ORGANOZINC DERIVATIVES OF DIAZINES, METALATION OF DIAZINES XXIII

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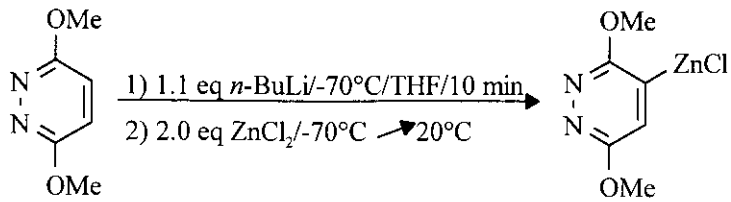
Abstract - Some organozinc derivatives of diazines have been prepared from lithiated diazines and zinc chloride. They reacted in cross coupling reactions with iodobenzene, 2-bromopyridine and 5-bromopyrimidine. The use of sonication, for the first time in a Negishi reaction, lowered the reaction times significantly and improved the yields.

Since ten years we have investigated the synthesis of organometallics of diazines *via* lithio derivatives.[1-8] These metalations were very often successful but, except in few cases, the lithio derivatives were reacted at -75°C because they are not stable at higher temperatures. In order to perform reactions at higher temperatures we were looking for diazinic organometallic derivatives with another metal than lithium. As it is reported by Knochel and Singer that organozinc compounds are more stable and much less reactive toward electrophiles than lithium or magnesium organometallics, [9] we decided to synthesize and test organozinc derivatives of diazines. Recently Knochel described the preparation of organozinc derivatives of uracil and purine, by direct insertion of zinc dust from the correspondent heteroaryl iodides.[10] In order to obtain easily the diazinic organozinc compounds we started from the lithio derivatives and performed a transmetallation reaction with zinc chloride. In a first approach we wanted to avoid the presence of an amine in the reaction mixture so we chosed as a substrate one of the few diazinic compounds which could be metalated with *n*-butyllithium : 3,6-dimethoxypyridazine (**1**) and we synthesized its organozinc derivative as described in Scheme 1.

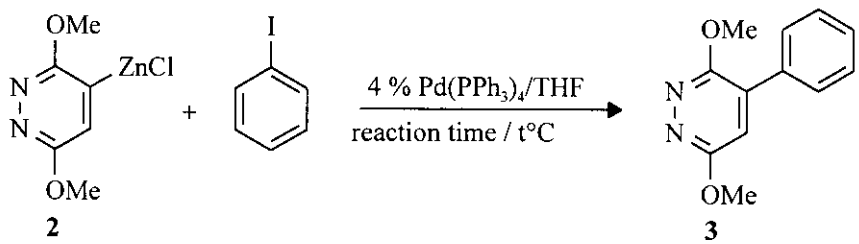
Scheme 1



1 **2**

Compound (**2**) was stable at room temperature and could be stored and reacted at this temperature, it was reacted with some electrophiles : acetaldehyde, benzoyl chloride, acetic anhydride without result as only starting material was recovered. Then some activation methods were tested : addition of $Pd(PPh_3)_4$ as indicated by Sakamoto for pyridine,[11] addition of either $BF_3.EtO_2$, or $ClSiMe_3$, in most cases the starting material was recovered. These results could also be explained by a lack of formation of the organometallic compound (**2**). Knochel and Singer,[9] showed that organozinc derivatives reacted well in cross coupling reaction, so we investigated the reaction of **2** with iodobenzene. Scheme 2, Table 1 :

Scheme 2



2 **3**

Table 1

entry	reaction time (h)	temp. (°C)	Yield (%)	sonication
1	8.5	65	90	no
2	3	65	90	))))
3	5	25	58	))))

The excellent yield obtained in entry 1 was a proof that the organozinc compound (**2**) was actually obtained. However the reaction time was long , consequently we tested an ultrasonic activation in order to accelerate the coupling reactions, indeed Cheng and Luo,[12] described that a Heck reaction was improved by sonication. We used a simple ultrasound cleaning device with heating. The reaction time was much reduced (entry 2). Furthermore this reaction could even be performed at room temperature (entry 3). The same coupling reaction was then tested with 2-bromopyridine and 5-bromopyrimidine : Scheme 3, Table 2.

Scheme 3

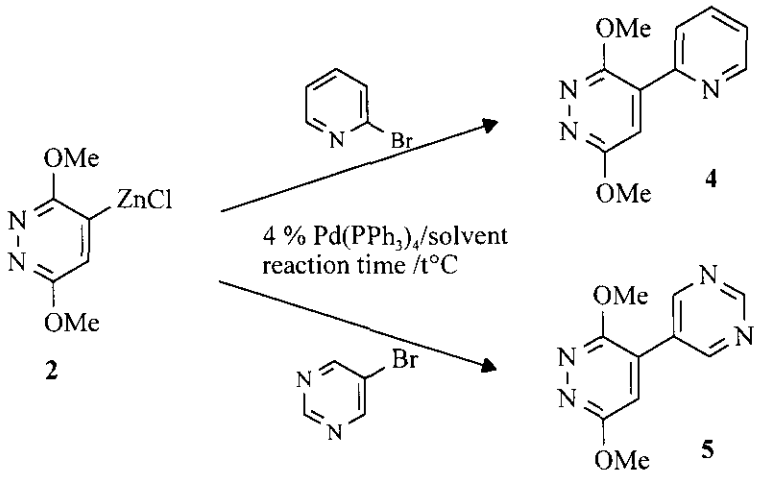


Table 2

entry	coupling substrate	reaction time (h)	temp. (°C)	solvent	Yield (%)	sonication
1	2-Br-pyridine	5	65	THF	51	no
2	//	8.5	65	//	62	no
3	//	1	125	NMP	10	no
4	//	5	125	NMP	60	no
5	//	3	25	THF	37	))))
6	//	3	45	//	60	))))
7*	//	3	45	//	70	))))
8	//	3	65	//	77	))))
9	//	2	65	//	59	))))
10	5-Br-pyrimidine	5	65	//	55	no
11	//	8.5	65	//	55	no
12	//	12	40	//	15	no
13	//	3	65	//	61	))))

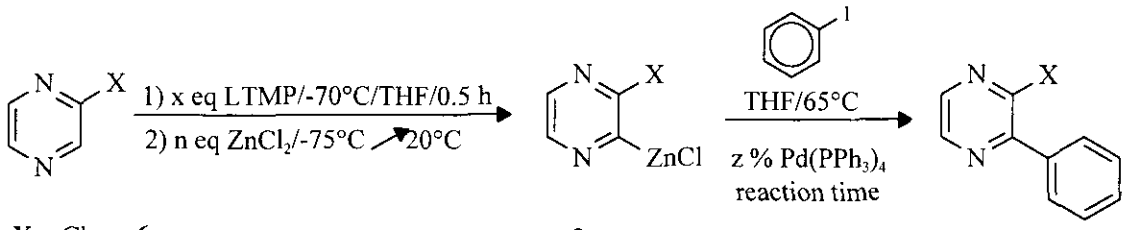
NMP : *N*-methylpyrrolidinone ; 7* : Metalating agent : LTMP.

The yields of the coupling reaction were lower than with iodobenzene, the reaction rate and the yields were enhanced when sonication was used. As most diazines cannot be metalated with *n*-butyllithium we tested the same coupling reaction with **1** metalated with LTMP (entry 7), the yields were close so it can be assumed that the presence of an amine in the reaction medium had no adverse effect on the reaction.

Another hypothesis about these successful coupling reactions must be accounted for : the direct coupling of a lithio derivative with an halogeno compound. It was shown that some organolithium compounds could be coupled with alkyl halides, [13a,b,c] so it was necessary to test the coupling reaction with the lithio derivative. This experiment afforded neither the coupling product nor the initial reactives, indicating that the transmetalation reaction with $ZnCl_2$ was mandatory to perform the coupling reaction.

Some pyrazine derivatives were then coupled with iodobenzene : Scheme 4, Table 3.

Scheme 4



X = Cl **6** **8** **10**

X = OMe **7** **9** **11**

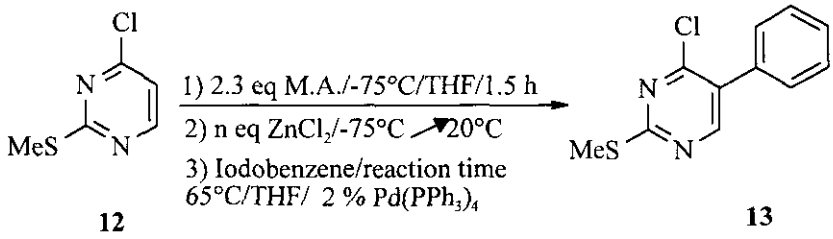
Table 3

entry	starting material	x eq LTMP	n eq $ZnCl_2$	reaction time (h)	z % of catalyst	compound	Yield (%)	sonication
1	6	1.3	1	20	1	10	67	no
2	//	1.3	2	20	1	//	85	no
3	//	1.3	3	20	1	//	84	no
4	//	1.3	3	7	1	//	27	))))
5	**//**	**1.3**	**3**	**7**	**4**	**//**	**36**	**no**
6	**//**	**1.3**	**3**	**7**	**4**	**//**	**99**	**))))**
7	7	2.3	2	20	4	11	84	no
8	//	2.3	2	3	4	//	88	))))

The zinc chloride amount was varied and a twofold excess was sufficient to obtain a good yield (entry 2). Here also sonication had a great influence on the yield and reaction time. With 2-chloropyrazine (**6**) we could obtain a quantitative yield (entry 6) under sonication whereas without sonication a 36% yield was obtained (entry 5). Karmas et Spoerri,[14] had yet described compounds (**10**) and (**11**), they synthesized them from 2-hydroxypyrazine and the yields were respectively 39% and 38%.

A pyrimidine derivative (**12**) was tested. Scheme 5, Table 4.

Scheme 5



12 **13**

M.A. : Metalating Agent : LTMP or LDA.

Table 4

entry	M.A.	n eq $ZnCl_2$	yield (%)	sonication	Reaction time (h)
1	LTMP	1.1	20	no	20
2	//	2.3	52	no	20
3	LDA	1.1	30	no	20
4	//	2.3	42	no	20
5	//	2.3	42	))))	10

Metalation of 2-thiomethyl-4-chloropyrimidine (**12**) was performed with LTMP or LDA as metalating agent. In the case of LTMP the lithiation was less regioselective at the 5 position than with LDA. The regioselectivity of this metalation at the 5 or 6 position has been previously studied[15] on the parent compound : 2,4-dichloropyrimidine. In the case of compound (**12**) a 52% yield with LTMP was obtained with a twofold excess of zinc chloride (entry 2) as usually. In the case of LDA the effect of the amount of zinc chloride is still verified (entries 3,4) ; however, yields are lower than with LTMP. To reach a similar yield we tested the crosscoupling reaction under sonication (entry 5). With ultrasonic wave, the same yields with LDA were obtained in half the time (entries 4,5).

In conclusion we have synthesized new organozinc derivatives in the diazine series (pyridazine, pyrazine, pyrimidine). These organozinc derivatives have proved to be very stable at room temperature and even at reflux of THF. These organozinc compounds could be used easily and gave good yields in crosscoupling reactions. It has been highlighted for the first time that the use of sonication could have a great interest for these Negishi reactions.

EXPERIMENTAL

Melting points were determined on a kofler hot stage and are uncorrected. The ^{1}H NMR spectra were recorded in deuteriochloroform with tetramethylsilan as internal standard on a Bruker AC 200 instrument. Microanalyses were performed on a Carlo Erba CHNOS 1106 apparatus.
Tetrahydrofuran was distilled from benzophenone sodium and used immediately. Water content of the solvent was estimated by the modified Karl-Fischer method (tetrahydrofuran less than 50 ppm water). Metalations were performed under an argon atmosphere which water content was regularly checked. Reagents were handled with syringes through septa. The cross coupling reactions with sonication were performed in an ultrasound cleaning bath (Lelievre, type 150T, 350 W).

Metalation reaction with lithium tetramethylpiperidide, A. A solution of *n*-butyllithium (2.5 M in hexane) was added to cold (-30°C), stirred, anhydrous tetrahydrofuran (20 mL) under an atmosphere of dry argon. 2,2,6,6-tetramethylpiperidine was added, the solution was then allowed to stand at 0°C for 15 min. Then the solution was cooled to -70°C. The diazine derivative dissolved in 5 mL of tetrahydrofuran was introduced and the mixture was stirred for a time t_1.

Metalation reaction with lithium diisopropylamide, C. A solution of *n*-butyllithium (2.5 M in hexane) was added to cold (-30°C), stirred, anhydrous tetrahydrofuran (20 mL) under an atmosphere of dry argon. Diisopropylamine was added, the solution was then allowed to stand at 0°C for 15 min. Then the solution was cooled to –70°C. The diazine derivative dissolved in 5 mL of tetrahydrofuran was introduced and the mixture was stirred for a time t_1.

Metalation reaction with *n*-butyllithium, B. A solution of *n*-butyllithium (2.5 M in hexane) was added to cold (-70°C), stirred, anhydrous tetrahydrofuran (20 mL) under an atmosphere of dry argon. The

diazine derivative dissolved in 5 mL of tetrahydrofuran was introduced and the mixture was stirred for 10 min.

Transmetalation reaction. A solution containing n equivalents of zinc chloride (previously dried under vaccum with a flameless heat gun) dissolved in 5 mL of tetrahydrofuran under an atmosphere of dry argon was added to the lithiated diazine at -70°C. The mixture was then gently warmed to rt.

Coupling reactions. A solution containing tetrakis(triphenylphosphine)palladium (z % mol), 1.1 equivalent of aromatic halide dissolved in 5 mL of tetrahydrofuran was added to the organozinc derivative of diazine and the mixture was warmed at 65°C during a time t_2 or placed in the sonication bath at the same temperature. The reaction mixture was then hydrolysed with a solution containing n equivalents of ethylenediamine tetraacetic acid (n was the same as the zinc chloride amount) and 10 mL of water, made slightly basic with a saturated aqueous solution of potassium carbonate. The aqueous layer was extracted with methylene chloride (3 x 15 mL) and the resulting organic layer was dried over magnesium sulphate and evaporated.

Testing few electrophiles with 3,6-dimethoxypyridazine (1). Metalation of **1** (1 mmol, 140 mg) according to the general procedure A (t_1 = 1.5 h, *n*-butyllithium : 2.3 mmol, 0.92 mL, 2,2,6,6-tetramethylpiperidine : 2.4 mmol, 0.41 mL) or to the general procedure B (*n*-butyllithium : 1.1 mmol, 0.45 mL) followed by the transmetalation reaction (zinc chloride : 2 mmol, 273 mg) gave a solution on which an excess of acetaldehyde (18 mmol, 1 mL) was added. After 3 h at rt no reaction occurred and the starting material was recovered quantitatively.

Other electrophiles on the same transmetalated diazine were tested : an excess of benzoyl chloride (4 mmol, 0.5 mL or 10 mmol, 1.2 mL) was introduced. After few h in refluxing tetrahydrofuran, the initial compound was recovered quantitatively. Nevertheless the compound resulting of the ring opening of the tetrahydrofuran by the benzoyl chloride was recovered as a byproduct. This result was previously described by Gaudemar and Normant. [16]

In order to avoid this side reaction, another electrophile was experimented : acetic anhydride. After a night at rt the starting material was recovered quantitatively. Some catalysts were used too with acetic anhydride in refluxing tetrahydrofuran during 1 to 12 h : tetrakis(triphenylphosphine)palladium (4 % mol, 46.2 mg) , boron trifluoride diethyl etherate (2 mmol, 0.3 mL), chlorotrimethylsilane (2 mmol, 0.1 mL) , or both tetrakis(triphenylphosphine)palladium (4 % mol, 46.2 mg) and boron trifluoride diethyl etherate (2 mmol, 0.3 mL); these experiments were always unsuccessfull and the starting material was recovered.

3,6-Dimethoxy-4-arylpyridazines (3), (4), (5). Metalation of **1** (1 mmol, 140 mg) according to the general procedure A (t_1 = 1.5 h, *n*-butyllithium : 2.3 mmol, 0.92 mL, 2,2,6,6-tetramethylpiperidine : 2.4 mmol, 0.41 mL) or to the general procedure B (*n*-butyllithium : 1.1 mmol, 0.45 mL) followed by the transmetalation reaction (zinc chloride : 2 mmol, 272 mg) gave a solution on which a coupling reaction was performed with tetrakis(triphenylphosphine)palladium (4 % mol, 46.2 mg), and an aromatic halide (V mL or m mg), in refluxing tetrahydrofuran (20 mL) or in a sonication bath at 65°C during a time t_2. After a flash chromatography on silica gel (petroleum ether : ethyl acetate; v/v : 5/5), products (**3**), (**4**), (**5**) were isolated.

3,6-dimethoxy-4-phenylpyridazine (**3**).

Iodobenzene : 1.2 mmol (0.11 mL) ; t_2 = 8.5 h, yield : 90 %; with sonication, t_2 = 3 h, yield : 90 %.

Product (**3**) was obtained as a white solid, mp 70°C. ^{1}H-NMR ($CDCl_3$) δ ppm : 4.0 (3H, s, OCH_3), 4.1 (3H, s, OCH_3), 7.1 (1H, m, H_5), 7.7 (5H, m, H_{phenyl}). Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.67 ; H, 5.07 ; N, 19.35. Found : C, 66.9; H, 5.2; N, 19.5.

3,6-dimethoxy-4-pyridinylpyridazine (**4**).

2-bromopyridine : 1.2 mmol (0.11 mL) ; t_2 = 8.5 h, yield : 62 %; with sonication, t_2 = 3 h, yield : 77 %.

Product (**4**) was obtained as a white solid, mp 80°C. ^{1}H-NMR ($CDCl_3$) δ ppm : 4.0 (3H, s, OCH_3), 4.1 (3H, s, OCH_3), 7.2 (1H, m, H'5), 7.5 (1H, s, H_5), 7.7 (1H, m, H'4), 8.0 (1H, d, H'3, J_{34} = 8 Hz), 8.6 (1H, d, H'6, J_{56} = 4 Hz). Anal. Calcd for $C_{11}H_{11}N_3O_2$: C, 60.83 ; H, 5.55 ; N, 12.96. Found : C, 61.0; H, 5.3; N, 12.7.

3,6-dimethoxy-4-pyrimidinylpyridazine (**5**).

5-bromopyrimidine : 1.1 mmol (179 mg) ; t_2 = 8.5 h, yield : 55 %; t_2 = 3 h, yield : 61 %.

Product (**5**) was obtained as a white solid, mp 148°C. ^{1}H-NMR ($CDCl_3$) δ ppm : 4.1 (6H, s, OCH_3); 7.0 (1H, s, H_5) ; 9.0 (2H, s); 9.3 (1H, s). Anal. Calcd for $C_{10}H_{10}N_4O_2$: C, 55.04; H, 4.59; N, 25.69. Found : C, 55.3 ; H, 4.7 ; N, 26.0.

2-Chloro-3-phenylpyrazine (10). Metalation of **6** (1 mmol, 0.09 mL) according to the general procedure A (t_1 = 30 min, *n*-butyllithium :1.3 mmol, 0.52 mL, 2,2,6,6-tetramethylpiperidine : 1.4 mmol, 0.24 mL) and transmetalation (zinc chloride : 1 mmol, 136 mg ; 2 mmol, 272 mg ; or 3 mmol, 408 mg) gave a solution on which a coupling reaction was performed with tetrakis(triphenylphosphine)palladium (1 % mol, 12 mg), and iodobenzene (1.2 mmol, 0.11 mL) ; (t_2 = 20 h) in refluxing tetrahydrofuran (20 mL). After a flash chromatography on silica gel (methylene chloride), product (**10**) was isolated as a white solid as described by Karmas and Spoerri.[14]

n = 1 mmol, yield = 67 % ; n = 2 mmol, yield = 85 % ; n = 3 mmol, yield = 84 %.

mp 78°C. ^{1}H-NMR ($CDCl_3$) δ ppm : 7.5 (3H, m, H'_3, H'_4, H'_5) ; 7.8 (2H, m, H'_2, H'_6) ; 8.4 (1H, d, H_5 or H_6, J_{56} = 2.5 Hz) ; 8.6 (1H, d, H_5 or H_6, J_{56} = 2.5 Hz). Anal. Calcd for $C_{10}H_7N_2Cl$: C, 62.99 ; H, 3.67 ; N, 14.70. Found : C, 62.7; H, 3.7; N, 14.6.

2-Methoxy-3-phenylpyrazine (11). Metalation of **7** (1 mmol, 0.10 mL) according to the general procedure A (t_1 = 30 min, *n*-butyllithium : 2.3 mmol, 0.92 mL, 2,2,6,6-tetramethylpiperidine : 2.4 mmol, 0.41 mL) followed by the transmetalation reaction (zinc chloride : 2 mmol, 272 mg) gave a solution on which a coupling reaction was performed with tetrakis(triphenylphosphine)palladium (4 % mol, 46 mg), and iodobenzene (1.2 mmol, 0.11 mL) ; (t_2 = 20 h) in refluxing tetrahydrofuran (20 mL) or (t_2 = 3 h) in a sonication bath at 65°C. After a flash chromatography on silica gel (methylene chloride), product (**11**) was isolated as a colorless liquid as described by Karmas and Spoerri.[14]

With refluxing, yield : 84 %; with sonication, yield : 88 %.

^{1}H-NMR ($CDCl_3$) δ ppm : 4.0 (3H, s, OCH_3); 7.5 (3H, m, H'_3, H'_4, H'_5); 8.1 (4H, m, H'_3, H'_4, H'_5, H_5 or H_6) ; 8.2 (1H, d, H_5 or H_6, J_{56} = 3 Hz). Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.97; H, 5.38; N, 15.05. Found : C, 70.7 ; H, 5.4 ; N, 15.0.

4-Chloro-2-methylthio-5-phenylpyrimidine (13). Metalation of **1** (1 mmol, 0.11 mL) according to the general procedure A (t_1 = 1.5 h, *n*-butyllithium : 2.3 mmol, 0.92 mL, 2,2,6,6-tetramethylpiperidine : 2.4 mmol, 0.41 mL) or to the general procedure C (t_1 = 1.5 h, n-butyllithium : 2.3 mmol, 0.92 mL, diisopropylamine : 2.4 mmol, 0.34 mL) and transmetalation (zinc chloride : 1.1 mmol, 150 mg ; 2.3 mmol, 313 mg ; 4.6 mmol, 626 mg ; or 6.9 mmol, 938 mg) gave a solution on which a coupling reaction was performed with tetrakis(triphenylphosphine)palladium (2 % mol, 23 mg), and iodobenzene (1.2 mmol, 0.11 mL) ; (t_2 = 20 h) in refluxing tetrahydrofuran (20 mL) or (t_2 = 10 h) in a sonication bath at 65°C. After a flash chromatography on silica gel (petroleum ether : diethyl ether; v/v : 9/1), product (**13**) was isolated as a white solid.

n = 1.1 mmol, yield = 20 % ; n = 2.3 mmol, yield = 52 % ; n = 4.6 mmol, yield = 52 %; n = 6.9 mmol, yield = 52 %.

mp 102°C. ^{1}H-NMR ($CDCl_3$) δ ppm : 2.6 (3H, s, SCH_3) ; 7.5 (5H, s, H_{phenyl}) ; 8.4 (1H, s, H_6). Anal. Calcd for $C_{11}H_9N_2ClS$: C, 55.81; H, 3.81; N, 11.84. Found : C, 55.7 ; H, 3.8 ; N, 11.7.

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