Transition-metal-free halocarbocyclisation of acrylamides using $K_2S_2O_8$

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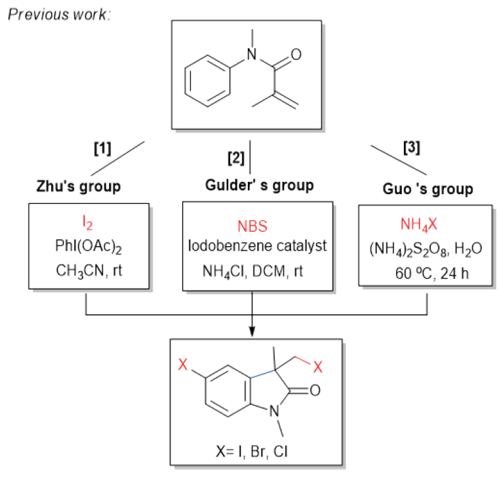
A novel and direct transition-metal-free oxidative halocarbocyclisation of acrylamides using inexpensive KX (X= I, Br, Cl) and $K_2S_2O_8$ has been developed. This methodology not only provides an efficient way to construct valuable halogenated oxindoles in good to excellent yields, but also represents a novel strategy for C–X and C–C bond formation.

Keywords: transition-metal-free, halocarbocyclisation, acrylamides, oxindoles

Oxindole frameworks have demonstrated significant potential for use in a wide range of pharmaceutical and biological applications such as an *N*-methyl-D-aspartic acid antagonist[1] and calcium channel blocker[2] as well as having anti-angiogenic,[3] anti-cancer[4] and analgesic effects.[5] Therefore, many methodologies for the synthesis of oxindoles have been developed.[6–9] It is worth noting that the direct transition-metal-free tandem C–H functionalisation/cyclisation of unactivated alkenes for the synthesis of various halogenated oxindoles is still an extremely attractive yet challenging task.[10–13] Recently Zhu and co-workers[14] realised an elegant approach for the synthesis of iodooxindoles by using $PhI(OAc)_2$ and I_2 [Scheme 1, Eqn (1)]. Gulder's group[15,16] have developed the first organocatalytic bromocarbocyclisation utilised in an effective method for the synthesis of bromooxindoles using NBS as the Br source [Scheme 1, Eqn (2)]. When our independent studies were being carried out, Guo's group[17] reported a similar method for the synthesis of halogenated oxindoles by using $(NH_4)_2S_2O_8$ as the oxidant and NH_4X (X= I, Br or Cl) as the halide source [Scheme 1, Eqn (3)].

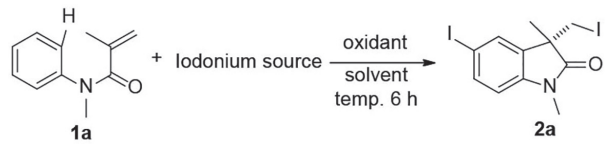
Although several elegant studies on the halocarbocyclisation of *N*-arylacrylamides have been accomplished, it is still highly desirable to develop new strategies to prepare halogenated oxindoles that are highly efficient and utilise cheap substrates and oxidants. Here we report a transition-metal-free cascade halocarbocyclisation of arylacrylamides using the very cheap KX (X= I, Br, Cl) and $K_2S_2O_8$ in aqueous solution, which allows highly efficient access to oxindoles by cascade C–X and C–C bond formation.



Scheme 1 Halocarbocyclisation of acrylamides.

In an initial study, we chose the *N*,2-dimethyl-*N*-phenylacrylamide (**1a**) and KI as the model reactants. $K_2S_2O_8$ was used as the oxidant to examine suitable reaction conditions and the results are summarised in Table 1. A number of solvents, including H_2O, THF/H_2O, DMF/H_2O, acetone/H_2O, CH_3CN/H_2O and CH_3CN, were screened at 80 °C for 8h (Table 1, entries 1–7). Moderate yields of the desired product **2a** were obtained using H_2O, THF/H_2O, DMF/H_2O and CH_3CN as solvent (Table 1, entries 1–3 and 6). It should be noted that a good yield of the desired product **2a** was obtained using acetone/H_2O as the solvent (Table 1, entry 4). To our delight, further optimisation showed that CH_3CN/H_2O (1:1) gave the best yield of 94% (Table 1, entry 5). To establish the reaction conditions that improve the reaction, several oxidants such as $K_2S_2O_8$, phenyliodinium diacetate, PhIO, *tert*-butyl hydroperoxide (TBHP) and O_2 were screened in CH_3CN/H_2O (1:1) at 80 °C for 8h (Table 1, entries

Table 1 Screening of reaction conditions[a]



Entry	Oxidant	Solvent	T (°C)	Yield (%)[b]
1	$K_2S_2O_8$	H_2O	80	47
2	$K_2S_2O_8$	THF/H_2O (1:1)	80	31
3	$K_2S_2O_8$	DMF/H_2O (1:1)	80	52
4	$K_2S_2O_8$	Acetone/H_2O (1:1)	80	82
5	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	80	94
6	$K_2S_2O_8$	CH_3CN	80	54
7	–	CH_3CN/H_2O (1:1)	80	n.d.
8	TBHP	CH_3CN/H_2O (1:1)	80	n.d.
9	O_2[c]	CH_3CN/H_2O (1:1)	80	n.d.
10	PIDA	CH_3CN/H_2O (1:1)	80	73
11	PhIO	CH_3CN/H_2O (1:1)	80	54
12	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	r.t.	n.d.
13	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	50	72
14	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	100	92
15	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	80	64[d]
16	$K_2S_2O_8$	CH_3CN/H_2O (1:1)	80	93[e]

[a]Reaction conditions: **1a** (0.25 mmol), $K_2S_2O_8$ (2 equiv.) and KI (2 equiv.) in CH_3CN/H_2O (1:1, 2.5 mL) with stirring at different temperature for 6 h. n.d. = not detected.
[b]Isolated yield.
[c]O_2 (1 atm).
[d]$K_2S_2O_8$ (1 equiv.).
[e]$K_2S_2O_8$ (3 equiv.).

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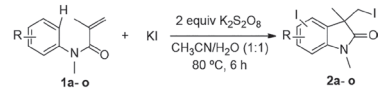
8–13). The transformation did not proceed with TBHP and O_2 (Table 1, entries 8–9). It was found that $K_2S_2O_8$ showed higher efficiency compared with the other oxidants and thus was chosen as the oxidant for further optimisation. Furthermore, screening of the reaction temperature revealed that 80 °C gave the best result (Table 1, entry 8). The ratios of **1a** to $K_2S_2O_8$ were also examined and it was found that the ratio **1a**/$K_2S_2O_8$ = 1:2 was preferable. Therefore, we chose the acrylamide together with KI (2 equiv.) and $K_2S_2O_8$ (2 equiv.) in CH_3CN/H_2O (1:1) at 80 °C for 6 h as our optimised reaction conditions.

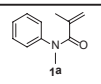
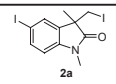
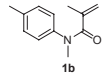
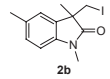
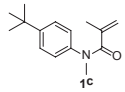
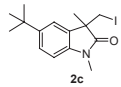
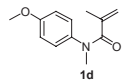
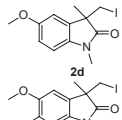
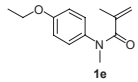
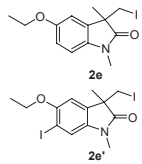
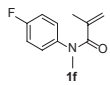
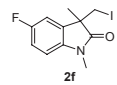
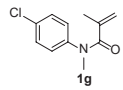
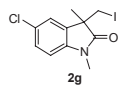
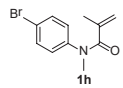
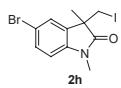
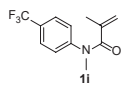
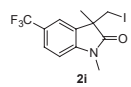
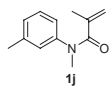
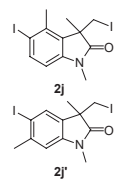
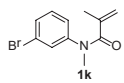
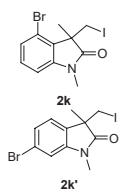
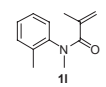
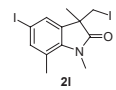
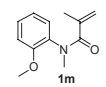
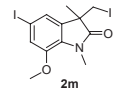
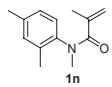
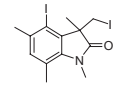
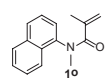
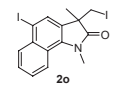
Various substrates were now subjected to the reaction under the optimised conditions and representative results are summarised in Table 2. For *N*-aryl-*N*,2-dimethylmethacrylamides bearing various electron-donating substituents (*e.g.* Me, *t*-Bu, OMe, OEt) in the *ortho*-position of the aromatic ring, the substrates could be converted successfully into the desired products in excellent yields (92–98%, Table 2, substrates **1b**–**e**). Interestingly, when a 4-methoxy or a 4-ethoxy group was present on the aromatic ring of the acrylamide, inseparable mixtures of regioisomers (**2d:2d' = 2:1, 2e:2e' = 1.5:1**) were isolated in 98% and 96% overall yields respectively. It is noteworthy that lower yields (trace–63%) were formed when electron-withdrawing groups (F, Cl, Br) were present in the *para*-position (Table 2, **2f**–**h**). However, *N*-arylacrylamides bearing a CF_3 substituent in the *para*-position failed to produce a corresponding product (Table 2, **2i**). Furthermore, the substrates bearing *meta* substituents on the *N*-arylacrylamides were well tolerated and readily converted into a mixture of two regioisomers in moderate to good yields (62–89%) with poor regioselectivity (Table 2, **2j–k** and **2j'–k'**). The *N*-arylacrylamides containing *ortho*-position substituent groups were compatible with the process and a steric hindrance effect was observed (Table 2, **2l**–**m**). For example, when the position of the methyl group on the aromatic ring of the *N*-arylacrylamide was changed from *para* to *meta* to *ortho*, the yields decreased from 95% to 89% to 79% (Table 2, **2b**, **2j** and **2l**). In addition, a 2,4-disubstituted *N*-arylacrylamide was well tolerated and afforded the desired oxindole in good yield (Table 2, **2n**). Gratifyingly, when the benzene ring was changed to a naphthalene one, the substrate also successfully formed the analogous product in 91% yield (Table 2, **2o**).

Encouraged by the above results, we subjected more *N*-arylacrylamides to the optimised conditions. To our delight, an investigation into different N-protecting groups revealed that the electron-donating protecting groups such as ethyl and *n*-butyl were appropriate for the reaction and furnished the corresponding oxindoles in very good yields (Table 3, **4a**, **4b**). A substrate bearing *N*-benzyl was tolerated but only a trace amount of the desired oxindole was isolated (Table 3, **4c**). Unfortunately, replacement of the methyl substituent with hydrogen, acetyl or Boc failed to produce the corresponding products (Table 3, **4d–f**). In addition, an α-substituted olefin bearing a phenyl group did provide the desired product in good yield (Table 3, **4g**). Tetrahydroisoquinoline structural motifs are common components in many biologically active compounds[18] and a tricyclic oxindole derivative was obtained in excellent yield from the corresponding tetrahydroquinoline substrate (Table 3, **4h**). However, when the framework of the substrate was changed by replacing the heteroatom N by O, none of the desired product was observed (Table 3, **4i**).

To realise such a transition-metal-free oxidative halocarbocyclisation, we tested different inorganic halogen salts in combination with $K_2S_2O_8$ for the conversion of model substrate **1a** into oxindoles **2a**, **5a** and **6c** (Table 4). Iodine salts, such as NaI and NH_4I were tolerated under the reaction conditions and afforded the corresponding diiodooxindoles in 94 and 52% yields

Table 2 Metal-free halocarbocyclisation of different *N*-arylacrylamides[a]

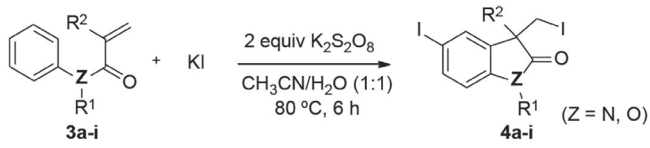


Entry	Substrate	Product	Yield (%)[b]
1			94%
2			95%
3			92%
4			98% **2d:2d'**= 2:1
5			96% **2e:2e'**= 1.5:1
6			Trace
7			51%
8			63%
9			Trace
10			89% **2j:2j'**= 1.7:1
11			62% **2k:2k'**= 3.1:1
12			79%
13			76%
14			79%
15			91%

[a]All reactions were carried out in the presence of **1a–o**, KI (0.5 mmol, 2.0 equiv.), $K_2S_2O_8$ (2.0 equiv.) in CH_3CN/H_2O (1:1, 5 mL) at 80 °C for 6 h.

[b]Isolated yield.

Table 3 Metal-free halocarbocyclisation of different arylacrylamides[a]

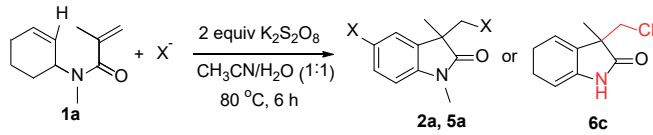


Entry	Substrate	Product	Yield (%)[b]
1	**3a**	**4a**	89%
2	**3b**	**4b**	82%
3	**3c**	**4c**	Trace
4	**3d**	**4d**	0%
5	**3e**	**4e**	0%
6	**3f**	**4f**	0%
7	**3g**	**4g**	87%
8	**3h**	**4h**	91%
9	**3i**	**4i**	0%

[a]All reactions were carried out in the presence of **3a–i**, KI (0.5 mmol, 2.0 equiv.), $K_2S_2O_8$ (2.0 equiv.) in CH_3CN/H_2O (1:1, 5 mL) at 80 °C for 6h.
[b]Isolated yield.

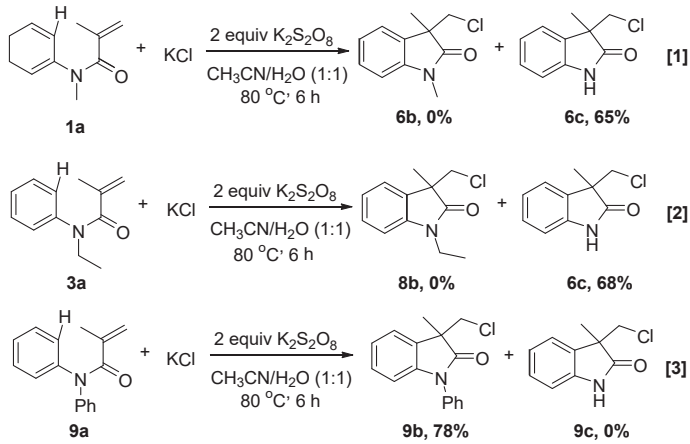
respectively (Table 4, entries 1 and 2). When KBr and NaBr were used as sources of bromide ion halocarbocyclisation went smoothly and the desired dibromooxindole **5a** was formed in good yields (Table 4, entries 3 and 4). Surprisingly, when KCl and NaCl were employed as chlorine sources, only product **6c** was isolated in moderate yields by an N-demethylation reaction (Table 4, entries 5 and 6). KF as a fluoride source demonstrated very poor activity and no fluorooxindole product was observed (Table 4, entry 7).

Table 4.Halocarbocyclisation of *N*,2-dimethyl-*N*-phenylacrylamide using different halogen salts[a]



Entry	Halide	Product	Yield (%)[b]
1	NaI	**2a**	94
2	NH_4I	**2a**	52
3	KBr	**5a**	87
4	NaBr	**5a**	84
5	KCl	**6c**	65
6	NaCl	**6c**	66
7	KF	**7a**	0

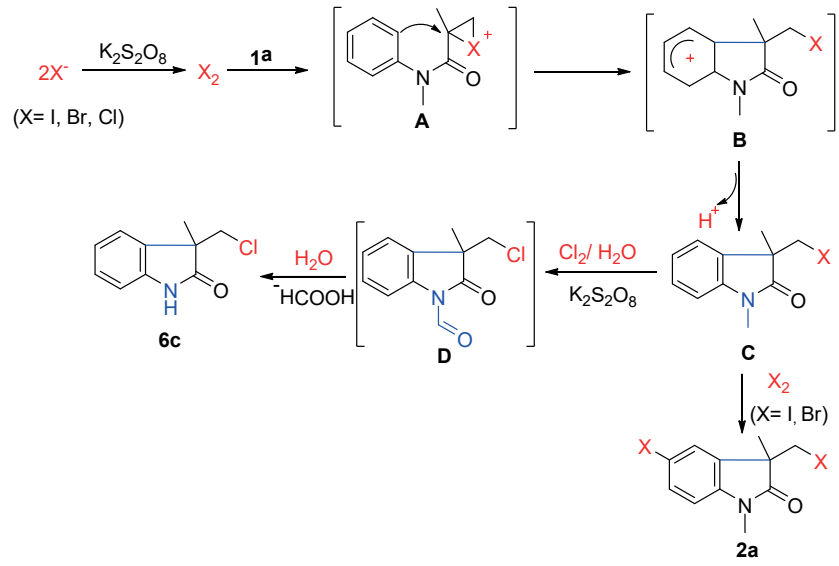
[a]Reaction conditions: **1a** (0.25 mmol), $K_2S_2O_8$ (2 equiv.) and halogen salt (2 equiv.) in CH_3CN/H_2O (1:1, 2.5 mL) with stirring at 80 °C for 6 h.
[b]Isolated yield.



Scheme 2 Investigation of the *N*-demethylation reaction.

To gain insight into the above N-demethylatiion reaction, several more experiments were conducted (Scheme 2). When the oxidative cyclisation of KCl and **1a** was carried out under the optimised conditions, the N-demethylated product **6c** was produced in 65% yield and the desired product **6b** was not observed [Scheme 2, Eqn (1)]. Similarly, replacement of **1a** with the *N*-ethylacrylamide (**3a**), gave the N-deethylated product **6c** in 68% yield and no **6b** was observed [Scheme 2, Eqn (2)]. Surprisingly, the *N,N*-diphenyl-2-methacrylamide (**9a**) could give the desired product **9b** with good yield and the N-dephenylated product **9c** was not found [Scheme 2, Eqn (3)]. We speculate that the N-demethylated and N-deethylated product **6c** may be generated by oxidation–hydrolysis of the *N*-methyl and *N*-ethyl group of the substrates with $K_2S_2O_8$ in CH_3CN/H_2O (1:1).

Based on the above experiments, a plausible mechanism for our methodology is hypothesised on the basis of literature[14–17]. Scheme 3 illustrates our proposed pathway. Initially, KX (X=I, Br, Cl) reacts with the persulfate ion to form the halogen. Then, the addition of the halogen to the activated alkene **1a** results in the formation of halonium ion **A**, followed by intramolecular carbocyclisation to generate the corresponding Wheland intermediate **B**, followed by proton loss to afford intermediate **C**. Further electrophilic halogenation of **C** affords the dihalogenated oxindoles **2a** and **5a**. In addition, with KCl as the halogen salt, the oxidation of the intermediate **C** using $K_2S_2O_8$ and HClO as the synergistic oxidants generates the intermediate



Scheme 3 Plausible mechanism for the formation of **2a** and **6c**.

D, followed by hydrolysis to afford the *N*-demethylated product **6c**.

In summary, we have demonstrated an efficient transition-metal-free oxidative halocarbocyclisation of acrylamides with halogen salts by sequential intermolecular addition and intramolecular substitution for the synthesis of monohalogenated and dihalogenated oxindoles using $K_2S_2O_8$ as oxidant. This methodology provides an economical and efficient way for the construction of halogen-containing oxindoles, which avoids expensive transition metals and oxidants. Further applications of this transformation to other simple substrates and the synthesis of more valuable compounds are underway in our group.

Experimental

Melting points were taken on a WRS-2A micro melting point apparatus and are uncorrected. All reagents and solvents were of analytical grade and purchased from Sigma-Aldrich Co. and used without additional purification. ^{1}H NMR and ^{13}C NMR spectra were obtained at 400 MHz and 100 MHz respectively on a Bruker AVANCE III HD 400MHz instrument. Chemical shifts (δ ppm) were referenced to tetramethylsilane, solvent or residual protio-solvent. Data for ^{1}H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet or unresolved, br = broad singlet, coupling constant(s) in Hz, integration). Mass spectra were recorded using a PE SCLEX QSTAR spectrometer. For Cl and Br containing products *m/z* values are given for the $[M + H]^+$ isotopomers. Purification was done by column chromatography on silica gel (200–300 mesh) with petroleum ether (30–60 °C)/ethyl acetate as the eluent.

An oven-dried Schlenk tube was charged with **1a–o**, **3a–i** or **9a** (0.5 mmol), KX (X = I, Br, Cl, 1 mmol) and $K_2S_2O_8$ (2.0 equiv.) in CH_3CN/H_2O (1:1, 5 mL). The reaction mixture was stirred at 80 °C for 6 h monitored by TLC. The mixture was then allowed to cool to room temperature and was quenched with H_2O (10 mL). This mixture was extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried with Na_2SO_4, concentrated under reduced pressure and dried under high vacuum. The residue was purified by flash chromatography on silica gel [petroleum ether (30–60 °C)/ethyl acetate] to obtain the desired products.

5-Iodo-3-(iodomethyl)-1,3-dimethylindolin-2-one (**2a**):[10] White solid; m.p. 130–131 °C (lit.[14] 129–130 °C); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.65 (dd, *J* =1.2, 8.0 Hz, 1H), 7.54 (d, *J* = 1.2 Hz, 1H), 6.67 (d, *J* = 8.4 Hz, 1H), 3.50 (d, *J* = 9.6 Hz, 1H), 3.37 (d, *J* = 9.6 Hz, 1H), 3.22 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.5, 143.4, 137.8, 135.4, 131.8, 110.5, 85.6, 50.1, 26.8, 23.4, 10.2; HRMS *m/z* (ESI) calcd for $C_{11}H_{11}NOI_2$: $[M + Na]^+$: 449.8828; found: 449.8838.

3-(Iodomethyl)-1,3,5-trimethylindolin-2-one (**2b**):[14] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.14 (d, *J* = 8.0 Hz, 1H), 7.08 (s, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 3.52 (d, *J* = 10.0 Hz, 1H), 3.41 (d, *J* = 10.0 Hz, 1H), 3.23 (s, 3H), 2.37 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.9, 140.8, 132.6, 132.3, 128.9, 123.5, 108.0, 48.7, 26.4, 23.0, 21.2, 11.0; HRMS *m/z* (ESI) calcd for $C_{12}H_{14}NOI$: $[M + Na]^+$: 338.0018; found: 337.9997.

*5-*tert*-Butyl-3-(iodomethyl)-1,3-dimethylindolin-2-one* (**2c**): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.34 (dd, *J* = 2.0, 8.0 Hz, 1H), 7.24 (d, *J* = 2.0 Hz, 1H), 6.81 (d, *J* = 8.4 Hz, 1H), 3.83 (d, *J* = 9.6 Hz, 1H), 3.75 (d, *J* = 9.6 Hz, 1H), 3.22 (s, 3H), 1.43 (s, 3H), 1.33 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.9, 146.5, 141.4, 131.7, 125.6, 120.5,108.1, 58.0, 49.3, 34.9, 31.8, 26.7, 10.9; HRMS *m/z* (ESI) calcd for $C_{15}H_{20}NOI$: $[M + Na]^+$: 380.0487; found: 380.0494.

3-(Iodomethyl)-5-methoxy-1,3-dimethylindolin-2-one (**2d**),[14] *6-iodo-3-(iodomethyl)-5-methoxy-1,3-dimethylindolin-2-one* (**2d'**),[10] **2d/2d'** = *2:1*: Yellow oil.

For **2d**: ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.90 (d, *J* = 2.4 Hz, 1H), 6.84 (d, *J* = 2.0 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 3.82 (s, 3H), 3.51 (d, *J* = 9.6 Hz, 1H), 3.40 (d, *J* = 9.6 Hz, 1H), 3.22 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.9, 156.5, 137.0, 134.5, 113.0, 110.7, 108.8, 56.3, 49.4, 26.8, 23.3, 11.1; HRMS *m/z* (ESI) calcd for $C_{12}H_{14}NO_2I$: $[M + Na]^+$: 353.9967; found: 353.9975.

For **2d'**: ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.29 (s, 1H), 6.87 (s, 1H), 3.90 (s, 3H), 3.49 (d, *J* = 9.6 Hz, 1H), 3.41 (d, *J* = 9.6 Hz, 1H), 3.21 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.7, 155.1, 138.2, 134.6, 119.3,107.3, 85.2, 57.6, 49.3, 26.8, 23.2, 10.8; HRMS *m/z* (ESI) calcd for $C_{12}H_{13}NO_2I_2$: $[M + Na]^+$: 479.8933; found: 479.8942.

5-Ethoxy-3-(iodomethyl)-1,3-dimethylindolin-2-one (**2e**), *5-ethoxy-6-iodo-3-(iodomethyl)-1,3-dimethylindolin-2-one* (**2e'**), **2e/2e'** = *1.5:1*: Yellow solid; m.p. 98 °C.

For **2e**: ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.90 (d, *J* = 2.4 Hz, 1H), 6.83 (d, *J* = 2.4 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 4.02 (q, *J* = 6.8 Hz, 2H), 3.51 (d, *J* = 9.8 Hz, 1H), 3.40 (d, *J* = 9.8 Hz, 1H), 3.22 (s, 3H), 1.50 (s, 3H), 1.42 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.6, 155.4, 137.9, 134.1, 113.4, 111.0, 108.6, 64.1, 49.0, 26.4, 23.1,15.0, 10.9; HRMS *m/z* (ESI) calcd for $C_{13}H_{16}NO_2I$: $[M + Na]^+$: 368.0123; found: 368.0135.

For **2e'**: ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.29 (s, 1H), 6.86 (s, 1H), 4.10 (q, *J* = 6.8 Hz, 2H), 3.48 (d, *J* = 10.0 Hz, 1H), 3.41 (d, *J* = 10.0 Hz, 1H), 3.20 (s, 3H), 1.51 (s, 3H), 1.48 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR

(100 MHz, $CDCl_3$, ppm): δ 177.3, 154.1, 136.6, 133.9, 118.8, 107.3, 86.0, 66.2, 49.0, 26.5, 23.1, 15.0, 10.5; HRMS *m/z* (ESI) calcd for $C_{13}H_{15}NO_2I_2$: [M + Na]$^+$: 493.9090; found: 493.9098.

5-Chloro-3-(iodomethyl)-1,3-dimethylindolin-2-one (**2g**):[17] White solid; m.p. 80–81 °C (lit.[17] 79–81 °C); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.31 (d, *J* = 8.0 Hz, 1H), 7.25 (s, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 3.51 (d, *J* = 9.8 Hz, 1H), 3.39 (d, *J* = 9.8 Hz, 1H), 3.24 (s, 3H), 1.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.4, 142.5, 133.4, 129.1, 128.7, 123.5,109.1, 49.2, 26.9, 23.6, 10.1; HRMS *m/z* (ESI) calcd for $C_{11}H_{11}NOICl$: [M + Na]$^+$: 357.9472/359.9422 (100:32); found: 357.9486/359.9428 (56:19).

5-Bromo-3-(iodomethyl)-1,3-dimethylindolin-2-one (**2h**): Yellow solid; m.p. 102–104 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.47 (dd, *J* = 1.8, 8.0 Hz, 1H), 7.38 (d, *J* = 1.8 Hz, 1H), 6.78 (d, *J* = 8.0 Hz, 1H), 3.53 (d, *J* = 9.8 Hz, 1H), 3.42 (d, *J* = 9.8 Hz, 1H), 3.23 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.6, 142.6, 133.2, 130.8, 127.7, 116.5,109.5, 48.9, 26.7, 23.8, 10.3; HRMS *m/z* (ESI) calcd for $C_{11}H_{11}NOIBr$: [M + Na]$^+$: 401.8966/403.8946; found: 401.8976/403.8952 (27:31).

5-Iodo-3-(iodomethyl)-1,3,4-trimethylindolin-2-one (**2j**),[14] *5-iodo-3-(iodomethyl)-1,3,6-trimethylindolin-2-one* (**2j'**),[14] **2j/2j'** = *1.7:1*: Yellow oil.

For **2j**: ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.63 (s, 1H), 6.79 (s, 1H), 3.49 (d, *J* = 9.8 Hz, 1H), 3.37 (d, *J* = 9.8 Hz, 1H), 3.21 (s, 3H), 2.48 (s, 3H), 1.49 (s, 3H).

For **2j'**: ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.82 (d, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 1H), 3.65 (d, *J* = 10.0 Hz, 1H), 3.59 (d, *J* = 10.0 Hz, 1H), 3.22 (s, 3H), 2.42 (s, 3H), 1.59 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.8, 177.7, 144.0, 143.9, 142.0, 139.3, 137.3, 132.8, 132.3, 131.0, 110.6, 108.3, 95.1, 92.0, 51.0, 48.6, 28.9, 26.6, 26.5, 23.7, 23.2, 10.5, 8.2; HRMS *m/z* (ESI) calcd for $C_{12}H_{13}NOI_2$: [M + Na]$^+$: 463.8984; found: 463.8997.

4-Bromo-3-(iodomethyl)-1,3-dimethylindolin-2-one (**2k**), *6-bromo-3-(iodomethyl)-1,3-dimethylindolin-2-one* (**2k'**), **2k/2k'** = *3.1:1*: Yellow solid; m.p. 104 °C.

For **2k**: ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.21 (d, *J* = 4.0 Hz, 2H), 6.85–6.81 (m, 1H), 4.02 (d, *J* = 9.8 Hz, 1H), 3.55 (d, *J* = 9.8 Hz, 1H), 3.25 (s, 3H), 1.68 (s, 3H).

For **2k'**: ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.25 (dd, *J* = 1.8, 8.0 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 1.8 Hz, 1H), 3.50 (d, *J* = 10.0 Hz, 1H), 3.39 (d, *J* = 10.0 Hz, 1H), 3.23 (s, 3H), 1.51 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.7, 145.4, 144.6, 131.5, 130.5, 130.0, 128.8, 125.5, 124.0, 122.3, 119.0,111.9, 107.3, 51.6, 48.5, 26.5, 26.4, 22.9, 20.0, 10.0, 6.9; HRMS *m/z* (ESI) calcd for $C_{11}H_{11}NOBrI$: [M + Na]$^+$: 401.8966/403.8946; found: 401.8977/403.8949 (47:52).

5-Iodo-3-(iodomethyl)-1,3,7-trimethylindolin-2-one (**2l**):[14] Yellow solid; m.p. 159–161 °C (lit.[14] 160 °C); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.41 (s, 1H), 7.34 (s, 1H), 3.49 (s,1H), 3.48 (d, *J* = 10.0 Hz, 1H), 3.32 (d, *J* = 10.0 Hz, 1H), 2.55 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 178.0, 141.0, 140.7, 135.5, 129.3, 122.4, 100.0, 85.2, 48.1, 29.7, 23.2, 18.7, 10.2; HRMS *m/z* (ESI) calcd for $C_{12}H_{13}NOI_2$: [M + Na]$^+$: 463.8984; found: 463.8988.

5-Iodo-3-(iodomethyl)-7-methoxy-1,3-dimethylindolin-2-one (**2m**): White solid; m.p. 97–99 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.40 (d, *J* = 2.0 Hz, 1H), 6.70 (d, *J* = 2.0 Hz, 1H), 3.87 (s, 3H), 3.68 (d, *J* = 10.8 Hz, 1H), 3.43 (d, *J* = 10.8 Hz, 1H), 3.39 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.6, 156.1, 138.3, 134.1, 119.3, 108.1, 85.4, 58.0, 49.3, 26.7, 23.4, 10.9; HRMS *m/z* (ESI) calcd for $C_{12}H_{13}NO_2I_2$: [M + Na]$^+$: 479.8933; found: 479.8939.

4-Iodo-3-(iodomethyl)-1,3,5,7-tetramethylindolin-2-one (**2n**): White solid; m.p. 112–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 6.90 (s, 1H), 3.64 (d, *J* = 10.0 Hz, 1H), 3.58 (d, *J* = 10.0 Hz, 1H), 3.48 (s, 3H), 2.54 (s, 3H), 2.31 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.8, 141.2, 138.6, 134.1, 131.3, 121.6, 85.3, 49.7, 26.9, 23.5, 21.3, 19.9, 10.9; HRMS *m/z* (ESI) calcd for: $C_{13}H_{15}NOI_2$: [M + Na]$^+$: 477.9141; found: 477.9152.

*7-Iodo-1-(iodomethyl)-1,3-dimethyl-1*H*-benzo[*e*]indol-2(3*H*)-one* (**2o**):[14] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 8.38 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.91 (s, 1H), 7.76–7.48 (m, 3H), 3.81 (s, 3H), 3.56 (d, *J* = 10.0 Hz, 1H), 3.40 (d, *J* = 10.0 Hz, 1H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 179.5, 140.1, 135.1, 134.2, 131.6, 129.8, 128.0, 126.8, 122.6, 122.4,92.1, 48.7, 31.2, 23.7, 9.8; HRMS *m/z* (ESI) calcd for $C_{15}H_{13}NOI_2$: [M + Na]$^+$: 499.8984; found: 499.8995.

1-Ethyl-5-iodo-3-(iodomethyl)-3-methylindolin-2-one (**4a**): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.64 (dd, *J* = 1.2, 8.0 Hz, 1H), 7.53 (d, *J* = 1.2 Hz, 1H), 6.69 (d, *J* = 8.0 Hz, 1H), 3.91–3.82 (m, 1H), 3.71–3.62 (m, 1H), 3.52 (d, *J* = 10.0 Hz, 1H), 3.36 (d, *J* = 10.0 Hz, 1H), 1.50 (s, 3H), 1.27 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ ppm 177.8, 142.9, 137.5, 134.8, 132.3, 109.8, 85.8, 49.7, 34.7, 23.5, 12.8, 10.2; HRMS *m/z* (ESI) calcd for $C_{12}H_{13}NOI_2$: [M + Na]$^+$: 463.8984; found: 463.8991.

*1-*n*-Butyl-5-iodo-3-(iodomethyl)-3-methylindolin-2-one* (**4b**): Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.66 (dd, *J* = 1.6, 8.0 Hz, 1H), 7.56 (d, *J* = 1.6 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 3.84–3.65 (m, 2H), 3.51 (d, *J* = 10.0 Hz, 1H), 3.35 (d, *J* = 10.0 Hz, 1H), 1.72–1.63 (m, 2H), 1.43–1.33 (m, 2H), 1.50 (s, 3H), 0.96 (t, *J* = 7.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.7, 143.1, 137.8, 135.1, 131.9, 109.5, 85.5, 49.6, 38.9, 29.5, 20.1, 13.6, 9.8; HRMS *m/z* (ESI) calcd for $C_{14}H_{17}NOI_2$: [M + Na]$^+$: 491.9297; found: 491.9306.

5-Iodo-3-(iodomethyl)-1-methyl-3-phenylindolin-2-one (**4g**):[14] White solid; m.p. 145–147 °C (lit.[14] 147–148 °C); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.75 (dd, *J* = 1.4, 8.0 Hz, 1H), 7.67 (d, *J* = 1.4 Hz, 1H), 7.43–7.41 (m, 2H), 7.38–7.33 (m, 3H), 6.75 (d, *J* = 8.0 Hz, 1H), 4.03 (d, *J* = 9.6 Hz, 1H), 3.74 (d, *J* = 9.6 Hz, 1H), 3.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 175.8, 143.8, 137.9, 137.0, 133.4, 133.1, 128.9, 128.2, 126.8, 110.6, 85.3, 56.5, 26.6, 9.8; HRMS *m/z* (ESI) calcd for $C_{16}H_{13}NOI_2$: [M + Na]$^+$: 511.8984; found: 511.8995.

*8-Iodo-1-(iodomethyl)-1-methyl-5,6-dihydro-1*H*-pyrrolo[3,2,1-*ij*]quinolin-2(4*H*)-one* (**4h**):[14] Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.44 (s, 1H), 7.41 (s, 1H), 3.79–3.65 (m, 2H), 3.48 (d, *J* = 9.6 Hz, 1H), 3.38 (d, *J* = 9.6 Hz, 1H), 2.81–2.72 (m, 2H), 2.03–1.97 (m, 2H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 176.0, 138.7, 136.2, 133.4, 129.5, 122.8, 84.7, 49.9, 38.9, 24.3, 22.7, 20.9, 10.3; HRMS *m/z* (ESI) calcd for $C_{13}H_{15}NOI_2$: [M + Na]$^+$: 475.8984; found: 475.8998.

5-Bromo-3-(bromomethyl)-1,3-dimethylindolin-2-one (**5a**):[16] Brown solid; m.p. 92–93 °C (lit.[16] 91 °C); ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.44 (dd, *J* =1.6, 8.0 Hz, 1H), 7.41 (d, *J* = 1.6 Hz, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 3.65 (d, *J* = 10.0 Hz, 1H), 3.57 (d, *J* = 10.0 Hz, 1H), 3.22 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.1, 142.5, 133.7, 131.4, 126.3, 115.4, 109.6, 49.4, 36.5, 26.5, 22.2; HRMS *m/z* (ESI) calcd for $C_{11}H_{11}NOBr_2$: [M + Na]$^+$: 353.9105/355.9085/357.9064; found 353.9111/355.9094/357.9070 (23:43:19).

3-(Chloromethyl)-3-methylindolin-2-one (**6c**): White solid; m.p. 67–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 9.08 (br, 1H), 7.34–7.27 (m, 2H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 7.6 Hz, 1H), 3.87 (d, *J* = 10.8 Hz, 1H), 3.80 (d, *J* = 10.8 Hz, 1H), 1.51 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 178.1, 143.1, 132.6, 129.4, 126.3, 121.8, 115.4, 59.7, 49.4, 21.8; HRMS *m/z* (ESI) calcd for $C_{10}H_{10}NOCl$: [M + Na]$^+$: 218.0349/220.0319; found: 218.0357/220.0327 (39:12).

3-(Chloromethyl)-3-methyl-1-phenylindolin-2-one (**9b**): White solid; m.p. 129–131 °C; ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ 7.53 (t, *J* = 8.0 Hz, 2H), 7.43–7.42 (m, 3H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.15 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 3.95 (d, *J* = 10.4 Hz, 1H), 3.84 (d, *J* = 10.4 Hz, 1H), 1.57 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, ppm): δ 177.9, 143.5, 133.6, 130.4, 129.3, 128.4, 128.1, 126.2, 123.8, 123.7, 110.4, 59.5, 49.8, 21.9; HRMS *m/z* (ESI) calcd for $C_{16}H_{14}NOCl$: [M + Na]$^+$: 294.0662/296.0632; found: 294.0651/296.0624 (27:8).

Acknowledgements

We thank the Taizhou Technology Plan Projects (No. 162gy54), the College Students' Science and Technology Innovation Project of Zhejiang Province (No. 2016R462005) and the Scientific Research Projects of Zhejiang Education Department (Y201636395) for financial support.

Received 19 December 2016; accepted 30 April 2017
Paper 1604490
https://doi.org/10.3184/174751917X14944355549177
Published online: 23 May 2017

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