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The Reaction of 2,3-Dimethylimidazole-1-sulfonyl Azide Triflate with 3-Substituted Indoles: Reactivity and Scope

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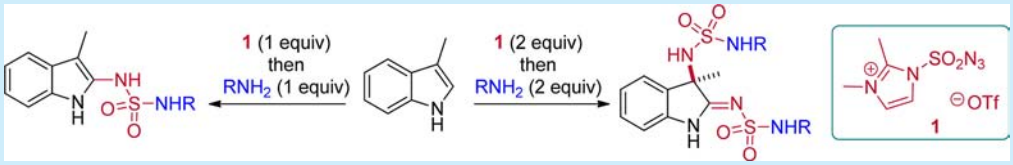
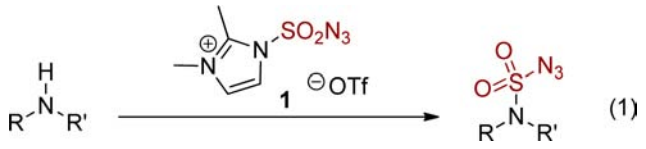
Supporting Information



ABSTRACT: 2,3-Dimethylimidazole-1-sulfonyl azide triflate reacts with 3-substituted indoles to deliver 2-iminoindolines, 2-aminoindoles, or 2-imino-3-aminoindolines by using different conditions. This imidazolium sulfonyl azide shows higher reactivity toward carbon nucleophile indoles than ordinary alkyl/aryl sulfonyl azides.

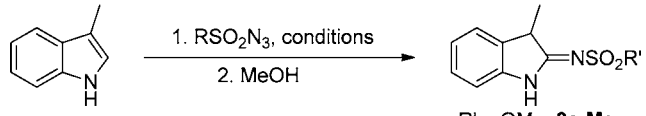
2,3-Dimethylimidazole-1-sulfonyl azide triflate **1**, a crystalline solid, was first introduced by the Fokin research group for the purpose of transferring a sulfonyl azide group to make sulfamoyl azide (eq 1) where, due to the cationic nature of



the imidazoulium group, this sulfonyl azide group transferring capability outcompetes its dinitrogen transferring ability for a sulfonyl azide.[1] Common azides[2] were also reported to react with electron-rich double bonds such as enamine without the aid of transition metals;[3] particularly, the Wang group has recently studied the reaction of sulfonyl azide with indole derivatives.[4]

In the course of our research, we quickly noticed that this reagent is more reactive toward nucleophiles than ordinary aromatic sulfonyl azide. When salt **1** was added to a solution of 3-methylindole in dichloroethane (DCE) at 20 °C, vigorous gas bubbling occurred and the indole **2a** was consumed in 5 min. The reaction mixture was then treated with excess methanol to give rise to 2-iminoindoline **3a-Me** in 67% yield (Table 1, entry 3). When the temperature was elevated to higher than 40 °C, the yield of **3a-Me** was improved to a maximum of 75% (entries 4−6). The same events also took place at 0 °C, though with a slower rate and lower yield (entry 1). Both dichloromethane (DCM) and chloroform as solvent gave inferior results. No reaction of **2a** was observed in toluene or DMSO at 10 °C, probably due to poor solubility or instability of **1** in these solvents respectively (entries 9−10). For comparison, TsN_3 was submitted to the identical conditions to find both reagents were nearly intact even in reflux DCE for 30 min. These data indicated that sulfonyl azide **1** is more reactive than

Table 1. Reaction of Indole 2a with Sulfonyl Azide 1 in Various Conditions[a]



entry	RSO_2N_3	solvent	temp.	time	prod., yield[b]
1	**1**	DCE	0 °C	20 min	**3a-Me**, 48%
2	**1**	DCE	10 °C	5 min	**3a-Me**, 64%
3	**1**	DCE	20 °C	5 min	**3a-Me**, 67%
4	**1**	DCE	40 °C	5 min	**3a-Me**, 75%
5	**1**	DCE	60 °C	5 min	**3a-Me**, 73%
6	**1**	DCE	80 °C	5 min	**3a-Me**, 73%
7	**1**	DCM,	10 °C	5 min	**3a-Me**, 58%
8	**1**	$CHCl_3$	10 °C	5 min	**3a-Me**, 48%
9	**1**	toluene	10 °C	5 min	**3a-Me**, –
10[c]	**1**	DMSO	10 °C	5 min	**3a-Me**, –
11[d]	TsN_3	DCE	20−80 °C	30 min	**3a-Ts**, –

[a]Conditions: RSO_2N_3 (0.5 mmol), **2a** (0.5 mmol, 1.0 equiv), solvent (4 mL), nitrogen atmosphere, then methanol (2.5 mmol, 5.0 equiv), 20 min. [b]Isolated yields. [c]Gas emission was observed whereas **2a** remained unchanged. [d]Both reagents remained intact.

common alkyl and aromatic sulfonyl azides and also suggested a potential method to access indolin-2-imine derivatives. Next, reactions of a variety of 3-substituted indoles with azide **1** were performed to exploit the generality of this two-step protocol. The results are tabulated below (Table 2). Alcohols other than methanol can also be used to trap an intermediate generated from the first step to give corresponding indolinyl imines

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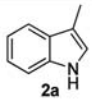
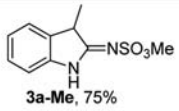
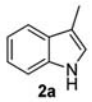
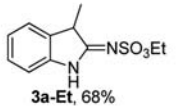
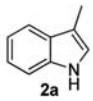
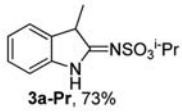
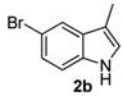
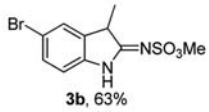
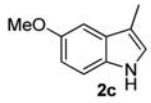
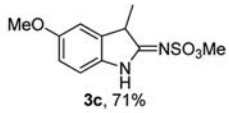
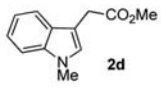
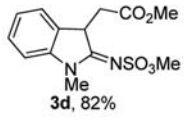
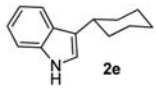
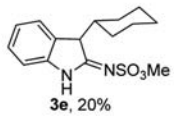
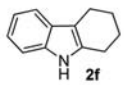
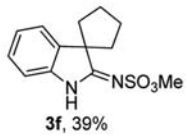
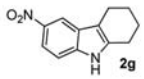
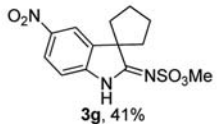
Table 2. Reactions of 2 with Azide 1 and Alcohols[a]

entry	indole	alcohol	product, yield[b]
1	 2a	MeOH	 3a-Me, 75%
2	 2a	EtOH	 3a-Et, 68%
3	 2a	^{i}PrOH	 3a-Pr, 73%
4	 2b	MeOH	 3b, 63%
5	 2c	MeOH	 3c, 71%
6	 2d	MeOH	 3d, 82%
7	 2e	MeOH	 3e, 20%
8	 2f	MeOH	 3f, 39%
9	 2g	MeOH	 3g, 41%

[a]Conditions: **1** (0.5 mmol), **2a** (0.5 mmol, 1.0 equiv), DCE (4 mL), 40 °C, 5 min, N_2, then alcohol (2.5 mmol, 5.0 equiv), 20 min. [b]Isolated yields.

(entries 2 and 3). It is not surprising that 6-substituted indoles **2b** and **2c** gave comparable yields. *N*-Methylindolylacetate **2d** is also an excellent substrate illustrating that carboxylate is compatible with this reaction (entry 6). The low yield of **3e** from **2e** indicates that the reaction somehow is hindered by the bulkiness at the 3-position. Interestingly, spiroindolinyl **3f** and **3g** were obtained smoothly from the reaction of tetrahydrocarbazoles **2f** and **2g** with **1** in moderate yields. The structure of **3f** was established unequivocally by X-ray crystallography (Figure 1).

In view of the present data and previous reports,[3f,4] a mechanism as shown in Scheme 1 has been proposed. Initially, [3 + 2] 1,3-dipolar cycloaddition takes place between 3-substituted indole **2** and sulfonyl azide **1** to afford fragile 1-sulfonyl triazoline **4**, which in turn undergoes ring contracting rearrangement to sulfonyl aziridine **5** driven by simultaneous

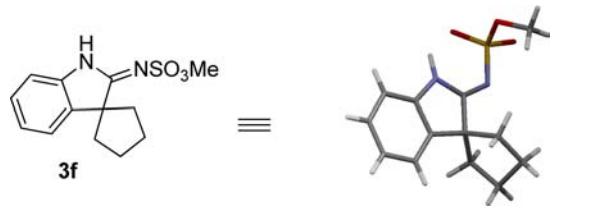
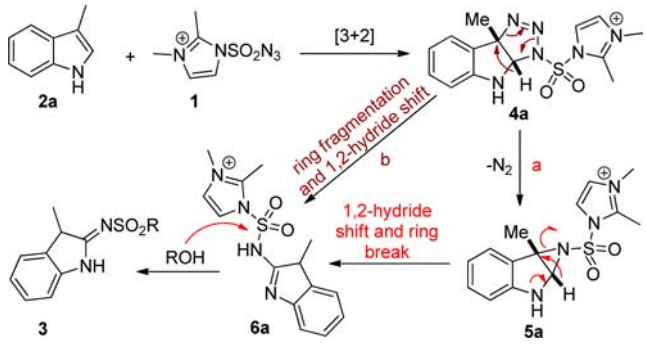


Figure 1. X-ray crystal structure of **3f**.

Scheme 1. Proposed Mechanism for the Reaction of Indole 2 with Azide 1



N_2 extrusion (route a). Strain releasing ring opening of the sulfonyl aziridine **5** is accompanied by a concomitant 1,2-hydride shift to give intermediate **6** which is alcoholysized and equilibrated to product **3**. Alternatively and probably more likely, fragile **4** directly decomposes to **6a** through a concerted nonsynchronous ring fragmentation−hydride shift process (route b). In the cases of **2f** and **2g**, a 1,2-alkyl shift event occurs instead to finish the spiro architecture in **3f** and **3g**. The strong electron-withdrawing nature of the imidazolium sulfonyl group was thought to facilitate all these steps, therefore accounting for the readiness of this reaction.

According to the above mechanistic analysis, we envisioned that the more nucleophilic amine should also be effective to substitute the imidazolium segment in intermediate **6**. Indeed, by replacement of alcohol with an amine in step 2 to treat the reaction mixture resulting from step 1, indolyl sulfuric diamide **7** was favorably obtained with high selectivity (Figure 2). Sulfuric diamides **7** were all obtained in good yields with small amounts of over-reacted products bisdiamides **8**. More fascinatingly, when excess amine was employed to quench the reaction, indolyl sulfuric 2,3-bisdiamide **8** was exclusively isolated in high yields. Obviously, **7** experiences a second round Huisgen cycloaddition with reactive 1,3-dipole **1**, ring contraction, and aziridine ring opening sequence to give rise to **8**, further demonstrating the uniqueness of **1** as a sulfonyl azide.

In order to gain more information about this reaction, indole **2h** and *N*-methylindole **2i** were submitted to conditions for method b. Upon addition of triazole salt **1**, both reactions finished in 90 s with N_2 bubbling. Subsequent treatment with *n*-butyl amine afforded **8h-Bu** and **8i-Bu** in 83% and 18% yields respectively (Scheme 2). These data also were in line with the working mechanism shown in Scheme 1 but with a further oxidation step which is common for an indoline and indole system.

In summary, the reactivity of 2,3-dimethylimidazole-1-sulfonyl azide triflate has been investigated and it was found that this highly electron-deficient sulfonyl azide is more reactive toward electron-rich carbon nucleophiles, namely indoles, than

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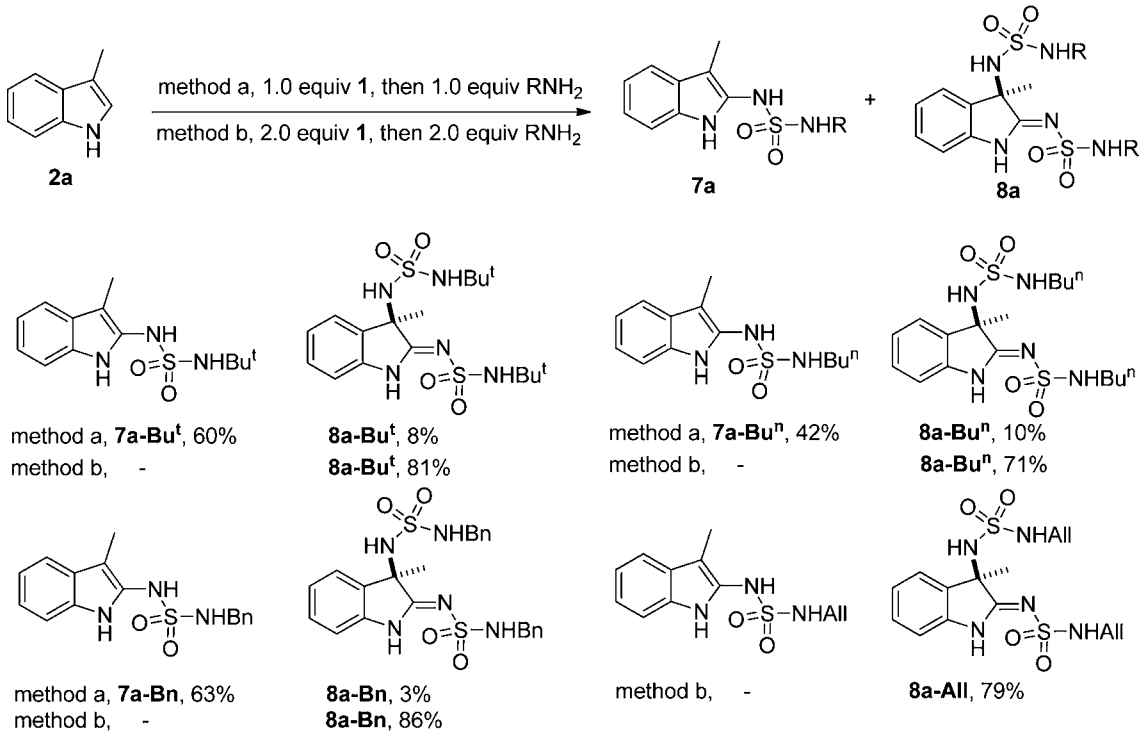
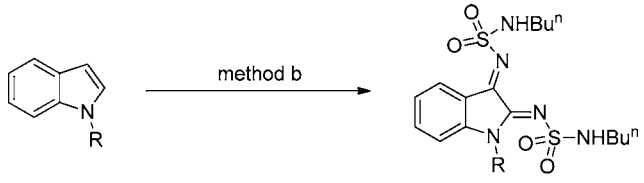


Figure 2. Preparation of indolyl sulfuric diamide **7** and 2,3-bisdiamide **8**. Conditions: (method a) **1** (0.5 mmol), **2a** (0.5 mmol, 1.0 equiv), DCE (4 mL), 40 °C for 5 min, N_2, then RNH_2 (0.5 mmol, 1.0 equiv), 20 min; (method b) same as method a except 2 equiv of **1** and 2 equiv of amine were used instead. Isolated yields are provided.

Scheme 2. Reaction of Indole and *N*-Methyl Indole with 2,3-Dimethylimidazole-1-sulfonyl Azide Triflate



common alkyl/aryl analogues. The imidazolium intermediate formed in the first step has been harvested by alcohols and amines to give related 2-iminoindolines and 2-aminoindoles, respectively. Moreover, exhaustive reaction of 2-methylindole with 2 equiv of this reactive amide and amines delivers corresponding 2-imino-3-aminoindolines which bears a density of nitrogen sites and hydrogen bonding donors/acceptors in close proximity indicating potential applications in metal coordination chemistry[5] and organocatalysis.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b01464.

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Notes

The authors declare no competing financial interest.

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