VIP Cycloaddition

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Silver-Catalyzed Isocyanide-Alkyne Cycloaddition: A General and Practical Method to Oligosubstituted Pyrroles**

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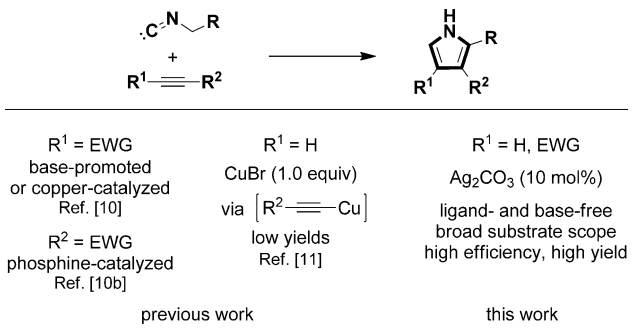
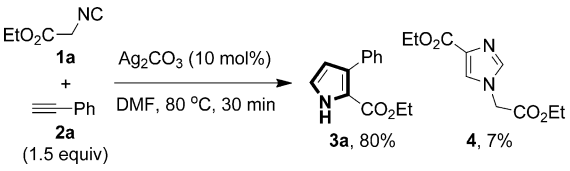
Oligosubstituted pyrroles are important as components in natural products, pharmaceuticals, and functional materials, and also serve as valuable intermediates in organic synthesis.[1,2] In the past, substantial advances in the development of transition-metal-catalyzed synthetic methods for these compounds have been achieved.[3] Compared to the traditional-metal-free reactions,[4] most of these protocols showed high efficiency with remarkable functional-group tolerance. However, the synthetic methods reported so far largely relied on elaborately designed substrates that are not readily accessible.[5,6] Thus, the direct assembly of pyrroles from basic chemicals remains an important research objective.[7] Isocyanides[8] and alkynes[9] are two classes of commercially available and versatile starting materials. The atom-economic nature of the reaction makes the cycloaddition of these substrates an ideal route to oligosubstituted pyrroles (Scheme 1). However, such reactions are mostly limited to



Scheme 1. Isocyanide–alkyne cycloaddition.

the use of electron-deficient alkynes under base or copper catalysis, and are hitherto underexploited.[10,11] Copper catalysis is the sole, synthetically useful transition-metal-catalyzed version reported so far, stemming from the seminal, independent work of the groups of Yamamoto and de Meijere in 2005.[10b,c] With regard to the more abundant unactivated terminal alkynes, a catalytic protocol remains elusive.[11] Herein, we wish to report a novel silver-catalyzed isocyanide–alkyne cycloaddition, which works with a broad range of alkynes, particularly unactivated terminal alkynes.

The search for a robust catalyst that achieves the cycloaddition of isocyanides with unactivated terminal alkynes has always been met with challenges, that is 1) the facile homocoupling of terminal alkynes (Glaser–Hay coupling) under oxidative conditions,[12] and 2) the easy dimerization of isocyanides to produce imidazoles in the presence of a base or transition-metal catalyst.[13] Recently, a rapidly growing number of reports on alkyne-involving organic reactions that make use of silver salts as the catalyst have been reported.[14] One advantage of silver catalysis is the avoidance of the Glaser–Hay coupling commonly encountered with terminal alkynes. A typical example is the recent pioneering work of Lei and co-workers, who reported the Ag_2CO_3-mediated oxidative cyclization of terminal alkynes with 1,3-dicarbonyl compounds or 2-aminopyridines,[15] in which no homocoupling products were observed. In addition, the silver-catalyzed cycloadditions of isocyanides with aldehydes or α,β-unsaturated carbonyl compounds are known.[16] On the basis of these precedents and our continued efforts in metal-catalyzed cyclizations,[17] we envisaged that Ag_2CO_3 might be the right catalyst for the cycloaddition of isocyanides with terminal alkynes. Delightfully, 2,3-disubstituted pyrrole **3a** was isolated in 82% yield from the reaction of ethyl isocyanoacetate (**1a**) and phenylacetylene (**2a**) in DMF at 80°C, with only a small amount of imidazole **4** [7%; Eq. (1)]. To our knowledge, this is the first example of a transition-metal-catalyzed cycloaddition of isocyanides with unactivated terminal alkynes.[10,11]



(1)

Encouraged by this finding, we continued our investigations by optimizing the reaction conditions (Table 1). A variety of silver salts were initially examined for the reaction of **1a** and **2a** in DMF at 80°C (entries 1–8). The counter anion of the silver salts turned out to play a critical role in the product distribution of pyrrole **3a** and imidazole **4**. For example, although AgOAc, AgOTf, Ag_2O, AgF, and $AgNO_2$

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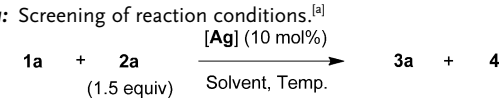
Table 1: Screening of reaction conditions.[a]

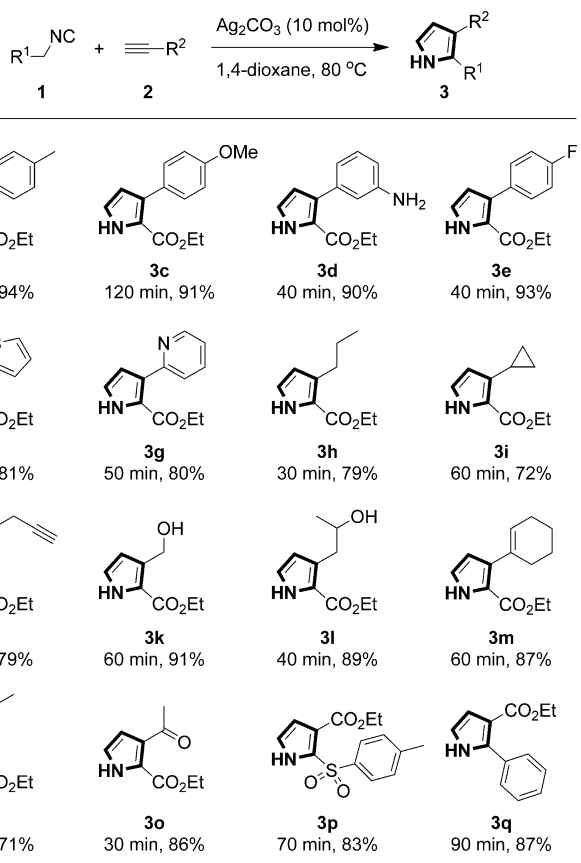


Entry	[Ag]	Solvent	T [°C]	t [min]	Yield [%][b] 3a	4
1	AgOAc	DMF	80	30	0	80
2	AgOTf	DMF	80	30	0	84
3	Ag_2O	DMF	80	30	trace	86
4	AgF	DMF	80	30	trace	82
5	$AgNO_2$	DMF	80	30	trace	81
6	$AgNO_3$	DMF	80	30	0	0
7	$AgBF_4$	DMF	80	30	0	0
8	$AgClO_4$	DMF	80	30	0	0
9	Ag_2CO_3	1,4-dioxane	80	30	90	trace
10	Ag_2CO_3	$(CH_2Cl)_2$	80	30	78	13
11	Ag_2CO_3	DMSO	80	30	trace	78
12	Ag_2CO_3	CH_3CN	80	30	trace	87
13	–	1,4-dioxane	80	30	0	0
14	Ag_2CO_3	1,4-dioxane	40	24 h	trace	88
15	Ag_2CO_3	1,4-dioxane	25	24 h	trace	93

[a] Reactions were performed on 1.0 mmol scale, at a concentration of 0.25 M (with respect to **1a**). [b] Yields of isolated products. DMF = *N*,*N*-dimethylformamide, DMSO = dimethyl sulfoxide.

all catalyzed the reaction to afford imidazole **4** in high yields (81–86%), only the latter three silver salts led to trace amounts of pyrrole **3a** (entries 1–5). Remarkably, no reaction took place with $AgNO_3$, $AgBF_4$, and $AgClO_4$ catalysts (entries 6–8). These results clearly demonstrate that Ag_2CO_3 is a unique and robust catalyst for the cycloaddition of **1a** and **2a**.[18] A better ratio of **3a** (90%) to **4** (trace) was achieved when 1,4-dioxane was employed as solvent (entries 9–12). Interestingly, no homocoupling of phenylacetylene (**2a**) was observed, which is consistent with the observation of Lei and co-workers.[15] The necessity of using Ag_2CO_3 was confirmed in a control experiment (entry 13). The reaction temperature also distinctly influenced the product distribution. A decrease in the temperature from 80 to 40°C or 25°C afforded imidazole **4** as the major product (entries 14 and 15, respectively).

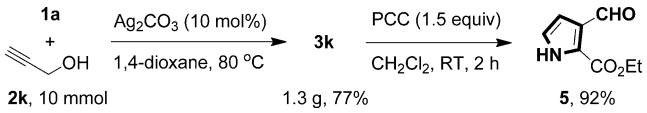
With the optimal conditions in hand (10 mol% Ag_2CO_3, 1,4-dioxane, 80°C; see Table 1, entry 9), the scope of the reaction with regard to the terminal alkyne and isocyanide components was investigated (Scheme 2). Ethyl isocyanoacetate **1a** effectively reacted with arylalkynes (**2b**–**2e**) within 40–120 min to give the corresponding 2,3-disubstituted pyrroles (**3b**–**3e**) in high yields. Specifically, the free amino group at the *meta* position of the phenyl ring of **2d** was well tolerated. Electron-rich and electron-poor heteroarylalkynes that contain 2-thienyl and 2-pyridyl groups (**2f** and **2g**, respectively) were also subjected to the cycloaddition, leading to the corresponding products **3f** and **3g**, respectively, in high yields. These high product yields demonstrate the superior catalytic activity of the current silver catalyst system.[11] Next, we focused our attention on investigating the scope of terminal alkynes by using a range of aliphatic alkynes (**2h**–**2o**). To our delight, these reactions efficiently afforded the 2,3-disubstituted pyrroles (**3h**–**3o**) in good to high yields within 30–60 min. Several representative functional groups,



Scheme 2. Scope of terminal alkynes.

including cyclopropyl, alkynyl, hydroxyalkyl, alkenyl, alkoxy, and acetyl, were well tolerated. These functionalities in the pyrrole products might be useful for further synthetic modifications. The results of our study impressively illustrate the negligible influence of the intrinsic electronic character of aliphatic alkynes, that is, whether they are electron-rich or electron-poor, on their cycloadditions with isocyanoacetates. Also worthy of note is the observation that in place of ethyl isocyanoacetate (**1a**), both toluenesulfonylmethyl isocyanide (TosMIC, **1b**) and benzyl isocyanide (**1c**) readily participated in the cycloaddition with ethyl propiolate **2p**, giving rise to products **3p** and **3q** in 83 and 87% yield, respectively. Thus, the silver-catalyzed cycloaddition of isocyanides with a broad range of unactivated terminal alkynes provides a powerful method for the synthesis of 2,3-disubstituted pyrroles.[19]

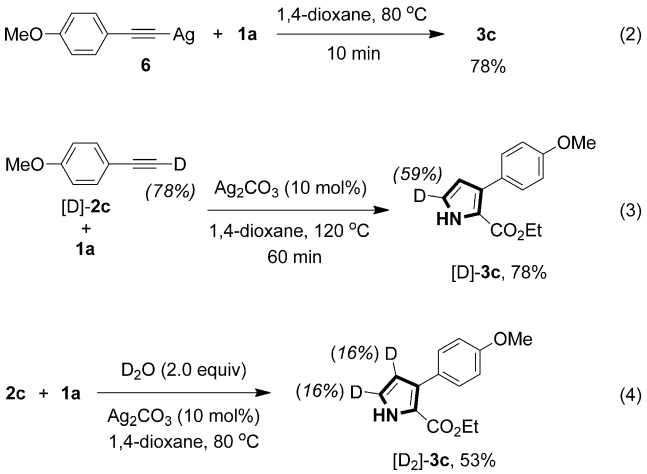
Structurally, products **3** contain one nonsubstituted 5-position and an ester group at the 2-position of the pyrrole ring. Such α-nonsubstituted pyrrole-2-carboxylates have been widely utilized in the preparation of pyrrole alkaloids, porphyrins, polypyrroles, and BODIPY dyes.[20] To unravel the synthetic potential of the method, the reaction of ethyl isocyanoacetate **1a** and propargyl alcohol **2k** was carried out on a gram scale (Scheme 3). To our delight, the corresponding 3-hydroxymethyl pyrrole **3l** was isolated in 77% yield. Furthermore, the high-yielding conversion of **3l** to ethyl 3-formyl-1*H*-pyrrole-2-carboxylate **5** was achieved in the presence of 1.5 equivalents of pyridinium chlorochromate (PCC).[21] Notably, formylation at the 3-position of pyrroles



Scheme 3. Experiment on a gram scale and further synthetic derivation.

is hard to realize through the most commonly used Vilsmeier–Haack reaction, which preferentially introduces the formyl group at the 2-position rather than the 3-position of the pyrrole ring.[22]

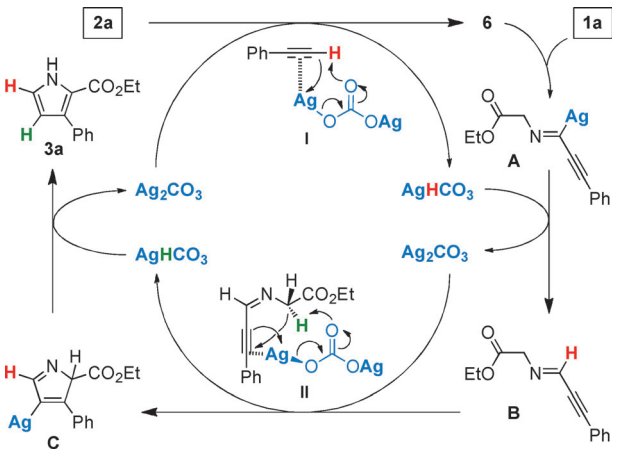
Some critical mechanistic information for the reaction of a terminal alkyne with an isocyanide was collected by experimental investigations (Scheme 4). Firstly, silver acetylide[23] **6** could efficiently react with ethyl isocyanoacetate **1a**



Scheme 4. Mechanistic investigations.

without the aid of Ag_2CO_3 as catalyst, giving pyrrole **3c** in 78% yield [Eq. (2)]. This result suggests that silver acetylide could be the intermediate in the reaction. Furthermore, the deuterium-labeling experiments clearly revealed the source of the α-hydrogen atom on pyrroles **3**. When deuterated 4-ethynylanisole ([D]-**2c**, 78% deuterium content) was reacted with **1a**, the deuterium atom was exclusively incorporated at the α-position of pyrrole **3c** to an extent of 59% [Eq. (3)]. This outcome is different from the experiment of de Meijere and co-workers, in which equal incorporation of deuterium at positions 4 and 5 (43% each) was observed,[11] hence implying a different catalytic mechanism for the Ag_2CO_3 catalyst. In addition, an elevated temperature of 120 °C was necessary for the reaction of the deuterated substrate [D]-**2c**, thus indicating that the C–H bond cleavage of terminal alkynes was involved in the rate-limiting step. With 2.0 equivalents of D_2O added to the reaction of 4-ethynylanisole **2c** and **1a** under the standard conditions, approximately equal incorporation of deuterium at positions 4 and 5 (16% each) was obtained [Eq. (4)].

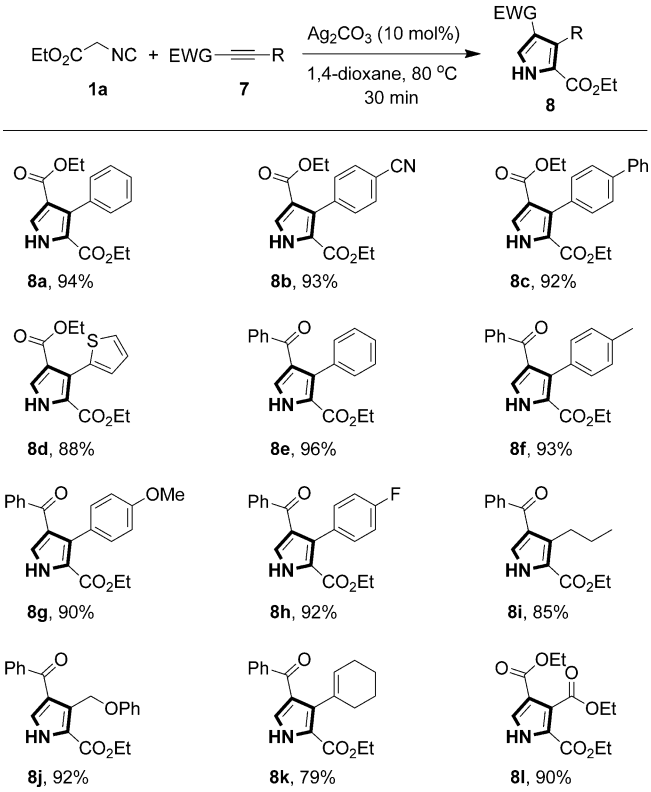
A plausible reaction mechanism (Scheme 5) is proposed on the basis of the above experiments and literature



Scheme 5. Mechanistic proposal for the cycloaddition of isocyanides and terminal alkynes.

precedents.[11,13] The initial step is the formation of a silver–acetylide intermediate **6** through the agostic interaction (**I**) between phenylacetylene and Ag_2CO_3, resulting in the transfer of a proton (H^+) to Ag_2CO_3 with the release of $AgHCO_3$.[24] Subsequent 1,1 insertion of the isocyanide into the metal–carbon bond takes place, giving the acetylenic imido complex **A**,[25] which readily undergoes protonolysis with $AgHCO_3$ to result in the acetylenic imide **B** and regenerates Ag_2CO_3 as the active species in the catalytic cycle. This step accounts for the destination of the acetylenic hydrogen observed in the above deuterium-labeling experiment [Scheme 4, Eq. (2)]. Subsequently, a possible interaction (**II**) between intermediate **B** and Ag_2CO_3 occurs, giving the metallic 2*H*-pyrrolenine species **C** through the intramolecular cyclization of acetylenic imide.[5h] Intermediate **C** then experiences a subsequent 1,5-hydrogen shift and protonation by the $AgHCO_3$ to yield **3a**, thus completing the catalytic cycle for Ag_2CO_3.

To examine the generality of the silver-catalyzed isocyanide–alkyne cycloaddition, we further investigated the scope of internal alkynes that have been previously used in base- or copper-catalyzed procedures.[10] An array of ethoxylcarbonyl- and benzoyl-activated internal alkynes reacted well with ethyl isocyanoacetate **1a** under the Ag_2CO_3-catalyed conditions (Scheme 6), generally affording 2,3,4-trisubstituted pyrroles (**8a–8k**) in high yields (up to 96%) with good functional-group tolerance. The structures of pyrroles **8**, substituted with electron-withdrawing groups (EWGs) at positions 2 and 4, were established with the aid of a 2D HMBC experiment on product **8a**. Notably, triethyl 2,3,4-pyrrole tricarboxylate **8l**, the precursor of a naturally occurring pyrrole acid in melanosomes,[26] was obtained in 90% yield by the cycloaddition of ethyl isocyanoacetate **1a** with diethyl acetylenedicarboxylate **7l**. However, 1,2-diphenylacetylene, a non-activated internal alkyne, did not react with ethyl isocyanoacetate **1a** under identical conditions. Consequently, a plausible mechanism for the silver-catalyzed reactions of electron-deficient internal alkynes involves the cycloaddition of α-metallated isocyanides to acetylenes, similar to the copper catalysis.[10,11]



Scheme 6. Scope of internal alkynes.

In conclusion, we have discovered Ag_2CO_3 as a unique and robust catalyst for the cycloaddition of isocyanides with a variety of alkynes, providing a general and practical method for the regioselective construction of synthetically useful 2,3-disubstituted and 2,3,4-trisubstituted pyrroles. For the first time, the transition-metal-catalyzed cycloaddition of isocyanides with unactivated terminal alkynes has been realized. A novel mechanism involving the catalytic cycle between Ag_2CO_3 and $AgHCO_3$ is proposed that satisfactorily accounts for the origin of the hydrogen atom on the pyrrole ring. In view of the broad scope of substrates, excellent functional-group tolerance, high reaction efficiencies, and high product yields, the silver-catalyzed isocyanide–alkyne cycloaddition can be expected to find wide synthetic applications.

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