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One-Step Synthesis of Diverse Pyridine-Containing Heterocycles with 3-Ethoxycyclobutanones at Room Temperature

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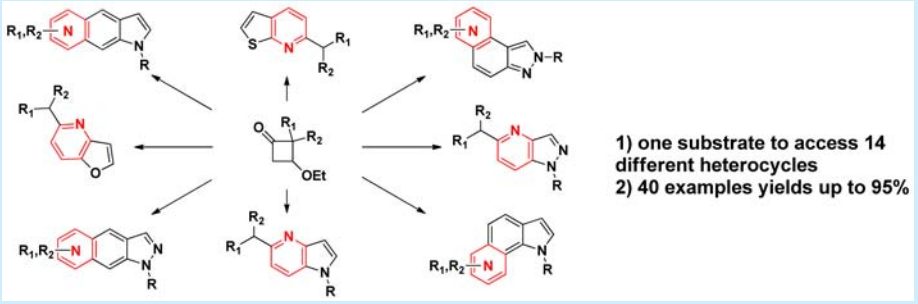
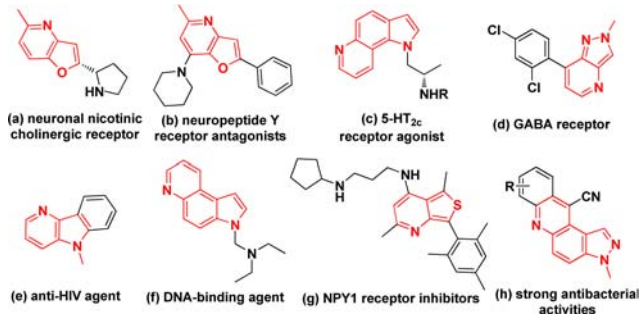
Supporting Information



ABSTRACT: An efficient and convenient approach toward a diversity-oriented synthesis of bioactive pyridine-containing fused heterocycles is described. Through a Lewis acid catalyzed union of 3-ethoxycyclobutanones with various heterocyclic amines, a broad range of heterocyclic compounds were prepared readily at ambient temperature with excellent regioselectivity.

Construction and screening of a chemically diverse heterocycle library plays an extremely important role in early drug discovery and chemical biology studies. Among those screened chemicals, pyridine-containing fused heterocycles are of particular interest because they exhibit a broad range of biological activities[1] due to the special rigid chemical conformation, π-stacking, and H-bond-forming ability (Scheme 1). Due to their great importance, the development of new general, efficient, and mild preparation methods for these scaffolds continues to be an important area of research effort. Although extensive investigations have been conducted on the construction of these heterocycles, important challenges still remain, especially for quickly accessing a focused small-molecule library containing these chemicals. For instance, the preparation of different pyridine-containing heterocycles usually needs different synthetic routes. In addition, current prevalent methods suffer from disadvantages that include harsh conditions, cumbersome steps, and operational difficulties. Furthermore, it is still difficult to prepare pyrido[3,2-*g*]indole,[2] thieno[3,2-*b*]pyridine,[3] pyrrolo[3,4-*b*]pyridine,[4] and 2*H*-pyrazolo[3,4-*f*]quinoline[5] via existing methods. Therefore, developing a versatile and efficient methodology to prepare these scaffolds from easily accessible building blocks is urgently needed.

Scheme 1. Pyridine-Containing Heterocycles as Potential Therapeutic Agents



Diversity-oriented synthesis (DOS)[6] represents a highly efficient and valuable strategy for the quick preparation of compound libraries of small molecules, with an emphasis on skeletal diversity from a readily available starting material. To date, a number of critical chemical modulators[7] of challenging biological targets have been discovered from DOS-derived compound libraries. Due to its convenience and significance, we wanted to employ DOS as a strategy to prepare a diverse heterocycle compound library which would be highly valuable for drug target screening. In recent years, 3-ethoxycyclobutanones[8] have been used as a versatile synthetic intermediate to prepare various types of compounds, including bicyclobutanes,[9] silyloxydienes,[10] six-membered ring compounds,[11] and pyrazoles.[12] Based on these studies, we therefore envisioned that a variety of pyridine-containing fused heterocycles might be accessed using 3-ethoxycyclobutanones and different heterocyclic amines via a DOS strategy. This new approach would allow

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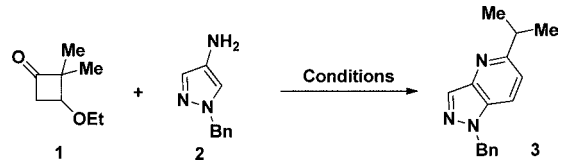
a rapid and facile fabrication of a unique fused heterocycle library in only one step. Herein, we report the development of an efficient one-step approach toward the synthesis of diverse heterocycles through Lewis acid promoted "3 + 3" annulation reactions between 3-ethoxycyclobutanones and substituted heterocyclic amines. Compared with traditional approaches, our reaction represents a highly effective method for the formation of pyridine-containing complex heterocycles with high yields and excellent regioselectivity.

To test our hypothesis, a model study was initiated with 2,2-dimethyl 3-ethoxycyclobutanone and *N*-benzyl-4-pyrazolamine (Table 1). First, different Lewis acids were tested as the reaction

Table 1. Optimization of the Reaction Conditions



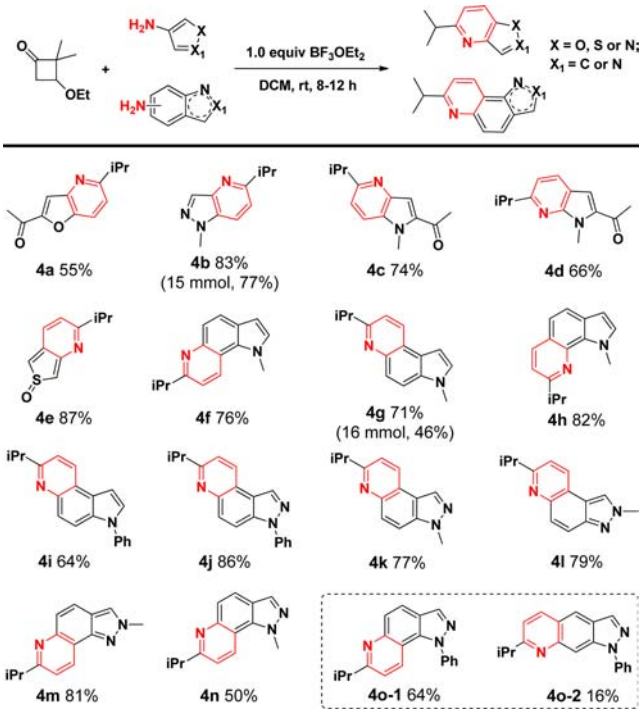
entry	catalyst	conditions	CR (%)[a]
1	$TiCl_4$	0.5 equiv, DCM, rt, Ar, 7 h	NR[b]
2	$SnCl_4$	0.5 equiv, DCM, rt, Ar, 7 h	18
3	BF_3OEt_2	0.5 equiv, DCM, rt, Ar, 7 h	49
4	BF_3OEt_2	0.7 equiv, DCM, rt, Ar, 7 h	63
5	BF_3OEt_2	1.0 equiv, DCM, rt, Ar, 7 h	86
6	BF_3OEt_2	1.5 equiv, DCM, rt, Ar, 7 h	89
7	BF_3OEt_2	1.0 equiv, MeCN, rt, Ar, 7 h	72
8	BF_3OEt_2	1.0 equiv, THF, rt, Ar, 7 h	31
9	BF_3OEt_2	1.0 equiv, DCE, rt, Ar, 7 h	36
10	BF_3OEt_2	1.0 equiv, MeOH, rt, Ar, 7 h	40
11	BF_3OEt_2	1.0 equiv, EtOH, rt, Ar, 7 h	34
12	BF_3OEt_2	1.0 equiv, 1,4-dioxane, rt, Ar, 7 h	57
13	BF_3OEt_2	1.0 equiv, EtOAc, rt, Ar, 7 h	52
14	BF_3OEt_2	1.0 equiv, DCM, rt, Ar, 10 h	84[c]

[a]Conversion ratio. [b]No reaction. [c]Isolated yield.

promoter. We found that $TiCl_4$ did not promote the reaction to give a desired product. When $SnCl_4$ or BF_3OEt_2 was used, the reaction afforded the desired 1*H*-pyrazolo[4,3-*b*]pyridine derivative **3** after 7 h at room temperature, and BF_3OEt_2 was superior to other Lewis acids (entries 1−3). Encouraged by these preliminary results, we started to optimize the reaction conditions. It was found that 1.0−1.5 equiv of BF_3OEt_2 was necessary to effectively promote the reaction (entries 4−6). It was observed that, besides DCM, the reaction proceeded smoothly in other solvents, such as MeCN, EtOAc, and 1,4-dioxane, and gave product **3** in fair conversion ratios (entries 7, 12, and 13). Interestingly, only one regioisomer **3** was observed under all different reaction conditions, which implied that this Lewis acid promoted "3 + 3" annulation reaction was very sensitive to the electronic distribution in the heterocycle partner. The influence of reagent stoichiometry was also evaluated. The 1:1 ratio of cyclobutanone **1** and 4-pyrazolamine **2** afforded **3** in a good isolated yield 84% (entry 14). Typically, the reaction proceeded to completion within 10 h in a clean manner at room temperature.

Having identified these optimal conditions, we set out to explore the scope for DOS of diverse complex bioactive heterocycles[13] using 2,2-dimethyl 3-ethoxycyclobutanone (Scheme 2). We found that a variety of heterocyclic amines were compatible with the optimal conditions, furnishing complex

Scheme 2. Reaction Scope with Respect to Heterocyclic Amines



pyridine-containing heterocycles. For example, by using 2-aceto-4-aminofuran, we obtained the furo[3,2-*b*]pyridine **4a**, a bicyclic compound, in a yield of 55%. With different amine-substituted five-membered heterocycles as substrates, other types of bicyclic heterocycles including thienopyridine, pyrazolopyridine, and pyrrolopyridine (**4b**−**4e**) were readily synthesized in good yields with excellent regioselectivity. Besides bicyclic compounds, tricyclic products (**4f**−**4o**) could smoothly be prepared, as well. For instance, it was found that varied pyrroloquinolines (**4f**−**4i**) were produced from corresponding indole derivatives. Similarly, different 1H- or 2H-substituted indazole amines can provide tricyclic pyrazoloquinoline products (**4j**−**4o**) in good to excellent yields. Annulation reactions always preferentially occurred at the more electron-rich position of the substrates to give just one regioisomer. The only exception was 1-methyl-1*H*-indazol-6-amine, which furnished both regioisomers with **4o-1** as the major product. To further prove the effectiveness and practicality of this new method, both **4b** and **4g** were prepared on a large scale (15−16 mmol) in good yields with only one regioisomer being obtained.

As illustrated in Scheme 3, the optimal reaction conditions were compatible with a variety of 3-ethoxycyclobutanones that reacted with heterocyclic amines to readily provide different novel heterocycles (compounds **5a**−**5x**). To our delight, a variety of substituents were readily introduced, such as methyl, ethyl, propyl, and cyclohexyl. In general, these reactions showed great reactivity, broad functional group tolerance, and satisfactory yields. In particular, a consistent complete regioselectivity of the reaction was observed. Interestingly, only single isomers were obtained in all examples.

It is noteworthy to point out that those pyridine-containing heterocycles are potentially valuable scaffolds for medicinal chemistry. In comparison to prevalent synthetic methods for these heterocycles, which normally require three or more steps for synthesis, our new method provides a general and efficient

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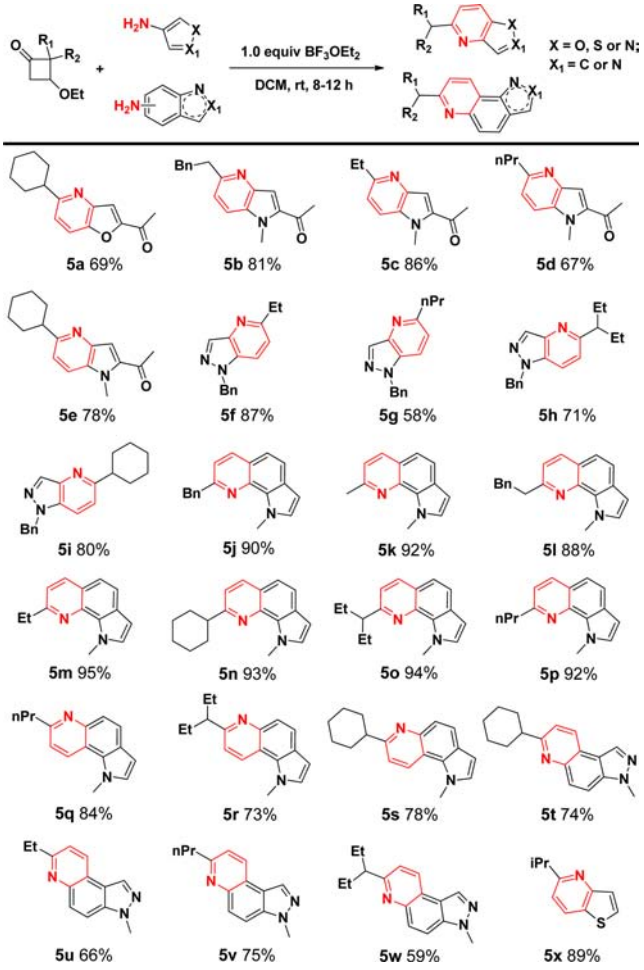
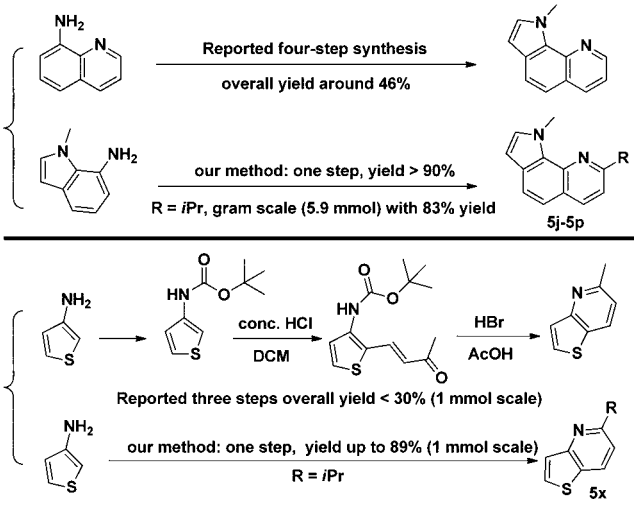
Scheme 3. Reaction Scope with Respect to 3-Ethoxycyclobutanones and Heterocyclic Amines



approach to these complex heterocyclic ring systems. For example, as shown in Scheme 4, pyrido[3,2-*g*]indoles can be prepared via a traditional protocol in four steps from 8-aminoquinolines in overall yields of 40−50%.[14] In contrast,

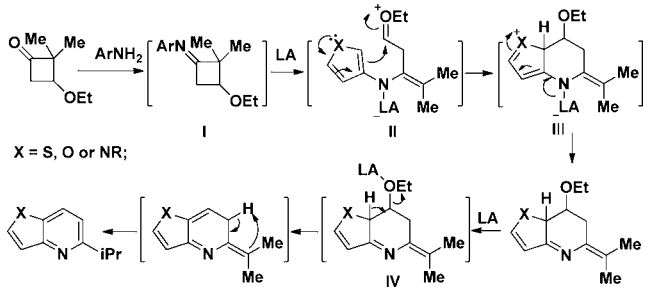
Scheme 4. Comparison between Traditional Methods and Our New Method for Pyrido[3,2-*g*]indole and Thieno[3,2-*b*]pyridine Synthesis



similar compounds **5j**−**5p** can be prepared in only one step with excellent yields up to 95% by our new method. Another case is provided by thieno[3,2-*b*]pyridines, which are typically prepared in three steps in low overall yield (<30%).[15] However, our protocol can readily provide thieno[3,2-*b*]pyridine derivatives in one step in yields up to 89%.

To account for the regioselectivity, a possible mechanism is illustrated in Scheme 5. Upon activation of the in situ generated

Scheme 5. Possible Mechanism of Regioselectivity with 3-Ethoxycyclobutanones



arylimine intermediate **I** from 2,2-dimethyl 3-ethoxycyclobutanone (**1**) with Lewis acids, the more substituted C2−C3 bond of the arylimine intermediate is broken down preferentially to form a zwitterionic intermediate **II**. Subsequently, intermediate **II** ring closes from the more electron-rich position to form the six-membered ring intermediate **III**. Following this intramolecular cyclization, a proton transfer provides intermediate **IV**. Finally, elimination of one molecule of EtOH from **IV** furnishes the corresponding pyridine-containing heterocyclic products.

In summary, we have developed a general, concise, one-pot method for DOS of bioactive pyridine-containing fused heterocycles from easily available starting materials at ambient temperature. A variety of complex heterocycles including substituted furopyridine, pyrazolopyridine, pyrrolopyridine, pyrazoloquinoline, pyrroloquinoline, and thienopyridines can be smoothly prepared. The method demonstrates excellent reactivity, good functional group tolerance, complete regioselectivity, and high yields. The resulting diverse heterocyclic scaffolds decorated with various substituents constituted a unique small-molecule library. Further expansion and biological screening of this focused heterocyclic library using 3-ethoxycyclobutanones is currently in progress.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01027.

Experimental procedures, characterization data, and copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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