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Report

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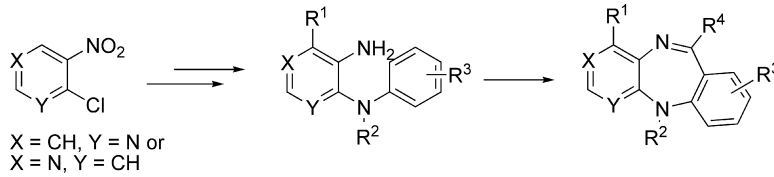

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Reports

Method Development for a Pyridobenzodiazepine Library with Multiple Diversification Points

Fuqiang Shi, Xianxiu Xu, Lianyou Zheng, Qun Dang, and Xu Bai*

The Center for Combinatorial Chemistry and Drug Discovery, Jilin University, 75 Haiwai Street, Changchun, Jilin 130012, P. R. China

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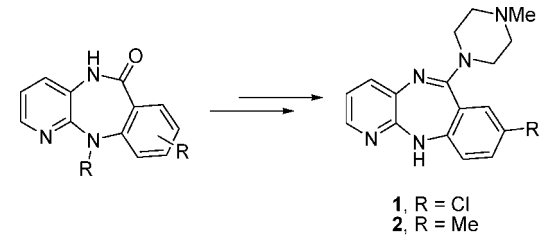
Pyridobenzodiazepines are an important class of compounds in central nervous system related diseases. For example, clozapine-like analogs such as pyrido[2,3-*b*]-[1,4]benzodiazepine **1** and pyrido[2,3-*b*][1,4]benzodiazepine **2** are reported as neuroleptics (Scheme 1).[1] In addition, pyridobenzodiazepine derivatives have been studied as potential agents to modulate activities of the central nervous system and vasopressin V_2 receptor.[2] Existing synthetic strategies to pyridobenzodiazepins have generally relied on preparation of the key lactam ring system and subsequent functionalization of the heterocyclic scaffold to introduce additional substituents (Scheme 1).[3] As such, most pyridobenzodiazepines reported contain an amino group at the 6-position of the heterocyclic nucleus. Kaczmarek et al. did report a sequential acylation and cyclization approach to C6-aryl and alkyl substituted pyridobenzodiazepines, but with very limited scope.[4]

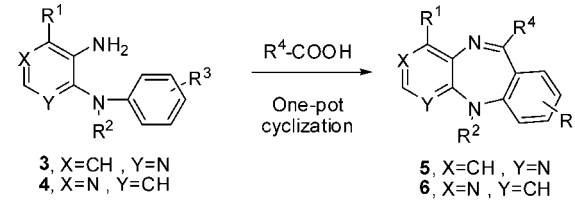
Given the interesting biological activities displayed by the benzodiazepine family of heterocyclic compounds, new methods enabling the efficient preparation of libraries based on the benzodiazepine scaffold should be useful for lead generation of various drug discovery programs.[5] We recently reported a series of synthetic methodologies, which relied on Bischler−Napeiralski type cyclization reactions as the key transformation step, that are useful to rapidly access various heterocyclic scaffolds with benzodiazepine as the core nucleus.[6] A logical expansion of these cyclization reactions leading to pyridobenzodiazepines could be envisioned as shown in Scheme 2.

The strategy outlined in Scheme 2 should allow ready access to pyridobenzodiazepines with various carbon-derived substituents at the 6-position of the central core. Given the large number of commercially available carboxylic acids and anilines, this method should be applicable to synthesis of libraries with high diversity enabling rapid exploration of the structure–activity relationship (SAR) of the 6-position and concurrently at several other positions. Herein, the investigation of this new strategy and method development toward a pyridobenzodiazepine library are reported.

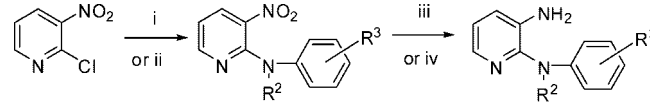
Scheme 1. Examples of Pyridobenzodiazepines as Neuroleptics



Scheme 2. Efficient Alternative Route to Pyridobenzodiazepines



Scheme 3. Preparation of Diaminopyridine Precursors **3**[a]



[a] Reagents and conditions: (i) Ar-N(R^2)H, K_2CO_3, *i*-PrOH, reflux; (ii) Ar-N(R^2)H, TEA, *n*-BuOH, reflux; (iii) Pd-C (10%), H_2, EtOH; (iv) Fe, NH_4Cl, EtOH, reflux.

Table 1. Summary for the Syntheses of Pyridines **8** and **3**

entry	R^2	R^3	**8a−j**	yield[a]	**3a−j**	yield[b]
1	Me	H	**8a**	70%[c]	**3a**	90%
2	Me	*p*-MeO	**8b**[f]	*c*	**3b**	71%[e]
3	Me	*p*-Me	**8c**[f]		**3c**	84%[e]
4	Me	*p*-F	**8d**[f]	*c*	**3d**	56%[e]
5	Me	*p*-Cl	**8e**	82%	**3e**	72%[d]
6	Me	*o*-Me	**8f**	62%[c]	**3f**	70%
7	Me	*m*-Me	**8g**	75%	**3g**	82%
8	Et	H	**8h**	85%	**3h**	75%
9	Bn	H	**8i**	85%	**3i**	70%[d]
10	H	H	**8j**	74%	**3j**	90%

[a] Based on isolated **8a−j**, condition ii, Scheme 1 (except where designated). [b] Based on isolated **3a−j**, condition iii, Scheme 1 (except where designated). [c] Condition i, Scheme 1. [d] Condition iv, Scheme 1. [e] Two steps. [f] Not purified.

The preparation of 2-substituted pyridines **3** required for the proposed synthetic route to pyridobenzodiazepines from 2-chloro-3-nitropyridine **7** is depicted in Scheme 3, and the results are summarized in Table 1.

Substitution of the chloro group in **7** with an amine was carried out using either potassium carbonate (entries 1, 2, 4, and 6) or TEA (entries 3, 5, and 7−9) as the base to give pyridines **8** in moderate to excellent yields. Reduction of

* To whom correspondence should be addressed. Tel: +86-431-85188955. Fax: +86-431-85188900. E-mail: xbai@jlu.edu.cn.

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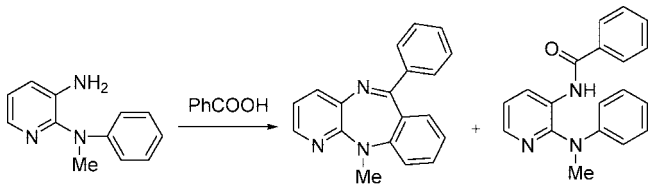
Table 2. Optimization of the Pyridobenzodiazepine Formation Reaction



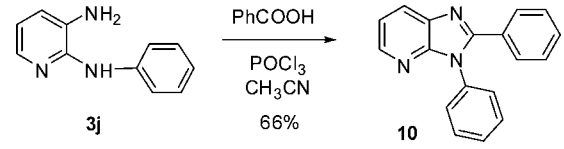
entry	conditions	yield (%) 5.1	9.1
1	PPA (1.5 equiv)/$POCl_3$, reflux, 40 min	58	
2	PPA (1.5 equiv)/$POCl_3$, 80 °C, 12 h then 90 °C, 7 h	64	
3	PPA (1.5 equiv)/$POCl_3$, 95 °C, 12 h	88	
4	PPA (1.5 equiv)/toluene, reflux, 24 h		91
5	PPA (1.5 equiv)/xylene, reflux, 24 h		90
6	$POCl_3$, reflux, 12 h	76	
7	$POCl_3$ (4 equiv)/CH_2Cl_2, reflux, 3 d		90
8	$POCl_3$ (4 equiv)/CH_3CN, reflux, 30 h	91	
9	$POCl_3$ (2 equiv)/CH_3CN, reflux, 24 h		90

the nitro group in **8** was accomplished under hydrogenation conditions although an iron-ammonium chloride reduction reaction was used to avoid potential dehalogenation and removal of benzyl when a chloro group or benzyl group is present (entries 5 and 9).[1a,6a]

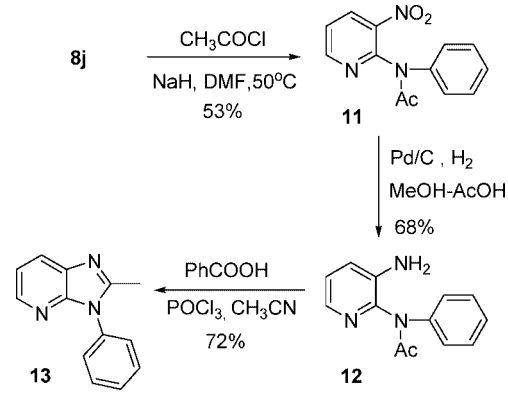
Pyridine **3a** was selected to test the proposed synthesis of pyridobenzodiazepines, and the results are shown in Table 2. Previously, the condition of polyphosphoric acid (PPA) in $POCl_3$ was reported to be effective at promoting Bischler−Napeiralski type cyclization reactions.[6a] Thus, treatment of pyridine **3a** and benzoic acid with PPA in refluxing $POCl_3$ (110 °C) gave the desired product **5.1** in moderate yield (58%, entry 1) on the first attempt. Lowering the reaction temperature to 95 °C improved the yield of compound **5.1** (88%, entry 3), indicating that perhaps milder reaction conditions could further improve the yield of the desired pyridobenzodiazepines. Therefore, optimization of reaction conditions was investigated. Further lowering the temperature led to lower yield (entry 2). The substitution of $POCl_3$ with either toluene or xylene as the solvent yielded intermediate amide **9.1** (entries 4 and 5), suggesting that $POCl_3$ is required to effect the cyclization reaction. When the cyclization reaction was conducted in $POCl_3$ without presence of PPA compound **5.1** was obtained in 76% yield after refluxing for 12 h (entry 6), which indicates that PPA is not required for the current cyclization reaction. To reduce the amount of $POCl_3$, the cyclization reaction was studied by introduction of solvents such as dichloromethane and acetonitrile (entries 7–9). Decreasing $POCl_3$ to 4 equiv and using acetonitrile as the solvent generated compound **5.1** in excellent yield (91%, entry 8). However, further reducing the amount of $POCl_3$ to 2 equiv (entry 9) or using dichloromethane as the solvent (entry 7) both gave only intermediate amide **9.1**. Therefore, the reaction conditions of 4 equiv of $POCl_3$ in refluxing acetonitrile were identified as optimum for the conversion of pyridines **3** to pyridobenzodiazepines **5**.

Since some N^{11}-H pyridobenzodiazepines showed interesting biological activities, we decided to investigate the possibility of generating N^{11}-H pyridobenzodiazepines as depicted in Scheme 4. When 3-amino-2-(*N*-phenylamino)-pyridine was subjected to the current reaction conditions, unfortunately only 3*H*-imidazo[4,5-*b*]pyridine was obtained. This result indicated that the intramolecular cyclization of either the amide or the chloroimine intermediate to the imidazole ring was much faster than the formation of the benzodiazepine ring.

Scheme 4. Reaction of Diaminopyridine **3j** with Benzoic Acid



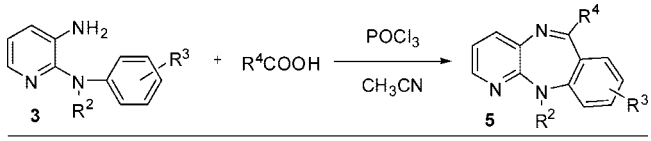
Scheme 5. Reaction of the Acetyl Protected Diaminopyridine **12** with Benzoic Acid



It is logical to explore a protecting group as R^2 that can be readily removed after the benzodiazepine ring is formed. Unfortunately, the acetyl protected pyridine **12**, prepared in two steps, did not give the desired benzodiazepine under the current conditions, but rather produced N^1-deaza purine **13** (Scheme 5). Evidently, the protecting acetyl group (not benzoic acid) participated the cyclization to form imidazole analog **13** instead of the desired benzodiazepine under the reaction conditions. On the basis of results of Schemes 4 and 5, a nonacyl protecting group should be used to access N^{11}-H analogs.

To demonstrate the suitability of this new method, a pyridobenzodiazepine library was prepared by reaction of 15 carboxylic acids with pyridine **3** with various substituents and the results are summarized in Table 3. In general, various carboxylic acids such as aromatic, aliphatic, and heterocyclic acids reacted well with precursors **3a** to give 6,11-disubstituted pyridobenzodiazepines **5.1**–**5.15** in moderate to high yields. This reaction appears to be sensitive to electronic effects. For example, an electron-donating group on the aromatic acid tends to speed up the reaction and to give higher yields (entries 2–5) while electron-withdrawing groups led to extended reaction time and lower yields (entries 6–7). When R^3 is a meta substituent there are two possible orientations for cyclization and indeed two regio-isomers were observed (entries 31–32). This reaction is also sensitive to steric effect of the aliphatic acids since the presence of a bulky group led to slower reactions (entries 11–14). Heteroaromatic acids, such as nicotinic acid, thiophene-3-

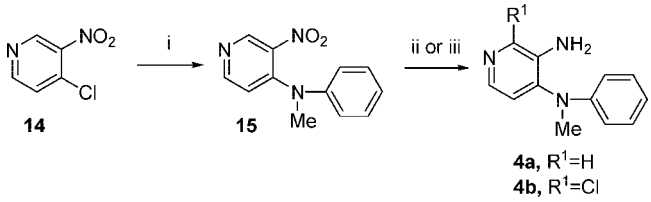
Table 3. Preparation of a Pyrido[2,3-*b*][1,4]benzodiazepine Library[a]



entry	Pdt	R^2	R^3	R^4	time (h)	yield (%)[b]
1	**5.1**	Me	H	Ph	30	91
2	**5.2**	Me	H	*p*-MeO-C_6H_4	33	96
3	**5.3**	Me	H	*m*-Me-C_6H_4	26	90
4	**5.4**	Me	H	*p*- Me-C_6H_4	28	82
5	**5.5**	Me	H	*o*- Me-C_6H_4	36	93
6	**5.6**	Me	H	*p*-NO_2-C_6H_4	85	74
7	**5.7**	Me	H	*p*-F-C_6H_4	36	63
8	**5.8**	Me	H	pyridin-3-yl	85	84[c]
9	**5.9**	Me	H	thiophen-3-yl	24	62
10	**5.10**	Me	H	furan-2-yl	14[d]	53
11	**5.11**	Me	H	Me	7	72
12	**5.12**	Me	H	Et	24	81
13	**5.13**	Me	H	*i*-Pr	24	44
14	**5.14**	Me	H	cyclohexyl	48	78
15	**5.15**	Me	H	*tert*-butyl	60	87[d]
16	**5.16**	Me	*p*-MeO	Ph	24	78
17	**5.17**	Me	*p*-MeO	*p*-MeO-C_6H_4	20	96
18	**5.18**	Me	*p*-MeO	*o*-MeO-C_6H_4	24	96
19	**5.19**	Me	*p*-MeO	Me	5	76
20	**5.20**	Me	*p*-Me	*p*-MeO-C_6H_4	40	94
21	**5.21**	Me	*p*-Me	Me	8	88
22	**5.22**	Me	*p*-F	Ph	40	88
23	**5.23**	Me	*p*-F	*p*-MeO-C_6H_4	35	85
24	**5.24**	Me	*p*-F	*m*-Me-C_6H_4	24	88
25	**5.25**	Me	*p*-F	Me	20	46
26	**5.26**	Me	*p*-Cl	*p*-MeO-C_6H_4	24	92
27	**5.27**	Me	*p*-Cl	Me	8	65
28	**5.28**	Me	*o*-Me	Ph	170	43[c]
29	**5.29**	Me	*o*-Me	*p*-F-C_6H_4	170	22[c]
30	**5.30**	Me	*o*-Me	Me	170	78[c]
31	**5.31**	Me	*m*-Me	*p*-MeO-C_6H_4	20	68[e]
32	**5.32**	Me	*m*-Me	Me	7	72[e]
33	**5.33**	Et	H	Ph	60	80
34	**5.34**	Et	H	*p*-MeO-C_6H_4	58	60
35	**5.35**	Et	H	*p*-NO_2-C_6H_4	190	93
36	**5.36**	Et	H	Me	24	93
37	**5.37**	Bn	H	Ph	170	48
38	**5.38**	Bn	H	Me	30	80

[a] Reagents and conditions (except designated): **8** (1.0 equiv), R^4COOH (1.5 equiv), and $POCl_3$ (4.0 equiv) in acetonitrile, reflux. [b] Isolated by flash chromatography. [c] **8** (1.0 equiv), R^4COOH (1.5 equiv), and PPA (1.5 equiv) in $POCl_3$, 95 °C. [d] Pivaloyl chloride was employed. [e] Mixture of two isomers, 1:1 ratio estimated by ^1H NMR.

Scheme 6. Preparation of Diaminopyridine Precursors **4**.[a]

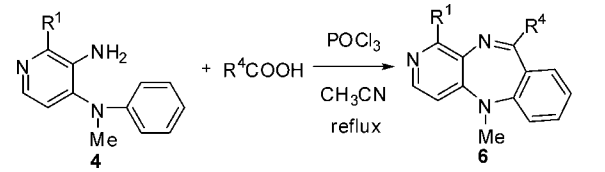


[a] Reagents and conditions: (i) Ph-NHMe, Et_3N, *n*-BuOH, reflux, 69%; (ii) Pd-C (10%), H_2, EtOH, **4a**, 87%; (iii) 12 N HCl, $SnCl_2 \cdot 2H_2O$, 90 °C, **4a**, 44%; **4b**, 35%.

carboxylic acid, and furan-2-carboxylic acid, could also provide the desired products in moderate yields (entries 8–10).

To expand the scope of the synthesis, diaminopyridine precursors **4** were prepared according to Scheme 6. Substitution of 4-chloro-3-nitropyridine **14** with *N*-methylaniline gave pyridine **15** in 69% yield. And chlorination of compound **15** using a reported method gave 2-chloro-N^4-methyl-N^4-phenylpyridine-3,4-diamine **4b**.[7]

Table 4. Synthesis of Pyrido[4,3-*b*][1,4]benzodiazepines[a]



entry	Pdt	R^1	R^4	time	yield[b]
1	**6.1**	H	Ph	30 h	77%
2	**6.2**	H	*p*-MeO-C_6H_4	24 h	76%
3	**6.3**	H	Me	7 h	87%
4	**6.4**	Cl	Ph	24 h	72%
5	**6.5**	Cl	Me	5 h	79%

[a] Reactions were conducted with 1.0 equiv of **4**, 1.5 equiv of R^4COOH, and 4.0 equiv of $POCl_3$ in refluxing acetonitrile. [b] Isolated by flash chromatography.

Application of the current benzodiazepine formation reaction conditions to both pyridines **4a** and **4b** gave the desired products **6.1**–**6.5** in good to high yields (Table 4).

In summary, a new synthetic route to pyridobenzodizepines using a one-pot Bischler−Napeiralski type cyclization reaction between pyridine-1,2-diamines and various carboxylic acids under mild acidic conditions was developed. The key cyclization reaction accommodates a large set of carboxylic acids. The method development for a pyridobenzodiazepine library was successfully completed as exemplified by the preparation of a 43-member library. Given that numerous anilines and carboxylic acids are readily available, the method demonstrated could be readily adopted to prepare large pyridobenzodiazepine libraries. The current strategy should complement existing methodologies to enable rapid exploration of this class of heterocycles.

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Supporting Information Available. Experimental details; 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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