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A new synthesis of 2-(hetero)aryl-substituted pyrazines

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ABSTRACT

2-Chloropyrazine showed remarkable reactivity towards $AlCl_3$-mediated heteroarylation of arenes and heteroarenes providing direct access to a variety of 2-aryl and heteroaryl-substituted pyrazines, respectively, in good to excellent yields under mild reaction conditions.

The first $AlCl_3$-induced C–C bond-forming reaction between 2-chloropyrazine and (hetero)arenes is described here, such reactions being only known using transition metal catalysts (Fig. 1).[1a]

Pyrazine derivatives have attracted wide pharmaceutical interests because of their potential uses in the treatment of psychiatric disorders, neurological diseases (e.g., stress, anxiety and depression), and cardiovascular disorders. They are reported to modulate the activity of CRF1 (corticotropin-releasing factor 1) receptors.[1b,1c] Besides, they are also versatile building blocks in the synthesis of VCAM-1 (vascular cell adhesion molecule-1) inhibitors,[2] pyrazine alkaloids (antineoplasmic activity),[3] and imidazopyrazin coelenterazine (bioluminescent).[4] Because of their medicinal and synthetic value, a number of methods have been developed for the synthesis of pyrazine derivatives, especially 2-(hetero)aryl pyrazines. These include the cross-coupling of 2-chloropyrazine with (a) ArMgX in the presence of $(PPh_3)_2PdCl_2/ZnCl_2$,[5] (b) $ArSnBu_3$ in the presence of $PdCl_2(PPh_3)_2/PPh_3$, (c) Ar_4Sn (generated in situ from ArMgX and $SnCl_4$) in the presence of $Pd(PPh_3)_4$,[6] (d) $ArBF_3K$ in the presence of $PdCl_2$(dppf), (e) ArZnCl in the presence of $PdCl_2(PPh_3)_2$[7], or (f) $ArB(OH)_3$ in the presence of $PdCl_2$(dppb)/Na_2CO_3.[8] 2-(Hetero)aryl pyrazines can also be prepared via the cross-coupling of vinyl triflate with 2-pyrazinylzincbromide in the presence of $Pd(PPh_3)_4$, coupling of 2-pyrazinylthioether with $ArSnBu_3$ in the presence of $Pd(PPh_3)_4$/Cu(I)-3-methylsalicylate, coupling of 2-pyrazinyl tributyltin with ArBr in the presence of $Pd(PPh_3)_4$. The utility of these methodologies, particularly the reaction under Suzuki conditions,[3] has been demonstrated in the synthesis of pyrazine alkaloids, for example, Botryllazines A–B that showed cytotoxicity against human tumor cells. While these methodologies involved mild conditions and displayed increased functional group tolerance, most of them, however, often required the use of expensive catalysts and reagents. Additionally, the required organo-metallic reagents are either not available commercially in many cases or their preparations often involve cumbersome procedures. Recently, we have reported a $AlCl_3$-induced heteroarylation of arenes and heteroarenes as an alternative, but less expensive strategy for the synthesis of various nitrogen-containing heterocyclic compounds.[9–13] A further exploration of

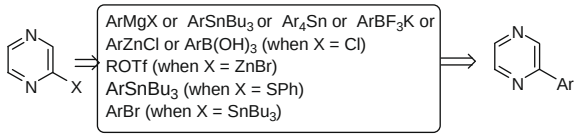
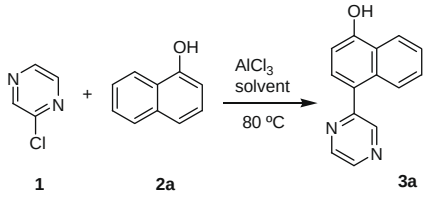


Figure 1. Pd-catalyzed C–C bond-forming reaction between 2-chloropyrazine and arenes.



Scheme 1. $AlCl_3$-Induced heteroarylation of 1-naphthol (**2a**) with **1**.

Table 1
Heteroarylation of **2a** with **1** under various conditions

Entry	Solvent	Time (h)	Yield[a] (%)
1	$ClCH_2CH_2Cl$	8	79
2	$CHCl_3$	14	70
3	CH_2Cl_2	24	66
4	CH_3CN	15	70
5	EtOAc	20	69
6	THF	32	20
7	Toluene	56	No reaction

[a] Yield of isolated products.

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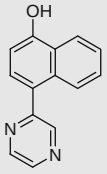
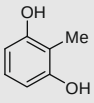
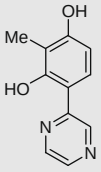
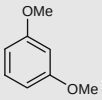
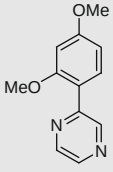
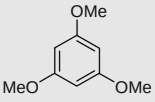
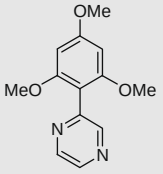
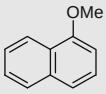
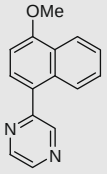
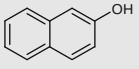
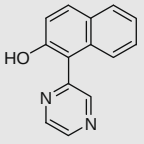
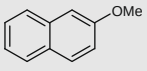
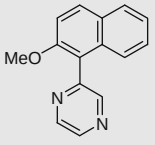
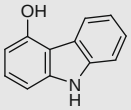
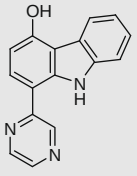
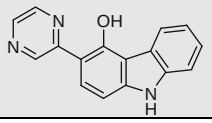
Table 2
Synthesis of 2-(hetero)aryl-substituted pyrazines (**3**)

Entry	Reactant (**2**)	Product (**3**)		Conditions	Yield[a] (%)
1	 **2a**		**3a**	80 °C, 8 h	79
2	 **2b**		**3b**	80 °C, 8 h	73
3	 **2c**		**3c**	80 °C, 12 h	69
4	 **2d**		**3d**	80 °C, 10 h	70
5	 **2e**		**3e**	80 °C, 14 h	76
6	 **2f**		**3f**	80 °C, 8 h	80
7	 **2g**		**3g**	80 °C, 15 h	76
8	 **2h**	 + 	**3h** **3ha**	80 °C, 10 h	53 35

[a] Yield of isolated products.

this strategy led us to develop a novel, inexpensive, and scalable method for the synthesis of 2-(hetero)aryl pyrazines.

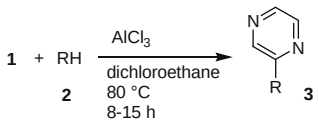
For our initial study, we chose commercially available 2-chloropyrazine (**1**) as a heteroaryl halide, and 1-naphthol (**2a**) as an arene component (Scheme 1) to examine the $AlCl_3$-induced heteroarylation reaction. The results are summarized in Table 1. Thus, when a mixture of **1** (1 equiv), **2a** (1 equiv), and $AlCl_3$ (1.2 equiv) in dichloroethane (5 ml) was stirred at 80 °C for 8 h, the desired 4-pyrazin-2-yl-naphthalen-1-ol (**3a**) was isolated in 79% yield (Table 1, entry 1). The compound **3a** was characterized by spectral data. To establish the optimum conditions, we then examined the effect of time and solvents on this heteroarylation process. A variety of solvents other than dichloroethane were examined (Table 1, entries 2–7). In spite of increasing and varying the reaction time from 14 to 56 h and maintaining the temperature at 80 °C, none of these solvents provided a better yield of **3a** than dichloroethane (70–20% vs 79%). The reaction did not proceed in toluene (Table 1, entry 7). Thus, dichloroethane was found to be the best suitable solvent for the heteroarylation of **2a** with 2-chloropyrazine.

Having established the optimum conditions for the $AlCl_3$-induced heteroarylation reaction of 2-chloropyrazine with **2a**, we then decided to examine the reactivity of 2-chloropyrazine with other arenes and heteroarenes. Accordingly, a number of arenes were reacted with 2-chloropyrazine (Scheme 2), and the results are summarized in Table 2. Arenes such as 2-methyl-benzene-1, 3-diol (**2b**), 1,3-dimethoxybenzene (**2c**), 1,3,5-trimethoxybenzene (**2d**), 1-methoxynaphthalene (**2e**), 2-naphthol (**2f**), and 2-methoxynaphthalene (**2g**) were employed successfully to afford the desired products **3b–g** (Table 2, entries 2–7) in good yields. Thus, in a typical procedure 1.0 equiv of 2-chloropyrazine was reacted with 1.0 equiv of arene (**2a–g**) in the presence of 1.2 equiv of anhydrous $AlCl_3$ using dichloroethane as solvent at 80 °C. The corresponding product 2-arylpyrazines (**3a–g**) was isolated in good yields after the usual work-up followed by purification using column chromatography.[14,15] The free phenolic hydroxyl group was well tolerated in the case of **2a, 2b**, **2f**, and **2h**, and the heteroarylation occurred at the ring carbon rather than oxygen (or nitrogen). The use of 4-hydroxycarbazole (**2h**) afforded a mixture of products, that is, **3h** and its regioisomer **3ha** in 53% and 35% yields, respectively (Table 2, entry 8).[16]

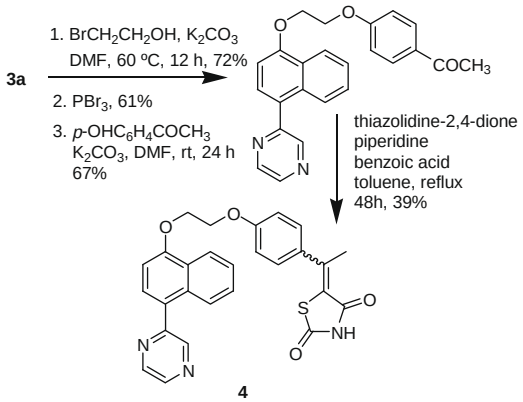
The presence of the free phenolic hydroxyl group in a number of products allowed us to use this as a handle for further chemical transformations. For example, compound **3a** was converted to a thiazolidinedione (TZD) derivative **4**, of potential pharmacological interest (Scheme 3).[17]

The heteroarylation reaction seems to proceed via the complexation of $AlCl_3$ with the nitrogen of –C(Cl)=N- moiety of **1**, thereby activating the chloro-group to facilitate a nucleophilic attack by arenes or heteroarenes (**2**) at the chlorine-bearing carbon atom (Fig. 2).[18] This nucleophilic attack is possibly favored by the electron-withdrawing effect of the second nitrogen of the pyrazine ring.

In conclusion, we have developed a novel, operationally simple and single-step method for the preparation of 2-(hetero)aryl pyrazines from readily available starting materials and reagents. The methodology does not require the use of expensive transition metal catalysts or organometallic reagents, and therefore has the potential to become useful alternative towards the direct synthesis of novel 2-(hetero)aryl pyrazines.



Scheme 2. $AlCl_3$-Induced heteroarylation of **2** with **1**.



Scheme 3. Synthesis of TZD derivative **4** from **3a**.

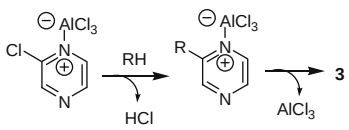


Figure 2. Proposed mechanism for $AlCl_3$-induced heteroarylation of **2** with **1**.

Acknowledgment

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.01.110.

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14. *Typical procedure for the synthesis of 2-(hetero)arylpyrazine* (**3**): A mixture of 2-chloropyrazine (1.0 equiv), arene/heteroarene (**2a–h**) (1.0 equiv), and

anhydrous $AlCl_3$ (1.2 equiv) in dichloroethane (5 mL) was stirred according to the conditions mentioned in Table 2. After completion of the reaction, the mixture was poured into ice-cold water (15 mL), stirred for 10 min, and then extracted with ethyl acetate (3 × 5 mL). The organic layers were collected, combined, washed with water (3 × 10 mL), dried over anhydrous Na_2SO_4, and concentrated under vacuum. The residue was purified by column chromatography to afford the expected products.

15. *Spectral data for selected compounds*: *Compound* **3a**: pale yellow solid; mp 188–190 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.57 (s, 1H, OH), 8.87 (s, 1H), 8.77 (s, 1H), 8.64 (d, J = 2.3 Hz, 1H), 8.27–8.24 (m, 1H), 8.14–8.11 (m, 1H), 7.57–7.50 (m, 3H), 7.01 (d, J = 7.8 Hz, 1H); ν_{max} (KBr, cm^{-1}): 1623, 1582, 1522, 1494, 1448; Mass (ESI method, i-butane): 223 (M$^+$+1, 100%); ^{13}C NMR (75 MHz, DMSO-d_6) 154.6, 154.5, 145.2, 143.7, 142.3, 131.7, 129.3, 127.0, 125.0, 124.8, 124.7 (2C), 122.4, 107.6; HPLC purity 98.41%. *Compound* **3b**: Pale yellow solid; mp 198–200 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 13.32 (s, 1H), 9.88 (s, 1H), 9.35 (s, 1H), 8.52 (m, 2H), 7.84 (d, J = 8.8 Hz, 1H), 6.48 (d, J = 8.8 Hz, 1H), 2.02 (s, 3H, CH_3); ν_{max} (KBr, cm^{-1}): 3427, 1613, 1518, 1468; Mass (ESI method, i-butane):203 (M$^+$+1, 100%); ^{13}C NMR (75 MHz, DMSO-d_6) 159.0, 158.8, 152.5, 141.7, 140.7, 139.6, 124.6, 111.2, 108.3, 107.1, 8.1; HPLC purity 99.29%. *Compound* **3d**: Off-white solid; mp 124–126 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.65 (d, J = 1.5 Hz, 1H), 8.48–8.46 (m, 2H), 6.34 (s, 2H), 3.84 (s, 3H, OCH_3), 3.67 (s, 6H, OCH_3); ν_{max} (KBr, cm^{-1}): 1610, 1587, 1471; Mass (ESI method, *i*-butane): 247 (M$^+$+1, 100%); ^{13}C NMR (75 MHz, DMSO-d_6) 161.7, 158.6 (2C), 150.3, 147.0, 144.0, 142.0, 108.0, 90.9 (2C), 55.7 (2C), 55.4; HPLC purity 99.99%.
16. While the corresponding isomeric products were not isolated from the reaction mixtures of **1** and **2a**–**g**, their formation cannot be ruled out completely as the yields of pure desired products, that is, **3a**–**g** were not very high.
17. Rao, Y. K.; Pal, M.; Sharma, V. M.; Venkateswarlu, A.; Pillaresetti, R. U.S. Patent Application US 2005/0119269 A1, June 2, 2005.
18. A possible alternative pathway for a phenol heteroarylation may be proposed which includes initial formation of an *O*-heteroaryl ether followed by its subsequent catalytic isomerization to the desired product. However, this pathway can be ruled out because of the fact that the intermediate ether was not isolated even in trace quantity from the reaction mixture of **1** and a phenol, for example, **2a** or **2b** or **2f**.