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Multicomponent [5 + 2] Cycloaddition Reaction for the Synthesis of 1,4-Diazepines: Isolation and Reactivity of Azomethine Ylides

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Supporting Information

ABSTRACT: Air-stable azomethine ylides with an unusual pattern of charge distribution were efficiently prepared via the rhodium-catalyzed reaction between pyridines and 1-sulfonyl-1,2,3-triazoles. This reaction allowed for the first example of the catalytic multicomponent [5 + 2] cycloaddition reactions, thus resulting in the formation of biologically active 1,4-diazepine compounds.

Diazepines represent one of the most prominent compound classes which are widely distributed in natural products and pharmaceuticals.[1] Especially, over 40 medications highlight 1,4-benzodiazepine as a privileged structure with a broad range of therapeutic treatment for the central nervous system (Figure 1).[2] More importantly, the bioactivity of these

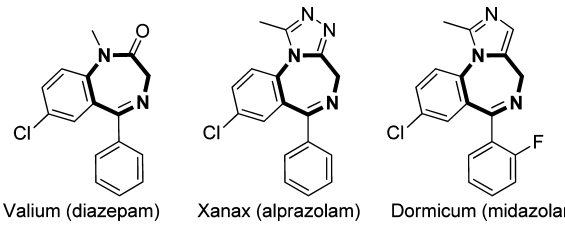


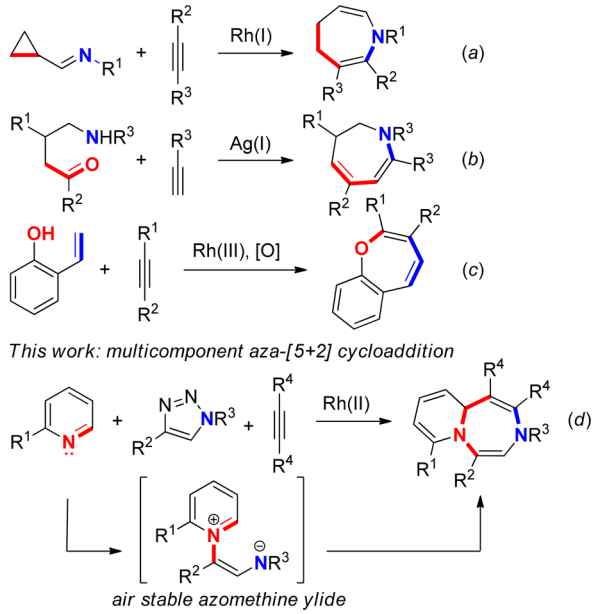
Figure 1. Psychoactive drugs containing the 1,4-diazepine core structure.

derivatives has been known to be significantly improved through the fusion of the 1,4-diazepine scaffold to various heterocycles. For example, marketed drugs such as triazole-fused Xanax and imidazole-fused Dormicum possess anxiolytic sedative and muscle relaxant properties. Therefore, an exciting new approach which has recently come into focus is to fuse the 1,4-diazepine moiety with heterocycles for further structure–activity relationship (SAR) studies. However, straightforward methods of core structure modification are still rare and restricted.

The [m + n] cycloaddition reaction has been established as a reliable and powerful tool for the synthesis of heterocycles from simple starting materials.[3] However, in contrast with catalytic [3 + 2] and [4 + 2] cycloadditions for preparing five- and six-membered heterocyclic rings, synthetic strategies using a [5 + 2] cycloaddition for the construction of seven-membered heterocycles have been less explored mainly owing to entropic factors and the presence of nonbonding interactions in the transition state.[4]

Despite the difficulties of the [5 + 2] cycloaddition, considerable progress has recently been made (Scheme 1).

Scheme 1. Hetero-[5 + 2] Cycloadditions with Alkyne



Wender and co-workers first reported the transition-metal-catalyzed hetero-[5 + 2] cycloaddition to synthesize azepine derivatives in 2002 (Scheme 1a).[5a] Li et al. reported the [5 + 2] cycloaddition between γ-amino ketones and alkynes in the presence of silver catalyst to give azepines (Scheme 1b).[5b] Most recently, Gulías and co-workers reported the Rh(III)-catalyzed [5 + 2] cycloaddition of 2-alkenylphenols with alkynes, leading to the corresponding benzoxepines (Scheme 1c).[5c] Although reported cycloaddition reactions toward seven-membered heterocycles are efficient, the development of multicomponent [5 + 2] cycloaddition reactions which have a great influence in discovery chemistry has been rather limited. Herein, we report new multicomponent cycloaddition reactions using simple pyridines, 1-sulfonyl-1,2,3-triazoles, and alkynes via an isolable azomethine ylide, which results in 1,4-diazepines (Scheme 1d). To the best of our knowledge, this is the first example of metal-catalyzed multicomponent [5 + 2] cycloaddition reactions.

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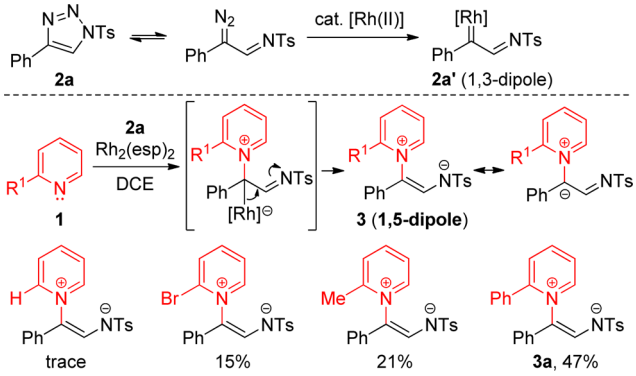
1-Sulfonyl-1,2,3-triazoles (Scheme 2, **2a**) have attracted a great deal of attention as precursors of Rh azavinyl carbene

Scheme 2. Isolable Azomethine Ylide Formation[a]



[a]Reaction conditions: 2-substituted pyridine (**1**; 0.2 mmol), 1-sulfonyl-1,2,3-triazole (**2a**; 0.4 mmol), $Rh_2(esp)_2$ (1.0 mol %), and 1,2-DCE (2.0 mL) at 100 °C for 12 h.

(**2a′**), which is a practical intermediate for the synthesis of N-heterocyclic complexes.[6] Most studies on the Rh catalysis of 1-sulfonyl-1,2,3-triazoles have been especially focused on [3 + 2] or [4 + 3] cycloaddition reactions.[7] Recently, our group and others reported a Rh(II)-catalyzed reaction of 1-sulfonyl-1,2,3-triazoles and amides to give enaminones via unstable azomethine ylide intermediates which are otherwise difficult to react with dipolarophiles.[8] Inspired by these studies, it was envisioned that relatively long-lived and stable azomethine ylides which have conjugated double bonds could participate in the annulation with reactive dipolarophiles.

To study the intrinsic aspects of such conjugated azomethine ylides, we conducted a reaction between the 2-substituted pyridine **1** and 1-sulfonyl-1,2,3-triazole **2a** with a catalytic amount of rhodium (Scheme 2). To our surprise, a mixture of 2-phenylpyridine, **2a**, and $Rh_2(esp)_2$ (1.0 mol %) in DCE at 100 °C afforded red crystalline **3a** together with a red solution. Even more surprisingly, **3a** was isolable by flash column chromatography (47%) and could be fully characterized, including by X-ray crystallography (Figure 2). Although azomethine ylides could be easily prepared in situ from a stable precursor,[9] the isolation of typical azomethine ylides is difficult in most cases because of their lability. Considering the limited applications of in situ generated azomethine ylides, this method presents a novel approach for the transformation of azomethine ylides.

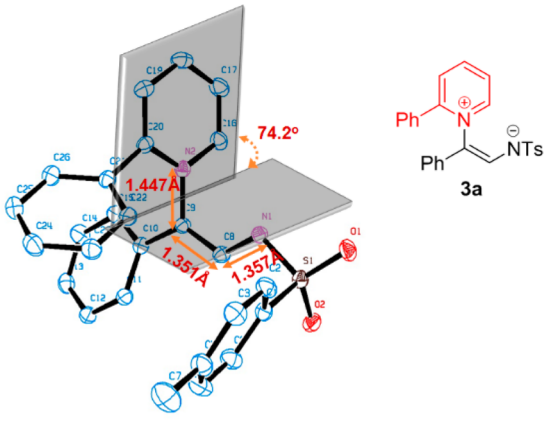
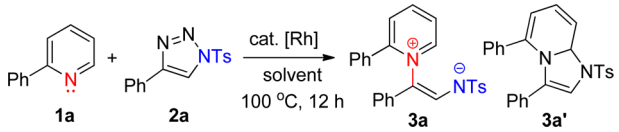


Figure 2. Molecular structure of azomethine compound **3a**.

An important feature of ylide **3** is the geometry of the dipole unit and planarity of the azomethine in contrast with typical azomethine ylides. As shown in Figure 2, two charges of the ylide **3a** are sufficiently stabilized similar to a 1,5-dipole. Azomethine ylide **3a** is twisted around the N(2)−C(9) bond with an angle of 74.2°, suggesting that the two components are arranged in an almost orthogonal manner. In view of the nonplanarity of the dipole, the unexpected stability of **3a** must be due to a particular electronic stabilization of the ionic centers and possibly steric effects.[10] Further tests of 2-substituted pyridine substrates also supported that azomethine ylide **3** was only isolable if particular electronic requirements were met (Scheme 2).[11] On the basis of the preliminary studies, we subsequently examined the reaction conditions and were pleased to find the optimum conditions (Table 1).

Table 1. Optimization of the Reaction Conditions[a]



entry	cat. [Rh] (amt, mol %)	solvent	yield, %[b]
1	$Rh_2(OAc)_4$ (1.0)	1,2-DCE	12
2	$Rh_2(oct)_4$ (1.0)	1,2-DCE	66
3	$Rh_2(S\text{-}PTAD)_4$ (1.0)	1,2-DCE	38
4	$Rh_2(esp)_2$ (1.0)	1,2-DCE	78[c]
5	$Rh_2(esp)_2$ (1.5)	1,2-DCE	82
6	$Rh_2(esp)_2$ (1.5)	toluene	75
7	$Rh_2(esp)_2$ (1.5)	benzene	95

[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.2 mmol), [Rh] (*x* mol %), and solvent (2.0 mL) at 100 °C. [b]Isolated yield of **3a**. [c]Reaction was carried out at 80 °C.

While a number of catalysts such as $Rh_2(OAc)_4$, $Rh_2(oct)_4$, and $Rh_2(S\text{-}PTAD)_4$ were less effective, the use of $Rh_2(esp)_2$ (1.0 mol %) in the reaction of 2-phenylpyridine (**1a**) with 1-sulfonyl-1,2,3-triazole (**2a**) in 1,2-DCE at 80 °C generated the desired product **3a** in 78% yield (entry 4).[12] While changing the solvent from 1,2-DCE to toluene led to diminished yield, the use of benzene allowed for the quantitative formation of **3a** (entries 6 and 7). Interestingly, the intramolecular 1,5-electrocyclized product **3a′**, imidazopyridine, was not observed at all during optimization examinations.

With the optimization conditions in hand, we decided to explore the scope of both substituted pyridines **1** and 1-sulfonyl-1,2,3-triazole **2** to obtain azomethine ylides **3**, which could be further utilized in other transformations (Table 2). We were pleased to see that a wide range of reactants smoothly underwent the process to afford the desired azomethine ylides in high yields. The efficiency of this reaction was not much influenced by either electronic or steric variation on 2-arylpyridines. Also, the reaction conditions tolerated a ketone functional group (**3o**). A substrate containing a naphthyl group was readily employed, resulting in almost quantitative yield (**3p**). Electronic variation of the sulfonyl group of 1-sulfonyl-1,2,3-triazoles **2** exhibited little effect on the product yields (**3t**−**v**).

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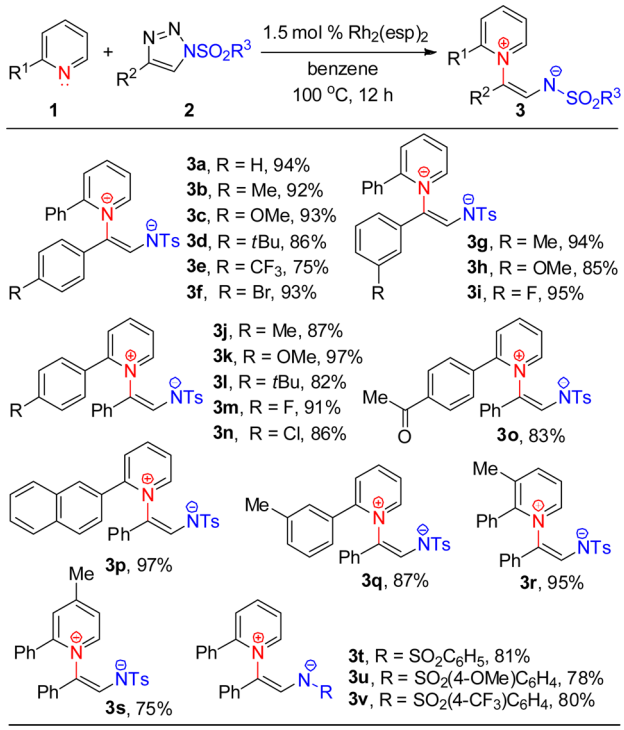
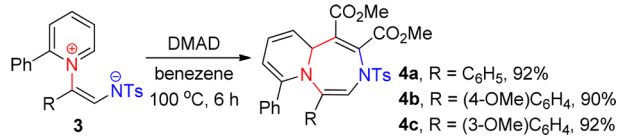
Table 2. Free Azomethine Formation Reactions[a,b]



[a]Reaction conditions: **1a** (2.5 equiv), **2a** (0.5 mmol), $Rh_2(esp)_2$ (1.5 mol %), and benzene (5.0 mL) at 100 °C for 12 h. [b]Isolated yield.

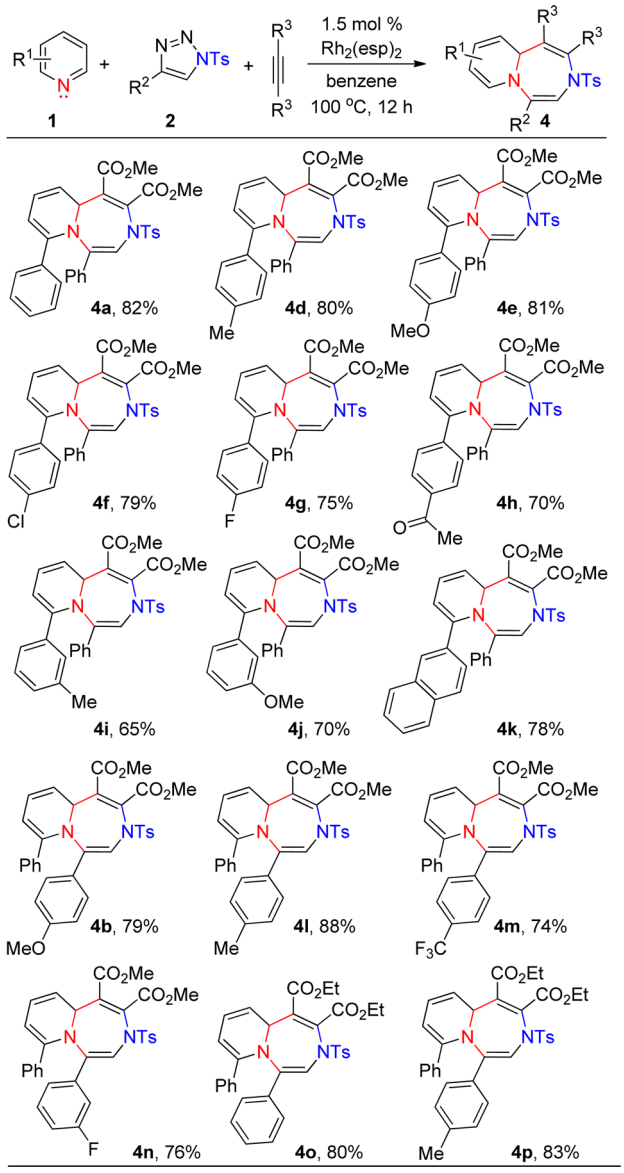
In general, azomethine ylides are known to undergo dipolar cycloaddition with π bonds, thus representing a tool for the construction of azacyclic complexes. [5 + 2] cycloaddition of isolated ylides **3** with dimethyl acetylenedicarboxylate (DMAD) was highly successful to afford the desired 1,4-diazepines with excellent yields (Scheme 3). As expected, metal mediation was unnecessary for annulation, and [3 + 2] cyclized adducts of ylides **3** with DMAD were not obtained under the reaction conditions.

Scheme 3. [5 + 2] Cycloaddition of Azomethines



Intrigued by the great value of purified azomethine ylides **3** as a 1,5-dipole, three-component [5 + 2] cycloaddition reactions of pyridines (**1**), 1-sulfonyl-1,2,3-triazole (**2**), and activated alkynes via in situ generated azomethine ylides (**3**) were conducted with the rhodium(II) catalyst in one pot (Table 3). As a result, this new protocol affords a practical, user-friendly, and operationally simple strategy for the systematic modification of the core structure of 1,4-diazepines. As shown for **4a**−**h**, the reaction was not hampered by para substituents on 2-arylpyridines. It was of interest that the presence of halogen-containing substrates posed no problems, delivering the corresponding 1,4-diazepines in good yields (**4f**,**g**). It is worth noting that the reaction conditions were compatible with an acetyl group (**4h**). The one-pot annulation system was not affected by steric variations (**4i**−**k**). Other 1-sulfonyl-1,2,3-triazoles could also be employed to expand the

Table 3. Multicomponent [5 + 2] Cycloaddition Reaction[a,b]



[a]Reaction conditions: **1** (2.5 equiv), **2a** (0.2 mmol), DMAD (3.0 equiv), $Rh_2(esp)_2$ (1.5 mol %), and benzene (2.0 mL) at 100 °C for 12 h. [b]Isolated yield.

scope of three-component reactions. This new three-component reaction was highly facile with a wide range of 1-sulfonyl-1,2,3-triazoles **2** to provide the desired products (**4l**−**n**). In addition, diethyl acetylenedicarboxylate gave the corresponding 1,4-diazepines in good yields (**4o**,**p**). However, when 2-methylpyridine was used as a reactant instead of the 2-arylpyridine derivative, the yield was significantly low. Also, 4-alkyl-substituted 1-sulfonyl-1,2,3-triazole was not a proper reactant for this [5 + 2] cycloaddition reaction.

For a further investigation, a multicatalytic system with four reactants was attempted, in which the first step was carried out by copper catalyst to afford 1-sulfonyl-1,2,3-triazoles **2** that are expected to be subjected to the rhodium catalyst for the formation of the ylides **3**. As a final step, in situ generated ylides were anticipated to undergo thermal annulation with alkynes (Scheme 4). Gratifyingly, the process exhibited the desired reactivity, which was relayed until the final [5 + 2]

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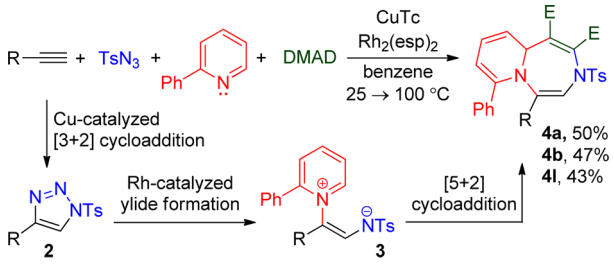
Scheme 4. Multicatalyzed Four-Component Reaction



cycloaddition step despite the challenges in the cooperative multicatalyst system with more than four reactants.[14] Preliminary test reactions smoothly proceeded with four reactants in an intermolecular fashion, offering a straightforward route to generate complexity and diversity of the core structure of 1,4-diazepines in acceptable yields.

In summary, we have described a new catalytic reaction of pyridines and 1-sulfonyl-1,2,3-triazoles for the generation of anomalous azomethine ylides which are isolable 1,5-dipoles. On the basis of this novel protocol, unprecedented catalytic multicomponent [5 + 2] cycloaddition reactions of pyridines, 1-sulfonyl-1,2,3-triazoles, and activated alkynes have been realized for the synthesis of 1,4-diazepines. Further related studies utilizing such azomethine ylides for the development of other methodologies are currently underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Text, tables, figures, and a CIF file giving experimental procedures and characterization data for new compounds and crystallographic data for **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) Other N-containing heterocycles including quinoline, indole, and pyrrole did not form corresponding isolable azomethine ylides under identical reaction conditions.

(12) See the Supporting Information for details.

(13) When asymmetrical alkynes, such as methyl propiolate or methyl 3-phenylpropiolate, and electron-rich alkynes were applied with **3**, the thermal annulation did not occur.

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