A One-Pot Domino Reaction for the Synthesis of 3-Arylindolizines from Pyridines, Benzyl Halides, and Dihalide-Substituted Electron-Deficient Alkenes

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Received 3 August 2010; revised 23 August 2010

Abstract: 3-Arylindolizines were prepared by one-pot domino reactions from benzyl halides with pyridine (or isoquinoline) and cyclic or acyclic dihalide-substituted electron-deficient alkenes in the presence of potassium carbonate via in situ generated N-ylide intermediate. Both electron-donating and electron-withdrawing groups are tolerated in the aryl ring of benzyl halides. The yields range from moderate to high.

Key words: N-ylides, indolizine polycycles, 1,3-dipolar cycloadditions, one-pot reaction, electron-deficient alkenes

Indolizine has been drawing continuous research interest of synthetic chemists because of the presence of this skeleton in many natural products[1,2] such as amorine,[1] erythraline,[1] swainonine,[1] slaframine,[1] crepidine,[1] gephyrotoxine,[1] cryptowoline,[2] and cryptowoline.[2] These natural products and many synthetic indolizine derivatives exhibit a variety of biological activities, such as antibacterial,[3a] phosphatase and aromatase inhibiting,[3b,c] antioxidant,[3d] antidepressant,[3g] and antitumor activities.[4] They are also known to be calcium entry blockers[3e] and 5-hydroxytryptamine receptor antagonists.[3f] In particular, 1,2-annulated indolizine frameworks are found in several naturally occurring alkaloids with important biological activity, such as camptothecin[5] and nuevamine.[6] A few synthetic 1,2-annulated indolizines have also displayed interesting biological activity to serve as brain protecting and anticancer agents.[7] Polycyclic indolizine compounds have been found to have long wavelength absorption and fluorescence in the visible region. The synthesis of these polycyclic indolizine derivatives has therefore attracted increasing research interest with the aim of developing new pharmaceuticals, novel classes of dyes, and biological markers.[8]

It is well recognized that 1,3-dipolar cycloaddition[9] is one of the most efficient methods for preparing indolizines,[10] since Boekelheide and his co-workers first applied this synthetic strategy in 1961.[11] However, the reactions reported before have some drawbacks relating to the reaction scope and the chemo- and regioselectivity control. First, the reaction scope is rather limited. The N-substituent in the ylide has almost always been an electron-deficient group such as acyl or cyanomethyl or 4-nitrophenyl,[12] while ylides with an electron-rich group such as a benzyl at the nitrogen atom, were rarely applied with success.[13] As a result, the regioselective synthesis of 3-arylindolizines and their annulated derivatives proved so far rather difficult and have to rely on some specific strategy other than 1,3-dipolar cycloadditions.[14] Also, only electron-deficient alkynes and electron-deficient alkenes (with oxidant) were used as dipolarophile. Moreover, they used isolated pyridinium salt instead of more effective one-pot domino reaction.[10–12]

We have previously reported that 2,3-annulated indolizines can be obtained as rearrangement products by the reaction of 2,3-dichloro-1,4-naphthoquinone with N-ylides.[15] In this paper, the successful use of *N*-benzyl ylides in the 1,3-dipolar cycloadditions and the regioselective synthesis of a series of 3-arylindolizines by an one-pot domino reaction of pyridines, benzyl halides, and cyclic or acyclic dihalide-substituted electron-deficient alkenes under oxidant-free conditions are described. A wide range of substituents, either electron-donating or electron-withdrawing, such as 4-nitro, 2-bromo, 3-fluoro, 3-chloro, 4-methyl, 4-methoxy, etc. are tolerated in the aryl ring of benzyl halides.

At first, the isolated *N*-benzylpyridinium bromide **2a** and 2,3-dichloronaphthoquinone (**3a**) were treated in DMF with sodium carbonate under room temperature for eight days. The reaction mixture was separated by chromatography to give **4a** in 23% yield as an orange solid. The structure of **4a** was unambiguously established by an X-ray diffraction measurement. The ORTEP diagram of **4a** is shown in Figure 1.[16]

Encouraged by this result, the reactivity in DMF with different bases under room temperature was investigated, and the results are given in Table 1 (entries 1–7). As shown in Table 1, potassium carbonate was found to be the best base, yielding **4a** in 65% yield at room temperature. The results on the search for a better solvent (Table 1, entries 7–18) show that the low polarity solvent 1,4-dioxane was the best with an increased yield of 79%. However, the reaction was too slow and took six days to reach completion. Therefore, the reaction temperature

SYNTHESIS 2010, No. 23, pp 4007–4014
Advanced online publication: 22.09.2010
DOI: 10.1055/s-0030-1258266; Art ID: F13510SS

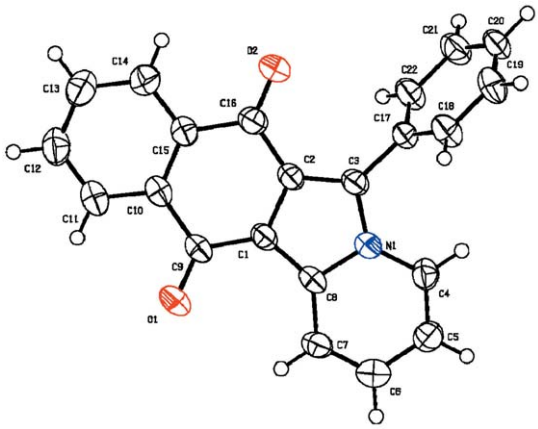


Figure 1 ORTEP diagram of compound **4a**

was raised and it was found that at 50 °C, the reaction could be finished within 24 hours with similar yield (entry 19).

After that, the one-pot reaction protocol was tried without preliminary preparation and isolation of the N-ylide. Pyridine and 5% excess of benzyl bromide were mixed first and kept at room temperature for 4 hours, then 1,4-dioxane, **3a**, and potassium carbonate were added to the mixture. The mixture was then reacted at 70 °C for 12 hours. To our delight, this was found to give an even better yield of the product **4a** (85%) (entry 20). By using 2.05 equivalents of benzyl bromide and 2.0 equivalents of pyridine, the yield of *N*-benzylpyridinium bromide (**4a**) was increased to 98% (entry 21).

The use of benzyl chloride instead of benzyl bromide was also examined. The result shows that benzyl chloride is less reactive than benzyl bromide and the formation of corresponding pyridinium salt needs higher temperature and longer time, but comparable overall yield as when using benzyl bromide can be obtained. Then, various substituted benzyl halides bearing function groups like 4-methoxy, 4-methyl, 2-bromo, 3-fluoro, 3-chloro, and 4-nitro were tried. The results shown in Table 2 indicate that electron-donating groups like 4-methyl and 4-methoxy and electron-withdrawing groups like halogen and 4-nitro were tolerated in the phenyl ring of benzyl halides. However, the N-ylides that are sterically hindered at the *ortho*-position of the N atom such as those derived from 2-methylpyridine, 2-bromopyridine, and quinoline, fail to give corresponding indolizines.

For the synthesis of 1,2 and 6,7-bisannulated indolizines, isoquinoline was used in place of pyridine. These reactions also proceeded smoothly by the one-pot protocol to give the products (Table 3).

For checking the scope of alkenes, several cyclic or acyclic dihalide-substituted electron-deficient alkenes **3b–f** and 2,3-dibromonaphthoquinone (**3g**) were applied to the standard reaction condition (Table 4).

Table 1 Screening of Reaction Conditions for the Synthesis of Indolizine **4a**

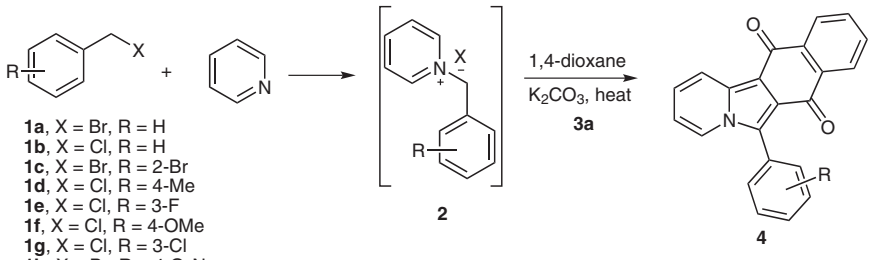
Entry[a]	Base	Solvent[b]	Temp (°C)	Time (h)	Yield (%)[c]
1	Na_2CO_3	DMF	r.t.	7 d	26
2	Et_3N	DMF	r.t.	30	0
3	Li_2CO_3	DMF	r.t.	7 d	trace
4	K_3PO_4	DMF	r.t.	16	23
5	*t*-BuOK	DMF	r.t.	3	trace
6	DBU	DMF	r.t.	3	trace
7	K_2CO_3	DMF	r.t.	24	65
8	K_2CO_3	DMA	r.t.	36	36
9	K_2CO_3	DMSO	r.t.	16	40
10	K_2CO_3	MeCN	r.t.	48	43
11	K_2CO_3	CH_2Cl_2	r.t.	29	61
12	K_2CO_3	acetone	r.t.	4 d	12
13	K_2CO_3	toluene	r.t.	8 d	47
14	K_2CO_3	benzene	r.t.	7 d	56
15	K_2CO_3	cyclohexane	r.t.	7 d	trace
16	K_2CO_3	hexane	r.t.	7 d	trace
17	K_2CO_3	THF	r.t.	4 d	78
18	K_2CO_3	1,4-dioxane	r.t.	6d	79
19	K_2CO_3	1,4-dioxane	50	24	81
20[d]	K_2CO_3	1,4-dioxane	70	12	85
21[e]	K_2CO_3	1,4-dioxane	70	12	98

[a] Unless otherwise stated, all the reactions were carried out using *N*-benzylpyridinium bromide (0.45 mmol), 2, 3-dichloronaphthoquinone (0.30 mmol), and base (1.20 mmol).
[b] All reactions were run at 0.10 M.
[c] Isolated yield.
[d] Pyridine (0.45 mmol) and benzyl bromide (0.47 mmol) were stirred at r.t. for 4 h, then 2,3-dichloronaphthoquinone (0.30 mmol), K_2CO_3 (1.20 mmol), and 1,4-dioxane (3 mL) were added.
[e] Pyridine (0.60 mmol) and benzyl bromide (0.63 mmol) were stirred at r.t. for 4 h, then 2,3-dichloronaphthoquinone (0.30 mmol), K_2CO_3 (1.20 mmol), and 1,4-dioxane (3 mL) were added.

Several cyclic dichloro-substituted unsaturated carbonyl compounds like 2,3-dichloro-1*H*-inden-1-one, 3,4-dichloro-1-phenyl-1*H*-pyrrole-2,5-dione, 2,3,5,6-tetrachlorocyclohexa-2,5-diene-1,4-dione, 4,5-dichloro-3,6-dioxocyclohexa-1,4-diene-1,2-dicarbonitrile, and 4a,6,7,8a-tetrachloro-1,4-methanonaphthalene-5,8-dione, have also been tried to react with the benzyl ylides, but they failed to give the corresponding indolizines (Figure 2).

It is interesting to note that the reactions of the *N*-benzoylpyridinium ylides with 2,3-dichloro-1,4-naphtho-

Table 2 Synthesis of Indolizines from Pyridine



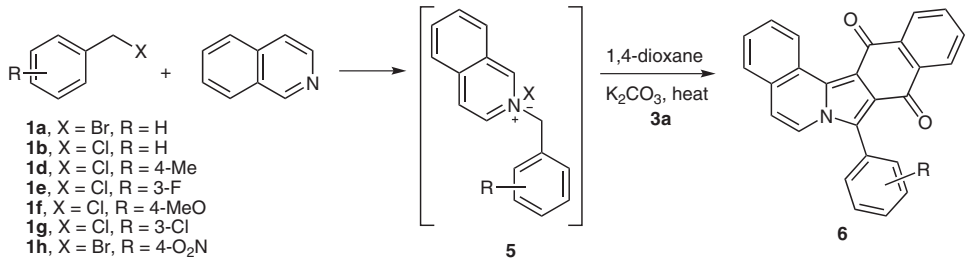
1a, X = Br, R = H
1b, X = Cl, R = H
1c, X = Br, R = 2-Br
1d, X = Cl, R = 4-Me
1e, X = Cl, R = 3-F
1f, X = Cl, R = 4-OMe
1g, X = Cl, R = 3-Cl
1h, X = Br, R = 4-O_2N

2 **4**

Benzyl halide	Temp (°C), time (h)[a]	Temp (°C), time (h)[b]	Product, yield (%)[c]
1a	r.t., 4	70, 12	**4a**, 98
1b	70, 6	70, 12	**4a**, 98
1c	r.t., 4	80, 12	**4c**, 82
1d	70, 6	70, 24	**4d**, 61
1e	70, 6	70, 24	**4e**, 81
1f	70, 6	70, 12	**4f**, 75
1g	70, 6	70, 24	**4g**, 73
1h	r.t., 4	80, 12	**4h**, 91

[a] Reaction temperature and time for forming the pyridinium salts.
[b] Reaction temperature and time for forming the indolizines.
[c] Isolated yield.

Table 3 Synthesis Indolizines from Isoquinoline



1a, X = Br, R = H
1b, X = Cl, R = H
1d, X = Cl, R = 4-Me
1e, X = Cl, R = 3-F
1f, X = Cl, R = 4-MeO
1g, X = Cl, R = 3-Cl
1h, X = Br, R = 4-O_2N

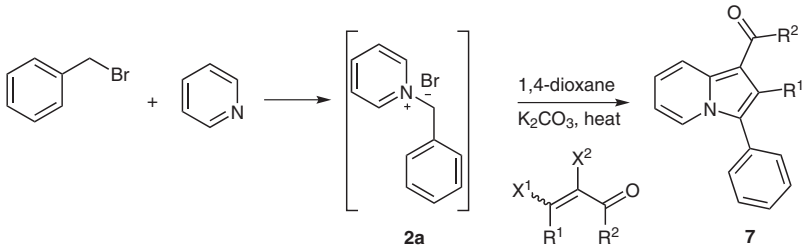
5 **6**

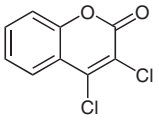
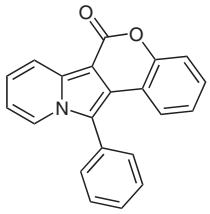
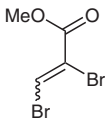
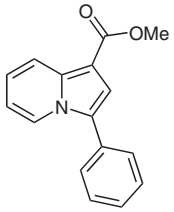
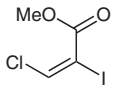
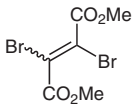
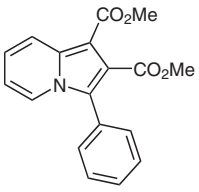
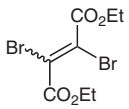
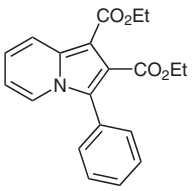
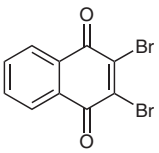
Benzyl halide	Temp (°C), time (h)[a]	Temp (°C), temp (h)[b]	Product, yield (%)[c]
1a	70, 4	70, 24	**6a**, 56
1b	70, 4	70, 24	**6a**, 57
1d	70, 4;	70, 20	**6d**, 63
1e	70, 4	70, 24	**6e**, 75
1f	70, 4	70, 29	**6f**, 65
1g	70, 4	70, 20	**6g**, 89
1h	50, 6	50, 15	**6h**, 90

[a] Time and temperature for forming the pyridinium salts.
[b] Time and temperature for forming the indolizines.
[c] Isolated yield.

quinone proceed by a novel reaction sequence not involving 1,3-dipolar cycloaddition to give 2,3-annulated indolizines; however, similar reactions of the *N*-benzylpyridinium ylides with the same quinone take place by normal 1,3-dipolar cycloadditions to give the regioisomeric 1,2-annulated indolizines as products. The mechanistic origin for this difference warrants further study.

Table 4 Synthesis Indolizines from Different Alkenes



Alkene	Temp (°C), time (h)[a]	Product, yield (%)[b]
 **3b**	70, 15	 **7a**, 66
 **3c**	70, 2.5	 **7b**, 22
 **3d**	70, 3	**7b**, 64
 **3e**	70, 4	 **7c**, 68
 **3f**	70, 3	 **7d**, 53
 **3g**	70, 18	**4a**, 40

[a] Compound **2a** was prepared from pyridine (0.60 mmol) and benzyl bromide (0.63 mmol) by stirring at r.t. for 4 h.
[b] Isolated yield.

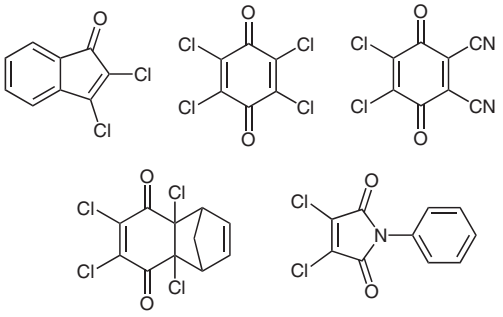


Figure 2 Dichloro-substituted unsaturated carbonyl compounds that fail to give indolizine products

In conclusion, we have developed a convenient one-pot procedure for the regioselective synthesis of 3-arylindolizine derivatives from easily available starting materials by the more general 1,3-dipolar cycloaddition strategy. This strategy takes advantage of the successful use of *N*-benzyl ylides as the dipoles in the reactions. Further research will focus on the mechanistic issue of the reactions and the fluorescent properties of these new polycyclic indolizine compounds.

All organic solutions were concentrated by rotary evaporation under reduced pressure. Flash column chromatography was performed employing 300–400 mesh silica gel. TLC was performed using plates precoated to a depth of 0.25mm with 300–400 mesh silica gel impregnated with a fluorescent indicator. All chemicals and solvents were obtained from commercial vendors and used without further purification. Melting points are uncorrected. IR spectra were obtained using a Nicolet Avator 360 spectrometer. Data were presented as frequency of absorption (cm^{-1}). Element analyses were obtained using an Elementar Vario MICRO analyzer. ^1H and ^{13}C NMR spectra were recorded on a Bruker 400 NMR spectrometer, chemical shifts are expressed in parts per million (δ scale) downfield from TMS and are referenced to residual hydrogen in the NMR solvent ($CHCl_3$: δ = 7.26). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances), coupling constant in hertz (Hz), integration.

Compounds 4, 6, and 7; General Procedure

A mixture of benzyl bromide (or chloride) (0.63 mmol) and pyridine (or isoquinoline) (0.60 mmol) was taken in a test tube with a stopper and stirred at the temperature and time shown in Table 2 (or Tables 3, 4). Then 2,3-dichloro-1,4-naphthoquinone (**3a**; 68.1 mg, 0.30 mmol) (or alkene **3b**–**g**, 0.3 mmol), K_2CO_3 (166 mg, 1.20 mmol), and 1,4-dioxane (3.0 mL) were added. The resulting mixture was heated at the temperature and time indicated in Table 2 (or Tables 3, 4), then allowed to cool to r.t. Brine (10 mL) was added and the mixture was extracted with $CHCl_3$ (3 × 15 mL). The combined organic layers were dried (Na_2SO_4). The solvent was evaporated, and the residue obtained was purified by column chromatography [silica gel, 30% $CHCl_3$ in petroleum ether (bp 60–90 °C)] to furnish the pure compound **4 (or 6 and 7)**.

6-Phenylbenzo[*f*]pyrido[2,1-*a*]isoindole-7,12-dione (4a)

Orange solid; mp 284–285 °C.

IR (KBr): 3069, 1658, 1632, 1593, 1539, 1501, 1432, 1236 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.55 (d, *J* = 8.8 Hz, 1 H), 8.33 (d, *J* = 7.6 Hz, 1 H), 8.19 (d, *J* = 6.8 Hz, 1 H), 8.09 (d, *J* = 6.8 Hz, 1 H), 7.88 (d, *J* = 7.2 Hz, 1 H), 7.74 (t, *J* = 7.2 Hz, 1 H), 7.55–7.70 (m, 5 H), 7.32 (dd, *J* = 8.4, 7.6 Hz, 1 H), 6.87 (t, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.8, 179.2, 136.4, 135.5, 133.4, 132.5, 130.6, 129.8, 129.0, 128.5, 128.4, 126.8, 126.4, 126.3, 124.5, 121.7, 121.5, 115.6, 110.8.

MS (MALDI-TOF): *m*/*z* = 324 ($M + H^+$).

Anal. Calcd for $C_{22}H_{13}NO_2$: C, 81.72; H, 4.05; N, 4.33. Found: C, 81.68; H, 4.01; N, 4.23.

6-(2-Bromophenyl)benzo[*f*]pyrido[2,1-*a*]isoindole-7,12-dione (4c)

Orange solid; mp 258–259 °C.

IR (KBr): 2922, 1658, 1537, 1500, 1238 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 9.0 Hz, 1 H), 8.33 (d, *J* = 8.4 Hz, 1 H), 8.16 (d, *J* = 8.4 Hz, 1 H), 7.83 (d, *J* = 8.1 Hz, 1 H), 7.75 (t, *J* = 7.2 Hz, 1 H), 7.68 (d, *J* = 7.5 Hz, 2 H), 7.44–7.58 (m, 3 H), 7.36 (dd, *J* = 8.7, 7.2 Hz, 1 H), 6.92 (t, *J* = 6.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.7, 179.1, 136.5, 135.2, 134.9, 133.54, 133.53, 133.4, 132.5, 131.5, 130.2, 128.0, 126.8, 126.54, 126.46, 126.39, 125.2, 124.8, 122.6, 121.4, 115.7, 110.5.

MS (MALDI-TOF): *m*/*z* = 402 ($M + H^+$).

Anal. Calcd for $C_{22}H_{12}BrNO_2$: C, 65.69; H, 3.01; N, 3.48. Found: C, 65.46; H, 3.21; N, 3.37.

6-*p*-Tolylbenzo[*f*]pyrido[2,1-*a*]isoindole-7,12-dione (4d)

Orange solid; mp 304–305 °C.

IR (KBr): 3120, 1664, 1628, 1593, 1538, 1506, 1436, 1236 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.53 (d, *J* = 9.2 Hz, 1 H), 8.32 (d, *J* = 7.6 Hz, 1 H), 8.18 (d, *J* = 7.6 Hz, 1 H), 8.09 (d, *J* = 7.2 Hz, 1 H), 7.74 (t, *J* = 6.8 Hz, 1 H), 7.66 (t, *J* = 7.2 Hz, 1 H), 7.53 (d, *J* = 8.0 Hz, 2 H), 7.42 (d, *J* = 8.0 Hz, 2 H), 7.30 (dd, *J* = 8.4, 7.6 Hz, 1 H), 6.85 (t, *J* = 6.8 Hz, 1 H), 2.50 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.8, 179.1, 139.9, 136.4, 135.6, 135.1, 133.3, 132.4, 130.5, 129.7, 128.7, 126.8, 126.4, 126.3, 125.4, 124.5, 121.6, 121.5, 115.5, 110.8, 21.6.

MS (MALDI-TOF): *m*/*z* = 338 ($M + H^+$).

Anal. Calcd for $C_{23}H_{15}NO_2$: C, 81.88; H, 4.48; N, 4.15. Found: C, 81.78; H, 4.41; N, 4.07.

6-(3-Fluorophenyl)benzo[*f*]pyrido[2,1-*a*]isoindole-7,12-dione (4e)

Orange solid; mp 287–288 °C.

IR (KBr): 3062, 1659, 1632, 1589, 1534, 1502, 1433, 1271, 1236 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 8.8 Hz, 1 H), 8.33 (d, *J* = 8.0 Hz, 1 H), 8.19 (d, *J* = 7.6 Hz, 1 H), 8.08 (d, *J* = 7.2 Hz, 1 H), 7.76 (t, *J* = 7.2 Hz, 1 H), 7.68 (t, *J* = 7.2 Hz, 1 H), 7.60 (dd, *J* = 14.0, 7.6 Hz, 1 H), 7.43 (d, *J* = 7.6 Hz, 1 H), 7.36 (d, *J* = 7.2 Hz, 1 H), 7.27–7.31 (m, 1 H), 6.91 (t, *J* = 6.8 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.7, 179.1, 160.3 (d, *J* = 246.2 Hz), 136.3, 135.4, 135.2, 133.5, 132.6, 130.6 (d, *J* = 8.4 Hz), 130.5 (d, *J* = 8.4 Hz), 126.8, 126.48, 126.47, 126.44, 126.40, 124.2, 122.0, 121.6, 117.8 (d, *J* = 22.1 Hz), 117.7 (d, *J* = 20.9 Hz), 115.9, 110.9.

MS (MALDI-TOF): *m*/*z* = 342 ($M + H^+$).

Anal. Calcd for $C_{22}H_{12}FNO_2$: C, 77.41; H, 3.54; N, 4.10. Found: C, 77.27; H, 3.60; N, 4.01.

6-(4-Methoxyphenyl)benzo[*f*]pyrido[2,1-*a*]isoindole-7,12-dione (4f)

Orange solid; mp 250–251 °C.

IR (KBr): 3108, 2960, 1658, 1635, 1593, 1551, 1505, 1432, 1237 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 9.2 Hz, 1 H), 8.32 (d, *J* = 7.6 Hz, 1 H), 8.18 (d, *J* = 7.6 Hz, 1 H), 8.10 (d, *J* = 6.8 Hz, 1 H), 7.73 (t, *J* = 7.6 Hz, 1 H), 7.66 (t, *J* = 7.6 Hz, 1 H), 7.58 (d, *J* = 8.4 Hz, 2 H), 7.27–7.31 (m, 1 H), 7.13 (d, *J* = 8.4 Hz, 2 H), 6.65 (t, *J* = 6.8 Hz, 1 H), 3.94 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.8, 179.1, 160.7, 136.4, 135.6, 135.0, 133.3, 132.4, 132.0, 128.6, 126.8, 126.4, 126.2, 124.5, 121.53, 121.48, 120.4, 115.5, 114.5, 110.7, 55.4.

MS (MALDI-TOF): *m*/*z* = 354 ($M + H^+$).

Anal. Calcd for $C_{23}H_{15}NO_3$: C, 78.17; H, 4.28; N, 3.96. Found: C, 78.09; H, 4.37; N, 3.99.

6-(3-Chlorophenyl)benzo[*f*]pyrido[2,1-*a*]isoindole-7,12-dione (4g)
Orange solid; mp 236–237 °C.

IR (KBr): 3054, 1659, 1632, 1592, 1536, 1500, 1429, 1269, 1235 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 8.4 Hz, 1 H), 8.30 (d, *J* = 7.6 Hz, 1 H), 8.16 (d, *J* = 7.6 Hz, 1 H), 8.04 (d, *J* = 7.2 Hz, 1 H), 7.73 (t, *J* = 7.6 Hz, 1 H), 7.68 (t, *J* = 7.2 Hz, 1 H), 7.62–7.70 (m, 2 H), 7.55 (s, 3 H), 7.30 (t, *J* = 6.4 Hz, 1 H), 6.88 (t, *J* = 6.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.66, 181.64, 179.0, 136.2, 135.3, 135.1, 134.9, 133.5, 132.6, 130.6, 130.31, 130.28, 129.9, 129.0, 126.8, 126.5, 126.4, 124.2, 122.0, 121.5, 115.9, 110.9.

MS (MALDI-TOF): *m*/*z* = 358 ($M + H^+$).

Anal. Calcd for $C_{22}H_{12}ClNO_2$: C, 73.85; H, 3.38; N, 3.91. Found: C, 73.87; H, 3.27; N, 3.78.

6-(4-Nitrophenyl)benzo[*f*]pyrido[2,1-*a*]isoindole-7,12-dione (4h)
Orange solid; mp 236–237 °C.

IR (KBr): 3108, 2925, 1666, 1635, 1593, 1510, 1436, 1347, 1236 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 8.4 Hz, 1 H), 8.30 (d, *J* = 7.6 Hz, 1 H), 8.16 (d, *J* = 7.6 Hz, 1 H), 8.04 (d, *J* = 7.2 Hz, 1 H), 7.73 (t, *J* = 7.6 Hz, 1 H), 7.68 (t, *J* = 7.2 Hz, 1 H), 7.62–7.70 (m, 2 H), 7.55 (s, 3 H), 7.30 (t, *J* = 6.4 Hz, 1 H), 6.88 (t, *J* = 6.4 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.66, 181.64, 179.0, 136.2, 135.3, 135.1, 134.9, 133.5, 132.6, 130.6, 130.31, 130.28, 129.9, 129.0, 126.8, 126.5, 126.4, 124.2, 122.0, 121.5, 115.9, 110.9.

MS (MALDI-TOF): *m*/*z* = 370 ($M + H^+$).

Anal. Calcd for $C_{22}H_{12}N_2O_4$: C, 71.74; H, 3.28; N, 7.61. Found: C, 71.74; H, 3.24; N, 7.48.

8-Phenylbenz[5,6]isoindolo[1,2-*a*]isoquinoline-9,14-dione (6a)
Orange solid; mp 285–286 °C.

IR (KBr): 3110, 3064, 1662, 1639, 1592, 1563, 1499, 1474, 1400, 1267, 1245 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.50 (d, *J* = 8.4 Hz, 1 H), 8.45 (d, *J* = 8.0 Hz, 1 H), 8.16 (d, *J* = 7.6 Hz, 1 H), 7.73–7.81 (m, 3 H), 7.59–7.71 (m, 8 H), 7.07 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.4, 179.0, 137.0, 134.8, 133.7, 133.4, 132.5, 131.8, 130.9, 129.9, 129.8, 129.6, 129.2, 129.0, 128.51, 128.48, 127.5, 126.9, 126.2, 126.1, 121.8, 121.6, 116.5, 114.7.

MS (MALDI-TOF): *m*/*z* = 374 ($M + H^+$).

Anal. Calcd for $C_{26}H_{15}NO_2$: C, 83.63; H, 4.05; N, 3.75. Found: C, 83.53; H, 3.81; N, 3.64.

8-*p*-Tolylbenz[5,6]isoindolo[1,2-*a*]isoquinoline-9,14-dione (6d)
Orange solid; mp 257–258 °C.

IR (KBr): 3112, 3066, 3022, 1662, 1639, 1592, 1563, 1499, 1473, 1400, 1266, 1242 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.50 (d, *J* = 8.4 Hz, 1 H), 8.45 (d, *J* = 8.0 Hz, 1 H), 8.16 (d, *J* = 7.6 Hz, 1 H), 7.72–7.81 (m, 3 H), 7.63–7.70 (m, 3 H), 7.50 (d, *J* = 8.0 Hz, 2 H), 7.45 (d, *J* = 8.0 Hz, 2 H), 7.06 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.4, 179.0, 139.9, 137.0, 134.8, 133.7, 133.4, 132.5, 132.1, 130.7, 129.9, 129.8, 129.6, 128.5, 128.4, 127.5, 126.8, 126.2, 126.1, 126.0, 121.73, 121.69, 118.2, 116.4, 114.7, 21.6.

MS (MALDI-TOF): *m*/*z* = 388 ($M + H^+$).

Anal. Calcd for $C_{27}H_{17}NO_2$: C, 83.70; H, 4.42; N, 3.62. Found: C, 83.57; H, 4.29; N, 3.52.

8-(3-Fluorophenyl)benz[5,6]isoindolo[1,2-*a*]isoquinoline-9,14-dione (6e)
Orange solid; mp 311–312 °C.

IR (KBr): 3112, 3065, 1664, 1640, 1588, 1500, 1474, 1428, 1400, 1270, 1224 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.47 (d, *J* = 7.6 Hz, 1 H), 8.44 (d, *J* = 7.6 Hz, 1 H), 8.14 (d, *J* = 7.6 Hz, 1 H), 7.29–7.82 (m, 8 H), 7.40 (d, *J* = 7.2 Hz, 1 H), 7.33 (t, *J* = 8.8 Hz, 2 H), 7.08 (d, *J* = 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.3, 178.9, 163.0 (d, *J* = 246.3 Hz), 136.9, 134.6, 133.8, 133.6, 132.6, 131.2 (d, *J* = 8.4 Hz), 130.7 (d, *J* = 8.5 Hz), 129.8, 129.7, 128.6, 128.5, 127.6, 126.9, 126.76, 126.73, 126.2, 126.0, 122.0, 121.3, 118.2 (d, *J* = 22.1 Hz), 116.9 (d, *J* = 20.5 Hz), 116.8, 114.7.

MS (MALDI-TOF): *m*/*z* = 392 ($M + H^+$).

Anal. Calcd for $C_{26}H_{14}FNO_2$: C, 79.79; H, 3.61; N, 3.58. Found: C, 79.97; H, 3.77; N, 3.61.

8-(4-Methoxyphenyl)benz[5,6]isoindolo[1,2-*a*]isoquinoline-9,14-dione (6f)
Orange solid; mp 277–278 °C.

IR (KBr): 3112, 2924, 1658, 1610, 1557, 1499, 1473, 1422, 1399, 1264, 1248 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.52 (d, *J* = 8.2 Hz, 1 H), 8.46 (d, *J* = 7.5 Hz, 1 H), 8.19 (d, *J* = 7.4 Hz, 1 H), 7.74–7.86 (m, 3 H), 7.64–7.73 (m, 3 H), 7.55 (d, *J* = 8.1 Hz, 2 H), 7.17 (d, *J* = 8.2 Hz, 2 H), 7.09 (d, *J* = 7.3 Hz, 1 H), 3.96 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.5, 179.0, 160.7, 137.1, 134.9, 133.7, 133.4, 132.5, 132.3, 132.0, 130.0, 129.6, 128.50, 128.47, 127.5, 126.9, 126.3, 126.1, 121.74, 121.73, 121.6, 120.9, 116.5, 114.7, 114.6, 55.4.

MS (MALDI-TOF): *m*/*z* = 404 ($M + H^+$).

Anal. Calcd for $C_{27}H_{17}NO_3$: C, 80.38; H, 4.25; N, 3.47. Found: C, 80.18; H, 4.37; N, 3.30.

8-(3-Chlorophenyl)benz[5,6]isoindolo[1,2-*a*]isoquinoline-9,14-dione (6g)
Orange solid; mp 253–254 °C.

IR (KBr): 3065, 2923, 2853, 1714, 1665, 1593, 1498, 1471, 1424, 1397, 1266, 1243 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 10.47 (d, *J* = 8.4 Hz, 1 H), 8.44 (d, *J* = 7.6 Hz, 1 H), 8.14 (d, *J* = 7.6 Hz, 1 H), 7.50–7.81 (m, 10 H), 7.09 (d, *J* = 7.2 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.3, 178.8, 136.9, 135.0, 134.6, 133.8, 133.6, 132.6, 130.96, 130.93, 129.81, 129.76, 129.75, 129.3, 128.6, 128.5, 127.6, 126.9, 126.2, 126.0, 123.4, 122.1, 121.3, 116.9, 114.7.

MS (MALDI-TOF): *m*/*z* = 408 (M + H$^+$).

Anal. Calcd for $C_{26}H_{14}ClNO_2$: C, 76.57; H, 3.46; N, 3.43. Found: C, 76.37; H, 3.54; N, 3.37.

8-(4-Nitrophenyl)benz[5,6]isoindolo[1,2-*a*]isoquinoline-9,14-dione (6h)
Orange solid; mp >330 °C.

IR (KBr): 3107, 1661, 1593, 1507, 1473, 1399, 1345, 1268, 1244 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.52 (d, *J* = 8.4 Hz, 1 H), 8.51 (d, *J* = 8.4 Hz, 2 H), 8.48 (d, *J* = 8.4 Hz, 1 H), 8.17 (d, *J* = 7.6 Hz, 1 H), 7.85 (d, *J* = 8.4 Hz, 2 H), 7.82 (t, *J* = 7.0 Hz, 2 H), 7.77–7.71 (m, 4 H), 7.18 (d, *J* = 7.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 181.5, 178.9, 148.5, 137.3, 136.9, 135.9, 134.40, 134.36, 133.3, 132.8, 132.3, 130.1, 129.8, 128.9, 128.6, 128.4, 127.7, 127.1, 126.3, 126.0, 124.2, 120.5, 117.4, 115.1.

MS (MALDI-TOF): *m*/*z* = 419 (M + H$^+$).

Anal. Calcd for $C_{26}H_{14}N_2O_4$: C, 74.64; H, 3.37; N, 6.70. Found: C, 74.57; H, 3.46; N, 6.53.

12-Phenyl-6*H*-chromeno[3,4-*a*]indolizin-6-one (7a)
Orange solid; mp 193–194 °C.

IR (KBr): 3059, 1706, 1638, 1606, 1504, 1408 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 8.8 Hz, 1 H), 7.98 (d, *J* = 8.8 Hz, 1 H), 7.52–7.72 (m, 6 H), 7.29–7.44 (m, 3 H), 7.01 (t, *J* = 7.4 Hz, 1 H), 6.92 (t, *J* = 6.6 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 159.0, 152.6, 134.6, 131.5, 130.2, 129.8, 128.7, 123.8, 123.55, 123.51, 123.4, 122.7, 119.7, 119.0, 117.8, 116.8, 114.7, 97.1

MS (ESI): *m*/*z* = 311 (M$^+$).

Anal. Calcd for $C_{21}H_{13}NO_2$: C, 81.01; H, 4.21; N, 4.50. Found: C, 81.10; H, 4.32; N, 4.45.

Methyl 3-Phenylindolizine-1-carboxylate (7b)
Orange solid; mp 86–87 °C.

IR (KBr): 3055, 2948, 1686, 1636, 1603, 1510, 1443, 1405 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.32 (d, *J* = 7.4 Hz, 1 H), 8.29 (d, *J* = 11.2 Hz, 1 H), 7.57 (d, *J* = 7.1 Hz, 2 H), 7.52 (t, *J* = 7.3 Hz, 2 H), 7.43 (t, *J* = 7.2 Hz, 1 H), 7.32 (s, 1 H), 7.10 (dd, *J* = 7.3, 8.3 Hz, 1 H), 6.73 (t, *J* = 6.8 Hz, 1 H), 3.94 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.4, 136.5, 131.3, 129.1, 128.7, 128.0, 126.5, 123.4, 122.3, 120.2, 116.1, 112.6, 104.0, 50.9.

MS (ESI): *m*/*z* = 251 (M$^+$).

Anal. Calcd for $C_{16}H_{13}NO_2$: C, 76.48; H, 5.21; N, 5.57. Found: C, 76.47; H, 5.27; N, 5.51.

Dimethyl 3-Phenylindolizine-1,2-dicarboxylate (7c)
Orange solid; mp 99–100 °C.

IR (KBr): 3060, 2993, 2949, 2853, 1731, 1698, 1635, 1601, 1512, 1449, 1396 cm^{-1}.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.25 (d, *J* = 9.1 Hz, 1 H), 8.06 (d, *J* = 7.1 Hz, 1 H), 7.60–7.44 (m, 5 H), 7.14 (dd, *J* = 8.7, 7.0 Hz, 1 H), 6.73 (t, *J* = 6.8 Hz, 1 H), 3.93 (s, 3 H), 3.82 (s, 3 H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 166.8, 164.2, 135.3, 130.0, 129.10, 129.06, 128.9, 125.1, 123.55, 123.54, 122.1, 120.4, 113.5, 102.0, 52.4, 51.3.

MS (ESI): *m*/*z* = 309 (M$^+$).

Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.84; H, 4.90; N, 4.46.

Diethyl 3-Phenylindolizine-1,2-dicarboxylate (7d)
Orange oil.

IR (KBr): 2978, 1729, 1695, 1512, 1443, 1396 cm^{-1}.

^{1}H NMR (400 MHz $CDCl_3$): δ = 8.27 (d, *J* = 9.1 Hz, 1 H), 8.04 (d, *J* = 7.0 Hz, 1 H), 7.59–7.43 (m, 5 H), 7.12 (dd, *J* = 8.8, 6.9 Hz, 1 H), 6.72 (t, *J* = 6.9 Hz, 1 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 4.28 (q, *J* = 7.1 Hz, 2 H), 1.41 (t, *J* = 7.1 Hz, 3 H), 1.23 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 163.8, 135.3, 130.1, 129.1, 129.01, 128.99, 124.9, 123.5, 123.3, 122.4, 120.4, 113.4, 102.2, 61.2, 59.9, 14.5, 14.0.

MS (ESI): *m*/*z* =337 (M$^+$).

Anal. Calcd for $C_{20}H_{19}NO_4$: C, 71.20; H, 5.68; N, 4.15. Found: C, 71.21; H, 5.64; N, 4.08.

Acknowledgment

This work was supported by the Jiangsu Key Laboratory for Chemistry of Low-Dimensional Materials (JSKC09067) and Huaiyin Normal University.

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