Journal of Organometallic Chemistry, 412 (1991) 301–310
Elsevier Sequoia S.A., Lausanne
JOM 21890

Metalation of diazines

IV *. Lithiation of *sym*-disubstituted pyrazines

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(Received December 26th, 1990)

Abstract

Conditions for the metalation of 2,6-dichloro- and 2,6-dimethoxy-pyrazine are defined and the lithio-derivatives are shown to react with some electrophiles. A convenient synthesis of a diazaxanthone from the lithio-derivative of the dichloro-compound is described. Couplings between phenylacetylene and iodo-derivatives of pyrazine have been carried out.

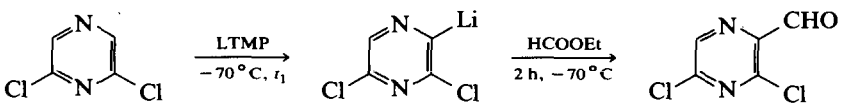
Introduction

In continuation of our work on the metalation of diazines [1–3] we describe here the lithiation of 2,6-dichloro- and 2,6-dimethoxy-pyrazines which are the first disubstituted pyrazines to be metalated. The metalation conditions are defined, and the lithio-derivatives used in the synthesis of some new pyrazine derivatives.

1. Determination of suitable metalation conditions

(a) 2,6-Dichloropyrazine (1)

It was shown previously [1], that lithium 2,2,6,6-tetramethylpiperidide (LTMP) (**2**) is a suitable metalating agent for this type of substrate. The outcome of the metalation was assessed by reaction with ethyl formate to give *o*-chloroaldehyde (**4**).



(**1**) (**3**) (**4**)

* For Part III see ref. 3.

0022-328X/91/$03.50

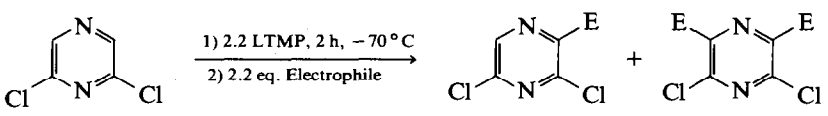
Table 1

Solvent	THF	THF	THF	THF	THF	Ether
LTMP eq. amount	1.2	1.2	1.2	1.2	2.2	1.4
t_1, h	0.5	1	1.5	2	2	2
Yield (%) of **3**	35	44	40	43	44	5

The reaction time t_1, the solvent, and the amount of LTMP were varied, and the results are summarized in Table 1.

The results indicate that after 1 h the reaction did not proceed further in THF and that ether is a poor reaction medium. It is noteworthy that neither unchanged **1** nor any product coming from a dimetalation reaction was recovered even when a large excess of LTMP (2.2 equivalent) was used.

The possible formation of a disubstitution product in the presence of an excess of the metalating agent was examined by treatment with electrophiles known not to be reactive towards the metalating agent, such as iodine, trimethyltin chloride, and benzaldehyde. The results are summarized in Table 2.



(1) **(5, 8)** **(6, 7, 9)**

In the case of iodine, some diiodo product is formed even when only 1.2 equivalent of the metalating agent is used. Since it was known that when acetaldehyde and an excess of LTMP were used there was no simultaneous dimetalation, the disubstitution products must have come from a subsequent dimetalation; i.e. the monosubstituted product was metalated *in situ* by LTMP and the remaining electrophile reacted with this lithio-derivative to give a disubstituted compound.

Table 2

Electrophile	Product	mono metalation (%)	Product	dimetalation (%)
PhCHO	**5**	53	**6**	17
$ClSn(CH_3)_3$	**27**		**9**	70
I_2		0	**7**	10
I_2 [a]	**8**	0	**7**	31

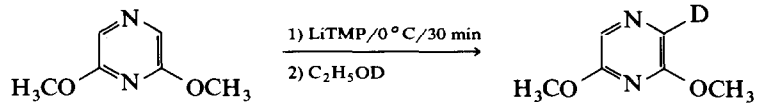
[a] Metalation performed with 1.2 eq. LTMP.

Table 3

Metalating agent eq.	1.2	1.2	1.2	2.2	2.2
t_1, min	15	30	60	15	30
Deuterated compound (%)	32	44	48	83	100

(b) 2,6-Dimethoxypyrazine (10)

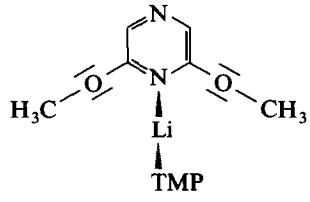
In this case it was possible to study the metalation by quenching with deuterated ethanol owing to the presence of the hydrogens of the methoxy group. The percentage of deuteration was assessed from the NMR spectrum (Table 3).



(10) **(11)**

The best conditions found for metalation at 0 °C were 2.2 equivalents of LTMP and a metalation time of more than 30 minutes.

The reason why it is necessary to use a two-fold excess of the metalating agent is not obvious. It is possible that the presence of two methoxy groups favours the formation of a complex such as **12** in which a LTMP molecules is trapped.

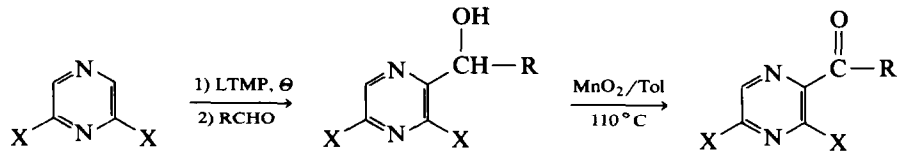


(12)

It is noteworthy that when metalation was carried out at −70 °C with 1.2 equivalents of LTMP for 15 min only 13% of deuterated product was obtained. Mattson and Sloan [4] using exactly the same conditions obtained good yields (57 to 92%) after adding the electrophile and leaving the mixture to warm overnight. This result was due to a shift in the metalation equilibrium. Such a procedure is limited to electrophiles which react slowly with LTMP.

2. Synthesis by metalation

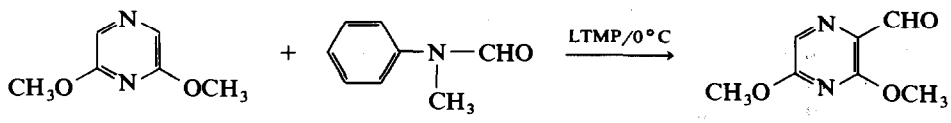
The conditions and procedure defined above various were used for reactions with electrophiles. Aldehydes were first used and yielded substituted alcohols.



(X = Cl, OCH_3) **(13–18)** **(20–24)**

Some of these alcohols were oxidized with manganese(IV) oxide in boiling toluene to give *o*-substituted ketones. The results are summarized in Table 4.

Reaction of the lithio-derivative with *N*-methylformanilide gave aldehyde **19**.



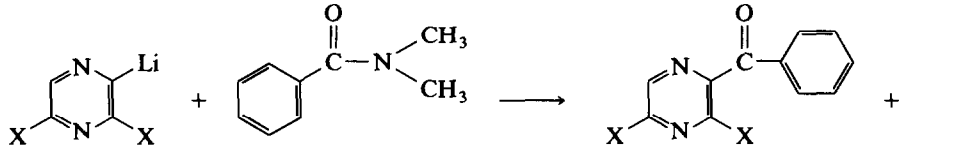
(10) **(19, 52%)**

Table 4

X [a]	R	Yield (%)	Compound	Yield (%)	Compound
Cl	Ph	62	**5**	84	**21**
Cl	CH_3	70	**13**	67	**20**
Cl	CH_3CH_2	57	**14**	–	–
Cl	$2MeOC_6H_4$	60	**15**	86	**22**
Cl	$2,4\ Cl_2C_6H_3$	64	**16**	84	**23**
OCH_3	Ph	72	**17** [b]	–	–
OCH_3	$2MeOC_6H_4$	75	**18**	77	**24**

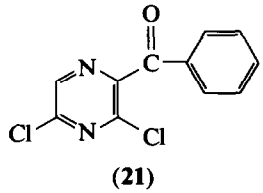
[a] $\theta = -70\,^{\circ}C$ for X = Cl; $0\,^{\circ}C$ for X = OCH_3. [b] Product described in ref. 4.

Another and more staightforward route to phenyl ketones is that developed by Watanabe [5], who used *N,N*-dimethylbenzamide as the electrophile. The same method was applied to **1** and **10**.

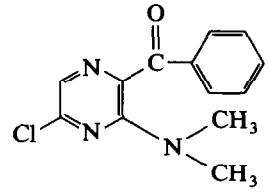


(X = OCH_3 (**25**); Cl (**21**))

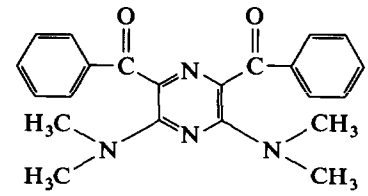
From dimethoxypyrazine a good yield (75%) of **25** was obtained but when 2,6-dichloropyrazine was used three products were isolated (Table 5).



(**21**)



(**26**)



(**27**)

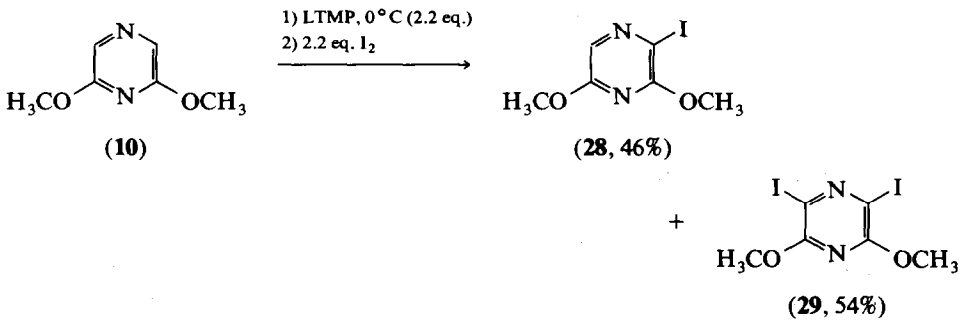
Product **25** is formed by nucleophilic displacement of chlorine by lithium *N,N*-dimethylamidide. To identify which chlorine atom, 2 or 6, had been replaced selective irradiation of the hydrogens of the NMe_2 moiety of **26** was performed, and a small but significant NOE was observed for the hydrogens of the phenyl ring, confirming that the NMe_2 group was close to the phenyl group. Product **27** is formed by metallation and disubstitution of **21**.

Table 5

	Compound (%)		
	21	**26**	**27**
After 1 h	31	27	3
After 12 h	6	55	13

Iodo compounds

Iodo derivatives are of interest because they can be used to create a carbon–carbon link in coupling reactions. The results for 2,6-dichloropyrazine (**1**) are shown in Table 2. When dimethoxypyrazine was used a quantitative yield was obtained.

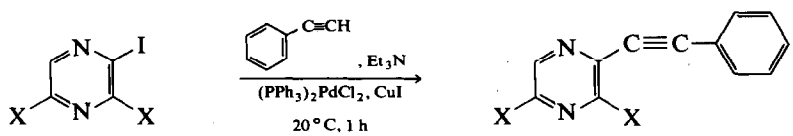


(**10**) (**28**, 46%)

+

(**29**, 54%)

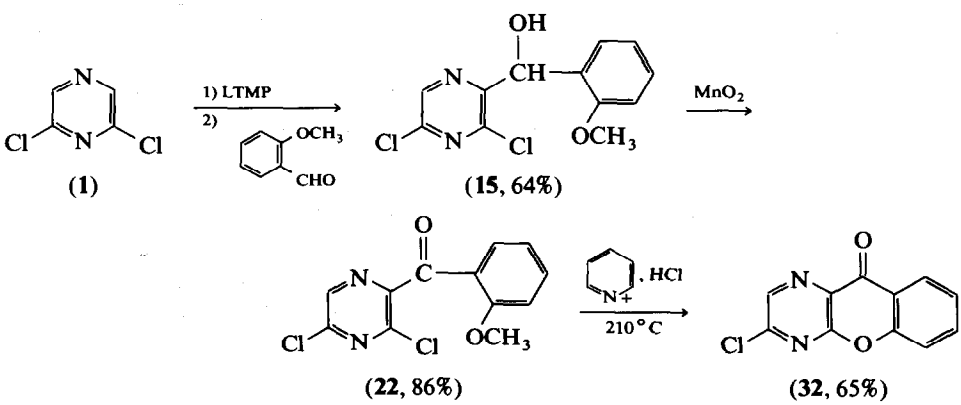
The two mono iodo compounds **7** and **28** were subjected to a coupling reaction with phenylacetylene and Pd as a catalyst.



(X = Cl (**8**); OCH_3 (**28**)) (X = Cl (**30**, 87%); OCH_3 (**31**, 80%))

Diazaxanthone

Some azaxanthone have antihistaminic properties and so an easy route to a diaza-analog was of interest, and the following sequence was successful:



(**1**) (**15**, 64%) (**22**, 86%) (**32**, 65%)

The last step involved a cyclisation brought about by heating in pyridinium hydrochloride as described by Royer [6]. The overall yield from **1** to **32** was 34%.

Conclusion

Metalation of dichloro- and dimethoxy-pyrazines has been successfully carried out, extending the scope of such metalation. Results of studies of compounds containing other *o*-directing groups will be published in the near future.

Experimental

All manipulations were carried out under argon. All reagents were freshly distilled. THF and ether were dried with a benzophenone-sodium mixture and distilled just before use. IR spectra were recorded on a Beckman 4250 spectrometer and NMR spectra on a Varian EM 360 L or Bruker spectrometer. All NMR spectra were carried out with $CDCl_3$ solutions and δ are given in ppm. Microanalysis were performed with a Carlo Erba 1106 apparatus. Melting points were determined with a Kofler hot-stage microscope.

General procedure for metalation

(a) Metalation of 2,6-dichloropyrazine (1)

Reactions were performed in a 100 ml three-necked flask equipped with a magnetic stirring bar, a pentane thermometer, and two septa. A stream of argon was maintained for 30 min. A 50 ml syringe was used to introduce 40 ml of dry THF or ether (water content < 40 ppm) and the solution was cooled to −30 °C and 2.5 ml (4 mmol) of n-butyllithium 1.6 *M* in hexane and 0.70 ml (4.1 mmol) of 2,2,6,6-tetramethylpiperidine were introduced. The mixture was allowed to warm to 0 °C and kept at this temperature for 30 min. The solution was cooled to −70 °C in a dry ice–acetone mixture, and a solution of 2,6-dichloropyrazine (0.5 g, 3.35 mmol) in 5 ml of THF was introduced from a syringe. The mixture became orange red. After the appropriate time t_1 the electrophile was added, and the mixture kept for 2 h at −70 °C. The mixture was then treated at this temperature with a mixture of 1 ml of HCl, 4 ml of ethanol, and 5 ml of THF. The solution was warmed slowly to 0 °C and neutralized with saturated aqueous sodium hydrogen carbonate. The solvent was evaporated in vacuum and the resulting slurry extracted three times with 25 ml of dichloromethane. The extract was dried over $MgSO_4$ then evaporated. The product was purified by sublimation, chromatography on silica gel, or by kugelrohr distillation.

2,6-Dichloropyrazine carboxaldehyde (4). The electrophile used was ethyl formate (0.4 ml, 4.88 mmol). Purification by chromatography on silica gel with CH_2Cl_2 as eluent gave 0.26 g (44%) of a pale yellow oil. ^1H NMR δ: 8.76 (s, 1H, H pyra); 10.21 (s, 1H, H(CHO)). IR (cm^{-1}): 1725 (ν(C=O)). Analysis. Found: C, 33.6; H, 1.4; N, 15.6. $C_5H_2Cl_2N_2O$ (M = 177) calc.: C, 33.93; H, 1.14; N, 15.82%.

(2,6-Dichloro-3-pyrazinyl)phenylmethanol (5). The electrophile used was benzaldehyde (0.5 ml, 5 mmol). Purification by chromatography on silica gel gave 0.53 g (62%) of a colourless oil. ^1H NMR δ: 4.55 (m, 1H, OH); 6.05 (m, 1H, CH); 7.35 (m, 5H, H phenyl); 8.52 (s, 1H, H pyra). Analysis. Found: C, 51.8; H, 3.0; N, 10.8. $C_{11}H_8Cl_2N_2O$ (M = 225) calc.: C, 51.79; H, 3.16; N, 10.93%.

2,6-Dichlorobis(hydroxyphenylmethyl)-3,5-pyrazine (6). Dichloropyrazine (**1**) (0.27 g, 1.8 mmol) and benzaldehyde (0.48 ml, 4.7 mmol) were used. The reaction time was 4 h. After chromatography on silica gel with CH_2Cl_2 as eluent (0.266 g, 58%) of **5** was obtained. With 1/4 CH_2Cl_2/CH_3COOEt mixture as eluent compound **6** was isolated (0.110 g, 17%) as a white solid. M.p. 161°C. ^1H NMR δ: 6.06 (m, 4H, H_{OH+CH}); 7.23 (s, 10H, H phenyl). Analysis. Found: C, 60.0; N, 7.7; H, 3.7. $C_{18}H_{14}Cl_2N_2O_2$ (M = 361.2) calc.: C, 59.85; N, 7.75; H, 3.90%.

2,6-Dichloro-3,5-diiodopyrazine (7). Metalation of **1** (0.27 g, 1.8 mmol), reaction with iodine (1.25 g, 4.92 mmol), and purification by chromatography on silica gel with a 7/3 hexane/CH_2Cl_2 mixture as eluent gave 0.22 g (31%) of a white solid. M.p. 122°C. No ^1H NMR spectrum. Analysis. Found: C, 12.2; N, 6.8. $C_4Cl_2I_2N_2$ (M = 400.8) calc.: C, 11.9; N, 6.99%.

2,6-Dichloro-3-iodopyrazine (8). The electrophile used was iodine (1.05 g, 4.15 mmol). After removal of the excess of iodine with a saturated solution of Na_2SO_3 and purification by chromatography on silica gel (with a 1/1 CH_2Cl_2/hexane mixture as eluent gave 0.25 g (27%) of a white solid. M.p. 89°C. ^1H NMR δ: 8.36 (s, 1H, H pyra). Analysis. Found: C, 17.4; H, 0.3; N, 9.9. $C_4HCl_2IN_2$ (M = 275) calc.: C, 17.48; H, 0.37; N, 10.19%.

The diodo compound **7** is also isolated (0.13 g, 10%).

2,6-Dichloro-3,5-di(trimethylstannyl)pyrazine (9). Metalation of **1** (0.27 g, 1.8 mmol) and reaction with trimethyltin chloride (0.83 g, 4.2 mmol) gave, after chromatography on silica gel with $CHCl_3$ as eluent a creamy solid (0.6 g, 70%). M.p. 68°C. ^1H NMR δ: 1.08 (s, 18H, H(CH_3)); Analysis. Found: C, 25.7; H, 3.8; N, 5.9. $C_{10}H_{18}Cl_2N_2Sn_2$ (M = 474.4) calc.: C, 25.31; H, 3.82; N, 5.90%.

(2,6-Dichloro-3-pyrazinyl)-1-ethanol (13). Metalation of **1** (0.27 g, 1.8 mmol) and reaction with trimethyltin chloride (0.83 g, 4.2 mmol) gave, after chromatography on silica gel with $CHCl_3$ as eluent a creamy solid (0.6 g, 70%). M.p. 68°C. ^1H NMR δ: 1.08 (s, 18 H, H(CH_3)); Analysis. Found: C, 25.7; H, 3.8; N, 5.9. $C_{10}H_{18}Cl_2N_2Sn_2$ (M = 474.4) calc.: C, 25.31; H, 3.82; N, 5.90%.

(2,6-Dichloro-3-pyrazinyl)-1-ethanol (13). Metalation was carried out as usual. The electrophile used was acetaldehyde (2 ml, 35 mmol). After chromatography on silica gel with CH_2Cl_2 as eluent a viscous oil was obtained (0.45 g, 70%). ^1H NMR δ: 1.53 (d, 3H, H(CH_3)); 3.56 (m, 1H, OH); 5.23 (s, 1H, H(CH)); 8.55 (s, 1H, H pyra); $J(H_{(CH_3)}-H_{(CH)}) = 6$ Hz. Analysis. Found: C, 37.3: H, 3.0; N, 14.6. $C_6H_6Cl_2N_2O$ (M = 193) calc.: C, 37.33; H, 3.13; N, 14.5%.

(2,6-Dichloro-3-pyrazinyl)-1-propanol (14). Metalation was followed by treatment with propionaldehyde (2 ml, 27 mmol). A viscous oil was obtained (0.40 g, 57%). ^1H NMR δ: 1.03 (t, 3H, H(CH_3)); 1.78 (q, 2H, H(CH_2)); 3.5 (m, 1H, OH); 4.96 (m, 1H, H(CH)); 8.5 (s, 1H, H pyra); $J(H_{CH_3}-H_{CH_2}) = 7$ Hz. Analysis. Found: C, 40.5; H, 3.9; N, 13.3. $C_7H_8Cl_2N_2O$ (M = 207) calc.: C, 40.60; H, 3.89; N, 13.53%.

(2,6-Dichloro-3-pyrazinyl)-2'-methoxyphenyl methanol (15). The electrophile used was *o*-anisaldehyde (0.52 ml, 4.3 mmol). After chromatography on silica gel with CH_2Cl_2 as eluent a white solide was obtained (0.57 g, 60%). M.p. 85°C. ^1H NMR δ: 3.77 (s, 3H, H(OCH_3)); 4.18 (m, 1H, OH); 6.3 (m, 1H, H(CH)); 7.0 (m, 4H, H phenyl); 8.47 (s, 1H, H pyra). Analysis. Found: C, 50.4; H, 3.2; N, 9.6. $C_{12}H_{10}Cl_2N_2O_2$ (M = 285) calc.: C, 50.55; H, 3.53; N, 9.82%.

(2,6-Dichloro-3-pyrazinyl)-(2',4'-dichlorophenyl)methanol (16). The electrophile

used was 2,4-dichlorobenzaldhyde (0.8 g, 4.55 mmol). After chromatography on silica gel with CH_2Cl_2 as eluent a yellow oil was obtained (0.69 g, 64%). ^1H NMR δ: 4.45 (m, 1H, OH); 6.37 (m, 1H, H(CH)); 7.2 (s, 2H, H phenyl); 7.38 (s, 1H, H phenyl); 8.50 (s, 1H, H pyra). Analysis. Found: C, 41.0; H, 1.9; N, 8.3. $C_{11}H_6Cl_4N_2O$ ($M = 324$) calc.: C, 40.78; H, 1.86; N, 8.64%.

(b) Metalation of 2,6-dimethoxypyrazine (10)

Lithium 2,2,6,6-Tetramethylpiperidide was prepared by adding butyllithium (2 ml, 3.2 mmol) and TMP (0.56 ml, 3.3 mmol) to anhydrous THF (40 ml). After 30 min stirring at 0 °C a solution of 2,6-dimethoxypyrazine (0.21 g, 1.5 mmol) in 5 ml of THf was added. The temperature was kept at 0 °C for 45 min and the electrophile then added. After 2 h at 0 °C the solution was treated with a mixture of 1 ml of water and 4 ml of ethanol. The THF was evaporated and the residual slurry extracted with chloroform (3 × 25 ml). The combined extracts were dried over $MgSO_4$ and then evaporated. The products obtained were purified by chromatography on silica gel.

3-Deutero-2,6-dimethoxypyrazine (11). The electrophile used was C_2H_5OD (0.5 ml with 2 ml of THF). After chromatography with CH_2Cl_2 as eluent, a white solid was obtained (0.18 g, 87%). M.p. 45 °C. ^1H NMR δ: 3.9 (s, 6H, H(OCH_3)); 7.77 (s, 1H, H pyra). Analysis. Found: C, 51.3; H, 5.3; N, 19.3. $C_6H_7DN_2O_2$ ($M = 141$) calc.: C, 51.06; H, 4.99; N, 19.85%.

(2,6-Dimethoxy 3-pyrazinyl)phenylmethanol (17). The electrophile used was benzaldehyde (0.36 ml, 3.5 mmol). After purification by chromatography on silica gel with a 9/1 CH_2Cl_2/CH_3COOEt mixture as eluent a pale yellow solid was obtained (0.26 g, 72%), with physical characteristics identical to those reported by Mattson and Sloan [4].

(2,6-Dimethoxy-3-pyrazinyl)-2'-methoxyphenyl methanol (18). The electrophile used was *o*-anisaldehyde (0.4 ml, 3.3 mmol). After purification by chromatography on silica gel with ether as eluent a pale yellow solid was obtained (0.31 g, 75%). M.p. 101 °C. ^1H NMR δ: 3.9 (s, 9H, H(OCH_3)); 4.4 (d, 1H, OH); 6.2 (d, 1H, H(CH)); 7.1 (m, 4H, H phenyl); 7.77 (s, 1H, H pyra); $J(H_{CH}-H_{OH}) = 6$ Hz. Analysis. Found: C, 61.4; H, 5.9; H, 9.8. $C_{14}H_{16}N_2O_4$ ($M = 276.3$) calc.: C, 60.87, H, 5.83; N, 10.14%.

2,6-Dimethoxy-3-pyrazinecarboxaldehyde (19). The electrophile used was *N*-methylformaniline (0.32 ml, 3.7 mmol). After purification by chromatography on silica gel with a 9/1 CH_2Cl_2/CH_3COOEt mixture as eluent and sublimation a pale yellow solid was obtained (0.13 g, 52%) M.p. 64 °C. ^1H NMR δ: 4.10 (s, 6H, H(OCH_3)); 7.92 (s, 1H, H pyra); 10.12 (s, 1H, H(CHO)). IR (cm^{-1}): ν(CO) = 1705. Analysis. Found: C, 49.9; H, 4.5; N, 16.4. $C_7H_8N_2O_3$ ($M = 168$) calc.: C, 50.00; H, 4.79; N, 16.66%.

(c) Procedure for the oxidation of alcohols to ketones

In a 100 ml flask fitted with a Dean Stark apparatus were placed 50 ml of dry toluene, the alcohol (n mmol), and freshly prepared manganese(IV) oxide (> 10 n mmol). The suspension was magnetically stirred and refluxed for 1 h, cooled, and filtrated. The precipitate was washed with 100 ml of chloroform. The combined organic phases were dried over $MgSO_4$ then evaporated, and the product purified by chromatography on silica gel with CH_2Cl_2 as eluent.

2,6-Dichloro-3-pyrazinyl ethanone (20). Compound **13** (0.48 g, 2.5 mmol) was

oxidized with 5 g of MnO_2 to yield a yellow oil **20** (0.32 g, 67%). ^1H NMR δ: 2.71 (s, 3H, $H(CH_3)$); 8.58 (s, 1H, H pyra). IR (cm^{-1}): $\nu(CO)$ = 1710. Analysis. Found: C, 37.40; H, 2.4; N, 14.6. $C_6H_4Cl_2N_2O$ (M = 191) calc.: C, 37.73; H, 2.11; N, 14.66%.

2,6-Dichloro-3-pyrazinyl phenylmethanone (21). Compound **5** (0.41 g, 1.6 mmol) was oxidized with 3 g of MnO_2 to give a pale yellow solid (0.34 g, 84%). M.p. 91°C. ^1H NMR δ: 7.6 (m, 3H, HPh); 7.8 (m, 2H, H phenyl); 8.58 (s, 1H, H pyra). IR (cm^{-1}): $\nu(CO)$ = 1670. Analysis. Found: C, 52.2: H, 2.2; N, 11.0. $C_{11}H_6Cl_2N_2O$ (M = 253) calc.: C, 52.20; H, 2.39; N, 11.07%.

(2,6-Dichloro-3-pyrazinyl)-2'-methoxy phenylmethanone (22). Compound **15** (0.43 g, 1.5 mmol) was oxidized with 4 g of MnO_2 to give a white solid (0.36 g, 86%). M.p. 109°C. ^1H NMR δ: 3.58 (s, 3H, $H(OCH_3)$); 7.0 (m, 2H, $H_5 + H_4$); 7.56 (d, 1H, H_3); 7.96 (d, 1H, H_6); 8.48 (s, 1H, H pyra). IR (cm^{-1}): $\nu(CO)$ = 1660. Analysis. Found: C, 50.6; H, 2.6; N, 9.8. $C_{12}H_8Cl_2N_2O_2$ (M = 283) calc.: C, 50.91; H, 2.84; N, 9.89%.

(2,6-Dichloro-3-pyrazinyl)-2',4'-dichlorophenyl methanone (23). Compound **16** (0.32 g, 1 mmol) was oxidized with 4 g of MnO_2 is give a pale yellow solid (0.27 g, 84%). M.p. 112°C. ^1H NMR δ: 7.43 (s, 2H, H phenyl); 7.62 (s, 1H, H phenyl); 8.50 (s, 1H, H pyra). IR (cm^{-1}): $\nu(CO)$ = 1680. Analysis. Found: C, 41.1; H, 1.2; N, 8.4. $C_{11}H_4Cl_4N_2O$ (M = 322) calc.: C, 41.03; H, 1.25; N, 8.70.

(2,6-Dimethoxy-3-pyrazinyl)-2'-methoxyphenyl methanone (24). Compound **18** (110 mg, 0.4 mmol) was oxidized with 1 g of MnO_2 to give a white solid (84.5 mg, 77%). M.p. 103°C. ^1H NMR δ: 3.63 (s, 3H, $H(OCH_3)$); 4.03 (s, 6H, $H(OCH_3)$); 6.96 (m, 2H, H phenyl); 7.45 (m, 2H, H phenyl); 7.75 (s, 1H, H pyra). IR (cm^{-1}): $\nu(CO)$ = 1660. Analysis. Found: C, 61.5; H, 4.8; N, 10.2. $C_{14}H_{14}N_2O_4$ (M = 274.3) calc.: C, 61.31; H, 5.14; N, 10.21%.

(2,6-Dimethoxy-3-pyrazinyl)phenylmethanone (25). Metalation of 2,6-dichloropyrazine **1** (0.21 g, 1.5 mmol) was carried out in the usual way. The electrophile used was *N,N*-dimethylbenzamide (0.5 g, 3.3 mmol). After chromatography on silica gel with CH_2Cl_2 as eluent a brown oil was isolated, and crystallised slowly (0.27 g, 75%). M.p. 64°C. ^1H NMR δ: 4.03 (s, 6H, H OCH_3); 7.53 (m, 3H, H phenyl); 7.86 (m, 3H, 2H phenyl + 1H pyra). IR (cm^{-1}): $\nu(CO)$ = 1670. Analysis. Found: C, 63.9; H, 5.0; N, 11.4. $C_{13}H_{12}N_2O_3$ (M = 244.2) calc.: C, 63.93; H, 4.95; N, 11.47%.

2-Benzoyl-5-chloro 3-dimethylaminopyrazine (26) and 2,6-dibenzoyl-3,5-bis-dimethylaminopyrazine (27). The usual metalation of 2,6-dichloropyrazine **1** (0.3 g, 2 mmol) was followed by treatment with *N,N*-dimethylbenzamide (0.42 g, 2.8 mmol) for 12 h. Elution with a 7/3 mixture of CH_2Cl_2/hexane afforded product **21**, then product **26** as a pale yellow solid (0.29 g, 55%). M.p. 145°C. ^1H NMR δ: 3.03 (s, 6H, H $N(CH_3)_2$); 7.50 (m, 3H, H phenyl); 7.77 (s, 1H, H pyra); 8.0 (m, 2H, H phenyl). IR (cm^{-1}): $\nu(CO)$ = 1640. Analysis. Found: C, 59.3; H, 4.5; N, 15.7. $C_{13}H_{12}ClN_3O$ (M = 261.7) calc.: C, 59.66; H, 4.62; N, 16.05%. Further elution with CH_2Cl_2 gave product **27** as an orange yellow solid (0.1 g, 13%). M.p. 126°C. ^1H NMR δ: 3.15 (s, 6H, H $N(CH_3)_2$); 7.3–7.9 (m, 10H, H phenyl). IR (cm^{-1}): $\nu(CO)$ = 1650. Analysis. Found: C, 70.2; H, 5.9; N, 15.3. $C_{22}H_{22}N_4O_2$ (M = 374.4) calc.: C, 70.57; H, 5.92; N, 14.96%.

2,6-Dimethoxy-3-iodopyrazine (28) and 3,5-diiodo-2,6-dimethoxypyrazine (29). The usual metalation of 2,6-dimethoxypyrazine **10** (0.36 g, 2.5 mmol) was followed by reaction with iodine (1.43 g, 5.5 mmol). After chromatography on silica gel with CH_2Cl_2 as eluent two products, **28** and **29**, were isolated. **28**: white solid (0.3 g,

46%). M.p. 114°C. ^{1}H NMR δ: 4.0 (s, 6H, H(OCH_3)); 7.72 (s, 1H, H pyra). Analysis. Found: C, 27.0; H, 2.5; N, 10.3. $C_6H_7IN_2O_2$ (M = 266) calc.: C, 27.09; H, 2.65; N, 10.53%. **29**: white solid (0.53 g, 54%). M.p. 194°C. ^{1}H NMR δ: 4.02 (s, 6H, H(OCH_3)). Analysis. Found: C, 18.4; H, 1.2; N, 7.0. $C_6H_6I_2N_2O_2$ (M = 392) calc.: C, 18.39; H, 1.54; N, 7.15%.

(d) Coupling reactions

Triethylamine (10 ml) was placed in a 50 ml flask equipped with magnetic stirring and flushed with argon. The solution was degassed for 30 min with argon. Copper iodide (10 min stirring), then phenylacetylene (10 min stirring), then the catalyst $PdCl_2(PPh_3)_2$ were added. The mixture was stirred for 30 min and the iodopyrazine was then introduced. The reaction was monitored by TLC. After completion of the reaction, the triethylamine iodide was filtered off and washed with ether (2 × 25 ml). The filtrate was dried over $MgSO_4$ and evaporated. The crude product was purified by chromatography on silica gel with a 7/3 hexane/CH_2Cl_2 mixture as eluent for product **30** and a 7/3 CH_2Cl_2/hexane mixture as eluent for product **31**. The latter was then sublimed under vacuum.

2,6-Dichloro-3-phenylethynylpyrazine (30). 2,6-Dichloro-3-iodopyrazine **8** (0.1276 g, 0.46 mmol), copper iodide (1.8 mg, $9.5 \cdot 10^{-6}$ mol), catalyst $PdCl_2(PPh_3)_2$ (5.2 mg, $7.5 \cdot 10^{-6}$ mol), and phenylacetylene (0.07 ml, 0.6 mmol) were used. The reaction time was 1 h. Product **30** was obtained as a white solid (99.7 mg, 87%). M.p. 121°C. ^{1}H NMR δ: 7.5 (m, 5H, H phenyl); 8.5 (s, 1H, H pyra). Analysis. Found: C, 57.9; H, 2.3; N, 11.1. $C_{12}H_6Cl_2N_2$ (M = 249) calc.: C, 57.86; H, 2.42; N, 11.24%.

2,6-Dimethoxy-3-phenylethynylpyrazine (31). 2,6-Dimethoxy 3-iodopyrazine **28** (0.133 g, 0.5 mmol), copper iodide (31 mg, $16 \cdot 10^{-6}$ mol), catalyst $PdCl_2$ $(PPh_3)_2$ (7.8 mg, $10 \cdot 10^{-6}$ mol), and phenylacetylene (0.07 ml, 0.6 mmol) were used. The reaction time was 2 h. Product **31** was obtained as a pale yellow solid (96 mg, 80%). M.p.: 144°C. ^{1}H NMR δ: 4.0 (d, 6H, H(OCH_3)); 7.5 (m, 5H, H phenyl); 7.85 (s, 1H, H pyra). Analysis. Found: C, 69.9; H, 5.0; N, 11.5. $C_{14}H_{12}N_2O_2$ (M = 240.3) calc.: C, 70.00; H, 5.03; N, 11.66%.

*2-Chloro-5-oxo(5*H*)benzopyranno[2,3-*b*]pyrazine (32).* Pyridinium chloride (10 ml) was first boiled (210°C) to remove any pyridine and water. Ketone **22** (0.090 g, 0.32 mmol) was added to the hot liquid and the mixture boiled for 15 min. The solution was poured on to ice (100 mg) and the mixture extracted with $CHCl_3$ (3 × 20 ml). After drying over $MgSO_4$ and evaporation of the solution the crude product was purified by chromatography on silica gel with CH_2Cl_2 as eluent. A greyish solid was obtained (48 mg, 65%). M.p.: 251°C (dec.). ^{1}H NMR δ: 7.68 (m, 3H, HPh); 8.41 (s, 1H, HPh); 8.82 (s, 1H, H pyra). IR (cm^{-1}): ν(CO) = 1685. Analysis. Found: C, 56.8; H, 2.4; N, 11.8. $C_{11}H_5ClN_2O_2$ (M = 232.6) calc.: C, 56.80; H, 2.16; N, 12.04%.

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