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Regio- and Chemoselective Multiple Functionalization of Chloropyrazine Derivatives. Application to the Synthesis of Coelenterazine

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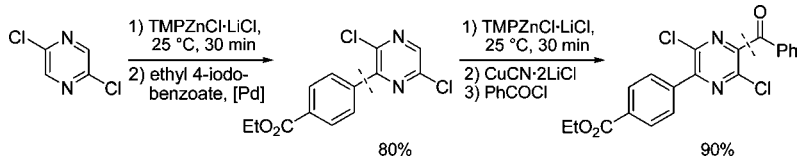
ABSTRACT



Successive regio- and chemoselective metalations of chloropyrazines using TMPMgCl·LiCl and TMPZnCl·LiCl furnish, after trapping with electrophiles, highly functionalized pyrazines in high yields. Application to a synthesis of coelenterazine, a bioluminescent natural product in jellyfish *Aequorea victoria*, in nine steps (9% overall yield) is reported.

Pyrazines are important biologically active metabolites. They are widely distributed in flavorings, formed either thermally like alkylpyrazines present in coffee, meat, and potatoes or biosynthetically like 2-alkyl-3-methoxy-pyrazines present in wines such as Cabernet-Sauvignon. Some pyrazine natural products such as coelenterazine (**1**), a natural occurring bioluminescent imidazopyrazine of marine origin isolated from the jellyfish *Aequorea victoria*, bear a trisubstituted pyrazine unit. Coelenterazine is used in new optical technologies for studying the complexity, diversity, and in vivo behavior of cancers (Figure 1).[1] The direct functionalization of these heterocycles by lithiation is difficult due to the electrophilic character of the ring, which readily undergoes addition of various organometallics.[2] The electrophilicity of these heterocycles requires low temperatures for their metalation.[3]

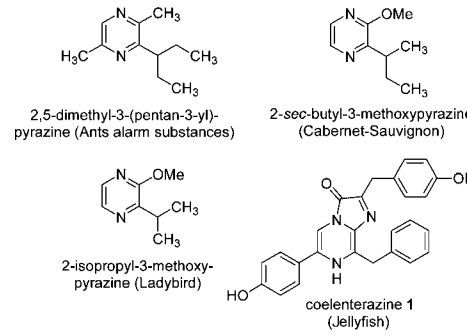


Figure 1. Natural products containing a pyrazine scaffold.

Recently, we and others have reported a range of new powerful bases.[4−6] Thus, TMPMgCl·LiCl[5] (**2a**; TMP = 2,2,6,6-tetramethylpiperidyl) allows the direct magnesiation

(1) (a) Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V. *Comprehensive Heterocyclic Chemistry II*; Pergamon: Oxford, 1996. (b) Gribble, G.; Joule, J. *Progress in Heterocyclic Chemistry*, *18*; Elsevier: Oxford, 2007. (c) Weissleder, R.; Pittet, M. J. *Nature* **2008**, *452*, 580. (d) Vance, E. *Nature* **2008**, *455*, 726.

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(3) (a) Zhang, C. Y.; Tour, J. M. *J. Am. Chem. Soc.* **1999**, *121*, 8783. (b) Liu, W.; Wise, D. S.; Townsend, L. B. *J. Org. Chem.* **2001**, *66*, 4783. (c) Buron, F.; Plé, N.; Turck, A.; Quéguiner, G. *J. Org. Chem.* **2004**, *70*, 2616. (d) Chevallier, F.; Mongin, F. *Chem. Soc. Rev.* **2008**, *37*, 595.

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of a number of arenes and heteroarenes even bearing esters or ketones. TMPZnCl·LiCl[6] (**2b**) permits a direct zincation of much more sensitive aromatics and heteroaromatics and tolerates aldehydes and nitro groups. Herein, we report a procedure allowing the *selective functionalization of all positions* of the pyrazine ring starting from simple compounds such as dichloropyrazines by performing successive metalations using TMPMgCl·LiCl (**2a**) or TMPZnCl·LiCl (**2b**).

Thus, the treatment of 2,3-dichloropyrazine (**3**) with TMPMgCl·LiCl (**2a**; 1.1 equiv, 25 °C, 15 min) leads to the 5-magnesiated pyrazine (**4**), which is trapped by electrophiles such as $MeSO_2SMe$ and 3-bromocyclohexene (after transmetalation with $ZnCl_2$ and addition of a catalytic amount of CuCN·2LiCl), leading to the expected pyrazines of type **5a** and **5b** in 67% and 72% yield (Scheme 1 and entries 1 and 2 of Table 1). The formation of a new carbon−carbon bond is readily performed by a Negishi cross-coupling[7] or a Sonogashira reaction[8] of in situ generated 2,3-dichloro-5-iodopyrazine providing the 5-substituted heterocycles **5c** and **5d** in 78% and 77% yield (entries 3 and 4).

A further magnesiation was achieved at the last position by the addition of TMPMgCl·LiCl (**2a**; 1.1 equiv). Thus, 2,3-dichloro-5-(methylthio)pyrazine[9] **5a** is converted within 30

Scheme 1. Magnesiation of 2,3-Dichloropyrazine (**3**) at Positions 5 and 6 Using TMPMgCl·LiCl (**2a**; 1.1 equiv) and Trapping with Electrophiles

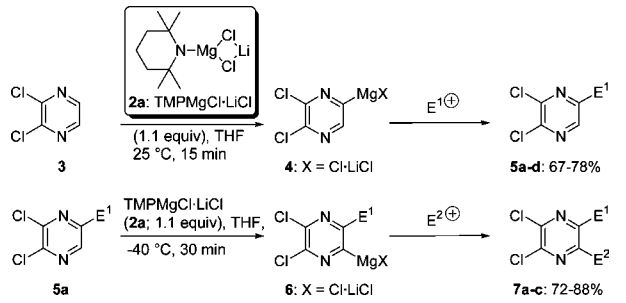
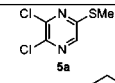
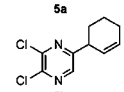
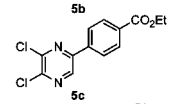
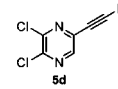
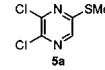
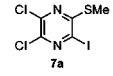
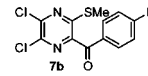
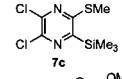
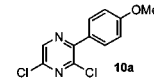
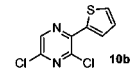
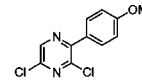
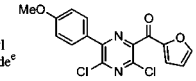
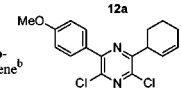
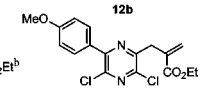
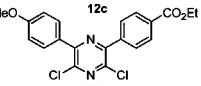
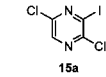
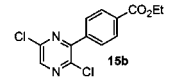
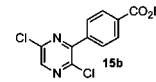
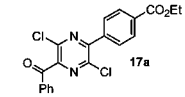
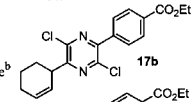
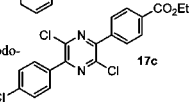


Table 1. Products Obtained by Regio- and Chemoselective Metalation of Chloropyrazines with TMPMgCl·LiCl (**2a**) or TMPZnCl·LiCl (**2b**) and Quenching with Electrophiles

entry	substrate	electrophile	product	yield, %[a]
1	 **3**	$MeSO_2SMe$	 **5a**	67
2	**3**	3-bromo-cyclohexene[b]	 **5b**	72
3	**3**	ethyl 4-iodo benzoate[c]	 **5c**	78
4	**3**	I_2 then phenylacetylene[d]	 **5d**	77
5	 **5a**	I_2	 **7a**	80
6	**5a**	4-fluorobenzoyl chloride[e]	 **7b**	72
7	**5a**	Me_3SiCN	 **7c**	88
8	 **8**	4-iodoanisole[c]	 **10a**	86
9	**8**	2-iodothiophene[c]	 **10b**	83
10	 **10a**	furoyl chloride[e]	 **12a**	84
11	**10a**	3-bromo-cyclohexene[b]	 **12b**	93
12	**10a**		 **12c**	74
13	**10a**	ethyl 4-iodo benzoate[c]	 **12d**	94
14	 **13**	I_2	 **15a**	76
15	**13**	ethyl 4-iodo benzoate[c]	 **15b**	80
16	 **15b**	PhCOCl[e]	 **17a**	90
17	**15b**	3-bromo-cyclohexene[b]	 **17b**	85
18	**15b**	1-chloro-4-iodo-benzene[c]	 **17c**	78

[a] Isolated, analytically pure product. [b] Catalyzed by 5 mol % of CuCN·2LiCl. [c] Obtained by Pd-catalyzed cross-coupling using $Pd(dba)_2$ (3 mol %) and $(o\text{-furyl})_3P$ (6 mol %). [d] Obtained by Pd-catalyzed cross-coupling using $Pd(dba)_2$ (3 mol %), $(o\text{-furyl})_3P$ (6 mol %), CuI (4 mol %), and NEt_3. [e] Transmetalation performed with 1.1 equiv of CuCN·2LiCl.

(4) For an excellent review, see: (a) Mulvey, R. E.; Mongin, F.; Uchiyama, M.; Kondo, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3802. (b) L'Helgoual'ch, J.-M.; Bentabed-Ababsa, G.; Chevallier, F.; Yonehara, M.; Uchiyama, M.; Derdour, A.; Mongin, F. *Chem. Commun.* **2008**, 5375. (c) Seggio, A.; Chevallier, F.; Vaultier, M.; Mongin, F. *J. Org. Chem.* **2007**, *72*, 6602.

(5) (a) Krasovskiy, A.; Krasovskaya, V.; Knochel, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 2958. (b) Lin, W.; Baron, O.; Knochel, P. *Org. Lett.* **2006**, *8*, 5673. (c) Mosrin, M.; Knochel, P. *Org. Lett.* **2008**, *10*, 2497. (d) Mosrin, M.; Knochel, P. *Chem.—Eur. J.* **2009**, *15*, 1468. (e) Piller, F.; Knochel, P. *Org. Lett.* **2009**, *11*, 445. (f) Clososki, G. C.; Rohbogner, C. J.; Knochel, P. *Angew. Chem., Int. Ed.* **2007**, *46*, 7681. (g) Rohbogner, C. J.; Clososki, G. C.; Knochel, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 1503. (h) Garcia-Alvarez, P.; Graham, D. V.; Hevia, E.; Kennedy, A. R.; Klett, J.; Mulvey, R. E.; O'Hara, C. T.; Weatherstone, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 8079.

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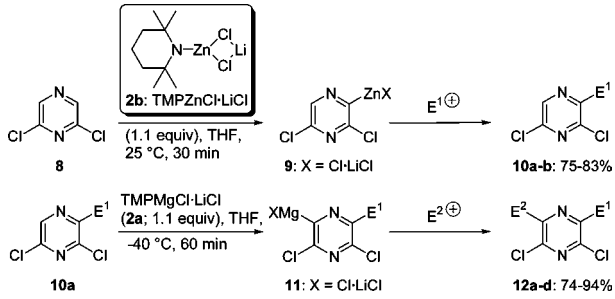
(7) (a) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (b) Negishi, E.; Kobayashi, M. *J. Org. Chem.* **1980**, *45*, 5223. (c) Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.

(8) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *50*, 4467. (b) Sonogashira, K. *Comprehensive Organic Synthesis*; Pergamon Press: New York, 1991; Vol. 3.

min at −40 °C to the 6-magnesiated species **6** which is iodinated by reaction with I_2 leading to the iodopyrazine **7a** in 80% yield (entry 5). Reaction with 4-fluorobenzoyl chloride (after transmetalation with CuCN·2LiCl)[10] furnishes the ketopyrazine **7b** in 72% yield (entry 6). Trapping with TMSCN leads to the fully substituted pyrazine **7c** in 88% yield (entry 7).

Other dichloropyrazines are metalated as well under mild conditions. Thus, 2,6-dichloropyrazine (**8**) is zincated quantitatively with TMPZnCl·LiCl (**2b**; 1.1 equiv, 25 °C, 30 min) giving the zinc species **9**, which undergoes a Negishi cross-coupling[7] providing the 3-substituted heterocycles **10a** and **10b** in 86% and 83% (Scheme 2 and entries 8 and 9).

Scheme 2. Metalation of 2,6-Dichloropyrazine (**8**) at Positions 3 and 5 Using TMPMgCl·LiCl (**2a**; 1.1 equiv) and TMPZnCl·LiCl (**2b**; 1.1 equiv) and Trapping with Electrophiles

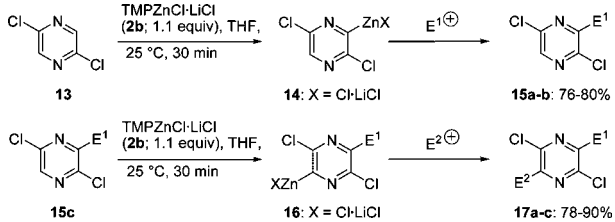


Subsequent metalation of the arylpyrazine **10a** using TMPMgCl·LiCl (**2a**; 1.1 equiv, −40 °C, 60 min) provides the magnesium reagent **11**, which affords after transmetalation with CuCN·2LiCl,[10] and trapping with furoyl chloride, the ketopyrazine **12a** in 84% yield (entry 10).

Quenching with 3-bromocyclohexene or ethyl 2-(bromomethyl)acrylate[11] gives fully substituted pyrazines **12b** and **12c** in 93% and 74% yield, respectively (entries 11 and 12). Negishi cross-coupling[7] using ethyl 4-iodobenzoate provides the substituted heterocycle **12d** in 94% (entry 13).

Similarly, 2,5-dichloropyrazine[12] (**13**) undergoes smooth zincation using TMPZnCl·LiCl (**2b**; 1.1 equiv, 25 °C, 30 min), affording the zinc reagent **14**. An iodolysis leads to the 2,5-dichloro-3-iodopyrazine **15a** in 76% (Scheme 3 and

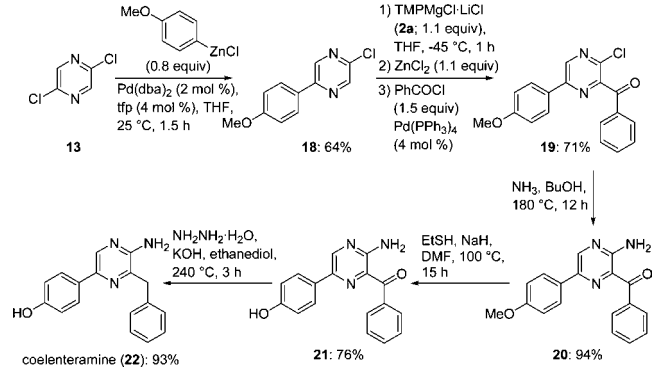
Scheme 3. Zincation of 2,5-Dichloropyrazine (**13**) at Positions 3 and 6 Using TMPZnCl·LiCl (**2b**; 1.1 equiv) and Trapping with Electrophiles



entry 14). Negishi cross-coupling[7] with ethyl 4-iodobenzoate provides the substituted heterocycle **15b** in 80% yield. Subsequent metalation of the ester derivative **15b** using TMPZnCl·LiCl (**2b**; 1.1 equiv, 25 °C, 30 min) gives the zinc species **16**, which was benzoylated (after transmetalation with CuCN·2LiCl)[10] giving the ketopyrazine **17a** in 90% yield. An allylation with 3-bromocyclohexene (in the presence of CuCN·2LiCl (5 mol %)) or a Negishi[7] cross-coupling is furnishing the fully substituted pyrazines **17b** and **17c** in 85% and 78% yield (entries 17 and 18).

As an application, we have carried out the total synthesis of coelenterazine (**1**)[1a,13] in nine steps and 9% overall yield. Thus, a Negishi cross-coupling[7] using 2,5-dichloropyrazine (**13**) as an electrophile provides the arylpyrazine **18** in 64% yield. A magnesiation using TMPMgCl·LiCl (**2a**; 1.1 equiv, −45 °C, 1 h) gives after transmetalation with $ZnCl_2$ and acylation[14] with benzoyl chloride the ketopyrazine **19** in 71% yield. The chlorine substitution is then achieved using NH_3 in BuOH[15] furnishing the aminopyrazine **20** in 94% yield. Cleavage of the methyl ether with sodium thioethanolate in DMF[16] yields the corresponding alcohol **21** in 76% yield. The reduction of the ketone is finally carried out using a Wolff−Kishner[17] reduction affording coelenteramine (**22**) in 93% yield (Scheme 4).

Scheme 4. Synthesis of Coelenteramine (**22**)



The preparation of the diazine ring in coelenterazine (**1**) requires a condensation of coelenteramine (**22**) with the ketoaldehyde **26** (Scheme 5). The addition of 4-(chloromethyl)phenyl acetate (**23**) to commercial Zn dust (2.5 equiv) in the presence of LiCl (2.5 equiv) at 25 °C is complete within 24 h.[18] Trapping with bromoacetyl chloride after transmetalation with CuCN·2LiCl[10] furnishes the acylated derivative **24** in 61% yield. Addition of silver nitrate at 25 °C gives after 18 h the nitrate ester **25** in 98% yield.[19] Subsequent reaction of **25** with NaOAc·$3H_2O$ in DMSO at

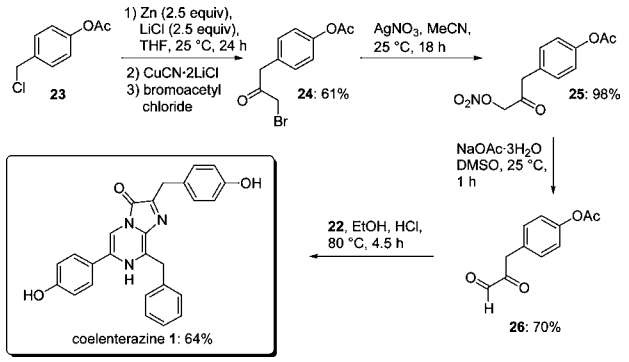
(9) The thiomethyl group can serve as a leaving group in cross-coupling reactions: (a) Liebeskind, L. S.; Srogl, J. *Org. Lett.* **2002**, *4*, 979. (b) Prokopcová, H.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2009**, *48*, 2276.

(10) Knochel, P.; Yeh, M. C. P.; Berk, S. C.; Talbert, J. *J. Org. Chem.* **1988**, *53*, 2390.

(11) Villiéras, J.; Rambaud, M. *Org. Synth.* **1988**, *66*, 220.

(12) Preparation of 2,5-dichloropyrazine, see: Klein, B.; Hetman, N. E.; O'Donnell, M. E. *J. Org. Chem.* **1963**, *28*, 1682.

Scheme 5. Synthesis of 3-(4-Methoxyphenyl)-2-oxopropanal (**26**) and Coelenterazine (**1**)



25 °C for 1 h affords the corresponding acetoxy α-keto aldehyde **26** in 70% yield.[19] Finally, the condensation of the 1,2-dicarbonyl derivative **26** with coelenteramine (**22**) provides the bioluminescent natural product coelenterazine (**1**) in 64% yield.[19]

In summary, we have reported the multiple functionalization[20] of the pyrazine scaffold using TMPMgCl·LiCl (**2a**) and TMPZnCl·LiCl (**2b**) as effective bases and reported a nine-step synthesis of the natural product coelenterazine (**1**). Further extensions and applications of this method are currently underway in our laboratories.

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Supporting Information Available: Experimental procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Procedure for the synthesis of 3,5-dichloro-2-(4-methoxyphenyl)pyrazine (**10a**): A dry and argon flushed 50 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with 2,6-dichloropyrazine (**8**) (1,49 g, 10.0 mmol) dissolved in THF (10 mL). A solution of TMPZnCl·LiCl (**2b**) (1.4 M in THF, 7.9 mL, 11.1 mmol) at 25 °C was then added, and the reaction mixture was stirred at this temperature for 30 min. $Pd(dba)_2$ (113 mg, 2 mol %) and P(*o*-furyl)$_3$ (93 mg, 4 mol %) dissolved in THF (5 mL) and mixed with 4-iodoanisole (3.04 g, 13 mmol, 1.3 equiv) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred at 65 °C for 1 h, quenched with a sat. aq. NH_4Cl solution (100 mL), extracted with diethyl ether (3 × 100 mL), and dried over anhydrous Na_2SO_4. After filtration, the solvent was evaporated in vacuo. Purification by flash chromatography (CH_2Cl_2/pentane 1:3) furnished the compound **10a** (2.18 g, 86% yield) as a colourless solid.