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An Efficient One-Step Synthesis of Heterobiaryl Pyrazolo[3,4-*b*]pyridines via Indole Ring Opening

Sanghee Lee[†] and Seung Bum Park*[,†,‡]

Department of Chemistry and Department of Biophysics and Chemical Biology, Seoul National University, Seoul 151-747, Korea

sbpark@snu.ac.kr

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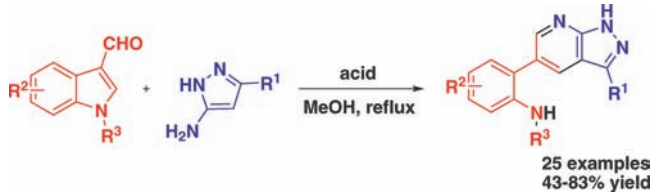
ABSTRACT



A mild one-step synthetic method to access privileged heterobiaryl pyrazolo[3,4-*b*]pyridines from indole-3-carboxaldehyde derivatives and a variety of aminopyrazoles has been developed. This novel method constructs heterobiaryls with the wide scope of substrate generality and excellent regioselectivity via indole ring opening.

Biaryls and heterobiaryls have attracted significant attention from the scientific community because of their relevance to various biological activities. Heterobiaryls frequently can be observed in numerous bioactive small molecules, and in particular, heterobiaryls fused with various heterocycles, such as pyrazole, pyridine, and pyrimidine, have been used as key pharmacophores.[1] As shown in Figure 1, a blockbuster drug, sildenafil citrate (Viagra),[2] and a potent anticancer agent, WYE-354,[3] contain heterobiaryls fused with privileged heterocycles as core skeletons. In addition, 1*H*-pyrazolo[3,4-*b*]pyridine is recognized as a privileged substructural motif of drug-like molecules and potential drugs. BAY 41-2272, which contains the heterobiaryl pyrazolopyridine substructure, stimulates soluble guanylate cyclase (sGC) via a nitric oxide independent regulatory site and induces vasodilation.[4] 6-Aryl pyrazolo[3,4-*b*]pyridines are also reported as potent inhibitors of glycogen synthase kinase-3 (GSK-3).[5] These examples emphasize the importance of pyrazol-fused heterobiaryls, as well as pyrazolopyridines, as key pharmacophores in bioactive small molecules.

The general synthetic method for the construction of biaryl and heterobiaryl compounds is via cross-coupling reactions catalyzed by transition metals. Although cross-coupling reactions offer several advantages such as broad reaction scope, high efficiency, and functional group compatibility, they have been reported to have some limitations: low efficiency with bulky substrates; environmental toxicity and safety of transition metals; laborious screening for proper catalysts, ligands, or additives; and high cost of transition metal catalysts.[6,7] Furthermore, the existing synthetic method requires multistep synthetic transformations to access im-

[†] Department of Chemistry.
[‡] Department of Biophysics and Chemical Biology.

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portant heterobiaryls, such as heterobiaryl pyrazolopyridines.[5] Therefore, synthetic organic chemists and medicinal chemists have been interested in the development of a novel synthetic pathway to access these molecular frameworks.

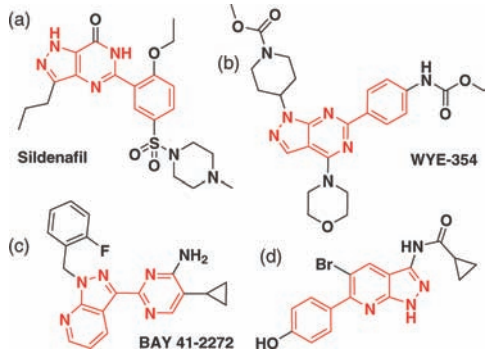
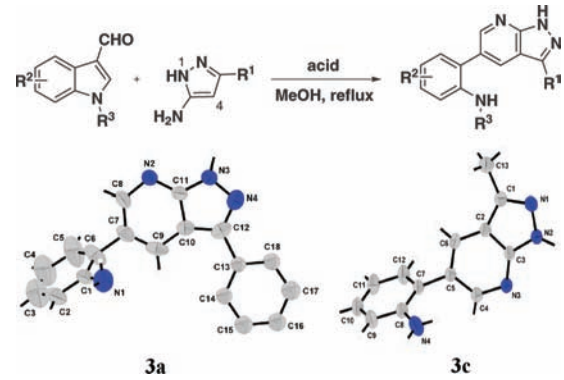


Figure 1. (a) Sildenafil, a potent and selective inhibitor of cGMP phosphodiesterase type 5 (PDE5), for the treatment of erectile dysfunction and pulmonary arterial hypertension (PAH). (b) WYE-354, ATP-competitive and selective inhibitors of the mammalian target of rapamycin (mTOR). (c) BAY 41-2272, stimulator of soluble guanylate cyclase (sGC). (d) Nonnucleoside glycogen synthase kinase-3 (GSK-3) inhibitor.

Here, we report a new synthetic method to access heterobiaryl pyrazolopyridines via an efficient one-step cyclization of aminopyrazoles with indole derivatives, as a part of our continuing efforts on the development of complexity-generating reactions (see Scheme 1).[8] An indole moiety is generally considered as a nucleophile in organic chemistry.[9] However, we induced indole to act as a dielectrophile by introducing an aldehyde moiety at the C-3 position and reacting it with dinucleophiles such as aminopyrazoles and hydrazines. The formation of imines followed by a second nucleophilic attack at the C-2 position of indoles leads to the formation of heterobiaryl pyrazolo[3,4-*b*]pyridines via indole ring opening. A similar indole ring opening approach was used by the Colotta group to construct 2-arylpyrazolo[3,4-*c*]quinoline derivatives using 3-ethoxalylindoles with hydrazines.[10] The Kolotaev group also observed that 2-substituted 3-acetylindoles can undergo indole ring opening by the treatment of hydrazine as an undesired side reaction.[11] In this study, we utilized aminopyrazoles as dinucleophiles for the one-step cyclization of indole derivatives to construct privileged heterobiaryl pyrazolopyridines. In fact, aminopyrazoles usually serve as N′/N-1 dinucleophiles to yield pyrazolo[1,5-*a*]pyrimidine, as has been reported in many cases.[12] However, in our system, aminopyrazole selectively attacked indole derivatives as N′/C-4 dinucleophiles to yield pyrazolo[3,4-*b*]pyridines with excellent regioselectivity, confirmed by X-ray crystallography (see Scheme 1). Moreover, we could readily access heterobiaryl pyrazolopyridines without the involvement of toxic transition metal catalysts or additives. Most importantly, our synthetic method allows the construction of sterically demanding 2,6-disubstituted biaryl pyrazolopyridines, which are difficult to obtain by transition-metal-catalyzed cross-coupling reactions.

Scheme 1. Synthetic Scheme of Heterobiaryl Pyrazolopyridines and Their X-ray Crystal Structures (**3a** and **3c**)



After we identified that one-step cyclization of indole-3-carboxaldehyde **1a** with 3-amino-5-phenylpyrazole **2a** yields heterobiaryl pyrazolo[3,4-*b*]pyridine **3a** via the indole ring opening, we attempted to optimize this transformation (see Table 1). First, we confirmed whether an acid catalyst could significantly enhance formation of the imine and was essential for this transformation (entry 1). Although various Brønsted-Lowry acids and Lewis acids can catalyze the formation of **3a** in moderate yield, $AlCl_3$ provides **3a** in better yield with cleaner reaction patterns (entries 2−10). By screening various solvents and quantities of the acid catalyst, we noted that polar protic solvents such as MeOH or EtOH were the better solvent systems, and 10 mol % $AlCl_3$ in MeOH was sufficient for achieving this transformation (entries 7, 11−17). When the reaction was conducted at room temperature, complete conversion of the starting materials was not achieved even after 24 h (entry 18).

After the reaction optimization, we investigated the reaction scope using 5-substituted aminopyrazoles (see Table 2). We successfully synthesized a series of desired products with aryl (**3a**), unsubstituted (**3b**), alkyl (**3c**), and hydroxy substituents (**3d**) in moderate to good yield. Aminopyrazoles

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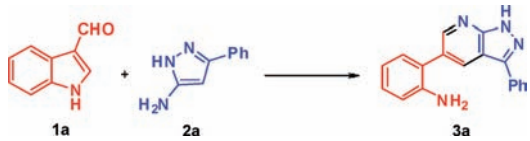
Table 1. Reaction Optimization for the Synthesis of Heterobiaryl Pyrazolo[3,4-*b*]pyridines[a]



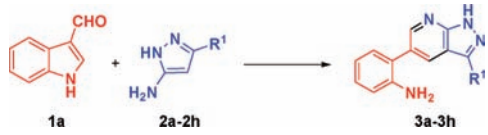
1a 2a 3a

entry	acid	solvent	conditions	yield (%)[b]
1		MeOH		7
2	AcOH	MeOH	5:95 v/v	46
3	formic acid	MeOH	5:95 v/v	60
4	TFA	MeOH	5:95 v/v	58
5	HCl	MeOH	5:95 v/v	30
6	HCl	MeOH	10 mol %	19
7	$AlCl_3$	MeOH	10 mol %	74
8	AgOAc	MeOH	10 mol %	0
9	$Cu(OAc)_2$	MeOH	10 mol %	0
10	AcOH	AcOH		41
11	$AlCl_3$	EtOH	10 mol %	63
12	$AlCl_3$	ACN	10 mol %	17
13	$AlCl_3$	THF	10 mol %	21
14	$AlCl_3$	toluene	10 mol %	29
15	$AlCl_3$	DCE	10 mol %	60
16	$AlCl_3$	DMF	10 mol %	44
17	$AlCl_3$	MeOH	30 mol %	51
18	$AlCl_3$	MeOH	10 mol %	22[c]

[a] All reactions employed indole-3-carboxadehyde **1a** (0.1 mmol) and 1.0 equiv of aminopyrazole **2a** in each solvent (50 mM) at 70 °C for 4 h. [b] Yield was determined by HPLC analysis using anthracene as an internal standard. [c] Reaction was performed at rt for 24 h.

with an electron-donating group (EDG) (**2e**) demonstrated slightly better yields than those with an electron-withdrawing group (EWG) (**2f**), because an EDG on pyrazole can increase the nucleophilicity of pyrazole at the C-4 position. The generality of this synthetic method was adequate to utilize heterocycle-substituted aminopyrazoles with furyl and thienyl groups (**3g**, **3h**).

Table 2. Synthesis of Heterobiaryl Pyrazolopyridines with Various Aminopyrazole Derivatives[a]



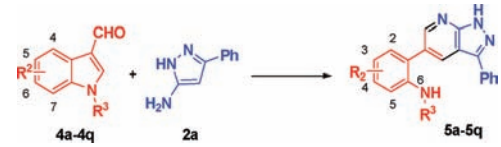
1a 2a-2h 3a-3h

product	R^1	yield(%)[b]
3a	phenyl	58
3b	H	71
3c	methyl	79
3d	hydroxy	62
3e	4-methoxyphenyl	78
3f	4-fluorophenyl	69
3g	2-furyl	72
3h	2-thienyl	65

[a] For the reaction condition and a detailed experimental operation, see Supporting Information. [b] Isolated yields.

Next, we validated the generality and efficiency of our synthetic methodology using a wide range of indole-3-carboxaldehyde derivatives, **4a**−**4q**. Most of the indole-3-carboxaldehyde derivatives were commercially available or could be easily prepared from indoles via the Vilsmeier−Haack reaction. As shown in Table 3, indole-3-carboxaldehyde derivatives were transformed to the corresponding heterobiaryl pyrazolopyridines (**5a**−**5n**) in reasonable to good yield. It is worth mentioning that our one-step indole cyclization could successfully yield 2,6-substituted heterobiaryl compounds (**5a**−**5f**), especially sterically congested **5f** with six consecutive quaternary carbons, which would be difficult to achieve by cross-coupling reactions because of the steric hindrance.[13]

Table 3. Synthesis of Heterobiaryl Pyrazolopyridines Using Indole-3-carboxaldehyde Derivatives **4a**−**4q**[a]



4a-4q 2a 5a-5q

5	yield(%)[a]	5	yield(%)[b]
5a	75	**5b**	61
5c	43	**5d**	76
5e	71	**5f**	61
5g	80	**5h**	82
5i	56	**5j**	68
5k	70	**5l**	61
5m	72	**5n**	71
5o	68	**5p**	83

[a] For detailed experimental procedures, see Supporting Information. [b] Isolated yields.

The electronic characters of the substituents on indole-3-carboxaldehydes contribute to this transformation: EWGs on

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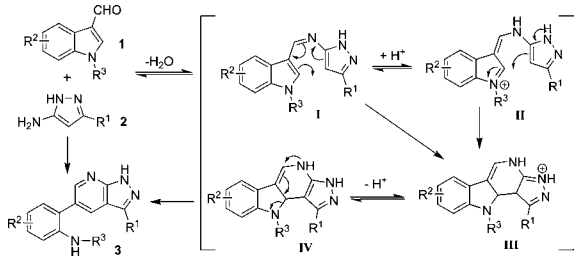
indole-3-carboxaldehydes enhance the efficiency of this transformation compared to EDGs (**5 g**, **5i**−**5k**), but the positional effects of substituents were marginal with *ortho* and *para* substitutents showing slight preferences toward the amine moiety (**5j**, **5l**, **5n**). We also confirmed that the *N*-modification of indole-3-carboxaldehydes did not hinder the acid-catalyzed one-step cyclization via the indole ring opening (**5o**−**5p**, **S-5a**).

Scheme 2. Postulated Mechanism



In Scheme 2, we postulate a mechanism for this one-step cyclization of indole-3-carboxaldehyde **1** with 5-aminopyrazole **2** to yield heterobiaryl pyrazolo[3,4-*b*]pyridine **3**. The first step is formation of the imine, as confirmed by TLC analysis, followed by intramolecular cyclization either via a pericyclic rearrangement of intermediate **I** or via C-4 nucleophilic addition of pyrazole to iminium electrophile (**II**) to generate a tetracyclic adduct (**III**). Finally, the resulting cyclic intermediate (**IV**) undergoes rearomatization, which leads to the opening of the indole ring, thereby yielding the desired heterobiaryl pyrazolo[3,4-*b*]pyridine **3**. Thus far, much previous literature has suggested that aminopyrazole serves as an N′/N-1 dinucleophile to yield pyrazolo[1,5-*a*]pyrimidine.[12] However, we did not observe the formation of pyrazolo[1,5-*a*]pyrimidines in our representative tested cases, which was confirmed by LC/MS using regioisomers of different masses (see Supporting Information). Therefore, we conclude that aminopyrazoles only serve as N′/C-4 dinucleophiles in this transformation to yield heterobiaryl pyrazolo[3,4-*b*]pyridines, which is supported by previous reports.[14] The regioisomer of heterobiaryl pyrazolo[3,4-*b*]pyridines was confirmed by X-ray crystallography (see Scheme 1) and ^{1}H nuclear Overhauser enhancement (NOE) NMR spectra (see Supporting Information). To confirm our conclusion, we tried the one-step cyclization of indole-3-carboxaldehyde **1a** either with 5-amino-3-methyl-1-phenylpyrazole **S-2a** or with 4-(4-fluorophenyl)-1*H*-pyrazol-5-amine **S-2b** to block N-1 nucleophilic attack or C-4 nucleophilic attack of pyrazoles, respectively. In fact, the modification on the N-1 position of pyrazole (**S-2a**) did not affect the one-step cyclization and C-4 nucleophilic addition producing the desired product **S-3a** in moderate yield. However, modification of the C-4 position of pyrazole (**S-2b**) did not lead to the formation of the product under the identical conditions. Interestingly, we did not observe any heterobiaryl pyrazolo[1,5-*a*]pyrimidine formation in the case of **S-2b** with **1a**, even after the extending the reaction time and elevating the temperature (see Supporting Information). These results support the notion that N′/C-4 dinucleophilic attack of aminopyrazole leads to the regioselectivity of this one-step cyclization. However, it is still unclear whether this one-step cyclization achieves this regioselectivity via N′/C-4 dinucleophilic addition of aminopyrozole or via the pericyclic rearrangement.

The resulting collection of heterobiaryl pyrazolo[3,4-*b*]pyridines was evaluated for their potential anticancer activity against various human cancer cell lines [lung carcinoma cell (A549) and cervical cancer cell (HeLa)] and normal cell lines [human embryonic kidney cell (293T) and muscle myoblast cell (C2C12)] (Table 2 in Supporting Information). The *in vitro* cell viability assay revealed that some compounds have cancer-cell specific inhibitory activity. Compound **5s** exhibited an excellent cancer-cell selectivity over normal cells as measured by mean % inhibition of cell proliferation at 10 μM (90% in A549, 81% in HeLa, 1% in 293T, 12% in C2C12). Compound **5r** also showed appreciable antiproliferative activities (IC_{50}) at 3.2 and 4.2 μM in HeLa and A549 cell lines (see Supporting Information).

In conclusion, we have developed a new one-step cyclization method for the synthesis of privileged heterobiaryl pyrazolo[3,4-*b*]pyridines from indole-3-carboxaldehyde derivatives and 5-aminopyrazoles. This transformation can efficiently generate heterobiaryl moieties without the limitations associated with the steric hindrance of substrates and we successfully demonstrated the wide scope of substrate generality, which is compatible with various functional groups, heteroaryl, and 2,6-substituted aryls with bulky substituents. We also observed excellent regioselectivity with 5-aminopyrazoles as the N′/C-4 dinucleophile to provide heterobiaryl pyrazolo[3,4-*b*]pyridines in moderate to good yield. The detailed mechanism of this regioselectivity and biological activities are currently being studied.

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Supporting Information Available: Experimental details, X-ray crystal structure, ^{1}H and ^{13}C NMR spectra of all new compounds, and LC/MS data for the confirmation of regioselectivity. This material is available free of charge via the Internet at http://pubs.acs.org.

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