

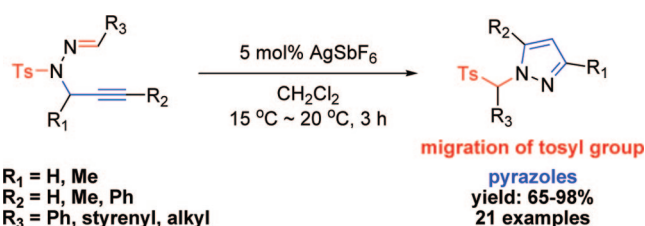
Silver(I)-Catalyzed Facile Synthesis of Pyrazoles From Propargyl *N*-Sulfonylhydrazones

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A silver(I)-catalyzed facile formation of pyrazoles from propargyl *N*-sulfonylhydrazones has been disclosed. During the reaction, a migration of sulfonyl groups (Ts, Ms) was observed. Good functional group compatibility was observed under mild reaction conditions (at room temperature for 3–5 h). This methodology allows for the efficient and regioselective synthesis of 1,3- and 1,5-disubstituted and 1,3,5-trisubstituted pyrazoles.

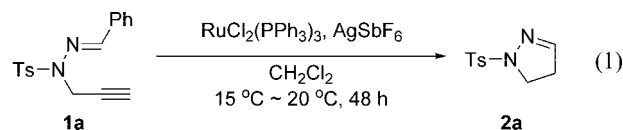
The synthesis of pyrazoles has received considerable attention because of their applications in pharmaceutical and agrochemical industries.¹ Recently, other applications in photoprotectors, ultraviolet stabilizers, and energetic materials also were reported.² Thus, various procedures for their synthesis have been

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developed.³ Among them, the condensation of hydrazine with 1,3-dicarbonyl compounds and the nitrene insertion reaction are widely employed strategies.⁴ However, the generality of these reactions is debased by the severe reaction conditions or multistep sequences usually required to access the starting materials. Moreover, the frequent formation of regioisomeric mixtures of unsymmetrical pyrazoles vitiates the appealing generality of the methods. As a result, efforts have been and are still being made to find and develop more general and versatile synthetic methodologies for pyrazoles.

While we studied a synthesis of Grubbs' catalyst, we found that a reaction of propargyl *N*-tosylhydrazone **1a** in the presence of ruthenium and silver salt led to an isolation of **2a** (eq 1).¹⁰



The formation of **2a** was confirmed by ¹H and ¹³C NMR, HRMass, and an X-ray diffraction study. However, very recently, the X-ray crystal structure of **2a** was reported by Makhova and his co-workers.¹¹ The formation of **2a** suggested that water molecules would take part in the reaction, presumably due to the handling of the chemicals in the air. We closely reexamined the reaction and found that the reaction was catalyzed by the silver salt alone in the presence of moisture. Thus, the formation of **2a** involves a 5-endo-dig ring closure

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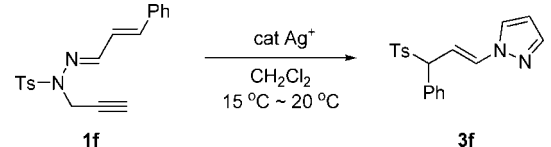
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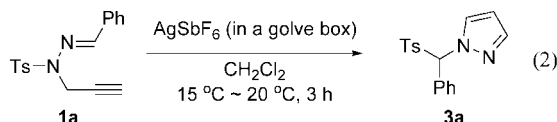
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TABLE 1. Screening the Reaction Conditions^a


entry	catalyst	solvent	T (°C)	time (h)	yield ^b (%)
1	10 mol % of AgSbF ₆	CH ₂ Cl ₂	15–20	3	89
2	5 mol % of AgSbF ₆	CH ₂ Cl ₂	15–20	3	88
3	5 mol % of AgBF ₄	CH ₂ Cl ₂	15–20	3	83
4	5 mol % of AgOTf	CH ₂ Cl ₂	15–20	3	66
5	5 mol % of AgPF ₆	CH ₂ Cl ₂	15–20	3	53
6	5 mol % of AgClO ₄	CH ₂ Cl ₂	15–20	3	76
7	10 mol % of [Au(PPh ₃) ₂]SbF ₆	CH ₂ Cl ₂	15–20	3	n.r. ^c
8	10 mol % of PtCl ₂	toluene	80	18	55

^a 0.5 mmol of **1f** (0.169 g) in 5 mL of CH₂Cl₂ was used. ^b Isolated yield. ^c n.r. = no reaction.

followed by addition of water to the iminium ion intermediate with a concomitant elimination of benzaldehyde. Under an exclusion of water, pyrazole **3a** was obtained in high yield (eq 2).



Compound **3a** was derived from an unprecedented sulfonamide migration to an alkenyl group. This is the first example of silver(I)-catalyzed formation of pyrazoles from propargyl *N*-sulfonylhydrazones. Four decades ago, a base-induced transformation of dypnone tosylhydrazone to pyrazole was reported by Sato and Watanabe.⁵ They used tosylhydrazones as diazo precursors in the presence of base. The diazo compounds were induced to react directly with alkenes or alkynes to synthesize pyrazoles after additional step.⁶ We herein report our recent results. Our newly developed reaction provides an efficient and selective formation of 1,3,5-trisubstituted pyrazoles in high yield.⁷

Using propargyl *N*-tosylhydrazone (**1f**) as a model compound, we screened silver catalysts, including AgClO₄, AgPF₆, AgOTf, AgBF₄, and AgSbF₆ (Table 1).

The reaction could be carried out under mild conditions: at room temperature for 3 h. After the reaction, pyrazole **3f** was obtained in reasonable to high yield. The formation of **3f** was confirmed by ¹H and ¹³C NMR. The yield was highly dependent upon the counteranion and the best yield (88%) employs only 5 mol % of the catalyst with AgSbF₆. We also used [Au(PPh₃)₂]SbF₆. However, no reaction was observed with it. When PtCl₂ was as a catalyst in toluene at 80 °C for 18 h, the product was obtained in 55% yield. Thus, the reaction was unique to silver catalysts. Formation of **3f** suggested a reaction involving a migration of the tosyl group.⁸ However, the migration of the tosyl group is not common as a detosylation.⁹

Using AgSbF₆ as a catalyst, we screened various propargyl *N*-sulfonylhydrazones with a terminal alkyne (Table 2).

The reactions of aryl hydrazones with various functional groups such as –Br, –F, –OMe, and –OH (entries 2–5) afforded the pyrazole products in high yields without forming any side reaction products. Treatment of alkenyl hydrazones (entries 8 and 9) with silver catalyst also produced pyrazoles

TABLE 2. AgSbF₆-Catalyzed Synthesis of Pyrazoles from Propargyl *N*-Sulfonylhydrazones^a

Entry	Reactant	Product	Time	Yield (%) ^b
1	1a (R = H)	3a	5 h	76(3a)
2	1b (R = Br)	3b	5 h	73(3b)
3	1c (R = F)	3c	5 h	71(3c)
4	1d (R = OMe)	3d	5 h	78(3d)
5	1e (R = OH)	3e	5 h	94(3e)
6	1f (R = Ts)	3f	3 h	88(3f)
7	1g (R = Ms)	3g	5 h	83(3g)
8	1h (R ₁ = H, R ₂ = H)	3h	3 h	85(3h)
9	1i (R ₁ = Me, R ₂ = H)	3i	3 h	80(3i)
10	1j (R ₁ = Me, R ₂ = Ph)	3j	3 h	65(3j)
11	1k (R = Ts)	3k	3 h	98(3k)
12	1l (R = Ms)	3l	5 h	98(3l)
13 ^d	1m	3m and 3m'	5 h	86 45(3m)/41(3m')
14	1n (R = <i>iso</i> -propyl)	3n	5 h	78(3n)
15	1o (R = cyclopropyl)	3o	5 h	80(3o)
16	1p (R = Bz)		10 h	n.r. ^c
17	1q (R = Ph)		10 h	n.r. ^c

^a 0.5 mmol of propargyl *N*-sulfonylhydrazone in 5 mL of CH₂Cl₂ was used. ^b Isolated yield. ^c n.r. = no reaction. ^d Reaction run using 10 mol % of AgSbF₆.

in high yields. Styrenyl hydrazones (entries 6, 7, 10, 11, and 12) were good substrates. The formation of a pyrazole derivative was confirmed by an X-ray diffraction study of single crystals of **3h** (Figure 2, Supporting Information).¹⁰ For a reaction of an aryl hydrazone containing a doubly substituted imine moiety (entry 13), a higher loading of the catalyst (10 mol %) was needed and two pyrazole compounds were obtained; the expected product (**3m**) was isolated in 45% yield and the other (**3m'**) derived from the expected product by elimination of toluenesulfonic acid (TsH) was obtained in 41%. When the hydrazones possessing an alkyl group (entries 14 and 15) were subjected to the reaction conditions, the expected products were also obtained in high yields. The reaction also worked well with an alkylsulfonyl group (entries 7 and 12). However, with the *N*-benzoyl- or *N*-phenylhydrazones (entries 16 and 17, respectively) treatment with AgSbF₆ gave none of the desired products.

We next investigated the synthesis of 1,3- and 1,5-disubstituted and 1,3,5-trisubstituted pyrazoles (Table 3).

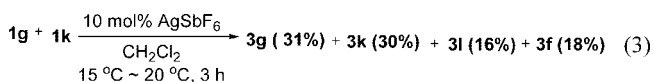
Treatment of styrenyl hydrazones (entries 1–3) in the presence of 5 mol % of the catalyst gave reasonable to high yields. Introduction of a methyl group to propargyl in styrenyl hydrazones (entry 3, 77%) slightly decreased the yield of the reaction. Interestingly, reactions of *p*-methoxystyrenyl hydrazones (entries 4–6) gave higher yields with shortening of the reaction time. Any side products were not isolated. Thus, 1,3- and 1,5-disubstituted and 1,3,5-trisubstituted pyrazoles were readily synthesized under mild reaction conditions.

TABLE 3. AgSbF₆-Catalyzed Synthesis of Substituted Pyrazoles from Propargyl *N*-Sulfonylhydrazones^a

Entry	Reactant	Product	Time	Yield (%) ^b
1			6 h	84(3r)
2			6 h	79(3s)
3			6 h	77(3t)
4			3 h	90(3u)
5			3 h	87(3v)
6			12 h	65(3w)

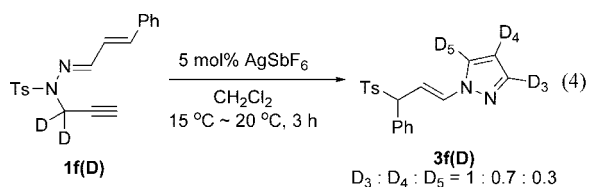
^a 0.5 mmol of propargyl *N*-sulfonylhydrazone in 5 mL of CH₂Cl₂ was used. ^b Isolated yield.

To find out whether the migration of the sulfonyl group occurs in an intramolecular or intermolecular fashion, we performed a crossover experiment (eq 3).



The reaction of a 1:1 mixture of **1g** and **1k** in the presence of a catalytic amount of AgSbF₆ gave the corresponding products **3g** and **3k** in 31% and 30% yields, respectively, and the crossover products **3l** and **3f** in 16% and 18% yields, respectively. This result clearly indicates that migration of the sulfonyl group proceeds in an intermolecular manner.

To get some insight about the reaction mechanism, a deuterated substrate **1f(D)** was subjected under the same reaction conditions (eq 4).



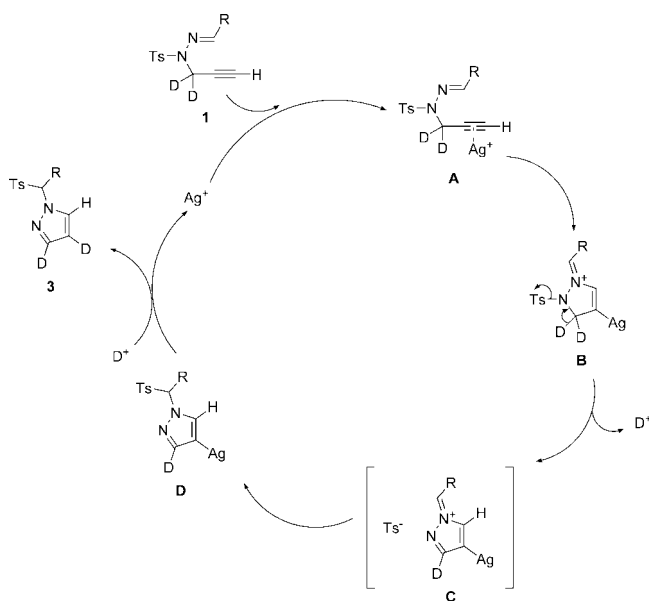
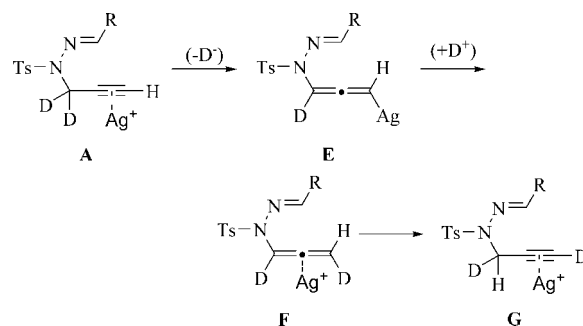
The ¹H NMR spectrum of the reaction product **3f(D)** showed two peaks at 7.59 and 6.37 ppm corresponding to the positions 4 and 5 of the pyrazole moiety, respectively, with a ratio of 0.3:0.7. Thus, the ratio of the deuterium at the positions at 3, 4, and 5 was 1:0.7:0.3. The ²H NMR of **3f(D)** showed two peaks at 7.65 and 6.40 ppm with a ratio of 1.5:0.7. Because of broadening, the two peaks corresponding to the positions 3 and 5 was merged in one peak at 7.65 ppm.

Although little mechanistic information has been obtained, the following mechanism is proposed on the basis of the above results (Scheme 1).

Upon coordination of the triple bond of **1**, the enhancement of electrophilicity of the alkyne gives rise to a subsequent nucleophilic attack of the imine nitrogen atom on the electron-deficient alkyne to yield the cyclized silver(I) intermediate **B**. Deprotonation leads to the generation of ion pairs **C**. An attack of the tosyl anion to the electron-deficient imine carbon followed by protonation give the product **3**.

The scrambling of the deuterium in the positions 4 and 5 of pyrazole in eq 4 can be understood by proposition of a Ag(I)-substituted allene intermediate, **E** (Scheme 2).

Removal of a deuterium allows the π -intermediate **A** to rearrange to a silver-substituted allene intermediate, **E**.

SCHEME 1. Proposed Mechanism for Ag-Catalyzed Pyrazole Synthesis**SCHEME 2.** Proposition of a Ag(I)-Substituted Allene Intermediate

of the liberated deuterium to **E** leads to **G** through an intermediate **F** and the intermediate **G** will undergo a subsequent nucleophilic cyclization to give pyrazole derivatives with a deuterium in 4 and 5 positions. An allenic intermediate was proposed in the some Cu(I) and Au(I)-catalyzed reactions.¹²

In summary, we have reported a simple and efficient procedure for the silver(I)-catalyzed formation of pyrazoles from propargyl *N*-sulfonylhydrazone, especially affording 1,3,5-trisubstituted pyrazoles. The procedures introduced here are practically useful and good functional group-compatibility was observed under mild reaction conditions. Further development of the silver(I) catalyzed reactions and extension of the approach to a wider range of valuable nitrogen heterocycles is underway.

Experimental Section

General Procedure for AgSbF₆-Catalyzed Synthesis of Pyrazoles from Propargyl *N*-Sulfonylhydrazones. To a flame-dried 10 mL Schlenk flask capped with a rubber septum containing 5 mL of dry CH₂Cl₂ were added 8.6 mg (5 mol %) of AgSbF₆ and 0.5 mmol of propargyl *N*-sulfonylhydrazone sequentially in a glovebox. The disappearance of the starting material was checked by TLC analysis. After the starting material had disappeared, the

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solvent was removed under reduced pressure. Flash chromatography on silica gel eluting with hexane and ethyl acetate (v/v, 5:1) gave the product.

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Supporting Information Available: Detailed experimental procedures, new characterization data, ^1H and ^{13}C NMR spectra of all compounds, and crystallographic data (CIF) of **3h**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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