



Silver-catalyzed chemoselective annulation of propargyl amines with alkynes for access to pyridines and pyrroles



Tauqir A. Nizami, Ruimao Hua*

Department of Chemistry, Tsinghua University, Beijing, 100084, China

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ABSTRACT

The annulation of propargyl amines with electron-deficient alkynes in the presence of silver salts affording pyridines and pyrroles has been developed. The chemoselective [4+2] or [3+2] annulation approach to pyridines or pyrroles depends on the structures of propargyl amines and the different reaction conditions.

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1. Introduction

Development of the synthetic methods for the formation of *multi*-substituted pyridines¹ and pyrroles² is one of the important and interesting research topics in the synthetic chemistry and heterochemistry. Both pyridines and pyrroles are the most important kinds of *N*-heterocyclic compounds, which have been applied in agrochemicals, pharmaceuticals, and organic materials. On the other hand, propargyl amines with the π -nucleophilic character of triple bond and vicinity of functional group have been used as the useful and versatile reactants in the synthesis of various *N*-heterocycles *via* their annulation with other unsaturated compounds.³ In our previous work, we have also developed the application of propargyl alcohols, and propargyl amines in the synthesis of 2*H*-chromenes,⁴ 4-vinyl-1,2,3-triazoles,⁵ 1,2-dihydroquinolines,⁶ and 2,5-dimethylpyrazines.⁷ As a continuation of our interest in developing synthetic methods for heterocyclic compounds *via* annulation process using alkynes as one of the reactants,⁸ and silver salts have been well applied in the synthesis of heterocycles *via* the annulation of alkynes.⁹ We report here the highly selective formation of *multi*-substituted pyridines and pyrroles *via* the

annulation of propargyl amines with electron-deficient alkynes catalyzed by silver salts under different conditions.

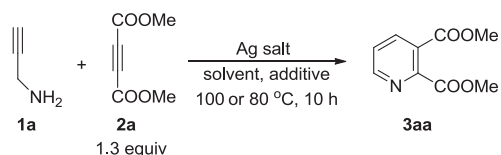
2. Results and discussion

The reaction of prop-2-yn-1-amine (**1a**) with the electron-deficient alkyne of dimethylacetylenedicarboxylate (DMAD) (**2a**) was detailed studied to optimize the reaction conditions. As shown in Table 1, in the presence of Ag₂CO₃, when a mixture of **1a** and **2a** (1.3 equiv.) in THF was heated at 100 °C for 12 h, dimethyl pyridine-2,3-dicarboxylate (**3aa**) could be isolated from the mixture in 39% yield (entry 1).¹⁰ Repeating the reaction in dioxane for 10 h and using an increased amount of catalyst (10 mol%) resulted in the slight increase of **3aa** yield (entry 2). Encouraged by this promising result, other silver salts such as silver acetate (AgOAc), silver nitrate (AgNO₃), silver iodide (AgI), silver tetrafluoroborate (AgBF₄), and silver hexafluoroantimonate (AgSbF₆) were screened. It was found that either **3aa** was formed in the fair yields or no reaction took place for the formation of **3aa** due maybe to their different solubility in dioxane (entries 3–7). However, **3aa** yield could be significantly increased to 62% when AgOTf was used as catalyst, and was further considerably increased by using K₂S₂O₈ as additive (entries 8–9). In addition, when toluene was used as solvent, **3aa** was obtained in 91% yield (entry 10). Although the decrease of the catalyst amount to 5 mol% resulted in great decrease of **3aa** yield

* Corresponding author.

E-mail address: ruimao@mail.tsinghua.edu.cn (R. Hua).

Table 1
Optimizing the reaction conditions for the formation of **3aa**.^a



Entry	Catalyst (mol%)	Solvent	Additive ^b	Yield (%) ^c
1	Ag ₂ CO ₃ (5)	THF	—	39
2	Ag ₂ CO ₃ (10)	dioxane	—	43
3	AgOAc (10)	dioxane	—	47
4	AgNO ₃ (10)	dioxane	—	28
5	AgI (10)	dioxane	—	15
6	AgBF ₄ (10)	dioxane	—	0
7	AgSbF ₆ (10)	dioxane	—	0
8	AgOTf (10)	dioxane	—	62
9	AgOTf (10)	dioxane	K ₂ S ₂ O ₈	74
10	AgOTf (10)	toluene	K ₂ S ₂ O ₈	91
11	AgOTf (5)	toluene	K ₂ S ₂ O ₈	56
12 ^d	AgOTf (10)	toluene	K ₂ S ₂ O ₈	93

^a Reactions were carried out using 1.0 mmol **1a**, 1.3 mmol of **2a** and silver salt in 5 mL of solvent.

^b 1 equiv.

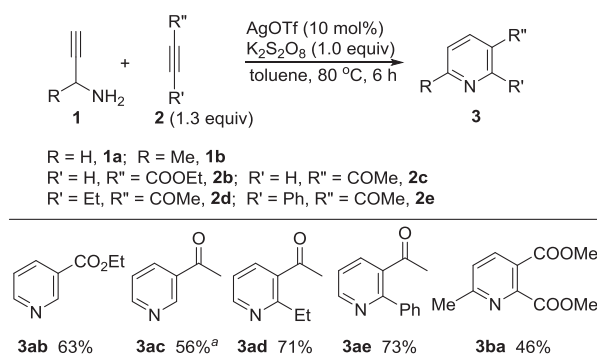
^c Isolated yield based on the amount of **1a** used.

^d At 80 °C for 6 h.

(entry 11), the further studies on the effect of reaction temperature and time in toluene were disclosed that the reaction performed at 80 °C for 6 h is the suitable choice for the formation of **3aa** in a satisfactory yield (entry 12), which were used as the optimal reaction conditions for the studies of substrate scope.

Several substituted pyridines could be synthesized in mild to good yields as summarized in Table 2 under the optimized conditions. Notably, when unsymmetric alkynes were used, the [4+2] cycloaddition reactions occurred with an excellent regioselective manner to afford **3ab–3ae** bearing electron-withdrawing group at 3-position of pyridine ring, as the sole regioisomer due to the first step of Michael addition of N–H bond of **1a** to alkynes taking place with excellent regioselectivity as shown in the proposed mechanism (*vide infra*). In addition, the reaction of but-3-yn-2-one (**2c**) with **1a** had to be carried out at room temperature to decrease the self-dimerization of **2c** affording the corresponding pyridine derivative **3ac** in a relatively low yield. In the case of 3-butyn-2-amine (**1b**) used, the annulation with **2a** also occurred to afford the corresponding pyridine derivative **3ba** in 46% yield. However, under

Table 2
The synthesis of pyridine derivatives.

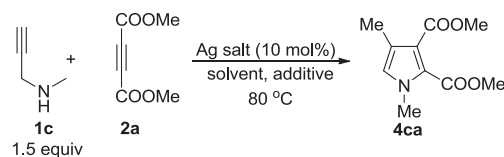


^a Reaction was carried out at room temperature.

the similar reaction conditions, the reactions of 3-substituted propargyl amines, such as 3-phenyl-2-propyn-1-amine and 2-heptyn-1-amine with **2a** could not produce the corresponding pyridine derivatives at all.

The reaction manner of N-substituted propargyl amines is expected to be different from **1a**, since the reaction must be unfavorable for the formation of pyridine ring due to the substituent at the nitrogen atom. Interestingly, as shown in Table 3, when a mixture of 1.5 equivalent of N-methyl propargyl amine (**1c**) and **2a** in toluene in the presence of 10 mol% of AgOTf was heated at 80 °C for 8 h, the four-substituted pyrrole ring **4ca** could be isolated in 13% yield from the reaction mixture (Table 3, entry 1). Although a [3+2] cycloaddition of N-propargylamines with activated alkynes by base-catalyzed reaction affording a variety of multi-substituted pyrroles was reported by Jin and co-worker,^{3f} in continuation of our previous work on the synthesis of pyrroles^{8d,8l,8q,8r} and with the purpose of providing an alternative catalyst system for the construction of pyrrole ring, we further optimized the reaction conditions for the synthesis of **4ca**. As concluded in Table 3, DMF is found the suitable solvent for the formation of **4ca**, and AgOAc shows higher catalytic activity than AgOTf and Ag₂CO₃. Moreover, the use of base is the key factor to promote the transformation, and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), an organic base is the better choice than inorganic bases, such as KOAc and K^tBu. After optimizing the reaction conditions, the yield of **4ca** could be

Table 3
Optimizing the reaction conditions for the formation of pyrrole derivative **4ca**.^a



Entry	Catalyst	Solvent	Time (h)	Additive ^b	Yield (%) ^c
1	AgOTf	toluene	8	—	13
2	Ag ₂ CO ₃	DMF	10	—	23
3	AgOAc	DMF	10	—	41
4	AgOAc	DMF	10	KOAc	64
5	AgOAc	DMF	10	<i>t</i> -BuOK	50
6	AgOAc	DMF	2	DBU	84

^a Reactions were carried out using 1.5 mmol of **1c**, 1.0 mmol of **2a** and silver salt in 5 ml of solvent.

^b 1 equiv.

^c Isolated yield based on the amount of **2a** used.

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