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Efficient synthesis of substituted 2-aminopyrazines: $FeCl_3$-promoted condensation of hydroxyiminoketones with aminoacetonitriles

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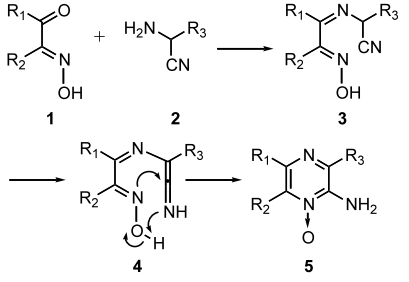
Abstract—$FeCl_3$-promoted condensation of hydroxyiminoketones with aminoacetonitriles followed by catalytic hydrogenation afforded the desired pyrazines in moderate–good yields. This protocol provides an efficient and practical synthesis of substituted 2-aminopyrazines.

Substituted pyrazines have gained increased attention in recent years due to their usefulness as important constituents either of biologically active compounds[1] or functional materials.[2] In particular, substituted 2-aminopyrazines are key synthetic intermediates to the luciferins and their analogues,[3] which have long been known as chemiluminescent and/or bioluminescent agents.[4,5] Irrespective of their importance, an efficient synthetic route to these key pyrazine intermediates has thus far not been fully developed. Of the several reported aminopyrazine preparation to date,[6] direct condensation of hydroxyiminoketones with aminoacetonitriles followed by reduction appears attractive; however, poor yields in the initial condensation step reduces the efficiency of this approach.[6,7] Stoichiometric $TiCl_4$ has been reported to accelerate the condensation with modest yield improvements.[8,9] These improvements, however, were still unsatisfactory for our preparative purposes and were highly dependent on the nature of the substituents on the product aminopyrazine.[6c] Furthermore, stoichiometric or excess use of $TiCl_4$ would not be practical for large-scale preparation due to its handling difficulty and environmentally-ill waste stream. In this article, we wish to report a novel, practical and economical synthesis of substituted 2-aminopyrazines by an $FeCl_3$-induced condensation of hydroxyiminoketones with aminoacetonitriles.

It has been postulated that Lewis acid such as $TiCl_4$ promotes not only formation of the Schiff base but also helps some of enolization of the resulting β-iminonitrile **3** to generate a reactive species such as aza-allene intermediate **4**. Cyclization of **4** should then occur relatively easily to afford the desired pyrazine *N*-oxide. This hypothesis can also be supported by the fact that the reaction of **1** with aminomalononitrile **2** (R_3 = CN) proceeds smoothly without assistance by Lewis acid (Scheme 1).[6c,d]

Therefore, development of a reagent, which can be more effective for accelerating both Schiff base formation and, in particular, enolization of iminonitrile **3** than $TiCl_4$, appears to be the key for successful condensation. We thus sought to find more effective conditions that would further accelerate both functions.

Recently Christoffers reported the $FeCl_3$-catalyzed Michael reactions of 1,3-dicarbonyl compounds with enones, presumably involving formation of stable 1,3-



Scheme 1.

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dionato iron chelate complexes which further activated the enones toward addition.[10] Interestingly and uniquely, in the presence of Fe(III) these complexes were instantly formed even under strongly Brønsted-acidic media without prior deprotonation. Thus, we envisioned that Fe(III) salts might promote not only formation but enolization of **3** to afford **4** effectively which would then cyclize to the desired pyrazine *N*-oxides **5**.

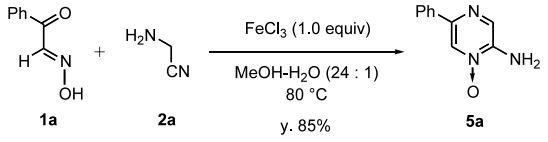
In fact, after neutralizing the aminoacetonitrile hydrochloride salt with NaOH, treatment of isonitrosoacetophenone **1a** with **2a** in MeOH–H_2O (24:1) at 80°C in the presence of anhydrous $FeCl_3$ (1 equiv.) afforded the *N*-oxide **5a**[6a] in 85% yield (Scheme 2). This condensation without $FeCl_3$ resulted in only 14% yield of **5a** according to the procedure of Sharp and Spring,[6a,7] and in 10% yield even $TiCl_4$ at 0°C. On the other hand, acidic conditions[6e,f] (TsOH, H_2SO_4 and HCl) gave miserable results.

Other alcohols and DMF were also acceptable as solvents, although aqueous MeOH afforded a homogeneous solution. Sodium carbonate and amine bases such as *N*-methylmorpholine and diisopropylethylamine were also tolerable for breaking the salt of aminoacetonitrile.

A variety of other metal chlorides were screened for promotion of this reaction sequence; however, $FeCl_3$ was proven to be the optimal promoter for this particular reaction.[11] $FeCl_2$ was much less effective than $FeCl_3$. Other Fe(III) salts such as $Fe(NO_3)_3$ and $Fe_2(SO_4)_3$ were also acceptable for this reaction.[12] Anhydrous $FeCl_3$ was compared with its hydrate in MeOH and they were not distinguishable.[13]

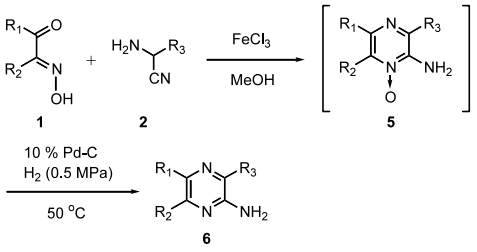
Table 1 provides results on the $FeCl_3$-induced condensation of α-ketoaldoximes with aminoacetonitriles followed by hydrogenation with 10% Pd–C in one flask under our typical conditions,[14] and also using Zn/aqueous NH_4Cl gave same result. Yields of pyrazines after hydrogenation are listed.[15] Reaction of isonitrosoacetophenone **1a** with unsubstituted aminoacetonitrile **2a** afforded the desired aminopyrazine in 80% yield. Condensation of **1a** with α-substituted aminoacetonitriles was also attempted. The reaction with 2-aminopropionitrile or 2-aminobutyronitrile **2b** or **2c** afforded the corresponding pyrazines in 63 and 67% yield, respectively (entries 2 and 3). It has also been reported that the 2-amino-3-methyl-5-phenylpyrazine **6b** was obtained in only 40% yield even when $TiCl_4$ was used.[8,16] The reaction with 2-phenylglycinonitrile **2d**, which is more difficult to control,[7] also worked relatively smoothly to afford the corresponding pyrazine **6d**[17] in ca. 60% yield (entry 4). For the benzyl substituted aminoacetonitrile, 72% of **6e**[18] was obtained by the present method, while ca. 60% of 2-amino-3-benzyl-5-(*p*-methoxy-phenyl)-6-methylpyrazine was produced with known $TiCl_4$ sequence (entry 5).[19] In addition to entry 1, condensations with unsubstituted aminoacetonitrile **2a**, which are known to be difficult due to its instability,[6a,16] were also evaluated. Two different oximes **1b** and **1c** were converted to the corresponding pyrazines **6f** and **6g**[20] in 60 and 55% yield, respectively (entries 6 and 7).

It was found that when the reaction was stirred with excess aminoacetonitrile (>5 equiv.) at higher temperature (reflux temp.) overnight, the product was the corresponding pyrazine and not the *N*-oxide (Table 2).



Scheme 2.

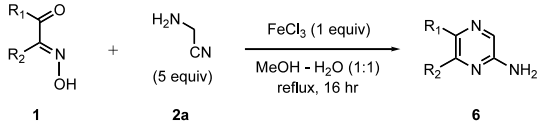
Table 1. $FeCl_3$-induced condensation of α-ketoaldoximes with aminoacetonitriles



Entry	Oximes **1**			Aminonitriles **2**		Yield[a] of **6** (%)	
	R_1	R_2		R_3			
1	Ph	H	**1a**	H	**2a**	80	**6a**
2			**1a**	Me	**2b**	63	**6b**
3			**1a**	Et	**2c**	67	**6c**
4			**1a**	Ph	**2d**	58	**6d**
5			**1a**	Bn	**2e**	72	**6e**
6	Ph	Me	**1b**	H	**2a**	60	**6f**
7	Me	H	**1c**	H	**2a**	55	**6g**

[a] Yields refer to the average isolated yield of two runs.

Table 2.



Entry	Oximes **1**			Yield[a] of **6** (%)	
	R_1	R_2			
1	Ph	H	**1a**	72	**6a**
2	Ph	Me	**1b**	68	**6f**
3	Me	H	**1c**	65	**6g**

[a] Yields refer to the average isolated yield of two runs.

Some results were slightly better than previous results of stepwise reaction. In contrast, treatment with 2 equiv. of aminoacetonitrile at 50°C gave only the *N*-oxide. These results indicate that direct reduction of the *N*-oxide intermediate, to spontaneously produce the desired pyrazine, can also be promoted under these reaction conditions.

Furthermore, when 0.1 equiv. of $FeCl_3$ was used, a prolonged reaction period gave the *N*-oxide **5a** in ca. 60% yield, indicating that $FeCl_3$ can work as a catalyst. However, the reaction did not lead to completion even after stirring for 2 days. The reason is still unclear but might be due to a lower valent iron generated from reduction of $FeCl_3$ with aminoacetonitrile.[21]

In conclusion, $FeCl_3$ promotes condensation of hydroxyiminoketones with aminoacetonitriles to give the desired pyrazine *N*-oxides, which are readily reduced to afford the desired pyrazines in reasonable yields. This protocol provides efficient and practical access to a variety of 3-mono or 3,5-disubstituted 2-aminopyrazines.

Acknowledgements

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9. Very recently, Kakoi reported that the condensation was dramatically improved with 5 equiv. of $TiCl_4$ in pyridine at −5°C after our study was completed, see: Kakoi, H. *Chem. Pharm. Bull.* **2002**, *50*, 301–302. Our study would be conceptually distinguishable from the work with $TiCl_4$. Results given with $FeCl_3$ are also equal or superior to those with $TiCl_4$. From a process chemistry perspective, our condition is more practical due to ease of handling and an environmentally friendly waste stream.
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11. Reactions with LiCl, $MgCl_2$, $AlCl_3$, $TiCl_4$, $NiCl_2$, CuCl, $CuCl_2$, $ZnCl_2$, $RuCl_3$, $SnCl_2$ and $CeCl_3$ were tested: results were not distinguishable with the one from the reaction without any additive.
12. Fe(III) citrate was less effective.
13. Powdered anhydrous $FeCl_3$ was used with water since the hydrate was a stony solid and difficult to handle.
14. **Typical procedure**. **The preparation of 2-amino-5-phenylpyrazine (6a)**. All experiments were operated under a nitrogen atmosphere. 12N aqueous NaOH (123 mL, 1.48 mol) was added to a mixture of aminoacetonitrile hydrochloride (124 g, 1.34 mol) in methanol (4 L), and then isonitrosoacetophenone (100 g, 0.67 mol) and ferric chloride (109 g, 0.67 mol) were added to the resulting solution below 20°C. The resulting mixture was stirred at 50°C for 2 h followed by stirring at reflux for 4 h. The reaction mixture was then cooled to ambient temperature and treated with palladium on carbon (10 w/w%) under a pressure of hydrogen (5.0 atm) at 50°C for 18 h. After checking consumption of *N*-oxide by HPLC, the reaction mixture was basified with 12N aqueous NaOH (pH ~ 10) and filtered through a plug of Celite. The filtrate was concentrated to remove MeOH under reduced pressure. The aqueous layer was extracted with EtOAc twice. The combined organic layers were washed with 7% aqueous NaCl and dried (Na_2SO_4). The filtered EtOAc solution was concentrated under reduced pressure to 1 L, pretreated with an activated carbon (Darco G-60) for 1 h at ambient temperature and filtered through Celite. The filter cake (activated carbon) was washed with EtOAc. The filtrate was concentrated to ca. 100 mL under reduced pressure which initiated crystallization of the product, and then the residue was stirred at ambient

temperature. To the resulting slurry was added dropwise *n*-heptane, and the resulting mixture was agitated for 1 h at ambient temperature. The solid product was collected by filtration, washed with *n*-heptane/EtOAc = 5:1 (200 mL) and dried in vacuo under nitrogen sweep at 30°C overnight to afford **6a** (77 g, 67%) as a yellow solid. HPLC analysis showed that **6a** in the mother liquor was obtained in 13% yield (15 g).

Compound **5a**: ^{1}H NMR (500 MHz, DMSO, ppm) δ 8.79 (s, 1H), 8.22 (s, 1H), 7.96 (d, J = 7.5 Hz, 2H), 7.44 (dd, J = 7.3, 7.5 Hz, 2H), 7.38 (dd, J = 7.3 Hz, 1H), 7.11 (s, 2H).

Compound **6a**: ^{1}H NMR (500 MHz, DMSO, ppm) δ 8.53 (s, 1H), 8.01 (s, 1H), 7.94 (d, J = 7.6 Hz, 1H), 7.93 (d, J = 7.6 Hz, 1H), 7.43 (dd, J = 7.4, 7.6 Hz, 2H), 7.32 (dd, J = 7.4 Hz, 1H), 6.59 (s, 1H); ^{13}C NMR (125 MHz, DMSO, ppm) δ 125.0, 127.7, 129.0, 131.8, 137.5, 139.2, 139.4, 155.3.

Compound **6b**: ^{1}H NMR (500 MHz, DMSO, ppm) δ 8.40 (s, 1H), 7.94 (d, J = 7.4, 8.3 Hz, 2H), 7.43 (d, J = 7.6 Hz, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 7.2 Hz, 1H), 6.35 (s, 2H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, DMSO, ppm) δ 21.1, 125.1, 127.6, 129.0, 136.8, 137.6, 138.8, 138.9, 153.6, 176.5.

Compound **6c**: ^{1}H NMR (270 MHz, $CDCl_3$, ppm) δ 8.32 (s, 1H), 7.93 (d, J = 7.3, 8.6 Hz, 2H), 7.45 (d, J = 7.3 Hz, 1H), 7.42 (d, J = 7.6 Hz, 1H), 7.34 (dd, J = 6.9, 7.6 Hz, 1H), 4.61 (s, 2H), 2.73 (q, J = 7.3, 7.6 Hz, 2H), 1.41 (t, J = 7.3, 7.6 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$, ppm) δ 11.0, 26.0, 125.0, 127.5, 129.0, 136.5, 137.8, 138.8, 142.5, 153.0.

Compound **6d**: ^{1}H NMR (270 MHz, DMSO, ppm) δ 8.57 (s, 1H), 8.00 (d, J = 7.3, 8.6 Hz, 2H), 7.82 (d, J = 6.9, 8.3 Hz, 2H), 7.57–7.47 (m, 4H), 7.43 (d, J = 7.6 Hz, 1H), 7.34 (dd, J = 6.9, 7.6 Hz, 1H), 6.31 (s, 2H); ^{13}C NMR (67.5 MHz, DMSO, ppm) δ 124.9, 127.8, 128.1, 128.5, 128.6, 128.8, 128.9, 129.0, 136.9, 137.5, 137.8, 137.9, 139.7, 152.0.

Compound **6e**: ^{1}H NMR (270 MHz, DMSO, ppm) δ 8.44 (s, 1H), 7.92 (d, d = 7.3 Hz, 2H), 7.44–7.17 (m, 8H), 6.41 (s, 2H), 4.11 (s, 2H); ^{13}C NMR (67.5 MHz, DMSO, ppm) δ 124.7, 126.1, 127.3, 128.2, 128.6, 128.9, 136.9, 137.1, 138.1, 138.7, 140.0, 152.7.

Compound **6f**: ^{1}H NMR (270 MHz, DMSO, ppm) δ 7.82 (s, 1H), 7.51 (d, J = 6.6 Hz, 1H), 7.43 (d, J = 6.6 Hz, 1H), 7.41 (d, J = 7.9 Hz, 1H), 7.34 (d, J = 6.6 Hz, 1H), 7.32 (d, J = 7.6 Hz, 1H), 6.40 (s, 2H), 2.35 (s, 3H); ^{13}C NMR (67.5 MHz, DMSO, ppm) δ 22.7, 127.2, 128.2, 129.1, 129.2, 139.7, 140.1, 147.8, 154.2.

Compound **6g**: ^{1}H NMR (500 MHz, DMSO, ppm) δ 7.81 (s, 1H), 7.78 (s, 1H), 6.10 (s, 2H), 2.25 (s, 3H); ^{13}C NMR (125 MHz, DMSO, ppm) δ 20.0, 131.4, 139.6, 140.7, 154.4, 176.5.

15. It is comparatively difficult to isolate pure pyrazine *N*-oxides. As hydrogenation of the *N*-oxide normally proceeds very cleanly to give the desired pyrazines in high yield (>90%), yields given in Table 1 should reflect to yields for *N*-oxides.
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21. Treatment of the oxide **5a** with $FeCl_2$ did not lead to the corresponding pyrazine **6a** while with Fe powder did work, giving **6a**.