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

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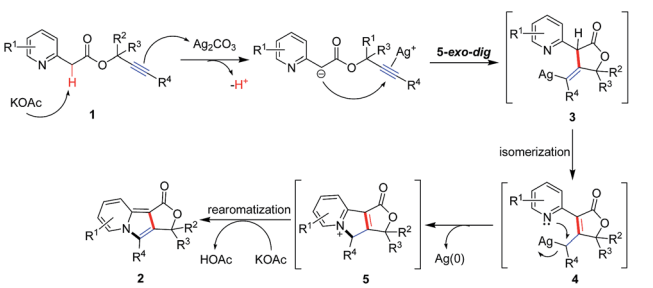
The treatment of a toluene solution of easily accessible 2-(pyridin-2-yl)acetic acid propargyl esters with 2.0 equiv. of Ag_2CO_3 in the presence of potassium acetate (2.0 equiv.) at 100 °C afforded fused tricyclic indolizines in good to excellent yields. The reaction proceeded through a domino silver-mediated double cyclization sequence involving a 5-*exo*-dig cyclization and 1,3-hydrogen shift followed by an intramolecular cycloisomerization.

The indolizine ring system is prevalent in a wide range of natural and synthetic compounds and possesses different biological and pharmacological activities,[1] such as anti-inflammatory,[1e] antimicrobial,[1g] antioxidant,[1h–i] and 5-HT3 receptor antagonist[1j] activities, to name a few. It is also used as a building block in the syntheses of many bioactive and heterocyclic compounds.[2] Among such compounds, fused polycyclic indolizines are particularly attractive since their analogues have been used as biologically interesting compounds[1a] and fluorescent molecules.[3] 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}.[4] Compound **B** (NNC 45-0095) possesses comparable estrogen agonist activity with IC_{50} = 9.5 nM when compared to standard drug moxestrol (IC_{50} = 2.5 nM).[5] Polycyclic indolizine **C** (Seoul-Fluor) is a novel full-color-tunable fluorescent core skeleton developed by Park and co-workers.[6] 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.[7] 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.[8] 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 Ag_2CO_3 and KOAc, compound **1** underwent deprotonation and 5-*exo*-dig cyclization[9] 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,[10] the silver-mediated intramolecular cascade annulations of 2-(pyridin-2-yl)acetic acid propargylesters



Scheme 1 Proposed silver-mediated double cyclization of substrate **1**.

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† 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

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

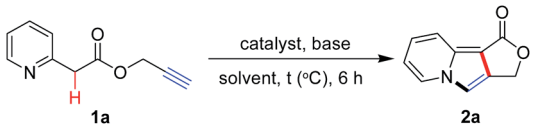
We began our studies using the easily accessible prop-2-ynyl 2-(pyridin-2-yl)acetate (**1a**)[11] as a model substrate for the survey of reaction conditions. As shown in Table 1, the double cyclization of **1a** proceeded efficiently in the presence of 2.0 equiv. of Ag_2CO_3 and 2.0 equiv. of KOAc in toluene at 100 °C to afford furo[3,4-*a*]indolizin-1(3*H*)-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 $Cu(OAc)_2$, $CdCO_3$, $Pd(OAc)_2$, $Pd[P(C_6H_5)_3]_4$ or $AgNO_3$, 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 CH_3CN 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 Ag_2CO_3 (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 R^1 in the pyridine ring has been substituted with 5-methyl, 6-methyl, 6-methoxy, 5-bromo and 5-trifluoromethyl groups whereas R^2 and R^3 in the propargyl group included alkyl and aryl moieties. The R^4 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 R^2 or R^3 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(3*H*)-one **2h** was formed in 86% yield (Table 2, entry 8). Additionally, substituting R^4 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-piperidinyloxy) 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 Ag_2CO_3 (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 CH_3CN. 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

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst (equiv.)	Base (equiv.)	Solvent	*t* (°C)	Yield[b] (%)
1	**Ag_2CO_3** (2)	**KOAc** (2)	**Toluene**	**100**	**90**
2	None	KOAc (2)	Toluene	100	0
3	$Cu(OAc)_2$ (2)	KOAc (2)	Toluene	100	0
4	$CdCO_3$ (2)	KOAc (2)	Toluene	100	0
5	$Pd(OAc)_2$ (2)	KOAc (2)	Toluene	100	0
6	$Pd[P(C_6H_5)_3]_4$ (2)	KOAc (2)	Toluene	100	0
7	$AgNO_3$ (2)	KOAc (2)	Toluene	100	0
8	AgOAc (2)	KOAc (2)	Toluene	100	66
9	Ag_2CO_3 (2)	None	Toluene	100	0
10	Ag_2CO_3 (2)	NaOH (2)	Toluene	100	Trace
11	Ag_2CO_3 (2)	*t*-BuOK (2)	Toluene	100	Trace
12	Ag_2CO_3 (2)	K_2CO_3 (2)	Toluene	100	Trace
13	Ag_2CO_3 (2)	KOAc (2)	PhCl	100	82
14	Ag_2CO_3 (2)	KOAc (2)	DMF	100	75
15	Ag_2CO_3 (2)	KOAc (2)	DMSO	100	28
16	Ag_2CO_3 (2)	KOAc (2)	CH_3CN	100	41
17	Ag_2CO_3 (2)	KOAc (2)	Toluene	60	53
18	Ag_2CO_3 (2)	KOAc (2)	Toluene	140	10
19	Ag_2CO_3 (1)	KOAc (2)	Toluene	100	42
20	Ag_2CO_3 (2)	KOAc (1)	Toluene	100	45

[a] Reactions conditions: **1a** (0.5 mmol), catalyst, base, solvent (2.0 mL), 100 °C (except for entry 17 and entry 18) for 6 h. [b] Isolated yield of pure product based on **1a**. Entry in bold highlights optimized reaction conditions.

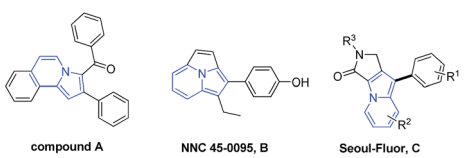
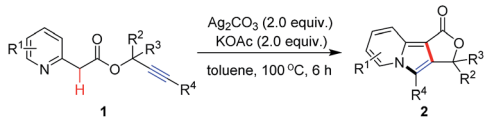


Fig. 1 Examples of fused polycyclic indolizines in pharmaceuticals and fluorescent molecules.

Table 2 Synthesis of fused tricyclic indolizine derivatives[a]



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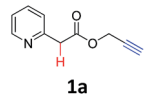
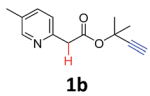
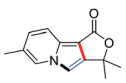
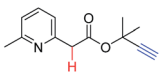
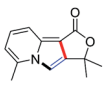
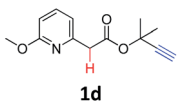
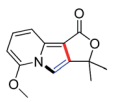
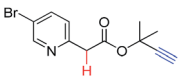
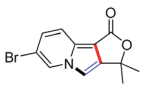
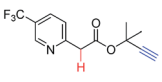
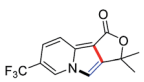
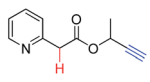
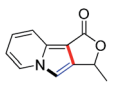
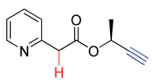
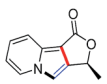
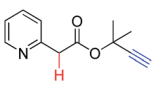
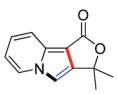
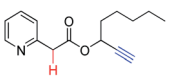
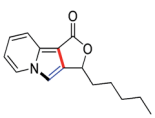
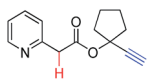
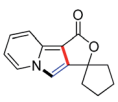
Entry	Substrate	Product	Yield[b] (%)
1	 1a	 2a	90
2	 1b	 2b	88
3	 1c	 2c	85
4	 1d	 2d	87
5	 1e	 2e	89
6	 1f	 2f	84
7	 1g	 2g	89
8	 1h	 2h	86
9	 1i	 2i	87
10	 1j	 2j	88
11	 1k	 2k	89

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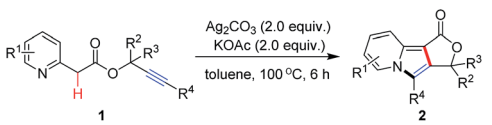

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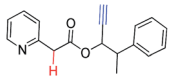
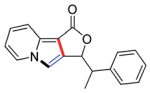
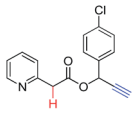
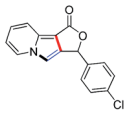
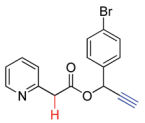
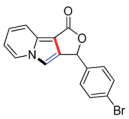
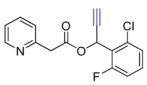
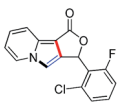
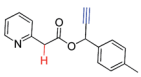
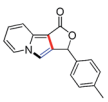
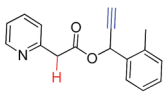
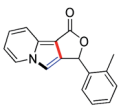
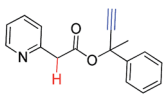
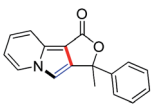
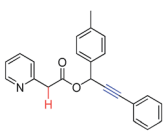
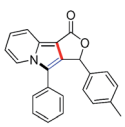
12	 1l	 2l	86
13	 1m	 2m	71
14	 1n	 2n	75
15	 1o	 2o	63
16	 1p	 2p	78
17	 1q	 2q	73
18	 1r	 2r	74
19	 1s	 2s	77
20	1t	2t	66

[a] Reaction conditions: **1a** (0.5 mmol), Ag_2CO_3 (2 equiv.), KOAc (2 equiv.), toluene (2.0 mL), 100 °C for 6 h. [b] Isolated yield of pure product based on **1a**.

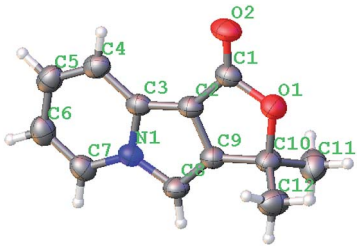


Fig. 2 X-ray crystal structure of fused tricyclic indolizine **2i** (CCDC 1501568).

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 cyclo-isomerization in one pot. Molecular biology studies involving derivatives of this scaffold are currently in progress.

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