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# Azomethine-Isocyanide [3+2] Cycloaddition to Imidazoles Promoted by Silver and DBU

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Xiaoshan Huang,[a] Xuefeng Cong,[a] Pengbing Mi[a] and Xihe Bi*[ab]

**A new silver-promoted [3+2] cycloaddition of azomethine ylides with isocyanides has been described. The methodology provides an efficient and modular approach to 1,2,4-trisubstituted imidazoles of vital bioactive molecules and atypical antipsychotics analogue.**

The 1,3-dipolar cycloaddition reaction is one of the most efficient methods of preparing five-membered heterocyclic compounds[1]. Remarkably, owing to its simplicity and atom efficiency, 1,3-dipolar [3+2] cycloaddition of azomethine ylides has been well established as a reliable and powerful tool for the construction of nitrogen-containing heterocyclic structural motifs with various π-systems[2,3,4,6]. For example, numerous alkenes[2,3] and imines[4] as dipolarophiles have been subsequently explored to achieve optically active pyrrolidines and imidazolidines by using either chiral metal-based catalysts or organocatalysts since the pioneering contribution of Allway and R. Grigg[5] (Fig 1a). Recently, the cycloaddition of azomethine ylides with ynones for construction of 2,5-dihydropyrroles and pyrroles also have been developed by Gong and Deng ect., respectively (Fig 1b)[6]. Isocyanides are versatile building blocks and have been widely applied in organic synthesis[7]. In particular, aryl isocyanides as dipolarophiles have proven to be a versatile functionality to undergo [3+2] cycloaddition for heterocycle synthesis[8]. However, the 1,3-dipolar [3+2] cycloaddition reaction of azomethine ylides with isocyanides to valuable heterocycles are rare.[7d,9]

Imidazoles, especially those with multiple functional groups, are considered to be special structural motifs, which are not only prevalent in various highly bioactive natural products[10], but also present in many enzymes and metalloenzymes in biological systems[11], and pharmaceutical compounds[12]. In addition, they also appeared as critical skeletons in functional materials[13]. Due to their characteristic properties, many impressive investigations have been developed for constructing imidazole scaffolds from basic chemical materials[14]. Despite these great achievements having been made, development of new methodologies for regioselective synthesis of functionalized imidazoles remains a challenging task[14,15]. Herein, we report the [3+2] cycloaddition of azomethine ylides with isocyanides promoted by silver and DBU for the efficient synthesis of 1,2,4-trisubstituted imidazoles (Fig 1c). In this transformation, silver plays a triple role: (1) serving as catalyst to activate isocyanides; (2) employing as oxidant to accomplish the aromatization; and (3) promoting the formation of metalated azomethine ylides.

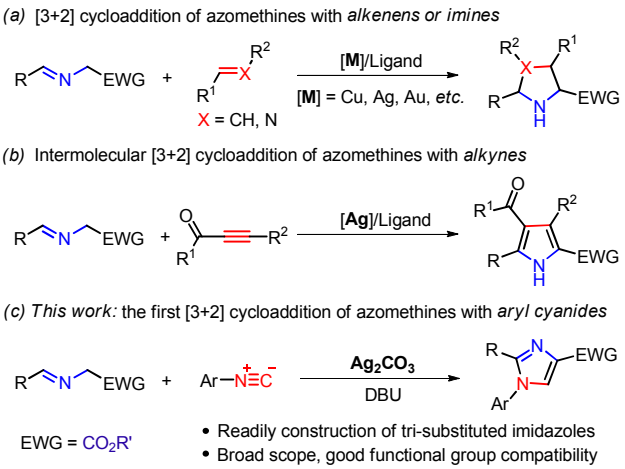


**Fig. 1** [3+2] Cycloaddition Reactions of Azomethine ylides

We initiated our investigation with the optimization studies of the [3+2] cycloaddition of (*E*)-methyl 2-((4-chlorobenzylidene)amino)acetate (**1a**) and 1-bromo-4-isocyanobenzene (**2a**). We were pleased to find that tri-substituted imidazole 3a was obtained in 30% isolated yield in the presence of 30 mol % of $Ag_2CO_3$ in 1,4-dioxane at 80 °C

[a] Jilin Province Key Laboratory of Organic Functional Molecular Design & Synthesis, Department of Chemistry, Northeast Normal University, 5268 Renmin Street, 130024 Changchun, China. Email: bixh507@nenu.edu.cn
[b] State Key Laboratory of Elemento-Organic Chemistry, Nankai University, 300071 Tianjin, China

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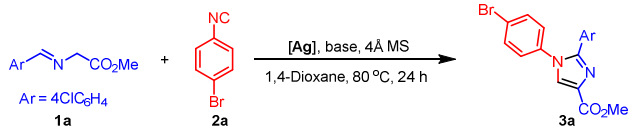
(Table 1, entry 1). The employment of 0.2 equiv of DBU as base only increased the yield to 38% (entry 2), but along with a significant amount of the hydrolytic aldehyde of **1a**. Thus, 4Å molecular sieves were employed to inhibit the hydrolysis of azomethine **1a**. As expected, yield of imidazole **3a** was improved to 72 % yield (entry 3). Compared to $Ag_2CO_3$, other silver salts such as $AgNO_3$, AgOTf, AgOTFA, and $Ag_2O$ were less effective or ineffective in this transformation. A base screening revealed that DBU remained the best choice in our case (ESI, Table S1)[16]. Other solvent such as DCE and toluene also gave the desired product but in low yield, while no reactions occurred in DMF (ESI, Table S1). In view of this reaction involving oxidative process, external oxidants were screened. However, $PhI(OAc)_2$, $K_2S_2O_8$ and $O_2$ could not improve the conversation (ESI, Table S1). To our delight, the amount of $Ag_2CO_3$ was increased to 0.5 equiv and 1.0 equiv in the reaction, and, yields of 3a were improved to 78% and 87%, respectively. The isolated yield can be up to 82% (Table 1, entries 8-9).

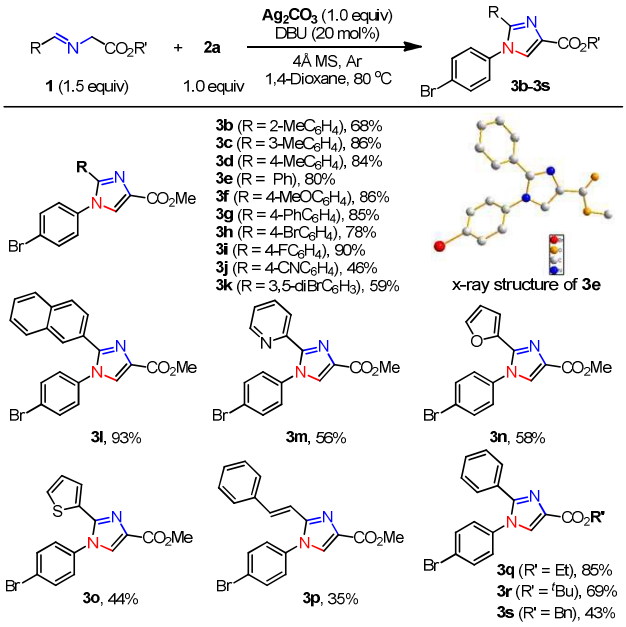
**Table 1** Optimization of the Reaction Conditions[a]




| entry | [Ag] | base | solvent | yield of **3a**[b] |
|---|---|---|---|---|
| 1[c] | $Ag_2CO_3$ | - | 1,4-Dioxane | 35% (30%) |
| 2[c] | $Ag_2CO_3$ | DBU | 1,4-Dioxane | 38% |
| 3 | $Ag_2CO_3$ | DBU | 1,4-Dioxane | 72% |
| 4 | $AgNO_3$ | DBU | 1,4-Dioxane | trace |
| 5 | AgOTf | DBU | 1,4-Dioxane | - |
| 6 | AgOTFA | DBU | 1,4-Dioxane | 17% |
| 7 | $Ag_2O$ | DBU | 1,4-Dioxane | 26% |
| 8[d] | $Ag_2CO_3$ | DBU | 1,4-Dioxane | 78% (76%) |
| 9[e] | $Ag_2CO_3$ | DBU | 1,4-Dioxane | 87% (82%) |

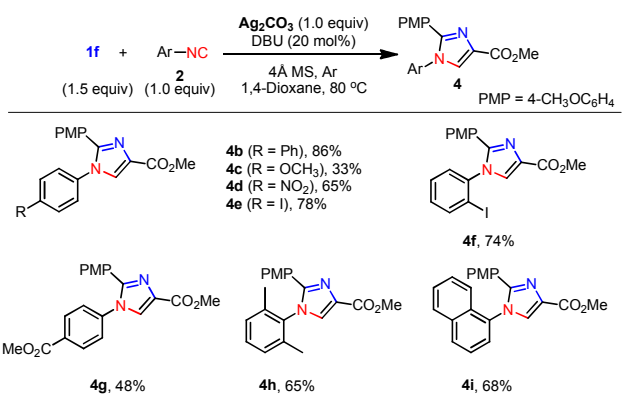
[a]Reaction conditions: **1a** (0.75 mmol), **2a** (0.5 mmol), [Ag] (30 mol %), DBU (20 mol %), 4Å MS (200.0 mg) in Dioxane (5 mL) at 80 °C for 24 h under Ar. [b]Determined by $^1$H-NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard; isolated yield are given in parentheses. [c]without 4Å MS; under air. [d]$Ag_2CO_3$ (0.5 equiv) was used. [e]$Ag_2CO_3$ (1.0 equiv) was used. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

With the optimal conditions in hand, the substrate scope toward this cycloaddition was further investigated, and the results were listed in scheme 2. A wide array of azomethines were examined in the reaction with **2a**, affording the corresponding 1,2,4-trisubstituted imidazoles in moderate to excellent yields (Scheme 1). Firstly, wide variation of the substituents on the benzene ring at para position including electron-donating (e.g., MeO and Me) and -withdrawing groups (e.g., Ph, F, Br, and CN) allowed the formation of diverse highly functionalized 1,2,4-trisubstituted imidazols (**3d–3j**) in 46-90% yields. This transformation is not sensitive to the ortho steric hindrance, affording the corresponding imidazole **3b** in 68% yield. Notably, 3,5-diboromo substituted azomethine could be readily introduced in the reaction, providing the corresponding product **3k** in a prepared useful yield. In addition, azomethine containing fused aromatic groups as well as heteroaromatic groups all reacted smoothly to give the desired products (**3l-3o**). The cinnamyl substituent **1p** was also allowed to react with isocyanide **2a**, providing alkenyled imidazole in an acceptable yield. Further, other azomethines with alkyl-substituted ester group were appreciated the products **3q** to **3s** under the optimal conditions (43-85%).




**Scheme 1** [3+2] Cycloaddition of **2a** with different Azomethines.

In view of these interesting results, we further extended the substrate scope of this strategy to isocyanides (Scheme 2). We found that varied aryl isocyanides bearing electron-donating and -withdrawing groups, could smoothly react with




**Scheme 2** [3+2] Cycloaddition of **1f** with different substituted aryl isocyanides.

azomethine **1f** to afford the corresponding 1,2,4-trisubstituted imidazoles in moderate to excellent yields (**4b, 4c, 4d**). It was

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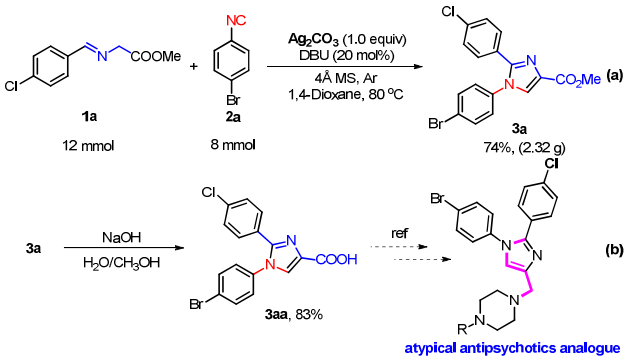
noticed that functional groups involving iodo (**4e, 4f**), methoxycarbonyl (**4g**), and nitro could be well tolerated in our case, affording the functionalized imidazole in 48-78% yields. 2,6-dimethyl phenyl (**4h**) and 1-naphenyl (**4i**) isocyanides were also readily employed under the optimal condition, thus suggesting our system was not influenced by steric factors. It is worth noting that trace amount of desired product was obtained with *tert*-butyl and benzyl isocyanides.

To further demonstrate the practical usefulness of the method, a gram-scale reaction was performed with azomethine ylide **1a** and **2a**. Under the optimized reaction conditions, the reaction could proceed smoothly, affording the desired product **3a** in 74% yield (Scheme 3a). It is worth mentioning that 1,2,4-trisubstituted imidazoles **3** and their derivatives are more specific $GABA_A$ receptor ligands in compared with classical anesthetics such as etomidate, propofol, and alphaxalone[17]. These imidazoles have previously been synthesized in a three-step process[17a]. By contrast, this cycloaddition strategy allowed the corresponding imidazoles **3** to be synthesized directly from readily available substrates in a single step in good isolated yield. The resulting ethyl ester **3a** can undergo the saponification with hydro alcoholic NaOH, giving the corresponding carboxylic acids **3aa** in 83% isolated yield. Notably, the product **3aa** is a known intermediate for accessing a series of atypical antipsychotics analogue in previous report[17b] (Scheme 3b).




**Scheme 3** Gram scale and Synthetic Applications

As shown in Figure 2a, the [3+2] cycloaddition still carries out smoothly when the addition of TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) into the system, implying that the radical pathway may be excluded in the this transformation. Therefore, a plausible reaction mechanism is proposed on the basis of the above experiments and related reports (Figure 2b)[8]. Initially, the intermediate **A**[2e,18] is formed and attacks to the complex $Ag_2CO_3(RNC)_n$ **B**, giving the imidoyl silver intermediate **C**[3a,18a]. After the protonation of intermediate **C**, the intermediate **D** is formed and followed by isomerisation and cyclization to give intermediate **E**. Intermediate **E** then experiences an oxidation to yield the desired product **3**. Compared to classical [3+2] cycloaddition, this process occurs in a stepwise manner and the complex $Ag_2CO_3(RNC)_n$ is formed initially to promote the nucleophilic attack of intermediate **A**.

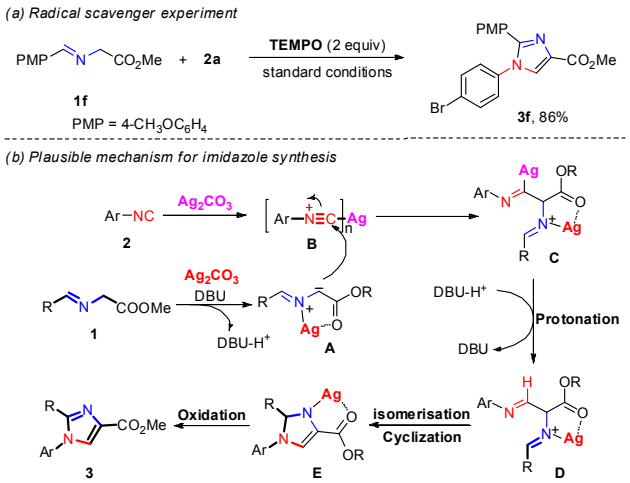



**Fig. 2** Plausible mechanism

In conclusion, we have developed the first azomethine-isocyanide [3+2] cycloaddition reaction promoted by silver and DBU to achive 1,2,4-trisubstituted imidazoles. This method allows modular access to 1,2,4-trisubstituted imidazoles starting from the readily available aryl isocyanides and azomethine ylides with broad substrate scope and good functional group compatibility. $Ag_2CO_3$ plays key role as the catalyst and oxidant in this transformation. Furthermore, the target scaffolds containing ester group at C4 position are more specific $GABA_A$ receptor ligands, and easily access to a series of atypical antipsychotics analogue. Considering the extreme importance of 1,2,4-trisubstituted imidazoles in medicinal chemistry, the methodology presented herein undoubtedly will find wide applications in future synthetic endeavors and pharmaceutical synthesis.

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