VIP Cycloaddition

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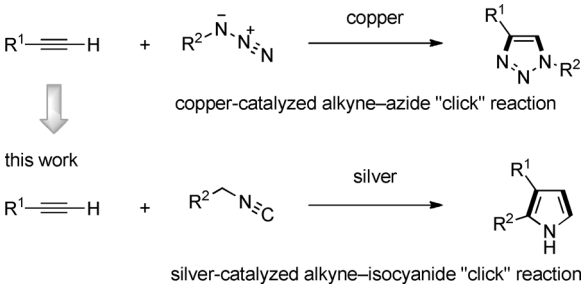
Synthesis of Pyrroles by Click Reaction: Silver-Catalyzed Cycloaddition of Terminal Alkynes with Isocyanides**

*Meng Gao, Chuan He, Hongyi Chen, Ruopeng Bai, Ben Cheng, and Aiwen Lei**

Dedicated to Professor Irina Petrovna Beletskaya

Pyrroles and their partially saturated derivatives represent an important class of five-membered heterocycles,[1] which are the basic constituents of numerous natural products, biologically active alkaloids, pharmaceuticals, and agrochemicals.[2] This key heterocyclic core has also found broad use in both organic synthesis and material science.[3] Because of their characteristic properties, numerous processes have been developed for the construction and modification of the pyrrole structure,[4] although most of these methods are limited to the use of elaborately designed starting materials and suffer from low efficiency and selectivity. Thus, the development of a straightforward, convenient, and regioselective route to pyrrole derivatives from basic chemical materials is highly attractive.

In 2001, Sharpless et al. introduced the concept of "click chemistry" for conducting organic reactions with high efficiency, selectivity, and yield under mild reaction conditions with a wide variety of readily available starting materials with orthogonal protecting groups.[5] It is well known that the copper-catalyzed azide–alkyne cycloaddition (CuAAC) has emerged as the premier example of click chemistry and plays a significant role not only in organic synthesis, but also in medicinal chemistry, surface and polymer chemistry, and bioconjugation applications.[5,6] Actually, isocyanides and azides have a certain structural similarity. Compared to the copper-catalyzed cycloaddition of azides to terminal alkynes for the synthesis of 1,4-triazoles, the co-cyclization of isocyanides with terminal alkynes will directly give pyrrole derivatives (Scheme 1). However, this strategy has been rarely used and cannot really be classified as a "click" synthesis of pyrroles.[7] Recently, based on the continued



Scheme 1. Proposed click synthesis of pyrroles.

efforts toward the C–H functionalization/alkynylation, silver salts have displayed a great potential in the mediation of highly selective chemical transformations involving terminal alkynes.[8] Herein, we communicate our efforts in the silver-catalyzed synthesis of pyrroles by the cycloaddition of terminal alkynes and isocyanides. This protocol addresses the previous limitations and furnishes a diverse collection of valuable substituted pyrroles with high efficiency and selectivity under mild conditions, thus complementing the click method for the rapid construction of multifunctional heterocycles.

Our initial efforts focused on the reaction of phenylacetylene **1a** and ethyl 2-isocyanoacetate **2a** by using one equivalent of Ag_2CO_3 as the mediator. To our delight, we indeed obtained the corresponding pyrrole cycloaddition product in moderate yield (Table 1, entry 1). Notably, in this reaction, no by-product resulting from the homocoupling of the terminal alkyne was observed. This interesting transformation to the pyrrole heterocycles encouraged us to further examine the feasibility of this efficient cycloaddition.

After many optimization efforts, the use of 10 mol% Ag_2CO_3 as the catalyst in *N*-methyl-2-pyrrolidone (NMP) at 80 °C turned out to give the best result (Table 1, entry 11). To enhance the conversion of the terminal alkyne, ethyl 2-isocyanoacetate **2a** (1.5 equiv) was employed in the reaction. Increasing the amount of Ag_2CO_3 did not improve the yield observably (Table 1, entries 1–5). The reaction also proceeded in other solvents, such as dimethyl sulfoxide (DMSO), toluene, *N*,*N*-dimethylformamide (DMF), and dioxane, but gave the products in lower yields (Table, entries 5–8). When the reaction temperature was lowered to 60 °C, a yield of only 59% could be achieved (Table 1, entry 9). It is noteworthy that Ag_2CO_3 played a critical role in the reaction; other silver salts, such as Ag_2O and $AgNO_3$, were totally ineffective (Table 1, entries 12 and 13). For comparison, copper salts were also tested in this reaction.

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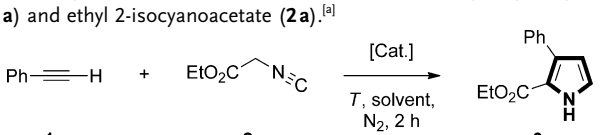
Table 1: Optimization of conditions for the reaction of phenylacetylene (**1a**) and ethyl 2-isocyanoacetate (**2a**).[a]



1a **2a** **3a**

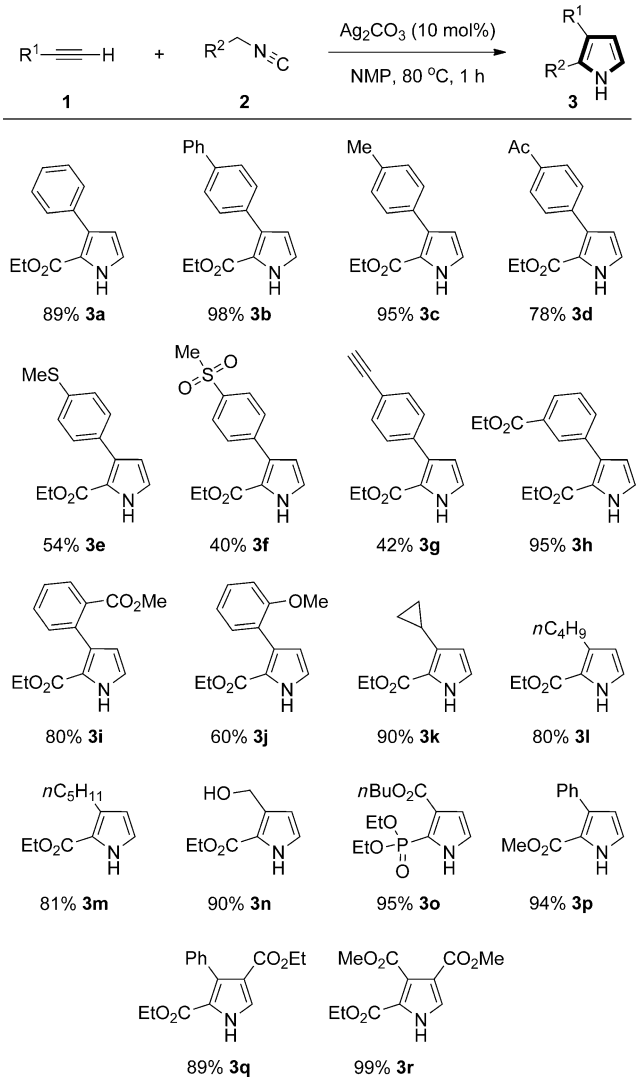
Entry	Cat. (equiv)	*T* [°C]	Solvent	Yield [%][b]
1	Ag_2CO_3 (1.0)	100	dioxane	60
2	Ag_2CO_3 (0.5)	100	dioxane	82
3	Ag_2CO_3 (0.2)	100	dioxane	80
4	Ag_2CO_3 (0.1)	100	dioxane	77
5	Ag_2CO_3 (0.05)	100	DMF	49
6	Ag_2CO_3 (0.2)	100	DMSO	31
7	Ag_2CO_3 (0.2)	100	NMP	87
8	Ag_2CO_3 (0.2)	100	toluene	77
9	Ag_2CO_3 (0.2)	60	NMP	59
10	Ag_2CO_3 (0.2)	80	NMP	88
11	**Ag_2CO_3 (0.1)**	**80**	**NMP**	**89**
12	$AgNO_3$ (0.2)	80	NMP	trace
13	Ag_2O (0.2)	80	NMP	trace
14	$Cu(OAc)_2$ (0.2)	80	NMP	trace
15	CuI (0.2)	80	NMP	0

[a] Reactions were carried out on a scale of 0.25 mmol of **1a** and 0.38 mmol of **2a** in the presence of silver or copper salts in 3 mL of solvent under N_2 atmosphere for 2 h. [b] Yields of isolated products. The entry in bold marks the optimized reaction conditions.

However, both Cu^{II} and Cu^{I} salts, such as $Cu(OAc)_2$ and CuI, respectively, turned out to be ineffective (Table 1, entries 14 and 15).

With the optimized conditions in hand, various terminal alkynes **1** were reacted with different isocyanides **2** to access the corresponding pyrrole products **3** (Scheme 2). The reaction was readily extended to a variety of aryl-substituted terminal alkynes, and both electron-withdrawing and electron-donating substituents were well tolerated under the reaction conditions (**3a**–**3j**). It is noteworthy that steric effects had little influence on this cycloaddition reaction. Regardless of the substitution pattern of the aryl ring (*ortho*, *meta*, or *para*) of the aryl acetylenes used in the reaction, the corresponding pyrrole products (**3b**–**3j**) were obtained in good yields. Several interesting functional groups, such as methylthio, methylsulfonyl, and ethynyl, were well tolerated in the cycloaddition (**3e**, **3f**, and **3g**). Moreover, alkyl-substituted terminal alkynes were also found to be suitable reaction partners. Various aliphatic terminal alkynes, including those with cyclopropyl, *n*-butyl, *n*-amyl, and terminal hydroxy groups, smoothly reacted with ethyl 2-isocyanoacetate **2a** to afford the corresponding pyrrole products in good yields (**3k**–**3n**). Meanwhile, internal alkynes **1q** and **1r** could also be employed to give the pyrrole scaffold without any difficulties (**3q**, **3r**, respectively). In addition, various isocyanides **2** could be used to access the pyrrole ring, both diethyl isocyanomethylphosphonate **2o** and methyl 2-isocyanoacetate **2p** could react satisfactorily and gave the products in excellent yields (**3o** and **3p**, respectively).

To elucidate the role of the silver catalyst in this cycloaddition, the stoichiometric reaction between phenylacetylene **1a** and ethyl 2-isocyanoacetate **2a** with Ag_2CO_3 was monitored by in situ IR spectroscopy (Figure 1, see the



Scheme 2. Cycloaddition of alkynes **1** and isocyanides **2.** Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), Ag_2CO_3 (10 mol%) in 2 mL of NMP at 80°C under N_2 atmosphere for 1 h. Yields of isolated products are given.

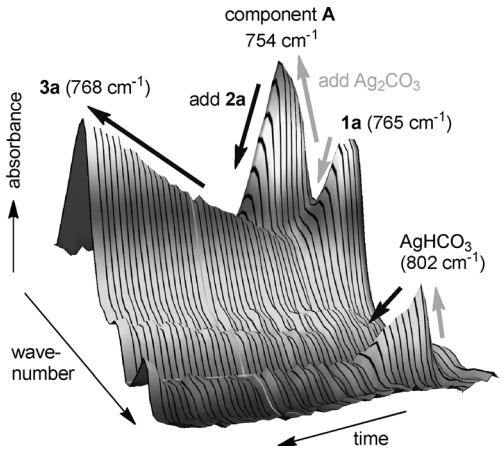
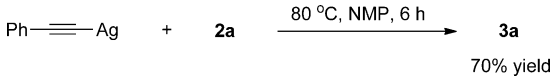


Figure 1. Profile of the stepwise stoichiometric reaction between **1a**, Ag_2CO_3, and **2a** in DMSO at 80°C monitored by in situ IR spectroscopy.

Supporting Information for more details). When one equivalent of Ag_2CO_3 was added to the solution of **1a** in DMSO, the band of **1a** (765 cm^{-1}) disappeared quickly with concomitant appearance of the band for $AgHCO_3$ (802 cm^{-1}) and a new component **A** (754 cm^{-1}). It is reasonable to assume that component **A** might be the silver–acetylide complex **A**. Then, one equivalent of **2a** was added to the solution. The concentration of component **A** decreased very fast while the concentration of product **3a** (768 cm^{-1}) increased slowly. This result indicated that when **2a** reacted with component **A**, a probably insoluble complex **C** was formed, which slowly released the product **3a** into the solution.

To verify the involvement of silver acetylide as a critical intermediate in the reaction, the prepared silver phenylacetylide[9] was reacted with **2a** under the standard conditions in the absence of silver catalyst (Scheme 3). The desired



Scheme 3. Reaction of silver phenylacetylide with **2a**.

product **3a** was obtained in 70% yield, thus suggesting that component **A** in Figure 1 is the silver–acetylide intermediate complex **A**.[10]

Moreover, we noticed that silver salts could also coordinate to the isocyano group and activate isocyanides **2** in some cycloaddition reactions.[11] Thus, the investigation of the stoichiometric reaction of ethyl 2-isocyanoacetate **2a** with Ag_2CO_3 was also monitored by in situ IR spectroscopy (Figure 2, see the Supporting Information for more details).

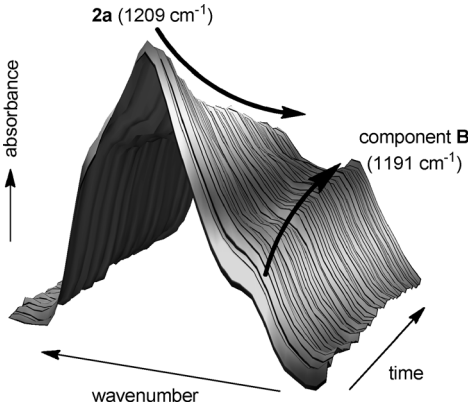
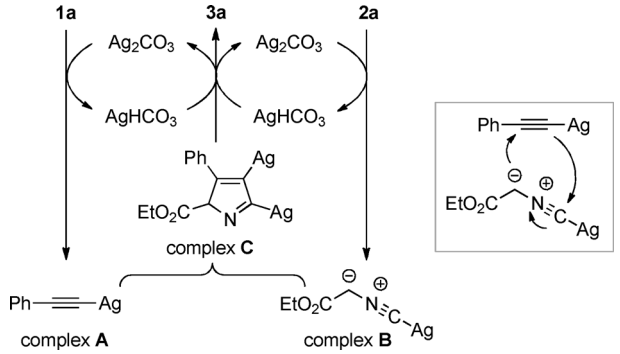


Figure 2. Profile of the stoichiometric reaction between **2a** and Ag_2CO_3 in DMSO at 80 °C monitored by in situ IR spectroscopy.

When one equivalent of Ag_2CO_3 was added to a solution of **2a** in DMSO, the band of **2a** (1209 cm^{-1}) disappeared upon the generation of a new component **B** (1191 cm^{-1}). This new component **B** could be identified as complex **B** of silver(I) and isocyanide. Based on these results, we believe that the silver(I) catalyst activates both the terminal alkyne and the isocyanide in the cycloaddition.



Scheme 4. Proposed mechanism for the silver-catalyzed cycloaddition of terminal alkynes with isocyanides.

According to the above information, a reaction mechanism is proposed in Scheme 4. In the presence of Ag_2CO_3 catalyst, both the silver–acetylide complex **A** and silver–isocyanide complex **B** would be generated from **1a** and **2a**, respectively.[10,12] Subsequently, the cycloaddition between complex **A** and complex **B** would afford the key intermediate complex **C**.[13] Finally, protonation and tautomerization gives the pyrrole product **3a**.

In summary, we have demonstrated a silver-catalyzed click synthesis of pyrroles by the co-cyclization of terminal alkynes and isocyanides. From a synthetic point of view, this protocol represents an extremely simple, efficient, and atom-economic way to construct substituted pyrroles in good yields with high selectivity, thus complementing the click method for the rapid formation of multifunctional heterocycles. Further detailed mechanistic studies about this transformation are currently under way in our laboratory.

Experimental Section

General procedure for the preparation of pyrroles (e.g., **3a**): A mixture of phenylacetylene **1a** (0.5 mmol), ethyl 2-isocyanoacetate **2a** (0.75 mmol), and Ag_2CO_3 (0.05 mmol) in NMP (3 mL) was stirred under an N_2 atmosphere at 80 °C for 1 h. After completion of the reaction, as indicated by TLC and GC-MS, the solid was filtered off and washed with dichloromethane. After removal of the solvent of the filtrate, the pure product was obtained by flash column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 8:1) to afford **3a** in 89% yield. The spectroscopic data of all products are presented in the Supporting Information. The spectroscopic features of all obtained compounds were analogous to the spectroscopic data reported in the literature. For **3a**: ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 9.42$ (brs, 1H), 7.59 (d, $J = 7.2$ Hz, 2H), 7.39 (t, $J = 7.4$ Hz, 2H), 7.32 (t, $J = 7.2$ Hz, 1H), 6.95 (t, $J = 2.8$ Hz, 1H), 6.37 (t, $J = 2.8$ Hz, 1H), 4.28 (q, $J = 7.1$ Hz, 2H), 1.26 ppm (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 161.2$, 135.3, 132.1, 129.6, 127.6, 126.9, 121.8, 118.2, 112.5, 60.3, 14.2 ppm. HRMS (ESI) calcd for $[C_{13}H_{14}NO_2]^+$ $[M+H]^+$: 216.1019; found: 216.1019.

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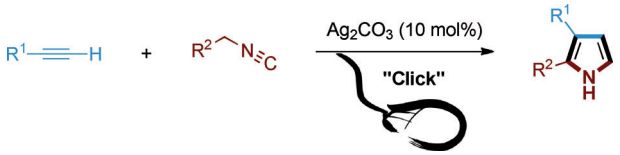
Communications

Cycloaddition

M. Gao, C. He, H. Chen, R. Bai, B. Cheng, A. Lei* ——— ■■■■–■■■■

Synthesis of Pyrroles by Click Reaction: Silver-Catalyzed Cycloaddition of Terminal Alkynes with Isocyanides



Just click with silver: Pyrroles are prepared by the co-cyclization of terminal alkynes and isocyanides in a silver-catalyzed click reaction. This protocol represents an extremely simple, efficient, and atom-economic approach to substituted pyrroles in good yields with high selectivity, thus complementing the click method for the rapid formation of multifunctional heterocycles.