

# Synthesis and reactivity of 5-Br(I)-indolizines and their parallel cross-coupling reactions

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## Abstract

Poorly available 5-iodo- and 5-bromoindolizines were prepared via regioselective lithiation of indolizines followed by halogenation. 5-Halogenoindolizines were found to be passive toward nucleophiles, whereas they may be trifluoroacetylated at C-3 and involved in reaction with DMAD giving cycl[3.2.2]azine. The first successful Suzuki-coupling of 5-bromo(iodo)indolizines with different arylboronic acids (performed as a parallel synthesis) led to a series of 5-arylindolizines; the effect of substituents on the reaction yield was examined.

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## 1. Introduction

Indolizines are an important class of heterocyclic compounds with interesting photophysical and biological properties.<sup>1,2</sup> There are nine non-equivalent positions around the bicyclic indolizine structure, and many strategies have been reviewed to prepare substituted indolizines with a different arrangement of functional groups.<sup>1–3</sup> However, one important class of substituted indolizine, namely the 5-halogenoindolizines **I**, remains poorly available.

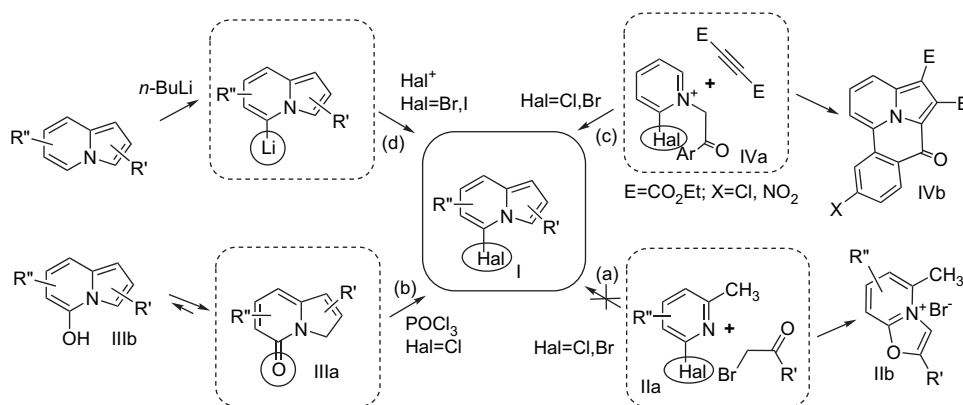
One would expect that the position of the halogen in the indolizines **I** should be equivalent to the  $\alpha$ -position in 2-halogenopyridines, and therefore a halogen could be easily substituted by nucleophiles. According to most theoretical calculations of indolizine reactivity (starting from earliest statements by Coulson<sup>4</sup> and Fukui<sup>5</sup>), position 5 should be most favorable for nucleophilic attack. However, nucleophilic attack at C-5 was confirmed only for indolizines with an additional electron-withdrawing group at position 6 or 8. Two reported examples involve direct S<sub>N</sub>H amination at C-5 of 8-nitroindolizines<sup>6</sup> and substitution of chlorine in 5-Cl-6-CN-indolizines by *O*-,

*N*- and *S*-nucleophiles;<sup>7</sup> the reactivity of simple 5-halogenoindolizines remained unclear.<sup>8</sup>

It is hard to introduce a halogen atom at position 5 of indolizine by common methods, and our earlier attempts are shown in **Scheme 1**. The Chichibabin reaction (route (a)), a standard way to substituted indolizines, is useless for the target class **I**. 5-Chloro-2-methylindolizine has been once mentioned in the old patent.<sup>9</sup> However, careful reinvestigation of reaction between 6-halogeno-2-picoline **IIa** and  $\alpha$ -bromoketones proved<sup>10</sup> that the condensation products have the structures **IIb**. The strategy that allows insertion of chlorine at position 5 (route (b)) is the reaction of 6-cyanoindolizine-5-ones **IIIa** (that are preferable tautomeric forms of 5-hydroxyindolizines **IIIb**) with POCl<sub>3</sub> leading to 5-chloro-6-cyanoindolizines.<sup>7</sup> Another strategy (route (c)) is the 1,3-dipolar cycloaddition of the pyridinium ylides derived from 2-chloro-*N*-phenacylpyridinium salts **IVa** leading to 3-aryl-5-chloroindolizines.<sup>11,12</sup> A similar reaction of 2-bromopyridinium ylide was also reported,<sup>13</sup> however both 5-Cl- and 5-Br-derivatives are unstable and quickly lose halogen atom due to an unusual cyclization to tetracyclic structures **IVb**.<sup>11–13</sup> In addition to the strategies listed in **Scheme 1**, a novel gold-assisted cycloisomerization of 2-propargylpyridines should be mentioned, since in a single example it led to a 1,2-substituted 5-bromoindolizine.<sup>14</sup>

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Scheme 1.

In 1992 Renard and Gubin<sup>15</sup> employed a promising method for the synthesis of a wide range of 5-substituted indolizines by direct lithiation of 2-phenylindolizine, and further reactions with different (mostly carbon) electrophiles. The only heteroatomic group inserted by this method was SiMe<sub>3</sub>. Earlier<sup>16</sup> we have reinvestigated this procedure, suggested the optimized protocol of indolizine lithiation (due to observed low yields of products), and succeeded in the preparation of a 5-iodoindolizine capable of Suzuki cross-coupling. In this paper we report applications of this strategy (route (d)) to the synthesis of a series of 5-Br(I)-indolizines (with additional groups in the pyrrole and pyridine rings). We found that such compounds can be involved in Suzuki-coupling, and developed a convenient parallel protocol for this reaction leading to a library of poorly investigated 5-arylindolizines. Reactivity of 5-Br(I)-indolizines toward simple nucleo-, electro- and dienophiles was also studied.

## 2. Results and discussion

### 2.1. Synthesis of 5-bromo(iodo)indolizines

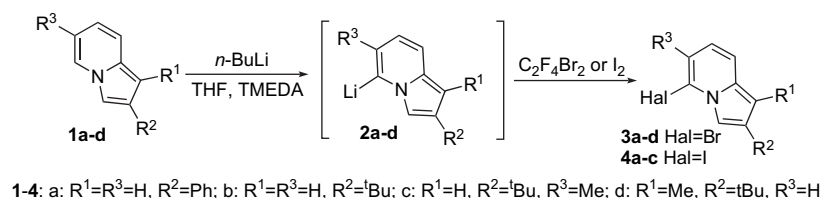
The starting indolizines **1a–d** were prepared by known procedures.<sup>17,18</sup> The corresponding lithium derivatives **2a–d** were formed in THF at  $-78$  to  $-80$  °C with *n*-BuLi (and TMEDA as co-reagent) using our optimized protocol for the direct lithiation of 2-substituted indolizines (Scheme 2).<sup>16</sup> Reaction of **2a–d** with 1,2-dibromotetrafluoroethane as brominating agent led to 5-bromoindolizines **3a–d** in high yields (80–98%). The reaction of lithium derivatives **2a–c** with a THF solution of I<sub>2</sub> gave 5-iodosubstituted indolizines

**4a–c** with 76–95% yields. Although the 5-Br(I)-indolizines (oils or solids) obtained are unstable in air, they gave satisfactory analytical and spectroscopic data (see Section 4). The <sup>1</sup>H NMR spectra of **3** and **4** were similar to the parent indolizines **1**, and the initial signal 5-H (observed in **1**) was absent in the spectra of **3** and **4**.

### 2.2. Reactions of indolizines **3**, **4** with common nucleo-, electro- and dienophiles

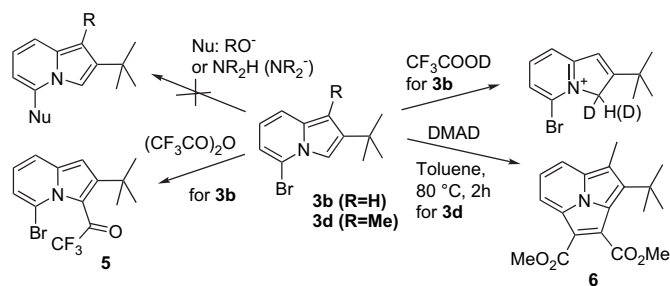
In contrast to the theoretical predictions mentioned above, 5-haloindolizines appeared to be completely passive in their reactions with nucleophiles. Thus, heating of indolizines **3a–c** and **4a–c** with <sup>1</sup>PrONa (in <sup>1</sup>PrOH) or with morpholine (in the presence of <sup>1</sup>BuOK) at reflux for 24 h led only to unchanged starting materials. Analogously, no changes were observed in the reaction of **3a** or **4a** with diethyl sodiomalonate (in EtOH, reflux for 24 h). The reason why 5-Br(I)-indolizines behave differently from 2-Br(I)-pyridines may be explained by the general  $\pi$ -excessive character of the indolizine nuclei preserved in structures **3** and **4**.

Electrophilic substitution in indolizines usually occurs at position C-3; some exceptions have been found for 5-substituted indolizines. (Thus, 5-methylindolizines usually give mixtures of 1- and 3-substituted products.) We found that reaction of 5-bromoindolizine **3b** with trifluoroacetic anhydride at 0 °C led exclusively to the 3-COCF<sub>3</sub> derivative **5** with 83% yield (Scheme 3). The regioselectivity of C-3 attack clearly followed from <sup>1</sup>H NMR spectroscopic data: the signal of proton H<sub>3</sub> disappeared, and all other peaks (excluding H<sub>8</sub>) underwent insignificant downfield shift.<sup>19</sup> It should be



Scheme 2.

mentioned that the 5-bromo substituent slightly increases the basicity of the pyrrole fragment: protonation of indolizine **3b** in  $\text{CF}_3\text{COOD}$  occurred at C-3 (Scheme 3), and after 2 days the proton H-3 was completely exchanged, whereas the parent 5-H indolizine **1b** during the same time underwent H/D exchange at C-3 only, in 25%.



Scheme 3.

Another well-known reactivity type of indolizine is [8+2] cycloaddition of dienophiles across the positions 3 and 5 (see review, Ref. 20). The reaction was usually studied for 5-unsubstituted indolizines, and initial cycloadducts (e.g., with alkynes) underwent spontaneous oxidation to aromatic cycl[3.2.2]azines. We found that 5-bromoindolizine **3d** does not react with ethyl acrylate, whereas its reaction with DMAD led to cycl[3.2.2]azine **6** in 87% yield (Scheme 3).

Evidently, this [8+2] cycloaddition (with HBr elimination) is non-oxidative, and is similar to the behavior of 3-cyanoindolizine.<sup>20</sup>

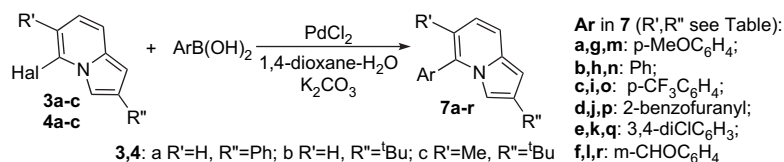
### 2.3. Parallel cross-coupling reactions

Although the halogen atom in indolizines **3** and **4** is not a leaving group in reactions with common nucleophiles, one would expect the possibility of its replacement in Suzuki-type cross-coupling reactions. We investigated the reactions of 5-Br(I)-indolizines **3a–c** and **4a–c** with several arylboronic acids (listed in Table 1) using  $\text{PdCl}_2$  as the catalyst, 1,4-dioxane/ $\text{H}_2\text{O}$  as the solvent, and  $\text{K}_2\text{CO}_3$  as the base. All 36 reactions were performed in parallel (heating, shaking, and filtration) using a SynCore parallel reactor. The resulting 5-arylindolizines **7a–r** were obtained in moderate to excellent yields (Scheme 4, Table 1).

The yields in Table 1 allowed qualitative comparison of the reactivity of indolizines in the cross-coupling reaction depending on the nature of the substituents at positions 2, 5, and 6. Firstly, the reactivity of 5-Hal-2-*tert*-butylindolizines was found to be generally higher than that of the corresponding 2-phenyl derivatives; this was evident for 5-bromo (**3a,b**) and 5-iodo (**4a,b**) pairs of compounds. Secondly, the appearance of the 6-methyl group in close vicinity to the halogen atom at C-5 caused a decrease of reactivity (probably due to steric effects). This trend was clear for 5-bromo derivative

Table 1  
The yields (%) for 5-arylindolizines

Boronic acid	Indolizine									
	76	<b>7a</b>	70	87	<b>7g</b>	49	87	<b>7m</b>	64	
	80	<b>7b</b>	73	78	<b>7h</b>	44	78	<b>7n</b>	41	
	97	<b>7c</b>	86	90	<b>7i</b>	47	96	<b>7o</b>	32	
	84	<b>7d</b>	72	79	<b>7j</b>	44	90	<b>7p</b>	68	
	93	<b>7e</b>	82	87	<b>7k</b>	36	87	<b>7q</b>	70	
	96	<b>7f</b>	84	91	<b>7l</b>	52	95	<b>7r</b>	72	



Scheme 4.

**3b** and its 6-methyl homologue **3c**, and for the homologous pair of 6-H/6-Me-5-iodo-derivatives **4b, c**. Interestingly, the difference in reactivity of 5-iodo and 5-bromo groups is negligible for 6-unsubstituted indolizines (cf. the yields for **3a** and **4a** or **3b** and **4b**), whereas for the 6-methyl series the yields of 5-iodoindolizine **4c** were 2–3 times higher against 5-bromoindolizine **3c**.

### 3. Conclusion

Regioselective lithiation followed by halogenation opens a new route to previously poorly available 5-bromo- and 5-iodoindolizines. Although these compounds are not stable in air, they can be involved in Suzuki-coupling reaction and serve as suitable precursors of a poorly investigated family of 5-aryloxyindolizines. 5-Br(I)-indolizines kept  $\pi$ -excessive properties: they can not be involved in nucleophilic substitution reactions, but can react with some electrophiles and dienophiles.

## 4. Experimental

### 4.1. General

All melting points are uncorrected. IR spectra were obtained using a UR-20 spectrometer. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on AM 400 Bruker spectrometer for <sup>1</sup>H at 360 MHz (in DMSO-*d*<sub>6</sub>) and for <sup>13</sup>C at 100 MHz (in DMSO-*d*<sub>6</sub> or acetone-*d*<sub>6</sub>). THF was distilled over benzophenone/sodium and used immediately. TMEDA was distilled over sodium. The freshly prepared solution of *n*-BuLi in hexane (1.19 M) was titrated according to a known procedure.<sup>21</sup> All boronic acids were supplied by Aldrich. All reactions involving air-sensitive reagents were performed using syringe–septum cap techniques in oven-dried glassware under a dry argon/nitrogen atmosphere. Parallel cross-coupling and parallel evaporation were performed and accelerated using the BÜCHI SynCore Reactor (with its filtration unit, vacuum pump V-501 and vacuum controller V-805).<sup>22</sup>

### 4.2. Preparation of 5-Br(I)-indolizines (general procedure)

To a solution of indolizine **1a–d** (20 mmol) and TMEDA (22 mmol) in anhydrous THF (70 mL) at –80 °C, a solution of *n*-BuLi (18.5 mL, 1.19 M, 1.1 equiv) was added with stirring. The mixture was allowed to warm to –20 °C, and kept at this temperature for a further 2 h. A yellow color appeared. Then the mixture was cooled to –80 °C, and 1,2-dibromo-tetrafluoroethane (BrCF<sub>2</sub>)<sub>2</sub> (22 mmol) or a dry THF (30 mL)

solution of I<sub>2</sub> (22 mmol) was slowly added. The mixture was allowed to warm to room temperature and treated with a saturated solution of ammonium chloride. The organic layer was separated and the aqueous layer was extracted with dichloromethane. After drying over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporation of the organic solvents, the crude product was purified by column chromatography on silica gel (eluent hexane).

#### 4.2.1. 5-Bromo-2-phenylindolizine (**3a**)

From 2-phenylindolizine (**1a**). Yield of **3a**: 80%; light yellow solid, mp: 85–87 °C; <sup>1</sup>H NMR:  $\delta$ =7.87 (1H, s, H<sub>3</sub>), 7.70–7.68 (2H, m, Ph-H), 7.42–7.38 (2H, m, Ph-H), 7.36 (1H, d, H<sub>6</sub>, *J*<sub>67</sub>=8.6 Hz), 7.29–7.24 (1H, m, Ph-H), 6.88 (1H, s, H<sub>1</sub>), 6.77 (1H, d, H<sub>8</sub>, *J*<sub>78</sub>=7.0 Hz), 6.58–6.54 (1H, m, H<sub>7</sub>); elemental analysis calcd (%) for C<sub>14</sub>H<sub>10</sub>BrN (272.14): C 61.79, H 3.70, N 5.15; found: C 61.99, H 3.62, N 5.28.

#### 4.2.2. 5-Iodo-2-phenylindolizine (**4a**)

From 2-phenylindolizine (**1a**). Yield of **4a**: 76%; light yellow solid, mp: 105–107 °C; <sup>1</sup>H NMR:  $\delta$ =7.85 (1H, s, H<sub>3</sub>), 7.68–7.66 (2H, m, Ph-H), 7.42–7.35 (3H, m, Ph-H), 7.24–7.22 (1H, m, H<sub>6</sub>), 7.06 (1H, d, H<sub>8</sub>, *J*<sub>78</sub>=7.7 Hz), 6.94 (1H, s, H<sub>1</sub>), 6.45–6.43 (1H, m, H<sub>7</sub>); elemental analysis calcd (%) for C<sub>14</sub>H<sub>10</sub>IN (319.14): C 52.69, H 3.16, N 4.39; found: C 53.01, H 3.43, N 4.58.

#### 4.2.3. 5-Bromo-2-*tert*-butylindolizine (**3b**)

From 2-*tert*-butylindolizine (**1b**). Yield of **3b**: 97%; a yellow oil that formed crystals upon standing at 9 °C; IR (neat): 1620, 1500, 1480 cm<sup>-1</sup>; <sup>1</sup>H NMR:  $\delta$ =7.35 (1H, s, H<sub>3</sub>), 7.28 (1H, d, H<sub>6</sub>, *J*<sub>67</sub>=8.9 Hz), 6.73 (1H, d, H<sub>8</sub>, *J*<sub>78</sub>=6.6 Hz), 6.55–6.50 (1H, m, H<sub>7</sub>), 6.48 (1H, s, H<sub>1</sub>), 1.35 (9H, s, <sup>t</sup>Bu); <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>): 140.9, 133.8, 117.4, 117.1, 113.6, 109.1, 99.5, 99.4, 31.5 (C(CH<sub>3</sub>)<sub>3</sub>), 30.8 (C(CH<sub>3</sub>)<sub>3</sub>); elemental analysis calcd (%) for C<sub>12</sub>H<sub>14</sub>BrN (252.15): C 57.16, H 5.60, N 5.55; found: C 56.95, H 5.63, N 5.77; <sup>1</sup>H NMR (CF<sub>3</sub>COOD):  $\delta$ =9.30 (1H, m), 8.95 (2H, m, H<sub>6</sub>+H<sub>8</sub>), 8.03 (1H, s, H<sub>1</sub>), 6.43 (1H, s, 3-CHD), 2.46 (9H, s, <sup>t</sup>Bu).

#### 4.2.4. 5-Iodo-2-*tert*-butylindolizine (**4b**)

From 2-*tert*-butylindolizine (**1b**). Yield of **4b**: 95%; light green solid, mp: 57–59 °C; IR (neat): 1615, 1490, 1475 cm<sup>-1</sup>; <sup>1</sup>H NMR:  $\delta$ =7.32 (1H, s, H<sub>3</sub>), 7.28 (1H, d, H<sub>6</sub>, *J*<sub>67</sub>=8.9 Hz), 6.96 (1H, d, H<sub>8</sub>, *J*<sub>78</sub>=6.8 Hz), 6.53 (1H, s, H<sub>1</sub>), 6.37–6.33 (1H, m, H<sub>7</sub>), 1.35 (9H, s, <sup>t</sup>Bu); <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>): 140.2, 132.7, 121.6, 118.0, 117.3, 113.1, 99.5, 88.4, 31.6 (C(CH<sub>3</sub>)<sub>3</sub>), 30.7 (C(CH<sub>3</sub>)<sub>3</sub>); elemental analysis calcd (%) for C<sub>12</sub>H<sub>14</sub>IN (299.15): C 48.18, H 4.72, N 4.68; found: C 48.03, H 4.93, N 4.57.

#### 4.2.5. 5-Bromo-6-methyl-2-*tert*-butylindolizine (**3c**)

From 6-methyl-2-*tert*-butylindolizine (**1c**). Yield of **3c**: 92%; light yellow solid, mp: 28–30 °C; <sup>1</sup>H NMR: δ=7.35 (1H, s, H<sub>3</sub>), 7.19 (1H, d, H<sub>8</sub>, *J*<sub>78</sub>=6.3 Hz), 6.52 (1H, d, H<sub>7</sub>, *J*<sub>78</sub>=6.3 Hz), 6.41 (1H, s, H<sub>1</sub>), 2.35 (3H, s, Me), 1.35 (9H, s, <sup>t</sup>Bu); elemental analysis calcd (%) for C<sub>13</sub>H<sub>16</sub>BrN (266.18): C 58.66, H 6.06, N 5.26; found: C 58.52, H 6.20, N 5.51.

#### 4.2.6. 5-Iodo-6-methyl-2-*tert*-butylindolizine (**4c**)

From 6-methyl-2-*tert*-butylindolizine (**1c**). Yield of **4c**: 87%; light yellow-green solid, mp: 39–41 °C; <sup>1</sup>H NMR: δ=7.38 (1H, s, H<sub>3</sub>), 7.18 (1H, d, H<sub>8</sub>, *J*<sub>78</sub>=6.2 Hz), 6.51–6.49 (2H, m, H<sub>1</sub>+H<sub>7</sub>), 2.37 (3H, s, Me), 1.35 (9H, s, <sup>t</sup>Bu); elemental analysis calcd (%) for C<sub>13</sub>H<sub>16</sub>IN (313.18): C 49.86, H 5.15, N 4.47; found: C 49.60, H 5.48, N 4.71.

#### 4.2.7. 5-Bromo-1-methyl-2-*tert*-butylindolizine (**3d**)

From 1-methyl-2-*tert*-butylindolizine (**1d**). Yield of **3d**: 98%; yellow oil; <sup>1</sup>H NMR: δ=7.30 (1H, d, H<sub>6</sub>, *J*<sub>67</sub>=9.8 Hz), 7.28 (1H, s, H<sub>3</sub>), 6.68 (1H, d, H<sub>8</sub>, *J*<sub>78</sub>=6.6 Hz), 6.54–6.51 (1H, m, H<sub>7</sub>), 2.43 (3H, s, Me), 1.37 (9H, s, <sup>t</sup>Bu); elemental analysis calcd (%) for C<sub>13</sub>H<sub>16</sub>BrN (266.18): C 58.66, H 6.06, N 5.26; found: C 58.71, H 6.22, N 5.51.

#### 4.3. 5-Bromo-2-*tert*-butyl-3-trifluoroacetylindolizine (**5**) by acylation reaction

Trifluoroacetic anhydride (1 mL) was added with stirring to a solution of indolizine **3b** (0.252 g, 1.0 mmol) in anhydrous THF (10 mL) at 0 °C. The mixture turned yellow. The solution was kept at 0 °C (1 h) and then treated with a saturated solution of ammonium chloride. The organic layer was separated and the aqueous layer was extracted with dichloromethane. After drying over anhydrous Na<sub>2</sub>SO<sub>4</sub> and evaporation of the organic solvents, the crude product was purified by column chromatography on silica gel (eluent hexane/CHCl<sub>3</sub>; 9:1). The isolated product was 5-bromo-3-trifluoroacetyl-2-*tert*-butylindolizine **5a** (0.291 g, 83%) as a deep yellow solid. Mp: 48–50 °C; IR (Nujol): 1695, 1525, 1490 cm<sup>-1</sup>; <sup>1</sup>H NMR: δ=7.36 (1H, d, H<sub>6</sub>, *J*<sub>67</sub>=7.6 Hz), 6.87 (1H, d, H<sub>8</sub>, *J*<sub>78</sub>=7.0 Hz), 6.80–6.76 (1H, m, H<sub>7</sub>), 6.53 (1H, s, H<sub>1</sub>), 1.38 (9H, s, <sup>t</sup>Bu); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): 177.8 (q, *J*<sub>C-F</sub>=34.4 Hz, CCOCF<sub>3</sub>), 148.3, 138.2, 123.8, 118.6, 118.5, 116.7 (q, *J*<sub>C-F</sub>=293.8 Hz, COCF<sub>3</sub>), 116.2, 115.8, 103.2, 32.3 (C(CH<sub>3</sub>)<sub>3</sub>), 30.8 (C(CH<sub>3</sub>)<sub>3</sub>); elemental analysis calcd (%) for C<sub>14</sub>H<sub>13</sub>BrF<sub>3</sub>NO (348.17): C 48.30, H 3.76, N 4.02; found: C 48.47, H 3.68, N 4.21.

#### 4.4. Dimethyl 3-*tert*-butyl-4-methylpyrrolo[2,1,5-*cd*]-indolizine-1,2-dicarboxylate (**6**) by [8+2] cycloaddition reaction

Dimethyl acetylenedicarboxylate (0.170 g, 0.146 mL, 1 mmol) was added to a solution of bromoindolizine **3d** (0.266 g, 1.0 mmol) in anhydrous toluene (10 mL) at room temperature. The mixture was heated to 80 °C and kept at this temperature for 2 h with stirring. The mixture was allowed

to cool to room temperature, the organic solvent was evaporated, and the crude product was purified by column chromatography on silica gel (eluent hexane/CHCl<sub>3</sub>; 9:1). The cycl[3.2.2]azine **6** was isolated as a deep yellow solid (0.260 g, 87%). Mp: 121–123 °C; IR (Nujol): 1745, 1700, 1545 cm<sup>-1</sup>; <sup>1</sup>H NMR: δ=8.27 (1H, d, H<sub>6</sub>, *J*<sub>67</sub>=8.0 Hz), 7.96 (1H, d, H<sub>8</sub>, *J*<sub>78</sub>=6.8 Hz), 7.91–7.86 (1H, m, H<sub>7</sub>), 3.94 (6H, s, 2COOMe), 2.76 (3H, s, Me), 1.57 (9H, s, <sup>t</sup>Bu); <sup>13</sup>C NMR (DMSO-*d*<sub>6</sub>): 167.5 (COOCH<sub>3</sub>), 163.8 (COOCH<sub>3</sub>), 142.7, 133.1, 127.1, 125.2, 124.5, 122.0, 121.9, 115.1, 112.0, 108.6, 52.9 (COOCH<sub>3</sub>), 51.7 (COOCH<sub>3</sub>), 33.9 (C(CH<sub>3</sub>)<sub>3</sub>), 31.1 (C(CH<sub>3</sub>)<sub>3</sub>), 12.2 (C(4)-CH<sub>3</sub>); MS *m/z* (%) 327 (66), 312 (6), 296 (20), 282 (5), 281 (18), 280 (100), 248 (6), 191 (6), 178 (8), 110 (9), 96 (5), 43 (11); elemental analysis calcd (%) for C<sub>19</sub>H<sub>21</sub>NO<sub>4</sub> (327.38): C 69.71, H 6.47, N 4.28; found: C 69.62, H 6.43, N 4.18.

#### 4.5. Parallel cross-coupling of 5-Br(I)-indolizines with arylboronic acids

The experiments were performed in a SynCore™ module. The solutions of 5-Br(I)-indolizine derivative (1 mmol), arylboronic acid (1.1 mmol), and K<sub>2</sub>CO<sub>3</sub> (2 mmol) in pure 1,4-dioxane (7 mL) and water (1 mL) at room temperature were placed in 24 Syncore flasks under a nitrogen atmosphere, and a solution of 0.1 M PdCl<sub>2</sub> in water (0.05 mL, 0.5 mol %) was added to each flask. The flasks were shaken and heated at 80 °C for 24 h. The flasks were cooled to room temperature and palladium black was removed by parallel filtration using a Buchi filtration unit under a nitrogen atmosphere. The filtrates were concentrated by parallel evaporation and water (5 mL) was added to each flask. Then the mixtures were manually extracted with CHCl<sub>3</sub>, the organic layers were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and evaporated. The residues were purified by column chromatography on silica gel. The parallel procedure was repeated for other 12 combinations of indolizines and boronic acids.

##### 4.5.1. 5-(4-Methoxyphenyl)-2-*tert*-butylindolizine (**7a**)

Column chromatography of residue using an eluent (hexane/CHCl<sub>3</sub>; 9:1) yielded **7a** from 4-methoxyphenylboronic acid and 5-bromoindolizine **3b** (70%) or 5-iodoindolizine **4b** (76%) as a white solid. Mp: 113–115 °C; <sup>1</sup>H NMR: δ=7.54–7.52 (2H, m, 5-Ar), 7.19 (1H, d, H<sub>6</sub>, *J*<sub>67</sub>=8.9 Hz), 7.08 (1H, s, H<sub>3</sub>), 7.05–7.03 (2H, m, 5-Ar), 6.67–6.64 (1H, m, H<sub>7</sub>), 6.32 (1H, s, H<sub>1</sub>), 6.26 (1H, d, H<sub>8</sub>, *J*<sub>78</sub>=5.0 Hz), 3.87 (3H, s, OMe), 1.28 (9H, s, <sup>t</sup>Bu); elemental analysis calcd (%) for C<sub>19</sub>H<sub>21</sub>NO (279.38): C 81.68, H 7.58, N 5.01; found: C 81.33, H 7.84, N 5.23.

##### 4.5.2. 5-Phenyl-2-*tert*-butylindolizine (**7b**)

Column chromatography of residue using hexane as an eluent yielded **7b** from phenylboronic acid and 5-bromoindolizine **3b** (73%) or 5-iodoindolizine **4b** (80%) as a white solid. Mp: 68–70 °C; <sup>1</sup>H NMR: δ=7.62–7.60 (2H, m, 5-Ph), 7.52–7.44 (3H, m, 5-Ph), 7.23 (1H, d, H<sub>6</sub>, *J*<sub>67</sub>=8.7 Hz), 7.10 (1H, s, H<sub>3</sub>), 6.69–6.65 (1H, m, H<sub>7</sub>), 6.35 (1H, s, H<sub>1</sub>), 6.30 (1H, d, H<sub>8</sub>,

$J_{78}=7.9$  Hz), 1.28 (9H, s, <sup>t</sup>Bu); elemental analysis calcd (%) for C<sub>18</sub>H<sub>19</sub>N (249.35): C 86.70, H 7.68, N 5.62; found: C 86.47, H 8.01, N 5.88.

#### 4.5.3. 5-(4-Trifluoromethylphenyl)-2-tert-butylindolizine (7c)

Column chromatography of residue using hexane as an eluent yielded **7c** from 4-trifluoromethylphenylboronic acid and 5-bromoindolizine **3b** (86%) or 5-iodoindolizine **4b** (97%) as a yellow-green solid. Mp: 123–125 °C; <sup>1</sup>H NMR:  $\delta=7.87$ – $7.86$  (4H, m, 5-Ar), 7.28 (1H, d, H<sub>6</sub>,  $J_{67}=9.0$  Hz), 7.11 (1H, s, H<sub>3</sub>), 6.69–6.65 (1H, m, H<sub>7</sub>), 6.39 (1H, s, H<sub>1</sub>), 6.37 (1H, d, H<sub>8</sub>,  $J_{78}=6.1$  Hz), 1.28 (9H, s, <sup>t</sup>Bu); elemental analysis calcd (%) for C<sub>19</sub>H<sub>18</sub>F<sub>3</sub>N (317.35): C 71.91, H 5.72, N 4.41; found: C 71.63, H 5.98, N 4.67.

#### 4.5.4. 5-(2-Benzofuranyl)-2-tert-butylindolizine (7d)

Column chromatography of residue using hexane as an eluent yielded **7d** from 2-benzofuranylboronic acid and 5-bromoindolizine **3b** (72%) or 5-iodoindolizine **4b** (84%) as a light yellow solid. Mp: 76–78 °C; <sup>1</sup>H NMR:  $\delta=7.78$  (1H, s, H<sub>3</sub>), 7.70 (1H, d, 5-Ar,  $J=7.2$  Hz), 7.58 (1H, d, 5-Ar,  $J=7.7$  Hz), 7.50 (1H, s, 5-H<sub>3</sub>), 7.41–7.34 (2H, m, 5-Ar), 7.31–7.27 (1H, m, 5-Ar), 7.12 (1H, d, H<sub>8</sub>,  $J_{78}=7.0$  Hz), 6.77–6.74 (1H, m, H<sub>7</sub>), 6.49 (1H, s, H<sub>1</sub>), 1.39 (9H, s, <sup>t</sup>Bu); elemental analysis calcd (%) for C<sub>20</sub>H<sub>19</sub>NO (289.37): C 83.01, H 6.62, N 4.84; found: C 82.74, H 6.91, N 5.09.

#### 4.5.5. 5-(3,4-Dichlorophenyl)-2-tert-butylindolizine (7e)

Column chromatography of residue using hexane as an eluent yielded **7e** from 3,4-dichlorophenylboronic acid and 5-bromoindolizine **3b** (82%) or 5-iodoindolizine **4b** (93%) as a yellow solid. Mp: 81–83 °C; <sup>1</sup>H NMR:  $\delta=7.78$  (1H, s, 5-H<sub>2</sub>), 7.70 (1H, d, 5-H<sub>2</sub>,  $J=7.4$  Hz), 7.62–6.59 (1H, m, 5-H<sub>3</sub>), 7.28 (1H, d, H<sub>6</sub>,  $J_{67}=8.8$  Hz), 7.09 (1H, s, H<sub>3</sub>), 6.69–6.66 (1H, m, H<sub>7</sub>), 6.39 (1H, s, H<sub>1</sub>), 6.36 (1H, d, H<sub>8</sub>,  $J_{78}=7.6$  Hz), 1.28 (9H, s, <sup>t</sup>Bu); elemental analysis calcd (%) for C<sub>18</sub>H<sub>17</sub>Cl<sub>2</sub>N (318.24): C 67.93, H 5.38, N 4.40; found: C 67.65, H 5.74, N 4.72.

#### 4.5.6. 5-(3-Formylphenyl)-2-tert-butylindolizine (7f)

Column chromatography of residue using an eluent (hexane/CHCl<sub>3</sub>; 9:1) yielded **7f** from 3-formylphenylboronic acid and 5-bromoindolizine **3b** (84%) or 5-iodoindolizine **4b** (96%) as a yellow solid. Mp: 62–65 °C; IR (neat): 1705, 1625, 1600, 1585 cm<sup>-1</sup>; <sup>1</sup>H NMR:  $\delta=10.05$  (1H, s, CHO), 8.11 (1H, s, 5-H<sub>2</sub>), 7.99 (1H, d, 5-H<sub>2</sub>,  $J=8.0$  Hz), 7.91 (1H, d, 5-H<sub>4</sub>,  $J=8.0$  Hz), 7.74–7.70 (1H, m, 5-H<sub>3</sub>), 7.27 (1H, d, H<sub>6</sub>,  $J_{67}=8.9$  Hz), 7.05 (1H, s, H<sub>3</sub>), 6.70–6.66 (1H, m, H<sub>7</sub>), 6.37 (1H, d, H<sub>8</sub>,  $J_{78}=6.2$  Hz), 6.36 (1H, s, H<sub>1</sub>), 1.24 (9H, s, <sup>t</sup>Bu); <sup>13</sup>C NMR (acetone-*d*<sub>6</sub>): 192.6 (CHO), 141.7, 138.5, 137.5, 136.1, 135.2, 134.9, 130.9, 130.5, 128.0, 119.1, 117.8, 111.8, 107.3, 98.8, 32.1 (C(CH<sub>3</sub>)<sub>3</sub>), 31.6 (C(CH<sub>3</sub>)<sub>3</sub>); elemental analysis calcd (%) for C<sub>19</sub>H<sub>19</sub>NO (277.36): C 82.28, H 6.90, N 5.05; found: C 78.27, H 6.96, N 4.60. LSMS: 278; 279.<sup>23</sup>

#### 4.5.7. 5-(4-Methoxyphenyl)-6-methyl-2-tert-butylindolizine (7g)

Column chromatography of residue using an eluent (hexane/CHCl<sub>3</sub>; 9:1) yielded **7g** from 4-methoxyphenylboronic acid and 5-bromoindolizine **3c** (49%) or 5-iodoindolizine **4c** (87%) as a white solid. Mp: 139–141 °C; <sup>1</sup>H NMR:  $\delta=7.28$ – $7.25$  (2H, m, 5-Ar), 7.15 (1H, d, H<sub>7</sub>,  $J_{78}=8.5$  Hz), 7.10–7.06 (2H, m, 5-Ar), 6.56 (1H, d, H<sub>8</sub>,  $J_{78}=8.5$  Hz), 6.51 (1H, s, H<sub>3</sub>), 6.24 (1H, s, H<sub>1</sub>), 3.86 (3H, s, OMe), 1.98 (3H, s, Me), 1.27 (9H, s, <sup>t</sup>Bu); elemental analysis calcd (%) for C<sub>20</sub>H<sub>23</sub>NO (293.41): C 81.87, H 7.90, N 4.77; found: C 82.02, H 7.83, N 4.92.

#### 4.5.8. 6-Methyl-5-phenyl-2-tert-butylindolizine (7h)

Column chromatography of residue using hexane as an eluent yielded **7h** from phenylboronic acid and 5-bromoindolizine **3c** (44%) or 5-iodoindolizine **4c** (78%) as a white solid. Mp: 79–81 °C; <sup>1</sup>H NMR:  $\delta=7.59$ – $7.55$  (2H, m, 5-Ph), 7.51–7.47 (1H, m, 5-Ph), 7.39–7.36 (2H, m, 5-Ph), 7.18 (1H, d, H<sub>7</sub>,  $J_{78}=8.7$  Hz), 6.58 (1H, d, H<sub>8</sub>,  $J_{78}=8.7$  Hz), 6.47 (1H, s, H<sub>3</sub>), 6.27 (1H, s, H<sub>1</sub>), 1.98 (3H, s, Me), 1.22 (9H, s, <sup>t</sup>Bu); elemental analysis calcd (%) for C<sub>19</sub>H<sub>21</sub>N (263.38): C 86.65, H 8.04, N 5.32; found: C 86.31, H 8.27, N 5.64.

#### 4.5.9. 5-(4-Trifluoromethylphenyl)-6-methyl-2-tert-butylindolizine (7i)

Column chromatography of residue using hexane as an eluent yielded **7i** from 4-trifluoromethylphenylboronic acid and 5-bromoindolizine **3c** (47%) or 5-iodoindolizine **4c** (90%) as a yellow-green solid. Mp: 151–153 °C; <sup>1</sup>H NMR:  $\delta=7.90$ – $7.86$  (2H, m, 5-Ar), 7.62–6.59 (2H, m, 5-Ar), 7.22 (1H, d, H<sub>7</sub>,  $J_{78}=8.5$  Hz), 6.60 (1H, d, H<sub>8</sub>,  $J_{78}=8.5$  Hz), 6.45 (1H, s, H<sub>3</sub>), 6.30 (1H, s, H<sub>1</sub>), 1.98 (3H, s, Me), 1.22 (9H, s, <sup>t</sup>Bu); elemental analysis calcd (%) for C<sub>20</sub>H<sub>20</sub>F<sub>3</sub>N (331.37): C 72.49, H 6.08, N 4.23; found: C 72.24, H 6.33, N 4.57.

#### 4.5.10. 5-(2-Benzofuranyl)-6-methyl-2-tert-butylindolizine (7j)

Column chromatography of residue using hexane as an eluent yielded **7j** from 2-benzofuranylboronic acid and 5-bromoindolizine **3c** (44%) or 5-iodoindolizine **4c** (79%) as a deep yellow solid. Mp: 77–79 °C; <sup>1</sup>H NMR:  $\delta=7.71$  (1H, d, 5-Ar,  $J=6.7$  Hz), 7.58 (1H, d, H<sub>7</sub>,  $J_{78}=8.6$  Hz), 7.40–7.35 (1H, m, 5-Ar), 7.32–7.26 (2H, m, 5-Ar), 7.17 (1H, s, 5-H<sub>3</sub>), 7.03 (1H, s, H<sub>3</sub>), 6.56 (1H, d, H<sub>8</sub>,  $J_{78}=8.6$  Hz), 6.35 (1H, s, H<sub>1</sub>), 2.25 (3H, s, Me), 1.27 (9H, s, <sup>t</sup>Bu); elemental analysis calcd (%) for C<sub>21</sub>H<sub>21</sub>NO (303.41): C 83.13, H 6.98, N 4.62; found: C 83.08, H 6.81, N 4.81.

#### 4.5.11. 5-(3,4-Dichlorophenyl)-6-methyl-2-tert-butylindolizine (7k)

Column chromatography of residue using hexane as an eluent yielded **7k** from 3,4-dichlorophenylboronic acid and 5-bromoindolizine **3c** (36%) or 5-iodoindolizine **4c** (87%) as a yellow solid. Mp: 153–155 °C; <sup>1</sup>H NMR:  $\delta=7.83$  (1H, s, 5-H<sub>2</sub>), 7.75 (1H, d, 5-H<sub>2</sub>,  $J=9.0$  Hz), 7.60–7.56 (1H, m, 5-H<sub>3</sub>), 7.21 (1H, d, H<sub>7</sub>,  $J_{78}=8.6$  Hz), 6.58 (1H, d, H<sub>8</sub>,

$J_{78}=8.6$  Hz), 6.51 (1H, s, H<sub>3</sub>), 6.30 (1H, s, H<sub>1</sub>), 1.99 (3H, s, Me), 1.23 (9H, s, <sup>t</sup>Bu); elemental analysis calcd (%) for C<sub>19</sub>H<sub>19</sub>Cl<sub>2</sub>N (332.28): C 68.68, H 5.76, N 4.22; found: C 68.85, H 5.75, N 4.27.

#### 4.5.12. 5-(3-Formylphenyl)-6-methyl-2-tert-butylindolizine (7l)

Column chromatography of residue using an eluent (hexane/CHCl<sub>3</sub>; 9:1) yielded **7l** from 3-formylphenylboronic acid and 5-bromoindolizine **3c** (52%) or 5-iodoindolizine **4c** (91%) as a yellow solid. Mp: 116–118 °C; IR (Nujol): 1690, 1600 cm<sup>-1</sup>; <sup>1</sup>H NMR:  $\delta=10.11$  (1H, s, CHO), 8.06 (1H, d, 5-H<sub>2</sub>,  $J=6.9$  Hz), 7.93 (1H, s, 5-H<sub>2</sub>), 7.83–7.89 (1H, m, 5-H<sub>3</sub>), 7.71 (1H, d, 5-H<sub>4</sub>,  $J=7.5$  Hz), 7.23 (1H, d, H<sub>7</sub>,  $J_{78}=9.0$  Hz), 6.61 (1H, d, H<sub>8</sub>,  $J_{78}=8.6$  Hz), 6.45 (1H, s, H<sub>3</sub>), 6.30 (1H, s, H<sub>1</sub>), 1.99 (3H, s, Me), 1.22 (9H, s, <sup>t</sup>Bu); elemental analysis calcd (%) for C<sub>20</sub>H<sub>21</sub>NO (291.40): C 82.44, H 7.26, N 4.81; found: C 82.38, H 7.38, N 4.85.

#### 4.5.13. 5-(4-Methoxyphenyl)-2-phenylindolizine (7m)

Column chromatography of residue using an eluent (hexane/CHCl<sub>3</sub>; 9:1) yielded **7m** from 4-methoxyphenylboronic acid and 5-bromoindolizine **3a** (64%) or 5-iodoindolizine **4a** (87%) as a white solid. Mp: 146–148 °C; <sup>1</sup>H NMR:  $\delta=7.66$ –7.54 (5H, m), 7.37–7.26 (3H, m), 7.18–7.06 (3H, m), 6.75–6.72 (2H, m), 6.37 (1H, d, H<sub>8</sub>,  $J_{78}=10.2$  Hz), 3.88 (3H, s, OMe); elemental analysis calcd (%) for C<sub>21</sub>H<sub>17</sub>NO (299.37): C 84.25, H 5.72, N 4.68; found: C 84.06, H 5.98, N 4.91.

#### 4.5.14. 2,5-Diphenylindolizine (7n)

Column chromatography of residue using hexane as an eluent yielded **7n** from phenylboronic acid and 5-bromoindolizine **3a** (41%) or 5-iodoindolizine **4a** (78%) as a white solid. Mp: 92–94 °C; <sup>1</sup>H NMR:  $\delta=7.95$ –7.88 (2H, m), 7.73–7.67 (3H, m), 7.44–7.35 (5H, m), 7.24–7.22 (1H, m), 7.11–7.10 (1H, m), 7.01 (1H, s, H<sub>1</sub>), 6.99–6.97 (1H, m), 6.66–6.64 (1H, m, H<sub>7</sub>); elemental analysis calcd (%) for C<sub>20</sub>H<sub>15</sub>N (269.34): C 89.19, H 5.61, N 5.20; found: C 88.86, H 5.90, N 5.54.

#### 4.5.15. 5-(4-Trifluoromethylphenyl)-2-phenylindolizine (7o)

Column chromatography of residue using hexane as an eluent yielded **7o** from 4-trifluoromethylphenylboronic acid and 5-bromoindolizine **3a** (32%) or 5-iodoindolizine **4a** (96%) as a white-green solid. Mp: 129–131 °C; <sup>1</sup>H NMR:  $\delta=7.94$ –7.86 (4H, m), 7.63–7.58 (3H, m), 7.42 (1H, d, H<sub>6</sub>,  $J_{67}=7.2$  Hz), 7.33–7.29 (2H, m), 7.20–7.16 (1H, m), 6.82 (1H, s, H<sub>1</sub>), 6.80–6.78 (1H, m, H<sub>7</sub>), 6.49 (1H, d, H<sub>8</sub>,  $J_{78}=10.8$  Hz); elemental analysis calcd (%) for C<sub>21</sub>H<sub>14</sub>F<sub>3</sub>N (337.34): C 74.77, H 4.18, N 4.15; found: C 74.37, H 4.38, N 4.43.

#### 4.5.16. 5-(2-Benzofuranyl)-2-phenylindolizine (7p)

Column chromatography of residue using hexane as an eluent yielded **7p** from 2-benzofuranylboronic acid and 5-bromoindolizine **3a** (68%) or 5-iodoindolizine **4a** (90%) as a deep

yellow solid. Mp: 169–171 °C; <sup>1</sup>H NMR:  $\delta=8.32$  (1H, s, 5-H<sub>3</sub>), 7.77–7.69 (4H, m), 7.63–7.61 (1H, m), 7.51–7.49 (1H, m), 7.40–7.35 (3H, m), 7.33–7.28 (1H, m), 7.25–7.20 (2H, m), 6.91 (1H, s, H<sub>1</sub>), 6.84 (1H, m, H<sub>7</sub>); elemental analysis calcd (%) for C<sub>22</sub>H<sub>15</sub>NO (309.36): C 85.41, H 4.89, N 4.53; found: C 85.28, H 5.06, N 4.71.

#### 4.5.17. 5-(3,4-Dichlorophenyl)-2-phenylindolizine (7q)

Column chromatography of residue using hexane as an eluent yielded **7q** from 3,4-dichlorophenylboronic acid and 5-bromoindolizine **3a** (70%) or 5-iodoindolizine **4a** (87%) as a yellow solid. Mp: 142–144 °C; <sup>1</sup>H NMR:  $\delta=7.83$  (1H, d, 5-H<sub>2</sub>,  $J=2.5$  Hz), 7.75 (1H, d, 5-H<sub>2</sub>,  $J=8.4$  Hz), 7.69–7.66 (1H, m, 5-H<sub>3</sub>), 7.61–7.58 (3H, m), 7.40 (1H, d, H<sub>6</sub>,  $J_{67}=10.8$  Hz), 7.33–7.30 (2H, m), 7.20–7.16 (1H, m), 6.82 (1H, s, H<sub>1</sub>), 6.78 (1H, m, H<sub>7</sub>), 6.45 (1H, d, H<sub>8</sub>,  $J_{78}=9.8$  Hz); elemental analysis calcd (%) for C<sub>20</sub>H<sub>13</sub>Cl<sub>2</sub>N (338.23): C 71.02, H 3.87, N 4.14; found: C 70.74, H 4.13, N 4.45.

#### 4.5.18. 5-(3-Formylphenyl)-2-phenylindolizine (7r)

Column chromatography of residue using an eluent (hexane/CHCl<sub>3</sub>; 9:1) yielded **7r** from 3-formylphenylboronic acid and 5-bromoindolizine **3a** (72%) or 5-iodoindolizine **4a** (95%) as a yellow solid. Mp: >132 °C (dec); IR (Nujol): 1695, 1605, 1580 cm<sup>-1</sup>; <sup>1</sup>H NMR:  $\delta=10.11$  (1H, s, CHO), 8.23 (1H, s, 5-H<sub>2</sub>), 8.07 (1H, d, 5-H<sub>2</sub>,  $J=7.4$  Hz), 7.99 (1H, d, 5-H<sub>4</sub>,  $J=6.3$  Hz), 7.81–7.77 (1H, m, 5-H<sub>3</sub>), 7.62–7.57 (2H, m), 7.44–7.16 (5H, m), 6.82 (1H, s, H<sub>1</sub>), 6.77 (1H, m, H<sub>7</sub>), 6.49 (1H, d, H<sub>8</sub>,  $J_{78}=9.4$  Hz); elemental analysis calcd (%) for C<sub>21</sub>H<sub>15</sub>NO (297.35): C 84.82, H 5.08, N 4.71; found: C 84.51, H 5.34, N 4.96.

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## Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.11.017.

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