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Oxidative cross-coupling/cyclization to build polysubstituted pyrroles from terminal alkynes and β-enamino esters†

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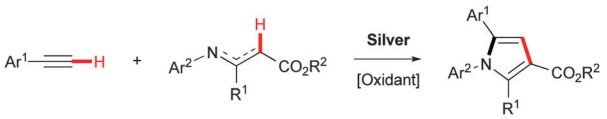
A novel silver-mediated highly selective synthesis of polysubstituted pyrroles by the C–H/C–H oxidative cross-coupling/cyclization of terminal alkynes with β-enamino esters has been developed. This protocol represents a simple, efficient and selective way to construct polysubstituted pyrroles in good yields from basic chemical materials.



Scheme 1 Proposal for a silver-mediated oxidative cyclization synthesis of polysubstituted pyrroles.

Inspired by the current requirements for green and sustainable chemistry, direct C–H functionalization has begun to alter the way towards the formation of C–C and C-heteroatom bonds in organic synthesis.[1] Compared to the classical transition-metal-catalyzed coupling reactions, the oxidative double C–H functionalization/cross-coupling has inherent advantages and represents an ideal chemical synthesis.[2] In this field, recently, the efficient and atom-economic synthesis of multifunctional heterocycles *via* direct oxidative C–H functionalization/cyclization has emerged as an attractive and challenging goal.

Heterocyclic compounds are of great chemical and biological significance in many fields. As important five-membered heterocycles,[3] pyrroles are the basic constituents of numerous natural products, biologically active alkaloids and pharmaceuticals,[4] and have also been found broad use in materials science.[5] Accordingly, substantial attention has been paid for the construction and modification of pyrroles,[6] although most of these methods involve multistep synthetic operations and suffer from low efficiency and low selectivity. The direct, region-defined syntheses of polysubstituted pyrroles from basic chemical materials are always highly attractive. Very recently, two efficient silver-catalyzed ''click'' syntheses of oligosubstituted pyrroles from cycloaddition of terminal alkynes with isocyanides have been reported.[7] Herein, we communicated our efforts in the silver-mediated synthesis of polysubstituted pyrroles through C–H/C–H oxidative cross-coupling/cyclization between terminal alkynes and β-enamino esters (Scheme 1). This protocol demonstrates a convenient approach for the construction of pyrrole frameworks, which expedites the facile synthesis of polyfunctional heterocycles.

Our initial studies focused on the reaction of phenylacetylene **1a** and (*Z*)-methyl 3-(2,6-diisopropylphenyl-amino)but-2-enoate **2a**. The employment of bulky groups around the aniline is to stabilize the imine towards hydrolytic cleavage.[8] Based on the continued efforts toward the C–H functionalization/alkynylation, silver salts have been found to display a critical potential to improve the selective transformation and avoid the homocoupling of terminal alkynes.[9] So several silver salts were firstly screened. When Ag_2CO_3 was employed as the mediator, the target pyrrole product **3a** was obtained in 54% yield in the presence of KOAc in DMSO at 80 °C (Table 1, entry 4). Notably, in this reaction, no terminal alkyne homocoupling byproduct was observed. Ag_2O could also provide the pyrrole product but AgOAc was ineffective (Table 1, entries 2 and 3). Without either silver salts or base, almost no reaction occurred (Table 1, entries 1 and 5). Then the influence of base on the reaction was also investigated. KO*t*Bu turned out to be effective while reducing the yield to 36% (Table 1, entry 6). The obvious improvement came from DBU, which afforded the desired oxidative cyclization product in 75% yield (Table 1, entry 7). While other organic amine bases, such as TBD, pyridine and DABCO, all turned out to be less effective (Table 1, entries 8–10).

With the optimized conditions in hand, substrate scope of this silver-mediated oxidative cross-coupling/cyclization was tested (Scheme 2). The reaction was readily extended to a variety of aryl-substituted terminal alkynes **1**. Both electron-withdrawing and -donating substituted groups were well tolerated under the

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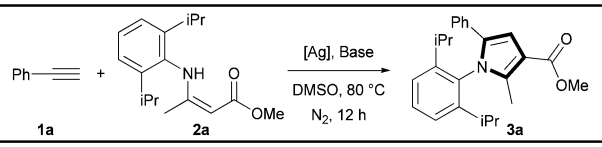
Table 1 Optimization of conditions for the reaction of **1a** with **2a**[a]



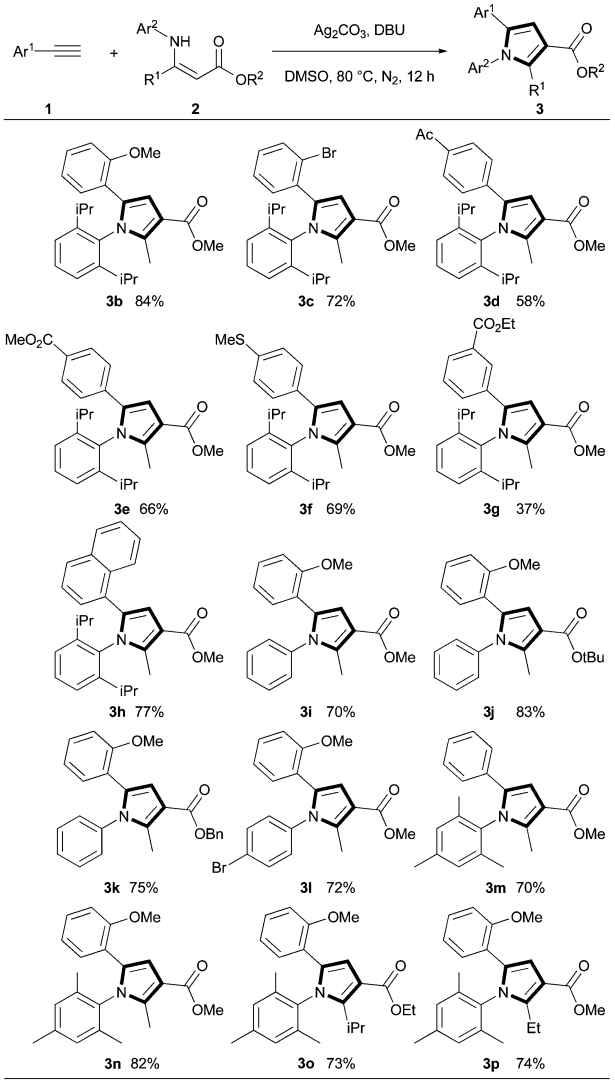
1a 2a 3a

Entry	[Ag]	Base	Yield[b] (%)
1	None	KOAc	0
2	AgOAc	KOAc	<5
3	Ag_2O	KOAc	32
4	Ag_2CO_3	KOAc	54
5	Ag_2CO_3	None	6
6	Ag_2CO_3	KO*t*Bu	36
7	Ag_2CO_3	DBU	75 (**71**)
8	Ag_2CO_3	TBD	29
9	Ag_2CO_3	Pyridine	10
10	Ag_2CO_3	DABCO	13

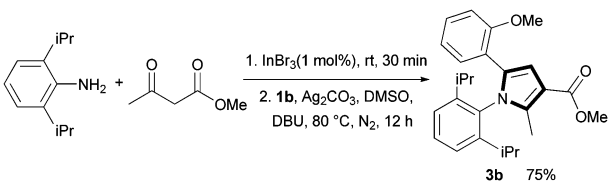
[a] Reaction conditions: **1a** (0.25 mmol), **2a** (0.5 mmol), [Ag] (2.0 equiv.), base (2.0 equiv.) in 6 mL of DMSO under N_2 at 80 °C for 12 h. [b] Yield determined by GC analysis with naphthalene as the internal standard; isolated yield for entry 7 in the parenthesis. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. TBD = 2,3,4,6,7,8-hexahydro-1*H*-pyrimido[1,2-*a*]pyrimidine. DABCO = 1,4-diazabicyclo[2.2.2]octane.

reaction conditions, such as OMe, SMe, Ac, CO_2Me, CO_2Et and Br (**3b**–**3g**). Meanwhile, regardless of the substitution pattern of the aryl ring (*ortho*, *meta*, *para*) of the aryl acetylenes used in the reaction, the corresponding pyrrole products were also obtained in good yields (**3b**–**3g**). Terminal alkynes containing a naphthalene moiety could also be employed to yield the pyrrole scaffold without any difficulties (**3h**). Moreover, various different substituted β-enamino esters **2** were also found to be suitable reaction partners with terminal alkynes **1** in this reaction. The ester group of **2** could be ranged from methyl to *tert*-butyl, benzyl or ethyl esters, all of which reacted with 1-ethynyl-2-methoxybenzene **1b** smoothly to afford the corresponding pyrrole pruducts in good yields (**3i**–**3k**, **3o**). In addition, the nitrogen protecting aryl groups of β-enamino esters **2** containing bromo or bulky substituents also allowed access to the pyrrole ring (**3b**, **3l**, **3n**). Meanwhile, the corresponding pyrroles with different substituents on the 2-position could also be successfully synthesized in good yields (**3o**, **3p**). Furthermore, a one-pot reaction sequence was performed successfully (Scheme 3). In the presence of the mild Lewis acid catalyst $InBr_3$ (1 mol%), the β-enamino ester was easily formed at room temperature by the condensation of 2,6-diisopropylaniline and methyl 3-oxobutanoate. Then, the *in situ* formed β-enamino ester underwent subsequent oxidative cross-coupling/cyclization with terminal alkyne **1b** under the standard conditions to give the desired pyrrole product **3b** in 75% yield. This efficient and modular one-pot construction of pyrrole scaffolds from three simple and commercially available starting materials complements the Hantsch-type pyrrole synthesis[10] and increases its practicality.

Usually, the reaction of terminal alkynes with silver(I) salts in the presence of a base could afford silver acetylides.[11] To elucidate the nature of the silver salt in this oxidative transformation, the stoichiometric reaction between phenylacetylene **1a** and Ag_2CO_3 was firstly monitored by using *in situ* IR spectroscopy (Fig. S2 in the ESI†). When an equivalent of

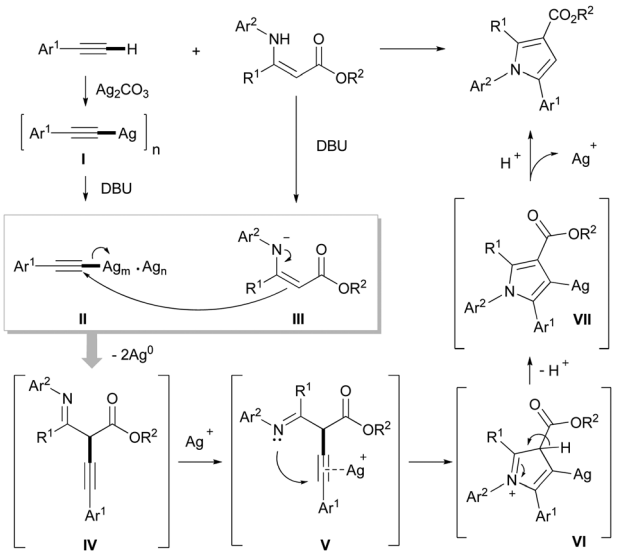


Scheme 2 Oxidative cyclization of terminal alkynes **1** and β-enamino esters **2**. Reaction conditions: **1** (0.25 mmol), **2** (0.5 mmol), Ag_2CO_3 (0.5 mmol), DBU (0.5 mmol) in 6 mL of DMSO under N_2 at 80 °C for 12 h, isolated yields.



Scheme 3 One-pot synthesis of pyrrole.

Ag_2CO_3 was added into the DMSO solution of **1a**, the peak of **1a** (765 cm^{-1}) consumed quickly upon the accumulation of the peak of $AgHCO_3$ (802 cm^{-1})[12] and a new component **I** (754 cm^{-1}). It is reasonable to figure out that component **I** might be the silver acetylide complex **I**. Actually, the large amount of white precipitate in the reaction solution has a similar characteristic to silver acetylide reported in the literature[11] and displays low solubility in DMSO. In addition, to get more information about the structure of component **I**, the Raman spectrum of this white precipitate was measured (Fig. S3 in the ESI†). The peak for the



Scheme 4 Proposed mechanism for the silver-mediated oxidative cross-coupling/cyclization.

C≡C stretching mode of phenylacetylene **1a** (2110 cm^{-1}) is red shifted to 1983 cm^{-1}. This suggests that alkynyl carbon binds covalently with silver and that the C≡C bond is weakened by electron transfer from the silver to the π* orbital of **1a**.[13] The above results clearly revealed that silver acetylide (complex **I**) was formed easily by the reaction of **1a** and Ag_2CO_3.

According to the above information, a proposed mechanism is outlined in Scheme 4. Initially, silver acetylide (complex **I**) was formed by the reaction of terminal alkyne and Ag_2CO_3. Then DBU could promote the monomerization of the polymeric silver acetylide yielding the active nonpolymeric species complex **II** (Fig. S4 in the ESI†), possibly aggregated with additional Ag(I). Meanwhile, β-enamino esters were deprotonated by DBU to afford intermediate **III** (Fig. S5 in the ESI†), which could undergo nucleophilic attack on complex **II** to give the oxidative cross-coupling intermediate **IV** *via* two single-electron oxidation. Finally, catalyzed by the silver species, the cycloisomerization process could be facile and afford the final pyrrole product.

In summary, we have developed a novel silver-mediated synthesis of polysubstituted pyrroles by the oxidative cross-coupling/cyclization of terminal alkynes with β-enamino esters. From the synthetic point of view, this protocol represents a simple, efficient and selective way to construct polysubstituted pyrroles in good yields, which complements the facile approach for the rapid construction of polyfunctional heterocycles. This work also demonstrates that silver can act as a ''key-mediator'' for the highly selective oxidative alkynylation, which will be quite important and of benefit for designing new reactions.

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