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Synthesis of Pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine Derivatives via Tandem Iminium Cyclization and Smiles Rearrangement

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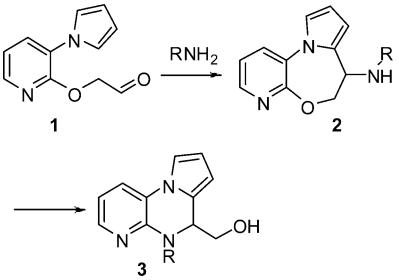

The tandem iminium cyclization and Smiles rearrangement of pyridinyloxyacetaldehyde **1** and a primary amine generated a novel pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine scaffold. TFA was discovered to be an efficient catalyst in the reactions with aromatic amines, whereas $TiCl_4$ was found to be superior in the case of aliphatic amines. This methodology proved to be efficient in the preparation of a library of diversified pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine derivatives.

Novel fused heterocyclic systems are often considered important scaffolds in medicinal chemistry.[1] Heterocyclic compounds possessing a pyrrolo[1,2-*a*]pyrazine moiety are of biological interest. For example, pyrrolo[1,2-*a*]quinoxalinones are reported to have oral antiallergic activity,[2] and thieno[3,2-*e*]pyrrolo[1,2-*a*]pyrazines[3] and pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazines[4] have been shown to be selective 5-HT_3 receptor agonists. However, few synthetic methodologies to access pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazines are available.[4,5]

Tandem reactions are developed as efficient strategies in the synthesis of complex organic molecules because they enable multiple transformations via a cascade of reactions.[6] Recently, we reported a unique cascade reaction of pyrimidine-derived aldehydes involving an iminium cyclization followed by a Smiles rearrangement leading to pyrrolo[1,2-*f*]pteridines (Scheme 1).[7] We envisioned that the pyridine analog **1** would react with an amine to follow a similar path of tandem iminium cyclization and Smiles rearrangement to yield novel pyrido[2,3-*e*]pyrrolo-[1,2-*a*]pyrazines **3** as shown in Scheme 2. Herein, the details of these studies are presented.

Aldehyde **1** was prepared as described in Scheme 3. Clauson−Kass reaction of **4** resulted in pyrrolopyridine[8] **5**, which reacted with ethyleneglycol under basic conditions to give **6**. Alcohol **6** was readily oxidized by Swern oxidation to give the corresponding aldehyde **1** in good yield.

Initially, the reaction of pyridine aldehyde **1** with *p*-chloroaniline was investigated, and results are summarized in Table 1.

We first tested a $TiCl_4/CH_3CN$ protocol employed in the analogous pyrimidine system (entry 1, Table 1),[7b] but unfortunately no desired pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine **3j** was obtained from the resulting complex mixture. Attempted optimization of the reaction conditions by varying the amount of $TiCl_4$ did not result in any significant improvement (entries 2 and 3, Table 1). Changing the acid to TFA in CH_2Cl_2 led to the desired product in 49% yield (entry 4, Table 1). The reasonable yield of the desired product generated under the TFA conditions indicated that further optimization by screening of reaction conditions including the solvent, amount of catalyst, and temperature might improve the yield. First, the solvents (dioxane, toluene, ethanol, THF, and acetonitrile) were investigated using TFA as the catalyst (entries 5−9, Table 1). To our delight, the desired product **3j** was obtained in 76% yield when acetonitrile was used (entry 9, Table 1). Second, the amount of TFA was varied. When the above reaction was carried out with 0.1 equiv of TFA at 8 °C, only iminium cyclization intermediate **2j** was produced (judging by LC-MS) after 4 h. However, 48% of **2j** and 7% of rearrangement product **3j** (which must have been generated from **2j** during removal of the solvent by a rotary evaporator) were isolated from the reaction mixture (entry 10, Table 1). This result is consistent with the proposed cascade reaction of iminium cyclization and Smiles rearrangement similar to the one reported in the pyrimidine systems.[7] Third, the reaction temperature was increased to refluxing acetonitrile, which led to the desired **3j** in 76% (entry 11, Table 1). Finally, aldehyde **1** was added dropwise to the solution of *p*-chloroaniline and TFA in CH_3CN to prevent potential side reactions similar to the aldol condensation that occurred in the pyrimidine systems under TFA conditions.[7b] Eventually, the desired **3j** was obtained in nearly quantitative yield under

(1) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893.

(2) Ager, I. R.; Barnes, A. C.; Danswan, G. W.; Hairsine, P. W.; Kay, D. P.; Kennewell, P. D.; Matharu, S. S.; Miller, P.; Robson, P.; Rowlands, D. A.; Tully, W. R.; Westwood, R. *J. Med. Chem.* **1988**, *31*, 1098.

(3) Rault, S.; Lancelot, J. C.; Prunier, H.; Robba, M.; Renard, P.; Delagrange, P.; Pfeiffer, B.; Caignard, D. H.; Guardiola-Lemaitre, B.; Hamon, M. *J. Med. Chem.* **1996**, *39*, 2068.

(4) Campiani, G.; Morelli, E.; Gemma, S.; Nacci, V.; Butini, S.; Hamon, M.; Novellino, E.; Greco, G.; Cagnotto, A.; Goegan, M.; Cervo, L.; Valle, F. D.; Fracasso, C.; Caccia, S.; Mennini, T. *J. Med. Chem.* **1999**, *42*, 4362.

(5) (a) Blache, Y.; Gueiffier, A.; Chavignon, O.; Teulade, J. C.; Milhavet, J. C.; Viols, H.; Chapat, J. P. *J. Heterocycl. Chem.* **1994**, *31*, 161. (b) Lancelot, J. C.; Ladurée, D.; Robba, M. *Chem. Pharm. Bull.* **1985**, *33*, 3122. (c) Abbiati, G.; Beccalli, E. M.; Broggini, G.; Paladino, G.; Rossi, E. *Synthesis* **2005**, 2881.

(6) (a) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167. (b) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195. (c) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137. (d) Moser, W. H. *Tetrahedron* **2001**, *57*, 2065.

(7) (a) Xiang, J.; Zheng, L.; Chen, F.; Dang, Q.; Bai, X. *Org. Lett.* **2007**, *9*, 765. (b) Xiang, J.; Zheng, L.; Xie, H.; Hu, X.; Dang, Q.; Bai, X. Unpublished results.

(8) Prunier, H.; Rault, S.; Lancelot, J. C.; Robba, M.; Renard, P.; Delagrange, P.; Pfeiffer, B.; Caignard, D. H.; Misslin, R.; Guardiola-Lemaitre, B.; Hamon, M. *J. Med. Chem.* **1997**, *40*, 1808.

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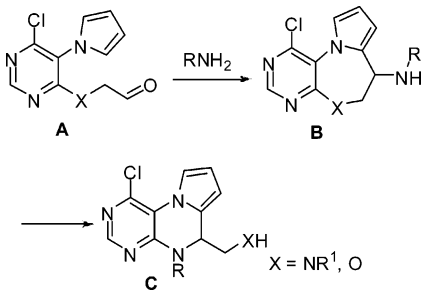
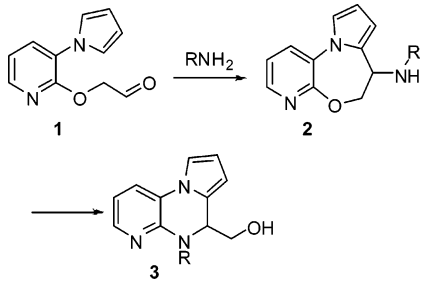
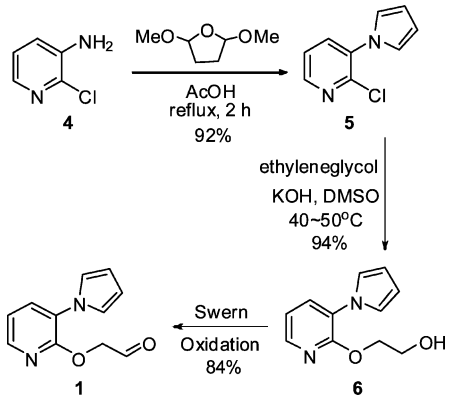
SCHEME 1. Tandem Iminium Cyclization and Smiles Rearrangement of Pyrimidines



SCHEME 2. Tandem Iminium Cyclization and Smiles Rearrangement of Pyridinyloxyacetaldehyde



SCHEME 3. Synthesis of 3-Pyrrolopyridin-2-yloxyacetaldehyde 1



conditions of 1.5 equiv of *p*-chloroaniline and 0.1 equiv of TFA in refluxing acetonitrile (entry 12, Table 1).

The above optimized conditions (entry 12, Table 1) were applied to a number of aromatic amines, and the results are summarized in Table 2.

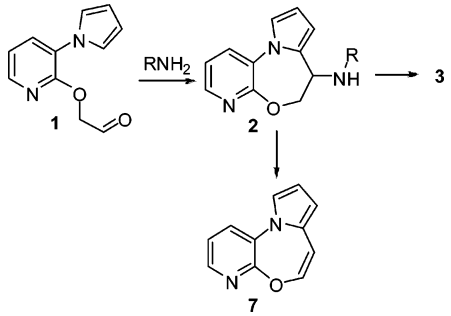
As shown in Table 2, the reactions of aldehyde **1** with aromatic amines gave the expected products **3** in good to excellent yields. The reaction appeared to be sensitive to both electronic and steric effects in the aromatic amines. When either a moderate electron-withdrawing or a mild electron-donating group (Cl, Br, H, and Me; entries 4−7 and 9−11) is present in the aromatic amine, higher yields were obtained compared to those with either a strong electron-donating group (R = *p*-MeO, entry 2) or a strong electron-withdrawing group (R = *p*-CN or *p*-NO_2; entry 12 or 13). When an *ortho* substituent is present in the aromatic amine, the product yield was lower (entries 1, 3, and 8). These results are consistent with the reaction mechanism that entailed a cascade of intramolecular electrophilic substitution of the iminium to an aromatic ring (iminium cyclization) and nucleophilic replacement (Smiles rearrangement). Aromatic amines form stable imines with an aldehyde

TABLE 1. Optimization of the Reaction of Pyridinyloxyacetaldehyde[a]

entry	acid (equiv)	solvent	temp (°C)	time (h)	yield **3j**[b] (%)
1	$TiCl_4$ (2.4)	CH_3CN	−15 to 24	5.5	0
2	$TiCl_4$ (0.6)	CH_3CN	−15 to 6	31	4
3	$TiCl_4$ (4.8)	CH_3CN	−11 to 11	4.5	0
4	TFA (0.6)	DCM	6	7.0	49
5	TFA (0.6)	dioxane	6	55	29
6	TFA (0.6)	toluene	6	11	24
7	TFA (0.6)	C_2H_5OH	6	168	48
8	TFA (0.6)	THF	reflux	12	31
9	TFA (0.6)	CH_3CN	6	12	76
10	TFA (0.1)	CH_3CN	8	4.0	0[c]
11	TFA (0.1)	CH_3CN	reflux	1.0	76
12	**TFA (0.1)**	**CH_3CN**	**reflux**	**3.0**	**97**[d]

[a] All reactions were conducted with 1.1 equiv of *p*-chloroaniline except for entry 12, for which 1.5 equiv was used. [b] Isolated yield. [c] Only **2j** was observed by LC-MS; after work-up 48% of **2j** and 7% of **3j** were isolated. [d] A solution of aldehyde **1** in CH_3CN was added dropwise into the reaction over 2.5 h.

TABLE 2. TFA-Catalyzed Cascade Reactions of Aldehyde 1[a]



entry	R	product	time (h)	yield[b] (%)
1	*o*-MeOPh	**3a**	6.0 (3.5[c])	46
2	*p*-MeOPh	**3b**	4.0 (2.5)	62
3	*o*-MePh	**3c**	10 (2.5)	26
4	*m*-MePh	**3d**	4.0 (2.5)	81
5	*p*-MePh	**3e**	3.5 (3.0)	80
6	Ph	**3f**	4.0 (2.5)	90
7	*p*-BrPh	**3g**	3.5 (2.5)	88
8	*o*-ClPh	**3h**	9.0 (2.0)	trace[d]
9	*m*-ClPh	**3i**	4.5 (3.0)	95
10	*p*-ClPh	**3j**	3.0 (2.5)	97
11	*p*-CH_3COPh	**3k**	4.5 (3.5)	80
12	*p*-CNPh	**3l**	3.5 (2.5)	58
13	*p*-NO_2Ph	**3m**	4.0 (2.0)	38

[a] All reactions were performed on 0.5 mmol scale. [b] Isolated yield. [c] Addition time of aldehyde **1** was indicated in the parenthesis. [d] 15% yield of **7** was isolated.

and thus are suitable reagents for the reaction process. However, a strong electron-withdrawing group, such as CN or NO_2, in the aromatic ring may stabilize the resulting imine and facilitate subsequent cyclization but reduce the nucleophilicity of the resulting secondary amine moiety so to disfavor Smiles rearrangement. In contrast, a strong electron-donating group, such as MeO, could increase the chance of side reactions, such as the ones of iminium ion with the electron-rich phenyl ring, thus reducing the overall yield. The presence of an *ortho* substituent in the aromatic amine led to lower yield of the final product **3** (entries 1, 3, and 8) compared to its corresponding *meta*- (entries 4 and 9) and *para*-substituted analogs (entries 2, 5 and 10), indicating that the steric effect of the amine is important in this reaction cascade. In entry 8, the combination of steric and electronic effects of the *ortho* chloro group prevented Smiles

TABLE 3. Optimization of the Reaction of Aldehyde 1 with *n*-Butylamine

entry	acid (aq)	solvent	temp (°C)	time (h)	yield **3n**[a] (%)
1	TFA (0.1)	CH_3CN	reflux	4.0[b]	0
2	TFA (1.2)/P_2O_5	CH_3CN	24	7.0	3
3	$TiCl_4$ (2.4)	CH_3CN	24	8.0	26
4	**$TiCl_4$ (2.4)**	**DCM**	**24**	**17**	**66**

[a] Isolated yield. [b] Aldehyde **1** was added into the reaction solution over 2.5 h.

TABLE 4. $TiCl_4$-Promoted Tandem Reactions of Aldehyde 1 with Aliphatic Amines[a]

entry	R	product	time (h)	yield[b] (%)
1	*n*-Bu	**3n**	17	66
2	*i*-Pr	**3o**	23	61
3	cyclohexyl	**3p**	21	38
4	Bn	**3q**	19	31[c]

[a] All reactions were performed on 0.5 mmol scale at 24 °C. [b] Isolated yield. [c] Reaction was carried out at 10 °C.

rearrangement and as a result the amine-elimination product pyrido[2,3-*b*]pyrrolo[1,2-*d*][1,4]oxazepine **7** was obtained.

The success of aldehyde **1** with aromatic amines encouraged us to expand the tandem iminium cyclization and Smiles rearrangement to aliphatic amines. Unfortunately, under the above optimized conditions reaction of aldehyde **1** with *n*-butylamine did not give the desired product **3n**. In consideration of the difficulty of imine formation with an aliphatic amine, P_2O_5 was added to trap the water formed by condensation of **1** and *n*-butylamine. This led to the desired product **3n** in 3% yield (entry 2, Table 3). Because $TiCl_4$ is generally regarded as an efficient catalyst and moisture trap, the $TiCl_4/CH_3CN$ reaction conditions were applied. To our delight, the desired product **3n** was isolated in 26% yield after 8 h (entry 3, Table 3). Eventually, product **3n** was obtained in 66% yield by using 2.4 equiv of $TiCl_4$ in dichloromethane (DCM) at ambient temperature (entry 4, Table 3). It is noteworthy that the iminium cyclization product **2n** was initially formed (judging by LC-MS), and the desired product **3** was obtained only after treatment with saturated aqueous $NaHCO_3$ solution. This observation is different from the cascade reaction of the pyrimidine system since the $TiCl_4$-catalyzed reaction of pyrimidines proceeded fully without the treatment by a base. This result may be attributed to the stronger pyridine−oxygen bond compared to the pyrimidine one, which is more favorable toward Smiles rearrangement.

Under the conditions of $TiCl_4$/DCM followed by $NaHCO_3$ treatment, aldehyde **1** reacted with several aliphatic amines to yield the desired pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazines **3** (Table 4).

As disclosed in Table 4, the tandem reaction products **3** were obtained in moderate to good yields when aliphatic amines were used. These reactions appeared to be influenced by steric effects as increasing the size of the aliphatic group decreased the yield (entries 1−3), although benzylamine gave lower yield compared to other aliphatic amines (entry 4 vs entries 1−3). These results demonstrated the feasibility of the reactions with aliphatic amines.

In summary, the tandem iminium cyclization and O−N Smiles rearrangement of a pyridinyloxyacetaldehyde has been successfully developed to generate novel pyrido[2,3-*e*]pyrrolo-[1,2-*a*]pyrazine derivatives. The pyridine system demonstrated reaction profiles slightly different from those in pyrimidine systems. Separate reaction conditions were developed for aromatic and aliphatic amines: TFA efficiently catalyzes the current cascade reaction with aromatic amines, whereas in case of aliphatic amines $TiCl_4$ is superior as the catalyst and follow-up treatment with a base is needed. This synthetic methodology complements existing pyridine chemistry by allowing access to libraries of policyclic pyridine derivatives.

Experimental Section

TFA-Reactions for the Synthesis of Pyrido[2,3-*e*]pyrrolo[1,2-*a*]pyrazine 3. The solution of aldehyde **1** (101 mg, 0.5 mmol) in CH_3CN (10 mL) was added dropwise into the solution of an aromatic amine (0.75 mmol) and TFA (4 μL, 0.05 mmol) in CH_3CN (10 mL) at 80 °C over 2.5 or 3.0 h. The resulting solution was stirred for the corresponding time at reflux. The solvent was removed in vacuo to give the crude product. Purification by flash chromatography (petroleum ether/EtOAc = 4:1, v/v) afforded the desired products.

5,6-Dihydro-6-hydroxymethyl-5-(4-chlorophenyl)pyrido [2,3-*e*]pyrrolo[1,2-*a*]pyrazine, 3j: 97%; mp 164−165 °C. ^{1}H NMR δ 7.96 (dd, 1H, J = 5.1, 1.2), 7.60 (dd, 1H, J = 8.1, 1.5), 7.32−7.29 (m, 4H), 7.20 (s, 1H), 6.89−6.85 (m, 1H), 6.42 (t, 1H, J = 3.0), 6.11−6.10 (m, 1H), 5.09 (t, 1H, J = 6.0), 3.78−3.59 (m, 2H); ^{13}C NMR δ 145.6, 143.5, 143.1, 129.4, 129.0, 125.1, 122.5, 121.5, 116.2, 114.6, 112.0, 105.9, 64.2, 59.8; MS (ESI) *m*/*z* 312.2 [M + H$^+$]. Anal. Calcd for $C_{17}H_{14}ClN_3O$: C, 65.49; H, 4.53; N, 13.48. Found: C, 65.58; H, 4.73; N, 13.32.

$TiCl_4$-Promoted Reaction for the Synthesis of Pyrido[2,3-*e*]-pyrrolo[1,2-*a*]pyrazine, 3. To a stirred solution of 2-(3-(1*H*-pyrrol-1-yl)pyridin-2-yloxy)acetaldehyde **1** (101 mg, 0.5 mmol) in DCM (20 mL) was added the aliphatic amine (0.55 mmol). After 10 min, $TiCl_4$ (132 μL, 1.2 mmol) was added. The resulting solution was stirred for the corresponding time at ambient temperature, quenched with saturated aqueous $NaHCO_3$, extracted with DCM (30 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (petroleum ether/EtOAc = 3:1, v/v) afforded the desired products.

5-(*n*-Butyl)-5,6-dihydro-6-hydroxymethylpyrido[2,3-*e*]pyrrolo-[1,2-*a*]pyrazine, 3n: 66%. ^{1}H NMR δ 7.88 (d, 1H, J = 4.2), 7.35 (d, 1H, J = 7.5), 7.10 (s, 1H), 6.59−6.55 (m, 1H), 6.33 (t, 1H, J = 3.0), 6.05 (d, 1H, J = 3.0), 4.69−4.65 (m, 1H), 4.27−4.20 (m, 1H), 3.71−3.49 (m, 2H), 3.15−3.06 (m, 1H), 1.64−1.55 (m, 2H), 1.39−1.29 (m, 2H), 0.88 (t, 3H, J = 7.2); ^{13}C NMR δ 147.2, 143.0, 125.0, 120.3, 119.3, 114.2, 112.1, 111.4, 105.2, 63.9, 57.2, 46.7 29.9, 20.0, 13.9; MS (ESI) *m*/*z* 258.1 [M + H$^+$].

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Supporting Information Available: Experimental details; ^{1}H and ^{13}C NMR and LC-MS-ELSD spectra for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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