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Silver-Mediated Synthesis of Indolizines via Oxidative C-H functionalization and *5- endo-dig* cyclization

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Abstract

An efficient strategy for the synthesis of indolizines from readily available starting materials via oxidative C-H functionalization and *5-endo-dig* cyclization in one step has been demonstrated. This protocol represents wide substrate scope, high functional group tolerance and selectivity. The structure of the product was confirmed by the X-ray crystallographic studies. The Ag_2CO_3 required of this tandem reaction can be recycled and reused after undergoing oxidative reaction.

Keywords

C-H functionalization; Indolizine; *5-endo-dig* cyclization

The study of the synthesis of small heterocyclic compounds and natural products using transition metal-catalyzed tandem reactions is a rapidly expanding area of interest in the field of synthetic organic chemistry. In recent years, various examples of direct oxidative C-

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Supplementary data

General experimental procedures, mass and NMR spectral data for compounds are provided in supporting information.

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H functionalization and subsequent C-C and C-N bond formation have improved the atom economy and efficiency of multistep synthesis.[1] Unfortunately, these approaches required expensive metal catalysts, such as Pd, Rh, and Ru, as well as pre-functionalized starting materials for both reactivity and selectivity. Limited progress has been made in the utilization of less expensive copper and silver salts as oxidative promoters of C-C bond formation via C-H activation. Recently, Lei et al.[2] reported stoichiometric silver-mediated oxidative C-H/C-H functionalization of 1,3-dicarbonyl compounds with terminal alkynes for the synthesis of polysubstituted furans and pyrroles. Duan[3] and Wu[4] independently disclosed silver-promoted oxidative C-H/P-H functionalization to construct benzo[b]phosphole oxides and 3-phosphorated coumarins, respectively.

The indolizine-based scaffolds are found in many natural alkaloids and biologically active compounds (Figure 1). Such derivatives have shown utility in anticancer,[5] antibacterial,[6] antituberculosis,[7] H3 receptor antagonist[8] and antifungal [9] applications. While numerous methods for the synthesis of indolizine scaffolds are known, the direct and region-selective synthesis of this class of scaffolds from readily available starting materials has drawn considerable attention.[10] Recently, we developed new synthetic methodologies for highly substituted imidazoles based on C-H functionalization.[11] Herein, we communicate our discovery of a silver-mediated indolizines synthesis via one pot oxidative C-H functionalization and 5-*endo-dig* cyclization in one step under mild reaction conditions (Scheme 1).

To identify suitable reaction conditions, various substrate ratios and solvent conditions were screened as summarized in Table 1. Initially, we carried out the reaction of ethyl 2-pyridylacetate (1 equiv.), phenylacetylene (1 equiv.), Ag_2CO_3 (1 equiv.) and KOAc (2 equiv.) in DMF solvent at room temperature (Table 1, entry 1). These conditions did not produce desired product **3a**, and lack the visual markers of the reaction initiation whereupon the reaction mixture turns black. Notably, after increasing the reaction temperature to 110°C this substrate ratio did produce the desired indolizine product with excellent region-selectivity, albeit low yield (Table 1, entry 2). Changing the reaction conditions to refluxing THF along with an increased ratio of silver salt (1.5 equiv.) afforded only moderate improvement in product yield (Table 1, entry 3). Further increase in the amounts of silver salt and compound **1a** to two equivalents improved the reaction outcome with KOAc base, showing the best overall yield among K_2CO_3 or Cs_2CO_3 alternatives (Table 1, entries 4–6).

After completing the standardization of the reaction conditions, we examined the scope of the reaction towards pyridine and alkyne substitution, as shown in scheme 2. This included CH_2COOEt, CH_2COOMe, CH_2CN groups substituted at the C2 position of pyridine and diverse electron withdrawing and donating aryl groups on the alkyne. Good overall tolerance was demonstrated by these reaction conditions, resulting in the formation of diverse products with excellent regio-selectivity in medium-to-high yield **(3a-3o)**. The presence of strong electron-withdrawing groups (COOEt, COOMe) at the C2 position of pyridine (R^3) provided higher yields relative to the less electron-withdrawing cyanide group (Scheme 2, **3a-3j** vs **3k-3o**). In contrast, no significant differences in yields were observed when aryl alkyne reactant substitution was varied with both electron-withdrawing (-Cl) and electron-donating substituents (-OMe, Me) affording similar outcomes. The evaporation of

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compound **3b** from dichloromethane gave a single crystal suitable for X-ray analysis. As illustrated in Figure 2, this proves unambiguously the heterocyclic and regio-isomeric identity of the reaction product being an indolizine ring substituted at the 2- and 4-positions. Furthermore, the structures were confirmed by 1D and 2D NMR spectrometry (Supporting Information).

Because two equivalents of Ag_2CO_3 are necessary to achieve high yields, this significantly increases the cost and chemical waste produced by this reaction. To address this issue, we examined whether Ag_2CO_3 could be regenerated from the reaction waste and successfully reused for this transformation. Upon completion of the reaction, the precipitated silver salts were separated by filtration, then treated with nitric acid followed by Na_2CO_3 at room temperature to provide Ag_2CO_3.[12] This regenerated Ag_2CO_3 was shown to mediate C-H functionalization for synthesizing indolizines with analogous activity to commercial Ag_2CO_3 salts (Scheme 3).

A plausible mechanism of this transformation is shown in scheme 4. One equivalent of Ag_2CO_3 activates ethyl 2-pyridylacetate by chelation to form **4.**[13] While a second equivalent of Ag_2CO_3 reacts with phenylacetylene to form silver phenylacetylide [2] **5.** Subsequent coupling of these two intermediates results in the formation of intermediate **6**, which undergo *5-endo-dig* cyclization to form the final product **3**.[14]

In summary, we have successfully developed a facile and highly selective synthesis of indolizines via silver-mediated oxidative C-H functionalization and *5-endo-dig* cyclization from readily available starting materials. This methodology provides a simple and direct way to access derivatives of the biologically important heterocycles. These reaction conditions display a wide range of functional group tolerance, including those that allow for further scaffold decoration. From an environmental point of view, this protocol represents good atom economy in that the expended Ag_2CO_3 can be recycled and reused to mediate this reaction. Molecular biology studies involving derivatives of this scaffold are currently underway in our laboratory.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. (a) Girard SA, Knauber T, Li CJ. Angew Chem, Int Ed. 2014; 53:74.(b) Yamaguchi J, Yamaguchi AD, Itami K. Angew Chem, Int Ed. 2012; 51:8960.(c) Song G, Wang F, Li X. Chem Soc Rev. 2012; 41:3651. [PubMed: 22377832] (d) Li BJ, Shi ZJ. Chem Soc Rev. 2012; 41:5588. [PubMed: 22782263] (e) Kuhl N, Hopkinson MN, Wencel-Delord J, Glorius F. Angew Chem, Int Ed. 2012; 51:10236.(f) Yeung CS, Hsieh TH, Dong VM. Chem Sci. 2011; 2:544.(g) Cho SH, Kim JY, Kwak J, Chang S. Chem Soc Rev. 2011; 40:5068. [PubMed: 21643614] (h) Bugaut X, Glorius F. Angew Chem, Int Ed. 2011; 50:7479.(i) Rossi R, Bellina F, Lessi M. Synthesis. 2010:4131.

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2. He C, Guo S, Ke J, Hao J, Xu H, Chen H, Lei A. J Am Chem Soc. 2012; 134:5766. [PubMed: 22428614]
3. Chen YR, Duan WL. J Am Chem Soc. 2013; 135:16754. [PubMed: 24160363]
4. Mi X, Wang C, Huang M, Zhang J, Wu Y, Wu Y. Org lett. 2014; 16:3356. [PubMed: 24921182]
5. Shen YM, Lv PC, Chen W, Liu PG, Zhang MZ, Zhu HL. Eur J Med Chem. 2010; 45:3184. [PubMed: 20304535]
6. Hazra A, Mondal S, Maity A, Naskar S, Saha P, Paira R, Sahu KB, Paira P, Ghosh S, Sinha C. Eur J Med Chem. 2011; 46:2132. [PubMed: 21440339]
7. Gundersen LL, Negussie AH, Rise F, Oestby OB. Arch der Pharm. 2003; 336:191.
8. Chai W, Breitenbucher JG, Kwok A, Li X, Wong V, Carruthers NI, Lovenberg TW, Mazur C, Wilson SJ, Axe FU. Bioorg Med Chem lett. 2003; 13:1767. [PubMed: 12729661]
9. Weide T, Arve L, Prinz H, Waldmann H, Kessler H. Bioorg Med Chem lett. 2006; 16:59. [PubMed: 16236508]
10. Zhao B. Org Biomol Chem. 2012; 10:7108. [PubMed: 22868382]
11. Pandya AN, Agrawal DK. Tetrahedron lett. 2014; 55:1835. [PubMed: 24882889]
12. Tang P, Ritter T. Tetrahedron Lett. 2011; 67:4449.
13. Wang X, Li S-y, Pan Y-m, Wang H-s, Liang H, Chen Z-f, Qin X-h. Org lett. 2013; 16:580. [PubMed: 24359214]
14. Aggarwal T, Kumar S, Dhaked DK, Tiwari RK, Bharatam PV, Verma AK. J Org Chem. 2012; 77:8562. [PubMed: 22950679]

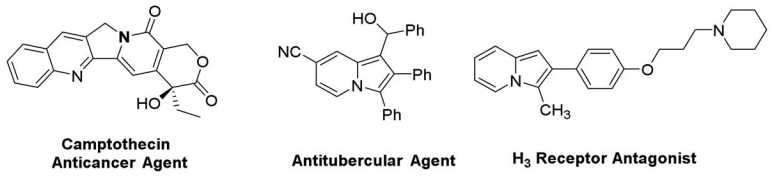

Figure 1.
Selected examples of biologically relevant indolizines derivatives

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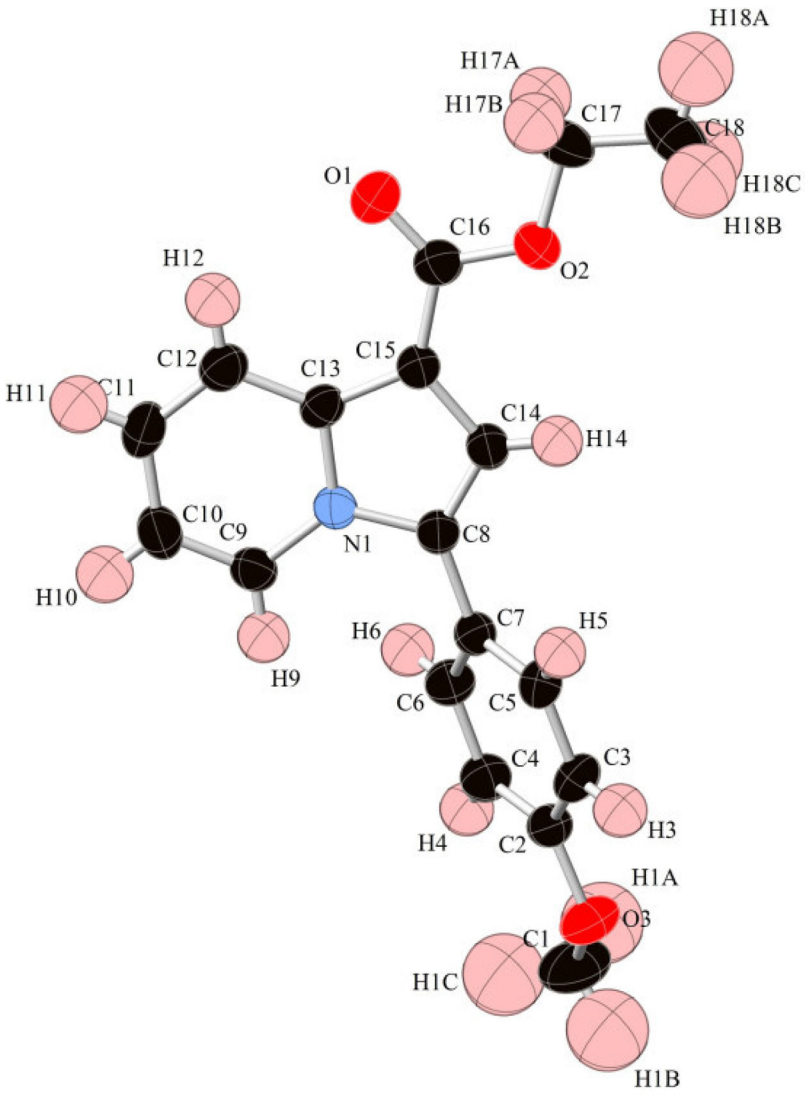
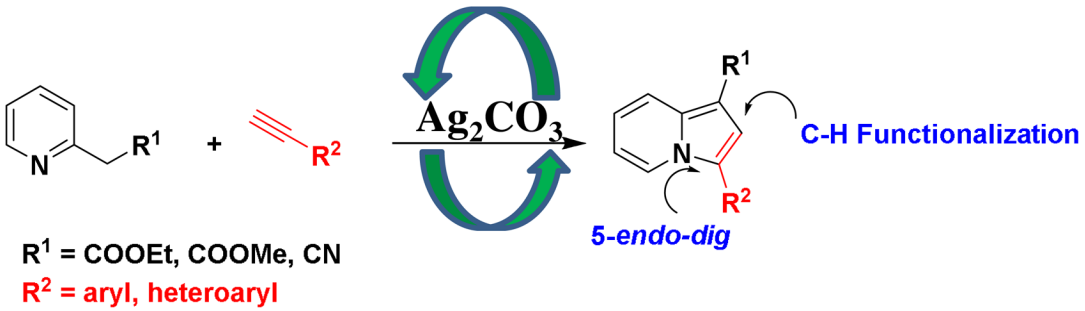


Figure 2.
X-ray crystal structure of indolizine **3b**



Scheme 1.
Silver-Mediated Oxidative C-H Functionalization to synthesize Indolizines

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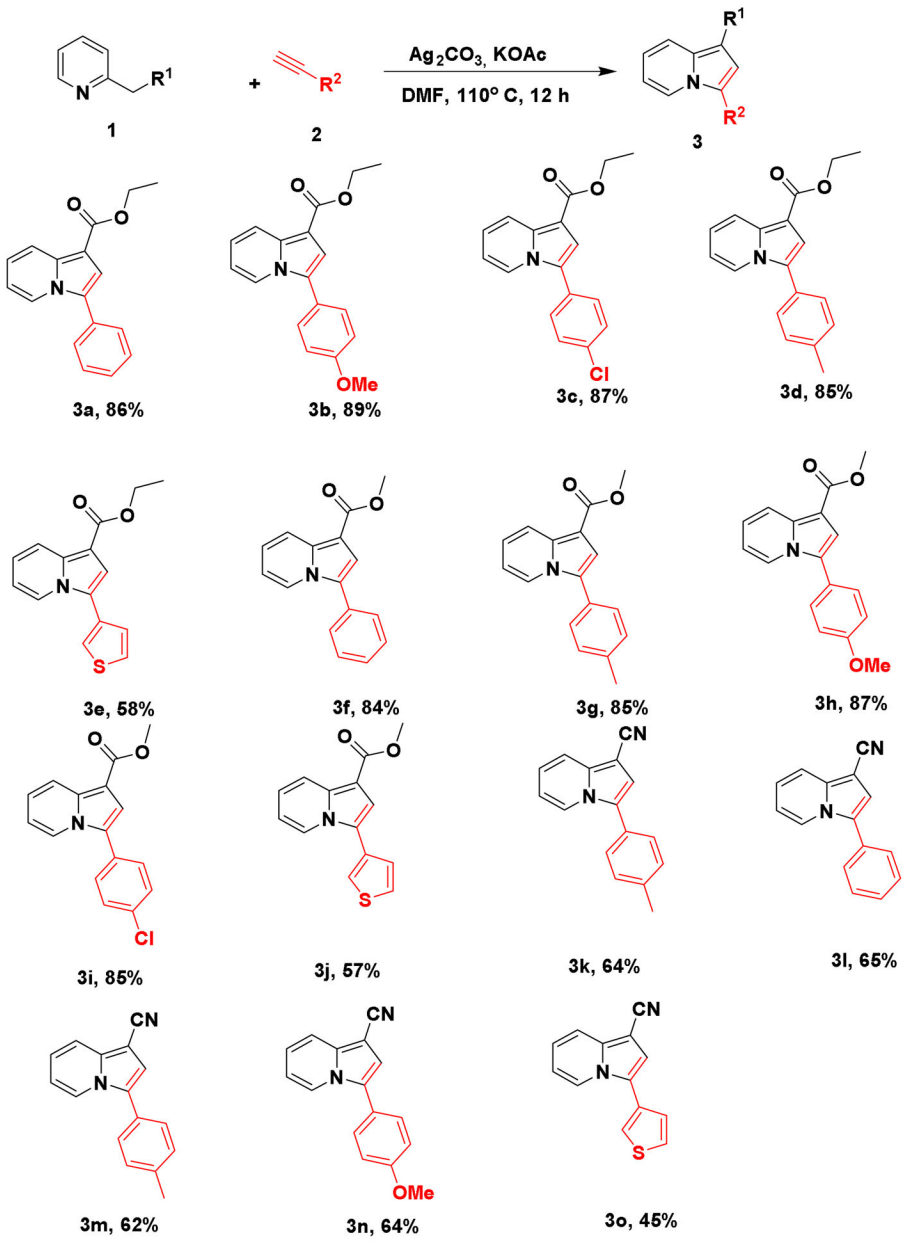
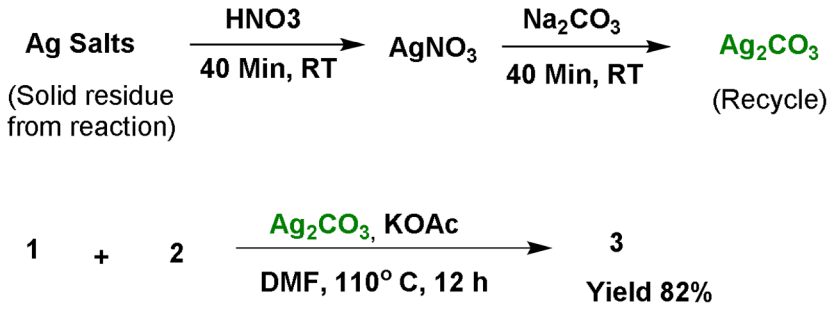


Scheme 2.

Substrate scope for the silver mediated synthesis of indolizines



Scheme 3.
Regeneration Ag_2CO_3 from reaction mixture

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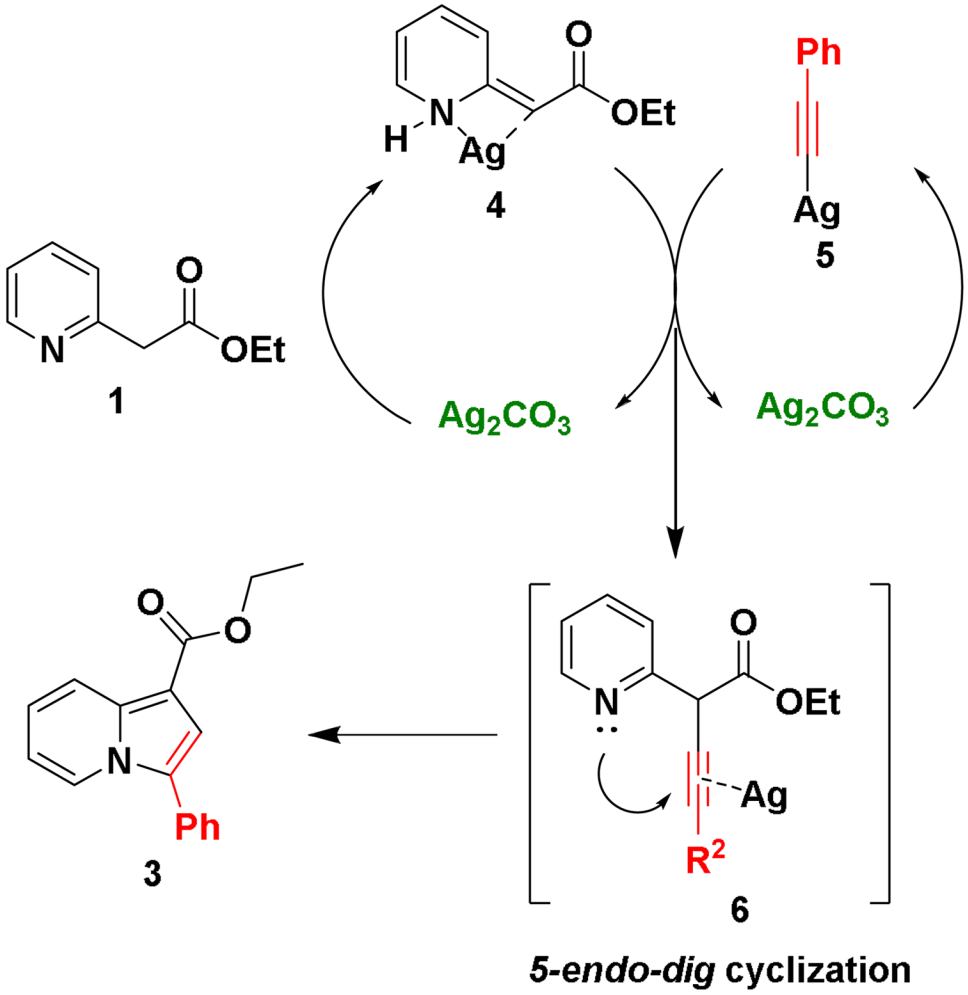

Scheme 4.
Plausible reaction mechanism

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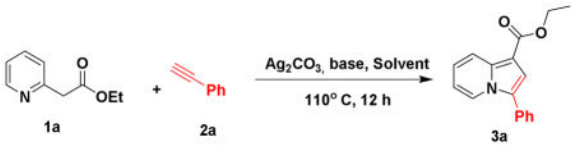
Table 1

Survey of reaction conditions for silver-mediated indolizine formation



entry	base	solvent	1a:2a:Ag_2CO_3	yields (%)[c]
1[a]	KOAc	DMF	1:1:1	0
2	KOAc	DMF	1:1:1	36
3[b]	KOAc	THF	1:1:1.5	57
4	K_2CO_3	DMF	2:1:2	69
5	Cs_2CO_3	DMF	2:1:2	72
6	KOAc	DMF	2:1:2	86

[a] Reaction carried out at room temperature.

[b] Reaction carried out at 80° C.

[c] Isolated Yields.