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Tandem Reaction of Propargyl Alcohol and *N*-Sulfonylhydrazone: Synthesis of Dihydropyrazole and Its Utility in the Preparation of 3,3-Diarylacrylonitrile

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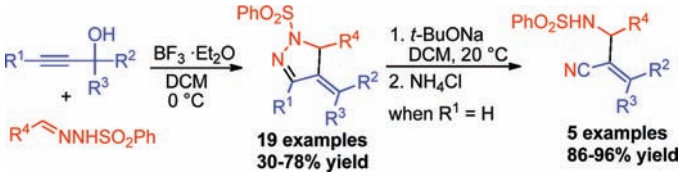
ABSTRACT



An efficient and straightforward strategy for the synthesis of 4-methylene-1-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrazole from propargyl alcohol and *N*-sulfonylhydrazone is described. *N*-Sulfonyl allenamide is postulated to be the key intermediate for this tandem transformation.

Allenamides, as a subclass of allenes, have shown impressive synthetic potentials in organic chemistry.[1] Many reactions based on allenamides were well established in the past decades, such as [4 + 2] cycloadditions,[2] [2 + 2] cycloadditions,[3] and radical cyclization.[4] The attendance of an allenamide motif enhances the diversity of reaction possibilities. In the formation of cyclic compounds, the allenamide serves as a nucleophilic reagent to undergo catalyzed cyclization with another electrophilic center such as organohalides.[5] More importantly, due to the electron-rich central carbon which can be easily activated in the presence of an electrophile and the unique geometry of allenamide, these reactions often proceed efficiently in highly stereoselective control, thus providing an attractive tool for the stereoselective synthesis of cyclic molecules.

As a part of our continuing research on the development of a tandem reaction of allenamide intermediates,[6] we herein report an efficient and general approach to the formation of 4-methylene-1-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrazoles (**3**) through a $BF_3 \cdot Et_2O$ catalyzed tandem reaction between propargyl alcohols (**1**) and *N*-sulfonylhydrazones (**2**). Structures of **3a** and **3f** were established by X-ray analysis.

Exhausive studies of the reaction conditions for the synthesis of **3a** from **1a** and **2a** were conducted (Table 1). These results showed that $BF_3 \cdot OEt_2$ was the most efficient catalyst for the transformation among others, such as HOTf, $Yb(OTf)_3$, $Cu(OTf)_2$, and AgOTf (Table 1, entries 1−5), whereas dichloromethane (DCM) was the most suitable solvent in comparison with others, such as tetrahydrofuran, acetonitrile, and toluene (Table 1, entries 6−8). In addition to these two key factors, further screening of the catalytic reaction conditions revealed that formation of **3a** largely depended on the reaction time and reaction temperature. Prolonging the reaction time would slightly influence the yield (Table 1, entry 9), while shortening the time made the reaction incomplete (Table 1, entry 10). A similar situation was observed for the reaction temperature survey (Table 1, entries 11 and 12). Thus, the most suitable reaction

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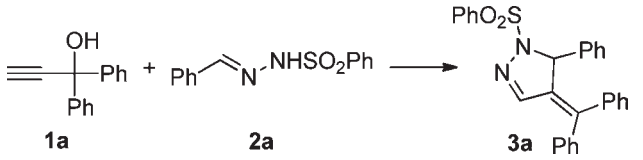
Table 1. Screening for the Reaction Conditions[a]



entry	catalyst	temp (°C)	time (h)	solvent	yield[b] (%)
1	$BF_3{\cdot}Et_2O$[c]	0	2	DCM	65
2	HOTf[d]	0	4	DCM	55
3	$Yb(OTf)_3$[d]	80	4	DCE	41
4	$Cu(OTf)_2$[d]	80	2	DCE	25
5	AgOTf[d]	80	1	DCE	36
6	$BF_3{\cdot}Et_2O$[c]	0	2	THF	nr[e]
7	$BF_3{\cdot}Et_2O$[c]	0	2	MeCN	42
8	$BF_3{\cdot}Et_2O$[c]	0	2	Toluene	0
9	$BF_3{\cdot}Et_2O$[c]	0	3	DCM	64
10	$BF_3{\cdot}Et_2O$[c]	0	1	DCM	52
11	$BF_3{\cdot}Et_2O$[c]	−20	12	DCM	59
12	$BF_3{\cdot}Et_2O$[c]	20	1	DCM	53

[a] Reaction conditions: **1a** (0.6 mmol), **2a** (0.5 mmol), solvent (5 mL). [b] Isolated yield referred to **2**. [c] Equivalent molar to **1**. [d] Catalyst (0.1 mmol) used. [e] nr = no reaction.

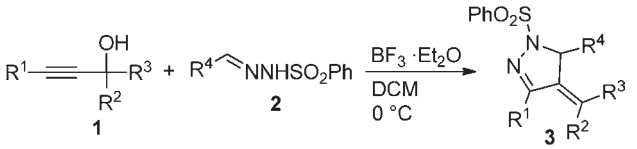
conditions for the formation of **3a** were established (Table 1, entry 1).

With the optimized reaction conditions in hand, we tested the substrate diversity for the transformation, and the results are presented in Table 2. Various propargyl alcohols (**1a**−**1f**) and *N*-sulfonylhydrazones (**2a**−**2j**) readily underwent this cascade process to afford **3a**−**3s** in moderate to good yields (30−78%), accordingly. With different aryl groups (R^2, R^3) occupied on the propargyl alcohol (**1a**−**1c**), reactions proceeded smoothly (Table 2, entries 1−3). When acetophenone derived propargylic alcohol (**1d**) was used as the substrate, *Z*-**3d** was obtained diastereoselectively (Table 2, entry 4). A *Z*-configuration was confirmed by the nuclear overhouser effect (NOE)[7] between methyl and hydrogen as we indicated in Figure 1. *E*-**3d** was not detected due to the steric hindrance of two phenyl rings in *E*-**3d** and its anticipated higher energy of the transition state of the formation of *E*-**3d**. In cases of **1e** and **1f**, with the internal triple bond, lower yields were observed (Table 2, entries 5 and 6). A substituent effect on the aryl of *N*-sulfonylhydrazones (**2b**−**2h**) was not apparent (Table 2, entries 7−13 and 16−19). However, when *N*-sulfonylhydrazones derived from aliphatic aldehydes (**2i**, **2j**) were used as substrates, reactions were not so effective (Table 2, entries 14 and 15).

A possible mechanism for the reaction is depicted in Scheme 1. Assisted by a Lewis acid, **1a** was converted to allenic carbocation **A** *via* Meyer−Schuster rearrangement.[8] It could be trapped *in situ* by **2a** to form *N*-sulfonylallenamide **B**. Because of the electron-donating nature of the

(7) For NOE experiments of **3d**, see Supporting Information.
(8) Swaminathan, S.; Narayanan, K. V. *Chem. Rev.* **1971**, *71*, 429.

Table 2. Tandem Synthesis of **3**[a]



entry	**1** (R^1/R^2/R^3)	**2** (R^4)	product/ yield[b] (%)
1	**1a** (H/C_6H_5/C_6H_5)	**2a** (C_6H_5)	**3a**/65
2	**1b** (H/4-ClC_6H_4/4-ClC_6H_4)	**2a**	**3b**/72
3	**1c** (H/4-MeC_6H_4/ 4-MeC_6H_4)	**2a**	**3c**/55
4	**1d** (H/C_6H_5/Me)	**2a**	**3d**/41
5	**1e** (*n*-Bu/C_6H_5/C_6H_5)	**2a**	**3e**/37
6	**1f** (C_6H_5/C_6H_5/C_6H_5)	**2a**	**3f**/50
7	**1a**	**2b** (3,4-$Me_2C_6H_3$)	**3g**/73
8	**1a**	**2c** (4-MeC_6H_4)	**3h**/74
9[c]	**1a**	**2d** (4-BrC_6H_4)	**3i**/63
10	**1a**	**2e** (3-BrC_6H_4)	**3j**/62
11	**1a**	**2f** (2-BrC_6H_4)	**3k**/60
12[c]	**1a**	**2g** (4-$NO_2C_6H_4$)	**3l**/43
13	**1a**	**2h** (1-naphthyl)	**3m**/74
14	**1a**	**2i** ($CH_2C_6H_5$)	**3n**/33
15	**1a**	**2j** (*n*-C_5H_{11})	**3o**/30
16	**1d**	**2b**	**3p**/78
17	**1d**	**2c**	**3q**/78
18[c]	**1d**	**2d**	**3r**/60
19[c]	**1d**	**2g**	**3s**/40

[a] Reaction conditions: **1** (0.6 mmol), **2** (0.5 mmol), $BF_3{\cdot}Et_2O$ (0.6 mmol), DCM (5 mL), reaction time (2 h). [b] Isolated yields refer to **2**. [c] 20 mL of solvent used.

nitrogen, the internal carbon of allene was electron-rich and could nucleophilically attack the electron-deficient carbon of the hydrazone. Thus, a cyclized intermediate **C** was constructed. Finally, intramolecular migration[9] of the sulfonyl group led to the formation of **3a.**

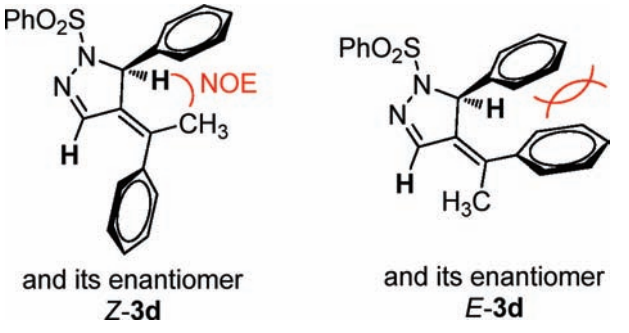
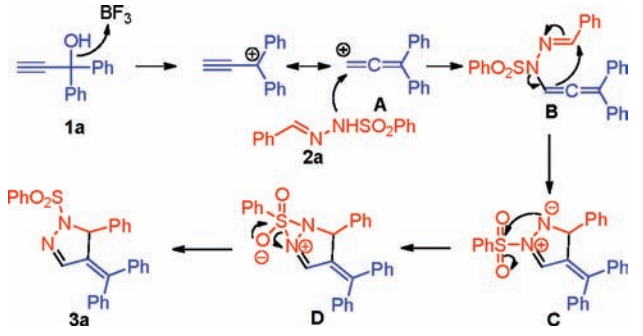


Figure 1. Diastereoselective formation of *Z*-**3d**.

(9) A controlled experiment was conducted to evidence the intramolecular migration of sulfonyl group. Sodium *p*-toluene sulfinate was added in the reaction between **1a** and **2a**. After workup, only **3a** was isolated (see Supporting Information for details). For one example for the intramolecular migration of sulfonyl group, see: Groszek, G.; Blazej, S.; Brud, A.; Swierczynski, D.; Lemek, T. *Tetrahedron* **2006**, *62*, 2622.

Scheme 1. Proposed Mechanism for the Tandem Transformation



Acrylonitriles have proven to be versatile building blocks in organic synthesis for nitrile-containing natural products, pharmaceuticals, and dyes.[10] For example, 3,3-diarylacrylonitriles could be served as tubulin polymerization inhibitors for potential utility in cancer chemotherapy (Figure 2).[11]

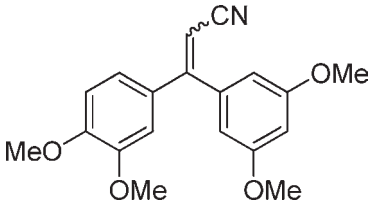
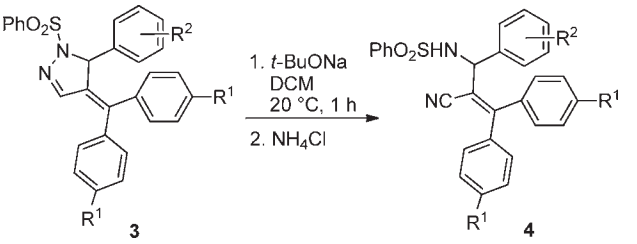


Figure 2. A potential inhibitor of tubulin polymerization.

In order to explore the reactivity of **3**, we first examined **3** in the presence of an acid. It was found that **3a** was stable to either a Lewis acid ($Cu(OTf)_2$[12]) or Bronsted acid (HOTf). However, compound **3a** was unstable under the basic conditions. When **3a** was treated with sodium *tert*-butoxide, a 3,3-diarylacrylonitrile derivative (**4a**) was unexpectedly obtained *via* N−N bond cleavage in a yield of 93%. The structure of **4a** was established by X-ray analysis. By similar treatment, **4b**−**4e** were prepared in yields between 86 and 96% (Table 3). Compounds **4a**−**4e** possessed a substructure of 3,3-diarylacrylonitrile, which might have potential utility in bioactivity.

Table 3. Synthesis of **4**[a]



entry	**3** (R^1/R^2)	product	yield (%)[b]
1	**3a** (H/H)	**4a**	93
2	**3b** (Cl/H)	**4b**	96
3	**3c** (Me/H)	**4c**	96
4	**3f** (H/3,4-Me_2)	**4d**	95
5	**3h** (H/4-Br)	**4e**	86

[a] Reaction conditions: **3** (0.25 mmol), DCM (5 mL). [b] Isolated yields refer to **3**.

In summary, we have developed an efficient method to synthesize 4-methylene-1-(phenylsulfonyl)-4,5-dihydro-1*H*-pyrazole *via* a Lewis acid catalyzed tandem reaction of propargyl alcohol and *N*-sulfonylhydrazone. A possible mechanism for this reaction was proposed, which involves the formation of a *N*-sulfonyl allenamide intermediate and the 1,2-sulfonyl group migration. More significantly, 3,3-diarylacrylonitriles could be efficiently obtained from the synthesized pyrazoles *via* N−N bond cleavage in excellent yields. Further research on the chemistry of *N*-sulfonyl allenamide is ongoing in our laboratory.

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Supporting Information Available. Detailed experimental procedures, characterizaton data, copies of ^1H, ^{13}C NMR spectra, and crystallographic information files (CIF) for compounds **3a**, **3f**, and **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) For an example of N−N cleavage, see: Nakamura, I.; Shiraiwa, N.; Kanazawa, R.; Terada, M. *Org. Lett.* **2010**, *12*, 4198.