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Synthesis of Novel Pyrimidine Fused 8-Membered Heterocycles via Iminium Ion Cyclization Reactions

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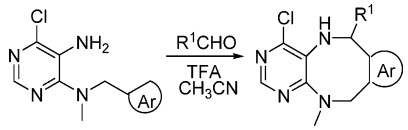
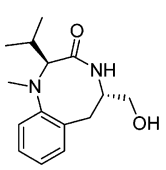
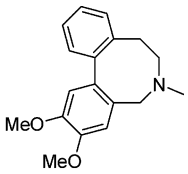


Novel tricyclic pyrimidine-fused 8-membered heterocycles were prepared by an iminium ion cyclization using pyrimidinediamine systems with electron-rich aromatic rings.

The search for novel compound libraries with potential biological activities is a major focus for chemical biology and medicinal chemistry. Therefore, efficient methodologies to access small molecules of privileged structures are of special interest.[1] Natural products are generated via an evolutionary selection process and represent the biologically relevant and prevalidated fractions of chemical spaces explored by nature. Waldmann et al. conducted a quantitative analysis of natural product scaffolds and showed that the ones with three rings are most often found in natural products.[2] 8-Membered nitrogen-containing heterocycles are among the natural products that exhibit important pharmacological effects.[3] For example, 9-decyl benzolactam-V8 was a potent PKC activator similar to the teleocidins,[4] and buflavine is shown to possess interesting adrenolytic and anti-serotonin activities.[5] However, 8-membered rings are generally more difficult to prepare due to their associated torsional, transannular, large-angle strain and the high activation energy needed for the ring closure.[6]

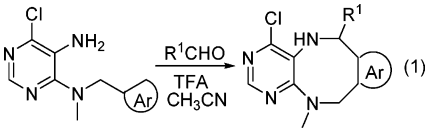


benzolactam-V8



Bulflavine

Pyrimidine is a key structural component in life molecules, and its derivatives are considered privileged structures in medicinal chemistry.[7] It is therefore logical to explore the utilities of pyrimidine-fused 8-membered heterocycles in chemical biology and medicinal chemistry. Recently, we reported a series of methodologies for the efficient synthesis of various novel tricyclic and tetracyclic scaffolds consisting of various pyrimidine-fused heterocycles.[8] For example, novel pyrimidine-fused benzodiazepines are prepared via a Pictet−Spengler-type cyclization.[8a] As part of an ongoing endeavor to create novel heterocyclic scaffolds, we have explored applications of iminium ion cyclization reactions to the synthesis of pyrimidine-fused 8-membered heterocycles (eq 1). Herein, we report the preliminary results from studies of this synthetic strategy, which is an efficient entry to unusual tricyclic systems consisting of an 8-membered heterocyclic ring.



2a-b **3-4**

The pyrimidines (**2a**,**b**) required for this study were readily prepared from commercially available 4,6-dichloro-5-nitropyrimidine or 5-amino-4,6-dichloropyrimidine as outlined in Scheme 1.[9]

Initially, the cyclization reaction of pyrimidine **2a** with *p*-nitrobenzaldehyde (eq 1) was investigated under trifluoroacetic acid (TFA) conditions, which proceeded smoothly to give the desired product 4-chloropyrimido[*b*,*f*][1,5]benzodiazocine **3a** in 86% yield (entry 1, Table 1). The structure of compound **3a** was unequivocally assigned through an X-ray diffraction analysis (details available in the Supporting Information), which indicates the formation of the 8-membered ring system. The scope of this cyclization reaction was then explored with other aldehydes, and the results are summarized in Table 1. In general, these reactions produced the desired 4-chloropyrimido[*b*,*f*][1,5]-benzodiazocines **3** in moderate to good yields.

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SCHEME 1. Synthesis of Substituted Pyrimidines

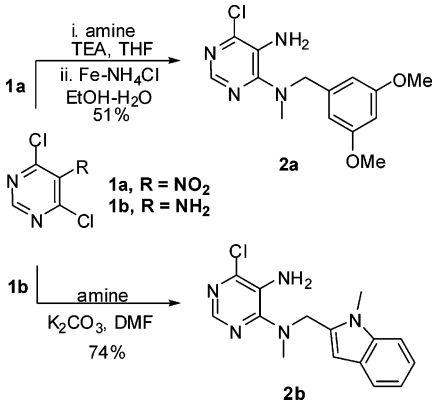
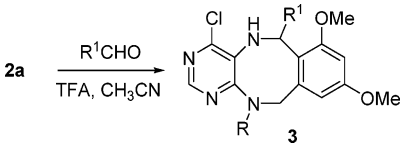


TABLE 1. Synthesis of 4-Chloropyrimido[*b*,*f*][1,5]benzodiazocines[a]



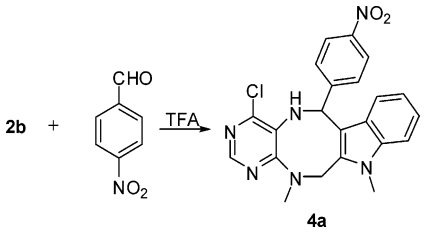
entry	product	R	R^1	time (h)	yield[b] (%)
1	**3a**	Me	*p*-$NO_2C_6H_4$-	12	86
2	**3b**	Me	*o*-$NO_2C_6H_4$-	12	54[c]
3	**3c**	Me	*m*-$NO_2C_6H_4$-	12	64
4	**3d**	Me	*p*-FC_6H_4-	12	72
5	**3e**	Me	*p*-NCC_6H_4-	12	62
6	**3f**	Me	Ph-	12	48
7	**3g**	Me	*p*-MeC_6H_4-	5	48
8	**3h**	Me	*p*-$MeOC_6H_4$-	7	26[d]
9	**3i**	Me	*m*-$MeOC_6H_4$-	4.5	66
10	**3j**	Me	*o*-$MeOC_6H_4$-	7	32
11	**3k**	Me	3,5-di-$MeOC_6H_4$-	7.5	64
12	**3l**	Me	*n*-Pr-	1	59
13	**3m**	Me	Et	1	64
14	**3n**	Me	2-thienyl	12	72
15	**3o**	Me	HOOC-	2	51
16	**3p**	*n*-Pr	*p*-$NO_2C_6H_4$-	12	79
17	**3q**	*n*-Bu	*p*-$NO_2C_6H_4$-	12	73
18	**3r**	Bn	*p*-$NO_2C_6H_4$-	12	90

[a] Reaction conditions: **2a** (1.0 equiv), R^1CHO (1.5−2.0 equiv), and TFA (excess) in acetonitrile, reflux. [b] Yields are based on pure products isolated by flash chromatography and unoptimized. [c] 8% imine intermediate was also isolated. [d] 6% imine intermediate was also isolated.

The results in Table 1 could be explained by a previously proposed mechanism that entailed an intramolecular electrophilic substitution of the benzene ring by an iminium ion intermediate.[8a] The cyclization reaction with an aliphatic aldehyde (R^1 = *n*-Pr-, Et-, or -COOH, entries 12, 13, and 15) proceeded faster compared to those with an aromatic aldehyde (entries 1−11, 14, and 16−18).

When R^1 was aromatic, an electron-withdrawing group (e.g., *p*-NO_2-) should increase the electron deficiency of the carbonyl, so to decrease the basicity of imine intermediate, therefore reducing the capability to form an iminium ion which may in turn slow down the intramolecular cyclization, while an aliphatic aldehyde forms a more reactive iminium ion for electrophilic substitution. This was supported by the fact that the reactions with aromatic aldehydes bearing an electron-withdrawing group were slower. Higher yields were obtained when electron-withdrawing groups were present in aromatic aldehydes (e.g., **3a**, **3c**, **3d**).

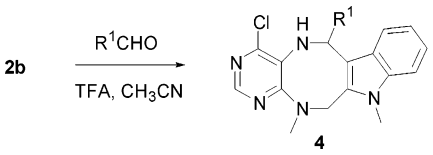
TABLE 2. Optimization of Reaction Conditions for Conversion of 2b to 4a[a]



entry	TFA (equiv)	[**2b**] (mmol/mL)	*T* (°C)	yield[b] (%)
1	excess	0.066	81	0
2	3	0.066	40	trace
3	1	0.066	40	43
4	1	0.066	25	59
5	1	0.132	25	61
6	0.1	0.132	25	64
7	0.1	0.33	25	70
8	0.1	0.5	25	81

[a] All reactions were conducted under nitrogen with acetonitrile as the solvent; 0.33 mmol of **2b**. [b] Yields are based on pure products isolated by flash chromatography.

TABLE 3. Synthesis of Pyrimidine-Fused Indolodiazocines (4a−h)[a]



entry	product	R^1	time (h)	yield[b] (%)
1	**4a**	*p*-$NO_2C_6H_4$-	3	73
2	**4b**	*o*-$NO_2C_6H_4$-	3	73
3	**4c**	*m*-$NO_2C_6H_4$-	3	76
4	**4d**	*p*-NCC_6H_4-	3	72
5	**4e**	*p*-MeC_6H_4-	3	71
6	**4f**	*n*-Pr-	0.33	86
7	**4g**	Et	0.33	83
8	**4h**	HOOC-	2	80

[a] Reaction conditions: **2b** (0.75 mmol, 1.0 equiv), R^1CHO (1.5 equiv), and TFA (10 mol %) in acetonitrile (1.5 mL), 25 °C. Yields are based on pure products isolated by flash chromatography and not optimized.

The cyclization was also tested with pyrimidine **2b**. When **2b** and *p*−nitrobenzaldehyde were treated under the above cyclization conditions, surprisingly no desired product was detected by LC−MS (Table 2, entry 1). Given that indole is an electron-rich heterocycle and may be liable under strong acidic conditions, we decided to closely examine the reaction conditions with regard to temperature, concentration, and the amount of TFA. The results from the optimization of reaction conditions are summarized in Table 2.

Reducing the amount of TFA to 3 equiv and lowering the reaction temperature to 40 °C led to generation of the desired product **4a** (entry 2). Reduction of TFA to 1 equiv at 40 °C increased the yield to 43% (entry 3). Further reducing the TFA amount, lowering temperature, and increasing the substrate concentration led to the optimized reaction conditions of 0.1 equiv of TFA, ambient temperature, and 0.5 M **2b** (entries 4−8).

The optimized conditions were extended to a variety of aldehydes, and the results are listed in Table 3. As shown in Table 3, pyrimidine **2b** reacted with various aldehydes to produce the desired products **4** in excellent yields. When R^1 was aliphatic (entries 6−8), the reaction proceeded faster and the yield was higher compared to the ones with an aromatic

aldehyde (entries 1−5). On the other hand, when an aromatic aldehyde was employed, the yield and the reaction rate were not influenced by the electronic properties of its substituents (entries 1, 4, and 5). In general, the cyclizations of substrate **2b** proceeded faster than those of substrate **2a** (Table 3 vs Table 1).

In conclusion, a new method was developed for the efficient preparation of novel tricyclic pyrimidine-fused 8-membered diazocines. Readily accessible pyrimidine derivatives and various aldehydes are within the scope of this new method; an acid-catalyzed iminium ion cyclization is introduced as the key step of the synthetic sequence. Two types of diazocines (pyrimidine-fused benzodiazocines and indolodiazocines) were readily prepared with a wide variety of substituents being tolerated by the mild reaction conditions. Application of this new method to preparation of diverse libraries of new heterocyclic scaffolds as useful tools in study of chemical biology and medicinal chemistry is in progress and will be reported in due course.

Experimental Section

General Procedure for the Synthesis of 4-Chloropyrimido[*b*,*f*][1,5]benzodiazocines 3. 5-Amino-6-chloro-4-*N*-methylbenzylaminopyrimidine (**2a**) (0.65 mmol), the appropriate aldehyde (0.975 mmol), and TFA (0.6 mL) were dissolved in CH_3CN (10.0 mL) and stirred under reflux for 1−12 h. The reaction mixture was concentrated in vacuo, diluted with EtOAc (15 mL), and washed with saturated $NaHCO_3$ (3 × 15 mL). The water layer was extracted with EtOAc (3 × 10 mL). The combined EtOAc layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated in vacuo, and purified by flash chromatography over silica gel to furnish the cyclized product **3**.

4-Chloro-7,9-dimethoxy-12-methyl-6-phenylpyrimido[*b*,*f*][1,5]-benzodiazocine (3f): white solid; yield 48% (elution with EtOAc/petroleum ether = 1:2); ES-MS 396.8 [$(M + 1)^+$]; mp 182−183 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.08−7.20 (m, 3H), 7.03 (d, J = 6.9 Hz, 2H), 6.42 (s, 2H), 6.14 (d, J = 6.0 Hz, 1H), 5.30(br., 1H), 4.87 (d, J = 15.6 Hz, 1H), 4.06 (br., 1H), 3.85 (s, 3H), 3.66 (s, 3H), 3.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 158.5, 151.3, 141.9, 137.9, 128.1, 127.9, 127.2, 124.8, 119.5, 107.1, 98.2, 60.9, 56.0, 55.6, 55.5, 38.1. Anal. Calcd for $C_{21}H_{21}ClN_4O_2$: C, 63.55; H, 5.33; N, 14.12. Found: C, 63.30; H, 5.23; N, 14.30.

General Procedure for 4-Chloropyrimido[*b*,*f*][1,5]indolodiazocines. Compound **2b** (0.75 mmol), the appropriate aldehyde (1.125 mmol), and TFA (10 mol %) were dissolved in CH_3CN (1.5 mL), and the mixture was stirred at room temperature for 0.3−3 h. After filtration and washing, the pure desired product **4** as a solid was obtained. The filtrate was concentrated in vacuo, and purification by flash chromatography on silica gel gave an additional part of **4**.

4-Chloro-15-methyl-6-propylpyrimido[*b*,*f*][1,5]indolodiazocine (4f): white solid; yield 86% (elution with EtOAc/petroleum ether = 1:2); ES-MS 356.1 [$(M + 1)^+$]; mp 178−180 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.48 (d, J = 8.1 Hz, 1H), 7.20−7.31 (m, 2H), 7.10 (td, J = 7.4, 1.5 Hz, 1H), 6.74 (d, J = 15.3 Hz, 1H), 4.84−4.87 (m, 1H), 4.18 (d, J = 15.6 Hz, 1H), 3.78 (s, 3H), 3.35 (s, 3H), 3.16 (br., 1H), 1.85−1.92 (m, 2H), 1.53−1.61 (m, 2H), 0.99 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.2, 157.4, 153.3, 137.1, 131.9, 125.9, 124.0, 122.1, 119.3, 118.7, 114.9, 109.5, 57.2, 46.8, 41.0, 40.6, 29.5, 19.0, 14.2. Anal. Calcd for $C_{19}H_{22}ClN_5$: C, 64.13; H, 6.23; N, 19.68. Found: C, 64.27; H, 6.26; N, 19.76.

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Supporting Information Available: Analytical data, spectroscopic data, copies of LC−MS, ^{1}H and ^{13}C NMR spectra of products **3** and **4**, and CIF files and crystallographic data of **3a** and **3l**. This material is available free of charge via the Internet at http://pubs.acs.org.

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