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Preparation of 3-Diazoindolin-2-imines via Cascade Reaction between Indoles and Sulfonylazides and Their Extensions to 2,3-Diaminoindoles and Imidazo[4,5-*b*]indoles

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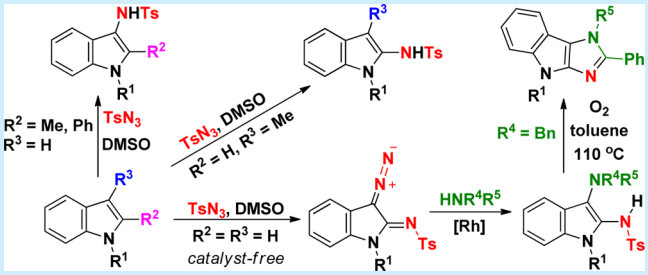
Supporting Information

ABSTRACT: 3-Diazoindolin-2-imines were constructed from indoles and sulfonylazides via an electronically matched 1,3-dipolar cycloaddition and a subsequent dehydroaromatization/ring-opening cascade. The reaction between 3-substituted indoles and sulfonyl azides provided 2-aminoindoles, while 2-substituted indoles furnished 3-aminoindoles. Moreover, 2,3-diaminoindoles could be prepared from the resulting 3-diazoindolin-2-imines and secondary amines via a rhodium-catalyzed amination. Further extension of 2,3-diaminoindoles led to the formation of imidazo[4,5-*b*]indoles.



Among the widely existing indole derivatives, compounds with a 2-aminoindole,[1] 3-aminoindole,[2] and 2,3-diaminoindole moiety[3] are much more attractive. Alkaloids possessing the 2- or 3-aminoindole framework exhibit a broad range of bioactivities, such as GSK-3β inhibiting,[2c] antibacterial, antimalarial, antitumor, and tubulin-inhibiting activities.[1,2,4] Due to their pharmaceutical importance and potential applications in the synthesis of more complicated indole derivatives, we became interested in the development of feasible strategies for the construction of 2-amino-, 3-amino-, and 2,3-diaminoindoles.

Recently, the fragile 1-sulfonyl-1,2,3-triazoles[5] have been demonstrated as α-imino metal carbene precursors in a variety of synthetically useful transformations,[6] such as transannulations,[7] ring expansions/rearrangements,[8] cyclopropanations,[9] C−H insertions,[10] and arylations.[11] Although Cu-catalyzed alkyne−azide cycloaddition proved to be a feasible and practical method in the preparation of 1-sulfonyl-1,2,3-triazoles with the help of suitable ligands,[12] development of metal-free formation of 1-sulfonyl-1,2,3-triazoles or their α-diazo imine forms remains formidably challenging.

In our previous work, we developed a Cu-catalyzed tandem synthesis of indolotriazoles,[13] which were later identified as 3-diazoindolin-2-imines in solid states by single crystal analysis (Figure 1, our previous work). We utilized them as rhodium carbene precursors for the synthesis of a series of valuable indole derivatives.

It was also reported that 1,2,3-triazoles could be constructed by the secondary amine-catalyzed inverse-electron-demand Huisgen 1,3-dipolar cycloadditions of ketones with azides.[14] Although the regioselectivity of this reaction was well controlled by the dipolar direction of enamines and azides, the variety of substituents at the 1-position of 1,2,3-triazoles was significantly limited to electron-donating groups. When

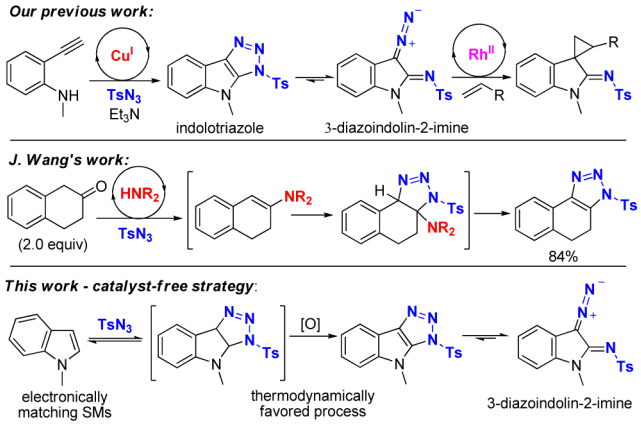


Figure 1. Our catalyst-free approach.

sulfonylazide was used for this 1,3-dipolar cycloaddition, the ring of 1-sulfonyl-1,2,3-triazoles was opened, affording amidines through a sequential alkyl shift.[15,14d] Only one exception was presented (Figure 1, J. Wang's work). In that case, the crowded amidine was not formed because the steric hindrance of the amine catalyst inhibited the alkyl shift as the authors claimed in their article.[14d]

Based on these reports, we proposed a novel strategy to prepare 3-diazoindolin-2-imines through a direct 1,3-dipolar cycloaddition of indoles with tosylazide (Figure 1, this work). It is anticipated that the dehydroaromatization of cycloaddition product could help the formation of thermodynamically favored indolotriazole and a catalyst could be reasonably avoided.

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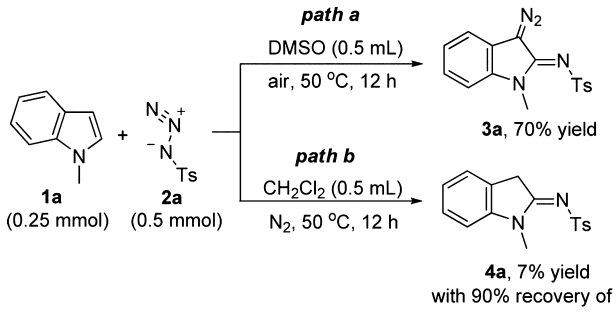
We initially examined the reaction between *N*-methylindole (**1a**, 0.25 mmol) and *p*-tosylazide (**2a**, 0.5 mmol) in DMSO (2 mL). After the mixture was stirred at 40 °C under air for 16 h, **3a** (Scheme 1) was isolated in 15% yield. We then screened the

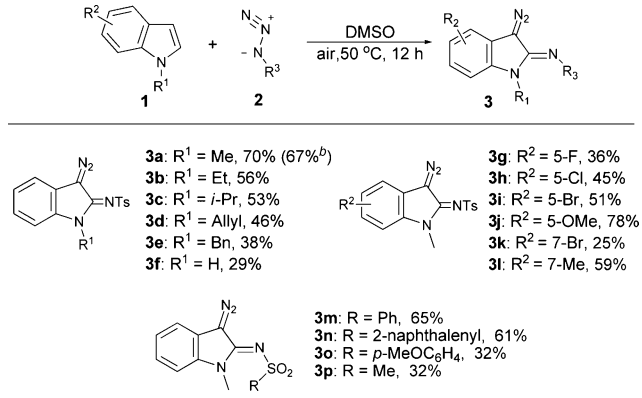
Scheme 1. Formation of 3a and 4a



reaction conditions (see Supporting Information, Table S1). The optimal reaction conditions were obtained when the reaction of **1a** (0.25 mmol) and **2a** (0.5 mmol) in DMSO (0.5 mL) was carried out under air at 50 °C for 12 h (Scheme 1, path a; Table S1, entry 19). We also performed the reaction in DCM under N_2, but isolated 2-iminoindoline **4a**[16] in 7% yield with 90% recovery of **1a** (Scheme 1, path b).

With the optimal reaction conditions, we examined the substrate scope (Scheme 2). The alkyl group on the 1-position

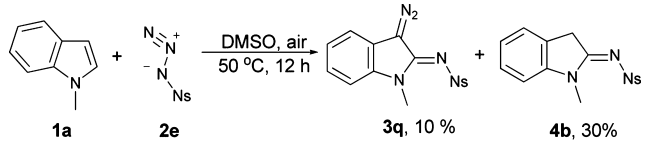
Scheme 2. Substrate Scope for the Preparation of 3[a]



[a]Reaction conditions: **1** (0.25 mmol), **2** (0.5 mmol), DMSO (0.5 mL), air, 50 °C, 12 h; isolated yields were reported. [b] For gram scale reaction: **1a** (0.655 g, 5 mmol), **2a** (1.97 g, 10 mmol), and DMSO (10 mL) were used, and 1.103 g (67% yield) of **3a** was isolated.

of indole could be varied from methyl (**3a**), ethyl (**3b**), isopropyl (**3c**), allyl (**3d**), and benzyl (**3e**) with moderate yields. It was worth noting that indole reacted with **2a** to afford **3f** (29% yield), which could not be prepared by our previous method.[13] The electronic effect of the substituent on the 5-position of indole was apparent. Electron-donating groups benefited the reaction and gave a higher yield (**3j**, 78%), but electron-withdrawing groups decreased the yields accordingly. As a result, 5-fluoro-, 5-chloro-, and 5-bromo-1-methylindoles produced **3g**, **3h**, and **3i** in 36%, 45%, and 51% yields, respectively. A substituent on the 7-position of indole presented a similar electronic effect. Compounds **3k** and **3l** were prepared in 25% and 59% yields, respectively. *p*-Tosylazide could be altered into benzenesulfonyl azide (**2b**), naphthalene-2-sulfonylazide (**2c**), 4-methoxybenzenesulfonyl-azide (**2d**), and methane-sulfonylazide (**2f**). Thus, **3m**–**p** were obtained in 32%–65% yields. For the reaction between 4-nitrobenzenesulfonylazide (**2e**) and **1a**, we isolated the desired product **3q**[13] (10% yield) along with 2-iminoindoline **4b**[16] (30% yield) as shown in Scheme 3. Single crystal analysis of **3d** and **3l** confirmed the existence of the 3-diazoindolin-2-imine skeleton.[17]

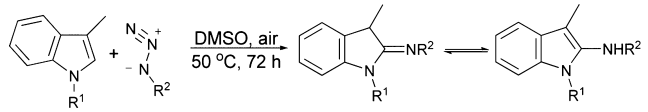
Scheme 3. Reaction of 1a with 2e



Electronically matching indole and azide is essential to a successful transformation. Neither phenyl azide nor benzyl azide reacted with *N*-methylindole (**1a**). The reaction also did not take place when *N*-tosylindole or *N*-acetylindole, instead of *N*-methylindole, was used.

In order to gain further insights into the reaction mechanism, we examined the 2- or 3- position blocked indoles **1b**–**f** (Table 1). 1,3-Dimethylindole (**1b**) readily reacted with **2a** to give **4c**

Table 1. Preparation of 2-Aminoindoles 4[a]



				4:4′	
entry	1 (R^1)	2 (R^2)	4/yield (%)	$CDCl_3$	DMSO-d_6
1	**1b** (Me)	**2a** (Ts)	**4c**/87	37:63	0:100
2	**1b**	**2b** (SO_2Ph)	**4d**/90	25:75	0:100
3	**1b**	**2c** (SO_2Np-β)	**4e**/94	100:0	0:100
4	**1b**	**2d** ($SO_2C_6H_4$OMe-*p*)	**4f**/89	29:71	0:100
5	**1b**	**2e** (Ns)	**4g**/84	100:0	0:100
6	**1c** (Et)	**2c**	**4h**/83	100:0	0:100
7	**1d** (Bn)	**2c**	**4i**/64[b]	46:64	0:100

[a]Reaction conditions: **1** (0.25 mmol), **2** (0.5 mmol), DMSO (0.5 mL), 50 °C, 72 h; isolated yields were reported. [b]48 h.

and its enamine form **4c**′ in 87% total yield (Table 1, entry 1). The ratio of **4c** (37%) and **4c**′ (63%) was determined on the basis of ^{1}H NMR in $CDCl_3$. When the ^{1}H NMR spectra were recorded in DMSO-d_6, the imine form **4c** disappeared and the enamine form **4c**′ was dominant. **1b**–**d** did react with sulfonyl azides **2b**–**e** to furnish **4d**–**i** in 64%–94% yields (Table 1, entries 2–7). In the cases of **4e** and **4g**, the ^{1}H NMR spectra in $CDCl_3$ presented a single imine form, while they showed a complete enamine form in DMSO-d_6. The solid structure of imine form **4g** was established by its single crystal analysis.[17] Tautoumerism occurred in some circumstances in $CDCl_3$, but all products existed in the enamine form in DMSO-d_6.

For 1,2-dimethylindole (**1e**), reactions with sulfonyl azides **2a**–**e** gave the corresponding 3-aminoindoles **5a**–**e** in excellent yields (Scheme 4). In these cases, the sulfonamide group migrated from the 2-position to the 3-position. Similar phenomena were observed in the reaction of 1-methyl-2-phenylindole (**1f**) with **2a**–**e**, which furnished **5f**–**j**.

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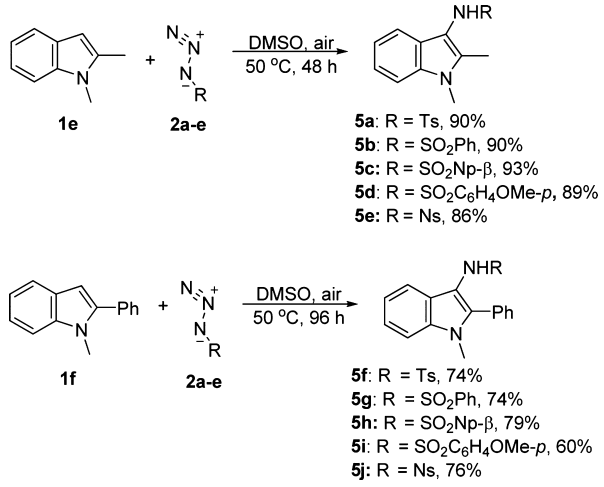
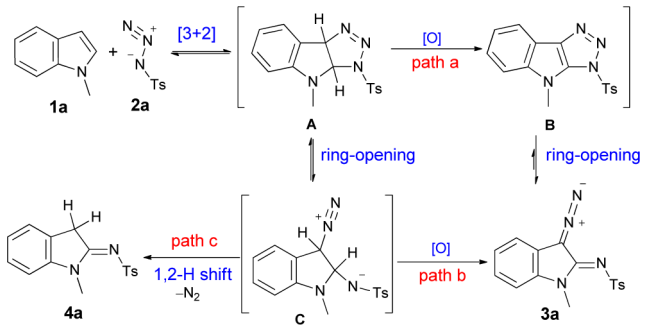
Scheme 4. Preparation of 3-Aminoindoles 5



Based on these results, we proposed a possible mechanism (Scheme 5). Despite the participation of the oxidant, the

Scheme 5. Possible Mechanism To Form 3a and 4a

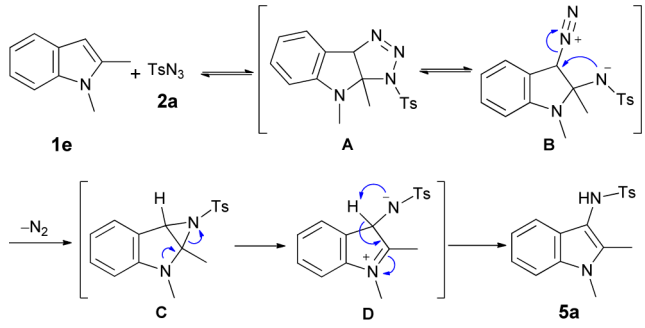


electronically matched Huisgen cycloaddition between **1a** and **2a** does occur to form **A** that can equilibrate with starting materials in the solution. Dehydroaromatization of **A** in the presence of O_2 generates **B** (path a). Subsequent ring opening of **B** leads to the formation of **3a**. Alternatively, the ring opening of **A** forms diazonium salt **C**, which undergoes dehydrogenation to give **3a** (path b). In the absence of an oxidant, **C** undergoes a 1,2-H shift with a loss of N_2 to afford **4a** (path c). In the case of 4-nitrobenzenesulfonylazide (**2f**, Scheme 3), the strong electron-withdrawing effect of the nitro group can facilitate the ring opening of the cycloaddition product **A** and the resulting diazonium salt **C** undergoes a 1,2-H shift to afford **4b**. When the 3-position of indole is blocked with methyl (Table 1), a 1,2-H shift occurs to generate **4**.[18]

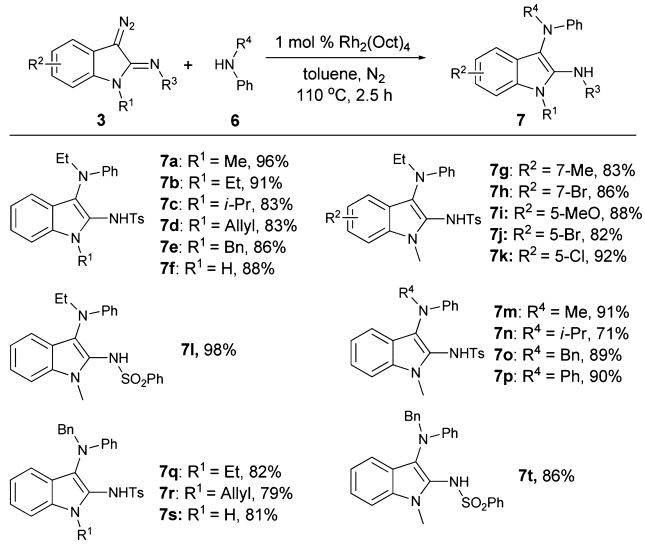
For 2-methylindole **1e** or 2-phenylindole **1f**, a 1,2-N shift occurs through an aziridine intermediate **C** (Scheme 6).[18] This rearrangement affords 3-aminoindole **5**.

As a synthetic application of 3-diazoindolin-2-imines (**3**), we tested the Rh-catalyzed amination of **3a** with *N*-ethylaniline (**6a**). After the mixture of **3a** (0.25 mmol), **6a** (0.5 mmol), and $Rh_2(Oct)_4$ (0.0025 mmol) reacted in toluene at 110 °C for 2.5 h, 2,3-diaminoindole **7a** was isolated in 96% yield (Scheme 7). No reaction was observed in the absence of the Rh catalyst. Toluene was the best solvent in comparison with others, such as benzene (81%), DCE (50%), and $CHCl_3$ (40%). With this satisfying result, we tested the reactivity of **3** with a series of secondary amines **6**. A variety of **3** were suitable to the

Scheme 6. Possible Mechanism for the Formation of 5a



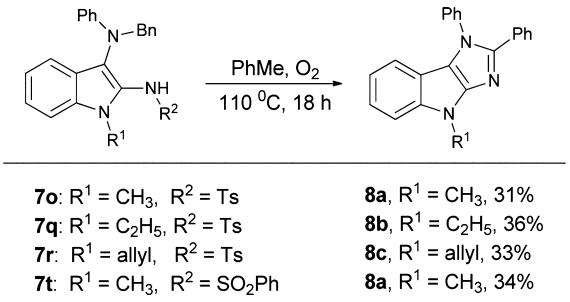
Scheme 7. Preparation of 2,3-Diaminoindoles 7



amination with **6a**, furnishing the corresponding 2,3-diaminoindoles **7a–l** in good to excellent yields. Substituents on the 1-position of **3** could be methyl (**7a**), ethyl (**7b**), isopropyl (**7c**), allyl (**7d**), benzyl (**7e**), or even hydrogen (**7f**). The substituent effect on the phenyl ring of indoles was not apparent (**7g–k**). Other secondary amines, such as *N*-methylaniline (**6b**), *N*-isopropylaniline (**6c**), *N*-benzylaniline (**6d**), and diphenylamine (**6e**) were also examined, and **7m–t** were obtained in 71% –91% yields.

The 2,3-diaminoindoles **7o**, **7q**, **7r**, and **7t** derived from *N*-benzylamine are stable in solid at room temperature, but instable in the solution under air at high temperature. By refluxing these compounds in toluene under O_2 for 18 h, imidazo[4,5-*b*]indoles **8a–c** were formed in yields varying from 31% to 36% (Scheme 8).

Scheme 8. Preparation of Imidazo[4,5-*b*]indoles 8



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In conclusion, we developed a general and practical approach to 3-diazoindolin-2-imines via the cascade reaction of indoles with sulfonyl azides. In comparison with Cu-catalyzed alkyne−azide cycloaddition, as well as the secondary amine-catalyzed enamine-azide cycloaddition, this method presented several advantages. First, the reaction is catalyst-free with excellent regioselectivity. Second, the starting materials are readily available with nice substrate diversity. Third, and most importantly, the electronically matched indoles and sulfonyl azides make the formation of diazoindolinimines feasible. Besides these featured characteristics, 2- and 3-aminoindoles could be prepared through the reactions of 3- or 2-substituted indoles with sulfonyl azides. Furthermore, the resulting 3-diazoindolin-2-imines could be applied as α-imino rhodium carbene precursors for the synthesis of diverse 2,3-diaminoindoles, which could be further extended into imidazo[4,5-*b*]indoles.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all new compounds, and crystallographic information files (CIF) for compounds **3d**, **3l**, and **4g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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