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Lewis Base Catalyzed Synthesis of Multisubstituted 4-Sulfonyl-1*H*-Pyrazole Involving a Novel 1,3-Sulfonyl Shift

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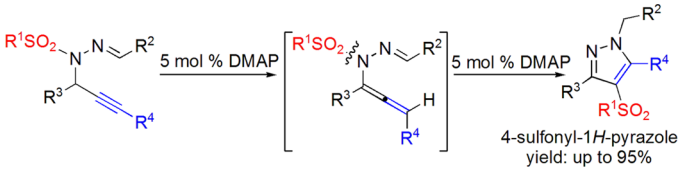
ABSTRACT



A facile synthesis of highly substituted 4-sulfonyl-1*H*-pyrazoles from *N*-propargylic sulfonylhydrazone derivatives has been developed. Allenic sulfonamide formation and 1,3-sulfonyl shift were established to be the critical steps of this transformation.

Pyrazoles and their derivatives have been recognized as important frameworks in pharmaceutical and agrochemical science,[1] and certain pyrazole derivatives including Celebrex (selective COX-2 inhibition) and Zoniporide (selective human NHE-1 inhibition) have been developed into clinical drugs. Owing to the attractive medicinal properties of pyrazoles, new approaches for the efficient assembly of different pyrazoles have attracted great interest. Efficient strategies have been developed with the aim of the preparation of diverse substitution pyrazoles.[2] Conventional approaches for the synthesis of compounds containing pyrazole skeletons involve either the modification of the pre-existing pyrazole precursors through the introduction of new groups[3] or synthesis of a new pyrazole ring from creation of C−N and C−C bonds.[4]

Previous studies from our group have reported a concise approach to prepared *N*-propargylic *N*-sulfonylhydrazones through $FeCl_3$-catalyzed nucleophilic substitution

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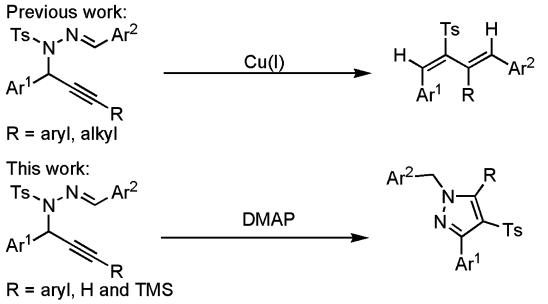
of propargylic acetates with *N*-sulfonylhydrazones.[6] The *N*-propargylic substitution products underwent a copper-(I)-catalyzed [3,3]-rearrangement affording (1*E*,3*E*)-2-sulfonyl-1,3-dienes (Scheme 1).[6a] As part of ongoing research on *N*-propargylic sulfonylhydrazones, we herein report a Lewis base catalyzed synthesis of 4-sulfonyl-1*H*-pyazoles in moderate to good yields. Allenic sulfonamide formation and 1,3-sulfonyl shift were established to be critical steps in this transformation.

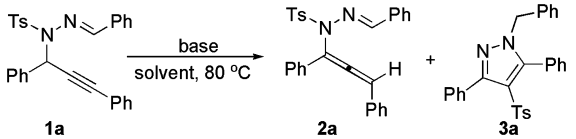
Scheme 1. Reaction of *N*-Propargylic Sulfonylhydrazones



Recently, base-promoted construction of pyrroles,[5a] oxazoles,[5b] and imidazoles[5c] from propargylic amides or propargylic amines involving sulfonyl group shift have been developed. Different from those transformations, which introduced the sulfonyl group to the exocyclic alkyl group of heterocycles,[5] here we report a sulfonyl group migration to the 4-position of 1*H*-pyrazole. The recent studies indicate that pyrazole derivatives containing a sulfonyl substituent display a variety of biological activities.[1g–i]

In our initial study, we decided to investigate the reaction conditions that would improve the yield of **3a** using **1a** as the reactant (Table 1). We treated the **1a** in 1,2-dichloroethane with 5 mol % of DMAP at 80 °C. The desired product **3a** was observed in 40% yield (Table 1, entry 1). The reaction also took place in solvents such as THF (52%), PhMe (47%), CH_3CN (50%), and dioxane (15%) (Table 1, entries 2, 3, 4, and 5). Subsequently, the synthesis of pyrazole was investigated in the mixed solvents of THF and NEt_3 (Table 1, entries 6–8). The best mixture volume ratio for THF and NEt_3 was 5:1, which afforded the product **3a** in 78% yield (Table 1, entry 7). When Lewis bases PPh_3 or DABCO were utilized in the same mix-solvent, the reaction proceeded to afford **3a** in 60% and 10% yields respectively (Table 1, entries 9 and 10). Other bases, such as DBU and Cs_2CO_3, were also screened but failed to promote this transformation (Table 1, entries 11 and 12). However, the reaction occurred to afford **2a** in 81% yield at room temperature for 0.5 h, and no desired product **3a** was detected after the reaction time was prolonged (Table 1, entry 13). Absence of catalyst led to complete recovery of **1a** (Table 1, entry 14). Thus, the most suitable reaction conditions for the formation of **3a** were established (Table 1, entry 7).

Table 1. Screening for the Reaction Conditions[a]



entry	catalyst (5 mol %)	solvent	time (h)	yield[b] (%) of **3a** (**2a**)
1	DMAP	DME	4	40
2	DMAP	THF	4	52
3	DMAP	PhMe	6	47
4	DMAP	CH_3CN	3	50
5	DMAP	dioxane	1	15
6	DMAP	V_T:V_N[c] = 3:1	3	76
7	DMAP	V_T:V_N = 5:1	3	78
8	DMAP	V_T:V_N = 100:1	4	56
9	PPh_3	V_T:V_N = 5:1	4	60
10	DABCO	V_T:V_N = 5:1	4	10
11	DBU	V_T:V_N = 5:1	4	trace
12	Cs_2CO_3	V_T:V_N = 5:1	4	trace
13	DMAP	V_T:V_N = 5:1	0.5	0 (81)[d]
14		V_T:V_N = 5:1	4	n.r.[e]

[a] Reaction conditions: **1a** (0.5 mmol), solvent (5 mL), 80 °C. [b] Isolated yield. [c] Mixture volume ratio of THF and NEt_3. [d] The reaction was performed at room temperature. [e] n.r. = no reaction.

To broaden the scope of this reaction, we carried out the reaction of the *N*-propargylic *N*-sulfonylhydrazone derivatives **1** under the optimized conditions (summarized in Table 2). The substrates **1a** (R^1 = 4-MeC_6H_4) and **1b** (R^1 = Ph) gave the desired results, providing **3a** and **3b** in 78% and 64% yields, respectively (Table 2, entries 1 and 2). The electron-donating *N*-sulfonylhydrazone **1c** (R^1 = 4-$MeOC_6H_4$) was also successfully employed in the reaction to give product **3c** in 61% yield (Table 2, entry 3). The electron-deficient *N*-sulfonylhydrazone **1d** (R^1 = 4-BrC_6H_4) reacted smoothly affording the product **3d** in 83% yield (Table 2, entry 4). The results suggested that reactant **1e** (R^1 = Me) failed to form 4-methylsulfonyl-1*H*-pyrazole (**3e**) (Table 2, entry 5). Gratifyingly, reactants (**1f**–**k**) bearing a terminal alkyne group (R^4 = H) successfully afforded the desired products (**3f**–**k**) in good isolated yields in a short reaction time (Table 2, entries 6–11). The reactant **1l** (R^4 = TMS) underwent protodesilylation under these base cyclization conditions with the same products **3f** obtained in 47% yield (Table 2, entry 12). No reaction of **1m** (R^3 = H) and **1n** (R^3 = C_2H_5) occurred under normal conditions (Table 2, entries 13 and 14). Unfortunately, the results suggested that internal alkynes **1o** (R^4 = *n*-C_4H_9) failed to form the corresponding pyrazole. Other internal alkynes **1p** and **1q** (R^4 = *t*-C_4H_9 and 1-cyclohexenal) afforded allenamides **2p** and **2q** as the major products (Table 2, entries 16 and 17).

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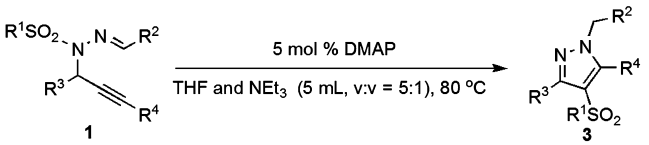
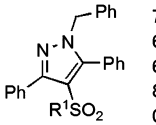
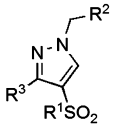
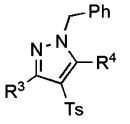
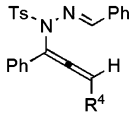
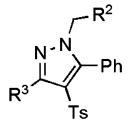
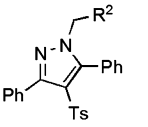
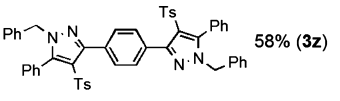
Table 2. DMAP-Catalyzed Formation of 4-Sulfonyl 1*H*-Pyrazoles[a]



1 3

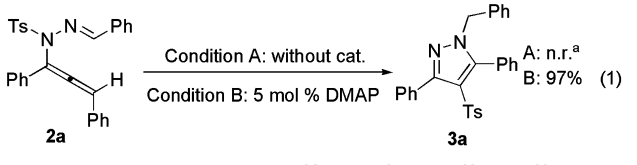
entry	reactant	product	yield[b]
1	**1a** (R^1 = 4-MePh)		78% (**3a**)
2	**1b** (R^1 = Ph)		64% (**3b**)
3	**1c** (R^1 = 4-MeOPh)		61% (**3c**)
4	**1d** (R^1 = 4-BrPh)		83% (**3d**)
5	**1e** (R^1 = Me)		0 (**3e**)
	(R^2 = R^3 = R^4 = Ph)		
6	**1f** (R^1 = 4-MeC_6H_4; R^2 = R^3 = Ph)		86% (**3f**)
7	**1g** (R^1 = 4-MeC_6H_4; R^2 = Ph, R^3 = 4-BrC_6H_4)		85% (**3g**)
8	**1h** (R^1 = R^2 = R^3 = Ph)		87% (**3h**)
9	**1i** (R^1 = R^2 = Ph; R^3 = 4-BrC_6H_4)		88% (**3i**)
10	**1j** (R^1 = 4-MeC_6H_4; R^2 = Ph; R^3 = 4-$MeOC_6H_4$)		82% (**3j**)
11	**1k** (R^1 = 4-MeC_6H_4; R^2 = 4-$NO_2C_6H_4$; R^3 = Ph)		83% (**3k**)
	(R^4 = H)		
12	**1l** (R^3 = Ph; R^4 = TMS)		47% (**3f**)
13	**1m** (R^3 = R^4 = H)		n.r.[c]
14	**1n** (R^3 = C_2H_5; R^4 = Ph)		n.r.[c]
15	**1o** (R^3 = Ph; R^4 = n-C_4H_9)		Complex
	(R^1 = 4-MeC_6H_4; R^2 = Ph)		
16	**1p** (R^4 = t-C_4H_9)		92% (**2p**)[d]
17	**1q** (R^4 = 1-Cyclohexenal)		87% (**2q**)[d]
	(R^1 = 4-MeC_6H_4; R^2 = R^3 = Ph)		
18	**1r** (R^2 = 4-CNC_6H_4; R^3 = Ph)		91% (**3r**)
19	**1s** (R^2 = 2-OHC_6H_4; R^3 = Ph)		0 (**3s**)
20	**1t** (R^2 = Ph; R^3 = 4-$MeOC_6H_4$)		50% (**3t**)
21	**1u** (R^2 = 4-$NO_2C_6H_4$; R^3 = 4-BrC_6H_4)		95% (**3u**)
22	**1v** (R^2 = Ph; R^3 = 4-BrC_6H_4)		85% (**3v**)
23	**1w** (R^2 = 2-BrC_6H_4; R^3 = 4-FC_6H_4)		88% (**3w**)
	(R^1 = 4-MeC_6H_4; R^4 = Ph)		
24	**1x** (R^2=1-Naphthyl)		86% (**3x**)
25	**1y** (R^2=2-Thiophenyl)		75% (**3y**)
	(R^1 = 4-MeC_6H_4; R^3 = R^4 = Ph)		
26	**1z**		58% (**3z**)

[a] Reaction conditions: **1** (0.5 mmol), DMAP (0.025 mmol), solvent (5 mL), 80 °C. [b] Isolated yield. [c] n.r. = no reaction. [d] No future reactions occurred by prolonging reaction time.

Electron-neutral, electron-deficient, and electron-rich aromatic groups (R^2 and R^3) on **1r** and **1t**–**w** were all tolerated, and the desired products (**3r and 3t**–**w**) were obtained in moderate-to-good yields (50–91%, Table 2, entries 18 and 20–23). The reaction of **1s** (R^2 = 2-OHC_6H_4) containing weakly acidic hydroxyl group failed to afforded **3s** (Table 2, entry 19). The substrates **1x** and **1y** bearing a fused ring or thiophene were also suitable for the transformations (Table 2, entries 24 and 25). Notably, starting from **1z**, we could finally obtain a symmetrical oligomer **3z** containing two pyrazole rings (Table 2, entry 26). However, when sulfonyl group on **1a** was replaced by an acetyl group, the reaction afforded allenic *N*-acetylhydrazones only, and the subsequent cyclization did not occur. It proved that migration of the sulfonyl group played a critical role in cyclization. The structure of **3w** was unambiguously demonstrated by X-ray diffraction analysis (see the Supporting Information).[7]

Attempts were made to probe the mechanism (Scheme 2, eq 1). In our previous study, allenic sulfonamide **2a** was obtained at room temperature (Table 1, entry 13). Therefore, we assumed that **2a** was the intermediate which led to **3a**. Indeed, **2a** completely converted into pyrazole **3a** (97% yield) under the standard conditions (Scheme 2, eq 1, conditionc B). No reaction occurred was obtained at room temperature without Lewis base, indicating that the allenamide formation and cyclization reactions were both catalyzed by a single catalyst DMAP (Scheme 2, eq 1, conditions A).

Scheme 2. Conversion of Allene to Pyrazole and Crossover Experiment of **1f** and **1i**[a]



[a] n.r. = no reaction.

On the basis of the above experiments and related reports,[8,9] we propose the following mechanism (Scheme 3). In the presence of base, the propargylic amide moiety of **1** is transformed into the allenic sulfonamide intermediate **2**. Two reasonable pathways accounting for the 1,3-sulfonyl

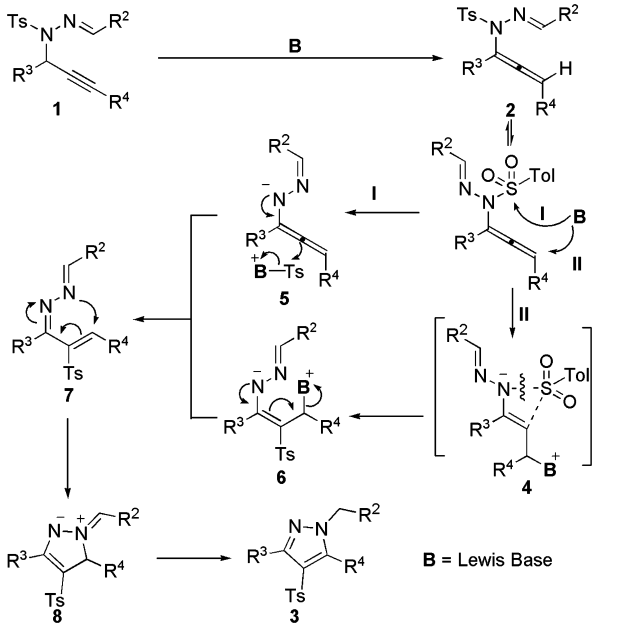
(7) CCDC 943608 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

shift and formation of **7** are shown. In path **I**, Lewis base facilitates the sulfonyl dissociation, and then intermolecular addition occurs to afford intermediate **7**. In path **II**, nucleophilic addition of Lewis base **B** such as DMAP to the terminal sp^2 carbon atom of allene pushs electron density into the sulfonamide moiety to afford transition state **4**, then the N−S bond is broken which allows the 1,3-sulfonyl shift and generates transition state **6**, and then electron transfer affords **7**. α,β-Unsaturated imine **7** undergoes intramolecular Michael addition providing zwitterionic species **8**. Finally, **8** rearranges to pyrolyze **3** via a 1,3-H shift and electron transfer.

In order to establish whether the shift of the sulfonyl group occurred in an intramolecular or intermolecular pathway, we performed a crossover experiment between equimolar amounts of reactants **1f** and **1i** which yields the corresponding products **3f** and **3i** in 82% and 83% yields, respectively, and the crossover products **3g** and **3h** were not detected (Scheme 2, eq 2, determined by HPLC). This result clearly indicated that migration of the sulfonyl group proceeds in an intramolecular manner. Therefore, path **II** might be the possible pathway envisioned for this 1,3-sulfonyl migration.

In summary, a facile approach for the synthesis of highly substituted multisubstituted 4-sulfonyl-1*H*-pyrazole from *N*-propargylic *N*-sulfonylhydrazone derivatives has been developed. A key feature of the reaction is the straightforward introduction of sulfonyl group to the 4-position of 1*H*-pyrazole. Studies aiming at exploring mechanistic aspects of this reaction and developing further transformations of *N*-propargylic *N*-sulfonylhydrazone derivatives are ongoing.

Scheme 3. Proposed Mechanism



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Supporting Information Available. Experimental procedures and characterization of compounds **3a**−**k**,**r**−**z** and **2a**,**p**,**q**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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