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Title: Silver(I)- and Base-Mediated 1,3-Dipolar [4+3] Cycloaddition of in Situ generated 1,2-Diaza-1,3-dienes with C,N-Cyclic Azomethine Imines: An Efficient Protocol for the Synthesis of Tetrazepine Derivatives

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Silver(I)- and Base-Mediated formal [4+3] Cycloaddition of *in Situ* generated 1,2-Diaza-1,3-dienes with *C,N*- Cyclic Azomethine Imines: An Efficient Protocol for the Synthesis of Tetrazepine Derivatives

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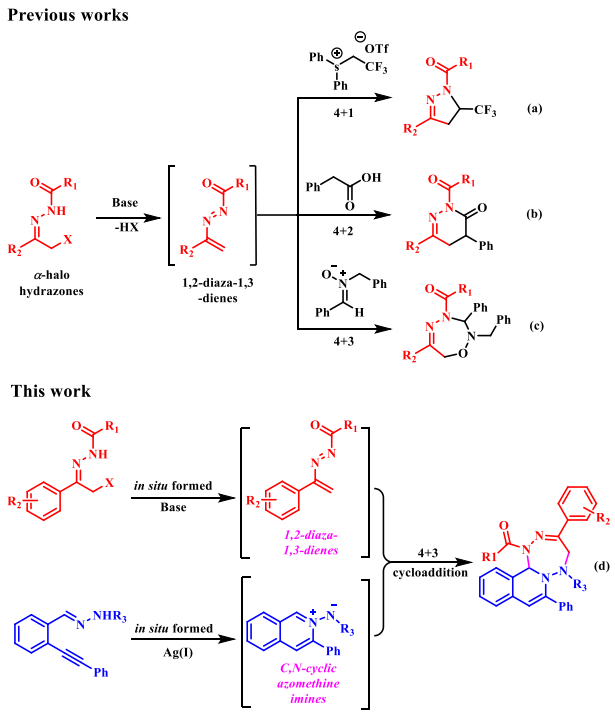
Abstract. A silver(I)- and base-mediated formal [4+3] cycloaddition reaction of in situ generated 1,2-diaza-1,3-dienes with in situ formed *C,N*- cyclic azomethine imines has been developed. This protocol provided a efficient method for the synthesis of biologically important 1,2,4,5-tetrazepine derivatives with a wild substrate scope and excellent functional group tolerance in moderate to excellent yields.

Keywords: Silver, 1,2-Diaza-1,3-dienes, Azomethine imines, [4+3] Cycloaddition, Tetrazepine derivatives

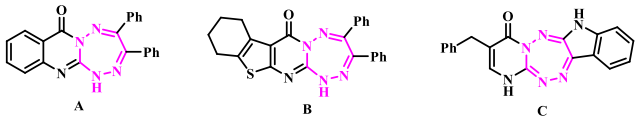
Nitrogen-containing seven-membered heterocyclic ring moieties exist extensively in many bioactive natural products, pharmaceuticals, agrochemicals and materials. Therefore, the chemical synthesis has received considerable attention from organic chemists worldwide.[1] However, compared with the well-established methodologies for the construction of five-membered and six-membered heterocyclic ring, the construction of seven-membered heterocycle is much less favourable. The main challenges are driven by the entropic factors derived from the changing of the rotation/translation of chemical bonds during the cyclization process and the non-bonding interactions in the transition states.[2] So far, the representative methods to construct seven-membered ring include [4+3] cycloaddition[3], [5+2] cycloadditions[4] and ring-closing metathesis[5]. As one of the useful and efficient protocols, the [4+3] cycloadditions have found many applications in the preparation of structurally complex and diverse seven-membered rings. In [4+3] cycloaddition, it is significant to design four-atom components to form dienes and three-atom dienophiles which undergo cycloadditions with the dienes.[6]

α-Halo hydrazones, as powerful and versatile building blocks, can generate electron-deficient dienes (1,2-diaza-1,3-dienes) *in situ* under basic reaction conditions.[7] In general, *α*-halo hydrazones can undergo [4+1][8], [4+2][9] and [4+3][10-11] cycloadditions with structurally different dienophiles and form structurally diverse *N*-containing heterocycles. For instance, Wang and co-workers realized the synthesis of 5- (trifluoromethyl)pyrazolines by formal [4+1] annulation of fluorinated sulfur ylides and *α*-halo hydrazones in good yields without any catalysts (**Scheme 1a**).[12] The Yao research group designed an isothiourea catalyzed formal [4+2] cycloaddition of *α*-halo hydrazones with arylacetic acids in a racemic version (**Scheme 1b**).[13] The Zhao research group reported the construction of 2,3,4,7-tetrahydro-1,2,4,5-oxatriazepines *via* [4+3] cycloadditions of *α*-halo hydrazones with nitrones (**Scheme 1c**).[14]



Scheme 1. Representative cycloadditions

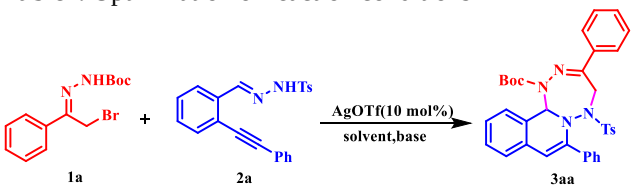
On the other hand, it is well known that azomethine imines are widely used for the synthesis of diverse *N*-containing heterocycles by 1,3-dipolar cycloadditions under thermal or catalyzed conditions.[15] Among those azomethine imines, we identified that *C,N*- cyclic azomethine imine generated *in situ* from *N'*-(2-alkynylbenzylidene)hydrazide is a useful building block for further [3+2][16] and [3+3][17]cycloadditions. However, in contrast to the widespread use of the [3+2] and [3+3] cycloadditions, no work has been reported on the [4+3] cycloadditions involving *N'*-(2-alkynylbenzylidene)hydrazides with the other four-atom component except for a few examples about NHC-catalyzed [4+3] cycloadditions of azomethine imines with enals.[11] For instance, the Xiao research group reported an [4+3] cycloaddition of in situ generated azoalkenes with *C,N*-cyclic azomethine imines without use of any catalyst.[11a] Encouraged by the above mentioned previously published works, we tried to develop the [4+3] cycloadditions of *N'*-(2-alkynylbenzylidene)hydrazides with *α*-halo hydrazones to construct the unique and biologically important 1,2,4,5-tetrazepine derivatives (**Scheme 2A**, **B** and **C**).[18] In this communication, we present our recent research on the [4+3] cycloaddition reaction of *in situ* generated 1,2-diaza-1,3-dienes with *in situ* formed *C,N*- cyclic azomethine imines (**Scheme 1d**). To our delight, under the optimized reaction conditions, the [4+3] cycloaddition product 1,2,4,5-tetrazepine derivatives could be obtained in satisfactory yields.



Scheme 2. Examples of biologically active compounds containing 1,2,4,5-tetrazepine core structures

The initial attempt was performed between the reaction of *α*-halo hydrazone **1a** as the 1,2-diaza-1,3-diene precursor and *N'*-(2-alkynylbenzylidene)-hydrazide **2a** as the *C,N*-cyclic azomethine imine precursor (**Table 1**). It was reported that *N'*-(2-alkynylbenzylidene)-hydrazide **2a** can be easily transferred to *C,N*-cyclic azomethine imine with the assistance of AgOTf.[19] To our delight, the desired cycloaddition occurred, giving the 1,2,4,5-tetrazepine **3aa** in a 78% combined yield by using 10 mol % AgOTf with Na_2CO_3 as the base in MeCN (**Table 1**, **entry 1**). The product was carefully characterized by ^{1}H NMR, ^{13}C NMR and HRMS spectral data. Besides, the chemical structure of **3aa** was unambiguously determined by single crystal X-ray analysis as depicted in **Figure 1**.[20] Encouraged by this preliminary result, other reaction medias were then systematically investigated. The yield could not be improved in toluene, DCE, THF, 1,4-dioxane, EtOAc, DMF and MeOH (**Table 1**, **entries 2-8**). Finally, MeCN was determined to be the best media. As the influence of base was crucial for the reaction, different bases were then screened. The yield was increased to 84% when the base was changed to K_2CO_3 (**Table 1**, **entry 9**). Other bases such as Cs_2CO_3, $NaHCO_3$, KOH and t-BuOK turned out to be less efficient for this cycloaddition reaction (**Table 1**, **entries 10-13**). Moreover, some organic bases were also examined (**Table 1**, **entries 14-16**). Replacement of K_2CO_3 to DIPEA, Et_3N and DBU decreased the yield to 72%, 52% and 10%, respectively. A further enhancement in the yield of **3aa** was observed upon varying the ratio of **1a** and **2a** (**Table 1**, **entries 17-19**). The highest yield was achieved when 1.2 equiv. of **1a** was used (88%) (**Table 1**, **entry 19**). Consequently, the standard reaction conditions used for further investigations were **2** (1.0 equiv.) and AgOTf (0.1 equiv.) in MeCN at 80 °C for 3 h and then adding **1** (1.2 equiv.) and K_2CO_3 (2.0 equiv.) at room temperature for 6 h under the protection of N_2.

Table1. Optimization of reaction conditions[a]



Entry	Solvent	Base	Yield[b]
1	MeCN	Na_2CO_3	78%
2	Toluene	Na_2CO_3	61%
3	DCE	Na_2CO_3	74%
4	THF	Na_2CO_3	52%
5	1,4-Dioxane	Na_2CO_3	65%
6	EtOAc	Na_2CO_3	67%
7	DMF	Na_2CO_3	32%
8	MeOH	Na_2CO_3	nd[f]
9	MeCN	K_2CO_3	84%
10	MeCN	Cs_2CO_3	68%
11	MeCN	$NaHCO_3$	45%
12	MeCN	KOH	62%
13	MeCN	*t*-BuOK	25%
14	MeCN	DIPEA	72%
15	MeCN	Et3N	52%
16	MeCN	DBU	10%
17[c]	**MeCN**	**K_2CO_3**	**88%**
18[d]	MeCN	K_2CO_3	80%
19[e]	MeCN	K_2CO_3	87%

[a]Reaction conditions: **1a** (0.20 mmol), **2a** (0.20 mmol), AgOTf (0.02mmol) and base (0.40 mmol) in solvent (3.0 mL). [b]Isolated yield. [c]The ratio of **1a**/**2a** = 1.2:1. [d]The ratio of **1a**/**2a** = 1:1.2. [e]The ratio of **1a**/**2a** = 1.5:1. [f]nd = not detected.

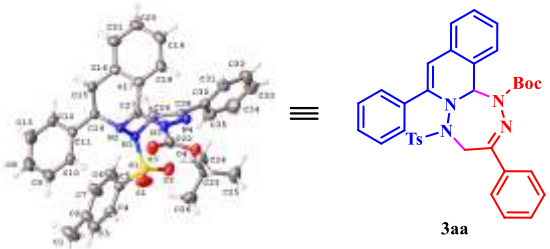


Figure1. X-ray single crystal structure of 3aa

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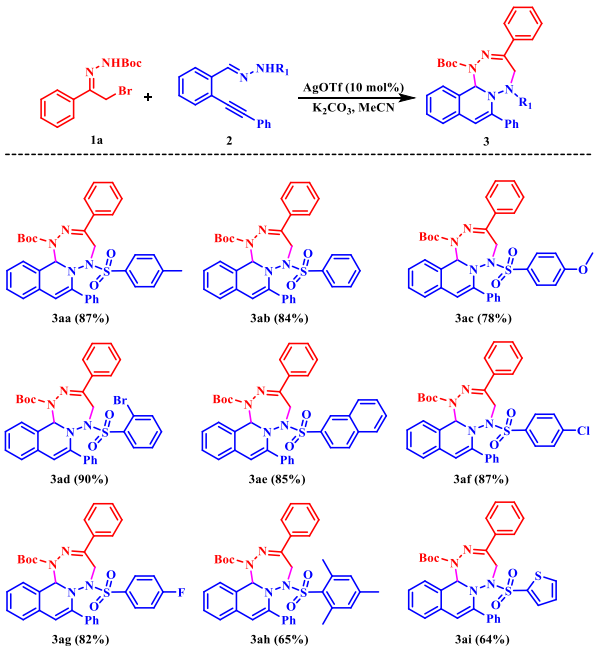
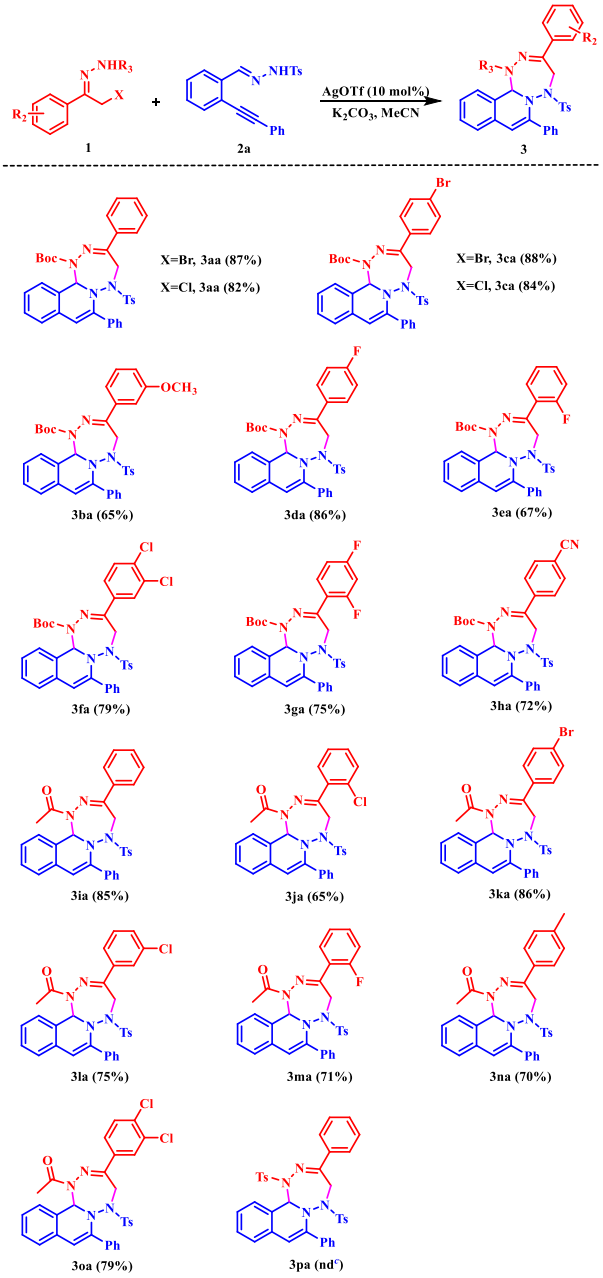
With the optimal reaction conditions in hand, further studies were focused on the evaluation of the substrate scope of this [4+3] cycloaddition process by reacting various of *N'*-(2-alkynylbenzylidene)-hydrazides **2** with *α*-halo hydrazone **1a**, and the results were summarized in **Scheme 3**. When there was no substituent in the benzene ring of the benzenesulfonyl moiety (R_1), the yield of corresponding product **3ab** was 84%. Both electron-donating (−Me, −OMe) and electron-withdrawing groups (−Br, −F, −Cl) were successfully introduced to the ortho- or para-positions of the phenyl ring, affording the corresponding cycloaddition products (**Scheme 3, 3aa**, **3ac**, **3ad**, **3af** and **3ag**) in moderate to excellent yields (78−90%). In addition, when 2,4,6-trimethyl benzenesulfonyl substituted hydrazide **2h** was used as a substrate, the corresponding product **3ah** was afforded in 65% yield. To our delight, the reaction performed well with 2-naphthalenesulfonyl and 2-thiophenesulfonyl protected hydrazide **2e** and **2i** to deliver the desired product **3ae** and **3ai** in 85% and 64% yield, respectively. These results clearly indicated that *N'*-(2-alkynylbenzylidene)-hydrazides **2** can endure the wide variation in R_1.



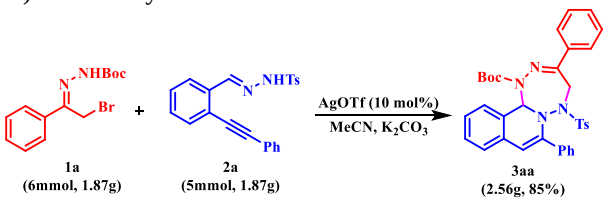
Scheme 3. Substrate scope of *N'*-(2-alkynylbenzylidene)-hydrazide $2^{a,b}$. [a]Reaction conditions: **1a** (0.24 mmol), **2a** (0.20 mmol), AgOTf (0.02mmol), and K_2CO_3 (0.40 mmol) in MeCN (3.0 mL). [b]Isolated yield.

To further expand the scope of the substrates, the diversity of *α*-halo hydrazones **1** were investigated under optimal conditions. As shown in **Scheme 4**, both *α*-chloro and *α*-bromo hydrazones **1** proved to be good 1,2-diaza-1,3-diene precursors in this annulation reaction (**Scheme 4**, **3aa** and **3ca**). Regardless of the electron property (electron-rich, -neutral, or -deficient) and the substituent pattern (*para-*, *meta-*, *or ortho-*position) on the benzene ring of *α*-bromo *N*-Boc hydrazones, the corresponding cycloaddition products **3** were obtained in moderate to excellent yields (**Scheme 4**, **3aa**−**3ha**). These results clearly indicated that there is no major electronic effect on the substitution pattern of the benzene ring. For instance, the electron-rich 3-methoxyl-substituted hydrazone **1b** worked well in this annulation, and the corresponding product **3ba** was obtained in moderate yield (65%). The electron-deficient 4-fluoro-substituted hydrazone **1d** was also compatible with the reaction conditions, leading to **3da** in 88% isolated yield. In addition, some disubstituted hydrazones **1** were also examined. For example, *N*-Boc 3,4-dichloro-substituted hydrazone **1f** was well tolerated in the cycloaddition reaction, leading to **3fa** in 79% yield. Furthermore, when *N*-acyl hydrazones were used to replace *N*-Boc hydrazones, the cycloaddition reactions also proceeded well in 65% to 86% yields (**Scheme 4**, **3ia**−**3oa**). However, *N*-tosyl hydrazine **1p** gave no product under these optimal conditions.



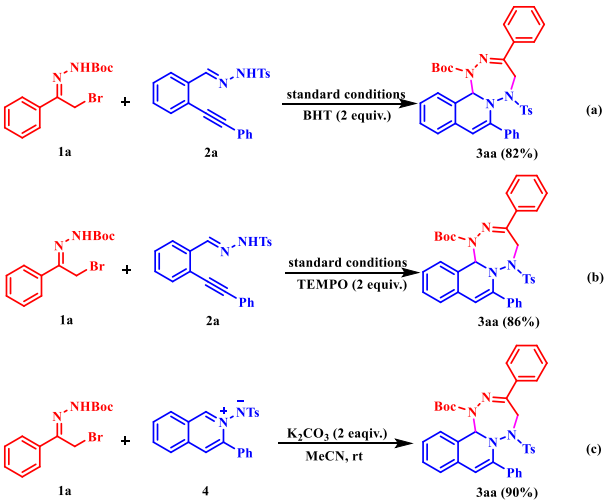
Scheme 4. Substrate scope of *α*-halo-hydrazone $2^{a,b}$. [a]Reaction conditions: **1a** (0.24 mmol), **2a** (0.20 mmol),

AgOTf (0.02mmol), and K_2CO_3 (0.40 mmol) in MeCN (3.0 mL). [b]Isolated yield. [c]nd = not detected.



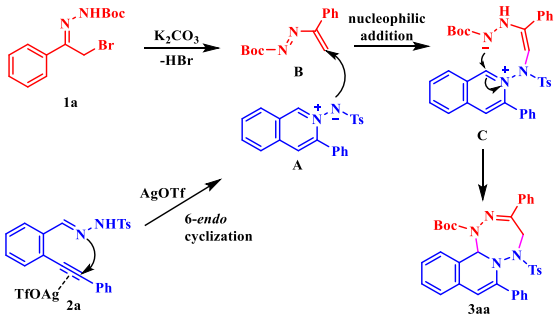
Scheme 5. Gram-scale experiment

To show the synthetic applicability of our present methodology, a gram-scale reaction was performed in a conventional laboratory. When 6.0 mmol *α*-halo hydrazone **1a** was reacted with 5.0 mmol *N'*-(2-alkynylbenzylidene)-hydrazide **2a**, the corresponding product **3aa** was obtained with a satisfactory yield of 75%, which confirmed the practicality of the method (**Scheme 5**).



Scheme 6. Control experiments

In order to explore the reaction mechanism, several control experiments were employed under the standard reaction conditions. When the radical scavengers butylated hydroxytoluene (BHT) and 2,2,6,6-tetramethylpiperidine oxide (TEMPO) were added to the mixture, the reaction proceeded smoothly and was not inhibited, which indicated that this reaction did not proceed *via* a radical mechanism (**Scheme 6a** and **3b**). To provide further support for the reaction pathway, treatment with **4** and **1a** under standard conditions gave the desired product **3aa** in 90% yield (**Scheme 6c**), suggesting that the reaction involves the *in situ* formation of **4**. Based on the above results and previous literature and studies, a plausible mechanism for this cyclization reaction was proposed (**Scheme 7**). Initially, *C,N*-cyclic azomethine imine **A** could be formed through the silver(I)-mediated 6-*endo* cyclization of *N'*-(2-alkynylbenzylidene)-hydrazide **2a**. *α*-Halo hydrazone **1a** reacted with K_2CO_3 to generate the reactive 1,2-diaza-1,3-dienes **B**. 1,4-Conjugated addition of *C,N*-cyclic azomethine imine **A** to **B** produced hydrazine intermediate **C**. Subsequently, intramolecular cyclization may be occurred to form 1,2,4,5-tetrazepine **3** from intermediate **C**.



Scheme 7. Plausible mechanism

In summary, an efficient method for the synthesis of 1,2,4,5-tetrazepine derivatives through a silver (I)-mediated [4+3] cycloaddition reaction between *in situ* formed 1,2-diaza-1,3-dienes and *C,N*-cyclic azomethine imines was devoloped. A variety of *α*-halo hydrazones and *N'*-(2-alkynylbenzylidene)-hydrazides were compatible under the mild reaction conditions, affording the corresponding biologically important and functionalized 1,2,4,5-tetrazepine derivatives in moderate to excellent yields. The further discovery of other cycloaddition reactions by using the *in situ* generated 1,2-diaza-1,3-dienes with other *in situ* formed reactive species is currently underway in our laboratory.

Experimental Section

General procedure for the synthesis of 4: Under a nitrogen atmosphere, MeCN (3.0 mL) was added to a sealed tube charged with **2** (1.0 equiv, 0.2 mmol), AgOTf (0.1 equiv, 0.02 mmol). The reaction mixture was then stirred at 80 °C for 3 h. After cooling to room temperature, **1** (1.2 equiv, 0.24 mmol) and K_2CO_3 (2.0 equiv, 0.4 mmol) were added and the mixture was stirred at room temperature for 0.5-6 h. The precipitated solid was filtrated and washed with water (3 x 3.0 mL) and diethyl ether (2 x 2.5 mL). The isolated product was dried without further purification (65% to 90% yield).

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Adv. Synth. Catal. **Year**, *Volume*, Page – Page

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