74 %	d	1/99
I_2	**6**	71 %	e	5/95
I_2	**7**	68 %	e	9/91

These yields were similar to those obtained with LTMP as metalating agent (table 1) and the regioselectivity was very good.

CONCLUSION

The use of very hindered bases as new metalating agents allowed us to achieve an almost regioselective metalation of 3-chloro-6-methoxypyridazine with a very good yield. Furthermore we could highlight the main factor governing the regioselectivity in a metalation reaction with alkylamides.

We are still investigating on this topic with the same alkylamides and other substrates.

EXPERIMENTAL

The ^1H NMR spectra were recorded in deuteriochloroform or in deuterated dimethylsulfoxide on a Bruker AC 200 instrument. Microanalyses were performed on a Carlo Erba CHNOS 1106 apparatus.

Tetrahydrofuran was distilled from benzophenone sodium and used immediatly. 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. The compounds to react were handled with syringues through septa. All reagents were of commercial quality and were purchased from Aldrich Chemical Co. or Janssen Pharmaceutica.

Typical procedure for metalation

A solution of *n*-butyllithium (1.6 M in hexane), (2 ml, 3.20 mmol) was added to cold (-30°C), stirred anhydrous tetrahydrofuran (30 ml) under an atmosphere of argon. The amine (3.20 mmol) was added, the mixture warmed to 0°C for LDA and LTMP and to 20°C for **6**, **7**, and **8** then allowed to stand 30 minutes at this temperature after which it was cooled to -75°C.

A solution of 3-chloro-6-methoxypyridazine (0.217g, 1.50 mmol) in tetrahydrofuran (5 ml) was slowly added at -75°C and the solution stirred at -75°C for 30 minutes. Acetaldehyde (1 ml, 18 mmol) was then added at -75°C and reacted for 1.5 h. Hydrolysis was carried out at -75°C using a mixture of 35% aqueous hydrochloric acid (1 ml), ethanol (4 ml) and tetrahydrofuran (5 ml). The solution was warmed to room temperature, made slightly basic with a saturated sodium hydrogenocarbonate solution (10 ml). Tetrahydrofuran was evaporated and the remaining mixture was extracted with dichloromethane (3 x 50 ml). The combined organic extracts were dried over magnesium sulfate and evaporated to dryness to afford the crude product which was purified by column chromatography on silica gel.

The reaction of the lithio derivatives **2** and **3** with methyl iodide and benzaldehyde has been described in a previous communication.[17] In order to evaluate the proportions of the **4** and **5** isomers with the best precision we have performed the ^{1}H NMR spectra in DMSO. Using this solvent we have no problem to integrate in the 7 - 8 ppm range where are the two hydrogen H_4 and H_5 signals.

Synthesis of 3-chloro-4-(1-hydroxyethyl)-6-methoxypyridazine 4b and 3-chloro-5-(1 hydroxyethyl)-6-methoxypyridazine 5b.

Metalation according to the typical procedure with amine **7** (0.734 g, 3.26 mmol) then reaction with acetaldehyde (1 ml, 18 mmol) gave after purification by column chromatography on silica gel [eluent ethyl acetate/cyclohexane (7: 3)] 0.252 g of mixture of the two alcohols **4b** and **5b**, yield 90%.

The proportion of the two isomers were determined by ^{1}H NMR and are 5/95 (**4b/5b**). ^{1}H NMR (DMSO) for **4b**: δ 1.32 (d, J = 6.5 Hz, 3H, CH_3), 4.00 (s, 3H, OCH_3), 4.76 (m, 1H, CH), 5.75 (d, J = 4.6 Hz, 1H, OH), 7.23 (s, 1H, H_5), ^{1}H NMR (DMSO) for **5b**: δ 1.29 (d, J = 6.5 Hz, 3H, CH_3), 4.04 (s, 3H, OCH_3), 4.76 (m, 1H, CH), 5.62 (d, J = 4.6 Hz, 1H, OH), 7.60 (s, 1H, H_4). Anal. calcd for $C_7H_9ClN_2O_2$: C, 44.56 ; H, 4.77 ; N, 14.85. Found: C, 44.5 ; H, 4.7 ; N, 14.5.

Synthesis of 3-chloro-4-iodo-6-methoxypyridazine 4e and 3-chloro-5-iodo-6-methoxypyridazine 5e.

Metalation according to the typical procedure with amine **6** (0.603 g, 3.26 mmol) then reaction with iodine (0.453 g, 1.78 mmol) gave after purification by column chromatography on silica gel [eluent dichloromethane/ethyl acetate (9: 1)] 0.285 g of mixture of the two iodo compounds **4e** and **5e**, yield 71%.

The proportion of the two isomers were determined by ^{1}H NMR and are 5/95 (**4e/5e**). ^{1}H NMR (DMSO) for **4e**: δ 4.03 (s, 3H, OCH_3), 8.00 (s, 1H, H_5), ^{1}H NMR (DMSO) for **5e**: δ 4.03 (s, 3H, OCH_3), 8.43 (s, 1H, H_4). Anal. calcd for $C_5H_4ClIN_2O$: C, 22.18 ; H, 1.48 ; N, 10.35. Found: C, 22.3 ; H, 1.4 ; N, 10.1.

Synthesis of the hindered bases 6, 7, 8.

1) *Synthesis of imines, general procedure.* In a three-necked flask fitted with a dropping funnel, stirrer and reflux condenser protected by a drying tube were placed 50 g of alumina (dried in an oven at 200°C for 48h) in 100 ml anhydrous pentane. Aldehyde (0.14 mol) and amine (0.26 mol), both freshly distilled were added. The mixture was stirred at 20°C during 12 hours, filtered and the alumine extracted again with pentane (2 x 50 ml). The filtrate was evaporated and the remaining oil was distilled.

***N*-isobutylen-*tert*-butylamine.**

Aldehyde: 2-methylpropanal, amine: *tert*-butylamine.

yield: 69%, bp 115°C; ^{1}H NMR ($CDCl_3$): δ 1.03 (d, J = 6Hz, 6H, CH_3), 1.13 (s, 9H, *t*Bu), 2.33 (m, 1H, CH), 7.32 (d, J = 6Hz, 1H, CH = N).

4 *N*-(cyclohexylmethylene) *tert*-butylamine.

Aldehyde: cyclohexylcarboxaldehyde, amine: *tert*-butylamine.

yield: 88%, bp 88°C/12mmHg ; ^{1}H NMR ($CDCl_3$): δ 1.13 (s, 9H, *t*Bu), 1.55 (m, 11H, cycle) 7.30 (d, J = 6Hz, 1H, CH=N).

***N*-(cyclohexylmethylene) neopentylamine.**

Aldehyde: cyclohexylcarboxaldehyde, amine: neopentylamine.

yield: 58%, bp 98°C/12mmHg ; ^{1}H NMR ($CDCl_3$): δ 0.90 (s, 9H, *t*Bu), 1.53 (m, 11H, cycle), 3.10 (s, 2H, CH_2), 7.30 (d, J = 6Hz, 1H, CH=N).

2) *Addition of butyllithium to imines, general procedure.* In a three-necked flask under an argon atmosphere was placed *n* or *tert*- butyllithium (0.2 mol). A solution of imine (0.1mol) in pentane (20 ml) was added slowly while keeping the temperature under 20°C. Stirring at room temperature was continued for 2h. The mixture was poured on ice (500 g) and the aqueous phase extracted with ether (3 x 100 ml). The organic phase was dried with magnesium sulfate and evaporated. The oily residue was purified by distillation under reduced pressure.

***N, N-tert*-butyl-(1-isopropylpentyl) amine 6.**

Alkyllithium: *n*-butyllithium, yield 78%, bp 82°C/12mmHg ; ^{1}H NMR ($CDCl_3$): δ 0.60 (m, 1H, NH), 0.80 (d, J = 6Hz, 6H, $(\underline{CH_3})_2CH$), 0.90 (m, 3H, CH_3), 1.10 (s, 9H, *t*Bu), 1.30 (m, 6H, CH_2), 1.70 (m, 1H, $\underline{CH}(CH_3)_2$), 2.40 (m, 1H, $\underline{CH}$-NH).

Anal. Calcd for $C_{12}H_{27}N$: C, 77.76 ; H, 14.68 ; N, 7.56. Found: C, 77.7 ; H, 14.8 ; N, 7.5.

***N, N-tert*-butyl-(1-cyclohexyl-2,2-dimethylpropyl) amine 7.**

Alkyllithium: *tert*-butyllithium, yield 67%, bp 115°C/0.7mmHg ; ^{1}H NMR ($CDCl_3$): δ 0.83 (s, 9H, *t*Bu), 1.05 (s, 9H, *t*Bu), 1.40 (m, 12H, cycle + $\underline{CH}$-NH), 2.00 (s, 1H, NH).

Anal. Calcd for $C_{15}H_{31}N$: C, 79.92 ; H, 13.86 ; N, 6.21. Found: C, 79.6 ; H, 14.1 ; N, 6.3.

***N, N*-neopentyl-(1-cyclohexyl-2,2 dimethylpropyl) amine 8.**

Alkyllithium: *tert*-butyllithium, yield 54%, bp 92°C/0.3mmHg ; ^{1}H NMR ($CDCl_3$): δ 0.90 (s, 18H, *t*Bu), 1.40 (m, 12H, cycle + NH), 1.85 (m, 1H, $\underline{CH}$-NH), 2.30 (d, J = 11Hz, 1H, $\underline{CH}$ *t*Bu), 2.50 (d, J = 11Hz, 1H,$\underline{CH}$ *t*Bu).

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(*Received in Belgium* 19 *February* 1996; *accepted* 17 *June* 1996)