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Report

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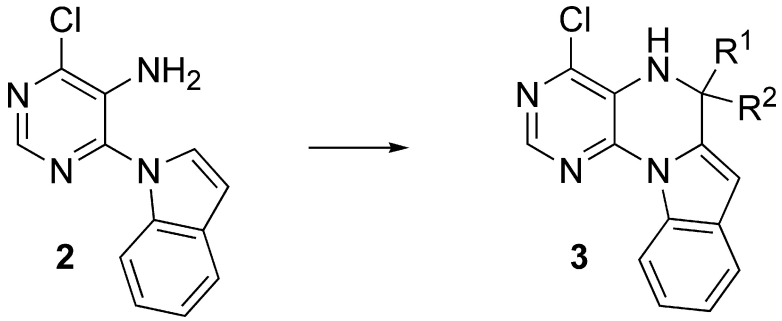

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Novel Heterocyclic Scaffold Consisting of Indole-Fused Pteridines

Lianyou Zheng, Jinbao Xiang, Qun Dang, Sigen Guo, and Xu Bai*

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

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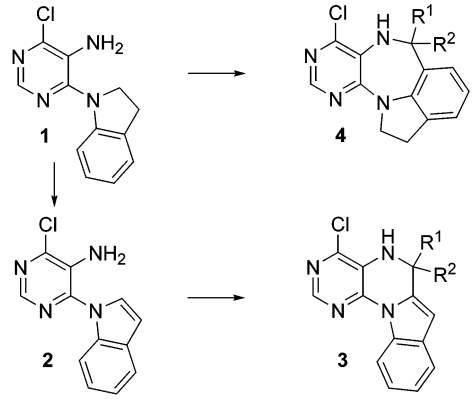
Novel fused heterocyclic ring systems are often considered important scaffolds in medicinal chemistry;[1] therefore, efficient methodologies leading to new scaffolds are always of interest to both organic and medicinal chemists. As a structural component of key biomolecules, a pyrimidine moiety was widely incorporated in the design of privileged structures. Consequently, the synthesis of various pyrimidine-fused heterocycles such as purines,[2] pyrrolopyrimidines,[3] pyrazolopyrimidines,[4] pyrimido-pyrimidines,[5] imidazopyrimidines,[6] and furopyrimidines[7] are frequently reported. For example, we recently introduced a new methodology for the efficient synthesis of pyrimidine-fused benzodiazepines,[8] and this methodology was further applied to the preparation of various fully substituted purine libraries.[2a,9] As part of an ongoing program to develop heterocyclic scaffolds, we investigated pyrimidine-fused pteridines because pteridines have been reported to exhibit a variety of biological activities and constitute the backbones of several marketed drugs. For example, the antifolate drug methotrexate (MTX) is used as an antitumor agent, and triamterene is used as a diuretic. Other pteridines are reported to have activities against biological targets such as alkyltransferase,[10] adenosine kinase,[11]mycobacterial FtsZ,[12] xanthine oxidase,[13] and neuronal nitric oxide synthase.[14]

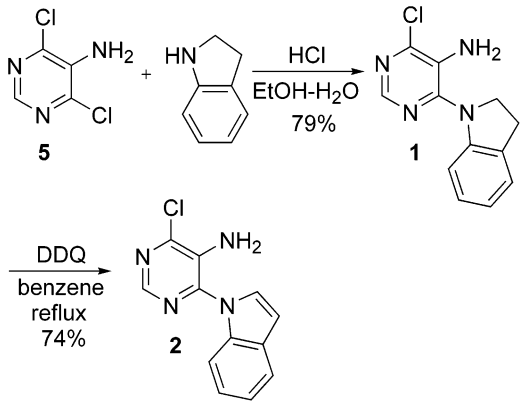
Although methods exist for the synthesis of their benzene-fused analogues, few examples of aromatic heterocycle-fused pteridines were reported.[15] To expand on our initial discovery of a novel cyclization reaction of pyrimidines leading to pyrimidine-fused benzodiazepines,[8] we envisioned that a 5-amino-6-(1-indolinyl)pyrimidine, **1**, should undergo an electrophilic cyclization with an aldehyde or a ketone at the phenyl ring, while a 5-amino-6-(1-indolyl)pyrimidine, **2**, should cyclize onto its electron-rich pyrrole ring (Scheme 1). Herein, the development and preliminary scope of the cyclization reactions of 5-amino-4-chloro-6-(1-indolyl)pyrimidine **2** with various aldehydes and ketones leading to a novel heterocyclic scaffold consisting of indole-fused pteridines are described.[16]

The key indole-substituted pyrimidine, **2**, was synthesized in a two-step sequence as depicted in Scheme 2. The treatment of commercially available 4,6-dichloride-5-aminopyrimidine **5** with indoline according to a literature procedure[17] gave pyrimidine **1** in a 79% yield. Subsequent

Scheme 1



Scheme 2



oxidation of the indoline moiety to its corresponding indole was achieved with DDQ in refluxing benzene[18] to yield the key aminopyrimidine, **2**.

The cyclization reaction of compound **2** with propionaldehyde was investigated under the conditions of refluxing acetonitrile in the presence of trifluoroacetic acid (TFA). As expected, the cyclization reaction occurred at the electron-rich pyrrole moiety of the indole ring to give the desired 4-chloro-5,6-dihydroindolo[2,1-h]pteridine (**3.1**) in an excellent yield of 93%. The scope of this reaction was further studied with various aldehydes and ketones and results are summarized in Table 1. The results show that compound **2** reacted with a wide range of aldehydes and ketones to give products, **3**, in moderate to excellent yields. The cyclization with aliphatic aldehydes proceeded quite fast and in excellent yields (Table 1, compounds **3.1** and **3.2**). The reactions with aromatic aldehydes and aliphatic ketones gave good to excellent yields although at a slower pace (Table 1, compounds **3.3**−**3.13**). Aromatic ketones reacted much slower and in a lower yield (Table 1, compounds **3.14**−**3.16**). The presence of an NO_2 group at the para position of phenyl methyl ketone resulted in losses of both reaction rate and yield (Table 1, compound **3.16**).

This cyclization could be rationalized to proceed through an iminium intermediate anagolously to the Pictet−Spengler reactions, as depicted in Scheme 3. Compound **2** reacted with an aldehyde or a ketone in the presence of TFA to give an

* To whom correspondence should be addressed. Phone: +86-431-5188955. E-mail: xbai@jlu.edu.cn.

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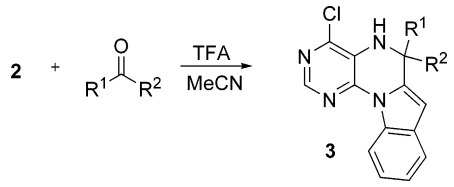
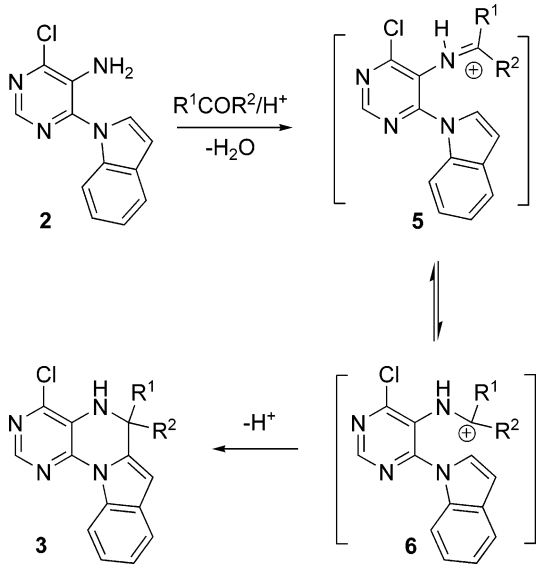
Table 1. Synthesis of 5,6-dihydroindolo[2,1-h]pteridines[a]



R^1	R^2	time (h)	product	yield (%)	mp (°C)
CH_3CH_2	H	0.5	**3.1**	93	139−140
$CH_3CH_2CH_2$	H	0.5	**3.2**	94	83−85
Ph	H	3	**3.3**	91	176−177
p-Me-C_6H_4	H	3	**3.4**	96	155−157
p-NO_2−C_6H_4	H	6	**3.5**	83	202−204
3′,4′-di-Cl−C_6H_3	H	5	**3.6**	82	225−227
o-MeO−C_6H_4	H	2.5	**3.7**	93	148−150
o-Cl−C_6H_4	H	8.5	**3.8**	98	142−144
o-NO_2−C_6H_4	H	28	**3.9**	72	154−156
m-NO_2−C_6H_4	H	18	**3.10**	87	214−216
CH_3CH_2	CH_3	6	**3.11**	93	135−136
$CH_3CH_2CH_2$	CH_3	15	**3.12**	90	110−112
R^1, $R^2 = -(CH_2)_5-$		3	**3.13**	89	153−154
Ph	CH_3	24	**3.14**	64	149−151
p-Me-C_6H_4	CH_3	45	**3.15**	70	134−136
p-NO_2−C_6H_4	CH_3	53	**3.16**	47	201−202

[a] All reactions were performed on 0.5 or 0.25 mmol scale.

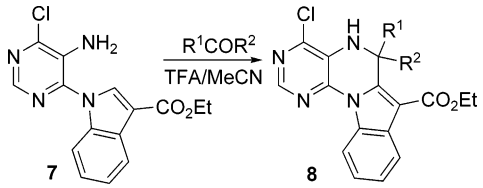
Scheme 3



imine which could be protonated under acidic conditions to yield an iminium ion, intermediate **5**, which resonates with carbon cation **6**. Electrophilic substitution of intermediate **6** at the electron-rich C-2 of the indole ring led to the final product, **3**.

Although the participation of indoles in Pictet−Spengler-type condensation reactions has often been reported,[19] most Pictet−Spengler reactions involve an aliphatic amine instead of the aromatic amine.[20] Compared to an aliphatic amine, an aromatic amine is less reactive in regard to imine formation with either an aldehyde or a ketone. In the current case, the combination of the pyrimidine ring and the indole ring systems provided some conformational restrictions compared to the classical Pictet−Spengler isoquinoline synthesis which has an aliphatic amine with more free-rotating bonds. These restrictions may help to speed up the cyclization step of the transformations. The rate-determining step seemed to be the formation of the iminium intermediate. Therefore, the reaction rate followed the order of reactivity of the carbonyl with the amino group: aliphatic aldehydes > aliphatic ketones ≥ aromatic aldehydes > aromatic aldehydes with electron-withdrawing groups > aromatic ketones > aromatic ketones with electron-withdrawing groups.

Table 2. Synthesis of 7-Ethoxycarbonyl-Substitued 4-Chloro-5,6-dihydroindolo[2,1-h]pteridines, **8**



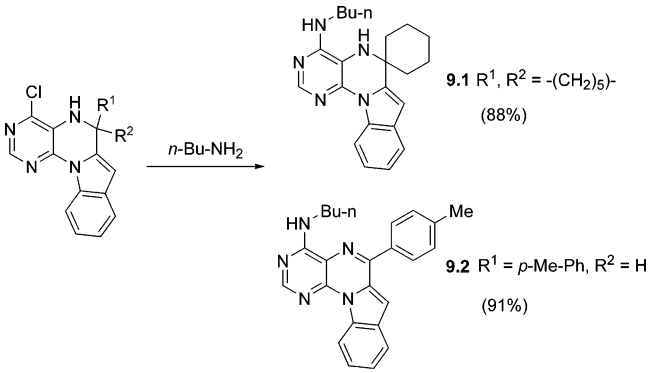
R^1	R^2	time (h)	compd	yield (%)	mp (°C)
Ph	H	20	**8.1**	86	210−213
p-Me-Ph	H	20	**8.2**	82	179−181
p−F−Ph	H	20	**8.3**	58	204−206
$CH_3(CH_2)_2$	H	20	**8.4**	82[a]	168−170
R^1, $R^2 = -(CH_2)_5-$		60	**8.5**	53	187−189

[a] About 5% of its stereoisomer was observed by LC-MS, and complete isolation of the minor isomer was not successful in the reaction scale.

It has been our long term goal to prepare large compound libraries of various heterocyclic scaffolds that are generally considered to be valuable assets to drug discovery programs. The indole moiety of the **3** compounds presents ample opportunity for five additional diversity points; therefore, it is important to determine the scope of the current reaction with regard to tolerability to the indole substituents. It is assumed that electron-donating groups should be permitted as substituents on the indole ring, while electron-withdrawing groups may reduce its reactivity toward an electrophile. To test the worst case scenario, we decided to prepare a pyrimidine with an electron-withdrawing group at C-3 of the indole ring that should reduce the electron density of the indole and present a steric hindrance. The 3-ethoxycarbonylindolylpyrimidine **7** (see Supporting Information for synthetic details) was subjected to the current cyclization conditions with several aldehydes and a cyclic ketone, and the results were listed in Table 2.

The reactions with pyrimidine **7** gave similarly cyclized products, **8**, albeit in slightly lower yields compared to those reactions with pyrimidine **2**. This observation could be attributed to the presence of an electron-withdrawing group (ethoxycarbonyl) which reduces the electron density at C-2 and, in turn, its propensity toward electrophiles. Furthermore, the ethoxycarbonyl at C-3 may also generate steric hindrance to its neighboring positions, thereby contributing to the slower reaction rate and slightly lower isolated yields. Nevertheless, it is important to demonstrate that the indole ring is tolerant of an electron-withdrawing group, which suggests that various other substituents (both electron-donating and electron-withdrawing groups) should be suitable for this type of cyclization. Consequently, this new meth-

Scheme 4



odology should be applicable to prepare a large library of novel indole-fused pteridine analogues.

The 4-Cl group was added by design to provide an entry to introduce an additional diversity point. For this purpose, two compounds (**3.4** and **3.13**) were selected to illustrate the propensity of the 4-Cl group toward nucleophilic substitutions (Scheme 4). The treatment of compound **3.13** with *n*-butylamine readily generated 4-(*n*-butylamino)-substituted pteridine **9.1** (R^1 and $R^2 = -(CH_2)_5-$) in an 88% yield, while aromatized compound **9.2** (R^1 = *p*-Me-Ph, R^2 = H) was obtained in a 91% yield from compound **3.4** under the same conditions. These results demonstrated the reactivity of the 4-Cl toward nucleophiles and the ease of aromatization (when R^2 = H) which is common among such types of compounds.

In conclusion, a novel heterocyclic scaffold consisting of indole-fused pteridines was readily prepared by the reaction of 5-amino-4-chloro-6-(indol-1-yl)pyrimidine with aldehydes or ketones. It was demonstrated that the indolylpyrimidine substrates had unusually high reactivity toward carbonyl compounds. The resulting 4-chloro-5,6-dihydroindolo [2,1-h]pteridines can undergo productive nucleophilic substitutions (demonstrated with an amine) to yield products with more diversity. This strategy provides an efficient way to access a library of compounds with privileged structures that are of interest in drug discovery.

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Supporting Information Available. Experimental details and compound characterization data are available as Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

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