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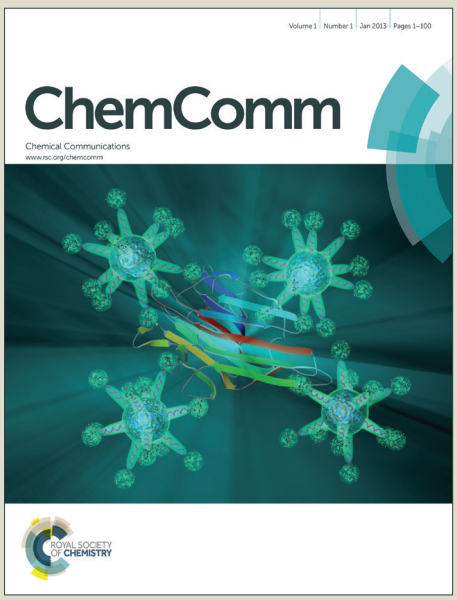

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Cyclization of Sulfide, Ether or Tertiary Amine Tethered N-sulfonyl-1,2,3-triazoles: A Facile Synthetic Protocol to 3-Substituted Isoquinolines or Dihydroisoquinolines

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A facile synthetic method to access 3-substituted isoquinoline or dihydroisoquinoline derivatives has been developed via a novel cyclization reaction from N-sulfonyl-1,2,3-triazole derivatives by thermally induced rearrangement.

Isoquinoline derivatives are an important kind of heterocyclic compounds[1] found in natural products,[2] pharmaceuticals,[3] and organic materials.[4] Accordingly, many useful synthetic methods to construct isoquinoline ring system have been developed, including the classic Pictet-Spengler reactions, Bischler-Napieralski reactions and so on.[5] Moreover, many 3-substituted isoquinolines, especially those with heteroatom substituent, are special agents with biological activities (Figure 1).[6] So far, many efforts have been made to synthesize isoquinoline derivatives,[7-9] but synthetic methods to access 3-heteroatom substituted isoquinolines are rare.[10] To this end, to develop a synthetic method that allows direct access of such isoquinolines with simple operation should be practically useful. In this paper, we wish to report an unprecedented rearrangement of sulfide, ether or tertiary amine-tethered N-sulfonyl-1,2,3-triazoles for the easy construction of 3-substituted isoquinoline derivatives.

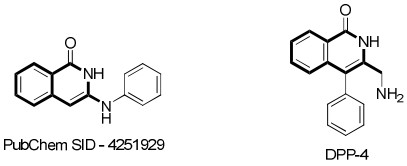
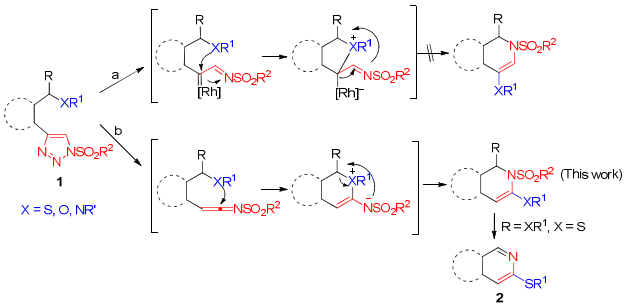


Figure 1. Representative Biologically Active Compounds.

N-sulfonyl ketenimines, derived from ring-opening of N-sulfonly triazoles, have been extensively explored in recent years for its diversified applications in organic synthesis.[11] As very active intermediate, N-sulfonly ketenimine can readily accept nucleophilic additions[12-14] or undergo pericyclic reactions.[15] During our ongoing investigations on ring-opening of N-sulfonly triazoles for the synthesis of heterocycles, we envisaged that dithioacetal-tethered N-sulfonyl-1,2,3-triazoles **1** could generate an aza-vinyl carbene intermediate, which then undergoes a tandem nucleophilic addition and ring-opening/recyclization process to form disubstituted isoquinoline derivative (Scheme 1, path a). To our surprise, the reaction of **1** gave an unprecedented isoquinoline derivative **2**, in which the sulfide substituent appears at the 3-position of isoquinoline backbone. Based on the structure of **2**, ketenimine intermediate was supposed to be the key intermediate, instead of aza-vinyl carbene. Moreover, it is also found that amine groups can also be used as the migrating group in the reaction.

Scheme 1. Hypothesized Rearrangement of Dithioacetal-tethered N-sulfonyl-1,2,3-triazoles.



We initially utilized 4-(2-(bis(ethylthio)methyl)phenyl)-1-tosyl-1*H*-1,2,3-triazole **1a** as model substrate to screen the reaction conditions. When the reaction was run at room temperature catalyzed in the presence of CuI, no reaction took

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place, while upon heating at 80 °C in a well-sealed tube under N_2, the reaction delivered isoquinoline derivative **2a** in 40% yield based on the ^{1}H NMR spectroscopy (Table 1, entries 1-2). Interestingly, if running the reaction of **1a** at 80 °C without catalyst, **2a** could also be obtained in 44% yield, indicating that the transformation may be a thermal-induced reaction (Table 1, entry 3). Subsequently, solvents and temperature were examined (entries 4-11). Consequently, it was found that DCE (1,2-dichloroethane) was better than other solvents as the isoquinoline derivative **2a** was obtained in 78% isolated yield (Table 1, entry 10). The structure has been unambiguously determined by the X-ray crystal structure of **2f**.[17, 18] Besides, the Rh catalyst[16] were also examined, but no influence was observed (entries 12-13).

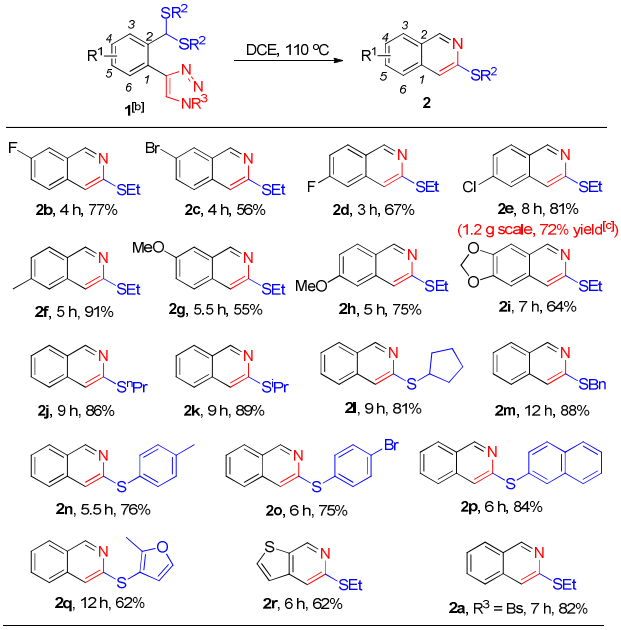
Table 1. Optimization of the Reaction Conditions.

entry[a]	catalyst	solvent	time (h)	T (°C)	yield (%)[b]
1[c]	CuI	DCE	10	rt	-
2[c]	CuI	DCE	10	80	40
3	-	DCE	20	80	44
4	-	Toluene	20	80	-[d]
5	-	CH_3Cl_3	20	80	40
6	-	DCM	20	80	33
7	-	CH_3CN	20	80	36
8	-	CH_3NO_2	20	80	33
9	-	DCE	8	100	71
10	-	DCE	4	110	80 (78)[e]
11	-	DCE	4	120	79
12	$Rh_2(OAc)_4$	DCE	20	80	43
13	$Rh_2(Piv)_4$	DCE	20	80	42

[a] Unless otherwise specified, all reactions were performed with **1a** (0.20 mmol) and catalyst (0.004 mmol) in a well-sealed tube under N_2. [b] Yields are determined by ^{1}H NMR using mesitylene as an internal standard. [c] 0.02 mmol of Et_3N was added. [d] No Reaction. [e] Isolated yields.

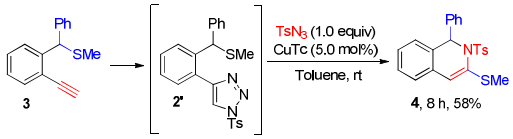
With the optimal reaction conditions in hand, we next surveyed the substrate scope of this reaction and the results are shown in Table 2. As for ethyl sulfides **1b**-**i** with different substituents on the aromatic ring, the reactions could all proceed smoothly to furnish the desired products **2b**-**i** in 55-91% yields. Other alkyl sulfides were well tolerated under the reaction conditions, providing the desired products **2j**-**m** in yields ranging from good to excellent. Furthermore, for aryl sulfides as well as furanyl sulfide, the desired products **2n**-**2q** were obtained in 62%-84% yields. When triazole **1r** was treated under the standard reaction conditions, **2r** was delivered in 62% yield. If the triazole was protected by Bs (4-bromophenylsulfonyl), the reaction also proceeded efficiently, giving the corresponding product **2a** in 82% yield. In addition, for the potential utility of this protocol, a gram scale reaction was carried out. As shown in Table 2, the reaction of **1e** (1.2g) proceeded smoothly to give the desired product **2e** in 72% yield.

Table 2. Reaction Scope: Synthesis of Isoquinolines **2**.[a]



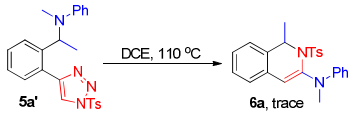
[a] Conditions: **1** (0.20 mmol) was heated in DCE (4 mL) at 110 °C for appropriate time. [b] As for substrates **1a**-**r**, R^3 = Ts (4-methylphenylsulfonyl). As for substrate **1s**, R^3 = Bs (4-bromophenylsulfonyl). [c] **2e** was obtained in 72% yield when the reaction was performed on a 1.2 g scale.

Scheme 2. Reaction of Phenylacetylene Derivative **3** with Tosyl Azide.



Since there was a thiolsulfonate eliminated in the above reaction, we therefore envisaged that the reaction of substrate with mono-sulfide would be different. Interestingly, upon treatment of mono-methylsulfide **3** with TsN_3 in the presence of CuTc, the CuAAC intermediate **2'** was very active and it readily underwent intramolecular rearrangement to afford the corresponding product **4**[19] in 58% yield at room temperature (Scheme 2).

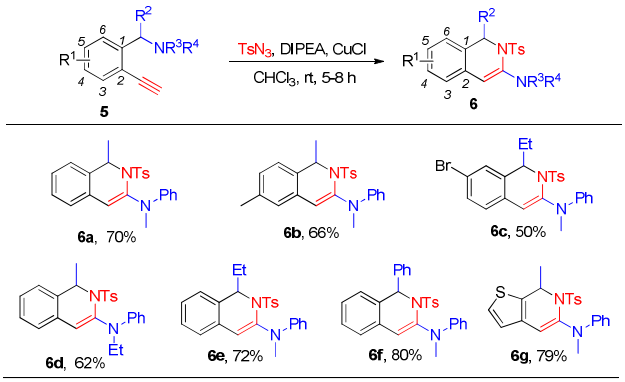
Scheme 3. Thermally Induced Reaction of **5a'**.



The next series of experiments were performed by using amine as a migrating group. N-methyl-N-(1-(2-(1-tosyl-1H-1,2,3-triazol-4-yl)phenyl)ethyl)aniline **5a'** was initially treated with the former reaction conditions, but only trace amount of dihydroisoquinoline derivative **6a** was obtained because the reaction system was complex (Scheme 3). To improve the yield

of **6a**, a one-pot procedure might be feasible. After screening the reaction conditions, it was found that upon stirring a mixture of **5a**, TsN_3 and DIPEA (ethyldiisopropylamine) in $CHCl_3$ at room temperature for 10 h in the presence of CuCl (5 mol %), the corresponding product **6a** could be obtained in 70% yield (for details, please see Table S1, in SI). As shown in Table 3, a broad range of phenylacetylene derivatives **5** reacted smoothly to provide the corresponding dihydroisoquinoline products **6** in moderate to good yields. For substrates with electron-donating or -withdrawing groups (R^1 = Me or Br), the reaction gave the desired product **6b** and **6c** in 66% and 50% yield, respectively. Meanwhile, for substrates bearing a Me, Et or Ph group (R^2) at the benzylic position, the corresponding dihydro-isoquinoline products **6d**-**6f** [20] were formed in 62%-80% yields. In addition, as for the thiophene-tethered phenylacetylene **5g**, the reactions also proceeded smoothly to afford the desired product **6g** in 79% yield.

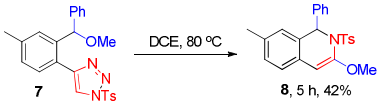
Table 3. Reaction Scope: Synthesis of Dihydroisoquinolins **6**.[a]



[a] Conditions: a mixture of **5** (0.20 mmol), TsN_3 (0.24 mmol), DIPEA (0.20 mmol), CuCl (0.01 mmol) in $CHCl_3$ (2 mL) was stirred at room temperature for appropriate time.

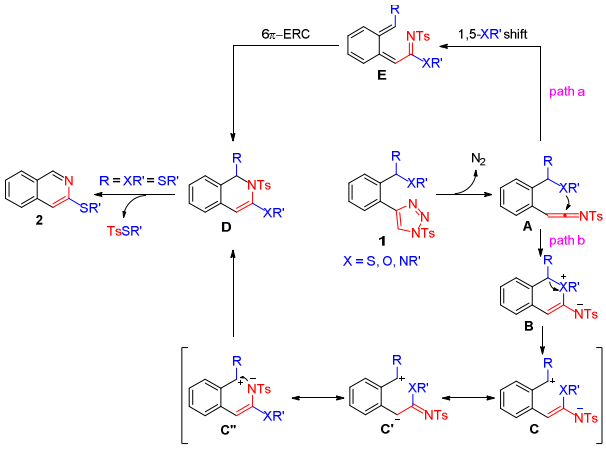
Methoxy group was also found to be a suitable migrating group in the reaction, as shown in Scheme 4, the reaction of methyl ether **7** could give the desired product **8** in 42% yield when it was stirred in DCE at 80 °C for 5h, demonstrating that this reaction could tolerate different migrating groups to give various 3-substituted isoquinoline derivatives.

Scheme 4. Reaction of methyl ether **7**.



Based on the above results and the previously reported literature,[11-14] two plausible mechanisms using substrate **1** as a model are outlined in Scheme 5. This reaction begins with a rapid formation of reactive ketenimine **A**. As shown in path b, followed by intramolecular nucleophilic addition, intermediate **B** is generated. The next ring-opening and rearrangement give the dihydroisoquinoline derivative **C** and its resonances **C'** and **C''**. Subsequent cyclization produces product **D**. While the ketenimine **A** also can undergo a 1,5-XR' shift to form dienimine **E**. A subsequent 6π-electrocyclic ring closure (6π-ERC) efficiently affords dihydroisoquinoline **D** (path a). Finally, the elimination of one molecule of thiolsulfonate results in the 3-sulfur substituted isoquinolines **2**.

Scheme 5. A plausible reaction mechanism.



In summary, we have developed a novel and efficient synthetic protocol to easily access 3-substituted isoquinoline or dihydroisoquinoline derivatives from cyclization reaction of sulfur, amino or alkoxy-tethered N-sulfonyl-1,2,3-triazoles. Notably, such 3-substituted isoquinolines were difficult to be synthesized by other traditional methods. The potential application and extension of the substrate scope of this novel synthetic methodology are currently underway in our laboratory.

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17 The crystal data of **2f** have been deposited in CCDC with number 1057819.

18 Interestingly, when the product **2c** was recrystallized in PE / EA, a novel dimeric product **9c** was obtained. The crystal data of **9c** have been deposited in CCDC with number 1037619.

5c **9c**

19 The crystal data of **4** have been deposited in CCDC with number 1400768.

20 The structure of **6** has been unambiguously determined by the X-ray crystal structure of **6f**, and the crystal data of **6f** have been deposited in CCDC with number 1421028.