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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.

1. Introduction

Indolizines are an important class of heterocyclic compounds with interesting photophysical and biological properties.[1,2] 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.[1–3] 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 α-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[4] and Fukui[5]), 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_NH amination at C-5 of 8-nitroindolizines[6] and substitution of chlorine in 5-Cl-6-CN-indolizines by *O*-, *N*- and *S*-nucleophiles;[7] the reactivity of simple 5-halogenoindolizines remained unclear.[8]

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.[9] However, careful reinvestigation of reaction between 6-halogeno-2-picolines **IIa** and α-bromoketones proved[10] 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 $POCl_3$ leading to 5-chloro-6-cyanoindolizines.[7] 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-aroyl-5-chloroindolizines.[11,12] A similar reaction of 2-bromopyridinium ylide was also reported,[13] however both 5-Cl- and 5-Br-derivatives are unstable and quickly lose halogen atom due to an unusual cyclization to tetracyclic structures **IVb**.[11–13] 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.[14]

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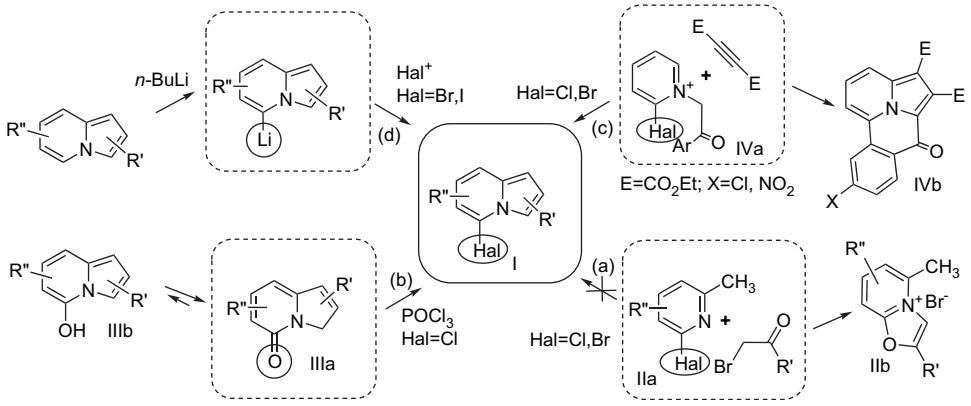


Scheme 1.

In 1992 Renard and Gubin[15] 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 $SiMe_3$. Earlier[16] 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

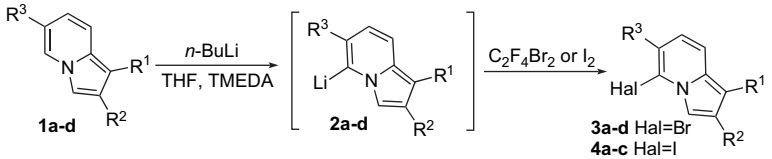
2.1. Synthesis of 5-bromo(iodo)indolizines

The starting indolizines **1a–d** were prepared by known procedures.[17,18] 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).[16] 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_2 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 ^{1}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-halogenoindolizines appeared to be completely passive in their reactions with nucleophiles. Thus, heating of indolizines **3a–c** and **4a–c** with ^{i}PrONa (in ^{i}PrOH) or with morpholine (in the presence of ^{t}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 π-excessive character of the indolizine nuclei preserved in structures **3** and **4**.

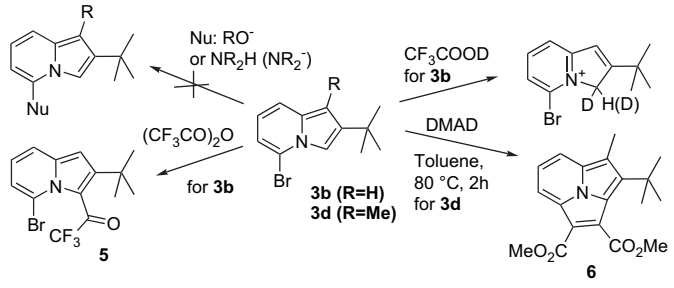
Electrophilic substitution in indolizines usually occurs at position C-3; some exceptions have been found for 5-substituted indolizines. (Thus, 5-methylindolizines usually give mixtures of 1- and 3-substituted products.) We found that reaction of 5-bromoindolizine **3b** with trifluoroacetic anhydride at 0 °C led exclusively to the 3-$COCF_3$ derivative **5** with 83% yield (Scheme 3). The regioselectivity of C-3 attack clearly followed from ^{1}H NMR spectroscopic data: the signal of proton H_3 disappeared, and all other peaks (excluding H_8) underwent insignificant downfield shift.[19] It should be



1-4: a: R^1=R^3=H, R^2=Ph; b: R^1=R^3=H, R^2=^{t}Bu; c: R^1=H, R^2=^{t}Bu, R^3=Me; d: R^1=Me, R^2=tBu, R^3=H

Scheme 2.

mentioned that the 5-bromo substituent slightly increases the basicity of the pyrrole fragment: protonation of indolizine **3b** in CF_3COOD 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.

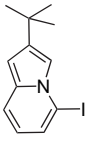
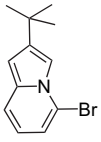
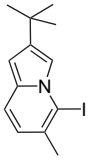
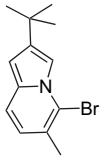
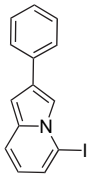
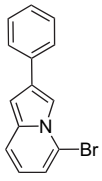
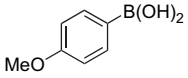
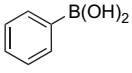
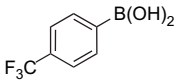
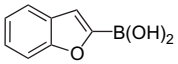
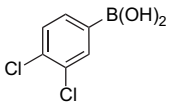
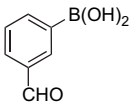
Another well-known reactivity type of indolizine is [8+2] cycloaddition of dienophiles across the positions 3 and 5 (see review, Ref. 20). The reaction was usually studied for 5-unsubstituted indolizines, and initial cycloadducts (e.g., with alkynes) underwent spontaneous oxidation to aromatic cycl[3.2.2]azines. 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.[20]

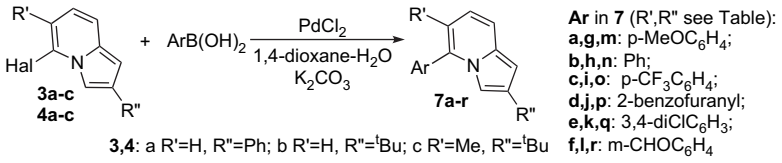
2.3. Parallel cross-coupling reactions

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 $PdCl_2$ as the catalyst, 1,4-dioxane/H_2O as the solvent, and K_2CO_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	**7a**	70	87	**7g**	49	87	**7m**	64
	80	**7b**	73	78	**7h**	44	78	**7n**	41
	97	**7c**	86	90	**7i**	47	96	**7o**	32
	84	**7d**	72	79	**7j**	44	90	**7p**	68
	93	**7e**	82	87	**7k**	36	87	**7q**	70
	96	**7f**	84	91	**7l**	52	95	**7r**	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-arylindolizines. 5-Br(I)-indolizines kept π-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. ^{1}H and ^{13}C NMR spectra were recorded on AM 400 Bruker spectrometer for ^{1}H at 360 MHz (in DMSO-d_6) and for ^{13}C at 100 MHz (in DMSO-d_6 or acetone-d_6). 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.[21] 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).[22]

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-dibromotetrafluoroethane $(BrCF_2)_2$ (22 mmol) or a dry THF (30 mL) solution of I_2 (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_2SO_4 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; ^{1}H NMR: δ=7.87 (1H, s, H_3), 7.70–7.68 (2H, m, Ph-H), 7.42–7.38 (2H, m, Ph-H), 7.36 (1H, d, H_6, J_{67}=8.6 Hz), 7.29–7.24 (1H, m, Ph-H), 6.88 (1H, s, H_1), 6.77 (1H, d, H_8, J_{78}=7.0 Hz), 6.58–6.54 (1H, m, H_7); elemental analysis calcd (%) for $C_{14}H_{10}BrN$ (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; ^{1}H NMR: δ=7.85 (1H, s, H_3), 7.68–7.66 (2H, m, Ph-H), 7.42–7.35 (3H, m, Ph-H), 7.24–7.22 (1H, m, H_6), 7.06 (1H, d, H_8, J_{78}=7.7 Hz), 6.94 (1H, s, H_1), 6.45–6.43 (1H, m, H_7); elemental analysis calcd (%) for $C_{14}H_{10}IN$ (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^{-1}; ^{1}H NMR: δ=7.35 (1H, s, H_3), 7.28 (1H, d, H_6, J_{67}=8.9 Hz), 6.73 (1H, d, H_8, J_{78}=6.6 Hz), 6.55–6.50 (1H, m, H_7), 6.48 (1H, s, H_1), 1.35 (9H, s, ^{t}Bu); ^{13}C NMR (acetone-d_6): 140.9, 133.8, 117.4, 117.1, 113.6, 109.1, 99.5, 99.4, 31.5 ($C(CH_3)_3$), 30.8 ($C(CH_3)_3$); elemental analysis calcd (%) for $C_{12}H_{14}BrN$ (252.15): C 57.16, H 5.60, N 5.55; found: C 56.95, H 5.63, N 5.77; ^{1}H NMR (CF_3COOD): δ=9.30 (1H, m), 8.95 (2H, m, H_6+H_8), 8.03 (1H, s, H_1), 6.43 (1H, s, 3-CHD), 2.46 (9H, s, ^{t}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^{-1}; ^{1}H NMR: δ=7.32 (1H, s, H_3), 7.28 (1H, d, H_6, J_{67}=8.9 Hz), 6.96 (1H, d, H_8, J_{78}=6.8 Hz), 6.53 (1H, s, H_1), 6.37–6.33 (1H, m, H_7), 1.35 (9H, s, ^{t}Bu); ^{13}C NMR (acetone-d_6): 140.2, 132.7, 121.6, 118.0, 117.3, 113.1, 99.5, 88.4, 31.6 ($C(CH_3)_3$), 30.7 ($C(CH_3)_3$); elemental analysis calcd (%) for $C_{12}H_{14}IN$ (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; ^{1}H NMR: δ=7.35 (1H, s, H_3), 7.19 (1H, d, H_8, J_{78}=6.3 Hz), 6.52 (1H, d, H_7, J_{78}=6.3 Hz), 6.41 (1H, s, H_1), 2.35 (3H, s, Me), 1.35 (9H, s, ^{t}Bu); elemental analysis calcd (%) for $C_{13}H_{16}BrN$ (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; ^{1}H NMR: δ= 7.38 (1H, s, H_3), 7.18 (1H, d, H_8, J_{78}=6.2 Hz), 6.51–6.49 (2H, m, H_1+H_7), 2.37 (3H, s, Me), 1.35 (9H, s, ^{t}Bu); elemental analysis calcd (%) for $C_{13}H_{16}IN$ (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; ^{1}H NMR: δ=7.30 (1H, d, H_6, J_{67}=9.8 Hz), 7.28 (1H, s, H_3), 6.68 (1H, d, H_8, J_{78}=6.6 Hz), 6.54–6.51 (1H, m, H_7), 2.43 (3H, s, Me), 1.37 (9H, s, ^{t}Bu); elemental analysis calcd (%) for $C_{13}H_{16}BrN$ (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_2SO_4 and evaporation of the organic solvents, the crude product was purified by column chromatography on silica gel (eluent hexane/$CHCl_3$; 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^{-1}; ^{1}H NMR: δ=7.36 (1H, d, H_6, J_{67}=7.6 Hz), 6.87 (1H, d, H_8, J_{78}= 7.0 Hz), 6.80–6.76 (1H, m, H_7), 6.53 (1H, s, H_1), 1.38 (9H, s, ^{t}Bu); ^{13}C NMR (DMSO-d_6): 177.8 (q, J_{C-F}=34.4 Hz, C*C*OCF_3), 148.3, 138.2, 123.8, 118.6, 118.5, 116.7 (q, J_{C-F}= 293.8 Hz, CO*C*F_3), 116.2, 115.8, 103.2, 32.3 (*C*$(CH_3)_3$), 30.8 (C(*C*$H_3)_3$); elemental analysis calcd (%) for $C_{14}H_{13}BrF_3NO$ (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 acetylendicarboxylate (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/$CHCl_3$; 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^{-1}; ^{1}H NMR: δ=8.27 (1H, d, H_6, J_{67}=8.0 Hz), 7.96 (1H, d, H_8, J_{78}=6.8 Hz), 7.91–7.86 (1H, m, H_7), 3.94 (6H, s, 2COOMe), 2.76 (3H, s, Me), 1.57 (9H, s, ^{t}Bu); ^{13}C NMR (DMSO-d_6): 167.5 (*C*$OOCH_3$), 163.8 (*C*$OOCH_3$), 142.7, 133.1, 127.1, 125.2, 124.5, 122.0, 121.9, 115.1, 112.0, 108.6, 52.9 (COO*C*H_3), 51.7 (COO*C*H_3), 33.9 (*C*$(CH_3)_3$), 31.1 (C(*C*$H_3)_3$), 12.2 (C(4)-*C*H_3); 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 $C_{19}H_{21}NO_4$ (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_2CO_3 (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 $PdCl_2$ 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 $CHCl_3$, the organic layers were dried over anhydrous Na_2SO_4, 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/$CHCl_3$; 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; ^{1}H NMR: δ= 7.54–7.52 (2H, m, 5-Ar), 7.19 (1H, d, H_6, J_{67}=8.9 Hz), 7.08 (1H, s, H_3), 7.05–7.03 (2H, m, 5-Ar), 6.67–6.64 (1H, m, H_7), 6.32 (1H, s, H_1), 6.26 (1H, d, H_8, J_{78}=5.0 Hz), 3.87 (3H, s, OMe), 1.28 (9H, s, ^{t}Bu); elemental analysis calcd (%) for $C_{19}H_{21}NO$ (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; ^{1}H NMR: δ=7.62–7.60 (2H, m, 5-Ph), 7.52–7.44 (3H, m, 5-Ph), 7.23 (1H, d, H_6, J_{67}=8.7 Hz), 7.10 (1H, s, H_3), 6.69–6.65 (1H, m, H_7), 6.35 (1H, s, H_1), 6.30 (1H, d, H_8,

J_{78}=7.9 Hz), 1.28 (9H, s, ^{t}Bu); elemental analysis calcd (%) for $C_{18}H_{19}N$ (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; ^{1}H NMR: δ=7.87–7.86 (4H, m, 5-Ar), 7.28 (1H, d, H_6, J_{67}=9.0 Hz), 7.11 (1H, s, H_3), 6.69–6.65 (1H, m, H_7), 6.39 (1H, s, H_1), 6.37 (1H, d, H_8, J_{78}=6.1 Hz), 1.28 (9H, s, ^{t}Bu); elemental analysis calcd (%) for $C_{19}H_{18}F_3N$ (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; ^{1}H NMR: δ=7.78 (1H, s, H_3), 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_3), 7.41–7.34 (2H, m, 5-Ar), 7.31–7.27 (1H, m, 5-Ar), 7.12 (1H, d, H_8, J_{78}=7.0 Hz), 6.77–6.74 (1H, m, H_7), 6.49 (1H, s, H_1), 1.39 (9H, s, ^{t}Bu); elemental analysis calcd (%) for $C_{20}H_{19}NO$ (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; ^{1}H NMR: δ=7.78 (1H, s, 5-H_2), 7.70 (1H, d, 5-$H_{2'}$, J=7.4 Hz), 7.62–6.59 (1H, m, 5-$H_{3'}$), 7.28 (1H, d, H_6, J_{67}=8.8 Hz), 7.09 (1H, s, H_3), 6.69–6.66 (1H, m, H_7), 6.39 (1H, s, H_1), 6.36 (1H, d, H_8, J_{78}=7.6 Hz), 1.28 (9H, s, ^{t}Bu); elemental analysis calcd (%) for $C_{18}H_{17}Cl_2N$ (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/$CHCl_3$; 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^{-1}; ^{1}H NMR: δ=10.05 (1H, s, CHO), 8.11 (1H, s, 5-H_2), 7.99 (1H, d, 5-$H_{2'}$, J=8.0 Hz), 7.91 (1H, d, 5-$H_{4'}$, J=8.0 Hz), 7.74–7.70 (1H, m, 5-$H_{3'}$), 7.27 (1H, d, H_6, J_{67}=8.9 Hz), 7.05 (1H, s, H_3), 6.70–6.66 (1H, m, H_7), 6.37 (1H, d, H_8, J_{78}=6.2 Hz), 6.36 (1H, s, H_1), 1.24 (9H, s, ^{t}Bu); ^{13}C NMR (acetone-d_6): 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 ($C(CH_3)_3$), 31.6 ($C(CH_3)_3$); elemental analysis calcd (%) for $C_{19}H_{19}NO$ (277.36): C 82.28, H 6.90, N 5.05; found: C 78.27, H 6.96, N 4.60. LSMS: 278; 279.[23]

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

Column chromatography of residue using an eluent (hexane/$CHCl_3$; 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; ^{1}H NMR: δ=7.28–7.25 (2H, m, 5-Ar), 7.15 (1H, d, H_7, J_{78}=8.5 Hz), 7.10–7.06 (2H, m, 5-Ar), 6.56 (1H, d, H_8, J_{78}=8.5 Hz), 6.51 (1H, s, H_3), 6.24 (1H, s, H_1), 3.86 (3H, s, OMe), 1.98 (3H, s, Me), 1.27 (9H, s, ^{t}Bu); elemental analysis calcd (%) for $C_{20}H_{23}NO$ (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; ^{1}H NMR: δ=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_7, J_{78}=8.7 Hz), 6.58 (1H, d, H_8, J_{78}=8.7 Hz), 6.47 (1H, s, H_3), 6.27 (1H, s, H_1), 1.98 (3H, s, Me), 1.22 (9H, s, ^{t}Bu); elemental analysis calcd (%) for $C_{19}H_{21}N$ (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; ^{1}H NMR: δ=7.90–7.86 (2H, m, 5-Ar), 7.62–6.59 (2H, m, 5-Ar), 7.22 (1H, d, H_7, J_{78}=8.5 Hz), 6.60 (1H, d, H_8, J_{78}=8.5 Hz), 6.45 (1H, s, H_3), 6.30 (1H, s, H_1), 1.98 (3H, s, Me), 1.22 (9H, s, ^{t}Bu); elemental analysis calcd (%) for $C_{20}H_{20}F_3N$ (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; ^{1}H NMR: δ=7.71 (1H, d, 5-Ar, J=6.7 Hz), 7.58 (1H, d, H_7, 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_3), 7.03 (1H, s, H_3), 6.56 (1H, d, H_8, J_{78}=8.6 Hz), 6.35 (1H, s, H_1), 2.25 (3H, s, Me), 1.27 (9H, s, ^{t}Bu); elemental analysis calcd (%) for $C_{21}H_{21}NO$ (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; ^{1}H NMR: δ=7.83 (1H, s, 5-H_2), 7.75 (1H, d, 5-$H_{2'}$, J=9.0 Hz), 7.60–7.56 (1H, m, 5-$H_{3'}$), 7.21 (1H, d, H_7, J_{78}=8.6 Hz), 6.58 (1H, d, H_8,

J_{78}=8.6 Hz), 6.51 (1H, s, H_3), 6.30 (1H, s, H_1), 1.99 (3H, s, Me), 1.23 (9H, s, ^{t}Bu); elemental analysis calcd (%) for $C_{19}H_{19}Cl_2N$ (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/$CHCl_3$; 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^{-1}; ^{1}H NMR: δ=10.11 (1H, s, CHO), 8.06 (1H, d, 5-$H_{2'}$, J=6.9 Hz), 7.93 (1H, s, 5-H_2), 7.83–7.89 (1H, m, 5-$H_{3'}$), 7.71 (1H, d, 5-$H_{4'}$, J=7.5 Hz), 7.23 (1H, d, H_7, J_{78}=9.0 Hz), 6.61 (1H, d, H_8, J_{78}=8.6 Hz), 6.45 (1H, s, H_3), 6.30 (1H, s, H_1), 1.99 (3H, s, Me), 1.22 (9H, s, ^{t}Bu); elemental analysis calcd (%) for $C_{20}H_{21}NO$ (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/$CHCl_3$; 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; ^{1}H NMR: δ= 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_8, J_{78}=10.2 Hz), 3.88 (3H, s, OMe); elemental analysis calcd (%) for $C_{21}H_{17}NO$ (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; ^{1}H NMR: δ=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_1), 6.99–6.97 (1H, m), 6.66–6.64 (1H, m, H_7); elemental analysis calcd (%) for $C_{20}H_{15}N$ (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; ^{1}H NMR: δ=7.94–7.86 (4H, m), 7.63–7.58 (3H, m), 7.42 (1H, d, H_6, J_{67}=7.2 Hz), 7.33–7.29 (2H, m), 7.20–7.16 (1H, m), 6.82 (1H, s, H_1), 6.80–6.78 (1H, m, H_7), 6.49 (1H, d, H_8, J_{78}= 10.8 Hz); elemental analysis calcd (%) for $C_{21}H_{14}F_3N$ (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; ^{1}H NMR: δ=8.32 (1H, s, 5-H_3), 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_1), 6.84 (1H, m, H_7); elemental analysis calcd (%) for $C_{22}H_{15}NO$ (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; ^{1}H NMR: δ=7.83 (1H, d, 5-H_2, J=2.5 Hz), 7.75 (1H, d, 5-$H_{2'}$, J=8.4 Hz), 7.69–7.66 (1H, m, 5-$H_{3'}$), 7.61–7.58 (3H, m), 7.40 (1H, d, H_6, J_{67}= 10.8 Hz), 7.33–7.30 (2H, m), 7.20–7.16 (1H, m), 6.82 (1H, s, H_1), 6.78 (1H, m, H_7), 6.45 (1H, d, H_8, J_{78}=9.8 Hz); elemental analysis calcd (%) for $C_{20}H_{13}Cl_2N$ (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/$CHCl_3$; 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^{-1}; ^{1}H NMR: δ=10.11 (1H, s, CHO), 8.23 (1H, s, 5-H_2), 8.07 (1H, d, 5-$H_{2'}$, J=7.4 Hz), 7.99 (1H, d, 5-$H_{4'}$, J=6.3 Hz), 7.81–7.77 (1H, m, 5-$H_{3'}$), 7.62–7.57 (2H, m), 7.44–7.16 (5H, m), 6.82 (1H, s, H_1), 6.77 (1H, m, H_7), 6.49 (1H, d, H_8, J_{78}=9.4 Hz); elemental analysis calcd (%) for $C_{21}H_{15}NO$ (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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