# Quick Access to Druglike Heterocycles: Facile Silver-Catalyzed One-Pot Multicomponent Synthesis of Aminoindolizines

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*Received May 22, 2010*

A direct and efficient approach to 1-aminoindolizines through three-component one-pot reaction of heteroaryl aldehydes, secondary amines, and terminal alkynes catalyzed by $AgBF_4$ has been developed. Desired products were obtained in moderate to excellent yields. Similar aminoindolizines products were afforded from trimethylsilyl protected alkyne substrates as well. This methodology provides a rapid access to construct a diversity-oriented library of indolizines.

## Introduction

Indolizines are a unique class of heterocycles. They are characterized by a N-bridgehead heterocyclic scaffold with an electron-rich pyrrole and an electron-poor pyridine.[1] Indolizines and their partially saturated derivatives have been widely found in natural products and synthetic pharmaceuticals[2] which are associated with a broad spectrum of biological activities such as antibacterial, antiviral, anti-inflammatory[3] and central nervous system (CNS) depressant activity.[4] They also have considerable potential applications which serve as phosphatase inhibitors,[5] aromatase inhibitors,[6] antioxidant reagents,[7] and calcium entry blockers.[8] As a consequence, great attention has been drawn to the synthesis of indolizine derivatives and a number of elegant synthetic methods have been developed.[9]

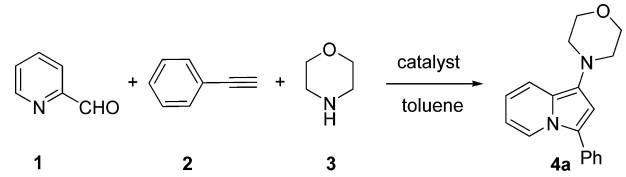
In recent years, multicomponent coupling reactions (MCRs) have been widely employed to develop efficient and practical methods for the diversity-oriented synthesis of structurally complex molecules.[10] Transition metal catalyzed MCRs involving cascade C−C and C−N bond formations have been widely used in the synthesis of heterocycles including indolizines.[11] In 2007, a novel and efficient method for synthesizing aminoindolizines from heteroaryl aldehydes, secondary amines, and terminal alkynes has been reported; however, this method involves an expensive gold catalyst, and it mainly focuses on the variation of amino substituents on the indolizine skeleton.[1b] In the past few years, we have been interested in developing new strategies to construct heterocyclic scaffolds with high synthetic efficiency.[12]

The viral enzyme neuraminidase (sialidase, NA) has recently attracted much attention in drug development because of its important role in pathogenesis, bacterial nutrition, and cellular interaction.[13] As part of our ongoing effort to screen new NA inhibitors, we plan to construct a library of aminoindolizines. In view of the dramatic bioactivities of indolizines, there is still need to develop a new method that allows functional group variation on the target molecule and minimizes cost to construct a combinatorial library of indolizines. To achieve this, herein we report a silver-catalyzed multicomponent synthesis of aminoindolizines with aldehydes, amines, and alkynes as starting materials.

## Results and Discussion

Our initial effort was focused on the evaluation of silver catalytic systems for the three-component reaction of pyridine-2-carboxaldehyde, morpholine, and phenylacetylene, and the results are summarized in Table 1. We found that silver catalyzes this one-pot multicomponent reaction efficiently. In the presence of 50 mol % AgOTf, the reaction proceeded smoothly in toluene, providing desired aminoindolizine in 81% yield at 60 °C (Table 1, entry 1). In addition, $AgClO_4$, CuI, $AgNO_3$/CuI, or $Ag_2O$ could also catalyze this reaction but led to lower yields (Table 1, entry 2−5). Catalyst screening confirmed that $AgBF_4$ was the most efficient catalyst. The reaction was completed in 3 h at 60 °C to

**Table 1.** Optimization of the Reaction Conditions[a]




1 2 3 4a

| entry | catalyst | equiv | temp (°C) | time | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | AgOTf | 0.5 | 60 | 3 h | 81 |
| 2 | $Ag_2O$ | 0.5 | 60 | 12 h | 25 |
| 3 | CuI | 0.5 | 60 | 12 h | 47 |
| 4 | $AgClO_4$ | 0.5 | 60 | 12 h | 51 |
| 5 | $AgNO_3$/CuI | 0.5 | 60 | 12 h | 29 |
| 6 | $AgBF_4$ | 0.5 | 60 | 3 h | 91 |
| 7 | $AgBF_4$ | 0.1 | 60 | 3 h | 90 |
| 8 | $AgBF_4$ | 0.05 | 60 | 5 h | 90 |
| 9 | $AgBF_4$ | 0.05 | 25 | 24 h | trace |
| 10 | $AgBF_4$ | 0.05 | 85 | 45 min | 89 |
| 11 | $AgBF_4$ | 0.05 | 110 | 45 min | 65 |

[a] Unless otherwise stated, reaction was carried out with pyridine-2-carboxaldehyde (1.0 mmol), morpholine (1.1 mmol), and phenylacetylene (1.5 mmol). [b] Isolated yields.

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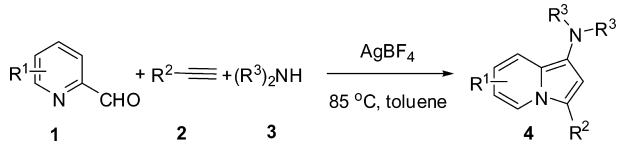
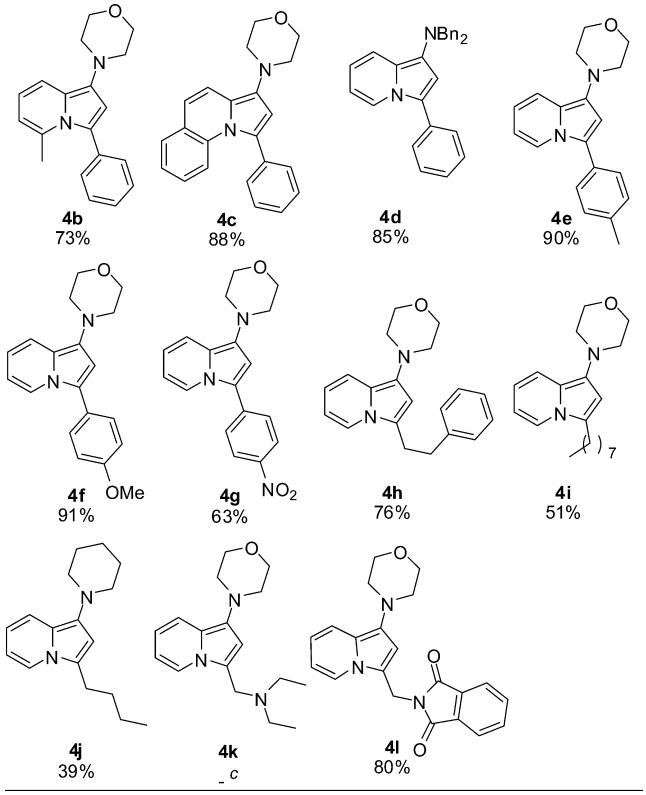
10.1021/cc100086h © 2010 American Chemical Society
Published on Web 07/22/2010

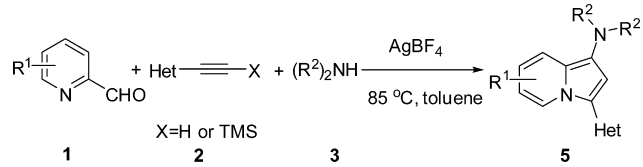
**Table 2.** Silver Catalyzed Three-Component Reactions to Synthesize Aminoindolizines[a,b]

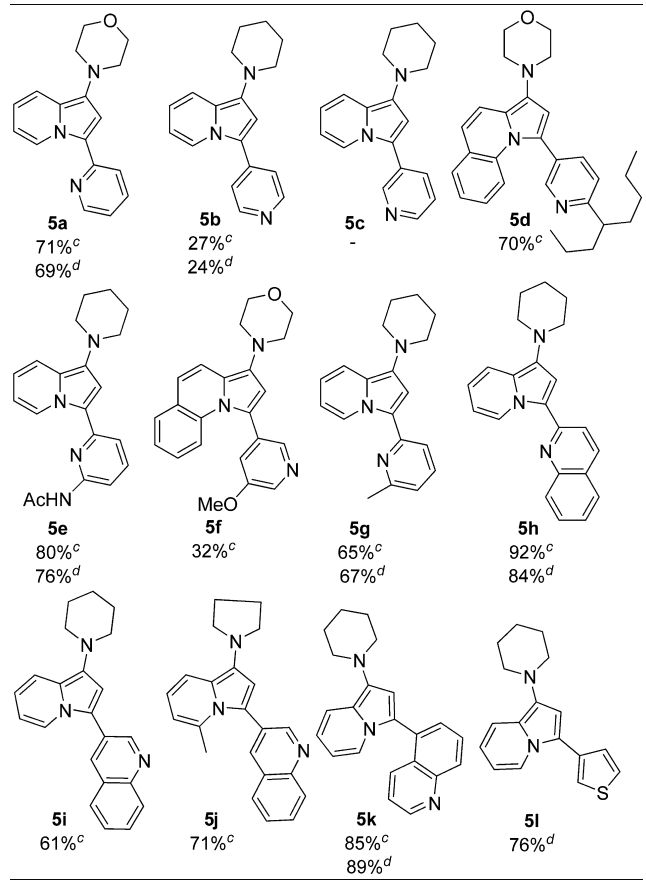



[a] Unless otherwise stated, reaction was carried out at 85 °C using aldehyde (1.0 mmol), amine (1.1 mmol), and acetylene (1.5 mmol) catalyzed by 0.05 equiv of $AgBF_4$. [b] Isolated yields. [c] No reaction, starting material recovered.

**Table 3.** Silver Catalyzed Formation of Heterocycle Substituted Aminoindolizines[a,b]



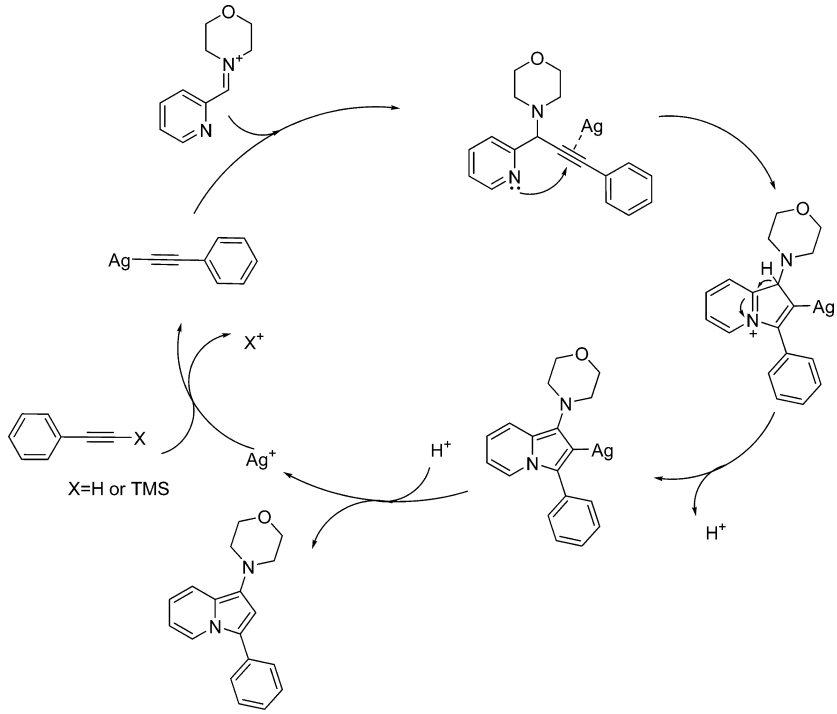




[a] Unless otherwise stated, reaction was carried out at 85 °C using aldehyde (1.0 mmol), amine (1.1 mmol), and acetylene (1.5 mmol) catalyzed by 0.05 equiv of $AgBF_4$. [b] Isolated yields. [c] Yields obtained by using terminal alkynes. [d] Yields obtained by using TMS protected alkynes.

furnish the product in 91% yield in the presence of 50 mol % $AgBF_4$ (Table 1, entry 6). Lowering the catalyst loading to 5 mol % resulted in a similar yield (Table 1, Entry 7, 8). Interestingly, the reaction time dramatically decreased from 3 h to 45 min when the reaction temperature increased to 85 °C, and the yield of 89% was obtained. Further increase in temperature (110 °C) and decrease in time (30 min) resulted in poor yields (Table 1, entry 9−11). The results were not satisfactory when dichloromethane (DCM), tetrahydrofuran (THF), and acetonitrile were used as solvents, where most of the compounds decomposed in the reaction mixture. Further investigations of the reaction conditions revealed that toluene was the best solvent, and a catalyst loading of 0.05 equiv could be used to afford indolizines in good yields.

With the optimized conditions, we started to examine the scope of this multicomponent reaction. As illustrated in Table 2, analogues of pyridine-2-carboxaldehyde were first tested under the optimized conditions. Reactions involving 6-methyl-pyridine-2-carboxaldehyde and 2-quinolinecarboxaldehyde proceeded smoothly and gave desired products in 73% and 88% yields, respectively (Table 2, **4b**, **4c**). With respect to amines, acyclic secondary amines such as dibenzylamine also afforded corresponding indolizine in good yield (Table 2, **4d**). However, a complex reaction mixture was observed when a primary amine such as benzylamine was used.[1b] Subsequently, a variety of alkynes, aldehydes, and amines were successfully transformed into the corresponding aminoindolizines in good to excellent yields. As evident from Table 2, besides simple phenylacetylene, other substituted aryl acetylenes also served as good substitutes for this reaction (Table 2, **4e**−**g**). Interestingly, aryl alkynes with electron-withdrawing substitutes furnished lower yields (Table 2, **4g**). On the other hand, alkyl alkynes gave the corresponding indolizines in poor to moderate yields (Table 2, **4 h-j**). This could be attributed to the instability of the compounds which decomposed quickly at room temperature.[14] No reaction occurred when *N*,*N*-diethylpropargylamine was used. However, to our surprise, reaction with phthalimide propargylamine furnished the corresponding indolizine in 80% yield (Table 2, **4k**−**4l**).

**Scheme 1.** Proposed Catalytic Cycle for the Silver Catalyzed Three-Component Reaction




The efficiency of this reaction prompted us to employ heterocycle substituted alkynes to synthesize a variety of 3-heterocycle substituted aminoindolizines (Table 3). We envisioned that these novel structures may present potential utilities in pharmacological areas. However, the yields of reactions using heterocycle alkynes as substrates varied according to the positions of the heteroatom and the functionalities on heterocycles. First, we checked the reactions of 2-ethynylpyridine and 2-ethynylquinoline, and it was found that the desired indolizines were rapidly formed in good to excellent yields (Table 3, **5a**, **5h**). In contrast, the reaction involving 4-ethynylpyridine was intriguing and resulted in poor yield (Table 3, **5b**). In addition, use of 3-ethynylpyridine could not give any product after refluxing for 12 h (Table 3, **5c**). When methyl and octyl substituted 3-ethynylpyridine were used, the reactions proceeded well, and high yields were achieved (Table 3, **5d**, **5g**). 3-Ethynylquinoline, 4-ethnylisoquinoline and 5-ethnylquinoline could be recognized as substituted pyridines, which reacted well to generate the corresponding indolizines in high yields (Table 3, **5i**−**k**).

Interestingly, trimethylsilyl (TMS) protected alkynes also tolerated these reaction conditions and yielded the same products as those of terminal alkynes (Table 3, **5a**, **5b**, **5e**, **5g**, **5h**, **5k**, and **5i**). Since both terminal alkyne and TMS protected alkyne generated the same alkynyl silver intermediate in the presence of silver salts,[15] we believe that these two types of reactions should have proceed through the same mechanism (Scheme 1). Thus, in situ generated alkynyl silver reacts with the activated imonium to afford N-substituted propargylic pyridine, which undergoes cyclization and deprotonation subsequently to generate indolizines. As all the heterocycle substituted TMS acetylenes could be easily synthesized from TMS acetylene and iodine or bromine substituted heterocycles via Sonogashira reaction developed by Thorand and Krause,[16] this method serves as a more rapid and direct approach to construct indolizines.

## Conclusion

In conclusion, we have reported the synthesis of functionalized aminoindolizines with the aid of one-pot three-component reaction catalyzed by a cheap and easily available catalyst $AgBF_4$. A library of 22 aminoindolizines has been prepared promptly. Furthermore, we also found that both TMS protected alkynes and terminal alkynes were well tolerated in this reaction to give the same products. Further efforts are currently underway to expand the library and also to evaluate the biological activity of these novel compounds.

## Experimental Section

**General Procedure for the Synthesis of 1-Aminoindolizines: Synthesis of 1-Morpholin-4-yl-3-phenyl-indolizine (4a).** To a solution of $AgBF_4$ (9.5 mg, 0.05 mmol) in toluene (1.0 mL) were added pyridine-2-carboxaldehyde (95 $\mu$L, 1.0 mmol), phenyl acetylene (130 $\mu$L, 1.2 mmol), and morpholine (86 $\mu$L, 1.0 mmol) successively. The resulting mixture was stirred at 85 °C until the reaction was completed as monitored by thin-layer chromatography. The mixture was then diluted with dichloromethane (5 mL) and washed with water (2 × 5 mL). The aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic phase was washed with saturated aqueous NaCl, dried over anhydrous $Na_2SO_4$, filtered and concentrated under vacuum. The residue was purified by flash chromatography on aluminum oxide to afford target product **4a** (243.5 mg, 89%) as a yellow oil. $^1$H NMR (300 MHz, $C_6D_6$, $Me_4Si$) 2.87 (t, $J$ = 1.5 Hz, 4H), 3.75 (t, $J$ = 1.5 Hz, 4H), 6.01−6.06 (m, 1H), 6.35 (dd, $J$ =

9.0, 6.3 Hz, 1H), 6.66 (s, 1H), 7.06−7.11 (m, 1H),7.16−7.22 (m, 2H), 7.34−7.37 (m, 2H), 7.43 (d, $J$ = 8.7 Hz, 1H), 7.91 (d, $J$ = 7.5 Hz,1H); $^{13}$C NMR (75 MHz, $C_6D_6$, $Me_4Si$) 54.6, 67.5, 106.4, 111.1, 114.9, 118.2, 121.8, 122.9, 125.9, 126.9, 128.1, 129.1, 130.5, 132.9; IR (neat) 2955, 2851, 1599, 1427, 1115, 737, 699 cm$^{-1}$; HRMS (ESI) calcd for $C_{18}H_{18}N_2O$ $[M+H]^+$ 278.1419, found 278.1424.

**Acknowledgment.** Financial supports from Nanyang Technological University (RG50/08) and the Ministry of Health, Singapore (NMRC, H1N1R/001/2009) are gratefully acknowledged. Y.B. is thankful for the grant from Nanyang Technological University under the Undergraduate Research Experience on Campus (URECA) programme.

**Supporting Information Available.** Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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CC100086H