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Expeditious synthesis of indolizine derivatives via iodine mediated 5-*endo-dig* cyclization

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Abstract—Iodine-mediated 5-*endo-dig* cyclization of propargylic esters **2** at room temperature proceeded smoothly to give highly functionalized indolizines **3** in excellent yields. A pyridine group was employed as a nucleophilic partner in this facile process for the first time.

Functionalized indolizines (Fig. 1) are common substructures found in biologically important natural products and synthetic pharmaceuticals. Due to the various biological functions associated with this skeleton, it has been frequently employed as a key scaffold in the drug industry.[1] Accordingly, many synthetic methods have been reported in the literature,[2,3] including Gevorgyan's cycloisomerization approach.[3f,4] However, in many cases, expensive and toxic metals, extended reaction times, and/or elevated reaction temperatures are required, providing opportunity for the further development of milder protocols. In continuation of our interest on the facile synthesis of heterocycles using mild and environment-friendly conditions,[5] we found a very convenient route to indolizine core structures facilitated by iodine. Here we wish to communicate our results on the synthesis of highly substituted indolizines via an efficient 5-*endo-dig* iodocyclization[6] of propargylic ester **2**.

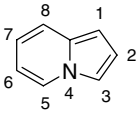
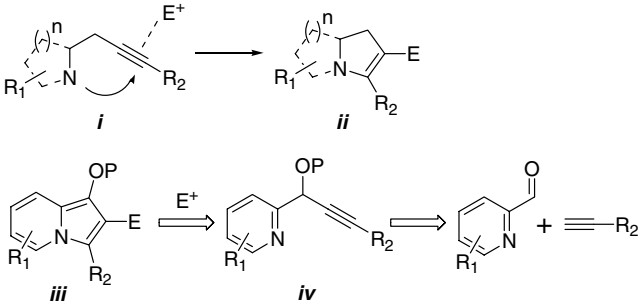


Figure 1. General structure of indolizine.



Scheme 1. Retrosynthetic analysis.

As a viable approach to five-membered, nitrogen-containing rings, 5-*endo-dig* type cyclization is well established.[7,8] Thus, the activation of triple bond in homopropargylic amine (i) by electrophiles is known to induce intramolecular attack by neighboring nitrogen-containing nucleophiles to give (ii) (Scheme 1). Along this line, we envisioned that the indolizine skeleton (iii) could be constructed via a 5-*endo-dig* electrophilic cyclization from an acyclic precursor (iv), which should be readily available from 2-pyridinecarboxaldehyde and terminal alkynes. Notably, the use of the pyridine moiety as a nucleophilic partner of iodocyclizations is unprecedented although it has been employed in the similar transition-metal catalyzed cycloisomerizations.[3c,f]

To validate this idea, propargylic acetate **2** was first prepared by the known procedure.[3c,f,9] Thus, the reaction of 2-pyridinecarboxaldehyde with 1-alkynyllithium

Keywords: Indolizine; Iodine; 5-*endo-dig* Cyclization; Environmently benign.
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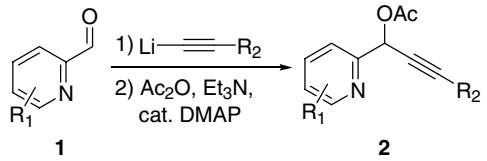
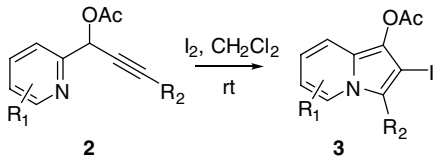


Scheme 2. Preparation of propargylic acetates **2**.



Scheme 3. Iodocyclization of propargylic acetates.

afforded propargylic alcohol which, upon acetylation, was converted to the corresponding ester **2** in excellent yield, setting the stage for the electrophilic cyclization (Scheme 2).

Initial screening of several electrophiles reveals that cyclization is electrophile-dependent. Exposure of acetate **2a** to iodine in methylene chloride at room temperature delivered the cyclized product **3a** in 92% yield (Scheme 3).[10] In contrast, other commonly used electrophiles such as Br_2, NBS, and PhSeCl failed to initiate the similar ring closure under the identical conditions.[11] It is not clear at this point what causes this difference, but we decided to focus on iodine-mediated cyclizations because it is more convenient to handle compared with

Table 1. Preparation of various indolizines via a 5-*endo-dig* iodocyclization

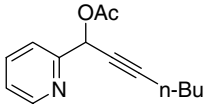
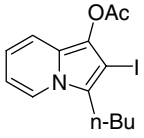
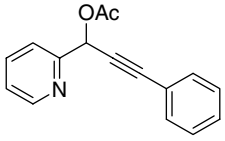
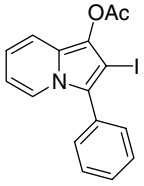
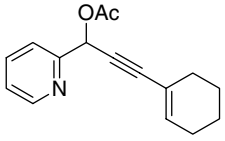
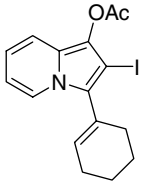
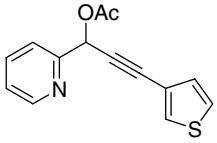
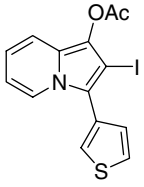
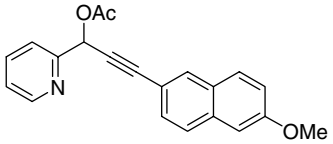
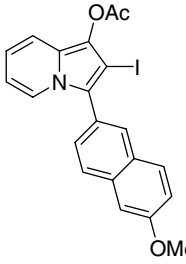
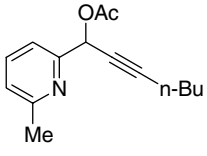
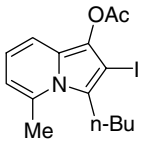
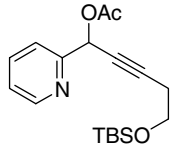
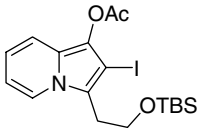
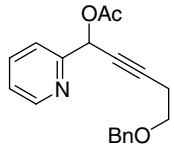
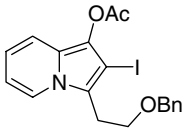
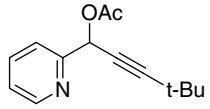
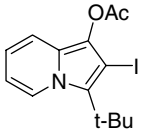
Entry	Substrate **2**		Product **3**		Isolated yield (%)
1		**2a**		**3a**	92
2		**2b**		**3b**	95
3		**2c**		**3c**	90
4		**2d**		**3d**	91
5		**2e**		**3e**	89
6		**2f**		**3f**	95

Table 1 (*continued*)

Entry	Substrate **2**		Product **3**		Isolated yield (%)
7		**2g**		**3g**	100
8		**2h**		**3h**	98
9		**2i**		**3i**	97

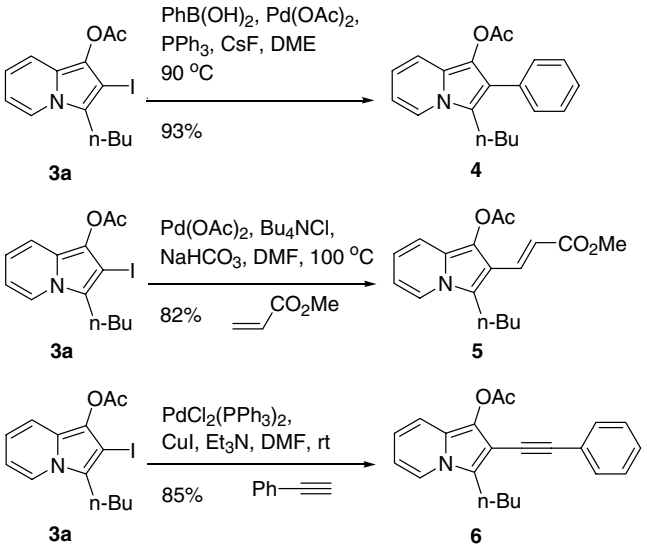
other electrophilic reagents. Therefore, other cyclization substrates were submitted to the identical conditions to demonstrate the generality of this process.

As outlined in Table 1, various indolizine derivatives were obtained in excellent yields, displaying a wide variety of functional tolerance. In all cases, the reaction was facile and completed within a couple of hours.

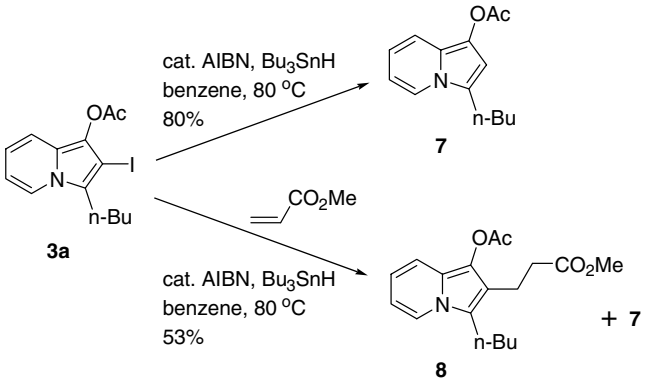
With this promising result in hand, we briefly investigated further functionalization of these indolizines to increase structural complexity. As an iodo group embedded in the cyclized products **3** could be a useful handle for further elaboration, we decided to use this for transition-metal catalyzed coupling reactions.[12] To this end, Suzuki–Miyaura coupling of **3a** was conducted with phenylboronic acid to yield **4** (Scheme 4). Similarly, Heck reaction of **3a** with methyl acrylate under Jeffery conditions[12b] cleanly afforded ester **5** in 82% yield. The phenylacetylene group was installed at C2 of **3a** via Sonogashira coupling to give **6**.

Besides, as an iodo group is a good precursor for radical generation,[13] two attempts have been made in this regard (Scheme 5). While **3a** was cleanly reduced to **7** under typical radical conditions, the reaction of **3a** with methyl acrylate in the presence of AIBN and Bu_3SnH produced ester **8** as a major product (unoptimized).

In summary, we achieved the expeditious synthesis of highly substituted indolizines via a facile and efficient iodocyclization of propargylic ester **2** where pyridine participated as a nucleophile for the first time. The operation is simple and environmentally benign. In addition, an iodo group incorporated at C2 of the cyclized product during the iodocyclization allowed subsequent functionalization possible, as exemplified by transition-metal catalyzed cross-coupling reactions and radical reactions of 2-iodoindolizines, and this group should be useful for other bond-forming reactions as well. Further studies to extend the scope of this reaction for the synthesis of other fused azacycles as well as to apply this process to the synthesis of natural products are underway and will be reported in due course.[14]



Scheme 4. Transition-metal catalyzed cross-coupling reactions of 2-iodoindolizines.



Scheme 5. Radical reactions of 2-iodoindolizines.

Acknowledgments

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Supplementary data

Supplementary data associated with this article (experimental details and characterization data for compounds **2**–**8**) can be found, in the online version, at doi:10.1016/j.tetlet.2007.07.180.

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9. *General procedure for the synthesis of propargylic acetates*: To a stirred solution of the appropriate alkyne (1.2 equiv) in THF was added *n*-BuLi (1.6 M solution in THF, 1.1 equiv) at −78 °C. After 15 min, a solution of 2-pyridinecarboxaldehyde (9.34 mmol) in THF was slowly added to this lithium acetylide solution at −78 °C. After the reaction was complete, the reaction mixture was quenched with saturated aqueous NH_4Cl at −78 °C. The organic layer was washed with brine and the aqueous layer was extracted with ethyl acetate one more time. The combined organic layers were dried over $MgSO_4$, filtered, and evaporated in vacuo. The resulting residue was purified by flash column chromatography (hexanes–ethyl acetate–methylene chloride = 5:1:2) to afford propargylic alcohol. To this alcohol dissolved in CH_2Cl_2 were added triethylamine (1.5 equiv), DMAP (0.1 equiv), and Ac_2O (1.2 equiv) at rt. After being stirred for 2 h at rt, the reaction mixture was diluted with CH_2Cl_2, and washed with aqueous citric acid and $NaHCO_3$, successively. The aqueous layer was extracted with CH_2Cl_2 one more time. The organic layer was dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash column chromatography (hexanes–ethyl acetate–methylene chloride = 7:1:2) to give propargylic acetate **2**. Compound **2a**: R_f 0.14 (hexanes–ethyl acetate = 7:1); ^1H NMR (300 MHz, $CDCl_3$) δ 8.62 (d, 4.8 Hz, 1H), 7.73 (dt, $J = 7.8$, 1.8 Hz, 1H), 7.68 (dd, 7.8, 1.5 Hz, 1H), 7.28–7.24 (m, 1H), 6.47 (t, 2.1 Hz, 1H), 2.27 (dt, $J = 6.9$, 2.1 Hz, 2H), 2.14 (s, 3H), 1.51 (quint, $J = 7.1$ Hz, 2H), 1.40 (sext, $J = 7.1$ Hz, 2H), 0.89 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8, 156.8, 149.8, 137.3, 123.7, 121.9, 89.1, 76.4, 67.4, 30.7, 22.2, 21.3, 18.8, 13.9; IR (thin film) 2923, 2860, 1738, 1220, 1016 cm^{-1}; HRMS (EI) calcd for $[C_{14}H_{17}NO_2]^+$: *m/z* 231.1259; found, 231.1262.
10. *General procedure for the synthesis of indolizines via iodocyclization*: To a stirred solution of propargylic acetate (0.5 mmol) in CH_2Cl_2 (2 mL) was added iodine (1.2 equiv) at room temperature. After 1hr, more iodine (0.5 equiv) was added if necessary by the judgement of tlc monitoring. After being stirred for another 30 min, the reaction mixture was diluted with CH_2Cl_2, and washed with $Na_2S_2O_3$ and $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 one more time. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography (hexanes–ethyl acetate–methylene chloride = 10:1:2) to give indolizine **3**. Compound **3a**: R_f 0.42 (hexanes–ethyl acetate = 10:1); ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (d, $J = 6.9$ Hz, 1H), 7.14 (d, $J = 9.0$ Hz, 1H), 6.57 (t, $J = 7.8$ Hz, 1H), 6.43 (dt, 7.2, 1.2 Hz, 1H), 2.91 (t, $J = 7.5$ Hz, 2H), 2.40 (s, 3H), 1.58 (quint,

$J = 7.2$ Hz, 2H), 1.43 (sext, $J = 7.1$ Hz, 2H), 0.95 (t, $J = 7.2$, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.7, 127. 7, 123.4, 123.0, 121.7, 116.2, 115.8, 110.8, 68.4, 29.8, 26.4, 22.8, 21.1, 14.3; IR (thin film) 2924, 2859, 1730, 1194, 1107 cm^{-1}; HRMS (EI) calcd for $[C_{14}H_{16}INO_2]^+$: *m/z* 357.0226; found, 357.0229.

11. In the case of Br_2, simple addition of Br_2 to alkyne unit of **2a** occurred without inducing ring closure.
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14. For example, indolizine **b** was obtained directly from an acyclic allylic acetate **a** upon treatment with I_2 and Et_3N at room temperature. Full details of this observation as well as other studies will be reported elsewhere.