Organic LETTERS

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TEMPO-Mediated Aza-Diels–Alder Reaction: Synthesis of Tetrahydropyridazines Using Ketohydrazones and Olefins

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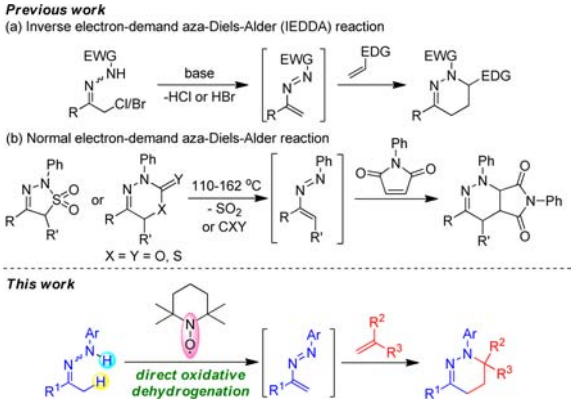
Supporting Information

ABSTRACT: A novel, facile, and efficient method for the synthesis of tetrahydropyridazines by a one-pot tandem reaction of easily accessible ketohydrazones and olefins in the presence of 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) has been successfully developed. The reaction involves the initial generation of azoalkenes from direct oxidative dehydrogenation of ketohydrazones using TEMPO as the commercially available oxidant, followed by a subsequent aza-Diels–Alder reaction with olefins.

Azoalkenes, also known as 1,2-diaza-1,3-dienes (DDs), have been established as valuable synthetic building blocks and have found broad applications in cyclization and cycloaddition reactions with a wide variety of partners for the preparation of various nitrogen-containing heterocyclic compounds.[1] Because azoalkenes are unstable and highly reactive, their generation and use usually proceeds by in situ transformation of the corresponding hydrazone derivatives. In general, there are two pathways for this transformation: one is elimination of hydrogen halide from α-halo ketohydrazones under basic conditions (Scheme 1a),[2] and the other is pyrolysis of hardly acquired heterocyclic precursors 2,5-dihydro-1,2,3-thiadiazole-1,1-dioxides, 3,6-dihydro-1-oxa-3,4-diazin-2-ones, and their sulfur analogues under harsh conditions (Scheme 1b).[3] However, the generation of azoalkenes by direct oxidative dehydrogenation of the most common hydrazones has rarely been documented.[4] In view of the aspects of atom economy and sustainable chemistry, herein we present a novel and efficient metal-, halogen-, and additive-free approach for the in situ formation of azoalkenes by the reaction of hydrazones with 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)[5] via a hydrazonyl radical-involved process.[6,7] By means of this protocol, tetrahydropyridazines have been successively synthesized by the subsequent reaction of the in situ-generated azoalkenes with olefins via an aza-Diels–Alder reaction.

Scheme 1. Strategies for in Situ Generation of Azoalkenes and Their Application in the Aza-Diels–Alder Reaction



Tetrahydropyridazines, as an important class of six-membered heterocycles, are widely found in many natural products and pharmaceutically active compounds.[8] To date, several efficient methods for the synthesis of tetrahydropyridazine motifs have been developed. Among them, the inverse-electron-demand hetero-Diels–Alder (IEDDA)[9] reaction of electrophilic azoalkenes with electron-rich alkenes is arguably one of the most effective and facile approaches for the synthesis of tetrahydropyridazines (Scheme 1a). Several normal aza-Diels–Alder reactions of electron-rich azoalkenes with alkenes have also been developed.[3] For example, Boeckman explored a normal aza-Diels–Alder reaction of alkenes with electron-rich azoalkenes generated through the pyrolysis of hardly acquired heterocyclic precursors (Scheme 1b).[3a] In this context, the present protocol provides a novel, mild, and efficient method for the synthesis of structurally important tetrahydropyridazines using ketohydrazones and olefins as easily accessible substrates and TEMPO as the commercially available oxidant as well as the first example of a TEMPO-mediated hydrazonyl radical-involved tandem oxidative dehydrogenation/aza-Diels–Alder reaction procedure.

We commenced our studies by the reaction of acetophenone phenylhydrazone (**1a**) with methyl acrylate (**2a**) (5 equiv) in the presence of TEMPO (3 equiv) in toluene under an argon atmosphere at 80 °C. To our delight, the desired product, methyl 2,6-diphenyl-2,3,4,5-tetrahydropyridazine-3-carboxylate

Received: March 10, 2016
Published: April 27, 2016

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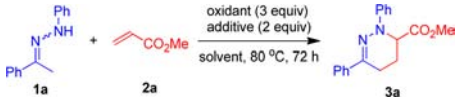
DOI: 10.1021/acs.orglett.6b00702
Org. Lett. 2016, 18, 2070–2073

(**3a**) was obtained in 65% yield (Table 1, entry 1). Significantly, increasing the amount of **2a** to 10 equiv improved the yield of

Table 1. Optimization Investigation[a]



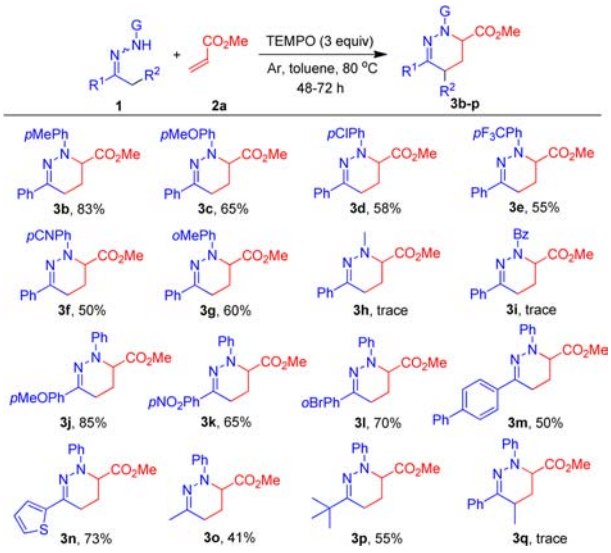
entry	oxidant	additive	solvent	yield (%)[b]
1[c]	TEMPO	–	toluene	65
2	**TEMPO**	–	**toluene**	**81**
3[d]	TEMPO	–	toluene	76
4	TEMPO	K_3PO_4	toluene	41
5	TEMPO	Cs_2CO_3	toluene	34
6	TEMPO	K_2CO_3	toluene	70
7	TEMPO	HOAc	toluene	42
8[e]	TEMPO	HOAc	toluene	73
9	TEMPO	–	neat	75
10	TEMPO	–	DMF	62
11	TEMPO	–	DMSO	52
12	4-HO-TEMPO	–	toluene	81
13	4-acetamido-TEMPO	–	toluene	70
14	4-oxo-TEMPO	–	toluene	50

[a]Reaction conditions: a mixture of **1a** (0.5 mmol), **2a** (5 mmol), and oxidant (1.5 mmol) in solvent (1 mL) was stirred under Ar at 80 °C for 72 h. [b]Isolated yields. [c]**2a** (5 equiv) was used. [d]At 110 °C. [e]HOAc (0.2 equiv) was used.

product **3a** to 81% (entry 2). In addition, a higher reaction temperature (110 °C) neither accelerated the reaction nor increased the yield of product **3a** (entry 3). Moreover, additives such as bases and acids did not further improve the yield of **3a** (entries 4–8). Furthermore, when the model reaction was carried out under solvent-free conditions, the desired product **3a** was obtained in 75% yield (entry 9). Unfortunately, the use of polar solvents such as DMSO and DMF resulted in lower yields of **3a** (entries 10 and 11). TEMPO derivatives such as 4-HO-TEMPO, 4-acetamido-TEMPO, and 4-oxo-TEMPO were also suitable for the reaction as the oxidant (entries 12–14), leading to the same or a slightly lower yield of **3a**.

With the optimized conditions in hand (Table 1, entry 2), a variety of ketohydrazones **1** were subjected to the reaction with **2a**. The results are summarized in Scheme 2. *N*-Phenyl-substituted acetophenone hydrazones with a broad range of electronic properties participated smoothly in the reaction, affording the corresponding tetrahydropyridazine derivatives **3a–g** in moderate to excellent yields. *N*-Methyl- and *N*-benzoyl-substituted acetophenone hydrazones were also tried. However, neither of them was suitable for the reaction, probably because of the lower stability of the in situ-generated alkyl azoalkene derived from compound **1h** and the strong N–H bond of acyl hydrazone **1i** to initiate the N-centered radical, respectively. In addition, both aromatic- and aliphatic-substituted *N*-phenyl ketohydrazones were also examined in the reaction. Acetophenone hydrazones bearing substituents such as *p*-MeO, *p*-NO_2, *o*-Br, and *p*-Ph on the phenyl groups of the ketone moieties furnished the corresponding products **3j–m** in 50–85% yield. 2-Acetylthiophene hydrazone participated swimmingly in the reaction as well, delivering the expected product **3n** in 73% yield. Notably, simple aliphatic ketohydrazones such as acetone phenylhydrazone and 3,3-dimethylbutan-2-one phenylhydrazone, were also good candidates for the reaction, providing the corresponding products **3o** and **3p**

Scheme 2. Scope of Ketohydrazones[a,b]

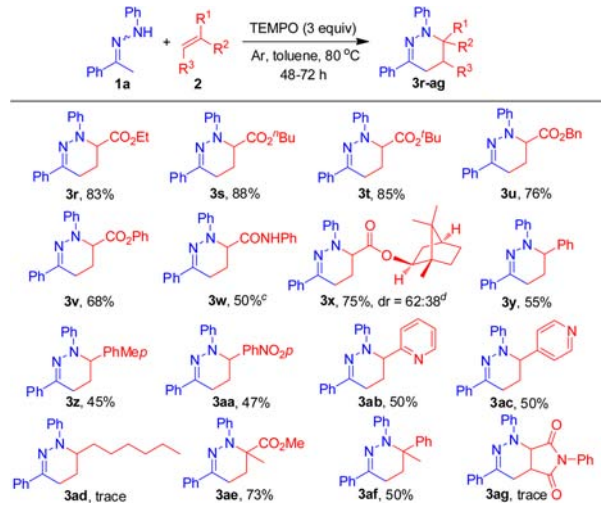


[a]Reaction conditions: a mixture of hydrazone **1** (0.5 mmol), **2a** (5 mmol), and TEMPO (1.5 mmol) in toluene (1 mL) was stirred under Ar at 80 °C for 48–72 h. [b]Isolated yields are shown.

in moderate yields. However, propiophenone hydrazone was inert in the reaction and hardly gave the desired product **3q**, probably because forming this kind of azoalkene via a Cope-like elimination of the TEMPO-trapped intermediate is difficult.[10]

Having successfully achieved the tandem reaction with various ketohydrazones, we then shifted our attention to investigate the scope of olefins (Scheme 3). A series of acrylates, such as Et, *n*Bu, *t*Bu, Bn, and phenyl esters, were well-tolerated in the reaction with hydrazone **1a**, giving rise to the corresponding products **3r–v** in good to excellent yields. *N*-Phenylacrylamide also proved to be suitable for this transformation, as demonstrated by the modest yield of **3w**. Remarkably, isobornyl acrylate also participated well in the

Scheme 3. Scope of Alkenes[a,b]



[a]Reaction conditions: a mixture of hydrazone **1a** (0.5 mmol), olefin **2** (5 mmol), and TEMPO (1.5 mmol) in toluene (1 mL) was stirred under Ar at 80 °C for 48–72 h. [b]Isolated yields are shown. [c]*N*-Phenylacrylamide (5 equiv) was used. [d]The diastereomeric ratio was determined by ^{1}H NMR analysis.

DOI: 10.1021/acs.orglett.6b00702
Org. Lett. 2016, 18, 2070–2073

reaction, delivering **3x** as an inseparable mixture of diastereomers in a combined 75% yield. In addition, styrenes with a range of electronic properties on the phenyl ring were also employed as the partners in the reaction, affording the desired products **3y**–**aa** in moderate yields. Significantly, the product **3y** was unequivocally determined to show *ortho*/*para* regioselectivity by single-crystal X-ray structural analysis (Figure 1). Furthermore, when 2-vinylpyridine and 4-vinylpyridine were allowed to react with **1a**, the reactions gave the corresponding products **3ab** and **3ac** in moderate yields. Unfortunately, the aliphatic olefin oct-1-ene, which is commonly used in the IEDDA reaction as the electron-rich dienophile, was inert in the reaction and gave only a trace amount of the desired product **3ad**. The phenomenon further revealed that the reaction is a normal-electron-demand aza-Diels–Alder reaction. The reaction was also successful with 1,1-disubstituted alkenes, as demonstrated in the cases of **3ae** and **3af**. Unfortunately, when the 1,2-disubstituted alkene 1-phenyl-1*H*-pyrrole-2,5-dione participated in the reaction, the corresponding product **3ag** was scarcely obtained.

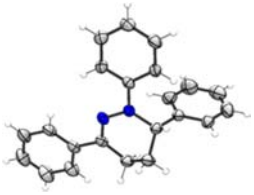
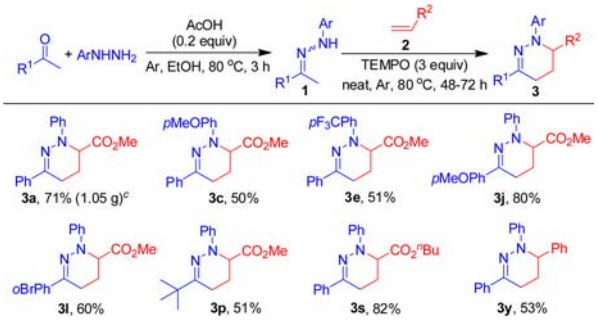


Figure 1. X-ray structure of **3y** (thermal ellipsoids are shown with 30% probability).

Considering that hydrazones are very readily formed by the condensation of ketones and hydrazines under acidic conditions, we examined the aza-Diels–Alder reaction of arylhydrazines, ketones, and alkenes with TEMPO in a one-pot manner. First, the condensation of ketones and arylhydrazines in the presence of 20% HOAc in EtOH almost quantitatively yielded ketohydrazones **1**. After removal of the solvent, TEMPO and alkenes were added, and then the mixture was stirred at 80 °C neat under argon for 48–72 h. As shown in Scheme 4, some representative substrates were found to be transformed into the desired products in comparable yields. It is noteworthy that the improved one-pot procedure could be performed on a gram scale without any difficulty, delivering compound **3a** in 71% yield (1.05 g) when 5 mmol of acetophenone was used.

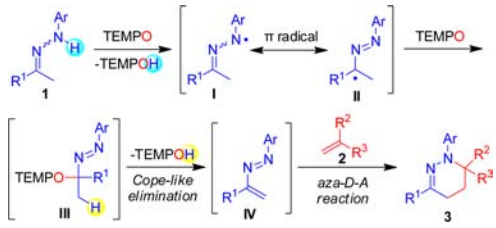
Scheme 4. One-Pot Reaction of Arylhydrazines, Ketones, and Alkenes[a,b]



[a]Reaction conditions: ketone **4** (1.0 mmol), arylhydrazine (1.05 mmol), alkene **2** (10 mmol), and TEMPO (3 mmol), Ar, 48–72 h. [b]Isolated yields are shown. [c]The reaction was carried out on a gram scale (5 mmol of ketone was used).

To account for the aforementioned results, the mechanism shown in Scheme 5 is proposed. We believe that TEMPO initially abstracts the H atom from the N–H bond of hydrazone **1** to produce the corresponding hydrazonyl radical.[6] Our previous results demonstrated that hydrazonyl radical serves as a π radical with the single electron spin density delocalized on both the N atom adjacent to a phenyl ring and the conjugated C atom of the ketone, which means that it can be drawn with resonance structures **I** and **II**.[6d,7g] Thus, the carbon-centered radical **II** would be trapped immediately by TEMPO to produce intermediate **III**, which would subsequently undergo Cope-like TEMPOH elimination to produce azoalkene **IV**.[10] Finally, the normal aza-Diels–Alder reaction of **IV** with alkene **2** would give the desired tetrahydropyridazine **3**.

Scheme 5. Proposed Mechanism



In conclusion, a facile one-pot metal- and halogen-free hydrazonyl radical-involved tandem oxidative dehydrogenation/aza-Diels–Alder reaction has been successively developed for the synthesis of tetrahydropyridazines using ketohydrazones and alkenes as the readily accessible substrates and commercially available TEMPO as the cheap oxidant. To the best of our knowledge, the reaction not only provides facile one-pot access to the biologically important and synthetically valuable tetrahydropyridazine derivatives under halide-free-substrate conditions but also provides the first example of the in situ generation of azoalkenes by direct oxidative dehydrogenation of ketohydrazones employing TEMPO as the hydrazonyl radical initiator as well as the β-hydrogen acceptor in the Cope-like elimination. Further studies of the hydrazonyl radical-promoted reaction are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00702.

Detailed experimental procedures and spectral data (^{1}H and ^{13}C NMR spectra) for all products (PDF)
Crystallographic data for **3y** (CIF)

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Notes

The authors declare no competing financial interest.

DOI: 10.1021/acs.orglett.6b00702
Org. Lett. 2016, 18, 2070–2073

■ ACKNOWLEDGMENTS

We thank the NNSFC (21422205 and 21272106), the Program for New Century Excellent Talents in University (NCET-13-0258), the "111" Project, the Changjiang Scholars and Innovative Research Team in University (IRT-15R28), and the Fundamental Research Funds for the Central Universities (lzujbky-2014-k03, lzujbky-2014-60) for financial support.

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