

A novel approach to 3-acylated indolizine structures via iodine-mediated hydrative cyclization

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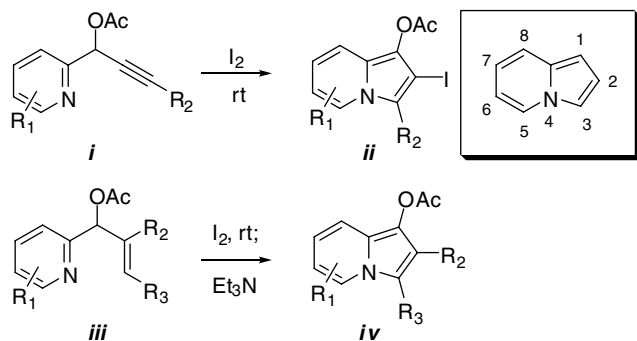
Received 21 September 2007; revised 12 October 2007; accepted 19 October 2007

Available online 24 October 2007

Abstract—We have discovered a new route to 3-acylated indolizine structures via iodine-mediated hydrative cyclization. Reaction mechanism is proposed for this novel transformation, which involves a 5-*exo-dig* iodocyclization, deprotonation, incorporation of another iodo group, deprotonation, and subsequent replacement of the diiodo group by H₂O. Various 3-acylated indolizine derivatives were obtained using this mild procedure in good yields.

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In the course of our research program on the facile synthesis of heterocycles using mild and environment-friendly conditions,¹ we recently reported on the convenient synthesis of indolizines based upon 5-*endo-dig* and 5-*endo-trig* iodocyclizations,^{1b,c,2} respectively (Scheme 1). These two complementary methods allowed us to synthesize a wide range of highly substituted indolizines under very mild conditions. Particularly, a pyridinyl nitrogen was employed as an internal nucleophile in these iodocyclizations for the first time.



Scheme 1.

Keywords: Indolizine; Iodine; 5-*exo-dig* Iodocyclization; Hydrative cyclization.

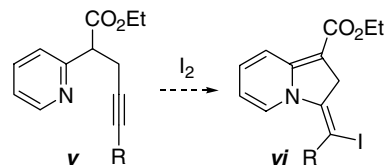
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Driven by these successful results as well as our interest in the indolizine nucleus^{3,4} for medicinal purpose,⁵ we decided to investigate 5-*exo-dig* iodocyclization⁶ of alkynes **v**. Herein we wish to describe a new method for the synthesis of 3-acylated indolizines facilitated by iodine.

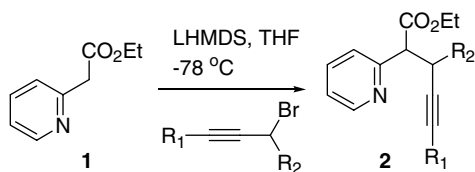
As shown in Scheme 2, we anticipated smooth cyclization of alkyne **v** to proceed in a 5-*exo* fashion to provide vinyl iodide **vi** which was envisioned to be useful for the synthesis of partially reduced indolizines.

To test this idea, cyclization precursors were first prepared by the reaction of ethyl pyridineacetate and appropriate propargylic bromides (Scheme 3). Thus, the treatment of **1** with LHMDS followed by the addition of propargylic bromides afforded **2** in good yields.⁷

To our surprise, when **2a** was initially exposed to 1.5 equiv of iodine in CH₂Cl₂ at rt, about 10% yield of **3a** was isolated (Table 1, entry 1). This compound was unambiguously identified by ¹H NMR, ¹³C NMR, IR, and mass spectra. The expected vinyl iodide was not isolated from the mixture. The reaction seemed to proceed



Scheme 2.



Scheme 3.

Table 1.

Entry	Equiv of iodine	Solvent	Time (h)	Yield (%)
1	1.5	CH ₂ Cl ₂	5	10
2	3	CH ₂ Cl ₂	5	22
3	1.5 ^a	CH ₂ Cl ₂	2	14
4	1.5 ^b	CH ₂ Cl ₂	2	16
5	2.5	CH ₃ CN	5	25
6	2.5	CH ₃ CN–H ₂ O (=10:1)	4	83
7	2.5	MeOH–H ₂ O (=10:1)	4	60

^a NBS was used instead of I₂.^b NIS was used instead of I₂.

cleanly by the judgement of TLC monitoring but the isolated yield of **3a** was in the range of 10–20%. The crude ¹H NMR indicated a complex mixture of products including **3a** which was actually formed upon I₂ treatment.

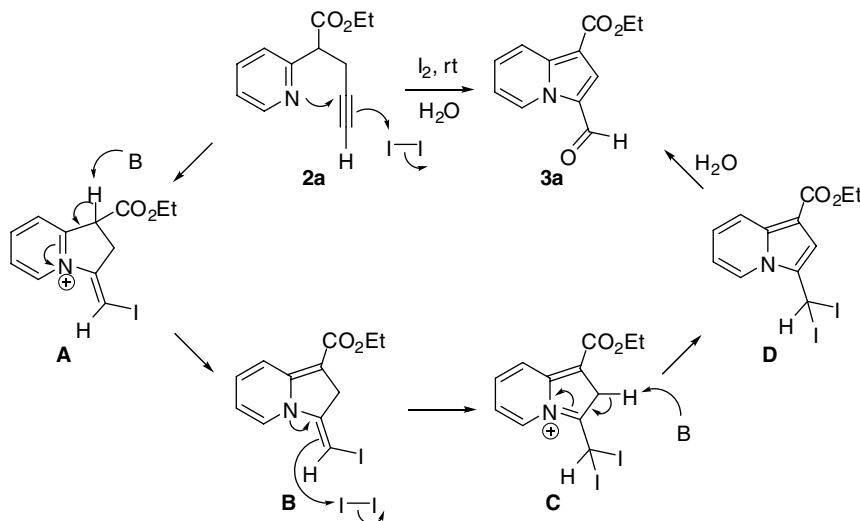
Increasing the amount of iodine did improve the yield albeit still low (entry 2). Interestingly, NBS or NIS also provided **3a** in 14% and 16% yields, respectively (entries 3 and 4). Acetonitrile gave a little better result than dichloromethane (entry 5). Since the newly generated

carbonyl functionality at C3 position of indolizine core was presumed to come from external H₂O source, we expected that the addition of H₂O to the reaction medium would facilitate the reaction. Pleasingly, when we employed CH₃CN–H₂O (=10:1) as the solvent, yield of **3a** increased to 83% (entry 6).⁸ Use of MeOH–H₂O (=10:1) led to inferior result (entry 7).

The formation of unexpected product **3a** can be rationalized by the sequence described in Scheme 4. Thus, initial 5-*exo-dig* type iodocyclization would generate vinyl iodide **A**. Deprotonation would lead to **B**. Attack of another iodine by the enamine unit in **B** would then produce a geminal diiodide **C** which loses proton to furnish 3-formylindolizine **3a** via substitution of the diiodo group of **D** by H₂O. Two equivalent of iodine is needed to complete the reaction, which is in agreement with our experimental result. Overall, iodine was used for hydrative cyclization⁹ and oxidation to gain aromaticity. Notably, only one example has been found in the literature, where iodine is used as a promoter in hydrative cyclizations.^{10,11}

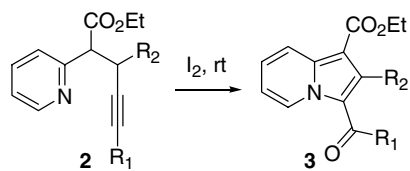
To demonstrate the reaction scope, other cyclization substrates were exposed to the above conditions (Table 2). Gratifyingly, various 3-acylated indolizine derivatives^{12,13} were successfully synthesized under these mild conditions. 4-Methoxyphenyl group attached to an alkyne unit inhibited the desired transformation (entry 5). However, 3-methoxyphenyl or 4-tolyl group did not affect the yield. Indolizine bearing a thiophene-2-carbonyl moiety at C3 position was obtained albeit in modest yield (entry 10). Substitution (R₂) at C2 position of alkynes **2** rather gave the low yield of products (entries 11 and 12).

For comparison, when **4**,¹⁴ **6**, and **8** were subjected to the identical conditions, respectively, pyridinium salts **5**, **7**, and **9** were isolated as major products (Scheme 5).¹⁵ It is not clear at this point what determines the reaction pathway, but relatively acidic proton next to



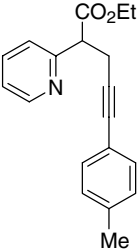
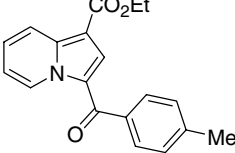
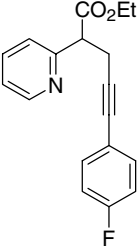
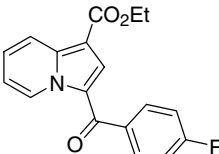
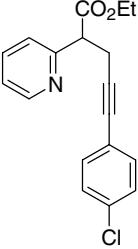
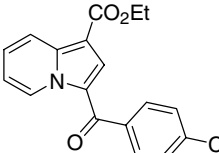
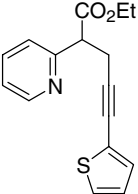
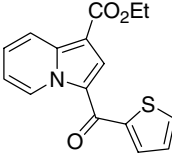
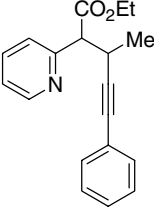
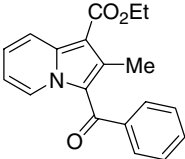
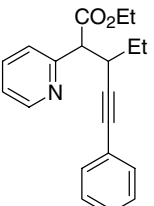
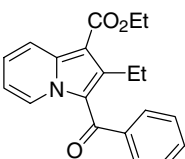
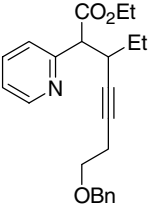
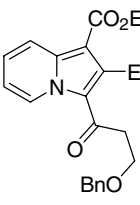
Scheme 4.

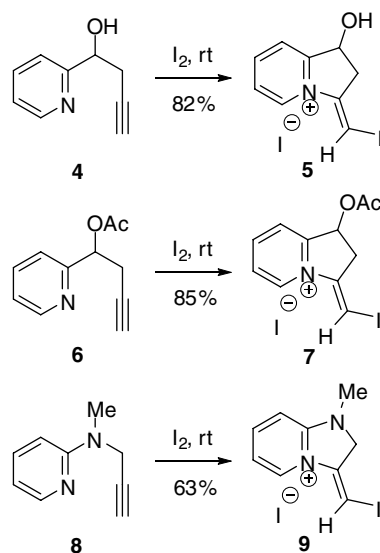
Table 2.



Entry	Substrate 2	Product 3	Isolated yield (%)
1			83
2			60
3			55
4			70
5			25
6			63

Table 2 (continued)

Entry	Substrate 2	Product 3	Isolated yield (%)		
7			3g	52	
8			2h	3h	62
9			2i	3i	77
10			2j	3j	40
11			2k	3k	27
12			2l	3l	35
13			2m	3m	22



Scheme 5.

the carboethoxy group of **3** seemed to be relevant to the above hydrative cyclization.

In conclusion, we have discovered a novel route to 3-acylated indolizines based upon a facile 5-*exo-dig* iodocyclization of alkynes **2** where a pyridinyl nitrogen was again engaged as an internal nucleophile. A series of reaction cascades after the cyclization allowed this hydrative cyclization to be feasible. Given the mildness and eco-friendliness of this procedure, it should be valuable for the synthesis of other structurally related compounds as well. Further studies are ongoing along this line and will be reported in due course.

Acknowledgments

We thank the Center for Biological Modulators and Korea Research Institute of Chemical Technology for generous financial support.

Supplementary data

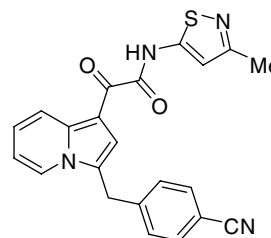
Characterization data and copies of ¹H and ¹³C NMR spectra for compounds **2–9**. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.101.

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- General procedure for the synthesis of alkynes 2*: To a stirred solution of ethyl pyridineacetate (1.5 mmol, 1 equiv) in THF was added LHMDS (1.0 M solution in THF, 1.1 equiv) at -78°C . After 15 min, a solution of the appropriate propargylic bromides (1.1 equiv) in THF was slowly added to this reaction mixture at -78°C . After being stirred for 16 h while slowly warming up to rt, the reaction mixture was quenched with saturated aqueous NH₄Cl at 0°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 MgSO₄, filtered, and evaporated in vacuo. The resulting residue was purified by flash column chromatography (hexanes–ethyl acetate = 10:1) to afford alkynes **2**. 2-Pyridin-2-yl-pent-4-ynoic acid ethyl ester (**2a**): ¹H NMR

- (300 MHz, CDCl₃) δ 8.59 (ddd, $J = 4.8, 1.8, 0.9$ Hz, 1H), 7.67 (dt, $J = 7.8, 2.1$ Hz, 1H), 7.33 (dd, $J = 7.8, 0.9$ Hz, 1H), 7.21 (ddd, $J = 7.5, 4.8, 0.9$ Hz, 1H), 4.24–4.13 (m, 2H), 4.01 (t, $J = 7.5$ Hz, 1H), 3.03 (ddd, $J = 16.8, 7.2, 2.7$ Hz, 1H), 2.86 (ddd, $J = 16.8, 8.1, 2.7$ Hz, 1H), 1.94 (t, $J = 2.6$ Hz, 1H), 1.21 (t, $J = 7.1$ Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 171.6, 157.2, 149.8, 136.9, 123.4, 122.7, 81.6, 70.2, 61.4, 52.9, 21.5, 14.3; IR (thin film) 3294, 2983, 1732, 1586, 1470, 1227 cm⁻¹; HRMS (EI) calcd for [C₁₂H₁₃NO₂]⁺: m/z 203.0949; found, 203.0947.
8. *General procedure for the hydrative cyclization of alkynes 2 to 3-acylated indolizines 3*: To a stirred solution of alkyne **2** (0.2 mmol, 1 equiv) in CH₃CN–H₂O (=10:1) was added iodine (2.5 equiv) at room temperature. After 1 h, more iodine (0.5 equiv) was added if necessary by the judgement of tlc monitoring. After being stirred for another 1 h, the reaction mixture was concentrated under reduced pressure. The residue was diluted with dichloromethane, and washed with Na₂S₂O₃ and NaHCO₃. The aqueous layer was extracted with dichloromethane one more time. The combined organic layers were dried over MgSO₄, filtered, and concentrated in vacuo. The resulting residue was purified by flash column chromatography (hexanes–ethyl acetate–dichloromethane = 15:1:2) to give the 3-acylated indolizine **3**. *3-Formyl-indolizine-1-carboxylic acid ethyl ester (3a)*: ¹H NMR (300 MHz, CDCl₃) δ 9.76 (s, 1H), 9.72 (d, $J = 6.9$ Hz, 1H), 8.37 (d, $J = 9.0$ Hz, 1H), 7.93 (s, 1H), 7.47 (ddd, $J = 8.1, 6.9, 1.1$ Hz, 1H), 7.08 (dt, $J = 6.9, 1.2$ Hz, 1H), 4.40 (q, $J = 7.2$ Hz, 2H), 1.43 (t, $J = 6.9$ Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 178.7, 163.9, 140.3, 129.7, 129.1, 128.5, 124.0, 119.8, 115.8, 107.6, 60.4, 14.7; IR (thin film) 3005, 1702, 1657, 1524, 1371, 1221 cm⁻¹; HRMS (EI) calcd for [C₁₂H₁₁NO₃]⁺: m/z 217.0739; found, 217.0742.
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