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One-Pot Highly Regioselective Synthesis of Indole-Fused Pyridazino[4,5-*b*][1,4]benzoxazepin-4(3*H*)-ones by a Smiles Rearrangement

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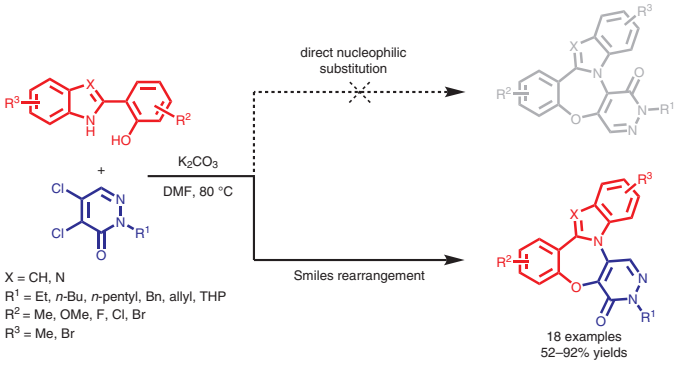

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Abstract A simple and convenient synthesis of indole-fused pyridazino[4,5-*b*][1,4]benzoxazepin-4(3*H*)-ones is described. A range of 2-(1*H*-indol-2-yl)phenols and 4,5-dichloropyridazin-3-ones are compatible with this reaction. A Smiles rearrangement is proposed as a key step in the highly regioselective construction of the products. The easy availability of the starting materials makes this an appealing method in organic synthesis.

Key words indoles, indolopyridazinobenzoxazepinones, regioselectivity, polycyclic heterocycles, Smiles rearrangement

Pyridazino[4,5-*b*][1,4]benzoxazepin-4(3*H*)-one analogues are among the most attractive structural motifs to the organic synthesis community, because these compounds are valued for their diverse biological activities.[1–6] In the recent decades, a great deal of effort has been devoted toward their synthesis.[7–10] However, heterocycle-fused pyridazino[4,5-*b*][1,4]benzoxazepin-4(3*H*)-ones have attracted surprisingly little attention. In this regard, indoles are important heterocyclic units that exhibit a wide range of biological activities.[11–12] Fusion of an indole skeleton with a pyridazino[4,5-*b*][1,4]benzoxazepin-4(3*H*)-one would lead to a new heterocycle library (Figure 1). To the best of our knowledge, no synthesis of this new fused heterocycle system has been reported and, consequently, the development of an economic and efficient method for their preparation is in high demand.

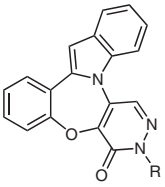
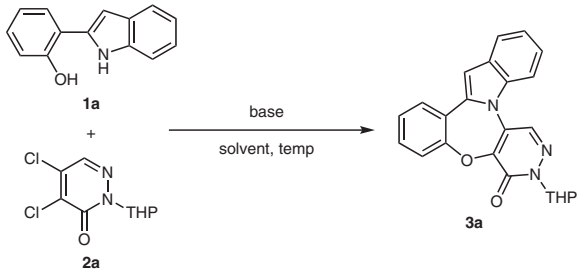


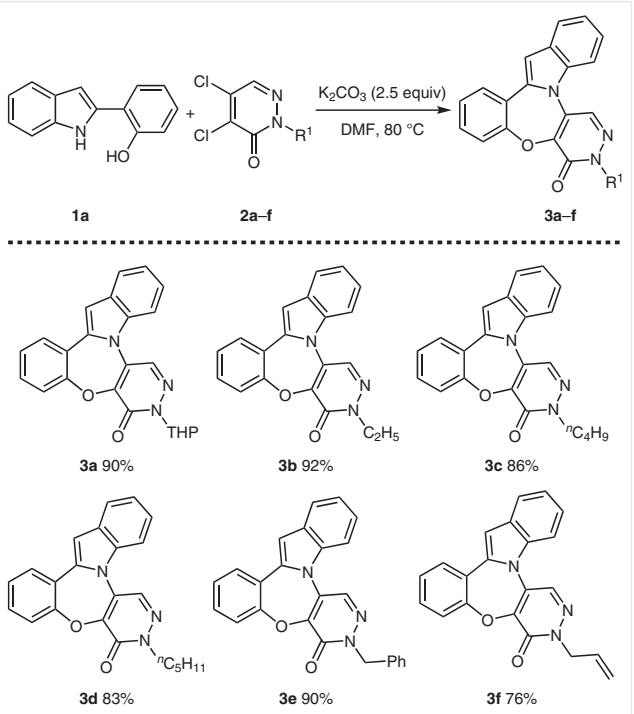
Figure 1 The structure of indole-fused pyridazino[4,5-*b*][1,4]benzoxazepin-4(3*H*)-ones

Table 1 Optimization of the Reaction Conditions[a]



Entry	Temp (°C)	Base	Solvent	Yield[b] (%)
1	50	K_2CO_3	DMF	81
2	80	K_2CO_3	DMF	90
3	100	K_2CO_3	DMF	87
4	80	Na_2CO_3	DMF	71
5	80	Cs_2CO_3	DMF	82
6	80	K_2CO_3	DMSO	71

[a] Reaction conditions: **1a** (0.3 mmol), **2a** (0.3 mmol), base (2.5 equiv), solvent, 3 h.
[b] Isolated yield after column chromatography.

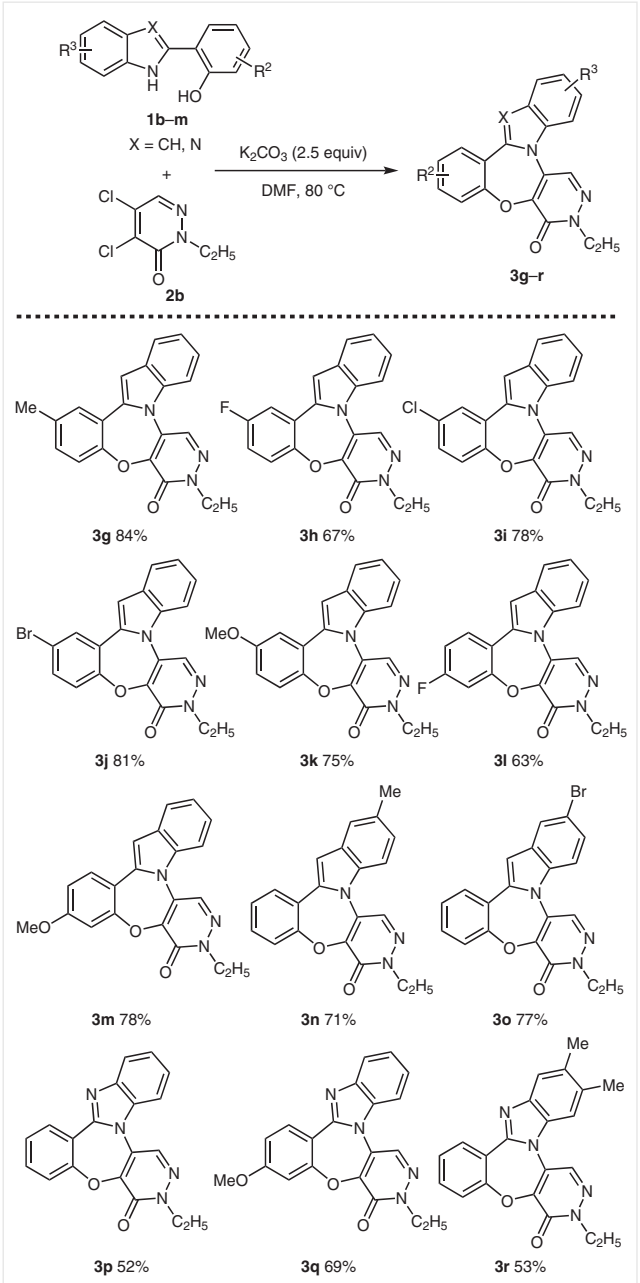


Scheme 1 The scope of 4,5-dichloropyridazin-3-ones. *Reaction conditions*: **1a** (0.3 mmol), **2a–f** (0.3 mmol), K_2CO_3 (2.5 equiv), DMF (2 mL), 80 °C, 3 h.

The Smiles rearrangement is a powerful and important tool for the construction of fused heterocycles.[13–17] In comparison with stepwise transformations, one-pot syntheses are much preferred due to their convenience. Consequently, the Smiles rearrangement has been introduced into one-pot syntheses of fused heterocycle systems.[18–21] On the basis of this concept, many N- and O-containing fused heterocycles have been conveniently produced with high efficiencies.[8,22–24] Inspired by the reported works,[9,10,25] we developed a one-pot, highly regioselective protocol for the construction of indole-fused pyridazino[4,5-*b*][1,4]benzoxazepin-4(3*H*)-ones through a Smiles rearrangement, using readily available starting materials.

We began our study by using 2-(1*H*-indol-2-yl)phenol (**1a**) and 4,5-dichloro-2-(tetrahydro-2*H*-pyran-2-yl)pyridazin-3(2*H*)-one (**2a**) as model substrates. To our delight, the desired product **3a** was obtained in 81% yield under our initial conditions (Table 1, entry 1). Raising the reaction temperature slightly improved the yield (entries 2 and 3), and the best result was achieved at 80 °C (entry 2). Next, a screen of bases indicated that potassium carbonate was the optimal base among those tested (entries 2, 4, and 5). The use of dimethyl sulfoxide as solvent gave an inferior result (entry 6). We therefore concluded that the best results were obtained with potassium carbonate as base and *N*,*N*-dimethylformamide as solvent at 80 °C, which gave the desired product **3a** in 90% yield.

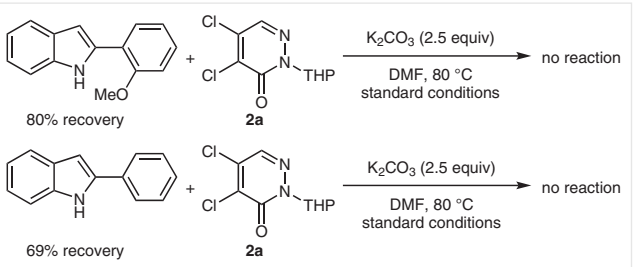
With the optimal reaction conditions in hand, we next examined the substrate scope. Various alkyl-substituted 4,5-dichloropyridazin-3-ones **2a–f** reacted smoothly with 2-(1*H*-indol-2-yl)phenol (**1a**) to give the corresponding products **3a–f** in good to excellent yields (Scheme 1). It was noteworthy that the allyl-substituted 4,5-dichloropyridazin-3-one **2f** was also tolerated in this transformation, giving the corresponding product **3f** in 76% yield.



Scheme 2 The scope of 2-(1*H*-indol-2-yl)phenols. *Reaction condition*: **1b–m** (0.3 mmol), **2b** (0.3 mmol), K_2CO_3 (2.5 equiv), DMF (2 mL), 80 °C, 3 h.

On the basis of these preliminary results, we then evaluated the scope of the 2-(1*H*-indol-2-yl)phenols with various substituents **1b–m** in this transformation (Scheme 2). To our satisfaction, all the tested 2-(1*H*-indol-2-yl)phenols worked well in the reaction, delivering the corresponding product **3g–o** in 63–84% yield. Remarkably, the structure of **3n** was unambiguously confirmed by X-ray crystallographic analysis (Figure 2).[26] The substrates were not limited to 2-(1*H*-indol-2-yl)phenols; interestingly, this method could also be extended to 2-(1*H*-benzimidazol-2-yl)phenols, and under the same reaction conditions, the product **3p** was produced in 52% yield. Similarly, substituents on the 2-(1*H*-benzimidazol-2-yl)phenol had no deleterious effect on the outcome (**3q**, **3r**).

To probe the reaction mechanism, two control experiments were carried out (Scheme 3). When attempts were made to react 2-(2-methoxyphenyl)-1*H*-indole or 2-phenyl-1*H*-indole with substrate **2a** under the standard conditions, no reaction occurred and the indole starting material was recovered in 80% and 69% yield, respectively. These experiments indicated that the indole nitrogen cannot serve as a nucleophilic center under the optimal reaction conditions, and that a hydroxy group in the substrate is indispensable



Scheme 3 Control experiments

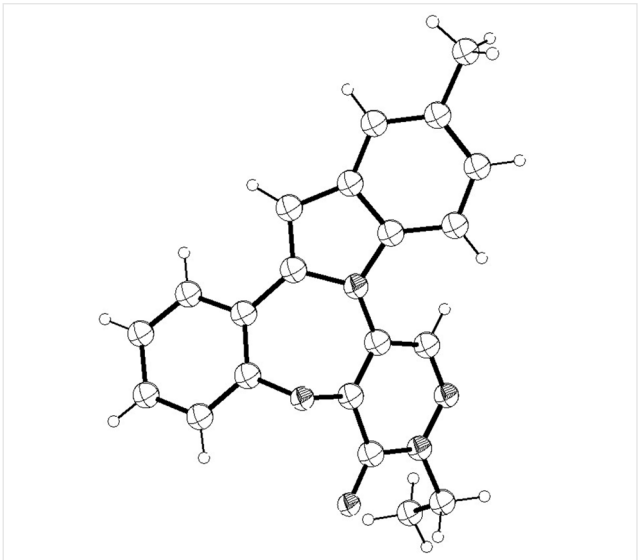
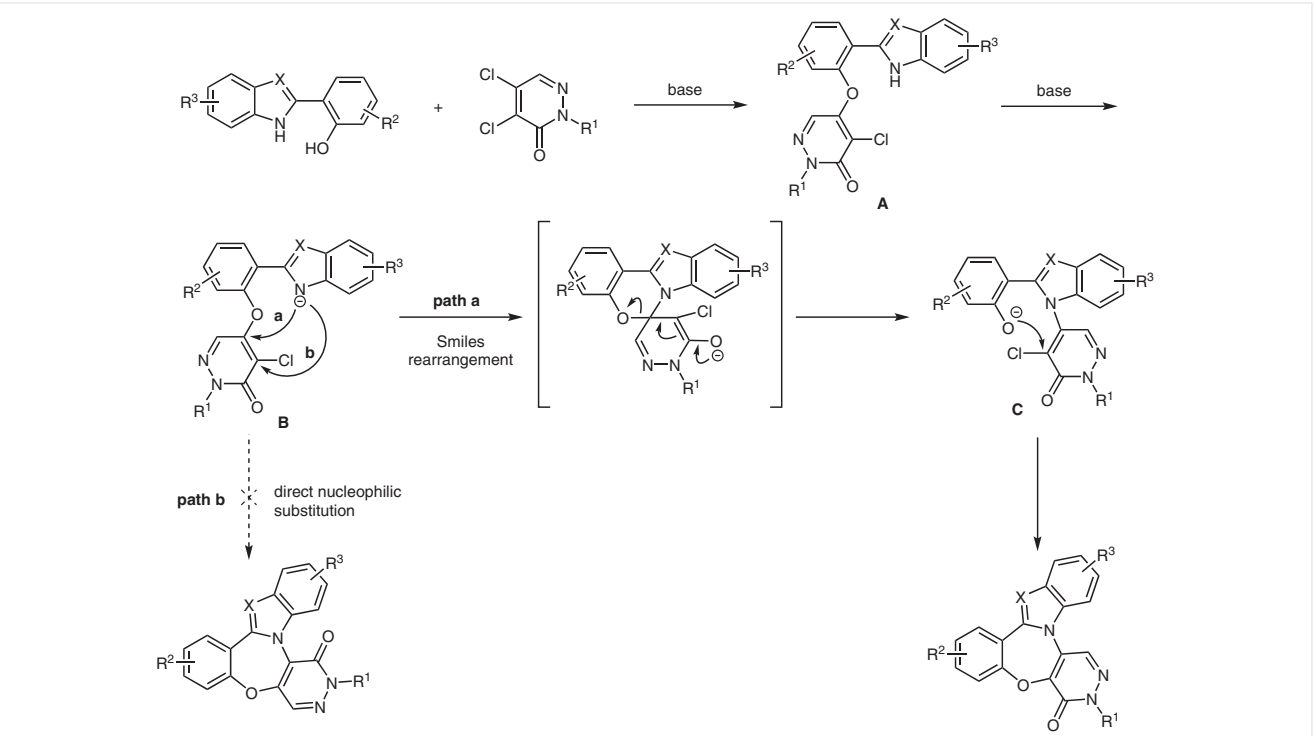


Figure 2 The X-ray structure of compound **3n**



Scheme 4 Possible reaction mechanism

for this transformation. We therefore deduced that a Smiles rearrangement is involved in this reaction.

Based on previous reports[8,25] and on our preliminarily mechanistic experiments, a possible reaction mechanism was proposed (Scheme 4). Under basic conditions, the intermediate **A** is initially formed through direct nucleophilic substitution of the phenolic oxygen anion with the 4,5-dichloropyridazin-3-one. The indole nitrogen anion **B** is then generated under the same reaction conditions. Next, a Smiles rearrangement occurs preferentially (path a), rather than direct nucleophilic cyclization (path b), to give intermediate **C**. Finally, the phenolic oxygen anion undergoes a second nucleophilic substitution to afford the desired product.

In summary, we have successfully developed a highly regioselective synthetic route for the construction of indolo[1,2-*d*]pyridazino[4,5-*b*][1,4]benzoxazepin-9(8*H*)-ones through a Smiles rearrangement under transition-metal-free conditions.[27] A range of substrates with various functional groups were compatible in this reaction and the corresponding products were obtained in good to high yields. A probable involvement of a Smiles rearrangement in this reaction was established by control experiments. Further studies on applications of this reaction in synthesizing other fused heterocyclic compounds are currently in progress.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1609338.

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(26) CCDC 1581528 contains the supplementary crystallographic data for compound **3n**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.
(27) **Indolo[1,2-*d*]pyridazino[4,5-*b*][1,4]benzoxazepin-9(8*H*)-ones 3a–r; General Procedure**
The appropriate 2-(1H-indol-2-yl)phenol **1** (0.30 mmol), 2-tetrahydropyranylpyridazin-3-one **2** (0.30 mmol), and K_2CO_3 (2.5 equiv.) were successively added to a 10 mL Schlenk tube. DMF (2 mL) was then added from a dropper and the resulting solution was stirred at 80 °C for 3 h. The mixture was cooled to r.t. then extracted with EtOAc (×3). The combined organic phase was washed with brine, dried (Na_2SO_4), and filtered. The solvent was then removed *in vacuo*to give a crude mixture that was purified by column chromatography (silica gel).
8-(Tetrahydro-2*H*-pyran-2-yl)indolo[1,2-*d*]pyridazino[4,5-*b*][1,4]benzoxazepin-9(8*H*)-one (3a)
Light-yellow solid; yield: 104 mg (90%); mp 122–124 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.43 (s, 1 H), 7.72–7.70 (m, 2 H), 7.66 (d, *J* = 8.2 Hz, 1 H), 7.54–7.52 (m, 1 H), 7.40–7.27 (m, 4 H), 6.98 (s, 1 H), 6.15–6.13 (m, 1 H), 4.17–4.14 (m, 1 H), 3.81–3.76 (m, 1 H), 2.23–2.15 (m, 1 H), 2.07–2.04 (m, 1 H), 1.80–1.71 (m, 3 H), 1.60–1.58 (m, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.55, 157.02, 144.65, 136.58, 135.94, 133.09, 131.39, 130.48, 129.45, 129.39, 126.36, 123.99, 123.54, 122.82, 122.15, 121.69, 111.56, 105.97, 83.32, 68.98, 28.99, 24.89, 22.83. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{23}H_{20}N_3O_3$: 386.1499; found: 386.1491.