Azomethine Ylide: An Isolable 1,5-Dipole for Affecting [5+2] Cycloaddition Reactions

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Abstract It was recently found that 1-sulfonyl-1,2,3-triazole can act as a 1,3-dipole in the presence of rhodium(II), leading to emergence of diverse rhodium(II)-catalyzed [3+n] cycloaddition reactions using 1-sulfonyl-1,2,3-triazole. Herein, we highlight development of another dipole, azomethine ylide, which was prepared from 1-sulfonyl-1,2,3-triazole with amide and pyridine derivatives, respectively. Notably, the rhodium(II)-catalyzed reaction of 1-sulfonyl-1,2,3-triazole with pyridines resulted in generation of uniquely isolable azomethine ylide. This azomethine ylide is the first example of an isolable 1,5-dipole that could be cyclized with 2π-dipolarophiles. The new 1,5-dipole provides an avenue for the development of new organic syntheses.

Key words metal catalysis, diazo compound, azomethine ylide, dipolar cycloaddition, multicomponent reaction

1 Introduction

Heterocycles are privileged structural units that are frequently encountered in natural products as well as in pharmaceuticals.1 Introducing a nitrogen atom into target cyclic compounds has been an important and challenging issue in organic chemistry. The dipolar cycloaddition reaction has become a powerful and widely used strategy for synthesizing heterocycles as it ensures high atom efficiency with a single operation.2 Ylide chemistry dates back to almost one century ago.3 Among the known ylides, azomethine ylide, consisting of an iminium ion adjacent to a carbanion, is an allyl-anionic-type dipole that can be applied to dipolar cycloaddition reactions.4 In general, azomethine ylides are short-lived reactive species, and are thus conventionally prepared in situ from easily accessible precursors such as iminium derivatives (Scheme 1, eq. 1).5 Other examples of protocols for generating such species include ring opening of aziridines or oxazolines by photolysis or thermolysis (Scheme 1, eq. 2 and 3).6,7 Transition-metal-catalyzed decomposition of diazo compounds and subsequent imine addition has recently gained popularity as a synthetic approach for generating azomethine ylides (Scheme 1, eq. 4).8 Despite steady advancement in the protocols for generation

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of azomethine ylides using diazo compounds, certain unexplored areas remain to be improved to expand the substrate scope. Herein, we briefly discuss an alternate route for generation of azomethine ylides from a simple precursor, 1-sulfonyl-1,2,3-triazole, and the applications of these species in reactions, including dipolar cycloadditions.

2 Reactions of 1-Sulfonyl-1,2,3-triazole with Aldehydes

In 2007, Chang, Fokin, and Sharpless reported regioselective generation of 1-sulfonyl-1,2,3-triazole via copper-catalyzed cycloaddition of sulfonyl azide and a terminal alkyne at 0 °C.⁹b Years later, Fokin reported an improved method for the synthesis of 1-sulfonyl-1,2,3-triazole using copper(I) thiophen-2-carboxylate (CuTc) as a catalyst at room temperature.⁹c These organic methods contributed significantly to the development of carbene chemistry, given that 1-sulfonyl-1,2,3-triazoles could be used as precursors for rhodium(II) carbenoids. As shown in Scheme 2, reversible ring-chain tautomerization of 1-sulfonyl-1,2,3-triazole generated α-diazo imine species that could react with rhodium(II) in an irreversible manner to afford an α-imino rhodium(II) carbenoid A with the release of nitrogen gas.¹⁰

The nucleophilic α-sulfonyl imine group of intermediate A enables the ylide intermediate B, generated from the α-imino Rh(II)-carbenoid, to participate in cycloaddition reactions (Scheme 2).¹¹ Moreover, the α-imino rhodium(II) carbenoids A are notable for their unique reactivity with aldehydes to produce 4-oxazolines depending on the reaction temperature (Scheme 2).

At room temperature, the reaction between the α-imino rhodium(II) carbenoid and aldehydes leads to the production of homochiral 4-oxazolines (Scheme 2,B).¹² The reaction proceeds via carbonyl ylide intermediates with excellent yields and enantioselectivity. Murakami and coworkers reported the reaction of α-imino rhodium(II) carbenoid with α,β-unsaturated aldehydes at 120 °C, leading to the stereoselective production of 2,3-dihydropyrroles D.¹³ Nucleophilic addition of the α,β-unsaturated aldehyde to the electrophilic rhodium(II) carbenoid occurred to furnish the 4-oxazoline via a carbonyl intermediate in the same manner. However, 4-oxazoline underwent ring opening at 120 °C to form azomethine ylide C, which was able to stereoselectively undergo 1,5-cyclization depending on the geometry of the azomethine ylide.

3. 1-Sulfonyl-1,2,3-triazole as a Precursor of Azomethine Ylide

Similar ring opening of 4-oxazoline to furnish azomethine ylide was observed in the reactions of α-imino rhodium(II) carbenoids with amide derivatives. Lee and Murakami independently published the rhodium(II)-catalyzed reaction of 1-sulfonyl-1,2,3-triazoles and DMF to produce α-amino enamines.¹⁴ Around the same time, a similar reaction of N,N-disubstituted benzamides to produce stereoselective α-amino enamines was also reported (Scheme 3).¹⁵ N,N-Dimethylbenzamide reacted with 1-sulfonyl-1,2,3-triazole leading to the formation of the fully substituted α-amido-enamine in yields up to 92% using Rh₂(esp)₃ as the catalyst in toluene at 80 °C; this product is a valuable building block of various medicinal compounds. The reaction conditions were successfully applied to a range of 1-sulfonyl-1,2,3-triazoles with high yields. Notably, various N,N-disubstituted benzamides could be employed in the reaction, allowing for the introduction of a variety of amine groups.
A plausible mechanism involves reaction of the N,N-disubstituted benzamides with $\alpha$-imino rhodium(II) carbenoid to form 4-oxazoline (Scheme 3, A). The unstable 4-oxazoline is then transformed into the short-lived azomethine ylide $B$ via ring opening of 4-oxazoline followed by intramolecular 1,3-cyclization and subsequent formation of aziridine $C$. Following ring opening of aziridine, the zwitterionic intermediate facilitated synthesis of the $Z$-selective $\alpha$-amino enamines $D$ via proton rearrangement. In the reaction of the $\alpha$-imino rhodium(II) carbenoid with the amide, formation of the azomethine ylide intermediate (Scheme 3, B) proceeded more readily at low temperature than formation of the azomethine ylide from reaction with the aldehyde (Scheme 2, C) because of the electronic effect. Furthermore, the generated azomethine ylide species was not amenable to the intermolecular cycloaddition reaction.

### 4 Generation of Free Azomethine Ylide

The reaction between the $\alpha$-imino rhodium(II) carbenoid (generated from 1-sulfonyl-1,2,3-triazole) and pyridine derivatives is totally distinct from the reaction with carbonyl compounds (aldehydes or amides). A mixture of 1-sulfonyl-1,2,3-triazole, 2-phenylpyridine, and Rh$_2$(esp)$_2$ catalyst in 1,2-DCE at 100 °C afforded the azomethine ylide in 47% yield. Unexpectedly, the azomethine ylide was table stable and could even be isolated as red crystals by silica gel column chromatography (Scheme 4).

Notably, whereas the typical azomethine ylide consists of an iminium ion adjacent to a carbanion, the isolated azomethine ylide, characterized by X-ray analysis, has a pyridinium 1,5-zwitterionic (1,5-dipole) structure. In addition, the pyridine backbone forms a torsion angle of 74.2° with the enamide moiety; hence, the two components are arranged in an almost orthogonal manner. Although further studies are needed, preliminary tests employing pyridine derivatives support the postulate that the stability of the azomethine ylide is dependent on the substituent at the 2-position of pyridine. 2-Alkyl- and 2-aryl-substituted pyridines exhibit high efficiency, whereas unsubstituted pyridine is ineffective. Simply changing the solvent and the pyridine equivalents enhanced the reaction efficiency to furnish 97% yield and the substrate scope was quite broad. In addition, the azomethine ylide was easily isolated and stored (Scheme 5).

To confirm that this azomethine ylide could be used as a dipole, the reaction of the isolated ylide with dimethyl acetylenedicarboxylate (DMAD), a highly active dipolarophile, was conducted at 100 °C. In general, azomethine ylides are known to undergo [3+2] cycloaddition with consequent construction of five-membered azacyclic compounds. For example, Jia and Li reported that azomethine ylides consistently undergo [3+2] cycloaddition reactions despite the similar charge distribution. However, in the present case, the [5+2] cycloaddition of azomethine ylides with DMAD was highly successful, giving rise to 1,4-diazepines due to the nucleophilicity of the nitrogen anion.
The present discovery is the first example of an isolable 1,5-dipole that can be used in a dipolar cycloaddition reaction. Considering the difficulty of the [5+2] cycloaddition, this is significant, not only for construction of seven-membered cyclic compounds, but also for other possible cycloaddition reactions. Notably, the continuing identification of biologically active natural products and pharmaceuticals that contain seven-membered heterocycles increases the importance of this contribution.

This breakthrough spurred the development of rhodium(II)-catalyzed, three-component [5+2] cycloaddition reactions of pyridines, 1-sulfonyl-1,2,3-triazoles, and activated alkynes via the in situ generated 1,5-dipole. Thus, a user-friendly and operationally simple strategy for systematization of the core structure of 1,4-diazepines was afforded. A variety of aryl substituents on the 2-position of pyridine were tolerated, and this new reaction proceeded readily with a wide range of 1-sulfonyl-1,2,3-triazoles to provide the desired products (Scheme 6).

Application of the developed protocol to a multicyclic four-component reaction starting from a terminal alkyne, sulfonyl azide, 2-substituted pyridine, and DMAD was assessed. Despite the challenges in the cooperative multicyclation system employing more than four reactants, we confirmed the possibility for further development of the reaction under nonoptimized conditions employing CuTc and Rh(esp)_2 (Scheme 7).

5 Outlook

Dipolar cycloaddition reactions employing simple and accessible dipoles have found extensive use as high-yielding, regio- and stereoselective methods for the synthesis of mono- or polyheterocycles. Reactions involving azomethine ylides are particularly valuable tools for generating N-containing heterocyclic compounds. However, because typical azomethine ylides function as three-atom 1,3-dipole units, the intrinsic limitation of the 1,3-dipolar cycloaddition reaction with azomethine ylides generally generates five-membered heterocycles via a [3+2] reaction model with a 2π-dipolarophile. For construction of non-five-membered heterocyclic compounds, the development of a new dipole that selectively matches the dipolarophile is a prospectively effective approach. Even though challenges still remain, the isolable azomethine ylide presented herein has been proven to be an unprecedented example of a 1,5-dipole for the synthesis of various azaheterocycles. Considering the slow development of [5+2] cycloaddition reactions despite intensive effort, this finding is a major breakthrough. This species provides an avenue for many prospective applications and is anticipated to contribute to advancements in the field of cycloaddition reactions.

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