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Selective synthesis of 4-(sulfonyl)-methyl-1*H*-pyrazoles and (*E*)-4,5-dihydro-1*H*-pyrazoles from *N*-allenic sulfonylhydrazones†

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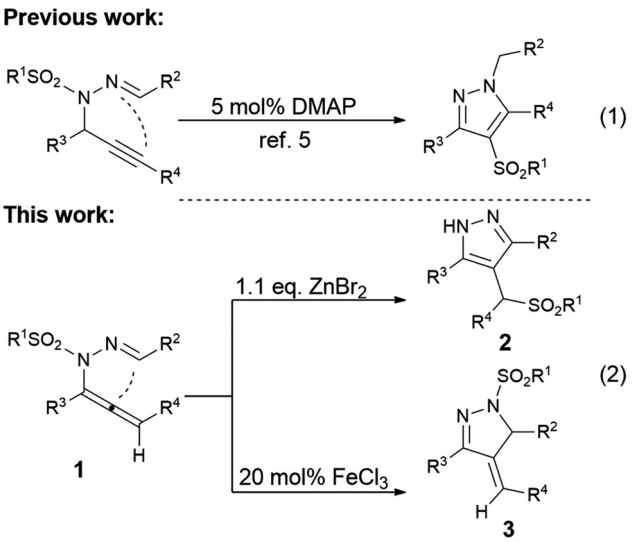
Selective synthesis of 4-(sulfonyl)-methyl-1*H*-pyrazoles and (*E*)-4,5-dihydro-1*H*-pyrazoles from *N*-allenic sulfonylhydrazones with sulfonyl group migrations has been developed. A key feature of these reactions is that the migrations of the sulfonyl groups to different positions can be controlled by changing the Lewis acids.

Pyrazoles are found in a variety of biologically active compounds,[1] such as celebrex, zoniporide, and fluzaolate. Owing to their wide applications in pharmaceutical and agrochemical sciences, substantial attention has been paid to development of efficient strategies for pyrazoles synthesis.[2] Although conventional approaches for the synthesis of pyrazole skeletons involving either modification of pre-existing pyrazole precursors[3] or assembly of new pyrazole rings[4] have been well studied, development of efficient methods to synthesize pyrazole derivatives which could lead to the discovery of new bioactive compounds is still a challenge in organic synthesis.

Allenic sulfonamides as a subclass of allenamides[5] have shown impressive synthetic potential in organic chemistry. A variety of transformations from allenic sulfonamides have been demonstrated which offer versatile access to a range of fascinating structures.[6]

Recently, our group has reported that a Lewis base catalyzed the synthesis of multisubstituted 4-sulfonyl-1*H*-pyrazoles from *N*-propargylic sulfonylhydrazones (Scheme 1, eqn (1)).[7] As a part of our continuing research, we conducted the reactions of *N*-allenic sulfonylhydrazones **1** as a subclass of allenic sulfonamides with Lewis acids. Interestingly, 4-(sulfonyl)-methyl-1*H*-pyrazoles **2** and (*E*)-4,5-dihydro-1*H*-pyrazoles **3** were obtained respectively involving regioselective migrations of sulfonyl groups[8] to different positions promoted by different Lewis acids (Scheme 1, eqn (2)).



Scheme 1 Cyclization of *N*-allenic sulfonylhydrazone and *N*-propargylic sulfonylhydrazone.

In the initial study, the activity of Lewis acids was screened with *N*-allenic sulfonylhydrazone **1a** as a substrate (Table 1). The reaction of **1a** in the presence of 20 mol% $FeCl_3$ in DCM at room temperature gave **3a** in 83% yield. The single product **3a** was isolated in 44% and 34% yields using Lewis acids $BF_3{\cdot}Et_2O$ and AgOTf, respectively (Table 1, entries 2 and 3). The rate of the reaction decreased dramatically catalyzed by 10 mol% $FeCl_3$, and a lower yield of **3a** was achieved (Table 1, entry 4). In the presence of 110 mol% $FeCl_3$, the reaction produced a 34 : 28 mixture of **2a** and **3a** (Table 1, entry 5). Prolonging the reaction time would not change the ratio of **2a** and **3a**. Subsequently, the reactions of **1a** were investigated with zinc salts. Interestingly, 20 mol% Lewis acid of $ZnCl_2$ and $ZnBr_2$ failed to promote those transformations (Table 1, entries 6 and 15). Nevertheless, the unique product **2a** was observed in 75% yield promoted by 1.1 equiv. of $ZnCl_2$ (Table 1, entry 7). To our delight, $ZnBr_2$ performed better in the formation of **2a** (Table 1, entry 8). Other metal Lewis acids, such as $AlCl_3$, $BiCl_3$

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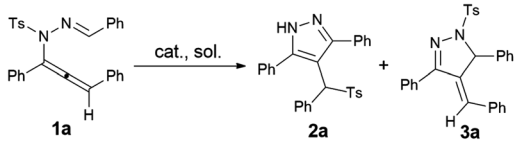
Table 1 Screening for the reaction conditions[a]



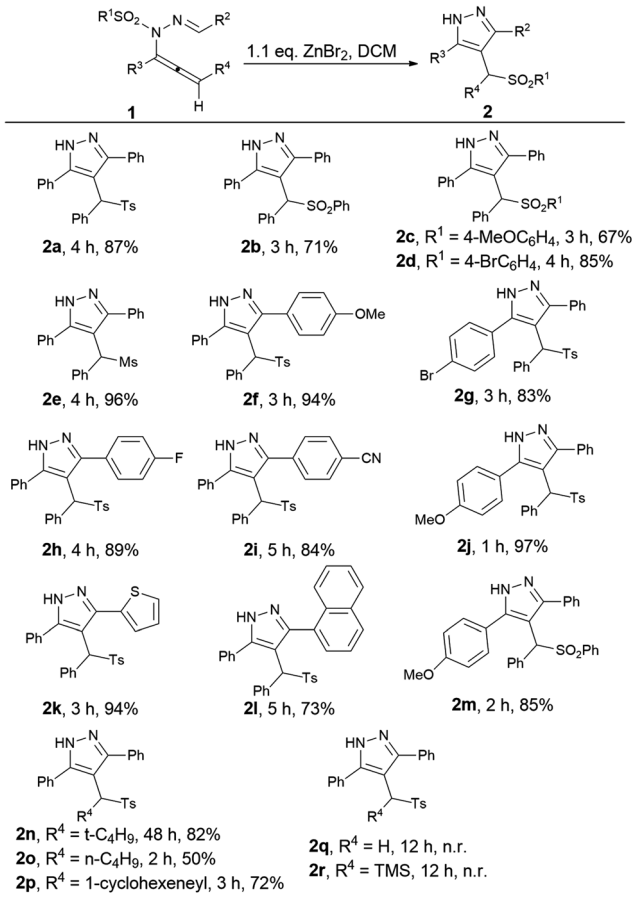
Entry	Catalyst (mol%)	Time	Temp.	Yield[b] (**2a**/**3a**)
1	**$FeCl_3$ (20)**	**5 min**	**r.t.**[c]	**0/83%**
2	$BF_3{\cdot}Et_2O$ (110)	5 min	0 °C	0/44%
3	AgOTf (20)	24 h	r.t.	0/34%
4	$FeCl_3$ (10)	10 h	r.t.	Trace/24%
5	$FeCl_3$ (110)	5 min	r.t.	34%/28%
6	$ZnCl_2$ (20)	12 h	r.t.	0/0[d]
7	$ZnCl_2$ (110)	4 h	r.t.	75%/0
8	**$ZnBr_2$ (110)**	**4 h**	**r.t.**	**87%/0**
9	$AlCl_3$ (20)	12 h	r.t.	0/trace[d]
10	$AlCl_3$ (110)	2 h	r.t.	Trace/36%
11	$BiCl_3$ (20)	12 h	r.t.	0/trace[d]
12	$BiCl_3$ (110)	2 h	r.t.	5%/30%
13	$InCl_3$ (20)	12 h	r.t.	0/0[d]
14	$InCl_3$ (110)	2 h	r.t.	10%/65%
15	$ZnBr_2$ (20)	12 h	r.t.	0/0[d]

[a] Reaction conditions: **1a** (232 mg, 0.5 mmol), DCM (5 mL). [b] Isolated yield. [c] r.t. = room temperature. [d] Recovery of substrate **1a**.

and $InCl_3$, were also screened. No reaction happened when 20 mol% catalysts were used, while increasing the amount of Lewis acids to 1.1 equiv. led to **3a** in comparatively low yields (Table 1, entries 9–14). The reaction took place in a less effective manner when solvents such as CH_3CN, THF and DCE were used. Thus, the most suitable conditions for the synthesis of **2a** and **3a** were established (Table 1, entries 1 and 8).

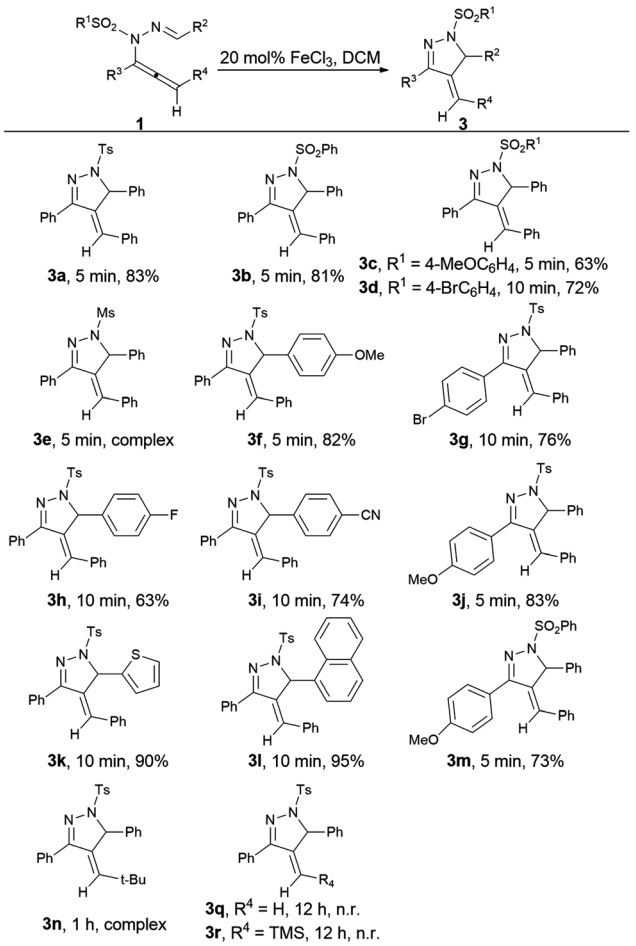
With the optimized reaction conditions in hand, the scope and generality of this zinc-promoted reaction was studied and the results are summarized in Scheme 2. The substrates **1a** (R^1 = 4-MeC_6H_4) and **1b** (R^1 = Ph) gave **2a** and **2b** in 87% and 71% yields, respectively. **1c** (R^1 = 4-$MeOC_6H_4$) and **1d** (R^1 = 4-BrC_6H_4) reacted smoothly affording the desired products **2c** and **2d** in 67% and 85% yields, respectively. **1e** was also successfully employed in the reaction to give the corresponding product **2e** in excellent yield (96%). Electron-neutral, electron-deficient, and electron-rich aromatic groups (R^2 and R^3) on the substrates **1** (**1f–j** and **1m**) were all well tolerated, and the desired products (**2f–j** and **2m**) were obtained in moderate to excellent yields (83–97%). The substrates **1k** and **1l** bearing a thiophene ring or a fused ring were also well suited for those transformations (**2k** and **2l**, 94% and 73% yields). Additionally, internal alkyne substrates **1n–p** (R^4 = *t*-C_4H_9, *n*-C_4H_9 and 1-cyclohexenyl) readily underwent those reactions to afford **2n–p** in moderate to good yields (50%–82%). The results suggested that **1q** (R^4 = H) and **1r** (R^4 = TMS) failed to form **2q** and **2r**.

Next, we investigated the reactions of *N*-allenic sulfonylhydrazones **1a–r** using 20 mol% $FeCl_3$ as a catalyst. The results are summarized in Scheme 3. **1a–d** were converted into **3a–d** in moderate to good yields (63–83%), while the reaction of **1e** led to a mixture. *N*-Allenic sulfonylhydrazones **1f–j** and **1m** bearing electron-deficient or electron-rich aromatic rings produced (*E*)-4,5-dihydro-1*H*-pyrazoles **3f–j** and **3m** in moderate to good yields (63–83%). The reactions of substrates **1k** and **1l** containing a 2-thiophenyl or 1-naphthyl group afforded desired products **3k** and **3l** in excellent yields (90% and 95%), respectively. Internal alkyne **1n** (R^4 = *t*-C_4H_9) failed in this transformation. No reaction of substrates **1q** (R^4 = H) and **1r** (R^4 = TMS) occurred under optimized conditions. The structure of **3l** was unambiguously demonstrated by X-ray diffraction analysis (see the ESI†).[9]

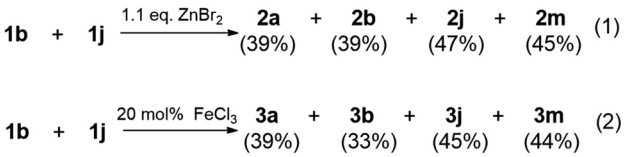


Scheme 2 Synthesis of 4-(sulfonyl)-methyl-(1*H*)-pyazole. Reaction conditions: substrate **1** (0.5 mmol), DCM (5 mL), $ZnBr_2$ (123 mg, 0.55 mmol), room temperature. n.r. = no reaction.

We performed a crossover experiment between equimolar amounts of *N*-allenic sulfonylhydrazones **1b** and **1j** in the presence of 1.1 equiv. of $ZnBr_2$ which yielded the corresponding pyrazoles **2b** and **2j** in 39% and 47% yields, respectively, and the crossover products **2a** and **2m** in 39% and 45% yields, respectively (Scheme 4 eqn (1), determined by HPLC). Furthermore, the $FeCl_3$-catalyzed reaction of a 1 : 1 mixture of **1b** and **1j** afforded the corresponding pyrazoles **3b** and **3j** in 33% and 45% yields, respectively, and the crossover products **3a** and **3m** in 39% and 44% yields, respectively (Scheme 4 eqn (2), determined by HPLC). These results clearly indicated that both migrations of the sulfonyl group proceeded in an intermolecular manner.



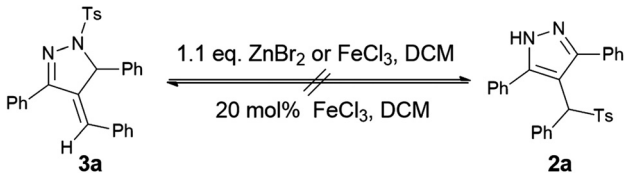
Scheme 3 Synthesis of (*E*)-4,5-dihydro-(1*H*)-pyrazole. Reaction conditions: substrates **1** (0.5 mmol, 232 mg), DCM (5 mL), $FeCl_3$ (16 mg, 0.1 mmol), room temperature. 50 mol% $FeCl_3$ was used. n.r. = no reaction.



Scheme 4 Crossover reactions of **1b** and **1j**.

The product **2a** or **3a** remained unchanged in the presence of $ZnBr_2$ or $FeCl_3$ in DCM at room temperature for 12 hours, thereby suggesting that interconversion between **2** and **3** does not take place under the optimized reaction conditions (Scheme 5).

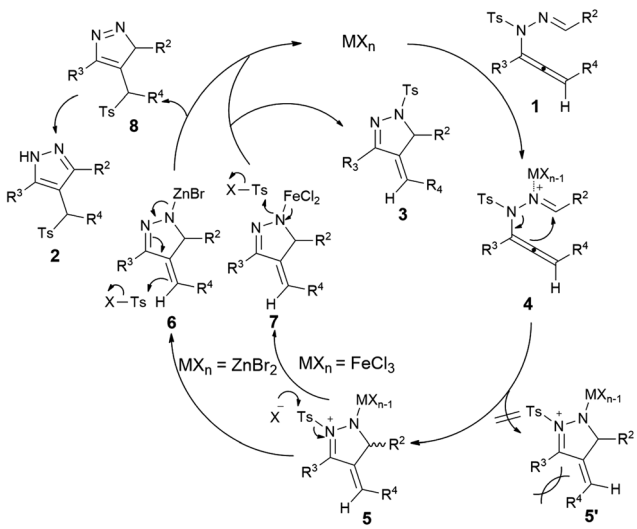
The above experimental results led us to propose a mechanism for the cyclization of **1**. The Lewis-acidic transition metal coordinates with the nitrogen atom of **1** to form complex **4**. The nitrogen atom donates its lone pair of electrons to the allenic moiety, followed by the addition of the central sp carbon to the azomethine carbon atom. The spatial arrangements of R^3 and R^4 are coplanar in intermediates **5** and **5′**. The



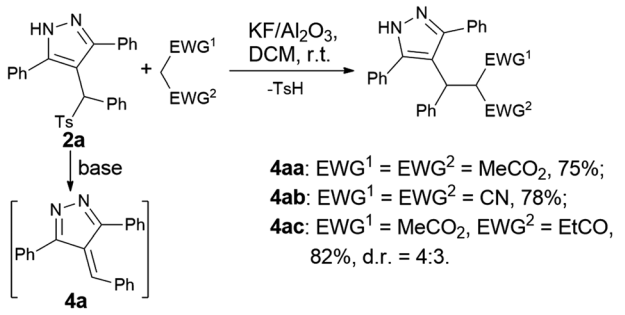
Scheme 5 Interconversion reactions between **2a** and **3a**.

small sterically hindered effect avails formation of (*E*)-configuration intermediate **5**. The halide ion promotes the N–S bond of **5** cleavage to give intermediate **6** or **7**. For zinc-promoted (MX_n = $ZnBr_2$) reaction of the substrates **1**, along with the departure of $ZnBr_2$ from **6**, electrons transfer to the exocyclic double bond to render sulfonylation reaction and intermediate **8** is formed. Finally, **8** rearranges to pyrazole **2** *via* 1,5-*H* shift and tautomerization. In iron-catalyzed (MX_n = $FeCl_3$) reaction, elimination of $FeCl_3$ on intermediate **7** and the new N–S bond formed give (*E*)-4,5-dihydro-1*H*-pyrazole **3**. The strength of the M–N bond might play a crucial role in selectively producing **2** and **3**. With such simple substrates, the real role of each catalyst for the different selectivity remains a puzzle (Scheme 6).

The ready availability of pyrazoles **2** bearing a sulfonyl moiety opens a new synthetic opportunity for a suitable transformation. Pyrazole derivative **4aa** was prepared from **2a** and dimethyl malonate in 75% yield. Malononitrile reacted with **2a** leading to the corresponding product **4ab** in 78% yield. Ethyl acetoacetate and **2a** reacted under basic conditions leading to the mixture **4ac** of two corresponding diastereoisomers in 82% yield. According to the above results, we presumed that under basic conditions pyrazole **2a** underwent elimination of arenesulfinic acid, leading to an intermediate vinylogous imine **4a** which when added with nucleophile reagents afforded 4-substituted pyrazole derivatives (Scheme 7).[10]



Scheme 6 Proposed mechanism.



Scheme 7 KF on basic alumina-promoted additions of active methylene compounds to pyrazole **2a**.

Conclusions

In summary, selective synthesis of 4-(sulfonyl)-methyl-1*H*-pyrazoles and (*E*)-4,5-dihydro-1*H*-pyrazoles from *N*-allenic sulfonylhydrazones has been developed. A key feature of those reactions is that the migration of the sulfonyl groups to different positions can be controlled. Employing inexpensive zinc or iron salt, operational simplicity, mild reaction conditions and absence of byproduct generation would be beneficial for their large-scale use. Studies aiming at exploring mechanistic aspects of these reactions and developing further transformations of *N*-allenic sulfonylhydrazones are ongoing.

Acknowledgements

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