Tetrahedron 68 (2012) 8198–8206

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Facile approach to diverse 3-acylated indolizines via a sequential Sonogashira coupling/iodocyclization process

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ARTICLE INFO

Article history:
Received 22 June 2012
Received in revised form 18 July 2012
Accepted 18 July 2012
Available online 31 July 2012

Keywords:
Indolizines
Palladium
Sonogashira coupling
Iodine-mediated cyclization

ABSTRACT

Successful implementation of a sequential Pd-catalyzed Sonogashira cross-coupling/iodine-promoted 5-*exo*-dig cyclization procedure with pyridines bearing a terminal alkyne moiety provided direct and straightforward access to a diverse array of 3-acylated indolizines under mild conditions.

1. Introduction

3-Acylated indolizine[1] is a useful scaffold known for a wide variety of biological activities including anticancer, anticonvulsant, anti-inflammatory, and antimalarial activities as shown in Fig. 1.[2] Despite its versatile use in drug discovery programs, however, not many synthetic methods toward 3-acylindolizines are available.[3] Most approaches to this skeleton rely on 1,3-dipolar cycloaddition reactions of pyridinium ylides with electron-deficient alkenes or alkynes.

Recently, we have reported a new synthetic method of 3-acylated indolizines using iodine-mediated[4] efficient hydrative cyclization.[5] Although the starting materials **2** for this transformation were easily prepared by propargylation of ethyl pyridineacetate **1** with appropriately functionalized propargylic bromides, we envisioned that a more succinct route to diversely propargylated starting materials **5** be feasible via palladium-catalyzed Sonogashira cross-coupling[6] of **4** with (hetero)aryl halides, thereby expanding the substrate scope more rapidly (Scheme 1). Due to a wide functional group tolerance of Sonogashira cross-coupling reactions, furthermore, we anticipated more substrate diversity by installing some aryl groups (Ar) containing functional groups, such as ketone or ester, which are sensitive to basic conditions (i.e., from **1** to **2**) under mild conditions.

As part of our continuing interest on nitrogen-fused heterocycles,[7] herein we describe our effort in this context with particular focus on rapid generation of 3-acylated indolizine library.

2. Results and discussion

We began our study with Sonogashira coupling of terminal acetylene **4** with iodobenzene in the presence of $(Ph_3P)_2PdCl_2$ (5 mol %), CuI (5 mol %), and Et_3N (5 equiv) in THF or CH_3CN as solvent at 45 °C to afford **5a** in 37 and 58% yield, respectively (Table 1, entries 1 and 2). Reactions in THF at room temperature rather improved the yield whereas similar result was observed in CH_3CN at ambient temperature (entries 3 and 4). Copper-free Sonogashira cross-coupling reactions did not produce the desired product with the starting material **4** remained even after 24 h (entries 5 and 6). To our delight, exposure of **4** and iodobenzene (1.3 equiv) to $(Ph_3P)_2PdCl_2$ (5 mol %), CuI (5 mol %) in Et_3N as solvent at 45 °C delivered **5a** in 78% yield (entry 7).

Several aryl iodides were subjected to these optimized conditions to provide the corresponding aryl-substituted alkynes (Table 2). Two other terminal alkynes, **6** and **7**, were coupled as well with several aryl iodides under these identical conditions to produce the internal alkynes. Not only aryl iodides bearing electron withdrawing group but also those with electron donating group participated well in Sonogashira cross-coupling reactions giving rise to the coupling products in good yields. Heterocycles, such as thiophene or pyridine were incorporated under these conditions without any event (entries 9, 10, and 17). As noted in the introduction section, it should be worthwhile to mention that some

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http://dx.doi.org/10.1016/j.tet.2012.07.068

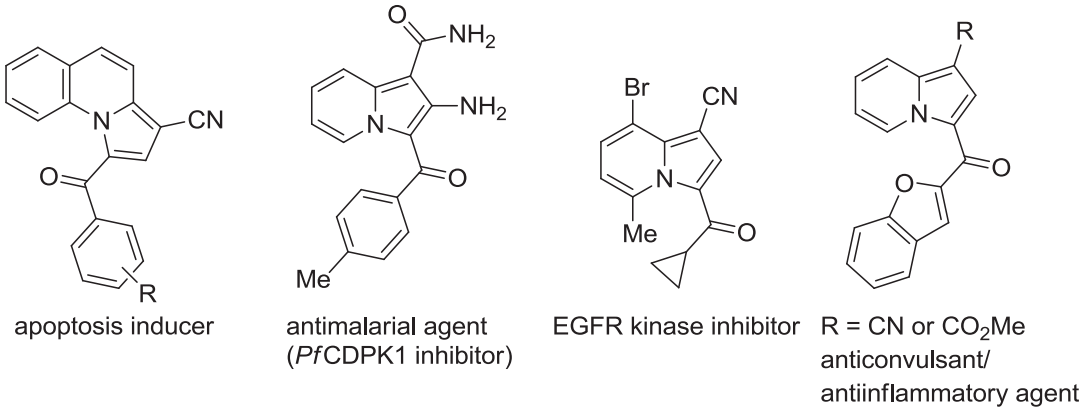
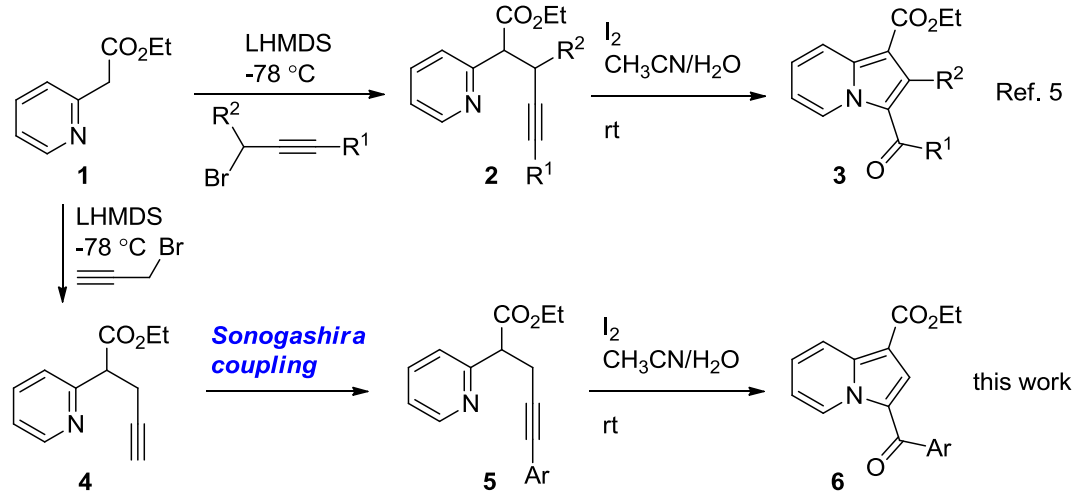
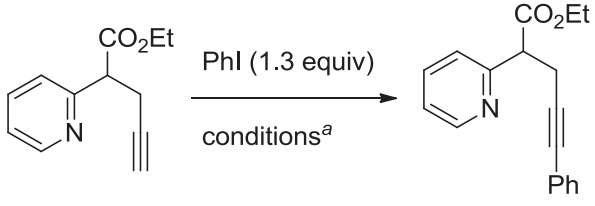


Fig. 1. Some biologically active 3-acylated indolizines.



Scheme 1. Synthetic approaches to 3-acylated indolizines.

Table 1
Sonogashira coupling of **4** with iodobenzene



4 **5a**

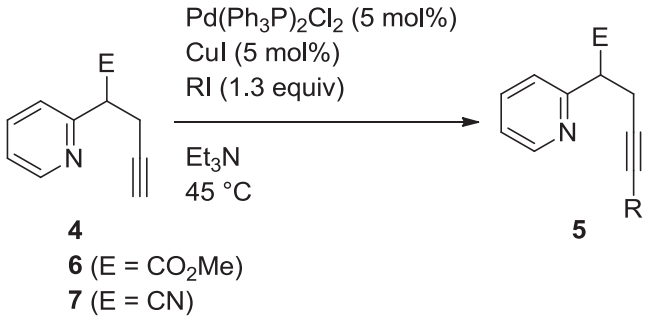
Entry	Pd	Cu	Base	Solvent	Temp (°C)	Yield[d]
1	$Pd(Ph_3P)_2Cl_2$	CuI	Et_3N	THF	45	37
2	$Pd(Ph_3P)_2Cl_2$	CuI	Et_3N	CH_3CN	45	58
3	$Pd(Ph_3P)_2Cl_2$	CuI	Et_3N	THF	25	52
4	$Pd(Ph_3P)_2Cl_2$	CuI	Et_3N	CH_3CN	25	57
5	$Pd(Ph_3P)_4$	[b]	Piperidine	THF	25	[e]
6	$Pd(Ph_3P)_2Cl_2$	[b]	Piperidine	[c]	45	[e]
7	$Pd(Ph_3P)_2Cl_2$	CuI	Et_3N	[c]	45	78

[a] A mixture of **4** (0.098 mmol), iodobenzene (1.3 equiv), Pd catalyst (5 mol %), Cu catalyst (5 mol %), and base (5 equiv) in solvent (1 mL) was stirred at the temperature indicated in the table for 13 h unless otherwise stated.
[b] No Cu catalyst was used.
[c] Base was used as solvent.
[d] Isolated yield (%).
[e] Starting material remained without formation of the desired product **5a** after 24 h.

iodocyclization substrates having functional groups incompatible with basic conditions, which could not be accessible by our previous approach, were readily prepared by this method (for example, entries 2–5).

Having secured a wide variety of internal alkynes in hand, we undertook iodine-mediated hydrative cyclization[8] to furnish the corresponding 3-acylated indolizines.[9] Thus, a number of new 3-acylated indolizines were rapidly synthesized under mild reaction conditions (Table 3). In general, alkynes bearing electron-deficient aryl groups as well as electron-rich aryl groups were converted to their corresponding 3-aroylindolizines in good yields. Indolizines with heterocycle substituents, such as thiophene and pyridine at the R site were readily prepared although yield was modest in case of thiophene-substituted alkyne **5j** (entries 10, 11, and 18). It turned out that position of substituent around the phenyl ring (R) could play a crucial role in this transformation, affecting the chemical yield. For instance, it was revealed that alkynes possessing 4-methoxyphenyl and 3-methoxyphenyl groups exhibited different chemical reactivities (entries 7 and 8). In contrast, similar results were obtained with **5e** and **5f** (entries 5 and 6). Exposure of 2-acetylphenyl-susbstituted alkyne **5o** to these conditions gave a low yield of the desired product presumably due to the interaction of acetyl group with the neighboring activated alkyne[8a,10] by the action of iodine whereas the reaction of 4-acetylphenyl-substituted alkyne **5p** delivered the desired product in good yield (entries 15 and 16). As good yield of the product **8e** was observed

Table 2
Sonogashira cross-coupling of **4**, **6**, and **7** with various (hetero)aryl iodides



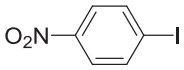
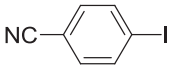
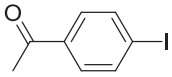
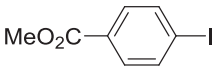
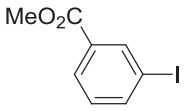
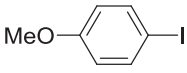
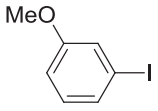
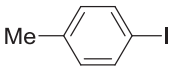
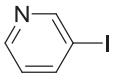
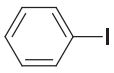
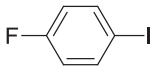
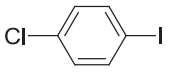
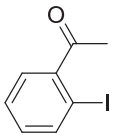
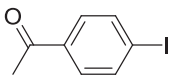
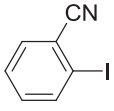
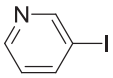
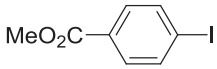
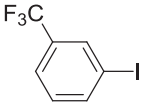
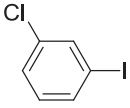
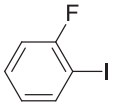
Entry	Starting material	RI	Product	Yield[a]
1	**4**		**5b**	87
2	**4**		**5c**	34
3	**4**		**5d**	93
4	**4**		**5e**	48
5	**4**		**5f**	57
6	**4**		**5g**	67
7	**4**		**5h**	66
8	**4**		**5i**	64
9	**4**		**5j**	70
10	**4**		**5k**	75
11	**6**		**5l**	57
12	**6**		**5m**	63
13	**6**		**5n**	73
14	**6**		**5o**	63
15	**6**		**5p**	87
16	**6**		**5q**	63

Table 2 (*continued*)

Entry	Starting material	RI	Product	Yield[a]
17	**7**		**5r**	83
18	**7**		**5s**	77
19	**7**		**5t**	88
20	**7**		**5u**	74
21	**7**		**5v**	67

[a] Isolated yield (%).

with **5e**, cyclization of **5s** was expected to proceed well but, surprisingly, poor result was observed (entries 5 and 19). Alkynes with 3-trifluoromethylphenyl and 3-chlorophenyl substituents, **5t** and **5u**, were transformed to their corresponding products in good yields (entries 20 and 21).

3. Conclusions

In conclusion, a new synthetic route to a variety of 3-acylated indolizines was developed by employing a sequential Pd-catalyzed Sonogashira cross-coupling/iodine-mediated 5-*exo*-dig cyclization procedure. Particularly, rapid and facile introduction of more diverse (hetero)aroyl moieties including base-sensitive functional groups at C3 position of an indolizine core was realized by employing Sonogashira cross-coupling technique, which was not possible by our previous approach. This was demonstrated in several examples. Biological evaluation of these 3-acylated indolizines is in progress and will be reported in due course.

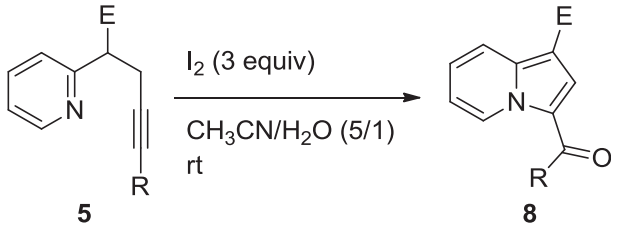
4. Experimental section

4.1. General procedure for the Sonogashira coupling of 4, 6 or 7 with aryl iodide

A mixture of **4**, **6**, or **7** (0.98 mmol),[11] aryl iodide (1.3 equiv), bis(triphenylphosphine)palladium(II) dichloride (5 mol %), and copper(I) iodide (5 mol %) in Et_3N (4 mL) was stirred at 45 °C. After the reaction was complete, the reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane) to give the internal alkyne **5**.

*4.1.1. Ethyl 5-phenyl-2-(pyridin-2-yl)pent-4-ynoate (**5a**).* Yellow gum; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (dd, J=1.0, 5.0 Hz, 1H), 7.67 (td, J=2.0, 8.0 Hz, 1H), 7.38 (d, J=8.0 Hz, 1H), 7.30–7.28 (m, 2H), 7.25–7.23 (m, 3H), 7.20 (ddd, J=1.0, 5.0, 7.5 Hz, 1H) 4.26–4.15 (m, 2H), 4.09 (t, J=8.0 Hz, 1H), 3.20 (dd, J=7.0, 17.0 Hz, 1H), 3.08 (dd, J=8.0, 17.0 Hz, 1H), 1.22 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 157.4, 149.7, 136.7, 131.6, 128.2, 127.9, 123.6, 123.3, 122.6, 87.2, 82.3, 61.3, 53.2, 22.5, 14.3; IR (ATR) 3055, 2980, 1731, 1589,

Table 3
Iodine-mediated cyclization of **5**



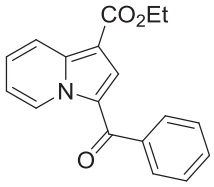
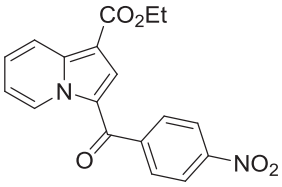
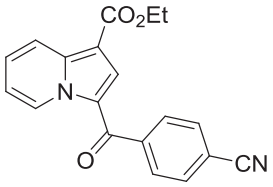
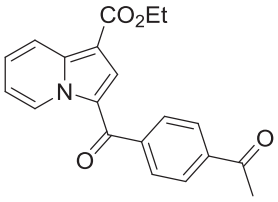
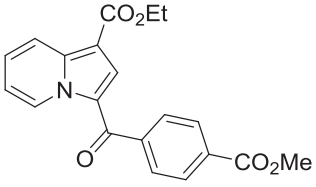
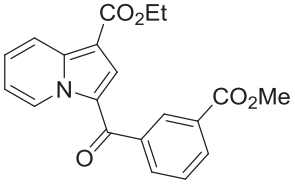
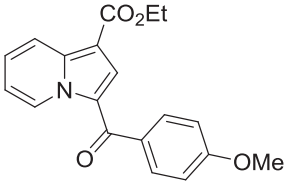
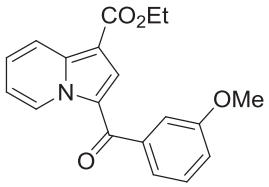
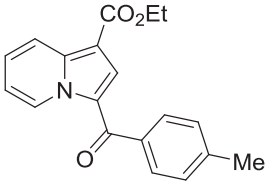
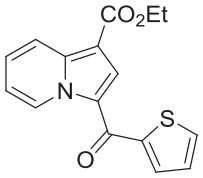
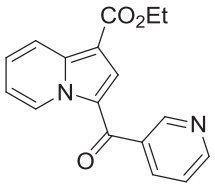
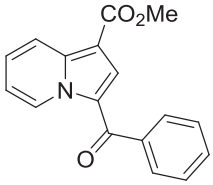
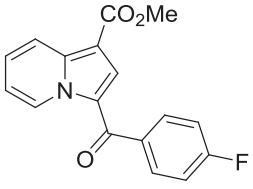
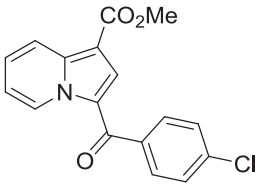
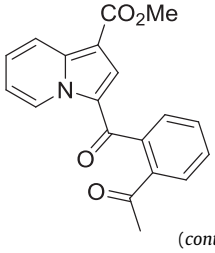
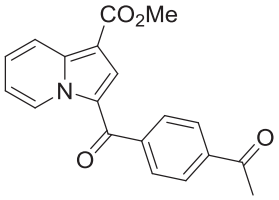
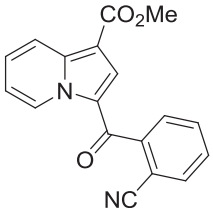
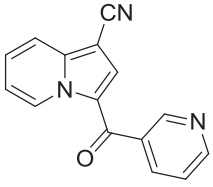
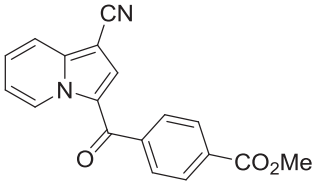
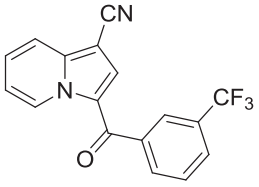
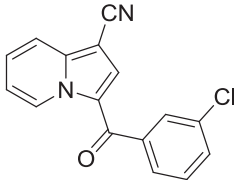
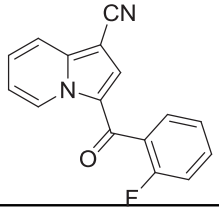
Entry	Starting material	Product		Yield[a]
1	**5a**		**8a**	70
2	**5b**		**8b**	83
3	**5c**		**8c**	58
4	**5d**		**8d**	68
5	**5e**		**8e**	73
6	**5f**		**8f**	65
7	**5g**		**8g**	25

Table 3 (*continued*)

Entry	Starting material	Product		Yield[a]
8	**5h**		**8h**	63
9	**5i**		**8i**	52
10	**5j**		**8j**	40
11	**5k**		**8k**	73
12	**5l**		**8l**	78
13	**5m**		**8m**	51
14	**5n**		**8n**	55
15	**5o**		**8o**	13

(*continued on next page*)

Table 3 (*continued*)

Entry	Starting material	Product	Yield[a]
16	**5p**	 **8p**	58
17	**5q**	 **8q**	66
18	**5r**	 **8r**	66
19	**5s**	 **8s**	35
20	**5t**	 **8t**	53
21	**5u**	 **8u**	58
22	**5v**	 **8v**	38

[a] Isolated yield (%).

1435, 1159 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{18}NO_2$ 280.1338 ($[M+H]^+$), found 280.1330.

*4.1.2. Ethyl 5-(4-nitrophenyl)-2-(pyridin-2-yl)pent-4-ynoate (**5b**).* Yellow gum; ^1H NMR (500 MHz, $CDCl_3$) δ 8.61 (ddd, J=1.0, 2.0, 5.0 Hz, 1H), 8.11 (d, J=9.0 Hz, 2H), 7.70 (td, J=1.5, 8.0 Hz, 1H), 7.41 (d, J=9.0 Hz, 2H), 7.37 (d, J=8.0 Hz, 1H), 7.24 (ddd, J=1.0, 5.0, 7.5 Hz, 1H), 4.26–4.16 (m, 2H), 4.11 (t, J=7.5 Hz, 1H), 3.26 (dd, J=7.5, 17.0 Hz, 1H), 3.14 (dd, J=8.0, 17.0 Hz, 1H), 1.23 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 157.0, 149.8, 146.8, 136.8, 132.3, 130.6, 123.5, 123.2, 122.7, 93.4, 80.8, 61.5, 52.7, 22.5, 14.2; IR (ATR) 3075, 2925, 2853, 1733, 1592, 1512, 1435, 1339, 1209 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{17}N_2O_4$ 325.1188 ($[M+H]^+$), found 325.1198.

*4.1.3. Ethyl 5-(4-cyanophenyl)-2-(pyridin-2-yl)pent-4-ynoate (**5c**).* Yellow gum; ^1H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, J=4.5 Hz, 1H), 7.69 (t, J=7.5 Hz, 1H), 7.53 (d, J=8.0 Hz, 2H), 7.36 (d, J=8.0 Hz, 3H), 7.23 (dd, J=5.5, 7.0 Hz, 1H), 4.26–4.16 (m, 2H), 4.09 (t, J=7.5 Hz, 1H), 3.24 (dd, J=7.5, 17.0 Hz, 1H), 3.12 (dd, J=8.0, 17.0 Hz, 1H), 1.22 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 157.1, 149.8, 136.8, 132.2, 132.0, 128.6, 123.2, 122.7, 118.6, 111.2, 92.4, 81.0, 61.5, 52.8, 22.5, 14.3; IR (ATR) 3052, 2980, 2928, 2226, 1731, 1589, 1435, 1161 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{17}N_2O_2$ 305.1290 ($[M+H]^+$), found 305.1295.

*4.1.4. Ethyl 5-(4-acetylphenyl)-2-(pyridin-2-yl)pent-4-ynoate (**5d**).* Yellow gum; ^1H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, J=5.0 Hz, 1H), 7.84 (d, J=8.5 Hz, 2H), 7.69 (td, J=1.5, 7.5 Hz, 1H), 7.37 (d, J=7.5 Hz, 1H), 7.36 (d, J=8.5 Hz, 2H), 7.22 (ddd, J=1.0, 5.0, 7.5 Hz, 1H), 4.26–4.16 (m, 2H), 4.10 (t, J=7.5 Hz, 1H), 3.24 (dd, J=7.5, 17.0 Hz, 1H), 3.12 (dd, J=8.0, 17.0 Hz, 1H), 2.57 (s, 3H), 1.23 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.4, 171.5, 157.2, 149.8, 136.7, 136.0, 131.8, 128.6, 128.2, 123.2, 122.7, 91.0, 81.7, 61.4, 52.9, 26.7, 22.6, 14.3; IR (ATR) 3053, 2980, 2931, 2223, 1732, 1680, 1600, 1435, 1260, 1162 cm^{-1}; HRMS (FAB) calcd for $C_{20}H_{20}NO_3$ 322.1443 ($[M+H]^+$), found 322.1447.

*4.1.5. Methyl 4-(5-ethoxy-5-oxo-4-(pyridin-2-yl)pent-1-yn-1-yl)benzoate (**5e**).* Pale yellow solid, mp: 72.2–73.3 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, J=5.0 Hz, 1H), 7.92 (d, J=8.0 Hz, 2H), 7.69 (t, J=8.0 Hz, 1H), 7.37 (d, J=8.0 Hz, 1H), 7.34 (d, J=8.0 Hz, 2H), 7.23–7.21 (m, 1H), 4.26–4.16 (m, 2H), 4.10 (t, J=7.5 Hz, 1H), 3.90 (s, 3H), 3.23 (dd, J=7.0, 17.0 Hz, 1H), 3.11 (dd, J=8.0, 17.0 Hz, 1H), 1.23 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 166.7, 157.2, 149.8, 136.7, 131.6, 129.5, 129.2, 128.4, 123.3, 122.7, 90.7, 81.8, 61.4, 53.0, 52.3, 22.6, 14.3; IR (ATR) 3062, 2983, 2920, 2224, 1730, 1710, 1604, 1438, 1279, 1209, 1174 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{20}NO_4$ 338.1392 ($[M+H]^+$), found 338.1392.

*4.1.6. Methyl 3-(5-ethoxy-5-oxo-4-(pyridin-2-yl)pent-1-yn-1-yl) benzoate (**5f**).* Yellow gum; ^1H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, J=4.0 Hz, 1H), 7.96 (s, 1H), 7.91 (d, J=8.0 Hz, 1H), 7.69 (td, J=2.0, 8.0 Hz, 1H), 7.46 (d, J=8.0 Hz, 1H), 7.38 (d, J=8.0 Hz, 1H), 7.32 (t, J=7.5 Hz, 1H), 7.24–7.21 (m, 1H), 4.26–4.16 (m, 2H), 4.10 (t, J=7.5 Hz, 1H), 3.91 (s, 3H), 3.22 (dd, J=7.5, 17.0 Hz, 1H), 3.09 (dd, J=8.0, 17.0 Hz, 1H), 1.23 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 166.6, 157.3, 149.8, 136.8, 135.9, 132.8, 130.4, 128.9, 128.4, 124.1, 123.3, 122.7, 88.3, 81.7, 61.4, 53.1, 52.3, 22.5, 14.3; IR (ATR) 3066, 2982, 2952, 1720, 1589, 1472, 1292, 1227, 1163 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{20}NO_4$ 338.1392 ($[M+H]^+$), found 338.1402.

*4.1.7. Ethyl 5-(4-methoxyphenyl)-2-(pyridin-2-yl)pent-4-ynoate (**5g**).* Yellow gum; ^1H NMR (500 MHz, $CDCl_3$) δ 8.58 (ddd, J=1.0, 1.5, 5.0 Hz, 1H), 7.66 (td, J=2.0, 8.0 Hz, 1H), 7.37 (d, J=8.0 Hz, 1H), 7.22 (d, J=9.0 Hz, 2H), 7.19 (ddd, J=1.0, 5.0, 7.5 Hz, 1H), 6.77 (d, J=9.0 Hz, 2H), 4.25–4.14 (m, 2H), 4.08 (t, J=7.5 Hz, 1H), 3.76 (s, 3H), 3.19 (dd, J=7.0, 17.0 Hz, 1H), 3.06 (dd, J=8.0, 17.0 Hz, 1H), 1.21 (t, J=6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 159.2, 157.4, 149.6, 136.6, 132.9, 123.2, 122.5, 115.7, 113.8, 85.5, 82.1, 61.2, 55.3, 53.2, 22.5, 14.2; IR (ATR) 3051, 2979, 2837, 1731, 1606, 1436, 1170 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{20}NO_3$ 310.1443 ($[M+H]^+$), found 310.1451.

*4.1.8. Ethyl 5-(3-methoxyphenyl)-2-(pyridin-2-yl)pent-4-ynoate (**5h**).* Yellow gum; ^1H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, J=4.5 Hz, 1H), 7.67 (t, J=8.0 Hz, 1H), 7.37 (d, J=8.0 Hz, 1H), 7.21–7.19 (m, 1H),

7.15 (t, J=7.5 Hz, 1H), 6.89 (d, J=7.5 Hz, 1H), 6.82–6.80 (m, 2H), 4.25–4.15 (m, 2H), 4.09 (t, J=7.5 Hz, 1H), 6.02 (s, 3H), 3.20 (dd, J=7.0, 17.0 Hz, 1H), 3.07 (dd, J=8.0, 17.0 Hz, 1H), 1.22 (t, J=7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 159.3, 157.4, 149.7, 136.6, 129.3, 124.6, 124.2, 123.3, 122.6, 116.6, 114.3, 87.0, 82.3, 61.3, 55.3, 53.1, 22.5, 14.3; IR (ATR) 3067, 2979, 2835, 1731, 1572, 1469, 1160 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{20}NO_3$ 310.1443 ([M+H]$^+$), found 310.1450.

*4.1.9. Ethyl 5-(4-methylcyclohexa-1,5-dien-1-yl)-2-(pyridin-2-yl) pent-4-ynoate (**5i**).* Orange gum; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, J=4.5 Hz, 1H), 7.66 (td, J=2.0, 8.0 Hz, 1H), 7.37 (d, J=8.0 Hz, 1H), 7.21–7.18 (m, 3H), 7.05 (d, J=7.5 Hz, 2H), 4.25–4.15 (m, 2H), 4.08 (t, J=7.5 Hz, 1H), 3.19 (dd, J=7.0, 17.0 Hz, 1H), 3.06 (dd, J=8.0, 17.0 Hz, 1H), 2.30 (s, 3H), 1.22 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 157.5, 149.7, 137.9, 136.6, 131.5, 129.0, 123.3, 122.5, 120.5, 86.3, 82.4, 61.3, 53.2, 22.6, 21.5, 14.3; IR (ATR) 3049, 2980, 2921, 1732, 1589, 1435, 1159 cm^{-1}; HRMS (FAB) calcd for $C_{19}H_{20}NO_2$ 294.1494 ([M+H]$^+$), found 294.1484.

*4.1.10. Ethyl 2-(pyridin-2-yl)-5-(thiophen-2-yl)pent-4-ynoate (**5j**).* Yellow gum; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, J=4.0 Hz, 1H), 7.67 (td, J=1.0, 7.5 Hz, 1H), 7.36 (d, J=7.5 Hz, 1H), 7.20 (ddd, J=1.0, 5.0, 7.0 Hz, 1H), 7.15 (dd, J=1.0, 5.0 Hz, 1H), 7.04 (d, J=3.5 Hz, 1H), 6.89 (dd, J=3.5, 5.0 Hz, 1H), 4.25–4.15 (m, 2H), 4.08 (t, J=7.5 Hz, 1H), 3.23 (dd, J=7.5, 17.0 Hz, 1H), 3.09 (dd, J=7.5, 17.0 Hz, 1H), 1.22 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 157.2, 149.7, 136.7, 131.4, 126.8, 126.3, 123.7, 123.3, 122.6, 91.2, 75.5, 61.4, 52.9, 22.8, 14.3; IR (ATR) 3076, 2980, 2933, 1730, 1588, 1434, 1160 cm^{-1}; HRMS (FAB) calcd for $C_{16}H_{16}NO_2S$ 286.0902 ([M+H]$^+$), found 286.0905.

*4.1.11. Ethyl 2-(pyridin-2-yl)-5-(pyridin-3-yl)pent-4-ynoate (**5k**).* Yellow gum; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, J=5.0 Hz, 1H), 8.51 (d, J=1.0 Hz, 1H), 8.47 (dd, J=1.5, 5.0 Hz, 1H), 7.69 (td, J=1.5, 8.0 Hz, 1H), 7.57 (dt, J=2.0, 8.0 Hz, 1H), 7.37 (d, J=8.0 Hz, 1H), 7.22 (ddd, J=1.0, 5.0, 7.5 Hz, 1H), 7.18 (dd, J=5.0, 8.0 Hz, 1H), 4.26–4.16 (m, 2H), 4.10 (t, J=7.5 Hz, 1H), 3.23 (dd, J=7.0, 17.0 Hz, 1H), 3.12 (dd, J=8.0, 17.0 Hz, 1H), 1.23 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.5, 157.2, 152.5, 149.8, 148.3, 138.5, 136.7, 123.3, 123.0, 122.7, 120.7, 90.9, 79.1, 61.4, 52.9, 22.5, 14.3; IR (ATR) 3049, 2980, 2934, 2226, 1731, 1588, 1473, 1161 cm^{-1}; HRMS (FAB) calcd for $C_{17}H_{17}N_2O_2$ 281.1290 ([M+H]$^+$), found 281.1280.

*4.1.12. Methyl 5-phenyl-2-(pyridin-2-yl)pent-4-ynoate (**5l**).* Brown solid, mp: 51.2–53.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, J=4.5 Hz, 1H), 7.67 (t, J=7.5 Hz, 1H), 7.37 (d, J=8.0 Hz, 1H), 7.29–7.27 (m, 2H), 7.24–7.19 (m, 4H), 4.11 (t, J=8.0 Hz, 1H), 3.73 (s, 3H), 3.21 (dd, J=7.0, 17.0 Hz, 1H), 3.09 (dd, J=8.5, 17.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 157.3, 149.8, 136.7, 131.6, 128.2, 127.9, 123.5, 123.4, 122.6, 87.0, 82.4, 53.0, 52.5, 22.5; IR (ATR) 3033, 2954, 2113, 1736, 1589, 1434, 1172 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{16}NO_2$ 266.1181 ([M+H]$^+$), found 266.1181.

*4.1.13. Methyl 5-(4-fluorophenyl)-2-(pyridin-2-yl)pent-4-ynoate (**5m**).* Yellow gum; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, J=4.0 Hz, 1H), 7.69 (td, J=2.0, 8.0 Hz, 1H), 7.36 (d, J=8.0 Hz, 1H), 7.27–7.22 (m, 3H), 6.94 (t, J=8.5 Hz, 2H), 4.10 (t, J=8.0 Hz, 1H), 3.74 (s, 3H), 3.20 (dd, J=7.0, 17.0 Hz, 1H), 3.07 (dd, J=8.0, 17.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 163.3, 161.3, 157.2, 149.8, 136.8, 133.5, 133.4, 123.4, 122.7, 119.6, 115.6, 115.4, 86.7, 81.3, 53.0, 52.6, 22.5; IR (ATR) 3056, 2952, 1736, 1590, 1505, 1434, 1218, 1155 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{15}FNO_2$ 284.1087 ([M+H]$^+$), found 284.1090.

*4.1.14. Methyl 5-(4-chlorophenyl)-2-(pyridin-2-yl)pent-4-ynoate (**5n**).* Yellow solid, mp: 81.8–83.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, J=5.0 Hz, 1H), 7.69 (td, J=2.0, 8.0 Hz, 1H), 7.36 (d, J=8.0 Hz, 1H), 7.24–7.19 (m, 5H), 4.10 (t, J=7.5 Hz, 1H), 3.73 (s, 3H), 3.20 (dd, J=7.0, 17.0 Hz, 1H), 3.08 (dd, J=7.0, 17.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.0, 157.1, 149.8, 136.8, 133.9, 132.9, 128.6, 123.3, 122.7, 122.0, 88.1, 81.3, 52.9, 52.6, 22.5; IR (ATR) 3052, 2947, 2230, 1732, 1588, 1432, 1164, 1084 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{15}ClNO_2$ 300.0791 ([M+H]$^+$), found 300.0791.

*4.1.15. Methyl 5-(2-acetylphenyl)-2-(pyridin-2-yl)pent-4-ynoate (**5o**).* Brown gum; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, J=4.5 Hz, 1H), 7.69 (td, J=2.0, 8.0 Hz, 1H), 7.63 (d, J=7.5 Hz, 1H), 7.39–7.35 (m, 3H), 7.34–7.31 (m, 1H), 7.23 (dd, J=5.0, 7.5 Hz, 1H), 4.14 (t, J=7.5 Hz, 1H), 3.73 (s, 3H), 3.28 (dd, J=7.0, 17.0 Hz, 1H), 3.18 (dd, J=8.0, 17.0 Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.1, 172.0, 157.0, 149.9, 141.2, 136.9, 134.2, 131.2, 128.4, 128.0, 123.5, 122.8, 121.8, 93.4, 81.3, 52.7, 52.6, 30.1, 22.7; IR (ATR) 3061, 2953, 2856, 1735, 1681, 1590, 1434, 1163 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}NO_3$ 308.1287 ([M+H]$^+$), found 308.1289.

*4.1.16. Methyl 5-(4-acetylphenyl)-2-(pyridin-2-yl)pent-4-ynoate (**5p**).* White solid, mp: 71.9–73.0 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, J=4.0 Hz, 1H), 7.84 (d, J=7.0 Hz, 2H), 7.70 (td, J=1.5, 7.5 Hz, 1H), 7.38–7.35 (m, 3H), 7.25–7.22 (m, 1H), 4.12 (t, J=8.0 Hz, 1H), 3.74 (s, 3H), 3.25 (dd, J=7.0, 17.0 Hz, 1H), 3.12 (dd, J=8.0, 17.0 Hz, 1H), 2.57 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.4, 171.9, 157.0, 149.8, 136.8, 136.0, 131.7, 128.5, 128.2, 123.3, 122.7, 90.9, 81.8, 52.8, 52.6, 26.7, 22.5; IR (ATR) 3070, 2998, 2927, 2223, 1734, 1678, 1588, 1436, 1172 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}NO_3$ 308.1287 ([M+H]$^+$), found 308.1297.

*4.1.17. Methyl 5-(2-cyanophenyl)-2-(pyridin-2-yl)pent-4-ynoate (**5q**).* Brown gum; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (d, J=4.0 Hz, 1H), 7.70 (td, J=2.0, 7.5 Hz, 1H), 7.58 (d, J=7.5 Hz, 1H), 7.48 (td, J=1.5, 8.0 Hz, 1H), 7.45 (d, J=7.5 Hz, 1H), 7.40 (d, J=7.5 Hz, 1H), 7.34 (td, J=1.0, 7.5 Hz, 1H), 7.22 (ddd, J=1.0, 5.0, 8.0 Hz, 1H), 4.17 (dd, J=7.0, 8.0 Hz, 1H), 3.75 (s, 3H), 3.33 (dd, J=7.0, 17.0 Hz, 1H), 3.18 (dd, J=8.0, 17.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 156.8, 149.8, 137.0, 132.6, 132.6, 132.5, 132.3, 128.0, 127.4, 123.8, 122.7, 117.7, 115.2, 94.4, 78.7, 52.6, 52.5, 22.55; IR (ATR) 3067, 2952, 2229, 1735, 1590, 1434, 1163 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{15}N_2O_2$ 291.1134 ([M+H]$^+$), found 291.1136.

*4.1.18. 2-(Pyridin-2-yl)-5-(pyridin-3-yl)pent-4-ynenitrile (**5r**).* Yellow gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J=2.8 Hz, 1H), 8.58 (s, 1H), 8.51 (d, J=3.2 Hz, 1H), 7.78 (td, J=1.2, 7.6 Hz, 1H), 7.66 (d, J=8.0 Hz, 1H), 7.56 (d, J=7.6 Hz, 1H), 7.32 (t, J=7.5 Hz, 1H), 7.24 (t, J=8.0 Hz, 1H), 4.29 (t, J=6.4 Hz, 1H), 3.26 (dd, J=6.4, 17.2 Hz, 1H), 3.19 (dd, J=7.2, 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 152.5, 150.2, 148.8, 137.4, 123.6, 122.3, 120.0, 118.9, 87.7, 81.1, 39.3, 24.9; IR (ATR) 3051, 2922, 2246, 1588, 1435 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{12}N_3$ 234.1031 ([M+H]$^+$), found 234.1021.

*4.1.19. Methyl 4-(4-cyano-4-(pyridin-2-yl)but-1-yn-1-yl)benzoate (**5s**).* Yellow solid, mp: 88.4–89.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, J=4.0 Hz, 1H), 7.95 (d, J=8.4 Hz, 2H), 7.78 (td, J=2.0, 8.0 Hz, 1H), 7.56 (d, J=7.6 Hz, 1H), 7.42 (d, J=8.4 Hz, 2H), 7.32 (ddd, J=0.8, 4.8, 7.6 Hz, 1H), 4.29 (t, J=6.4 Hz, 1H), 3.19 (s, 3H), 3.25 (dd, J=6.0, 16.8 Hz, 1H), 3.18 (dd, J=7.6, 16.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 153.5, 150.2, 137.4, 131.8, 129.7, 129.5, 127.5, 123.6, 122.3, 119.0, 87.3, 83.7, 52.4, 39.4, 25.0; IR (ATR) 3064, 2952, 2237, 1705, 1590, 1436, 1280 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{15}N_2O_2$ 291.1134 ([M+H]$^+$), found 291.1120.

*4.1.20. 2-(Pyridin-2-yl)-5-(3-(trifluoromethyl)phenyl)pent-4-ynenitrile (**5t**).* Yellow gum; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.64 (d, J=4.5 Hz, 1H), 7.77 (t, J=7.5 Hz, 1H), 7.60 (s, 1H), 7.56–7.53 (m, 3H),

7.41 (t, *J*=8.0 Hz, 1H), 7.32–7.30 (m, 1H), 4.29 (t, *J*=6.5 Hz, 1H), 3.24 (dd, *J*=6.0, 17.0 Hz, 1H), 3.18 (dd, *J*=7.0, 17.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 150.2, 137.4, 135.0, 131.4, 131.1, 130.8, 130.6, 128.9, 128.59, 128.56, 128.53, 128.5, 125.0, 124.99, 124.96, 124.9, 124.8, 123.8, 123.6, 122.7, 122.3, 119.0, 86.0, 82.9, 39.3, 24.8; IR (ATR) 3055, 2921, 2246, 1589, 1434, 1238, 1165, 1121 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{12}F_3N_2$ 301.0953 ($[M+H]^+$), found 301.0947.

*4.1.21. 5-(3-Chlorophenyl)-2-(pyridin-2-yl)pent-4-ynenitrile (**5u**).* Yellow gum; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, *J*=5.0 Hz, 1H), 7.77 (td, *J*=1.5, 7.5 Hz, 1H), 7.55 (d, *J*=7.5 Hz, 1H), 7.34–7.19 (m, 5H), 4.27 (t, *J*=7.0 Hz, 1H), 3.22 (dd, *J*=6.0, 17.0 Hz, 1H), 3.16 (dd, *J*=7.5, 17.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.5, 150.2, 137.4, 134.2, 131.7, 130.0, 129.6, 128.7, 124.5, 123.6, 122.3, 119.0, 85.5, 83.0, 39.4, 24.8; IR (ATR) 3060, 2919, 2246, 1590, 1472, 1151, 1094 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{12}ClN_2$ 267.0689 ($[M+H]^+$), found 267.0683.

*4.1.22. 5-(2-Fluorophenyl)-2-(pyridin-2-yl)pent-4-ynenitrile (**5v**).* Yellow gum; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.63 (d, *J*=4.0 Hz, 1H), 7.76 (td, *J*=1.5, 7.5 Hz, 1H), 7.57 (d, *J*=8.0 Hz, 1H), 7.36 (td, *J*=1.5, 7.5 Hz, 1H), 7.31–7.25 (m, 2H), 7.07–7.01 (m, 2H), 4.28 (t, *J*=6.5 Hz, 1H), 3.26 (dd, *J*=6.5, 17.0 Hz, 1H), 3.20 (dd, *J*=7.0, 17.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0, 162.0, 153.5, 150.1, 137.3, 133.74, 133.73, 130.13, 130.06, 123.98, 123.95, 123.5, 122.5, 119.0, 115.6, 115.4, 111.4, 111.3, 89.43, 89.40, 77.8, 39.3, 25.1; IR (ATR) 3060, 2923, 2245, 1588, 1491, 1215, 1104 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{12}FN_2$ 251.0985 ($[M+H]^+$), found 251.0982.

4.2. General procedure for iodine-mediated cyclization

To a stirred solution of alkyne **5** (0.14 mmol, 1 equiv) in CH_3CN/H_2O (=5:1) was added iodine (3 equiv) at room temperature. After the reaction was complete, the reaction mixture was concentrated under reduced pressure. The residue was diluted with dichloromethane, and washed with aqueous $Na_2S_2O_3$ and aqueous $NaHCO_3$. The aqueous layer was extracted with dichloromethane one more time. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The resulting residue was purified by silica gel column chromatography (hexane/ethyl acetate/dichloromethane) to afford the 3-acylated indolizine **8**.

*4.2.1. Ethyl 3-benzoylindolizine-1-carboxylate (**8a**).* Pale brown solid, mp: 80.7–83.1 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.98 (d, *J*=7.0 Hz, 1H), 8.40 (d, *J*=9.0 Hz, 1H), 7.86–7.78 (m, 3H), 7.62–7.55 (m, 1H), 7.55–7.49 (m, 2H), 7.46 (dd, *J*=7.5, 8.5 Hz, 1H), 7.10 (td, *J*=1.0, 7.0 Hz, 1H), 4.38 (q, *J*=7.0 Hz, 2H), 1.40 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.7, 164.2, 140.1, 131.6, 129.4, 129.2, 129.1, 128.5, 127.8, 122.7, 119.7, 115.4, 106.4, 60.3, 14.7; IR (ATR) 3061, 2979, 1689, 1632, 1611, 1477, 1209 cm^{-1}; HRMS (FAB) calcd for $C_{18}H_{16}NO_3$ 294.1130 ($[M+H]^+$), found 294.1135.

*4.2.2. Ethyl 3-(4-nitrobenzoyl)indolizine-1-carboxylate (**8b**).* Yellow solid, mp: 139.2–140.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (d, *J*=7.0 Hz, 1H), 8.44 (d, *J*=9.0 Hz, 1H), 8.38 (d, *J*=8.5 Hz, 2H), 7.96 (d, *J*=8.5 Hz, 2H), 7.74 (s, 1H), 7.54 (ddd, *J*=1.0, 7.0, 9.0 Hz, 1H), 7.17 (td, *J*=1.0, 7.0 Hz, 1H), 4.39 (q, *J*=7.0 Hz, 2H), 1.40 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.0, 163.8, 149.5, 145.5, 140.5, 129.9, 129.5, 129.3, 128.7, 123.8, 122.0, 119.8, 116.1, 107.4, 60.5, 14.7; IR (ATR) 3111, 2977, 1705, 1616, 1598, 1478, 1202 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{15}N_2O_5$ 339.0981 ($[M+H]^+$), found 339.0974.

*4.2.3. Ethyl 3-(4-cyanobenzoyl)indolizine-1-carboxylate (**8c**).* Pale yellow solid, mp: 135.7–136.4 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.98 (d, *J*=7.0 Hz, 1H), 8.43 (d, *J*=9.0 Hz, 1H), 7.90 (d, *J*=8.5 Hz, 2H), 7.83 (d, *J*=8.0 Hz, 2H), 7.74 (s, 1H), 7.52 (t, *J*=8.0 Hz, 1H), 7.16 (td, *J*=1.0, 6.5 Hz, 1H), 4.39 (q, *J*=7.0 Hz, 2H), 1.41 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.4, 163.9, 143.8, 140.5, 132.5, 129.49, 129.46, 129.3, 128.6, 122.0, 119.9, 118.3, 116.0, 115.0, 107.3, 60.5, 14.7; IR (ATR) 3120, 2974, 2229, 1680, 1614, 1513, 1484, 1212 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{15}N_2O_3$ 319.1083 ($[M+H]^+$), found 319.1075.

*4.2.4. Ethyl 3-(4-acetylbenzoyl)indolizine-1-carboxylate (**8d**).* Yellow solid, mp: 138.1–140.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.98 (d, *J*=7.0 Hz, 1H), 8.41 (d, *J*=9.0 Hz, 1H), 8.10 (d, *J*=8.0 Hz, 2H), 7.89 (d, *J*=8.0 Hz, 2H), 7.77 (s, 1H), 7.49 (t, *J*=7.5 Hz, 1H), 7.13 (t, *J*=7.0 Hz, 1H), 4.38 (q, *J*=7.0 Hz, 2H), 2.69 (s, 3H), 1.40 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 184.5, 163.9, 143.9, 140.2, 139.1, 129.4, 129.22, 129.15, 128.4, 128.3, 122.3, 119.7, 115.7, 106.9, 60.3, 27.0, 14.6; IR (ATR) 3120, 2995, 1681, 1603, 1513, 1480, 1271 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{18}NO_4$ 336.1236 ($[M+H]^+$), found 336.1231.

*4.2.5. Ethyl 3-(4-(methoxycarbonyl)benzoyl)indolizine-1-carboxylate (**8e**).* Brown solid, mp: 118.7–120.3 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (d, *J*=7.0 Hz, 1H), 8.42 (d, *J*=9.0 Hz, 1H), 8.19 (d, *J*=8.0 Hz, 2H), 7.86 (d, *J*=8.0 Hz, 2H), 7.77 (s, 1H), 7.50 (t, *J*=8.0 Hz, 1H), 7.14 (t, *J*=7.0 Hz, 1H), 4.38 (q, *J*=7.0 Hz, 2H), 3.98 (s, 3H), 1.33 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.6, 166.6, 164.0, 143.9, 140.3, 132.6, 129.8, 129.4, 129.3, 128.9, 128.3, 122.4, 119.7, 115.8, 106.9, 60.4, 52.6, 14.7; IR (ATR) 3000, 2926, 1721, 1700, 1603, 1436, 1274, 1217 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{18}NO_5$ 352.1185 ($[M+H]^+$), found 352.1184.

*4.2.6. Ethyl 3-(3-(methoxycarbonyl)benzoyl)indolizine-1-carboxylate (**8f**).* White solid, mp: 145.0–145.8 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (d, *J*=7.0 Hz, 1H), 8.46 (s, 1H), 8.41 (d, *J*=9.0 Hz, 1H), 8.25 (d, *J*=7.5 Hz, 1H), 7.99 (d, *J*=7.5 Hz, 1H), 7.77 (s, 1H), 7.61 (t, *J*=7.5 Hz, 1H), 7.48 (ddd, *J*=1.0, 7.0, 9.0 Hz, 1H), 7.12 (td, *J*=1.0, 7.0 Hz, 1H), 4.38 (q, *J*=7.0 Hz, 2H), 3.96 (s, 3H), 1.40 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.5, 166.5, 164.0, 140.4, 140.2, 133.1, 132.4, 130.0, 129.4, 129.2, 128.7, 128.1, 122.4, 119.7, 115.6, 106.8, 60.3, 52.5, 14.7; IR (ATR) 3128, 2981, 1731, 1709, 1614, 1484, 1288, 1206 cm^{-1}; HRMS (ESI) calcd for $C_{20}H_{18}NO_5$ 352.1185 ($[M+H]^+$), found 352.1181.

*4.2.7. Ethyl 3-(4-methoxybenzoyl)indolizine-1-carboxylate (**8g**).* Pale yellow solid, mp: 106.9–108.5 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.95 (d, *J*=7.0 Hz, 1H), 8.39 (d, *J*=9.0 Hz, 1H), 7.83 (s, 1H), 7.74 (d, *J*=8.0 Hz, 2H), 7.44 (t, *J*=7.5 Hz, 1H), 7.32 (d, *J*=8.0 Hz, 2H), 7.08 (t, *J*=8.5 Hz, 1H), 4.38 (q, *J*=7.0 Hz, 2H), 2.49 (s, 3H), 1.40 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.6, 164.3, 142.2, 139.9, 137.3, 129.3, 129.2, 128.9, 127.6, 122.8, 119.6, 115.3, 106.2, 60.2, 21.7, 14.7; IR (ATR) 3114, 2978, 1682, 1603, 1518, 1482, 1203 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}NO_4$ 324.1236 ($[M+H]^+$), found 324.1231.

*4.2.8. Ethyl 3-(3-methoxybenzoyl)indolizine-1-carboxylate (**8h**).* White solid, mp: 125.0–125.9 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (d, *J*=7.0 Hz, 1H), 8.40 (d, *J*=9.0 Hz, 1H), 7.85 (s, 1H), 7.50–7.36 (m, 3H), 7.34 (s, 1H), 7.16–7.06 (m, 2H), 4.38 (q, *J*=7.0 Hz, 2H), 3.88 (s, 3H), 1.40 (s, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.4, 164.2, 159.7, 141.4, 140.1, 129.5, 129.4, 129.2, 127.8, 122.6, 121.7, 119.7, 117.8, 115.4, 113.8, 106.5, 60.2, 55.6, 14.7; IR (ATR) 3122, 2920, 1693, 1606, 1577, 1425, 1217 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}NO_4$ 324.1236 ($[M+H]^+$), found 324.1232.

*4.2.9. Ethyl 3-(4-methylbenzoyl)indolizine-1-carboxylate (**8i**).* Green solid, mp: 104.6–106.7 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.95 (d, *J*=7.0 Hz, 1H), 8.39 (d, *J*=9.0 Hz, 1H), 7.83 (s, 1H), 7.74 (d, *J*=8.0 Hz, 2H), 7.44 (t, *J*=7.5 Hz, 1H), 7.32 (d, *J*=8.0 Hz, 2H), 7.08 (t, *J*=7.0 Hz, 1H), 4.38 (q, *J*=7.0 Hz, 2H), 2.46 (s, 3H), 1.40 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.6, 164.3, 142.2, 139.9, 137.3,

129.3, 129.2, 128.9, 127.6, 122.8, 119.6, 115.3, 106.2, 60.2, 21.7, 14.7; IR (ATR) 3124, 2980, 1633, 1604, 1518, 1481, 1202 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{18}NO_3$ 308.1287 ($[M+H]^+$), found308.1281.

*4.2.10. Ethyl 3-(thiophene-2-carbonyl)indolizine-1-carboxylate (**8j**).* Yellow solid, mp: 100.2–102.6 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.86 (d, J=7.0 Hz, 1H), 8.41 (d, J=9.0 Hz, 1H), 8.16 (s, 1H), 7.84 (dd, J=1.0, 3.5 Hz, 1H), 7.69 (d, J=4.5 Hz, 1H), 7.45 (t, J=8.0 Hz, 1H), 7.22 (dd, J=3.5, 5.0 Hz, 1H), 7.08 (t, J=7.0 Hz, 1H), 4.42 (q, J=7.0 Hz, 2H), 1.44 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.6, 164.2, 144.4, 140.0, 132.21, 132.16, 129.2, 127.9, 127.7, 127.4, 122.3, 119.7, 115.3, 106.5, 60.3, 14.7; IR (ATR) 3133, 2975, 1692, 1684, 1577, 1413, 1208 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{14}NO_3S$ 300.0694 ($[M+H]^+$), found 300.0690.

*4.2.11. Ethyl 3-nicotinoylindolizine-1-carboxylate (**8k**).* Brown solid, mp: 106.2–107.3 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.99 (d, J=7.0 Hz, 1H), 9.05 (d, J=1.5 Hz, 1H), 8.82 (dd, J=1.5, 5.0 Hz, 1H), 8.44 (d, J=9.0 Hz, 1H), 8.12 (dt, J=2.0, 8.0 Hz, 1H), 7.82 (s, 1H), 7.56–7.43 (m, 2H), 7.14 (td, J=1.5, 7.0 Hz, 1H), 4.39 (q, J=7.0 Hz, 2H), 1.40 (t, J=7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.1, 163.9, 152.2, 149.9, 140.4, 136.4, 135.7, 129.4, 129.2, 128.4, 123.6, 122.3, 119.8, 115.9, 107.1, 60.4, 14.7; IR (ATR) 3155, 2983, 1695, 1610, 1514, 1477, 1211 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{15}N_2O_3$ 295.1083 ($[M+H]^+$), found 295.1076.

*4.2.12. Methyl 3-benzoylindolizine-1-carboxylate (**8l**).* Brown solid, mp: 152.5–153.8 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.98 (d, J=7.0 Hz, 1H), 8.41 (d, J=9.0 Hz, 1H), 7.82 (s, 1H), 7.81 (d, J=7.0 Hz, 2H), 7.58 (t, J=7.5 Hz, 1H), 7.52 (t, J=7.5 Hz, 2H), 7.47 (t, J=7.5 Hz, 1H), 7.11 (t, J=7.0 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 185.8, 164.6, 140.0, 131.6, 129.4, 129.2, 129.1, 128.5, 127.9, 122.7, 119.6, 115.5, 106.0, 51.4; IR (ATR) 3033, 2924, 1691, 1619, 1516, 1451, 1199 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{14}NO_3$ 280.0974 ($[M+H]^+$), found 280.0967.

*4.2.13. Methyl 3-(4-fluorobenzoyl)indolizine-1-carboxylate (**8m**).* Yellow solid, mp: 168.9–170.0 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.93 (d, J=7.0 Hz, 1H), 8.40 (d, J=9.0 Hz, 1H), 7.85 (dd, J=5.0, 9.0 Hz, 2H), 7.79 (s, 1H), 7.47 (t, J=8.0 Hz, 1H), 7.20 (t, J=8.5 Hz, 2H), 7.11 (t, J=7.0 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.2, 166.0, 164.5, 163.9, 140.1, 136.2, 136.1, 131.5, 131.4, 129.3, 128.9, 128.0, 122.5, 119.6, 115.7, 115.57, 115.55, 106.1, 51.5; IR (ATR) 3062, 2951, 1689, 1606, 1510, 1455, 1342, 1199 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{13}FNO_3$ 298.0879 ($[M+H]^+$), found 298.0876.

*4.2.14. Methyl 3-(4-chlorobenzoyl)indolizine-1-carboxylate (**8n**).* White solid, mp: 155.7–156.2 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.94 (d, J=7.0 Hz, 1H), 8.41 (d, J=9.0 Hz, 1H), 7.78 (d, J=4.5 Hz, 2H), 7.76 (s, 1H), 7.52–7.45 (m, 3H), 7.11 (t, J=3.5 Hz, 1H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 184.2, 164.4, 140.2, 138.3, 138.0, 130.5, 129.3, 129.0, 128.8, 128.1, 122.4, 119.6, 115.7, 106.3, 51.5; IR (ATR) 3144, 2952, 1700, 1611, 1515, 1478, 1210, 1145, 1046 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{13}ClNO_3$ 314.0584 ($[M+H]^+$), found 314.0579.

*4.2.15. Methyl 3-(2-acetylbenzoyl)indolizine-1-carboxylate (**8o**).* Pale yellow solid, mp: 157.6–160.2 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 10.00 (d, J=6.5 Hz, 1H), 8.36 (d, J=9.5 Hz, 1H), 7.88 (d, J=8.0 Hz, 1H), 7.65–7.57 (m, 2H), 7.52 (d, J=7.0 Hz, 1H), 7.46 (t, J=8.0 Hz, 1H), 7.39 (s, 1H), 7.12 (t, J=6.5 Hz, 1H), 3.86 (s, 3H), 2.54 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.2, 186.8, 164.5, 140.8, 139.9, 137.9, 132.0, 129.9, 129.50, 129.46, 128.8, 127.93. 127.90, 123.3, 119.6, 115.6, 106.0, 51.4, 28.2; IR (ATR) 3123, 2923, 1697, 1678, 1614, 1522, 1443, 1215 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{16}NO_4$ 322.1079 ($[M+H]^+$), found 322.1073.

*4.2.16. Methyl 3-(4-acetylbenzoyl)indolizine-1-carboxylate (**8p**).* Yellow solid, mp: 181.1–182.0 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.98 (d, J=7.0 Hz, 1H), 8.41 (d, J=9.0 Hz, 1H), 8.09 (d, J=8.0 Hz, 2H), 7.88 (d, J=8.0 Hz, 2H), 7.77 (s, 1H), 7.50 (t, J=8.0 Hz, 1H), 7.14 (t, J=7.0 Hz, 1H), 3.90 (s, 3H), 2.69 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 184.5, 164.3, 143.8, 140.3, 139.1, 129.4, 129.3, 129.2, 128.43, 128.36, 122.4, 119.6, 115.8, 106.5, 51.5, 27.0; IR (ATR) 3135, 2924, 1697, 1680, 1612, 1515, 1442, 1207 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_{16}NO_4$ 322.1079 ($[M+H]^+$), found 322.1071.

*4.2.17. Methyl 3-(2-cyanobenzoyl)indolizine-1-carboxylate (**8q**).* Pale yellow solid, mp: 172.4–173.1 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 10.04 (d, J=7.0 Hz, 1H), 8.41 (d, J=9.0 Hz, 1H), 7.85 (d, J=8.0 Hz, 1H), 7.75–7.72 (m, 2H), 7.67–7.63 (m, 1H), 7.63 (s, 1H), 7.54 (t, J=8.0 Hz, 1H), 7.18 (t, J=7.0 Hz, 1H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.9, 164.1, 143.3, 140.6, 134.1, 132.4, 130.8, 129.7, 129.4, 129.0, 122.0, 119.7, 117.3, 116.2, 111.7, 107.1, 51.5; IR (ATR) 3100, 2955, 2227, 1712, 1694, 1609, 1439, 1209 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{13}N_2O_3$ 305.0926 ($[M+H]^+$), found 305.0925.

*4.2.18. 3-Nicotinoylindolizine-1-carbonitrile (**8r**).* White solid, mp: 223.6–225.1 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.97 (d, J=7.2 Hz, 1H), 9.02 (s, 1H), 8.84 (d, J=4.4 Hz, 1H), 8.10 (d, J=8.0 Hz, 1H), 7.88 (d, J=8.8 Hz, 1H), 7.64 (s, 1H), 7.56 (t, J=7.6 Hz, 1H), 7.50 (dd, J=5.2, 7.6 Hz, 1H), 7.20 (t, J=6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.8, 152.7, 149.7, 141.6, 136.3, 135.0, 129.7, 129.5, 128.7, 123.6, 122.7, 117.8, 116.5, 114.9, 85.7; IR (ATR) 3085, 2914, 2217, 1614, 1587, 1476 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{10}N_3O$ 248.0824 ($[M+H]^+$), found 248.0808.

*4.2.19. Methyl 4-(1-cyanoindolizine-3-carbonyl)benzoate (**8s**).* Yellow solid, mp: 238.5–240.2 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.98 (d, J=6.8 Hz, 1H), 8.20 (d, J=7.6 Hz, 2H), 7.87–7.84 (m, 3H), 7.60 (s, 1H), 7.54 (t, J=7.6 Hz, 1H), 7.21 (t, J=6.4 Hz, 1H), 3.99 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.3, 166.4, 143.1, 141.6, 133.1, 129.9, 129.7, 129.6, 128.9, 128.5, 122.8, 117.7, 116.4, 115.0, 85.5, 52.7; IR (ATR) 3119, 2921, 2219, 1718, 1614, 1478 cm^{-1}; HRMS (ESI) calcd for $C_{18}H_{13}N_2O_3$ 305.0926 ($[M+H]^+$), found 305.0921.

*4.2.20. 3-(3-(Trifluoromethyl)benzoyl)indolizine-1-carbonitrile (**8t**).* White solid, mp: 186.2–186.8 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.96 (d, J=7.0 Hz, 1H), 8.06 (s, 1H), 7.98 (d, J=7.5 Hz, 1H), 7.87 (d, J=8.0 Hz, 2H), 7.68 (t, J=8.0 Hz, 1H), 7.59 (s, 1H), 7.55 (t, J=8.0 Hz, 1H), 7.21 (t, J=7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.5, 141.6, 140.0, 132.1, 131.5, 131.3, 129.7, 129.4, 129.3, 128.57, 128.55, 125.9, 125.83, 125.80, 125.77, 122.6, 117.8, 116.4, 114.9, 85.6; IR (ATR) 3127, 2923, 2227, 1620, 1517, 1480, 1320, 1216, 1108 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{10}F_3N_2O$ 315.0745 ($[M+H]^+$), found 315.0735.

*4.2.21. 3-(3-Chlorobenzoyl)indolizine-1-carbonitrile (**8u**).* Pale brown solid, mp: 199.1–199.8 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 9.94 (d, J=7.0 Hz, 1H), 7.85 (d, J=8.5 Hz, 1H), 7.77 (s, 1H), 7.66 (d, J=7.5 Hz, 1H), 7.62 (s, 1H), 7.58 (d, J=8.5 Hz, 1H), 7.55–7.51 (m, 1H), 7.47 (t, J=8.0 Hz, 1H), 7.19 (t, J=7.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 183.5, 141.6, 140.9, 135.0, 132.1, 130.0, 129.7, 129.5, 129.0, 128.4, 127.1, 122.6, 117.8, 116.3, 115.0, 85.4; IR (ATR) 3135, 2925, 2226, 1615, 1564, 1478, 1219 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{10}ClN_2O$ 281.0482 ($[M+H]^+$), found 281.0473.

*4.2.22. 3-(2-Fluorobenzoyl)indolizine-1-carbonitrile (**8v**).* White solid, mp: 152.1–152.5 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 10.02 (d, J=7.0 Hz, 1H), 7.84 (d, J=9.0 Hz, 1H), 7.57–7.52 (m, 3H), 7.51 (d, J=2.0 Hz, 1H), 7.29 (t, J=7.5 Hz, 1H), 7.24–7.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.2, 160.6, 158.6, 141.6, 132.9, 132.8, 130.2, 130.2, 129.8, 129.8, 128.4, 124.5, 124.5, 117.8, 116.2, 116.5, 116.4, 114.9, 85.7, 77.4, 77.2, 76.9; IR (ATR) 3076, 2925, 2227, 1608, 1518, 1479, 1224, 1205 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{10}FN_2O$ 265.0777 ($[M+H]^+$), found 265.0773.

Acknowledgements

We thank Yonsei University for financial support.

Supplementary data

Copies of ^{1}H and ^{13}C NMR spectra of **5** and **8**. Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.tet.2012.07.068.

References and notes

1. For reviews on indolizines, see: (a) Uchida, T.; Matsumoto, K. *Synthesis* **1976**, 209; (b) Flitsch, W. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon: Oxford, 1984; Vol. 4, p 443; (c) Shipman, M. *Sci. Synth.* **2001**, 745; (d) Singh, G. S.; Mmatli, E. E. *Eur. J. Med. Chem.* **2011**, *46*, 5237.
2. (a) Krall, R. L.; Penry, J. K.; White, B. G.; Kupferberg, H. J.; Swinyard, E. A. *Epilepsia* **1978**, *19*, 409; (b) Porter, R. J.; Hessie, J. J.; Cereghino, J. J.; Gladding, G. D.; Kupferberg, H. J.; Scoville, B.; White, B. G. *Fed. Proc.* **1985**, *44*, 2645; (c) Weide, T.; Arve, L.; Prinz, H.; Waldmann, H.; Kessler, H. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 59; (d) Dawood, K.; Abel-Gawad, H.; Ellithey, M.; Mohamed, H. A.; Hegazi, B. *Arch. Pharm. (Weinheim, Ger.)* **2006**, *339*, 133; (e) Francoise, B.; Nathalie, G.; Jean-Pierre, M.; Pierre, F.; Jacob-Alsboek, O.; Gilles, A.-A. WO 2007080325 A1, 2007. (f) Kemnitzer, W.; Kuemmerle, J.; Jiang, S.; Zhang, H.-Z.; Sirisoma, N.; Kasibhatla, S.; Crogan-Grundy, C.; Tseng, B.; Drewe, J.; Cai, S. X. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6259; (g) Kemnitzer, W.; Kuemmerle, J.; Jiang, S.; Zhang, H.-Z.; Sirisoma, N.; Kasibhatla, S.; Crogan-Grundy, C.; Tseng, B.; Drewe, J.; Cai, S. X. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3481; (h) Lemercier, G.; Fernandez-Montalvan, A.; Shaw, J. P.; Kugelstadt, D.; Bomke, J.; Domostoj, M.; Schwarz, M. K.; Scheer, A.; Kappes, B.; Leroy, D. *Biochemistry* **2009**, *48*, 6379; (i) Shen, Y.-M.; Lv, P.-C.; Chen, W.; Liu, P.-G.; Zhang, M.-Z.; Zhu, H.-L. *Eur. J. Med. Chem.* **2010**, *45*, 3184.
3. For recent synthetic methods toward 3-acylated indolizines, see: (a) Liang, F.; Hu, J.; Zhang, L.; Hu, Y.; Hu, H. *J. Heterocycl. Chem.* **2001**, *38*, 853; (b) Coffinier, D.; El Kaim, L.; Grimaud, L. *Synlett* **2010**, 2474; (c) Yang, Y.; Chen, L.; Zhang, Z.; Zhang, Y. *Org. Lett.* **2011**, *13*, 1342; (d) Mao, Z.; Li, X.; Lin, X.; Lu, P.; Wang, Y. *Tetrahedron* **2012**, *68*, 85; (e) Liu, Y.; Sun, J.-W. *J. Org. Chem.* **2012**, *77*, 1191.
4. (a) Togo, H.; Iida, S. *Synlett* **2006**, 2159; (b) Mphahlele, M. J. *Molecules* **2009**, *14*, 4814; (c) Jereb, M.; Vrazic, D.; Zupan, M. *Tetrahedron* **2011**, *67*, 1355; (d) Parvatkar, P. T.; Parameswaran, P. S.; Tilve, S. G. *Chem.—Eur. J.* **2012**, *18*, 5460.
5. Kim, I.; Kim, S. G.; Kim, J. Y.; Lee, G. H. *Tetrahedron Lett.* **2007**, *48*, 8976.
6. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467; (b) Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46; (c) Negishi, E.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979; (d) Chinchilla, R.; Nájera, C. *Chem. Soc. Rev.* **2011**, *40*, 5084.
7. (a) Kim, I.; Choi, J.; Won, H. K.; Lee, G. H. *Tetrahedron Lett.* **2007**, *48*, 6863; (b) Kim, I.; Won, H. K.; Choi, J.; Lee, G. H. *Tetrahedron* **2007**, *63*, 12954; (c) Choi, J.; Lee, G. H.; Kim, I. *Synlett* **2008**, 1243; (d) Kim, I.; Choi, J.; Lee, S.; Lee, G. H. *Synlett* **2008**, 2334; (e) Kim, K.; Kim, I. *J. Comb. Chem.* **2010**, *12*, 379; (f) Kim, I.; Kim, K. *Org. Lett.* **2010**, *12*, 2500; (g) Cho, H.; Kim, I. *Tetrahedron* **2012**, *68*, 5464.
8. For recent papers on hydrative cyclization, see: (a) Du, X.; Chen, H.; Liu, Y. *Chem.—Eur. J.* **2008**, *14*, 9495; (b) Saito, A.; Anzai, T.; Matsumoto, A.; Hanzawa, Y. *Tetrahedron Lett.* **2011**, *52*, 4658; (c) Li, S.; Li, Z.; Yuan, Y.; Peng, D.; Li, Y.; Zhang, L.; Wu, Y. *Org. Lett.* **2012**, *14*, 1130; (d) Toh, K. K.; Sanjaya, S.; Sahnoun, S.; Chong, S. Y.; Chiba, S. *Org. Lett.* **2012**, *14*, 2290; (e) Cikotiene, I. *Eur. J. Org. Chem.* **2012**, 2766.
9. One-pot approach was also attempted. Thus, after the Sonogashira coupling of **4** in $CH^{3}CN$ (as solvent), iodine and water were added to directly obtain 3-acylindolizine. However, it was difficult to isolate the desired product since the R_f value of the product was similar to that of aryl halide used for cross-coupling. Moreover, yield was inferior to that from sequential process presumably due to the presence of excess base.
10. (a) Iwasawa, N.; Shido, M.; Kusama, H. *J. Am. Chem. Soc.* **2001**, *123*, 5814; (b) Asao, N.; Takahashi, K.; Lee, S.; Kasahara, T.; Yamamoto, Y. *J. Am. Chem. Soc.* **2002**, *124*, 12650; (c) Das, A.; Liao, H. H.; Liu, R. S. *J. Org. Chem.* **2007**, *72*, 9214; (d) Das, A.; Chang, H.-K.; Yang, C.-H.; Liu, R. S. *Org. Lett.* **2008**, *10*, 4061.
11. For the preparation of **4**, **6**, and **7**, see Ref. 5.