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Silver(I)-Catalyzed Conia-Ene Reaction: Synthesis of 3-Pyrrolines *via* a 5-*endo-dig* Cyclization

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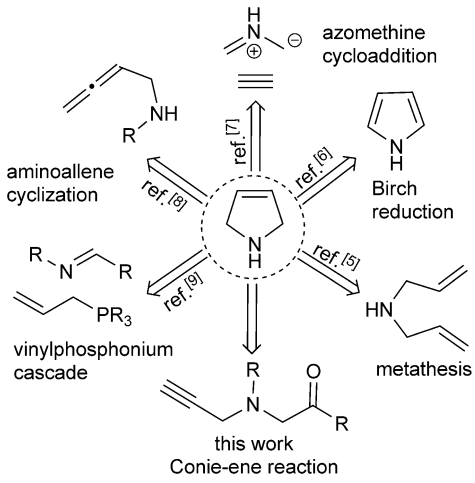
Abstract: A novel method has been developed for the synthesis of 3-pyrrolines from β-ketopropargylamines *via* a 5-*endo-dig* carbocyclization. This transformation involves a silver-catalyzed Conia-ene type reaction tolerating broad substrate scope with good to excellent yields. Furthermore, this methodology has been extended for the construction of 2-substituted pyrroles under base-mediated conditions.

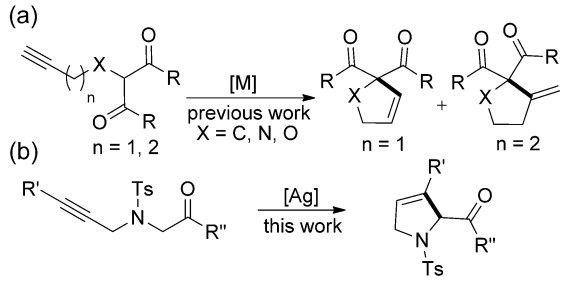
Keywords: alkynes; Conia-ene reaction; 2-pyrroles; 3-pyrrolines; silver

3-Pyrrolines are important heterocycles because of their broad applications in biology[1] and chemistry.[2] This class of heterocycles features in numerous bioactive molecules, natural products and pharmaceutical drugs. Of particular note are those molecules with 3,4-unsaturation, capable of being either oxidized to pyrroles[3] or reduced to pyrrolidines.[4] The most common methods in the literature for the synthesis of these molecules are ring closing metathesis,[5] Birch reduction of electron-deficient pyrroles,[6] 1,3-dipolar cycloaddition of azomethine ylides,[7] α-aminoallene cyclization,[8] and vinylphosphonium cascade reactions[9] (Scheme 1). However, some of these methods are limited by low reaction yields, poor substrate scope and the difficulty of preparing the necessary precursors. Therefore the development of a mild and complementary approach to the synthesis of 3-pyrrolines is highly desirable due to their widespread importance.[10]

The addition of enolates and enols to unactivated alkynes is a widely employed method for C–C bond formation.[11] In particular, Conia-ene reactions represent a robust strategy for synthesizing carbocycles, such as cyclopentane derivatives.[12] Over the last decade, transition metal-catalyzed Conia-ene reactions have been developed and replaced classic high temperature reactions, for the synthesis of such carbocycles.[12a] However, the synthesis of heterocycles by this method has been much less exploited. Recently, the syntheses of oxygen- and nitrogen-containing heterocycles were reported independently by Hatakeyama[13] and Burton[14] *via* indium and zinc catalysis, respectively. Although it should be noted that all of the reported metal-catalyzed reactions were restricted to dialkyl malonates or β-keto esters as precursors, as shown in Scheme 2a. To the best of our knowledge no other transition metal-catalyzed Conia-ene reactions have employed monocarbonyl groups as the starting material.[12a] Recently, we have been working on such cycloisomerization reactions in our group.[15] Herein we report a novel method for the synthesis of 3-pyrrolines from β-ketopropargylamines *via* 5-*endo-dig* cy-



Scheme 1. Previous reports and our strategy to synthesize 3-pyrrolines.

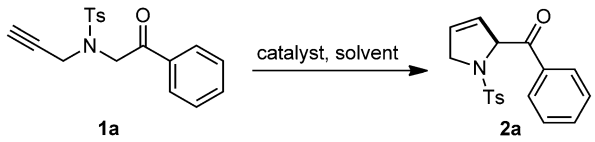


Scheme 2. Metal-catalyzed Conia-ene reactions.

clization[16] through a silver-catalyzed Conia-ene type reaction (Scheme 2b).

Our initial studies were carried out using **1a** as the model substrate to optimize the reaction conditions (Table 1). Evaluation of $AuCl(PPh_3)$ with silver co-catalysts resulted in hydration of alkyne (Table 1, entries 1 and 2). Further screening with various Lewis acids such as $FeCl_3$, $ZnCl_2$, CuI, $Cu(OAc)_2$, $Sc(OTf)_3$ and $In(OTf)_3$ failed to achieve the desired transformation (entries 3–9). To our delight, reaction with 20 mol% of $AgNO_3$ did give the desired product **1a**, in 29% yield (entry 9). Encouraged by this initial observation, various silver salts (entires 10–15) were screened. AgOTf and $AgNTf_2$ (entries 13 and 15) responded very well to this protocol; although of the two, we chose to use AgOTf as it is cheaper. Solvent screening revealed nitromethane to be the best solvent for this system, giving 85% yield (entries 16–19). Deviating from our optimum temperature (80 °C) in either direction appears to lower the yield (entries 20 and 21). From recent reports,[17] we were acutely aware of the fact that the Brønsted acid present in the triflate salts could also be catalyzing these reactions. To alleviate these concerns a control experiment was carried out with triflic acid (entry 22), but no reaction was observed, confirming that the reaction is indeed promoted by the metal catalyst.

Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst	Solvent	*t* [h]/ *T* [°C]	Yield [%][b]
1	$AuCl(PPh_3)$/AgOTf	DCE	2/r.t.	–[c]
2	$AuCl(PPh_3)$/$AgSbF_6$	DCE	2/r.t.	–[c]
3	$FeCl_3$	DCE	20/80	–
4	$ZnCl_2$	DCE	20/80	–
5	CuI	DMF	20/80	–
6	$Cu(OAc)_2$	DMF	20/80	–
7	$Sc(OTf)_3$	DCE	20/80	–
8	$In(OTf)_3$	DCE	20/80	traces
9[d]	$AgNO_3$	DCE	20/80	29%
10	Ag_2CO_3	DCE	16/80	traces
11	Ag_2O	DCE	20/80	traces
12	$AgSbF_6$	DCE	16/80	60%
13	$AgNTf_2$	DCE	16/80	68%
14	AgOAc	DCE	16/80	traces
15	AgOTf	DCE	16/80	66%
16	AgOTf	DMF	20/80	45%
17	AgOTf	toluene	24/80	40%
18	**AgOTf**	**CH_3NO_2**	**16/80**	**85%**
19	AgOTf	dioxane	20/80	60%
20	AgOTf	CH_3NO_2	16/100	58%
21	AgOTf	CH_3NO_2	16/60	20%
22[d]	TfOH	CH_3NO_2	16/80	–

[a] *Reaction conditions:* **1a** (1 mmol), catalyst (10 mol%) in solvent (1 mL) in a Schlenk tube at the mentioned temperature.
[b] Isolated yield of pure product.
[c] Hydration of the alkyne was observed to be quantitative.
[d] 20 mol% of catalyst was used.

Finally, we fixed upon entry 18 as the optimum reaction conditions to examine the substrate scope, with the results summarized in Table 2. Initially, a variety of terminal alkynes was screened with various R^1 groups. When R^1 is phenyl, the reaction tolerates both electron-donating (entries **2a**–**2c**) and electron-withdrawing substituents (entries **2k**–**2m**). With R^1 as an aryl halide the respective products were also formed in good yields (entries **2d**–**2j**). It is noteworthy that when R^1 is a fused aryl (**2n**), heterocycle (**2o**) or alkyl group (**2p**) the reaction progressed well under our standard reaction conditions.

The reaction was found to be compatible with both tosyl and nosyl substituents at the R^2 position. However, the expected product was not observed when the substitution on R^2 was alkyl, aryl and acyl. (Table 2, **2s**, **2t** and **2u**).

After exploring the scope with terminal alkynes, we turned our attention to investigating the feasibility of this reaction with internal alkynes. When R^3 is methyl (**2q**) and phenyl, (**2r**) the respective products were obtained in moderate yield. The structure of compound **2a** was unambiguously confirmed by X-ray analysis (Figure 1).[18]

To demonstrate the synthetic utility of our methodology, we sought to prepare pyrrole derivatives from

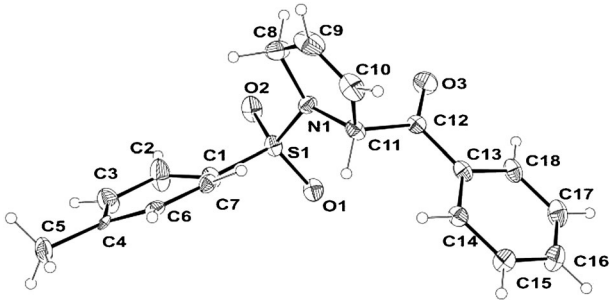
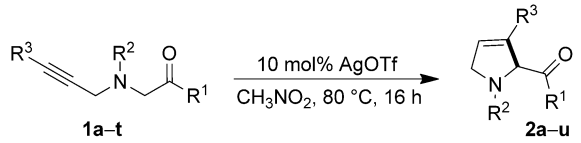
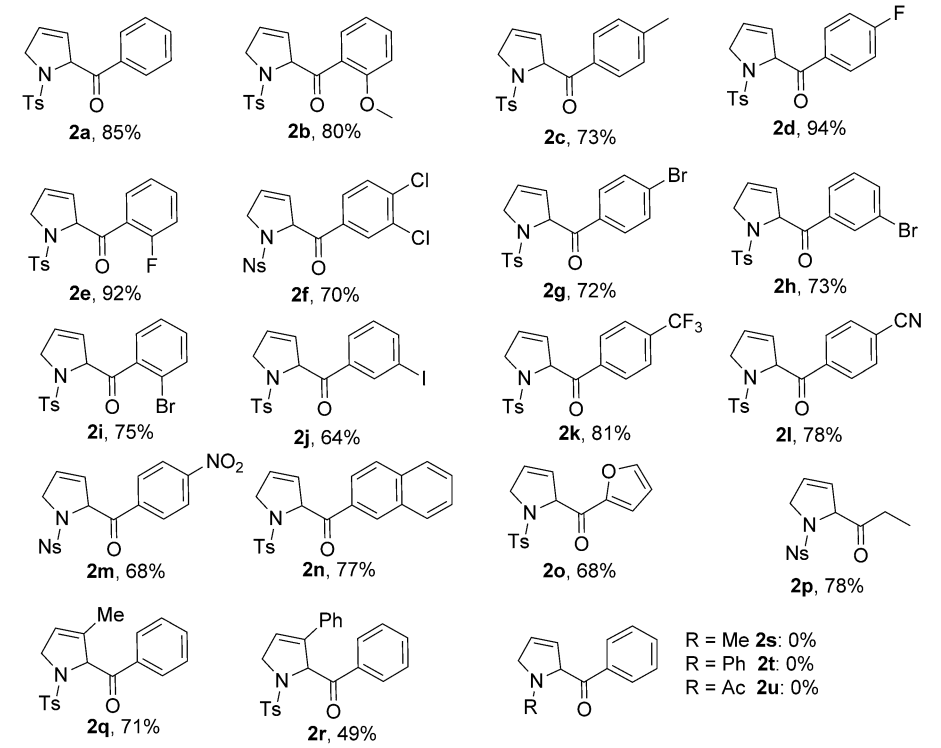


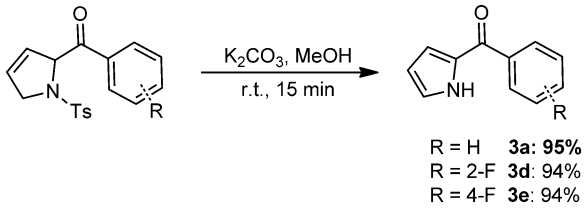
Figure 1. ORTEP diagram of **2a**.

Table 2. Substrate scope of 3-pyrroline derivatives.[a]





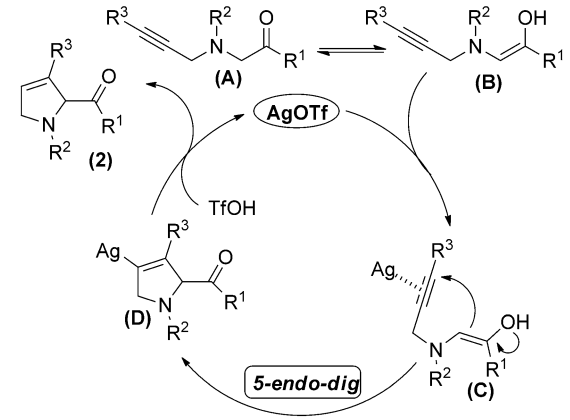
[a] *General reaction conditions*: **1** (1 mmol), AgOTf (10 mol%), CH_3NO_2 (1 mL), 80 °C, 16 h; yields refer to isolated products.



Scheme 3. Synthetic application to pyrrole derivatives.

the synthesized 3-pyrroline compounds (Scheme 3). The treatment of 3-pyrrolines with a stoichiometric amount of K_2CO_3 in methanol afforded the corresponding 2-substituted pyrroles (**3a**, **3d** and **3e**) in shorter times and excellent yields, *via* desulfonylation followed by an isomerization process.

Based on this observation and literature precedents,[8] a proposed mechanistic pathway was outlined, as shown in Scheme 4. Initially, the carbonyl group of compound **A** is in equilibrium with its enol form **B**. Compound **B** coordinates with the Lewis acid to produce an yne-Ag(I) intermediate **C**, which undergoes cyclization *via* a 5-*endo-dig* mode to produce intermediate **D**. In the end, protonation of **D** affords the final product **2**, regenerating the catalyst for the next cycle.



Scheme 4. Proposed mechanism.

In conclusion, a simple and convenient method of preparing 3-pyrrolines from β-ketopropargylamines *via* 5-*endo*-*dig* carbocyclization by a silver-mediated Conia-ene type reaction has been successfully developed. The attractive features of the work are wide functional group tolerance, high yields and easily available precursors. The synthetic utility of this method in affording 2-substituted pyrroles has also been demonstrated. Efforts to expand this strategy to other heterocycles are currently in progress.

Experimental Section

General Procedure for the Synthesis of 3-Pyrrolines (2a–2r)

An oven-dried, 15-mL Schlenk tube was charged with **1** (1 mmol) in nitromethane (1 mL) and silver triflate (10 mol%), then the reaction mixture was heated to 80 °C for 16 h. After reaction was completed (as detected by TLC), the reaction mass was partitioned between water and ethyl acetate, then the combined organic phases were dried and evaporated under vacuum. The resulting residue was purified by flash column chromatography on silica gel (100–200 mesh) with a suitable ratio of hexane and ethyl acetate to afford the desired product (**2**). The identity and purity of the compounds were determined by HR-MS, ^{1}H and ^{13}C NMR spectroscopy.

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[18] CCDC 948650 (**2a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

