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# PREPARATION OF 2-SULFONYL-1,2,3-TRIAZOLES BY BASE-PROMOTED 1,2-REARRANGEMENT OF A SULFONYL GROUP

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Dedicated to Professor Akira Suzuki on the occasion of his 80th birthday

**Abstract** – 1,2-Rearrangement of a sulfonyl group occurs on treatment of 1-sulfonyl-1,2,3-triazoles with a catalytic amount of 4-dimethylaminopyridine (DMAP) in acetonitrile to give an equilibrium mixture of 1-sulfonyl- and 2-sulfonyl derivatives, with considerable predominance of the latter. Subsequent acidic treatment of the mixture caused selective hydrolysis of the 1-sulfonyl derivative, which led to the isolation of the 2-sulfonyl-1,2,3-triazole in good total yield in a pure form.

1,2,3-Triazoles are five-membered ring heterocycles containing three nitrogen atoms of mixed hybridized forms in array, and substituted 1,2,3-triazoles constitute an important class of heterocyclic compounds of a variety of utilities, the area of which covers from pharmaceutical chemistry to materials science.[1] The synthesis of *C*,*N*-disubstituted 1,2,3-triazoles often suffers from a regiochemical issue. Thus, it has been the subject of particular interest in current heterocyclic chemistry to prepare them in a desired regiochemical form.[2] The 1,3-dipolar cycloaddition reaction of alkyl (or aryl) azide with terminal alkynes is one of the most reliable procedures for the synthesis of *C*,*N*-disubstituted 1,2,3-triazoles. Either 1,4- or 1,5-disubstituted 1,2,3-triazoles could be regioselectively prepared by the use of copper[3] or ruthenium[4] catalysts, respectively (Figure 1).

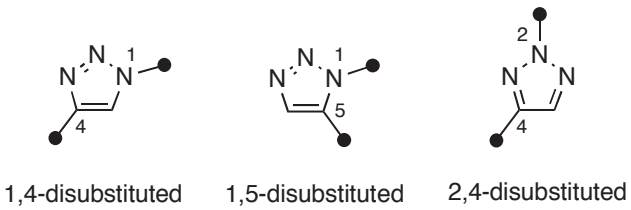
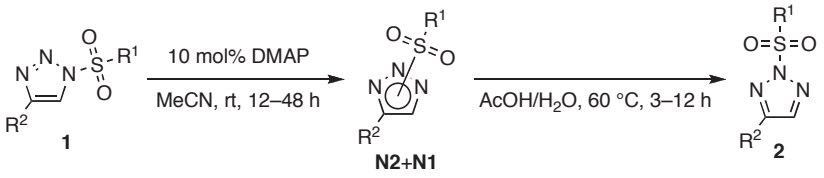



**Figure 1.** Spacial display of substituent in *C*,*N*-disubstituted 1,2,3-triazoles.

However, methods for the synthesis of 2,4-disubstituted 1,2,3-triazoles remain relatively undeveloped.[5,6] A substitution reaction of 4-substituted 1,2,3-triazoles with electrophiles often produces a mixture of regioisomers, *i.e.*, 1,4-disubstituted and 2,4-disubstituted 1,2,3-triazoles.[7] Higher electron density is allocated on the N1 nitrogen atom, which reacts better with an electrophile giving 1,4-disubstituted 1,2,3-triazoles under conditions of kinetic control.[8] On the other hand, 2,4-disubstituted 1,2,3-triazoles experience less steric hindrance than 1,4-disubstituted 1,2,3-triazoles, and therefore, the thermodynamically more stable 2,4-disubstituted 1,2,3-triazoles predominate under conditions of equilibrium control.[9] The thermodynamic preference for 2,4-disubstituted 1,2,3-triazoles was exploited by Fokin and co-workers in the regioselective synthesis of 4-substituted 2-hydroxymethyl-1,2,3-triazoles by a copper-catalyzed cycloaddition reaction of a terminal alkyne with sodium azide in the presence of formaldehyde.[10] During the course of our study on the nickel-catalyzed denitrogenative reaction of 4-substituted 1-sulfonyl-1,2,3-triazoles,[11] we found that the sulfonyl group underwent rearrangement from the N1 position to the N2 position to give 4-substituted 2-sulfonyl-1,2,3-triazoles,[12] which is the subject of the present communication.

4-Phenyl-1-tosyl-1,2,3-triazole (**1a**) could be readily prepared according to the literature procedure of the copper-catalyzed azide/alkyne cycloaddition.[13] The 1,2,3-triazole **1a** thus obtained was treated with a catalytic amount of 4-dimethylaminopyridine (DMAP, 10 mol%) in MeCN at room temperature for 12 h. An extractive work-up afforded a regioisomeric mixture of 4-phenyl-2-tosyl-1,2,3-triazole (**2a**) and **1a** (**2a**:**1a** = 88:12), suggesting that the sulfonyl group migrated from the N1 position to the N2 position (Table 1, entry 1).[14]

**Table 1.** Synthesis of 2-sulfonyl-1,2,3-triazoles.[a]

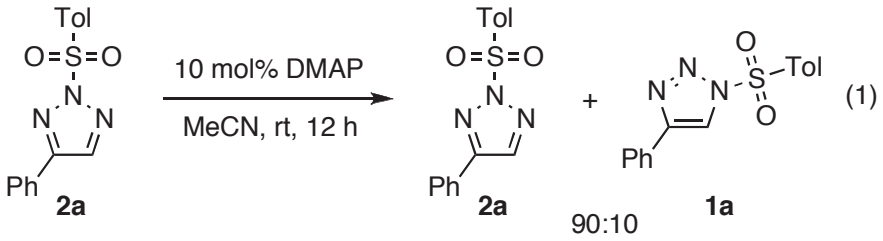



| Entry | **1** | $R^1$ | $R^2$ | **N2**:**N1**[b] | **2** | Yield[c] | Entry | **1** | $R^1$ | $R^2$ | **N2**:**N1**[b] | **2** | Yield[c] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | 4-$MeC_6H_4$ | Ph | 88:12 | **2a** | 82% | 6 | **1f** | 4-$MeC_6H_4$ | 4-$CF_3C_6H_4$ | 85:15 | **2f** | 75% |
| 2 | **1b** | 4-$FC_6H_4$ | Ph | 91:9 | **2b** | 86% | 7 | **1g** | 4-$MeC_6H_4$ | 4-$MeOC_6H_4$ | 92:8 | **2g** | 86% |
| 3 | **1c** | 4-$MeOC_6H_4$ | Ph | 87:13 | **2c** | 73%[d] | 8 | **1h** | 4-$MeC_6H_4$ | 2-Naphthyl | 92:8 | **2h** | 78% |
| 4 | **1d** | 2-Naphthyl | Ph | 88:12 | **2d** | 80% | 9 | **1i** | 4-$MeC_6H_4$ | 1-Cyclohexenyl | 89:11 | **2i** | 76%[d] |
| 5 | **1e** | *n*-Bu | Ph | 86:14 | **2e** | 72% | 10 | **1j** | 4-$MeC_6H_4$ | *n*-Hex | 90:10 | **2j** | 78%[e] |

[a] Reaction conducted on a 0.5 mmol scale. [b] Determined by $^1$H NMR analysis. [c] Isolated yield. [d] 20 mol% of DMAP was used. [e] The reaction was carried out with 50 mol% of DMAP at 60 °C, and then the isomeric mixture was heated at 70 °C.

Unfortunately, the regioisomeric mixture failed to be separated with flash column chromatography on silica gel. However, when the isomeric mixture was heated at 60 °C in AcOH/$H_2O$ (10/1), the N1 sulfonyl group of **1a** was selectively hydrolyzed in preference to the N2 sulfonyl group of **2a**. Subsequent chromatographic isolation readily afforded analytically pure **2a** in 82% overall yield.[15] The structure of **2a** was unambiguously confirmed by X-ray crystallographic analysis.

In order to gain a mechanistic insight, the isolated **2a** was subjected to the identical reaction conditions for the rearrangement [DMAP (10 mol%), acetonitrile, room temperature, 12 h] (eq 1). A regioisomeric mixture of **2a** and **1a** was again formed with the former predominating by 90:10. This result indicated that the sulfonyl group rearrangement was reversible under the reaction conditions and that **2a** was the thermodynamically more stable isomer. We presume that an *N*-sulfonyl(*p*-dimethylaminopyridinium) ion intermediate is involved in the rearrangement process as the intermediate. A computational study at the B3LYP/6-31G* level also suggested that **2a** was more stable than **1a** by 0.39 kcal/mol.[16]




We examined the rearrangement reaction of 4-phenyl-1,2,3-triazoles **1b**–**1e** having various sulfonyl groups ($R^1$) at the N1 position. Substituted benzenesulfonyl groups as well as a naphthalenesulfonyl group rearranged from the N1 position to the N2 position (Table 1, entries 2–4). Even a butanesulfonyl group successfully participated in the reaction (Table 1, entry 5). Variation of the substituent ($R^2$) at the C4 position was also examined. Aryl-and alkenyl-substituted substrates **1f**–**1i** worked well to afford the corresponding products **2f**–**2i** in yields ranging from 75% to 86% (Table 1, entries 6–9). The reaction of alkyl-substituted triazole **1j** required more forcing conditions to afford the product **2j** in 78% yield (Table 1, entry 10).

In summary, we have found a new base-promoted pathway starting from readily accessible 4-substituted 1-sulfonyl-1,2,3-triazoles leading to 4-substituted 2-sulfonyl-1,2,3-triazoles.

## ACKNOWLEDGEMENTS

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14. Other amines such as $NEt_3$, $NHEt_2$, and $NEt(i\text{-}Pr)_2$ were also effective for the rearrangement of sulfonyl group.
15. **Representative procedure**: To an oven-dried, Ar-purged flask was added **1a** (151 mg, 0.5 mmol), DMAP (6.5 mg, 0.05 mmol), and MeCN (5 mL). The reaction mixture was stirred at room temperature for 12 h, and then concentrated under reduced pressure. The residue was diluted with EtOAc (30 mL). The organic solution was washed with 1 M HCl (10 mL) and brine (10 mL), dried over $Na_2SO_4$, and evaporated. The residue was again dissolved in AcOH (5 mL) and $H_2O$ (0.5 mL). The reaction mixture was stirred at 60 °C for 3 h, and then concentrated under reduced pressure. The crude product was purified by flash column chromatography (hexane/EtOAc = 5/1) to yield **2a** as a white solid (124 mg, 0.41 mmol, 82%). **2a**: IR (KBr): 1391, 1196, 1163, 1086 $cm^{-1}$; $^1H$ NMR: δ = 2.41 (s, 3H), 7.34 (d, *J* = 8.7 Hz, 2H), 7.39–7.48 (m, 3H), 7.79–7.86 (m, 2H), 8.00 (d, *J* = 8.7 Hz, 2H), 8.08 (s, 1H); $^{13}C$ NMR: δ = 21.7, 126.6, 128.2, 128.6, 128.9, 129.9, 130.1, 132.9, 135.6, 146.6, 151.4; HRMS ($FAB^+$): Calcd for $C_{15}H_{14}N_3O_2S$, $M+H^+$ 300.0807. Found *m*/*z* 300.0801.
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