Synthesis of fused tricyclic indolizines by intramolecular silver-mediated double cyclization of 2-(pyridin-2-yl)acetic acid propargyl esters†

Hai-Yuan Zhao,†a Ying-chun Wang,†b Xiao-Lin Cao,a Qiu-Fang Pang,a Heng-shan Wangb† and Ying-ming Pan*a

The indolizine ring system is prevalent in a wide range of natural and synthetic compounds and possesses different biological and pharmacological activities, such as anti-inflammatory, antimicrobial, antioxidant, and 5-HT3 receptor antagonist activities, to name a few. It is also used as a building block in the syntheses of many bioactive and heterocyclic compounds. Among such compounds, fused polycyclic indolizines are particularly attractive since their analogues have been used as biologically interesting compounds and fluorescent molecules. For example, compound A exhibited dual antifungal and antibacterial activity with MIC values in the range of 500–1000 µg mL⁻¹ against fungal strains A. niger, C. albicans and C. tropicalis, while for bacterial strains MIC values were in the range of 32–500 µg mL⁻¹. Compound B (NNC 45-0095) possesses comparable estrogen agonist activity with IC₅₀ = 9.5 nM when compared to standard drug mestrol (IC₅₀ = 2.5 nM). Polycyclic indolizine C (Seoul-Fluor) is a novel full-color-tunable fluorescent core skeleton developed by Park and co-workers. Based on their structural and biological importance, the development of more direct and economical methods for their preparation is highly desirable.

Intramolecular cascade reactions are one of the most ideal processes in organic synthesis from an atom- and step-economical point of view, which can allow for the straightforward and selective construction of complex cyclic molecular structures in a one-pot manner. In our former study, we developed a silver-mediated sequential oxidative C–H functionalization and 5-endo-dig cyclization of 2-alkylpyridines with terminal and internal alkynes. This reaction provides a straightforward route to access biologically important 1,3-disubstituted and 1,2,3-trisubstituted indolizines. Inspired by this perspective and for the purpose of constructing the fused polycyclic indolizines skeleton, we designed substrate 1, 2-(pyridin-2-yl)acetic acid propargyl esters, and anticipated that in the presence of Ag₂CO₃ and KOAc, compound 1 underwent deprotonation and 5-endo-dig cyclization to produce intermediate 3, which thus yielded intermediate 4 followed by isomerization. Subsequent intramolecular aromatization of 4 would afford fused tricyclic indolizine product 2 as shown in Scheme 1. This silver-mediated double cyclization of 2-(pyridin-2-yl)acetic acid propargyl esters would provide a rapid, straightforward and atom-economic route to access biologically important fused tricyclic indolizines. Although extensive works have generated a significant number of approaches for the synthesis of indolizines, the silver-mediated intramolecular cascade annihilations of 2-(pyridin-2-yl)acetic acid propargylesters

The treatment of a toluene solution of easily accessible 2-(pyridin-2-yl)acetic acid propargyl esters with 2.0 equiv. of Ag₂CO₃ in the presence of potassium acetate (2.0 equiv.) at 100 °C afforded fused tricyclic indolizines in good to excellent yields. The reaction proceeded through a domino silver-mediated double cyclization sequence involving a 5-exo-dig cyclization and 1,3-hydrogen shift followed by an intramolecular cycloisomerization.

Scheme 1  Proposed silver-mediated double cyclization of substrate 1

† Electronic supplementary information (ESI) available: General experimental procedures, and spectral data, NMR spectra, high resolution mass spectra for all compounds, and X-ray crystallographic files (CIF) for 2g. CCDC 1501568. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c7ra00892a

‡ These authors contributed equally to this work.

1 State Key Laboratory for the Chemistry and Molecular Engineering of Medicinal Resources, School of Chemistry and Pharmaceutical Sciences of Guangxi Normal University, Guilin 541004, People’s Republic of China. E-mail: whengshan@163.com; panym2013@hotmail.com
2 College of Chemistry and Chemical Engineering, Jishou University, Jishou 416000, People’s Republic of China.

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have not been reported, and it offers an attractive alternative method for the synthesis of fused polycyclic indolizines (Fig. 1).

We began our studies using the easily accessible prop-2-ynyl 2-(pyridin-2-yl)acetate (1a) as a model substrate for the survey of reaction conditions. As shown in Table 1, the double cyclization of 1a proceeded efficiently in the presence of 2.0 equiv. of Ag2CO3 and 2.0 equiv. of KOAc in toluene at 100 °C to afford furo[3,4-a]indolizin-1(3H)-one (2a) in 90% yield (Table 1, entry 1). Without any metal salts, most of the starting material 1a was recovered (Table 1, entry 2), other metal salts, such as Cu(OAc)2, CdCO3, Pd(OAc)2, Pd[P(C6H5)3]4 or AgNO3, were totally ineffective for this conversion (Table 1, entries 3–7). Whereas AgOTf could also provide the fused tricyclic indolizine product 2a in 66% yield (Table 1, entry 8). The screening of bases revealed that the base played an important role in this transformation, and KOAc provided the best yield of 90% (Table 1, entry 1 vs. entries 10–12). In the absence of base, no reaction occurred (Table 1, entry 9). Solvent screening studies showed that none of the other solvents used, namely, PhCl, DMF, DMSO and CH3CN gave a higher yield than toluene (Table 1, entries 13–16). Additionally, 100 °C was found to be optimal reaction temperature. Although the reaction proceeded much more cleanly when the temperature was lowered to 60 °C, this resulted in a much lower yield of the product (Table 1, entry 17), and increasing the reaction temperature to 140 °C, the yield of 2a dramatically decreased to 10% (Table 1, entry 18). Unfortunately, the mediator and base loading (2.0 equiv.) could not be decreased. Running the reaction at a lower loading of Ag2CO3 (1.0 equiv.) or KOAc (1.0 equiv.) hampered the reaction efficiency (Table 1, entries 19 and 20).

A series of substrates 1 were prepared (see the ESI† for details) to investigate the scope of the double cyclization reaction under the optimized conditions (Table 2). The R1 in the pyridine ring has been substituted with 5-methyl, 6-methyl, 6-methoxy, 5-bromo and 5-trifluoromethyl groups whereas R2 and R3 in the propargyl group included alkyld and aryl moieties. The R4 in the alkyne has been substituted by a phenyl group. As shown in Table 2, all the reactions proceeded smoothly to afford the corresponding fused tricyclic indolizines in good to excellent yields (63–90%). It was found that the electronic properties of the substituent on the pyridine ring had a negligible effect on the yields of the final compounds (2b–2f). While replacing R2 or R3 with an aromatic ring (2m–2r) resulted in somewhat lower yields (63–78%) than an aliphatic moiety (2g–2k, 86–89%). Owing to the steric hindrance of the o-F and o-Cl (Table 2, entry 15), the substrate 1o gave the desired product 2o in a lower yield (63%) compared to the p-Cl-substituted 1m (71%) and p-Br-substituted 1n (75%). When optically active (S)-but-3-yn-2-yl 2-(pyridin-2-yl)acetate 1h was examined as a substrate, to our delight, (S)-3-methylfuro[3,4-a]indolizin-1(3H)-one 2h was formed in 86% yield (Table 2, entry 8). Additionally, substituting R4 with a phenyl group furnished 2s and 2t in reduced yields of 77 and 66% respectively (Table 2, entries 19 and 20). The crystallization of compound 2i from chloroform and ethanol gave a single crystal suitable for X-ray analysis. Fig. 2 illustrates the molecular structure of the fused tricyclic indolizine 2i.12

To further support the proposed reaction pathway, additional control experiments were carried out. It was observed that the presence of 2 equiv. of TEMPO (2,2,6,6-tetramethyl-1-piperidinonyloxy) did not suppress the double cyclization of substrate 1a under optimized conditions, suggesting that a radical mechanism was not likely involved. ESI/MS experiments were performed to gain evidence for the possible intermediates in the proposed mechanism. A mixture of 1a (0.5 mmol), KOAc (1.0 mmol) and Ag2CO3 (1.0 mmol) in toluene (2.0 mL) was reacted at 100 °C for 30 min and 50 µL of the mixture was used for the ESI analysis in CH3CN. The ESI/MS analyses showed a peak at m/z 174.0548, which was identified as intermediate 5a (see the ESI†).

In conclusion, we have developed a rapid, simple and efficient double cyclization reaction for the synthesis of fused tricyclic indolizines from easily available starting materials in

![Fig. 1](https://example.com/fused-polycyclic-indolizines.png)  
**Fig. 1** Examples of fused polycyclic indolizines in pharmaceuticals and fluorescent molecules.
Table 2 Synthesis of fused tricyclic indolizine derivatives

| Entry | Substrate | Product | Yield \(^b\) (%) |
|-------|-----------|---------|-----------------|
| 1     | 1a        | 2a      | 90              |
| 2     | 1b        | 2b      | 88              |
| 3     | 1c        | 2c      | 85              |
| 4     | 1d        | 2d      | 87              |
| 5     | 1e        | 2e      | 89              |
| 6     | 1f        | 2f      | 84              |
| 7     | 1g        | 2g      | 89              |
| 8     | 1h        | 2h      | 86              |
| 9     | 1i        | 2i      | 87              |
| 10    | 1j        | 2j      | 88              |
| 11    | 1k        | 2k      | 89              |

Table 2 (Contd.)

| Entry | Substrate | Product | Yield \(^b\) (%) |
|-------|-----------|---------|-----------------|
| 12    | 1l        | 2l      | 86              |
| 13    | 1m        | 2m      | 71              |
| 14    | 1n        | 2n      | 75              |
| 15    | 1o        | 2o      | 63              |
| 16    | 1p        | 2p      | 78              |
| 17    | 1q        | 2q      | 73              |
| 18    | 1r        | 2r      | 74              |
| 19    | 1s        | 2s      | 77              |
| 20    | 1t        | 2t      | 66              |

\(^a\) Reaction conditions: 1a (0.5 mmol), Ag$_2$CO$_3$ (2 equiv.), KOAc (2 equiv.), toluene (2.0 mL), 100 °C for 6 h. \(^b\) Isolated yield of pure product based on 1a.
good to excellent yields. The salient feature of this method involves a silver-mediated 5-exo-dig cyclization and 1,3-hydrogen shift followed by an intramolecular cyclization in one pot. Molecular biology studies involving derivatives of this scaffold are currently in progress.

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