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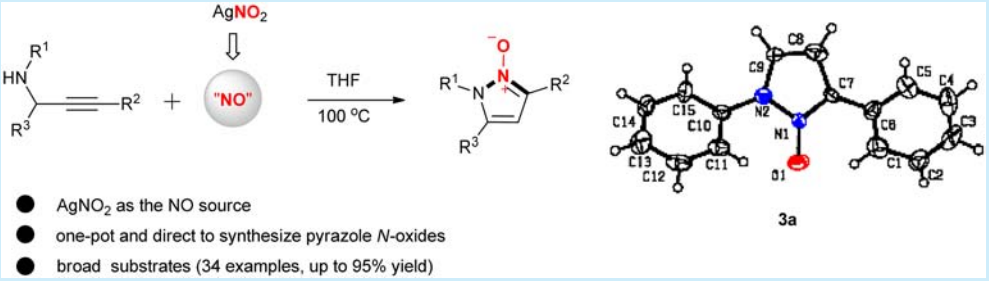
$AgNO_2$ as the NO Source for the Synthesis of Substituted Pyrazole *N*-Oxides from *N*-Propargylamines

Bingxiang Yuan,[†] Fuming Zhang,[†] Zhuomei Li,[‡] Shenghua Yang,[†] and Rulong Yan*[,†]

[†]State Key Laboratory of Applied Organic Chemistry, Key laboratory of Nonferrous Metal Chemistry and Resources Utiliztion of Gansu Province, Department of Chemistry, Lanzhou University, Lanzhou, Gansu, China

[‡]The Middle School Attached to Lanzhou University, Lanzhou, Gansu, China

Supporting Information

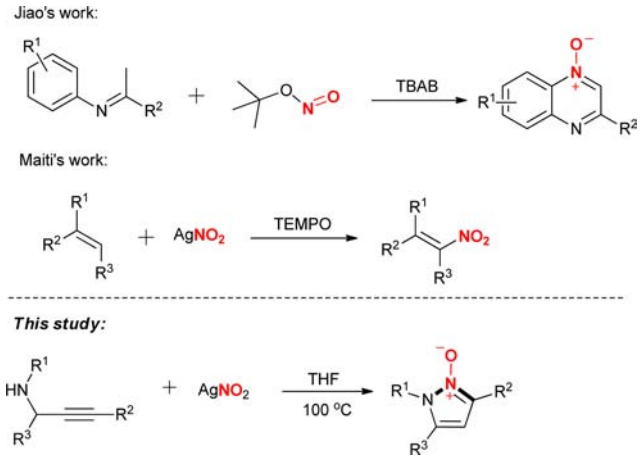


ABSTRACT: A straightforward method for synthesizing the pyrazole *N*-oxides from *N*-propargylamines and $AgNO_2$ through oxidation/cyclization reaction had been developed. $AgNO_2$ was used as the NO source for the first time to synthesize pyrazole *N*-oxides. Various substituted groups on *N*-propargylamines proceeded smoothly, and the desired products were obtained in good yields.

Nitrogen-containing compounds, such as pyrazoles, have great importance in chemistry, biology, and materials science.[1] Heterocyclic *N*-oxides are important structural scaffolds because of their significant biological activity in numerous natural and pharmacological compounds and in chiral ligands.[2] The typical approaches to synthesize *N*-oxides from corresponding *N*-heterocyclic compounds with various organic oxidants are well-documented.[3] However, these systems suffer from a similar disadvantage, which is that the substituted *N*-heterocycles need to be prepared in advance, and then the *N*-oxides are prepared by overoxidization. Alternatively, transition-metal-catalyzed reactions to form *N*-oxides through C−H bond functionalization have been well-studied recently, while most methods also required the parent *N*-heterocyclic compounds as the substrates.[4] The direct synthesis of *N*-oxides from simple substrates has rarely been exploited.

A variety of typical nitrogen sources, such as NaN_3, $TMSN_3$, and *t*BuONO, have been heavily investigated to provide the nitrogen atom to construct the scaffolds of heterocyclic compounds.[5] However, the sources for providing NO directly are very limited. In particular, Jiao's group reported that *tert*-butyl nitrite was employed as the NO source to generate the quinoxaline *N*-oxides under mild conditions (Scheme 1).[6] Maiti's group reported the efficient and stereoselective nitration of mono- and disubstituted olefins with $AgNO_2$ and 2,2,6,6,-tetramethylpiperidinooxy (TEMPO), with $AgNO_2$ serving as the NO_2 source.[7] Recently, Saikia's group developed an efficient method for synthesis of 4-iodopyrazole *N*-oxides from propargylamines through the $NaNO_2$/AcOH/I_2 reaction system.[8] Although $AgNO_2$ has been widely utilized as an oxidant and NO_2 source for the incorporation of functional groups into target molecules, there have been no reports about $AgNO_2$ as the NO source for the synthesis of heterocyclic compounds.[9] Herein, we report the first example of using $AgNO_2$ as the NO source for the direct synthesis of pyrazole *N*-oxides with simple substrates in a one-pot manner.

Scheme 1. Typical Approaches and the Reactions for Providing the NO Source



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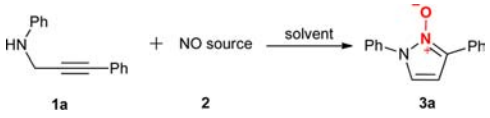
We began by treating *N*-(3-phenylprop-2-yn-1-yl)aniline (**1a**) and $AgNO_2$ (**2**) in THF at 100 °C for 6 h. We found that 1,3-diphenyl-1*H*-pyrazole *N*-oxide (**3a**) was obtained in 85% yield (Table 1, entry 1). The result was an interesting discovery because the method for direct synthesis of pyrazole *N*-oxides is very rare. The structure of **3a** was confirmed by spectroscopic analysis and further confirmed by single crystal X-ray analysis. Thus, the substrate **1a** was chosen as the model substrate to optimize the reaction conditions. First, some compounds, such as $AgNO_3$ and $NaNO_2$, were tested for this process, and $AgNO_2$ proved to be optimal (Table 1, entries 1−3). Then, various solvents were evaluated for this reaction; THF exhibited the highest efficiency and gave the corresponding product in 85% yield (Table 1, entries 4−8). After screening for temperature, light, and equivalent of substrates, the optimized conditions were established as shown in Table 1, entry 1.

Table 1. Optimization of Reaction Conditions[a]



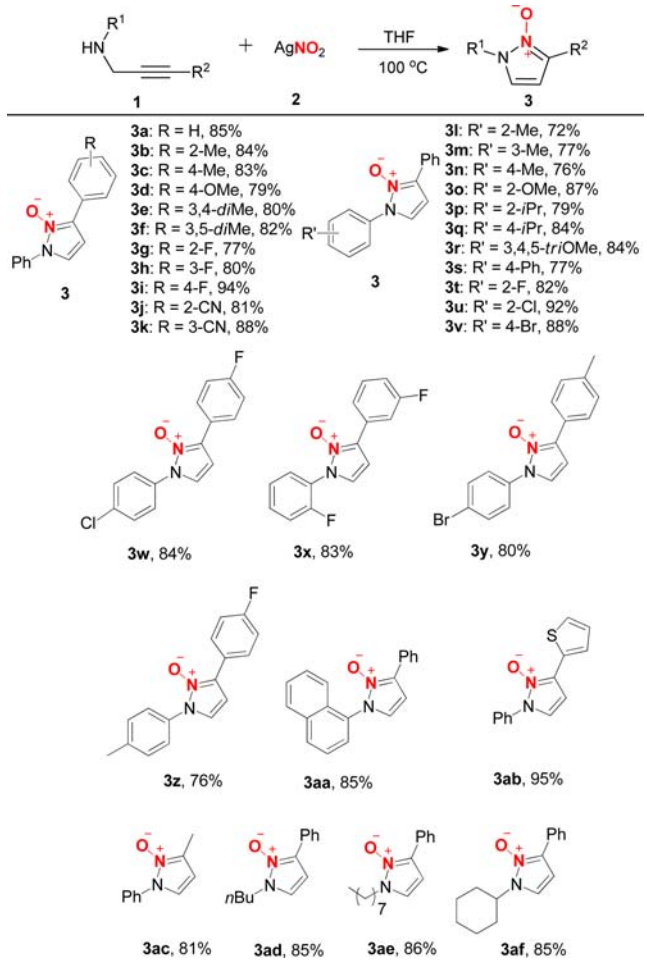
entry	additive	solvent	yield (%)[b]
1	**$AgNO_2$**	**THF**	**85**
2	$AgNO_3$	THF	80
3	$NaNO_2$	THF	–
4	$AgNO_2$	EtOH	56
5	$AgNO_2$	DMF	53
6	$AgNO_2$	DMSO	25
7	$AgNO_2$	PhMe	31
8	$AgNO_2$	CH_3CN	79
9[c]	$AgNO_2$	THF	83

[a]Reaction conditions: **1a** (0.5 mmol), NO sources (0.6 mmol), solvent (2 mL), 100 °C. [b]Yields of isolated products. [c]Kept in the dark. Entry in bold highlights the optimized reaction conditions, and the reaction time was monitored by TLC.

Using the optimized reaction conditions, the scope and generality of this reaction were investigated, and the results are illustrated in Scheme 2. A series of *N*-propargylamines with electron-donating or -withdrawing groups reacted with $AgNO_2$ efficiently, and the desired substituted pyrazole *N*-oxides were obtained in good to excellent yields. As shown in Scheme 2, the reaction was not significantly affected by the nature of the groups in the aromatic ring of the *N*-propargylamines. Additionally, the results indicated that the reaction was insensitive to the steric effect of the *ortho*-position. The substituent in the benzene ring of R^1 and R^2 gave the desired products in satisfactory yields (Scheme 2, **3w**−**3aa**). The *N*-(3-(thiophen-2-yl)prop-2-yn-1-yl)aniline **1ab** was also compatible in this transformation, producing the desired furans **3ab** in 95% yield. The substrates of *N*-propargylamines based on alkyl groups also performed well in this transformation, and the desired products were isolated in high yields (Scheme 2, **3ac**−**3af**).

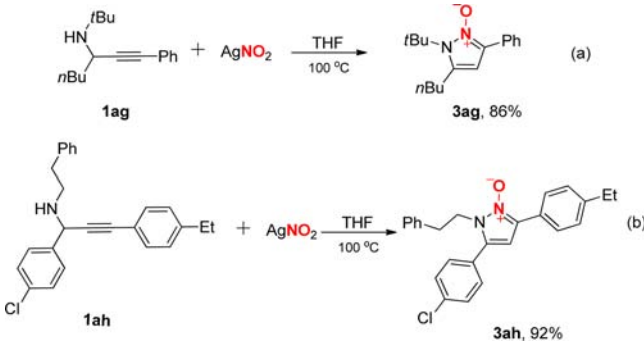
The more challenging substrates, 1-substituted-*N*-propargylamines, were employed for this procedure. When the polysubstituted *N*-propargylamines, such as **1ag** and **1ah**, were subjected to the optimized conditions, the target products **3ag** and **3ah** were isolated in 86% and 92% yields, respectively (Scheme 3).

Scheme 2. Synthesis of Substituted Pyrazole *N*-Oxides[a]



[a]Reaction conditions: **1a** (0.5 mmol), $AgNO_2$ (0.6 mmol), THF (2 mL), 100 °C.

Scheme 3. Reactions of 1-Substituted *N*-Propargylamines and $AgNO_2$



In order to gain further insight into this reaction, several control experiments were investigated (Scheme 4). The radical scavenger of TEMPO was used for this transformation, and the yield of **3a** sharply decreased (Scheme 4a). An important intermediate **4a**, which was synthesized with the substrate **1a** and *t*BuONO following the reported method,[10] was subjected to the standard conditions, and the desired product **3a** was obtained in 95% yield (Scheme 4b). The results showed that the *N*-nitrosamine **4a** should be the intermediate for this transformation. Subsequently, the *N*-nitrosamine **4a** was

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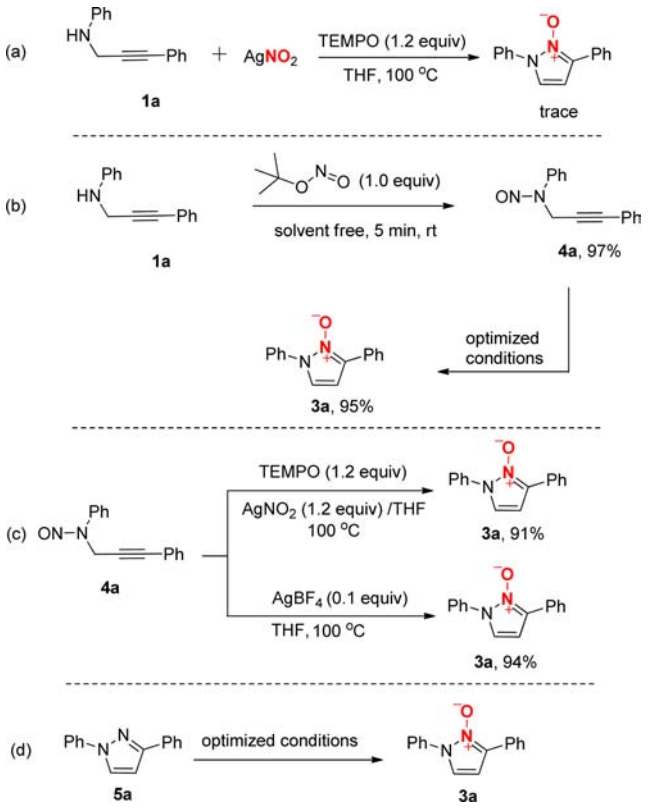
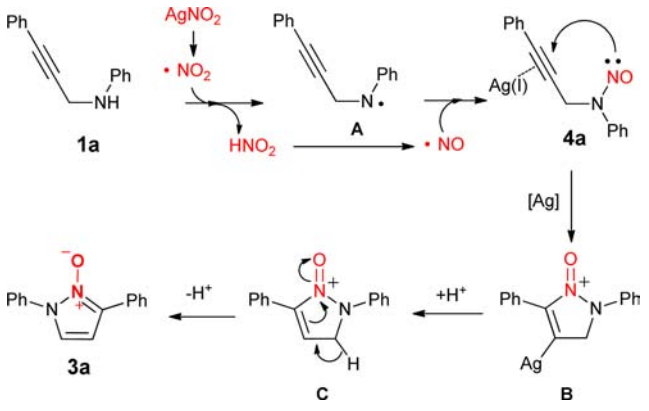
Scheme 4. Control Experiments



studied under the standard conditions with TEMPO, and the yield of **3a** had a slight decrease. Then, the *N*-nitrosamine **4a** was studied with 0.1 equiv of $AgBF_4$ in THF at 100 °C, and the desired **3a** was isolated in 94% yield (Scheme 4c). These results demonstrated that the transformation of the *N*-nitrosamine **4a** to **3a** was not a radical process. 1,3-Diphenyl-1*H*-pyrazole **5a** was also employed for this process, and the target molecule **3a** was not detected (Scheme 4d).

Based on the control experiments, a possible mechanism is proposed in Scheme 5. Under these conditions, a nitro radical might be generated though the decomposition of $AgNO_2$ first. Then the substrate **1a** reacted with the nitro radical to produce HNO_2 and the nitrogen radical **A**. The nitrogen radical **A** coupled with the ·NO radical, which was produced from HNO_2, to give the important intermediate *N*-nitrosamine **4a**. The coordination of **4a** with the silver catalyst gave the coordinated complex, which underwent subsequent cyclization to generate species **B**.[11] **B** was protonated to generate intermediate **C**, and finally, the desired product **3a** was produced through proton elimination.

Scheme 5. Proposed Mechanism



In conclusion, we developed a direct method to synthesize pyrazole *N*-oxides from *N*-propargylamines via a tandem oxidation/cyclization reaction. $AgNO_2$ was used for the first time as the NO source for the synthesis of pyrazole *N*-oxides. Various substituted groups on *N*-propargylamines proceeded smoothly, and the desired pyrazole *N*-oxides were obtained in good yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03021.

Experimental methods; ^1H and ^{13}C NMR spectra of all compounds (PDF)

X-ray data for **3a** (ZIP)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yanrl@lzu.edu.cn.

Notes

The authors declare no competing financial interest.

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