Iron-catalysed C-3 functionalisation of indolizines via C–H bond cleavage

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The synthesis of 3,3′-(arylmethylene)diindolizine with a $FeCl_3{\cdot}6H_2O$ catalyst has been achieved with excellent efficiency at room temperature. Various indolizines were prepared by the reaction with either aromatic or aliphatic aldehydes to produce di- or triheteroarylmethanes.

Keywords: indolizine, C-3 functionalisation, benzylation, iron-catalysed synthesis

Transition metal-catalysed C–C bond formation reactions involving C–H bond activation[1–5] are distinquished from the traditional transition metal-catalysed reactions by fewer steps and less wastage. The older methods need prefunctionalisation of both reaction partners. These transformations exhibit even more advantages for arylation, alkenylation, alkynylation and alkylation of heteroaromatics, because some important types of heteroaryl organometallic compounds have proven challenging to synthesise and may even be insufficiently stable to participate in cross-coupling processes. The regioselective conversion of C–H to C–C bonds would result in shortening of synthetic schemes by allowing the use of readily available starting materials.[6–11]

Indolizines are interesting structures in a wide variety of natural products with useful biological activities[11–16] and pharmaceutical properties.[17–22] The functionalisation of indolizines have attracted considerable interest in the past and metal-catalysed direct functionalisation of indolizines has been explored recently.[17–29]

Triaryl- and triheteroarylmethanes have attracted much attention from organic chemists and many such compounds have found widespread applications in synthetic, medicinal, and industrial chemistry.[30–32] Triarylmethanes can be synthesised by a number of methods, but most of them are multi-step processes and require harsh conditions, while Friedel–Crafts arene alkylation is a major technique in the formation of new arene-alkane C–C bonds.[33–38] Bis-indolylalkanes obtained by the condensation of indoles with aromatic or aliphatic aldehydes requires the use of several Brønsted and Lewis acids.[39–41] In the quest to develop a mild and practical protocol for the synthesis of triaryl-/triheteroarylmethanes, we speculated that iron(III) catalyst, which has recently been shown to catalyse a variety of C–C/C–N bond forming reactions,[42–47] might be ideal for effecting the condensation of aldehydes and activated arenes.

We investigated the electrophilic substitution reaction of indolizines with aldehydes in the presence of a catalytic amount of iron(III) chloride at room temperature to form triheteroarylmethane derivatives, the preparation of which usually requires multi-step processes and harsh conditions.

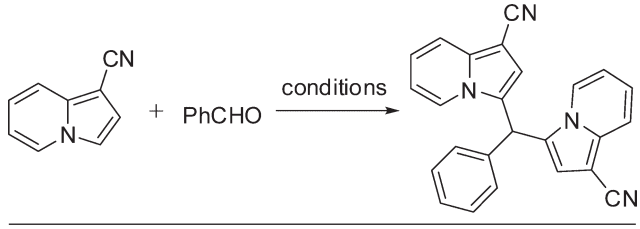
Results and discussion

The preliminary results that illustrate the efficiency and versatility of $FeCl_3$-promoted indolizines' condensation with aldehydes to afford triheteroarylmethanes-3,3′-(phenylmethylene) diiindolizine-1-carbonitrile are described in this work.

The formation of a 1,1-bis-indolizine-methane product was not observed in the presence of $FeCl_2$, $FeBr_2$, $FeSO_4$, $Fe(acac)_2$ and Fe_2O_3 (Table 1, entries 1–5). Comparable yields were obtained when $CuCl_2{\cdot}2H_2O$ and $Cu(OAc)_2{\cdot}H_2O$ were used as catalysts under 60 °C for 2 h in CH_3CN (Table 1, entries 6 and 7). However, $AlCl_3$ was a much more effective catalyst and $FeCl_3$ gave the best results at room temperature (Table 1, entries 8 and 9). The transformation completed under 60 °C in 2h in 96 % isolated yield (Table 1, entry 10). Otherwise, CH_3CN performed better than other apolar aprotic solvents (CCl_4, THF, Et_2O) and aprotic polar solvents (DMF, DMSO) (Table 1, entries 11–18). Furthermore, this transformation was very practical as it does not need the use of bases or ligands and the rigorous exclusion of air/moisture was not required.

These optimised conditions have been applied successfully for the condensation of a variety of indolizines with aldehydes. The results are summarised in Table 2. They showed that both electron-withdrawing and electron-donating substituents had no significant effect on the yields (Table 2, entries 1–3). The presence of a substituent on the *ortho*-position of aromatic aldehydes did not cause any decrease in the reaction yields (Table 2, entry 4). In the case of aliphatic aldehydes such as *n*-butyraldehyde, the reaction proceeded satisfactory in comparison with aromatic aldehydes (Table 2, entry 5). Attempts to use other indolizine derivatives in the reaction with benzaldehyde were mostly successful. Methyl, ethyl and *n*-butyl indolizine-1-carboxylate were all compatible with the catalyst system (Table 2, entries 6–8).

Table 1 Optimisation of reaction conditions[a]



Entry	Catalyst	Solvent	Yield/%[b]
1	$FeCl_2{\cdot}4H_2O$	CH_3CN	0
2	$FeBr_2$	CH_3CN	0
3	$FeSO_4$	CH_3CN	0
4	$Fe(acac)_2$	CH_3CN	0
5	Fe_2O_3	CH_3CN	0
6	$CuCl_2{\cdot}2H_2O$	CH_3CN	30[c]
7	$Cu(OAc)_2{\cdot}H_2O$	CH_3CN	22[c]
8	$FeCl_3{\cdot}6H_2O$	CH_3CN	92
9	$AlCl_3$	CH_3CN	81
10	$FeCl_3{\cdot}6H_2O$	CH_3CN	96[c]
11	$FeCl_3$	CH_2Cl_2	46
12	$FeCl_3$	$CHCl_3$	51
13	$FeCl_3$	CCl_4	60
14	$FeCl_3$	THF	39
15	$FeCl_3$	Et_2O	38
16	$FeCl_3$	EtOAc	23
17	$FeCl_3$	DMF	16
18	$FeCl_3$	DMSO	17

[a]Reaction conditions: indolizine-1-carbonitrile (0.4 mmol), benzaldehyde (0.2 mmol), catalyst (0.01 mmol), solvent (2 mL), RT, 2 h. [b]Isolated yield. [c]Performed at 60 °C for 2 h.

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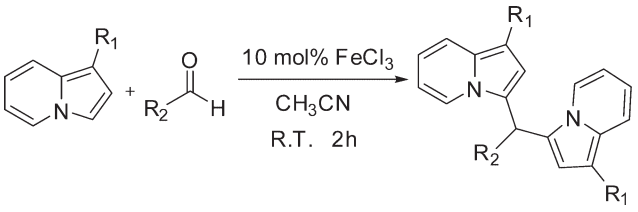
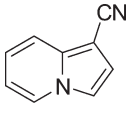
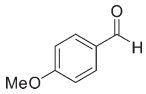
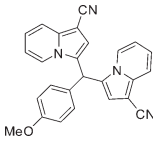
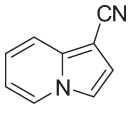
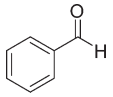
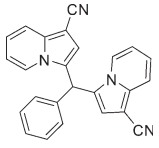
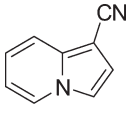
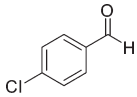
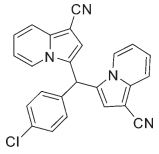
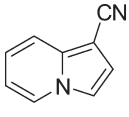
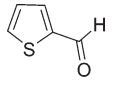
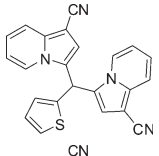
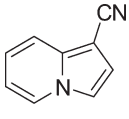
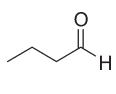
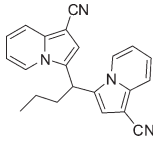
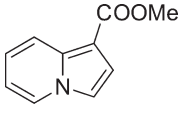
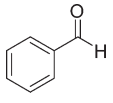
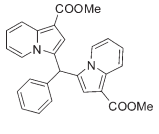
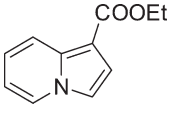
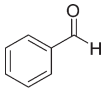
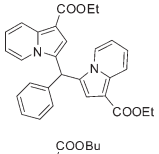
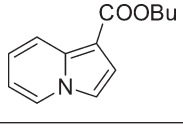
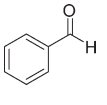
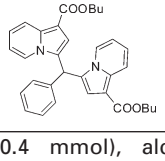
Table 2 The reaction of aldehydes with various indolizines[a]



Entry	Indolizine	Aldehydes	Products	Yield /%[b]
1				91
2				95
3				98
4				96
5				93
6				94
7				78
8				71

[a]Reaction conditions: Indolizines (0.4 mmol), aldehydes (0.2 mmol), $FeCl_3{\cdot}6H_2O$ (0.01 mmol),CH_3CN (2 mL), RT, 2h.
[b]Isolated yield.

Conclusion

In conclusion, we report our results concerning the study of indolizines' C-3 functionalisation involving C–H activation afford a diversity of C-3 substitution by benzylation. We have introduced a well-precedented electrophilic substitution reaction of indolizines with aldehydes in the presence of a catalytic amount of $FeCl_3{\cdot}6H_2O$ under mild conditions to afford triheteroarylmethane derivatives. As part of the continuing exploration of new chemistry of the indolizine ring, this reaction has potential applications in organic syntheses and industrial processes.

Experimental

Starting materials were purchased from common commercial sources and solvents were all purified and dried according to standard methods prior to use. Column chromatography was carried out on SiO_2 (300–400 mesh). ^{1}H NMR spectra were recorded with a Bruker 400 MHz spectrometer using TMS as internal standard. ^{13}C NMR spectra were recorded at 100 MHz using TMS as internal standard. The multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), multiplet (m). Mass spectroscopy data were collected with HRMS-EI and HRMS-ESI instrument.

Synthesis of triheteroarylmethane

A mixture of indolizines (0.4 mmol), aldehydes (0.2 mmol), $FeCl_3$ (5 mol%), in CH_3CN (2 mL) was stirred at room temperature for 2 h. Afterward, the mixture was filtered through a pad of Celite. The solvent was evaporated under reduced pressure, and the residue was subjected to flash column chromatography to obtain the desired product.

3,3′-((4-Methoxyphenyl)methylene)diindolizine-1-carbonitrile (**T 2-1**): Purification by column chromatography (silica gel, ethyl acetate/petroleum ether = 1/3, v/v) gave a white solid; m.p. 257–259 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.63–7.69 (m, 4 H), 7.11 (t, *J* = 8.0 Hz, 2 H), 7.06 (d, *J* = 7.6 Hz, 2 H), 7.00 (d, *J* = 8.0 Hz, 2 H), 6.73 (t, *J* = 8.0 Hz, 2 H), 6.35 (s, 2 H), 5.69 (s, 1 H), 3.81 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 138.8, 129.4, 127.8, 123.7, 122.4, 118.2, 117.2, 116.6, 114.8, 113.3, 81.4, 55.3, 40.3. HRMS (EI) Calcd for $C_{26}H_{18}N_4O$ (M^+) 402.1481; found 402.1490.

3,3′-(Phenylmethylene)diindolizine-1-carbonitrile (**T 2-2**) Purification by column chromatography (silica gel, ethyl acetate/petroleum ether = 1/3, v/v) gave a white solid; m.p. 249–250 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.68 (t, *J* = 7.2 Hz, 4 H), 7.37 (t, *J* = 7.2 Hz, 3 H), 7.17 (t, *J* = 7.2 Hz, 2 H), 7.11–7.12 (m, 2 H), 6.74 (t, *J* = 7.2 Hz, 2 H), 6.34 (s, 2 H), 5.80 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.8, 136.1, 129.4, 128.5, 128.4, 123.7, 123.4, 122.4, 118.1, 117.3, 116.5, 113.4, 81.4, 41.0. HRMS (EI) Calcd for $C_{25}H_{16}N_4$ (M^+) 372.1375; found 372.1380.

3,3′-((4-Chlorophenyl)methylene)diindolizine-1-carbonitrile (**T 2-3**): Purification by column chromatography (silica gel, ethyl acetate/petroleum ether = 1/3, v/v) afforded as a white solid; m.p. 260–262 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.69 (d, *J* = 9.2 Hz, 2 H), 7.65 (d, *J* = 8.4 Hz, 2 H), 7.38 (t, *J* = 8.4 Hz, 2 H), 7.10–7.16 (m, 4 H), 6.76 (t, *J* = 8.4 Hz, 2 H), 6.35 (s, 2 H), 5.77 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9, 134.7, 134.4, 129.8, 129.7, 123.6, 122.8, 122.6, 118.2, 117.3, 116.4, 113.5, 81.6, 40.4. HRMS (EI) Calcd for $C_{25}H_{15}ClN_4$ (M^+) 406.0985; found 406.0989.

3,3′-(Thiophen-2-ylmethylene)diindolizine-1-carbonitrile (**T 2-4**): Purification by column chromatography (silica gel, ethyl acetate/petroleum ether = 1/3, v/v) gave a white solid; m.p. 213–215 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.66–7.72 (m, 4 H), 7.32 (d, *J* = 7.6 Hz, 2 H), 7.13 (t, *J* = 8.0 Hz, 2 H), 7.00 (t, *J* = 8.0 Hz, 1 H), 6.74–6.80 (m, 3 H), 6.51 (s, 2 H), 6.07 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 138.8, 127.4, 127.1, 126.3, 123.6, 123.1, 122.6, 118.3, 117.0, 116.5, 113.5, 81.5, 36.1. HRMS (EI) Calcd for $C_{23}H_{14}N_4S$ (M^+) 378.0939; found 378.0930.

3,3′-(Butane-1,1-diyl)diindolizine-1-carbonitrile (**T 2-5**): Purification by column chromatography (silica gel, ethyl acetate/petroleum ether = 1/3, v/v) gave a white solid; m.p. 187–189 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 7.80 (d, *J* = 7.2 Hz, 2 H), 7.63 (d, *J* = 7.2 Hz, 2 H), 7.07 (t, *J* = 7.6 Hz, 2 H), 6.89 (s, 2 H), 6.75 (t, *J* = 6.8 Hz, 2 H), 4.54 (t, *J* = 7.2 Hz, 1 H), 2.20–2.26 (m, 2 H), 1.44–1.49 (m, 2 H), 1.01 (t, *J* = 7.6 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 124.0, 123.3, 122.1, 118.2, 116.7, 115.4, 113.4, 81.2, 34.6, 33.6, 20.8, 13.9. HRMS (EI) Calcd for $C_{22}H_{18}N_4$ (M^+) 338.1531; found 338.1528.

Dimethyl 3,3′-(phenylmethylene)diindolizine-1-carboxylate (**T 2-6**): Purification by column chromatography (silica gel, ethyl acetate/petroleum ether = 1/3, v/v) gave a white solid; m.p. 211–212 °C. (lit:[48] 210–211 °C) ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.27 (d, *J* = 8.0 Hz, 2 H), 7.64 (d, *J* = 7.6 Hz, 2 H), 7.34–7.36 (m, 3 H), 7.19 (d, *J* = 7.6 Hz, 2 H), 7.09 (t, *J* = 8.0 Hz, 2 H), 6.67 (t, *J* = 6.8 Hz, 2 H), 6.63 (s, 2 H), 5.72 (s, 1 H), 3.82 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 137.1, 136.7, 129.2, 128.6, 128.0, 123.3, 123.2, 122.2, 120.0, 116.8, 112.8, 103.0, 50.9, 41.3. HRMS (EI) Calcd for $C_{27}H_{22}N_2O_4$ (M^+) 438.1580; found 438.1587.

Diethyl 3,3'-(phenylmethylene)diindolizine-1-carboxylate (**T 2-7**): Purification by column chromatography (silica gel, ethyl acetate/petroleum ether = 1/3, v/v) gave a white solid; m.p. 194–195 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.27 (d, *J* = 7.6 Hz, 2 H), 7.64 (d, *J* = 7.2 Hz, 2 H), 7.34–7.35 (m, 3 H), 7.18–7.20 (m, 2 H), 7.06–7.10 (m, 2 H), 6.64–6.67 (m, 4 H), 5.72 (s, 2 H), 4.29–4.33 (m, 2 H), 1.35 (t, *J* = 7.2 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 137.2, 136.5, 129.2, 128.6, 127.9, 123.3, 123.2, 122.1, 120.1, 116.9, 112.7, 103.5, 59.5, 41.3, 14.6. HRMS (EI) Calcd for $C_{29}H_{26}N_2O_4$(M^+) 466.1893; found 466.1899.

Dibutyl 3,3'-(phenylmethylene)diindolizine-1-carboxylate (**T 2-8**): Purification by column chromatography (silica gel, ethyl acetate/petroleum ether = 1/3, v/v) gave a yellow solid; m.p. 176–177 °C. ^{1}H NMR (400 MHz, $CDCl_3$, TMS) δ 8.27 (d, *J* = 7.6 Hz, 2 H), 7.64 (d, *J* = 7.2 Hz, 2 H), 7.34–7.35 (m, 3 H), 7.18–7.20 (m, 2 H), 7.06–7.10 (m, 2 H), 6.64–6.67 (m, 4 H), 5.72 (s, 2 H), 4.29–4.33 (m, 2 H), 1.35 (t, *J* = 7.2 Hz, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 137.2, 136.5, 129.2, 128.6, 127.9, 123.3, 123.2, 122.1, 120.1, 117.0, 112.6, 103.5, 63.5, 41.3, 31.0, 19.3, 13.8. HRMS (EI) Calcd for $C_{33}H_{34}N_2O_4$ (M^+) 522.2519; found 522.2510.

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