SYNTHESIS
Journal of
Synthetic Organic
Chemistry
REPRINT

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Thieme

Synthesis of 3-Heteroaryloxindoles through *t*-BuOCl-Mediated Oxidation of 3-Heteroarylindoles

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Received 23 July 2010

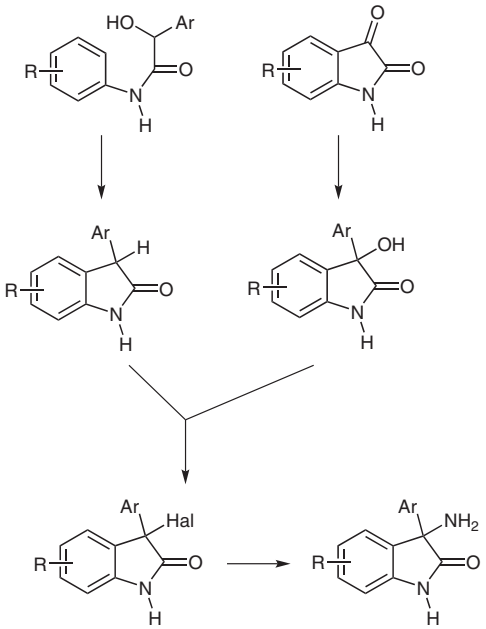
Abstract: The oxidation of 3-heteroarylindoles to the corresponding oxindoles with *t*-butyl hypochlorite has been investigated. Under carefully adjusted conditions, preparative scale of desired products can be achieved. Two competing pathways seem to contribute to the reaction mechanism, affording 3-heteroaryloxindoles bearing hydrogen or chlorine at C3, depending on stereoelectronic factors. The present methodology appears also generally applicable for the preparation of simple 3-aryloxindoles.

Key words: indole, oxindole, *t*-BuOCl, oxidation, heterocycles

Oxindole-containing heterocycles, particularly those substituted at the C3 position, are commonly encountered in natural products[1] and pharmaceutical compounds.[2] They display a wide range of biological properties, including antitumoral[3] and antiviral[4] activities.

Moreover, diverse oxindole derivatives are used as nonpeptide scaffolds[5] in the search for peptidomimetics either as enzyme inhibitors or as ligands of G-protein coupled receptors.[6] For instance, the oxindole framework is the essential feature of orally active nonpeptide arginine-vasopressin receptor antagonists,[7] of growth hormone secretagogue (ghrelin) receptors agonists,[8] and of a potent gastrin/CCK-B receptor antagonist.[9] As a consequence, the selective functionalization at C3 by alkyl, alkenyl, aryl, or heteroaryl groups of N-unsubstituted oxindoles has been a longstanding issue.[10]

In the course of a program directed toward the search for new pharmaceutically relevant oxindole scaffolds,[11] we became interested in developing the synthesis of several unprecedented 3-amino-3′-heteroaryloxindoles, especially those bearing chlorine on the aromatic ring. Preliminary attempts were directed to apply a few synthetic methodologies that are known for the preparation 3-amino-3′-aryloxindoles, such as Grignard addition to isatine[12] or intramolecular Friedel–Crafts cyclization onto α-hydroxyacetanilides,[13] according to Scheme 1. Widening the scope to 3-amino-3′-heteroaryloxindoles, we could point out that, unfortunately, these approaches proved to be quite often not applicable. In the case of Grignard addition, a limited range of organomagnesium heterocyclic compounds can be achieved. Reaction at the C3 isatine position with organolithium derivatives is moreover highly incompatible with halogenated isatine cores. On the other hand, the strongly acidic conditions and high temperatures required for Friedel–Crafts cyclization limit the range of tolerated functional groups. Also application of a palladium-catalyzed variant of the Friedel–Crafts procedure, starting from properly functionalized α-chloroacetanilides,[14] proved to be not applicable to obtain 3-heteroaryloxindoles, since nontrivial synthetic sequences are required to prepare the appropriate precursors for the reaction.



Scheme 1 Some approaches to 3-amino-3′-aryloxindoles

Therefore, our efforts turned toward setting up an alternative approach to 3-heteroaryloxindoles, based on the oxidation of the corresponding 3-heteroarylindoles by treatment with electrophilic halogenating agents. Subsequent conversion into 3-amino-3′-heteroaryloxindoles would be straightforward.[15]

While many methods exist for the construction of oxindole from non-indole precursors, fewer options are available for the direct conversion of indoles into the corresponding oxindoles.[16] These methods involve often

SYNTHESIS 2010, No. 23, pp 4075–4081
Advanced online publication: 07.10.2010
DOI: 10.1055/s-0030-1258289; Art ID: P12010SS

harsh conditions[17] or aqueous enzymatic systems[18] for the oxidation step and their applicability is sometimes restricted to a few substrates. To the best of our knowledge, this conversion has never been applied for the synthesis of 3-heteroaryloxindoles.

In our search for an efficient protocol, we drew our inspiration from the well-known oxidative rearrangement of indoles to oxindoles upon treatment with electrophilic halogenating agents, such as *tert*-butyl hypochlorite. This conversion has been investigated in simple indoles for several decades[19] and it has also found recent use in natural products chemistry.[20] The generally accepted mechanism is based on the key conversion of a 2,3-disubstituted indole into the corresponding 3-haloindolenine and also includes the migration of a R group from C2 to C3, affording the final 3,3′-disubstituted oxindole.

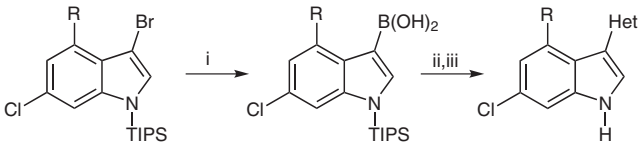
It was reasoned that *tert*-butyl hypochlorite could be a useful reagent also for our scope and so, in a first step, the preparation of a wide range of 3-heteroarylindoles as substrates was envisaged, with the aim of studying the potential applicability of this kind of oxidative process. Preparation of 3-heteroarylindoles was performed according to the general protocol reported in Table 1.[21]

The required 3-bromoindoles **1a**,**b** were prepared according to the literature.[22] Starting from **1a**,**b**, halogen–metal exchange with BuLi at –78 °C achieved highly selective 3-lithiation. Transmetalation of the resulting 3-lithioindoles with B(O-*i*Pr)$_3$ afforded indol-3-ylboronic acids **2a**,**b** in satisfactory yields.[23] With the obtained electron-rich indol-3-ylboronic acids **2a**,**b**, the coupling with bromide heterocycles, under the Suzuki–Miyaura conditions was then examined.[24] The desired cross-coupling products **3a**–**j** were readily obtained in a range of moderate to quantitative yields (Table 1).

With 3-heteroarylindoles in hand, the oxidation to the corresponding oxindoles (Table 2) was studied. To a freshly prepared 1 M solution of *t*-BuOCl in CH_2Cl_2 (1 equiv) was added a 0.3 M CH_2Cl_2 solution of **3a**. After consumption of the starting material, visualized by TLC, the solvent was removed under a nitrogen stream and the residue was dissolved in a 2:1 1,4-dioxane–aq 3 N H_2SO_4 solution. After two hours, only the corresponding 2-chloroindole **4a** was recovered quantitatively (Table 2, entry 1). Treatment of **4a** with one equivalent of *t*-BuOCl afforded **6a** in high yield (entry 2). Reasoning on the reaction mechanism, it was deduced that more *t*-BuOCl would be necessary in order to carry out the oxidation and so the reaction on **3a** with two equivalents of *t*-BuOCl (entry 3) was planned. In this case 3-chlorooxindole **6a** was isolated, together again with 20% of 2-chloroindole **4a**. The best result was then achieved with three equivalents of *t*-BuOCl, the reaction affording 3-chlorooxindole **6a** in almost quantitative yield (entry 4). With substrates **3b–e** the corresponding 3-chlorooxindoles were produced, without recovery of 2-chloroindole, already with two equivalents of *t*-BuOCl. Attempts to get higher yields employing more oxidant were not successful, since increasing amounts of chlorinated by-products started to appear (entries 5–8).

The reaction of substrate **3f**, bearing an additional chlorine substituent at C4 of the indole nucleus with one equivalent of *t*-BuOCl afforded a mixture of 2-chloroindole **4f** (53%) and oxindole **5f** (38%), suggesting that a slightly different reaction pathway would apply in this case (entry 9). In fact, when two equivalents of *t*-BuOCl

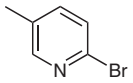
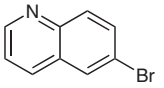
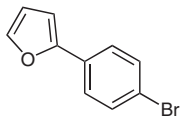
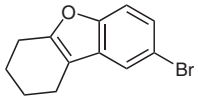
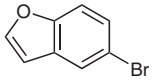
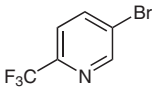
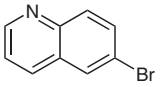
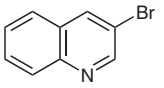
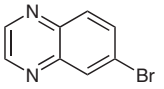
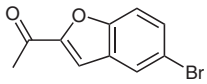
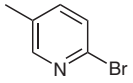
Table 1 Synthesis of 3-Heteroarylindoles **3a**–**j**[a]



1a R = H
1b R = Cl

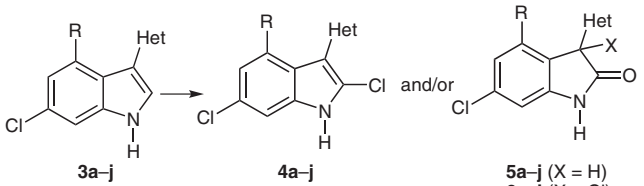
2a R = H
2b R = Cl

3a–j

3-Bromoindole	R	Het-Br	Product	Yield (%)
1a	H		**3a**	65
1a	H		**3b**	69
1a	H		**3c**	87
1a	H		**3d**	67
1a	H		**3e**	79
1b	Cl		**3f**	95
1b	Cl		**3g**	72
1b	Cl		**3h**	96
1b	Cl		**3i**	50
1b	Cl		**3j**	63
1a	H		**3a**	65

[a] Reaction conditions: (i) BuLi (1.6 M; 1.1 equiv), B(O*i*-Pr)$_3$ (3 equiv), THF, –78 °C; (ii) HetBr (1 equiv), Pd(PPh$_3$)$_4$ (0.05 equiv), toluene–MeOH, aq Na_2CO_3 (2 M), reflux; (iii) $Bu_4N^+F^-$ (1 M in THF), THF, 0 °C.

Table 2 Synthesis of 3-Heteroaryloxindoles **5** and **6**[a]

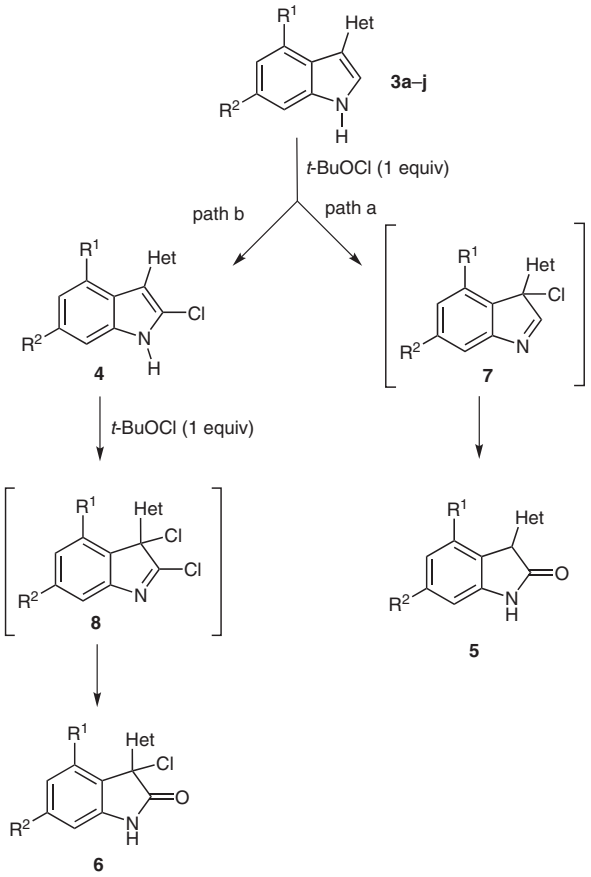


Entry	Substrate	R	*t*-BuOCl (equiv)	Yield (%) **4a–j**	Yield (%) **5a–j**	Yield (%) **6a–j**
1	**3a**	H	1	96	–	–
2	**4a**	H	1	–	–	96
3	**3a**	H	2	20	–	65
4	**3a**	H	3	–	–	91
5	**3b**	H	2	–	–	85
6	**3c**	H	2	–	–	66[b]
7	**3d**	H	2	–	–	64[b]
8	**3e**	H	2	–	–	60
9	**3f**	Cl	1	53	38	–
10	**3f**	Cl	2	–	40	55
11	**4f**	Cl	1	–	–	96
12	**3g**	Cl	2	–	81	16
13	**3h**	Cl	2	–	70	17
13	**3i**	Cl	2	–	78	18
14	**3j**	Cl	2	–	48	17

[a] Reaction conditions: (i) 1 M *t*-BuOCl in CH_2Cl_2, CH_2Cl_2, r.t.; (ii) then dioxane–aq 3 N H_2SO_4 (2:1).
[b] Some traces of halogenated by-products were detected.

were employed, almost the same amount of **5f** was obtained, together with 55% of 3-chlorooxindole **6f** (entry 10). Also in this case, quantitative conversion of 2-chloroindole **4f** into 3-chlorooxindole **6f** was realized with one equivalent of *t*-BuOCl (entry 11). Finally, starting from substrates **3g–j**, high conversions into the corresponding oxindoles were always observed, albeit as mixtures of compounds **5** and **6** (entries 12–15).

Reasoning on the reaction mechanism and in accordance with the well-known[25] oxidative rearrangement of indoles to oxindoles, promoted by electrophilic halogenating agents, the first chlorination step should afford preferentially the 3-chloroindolenine derivative **7** (Scheme 2, path a), which is the precursor of the oxindole **5**. From our results, however, it was deduced that the presence of a heteroaryl substituent at C3 affects deeply the outcome of this reaction, leading primarily the electrophilic attack of *t*-BuOCl at C2, probably for both steric and electronic reasons (path b). In particular, electronic effects would play a key role, due to the extensive conjugation of the all coplanar aromatic ring system. When an additional equivalent of *t*-BuOCl was added, the initially formed 2-chloroindole **4** was converted into the corresponding 3-chlorooxindole **6**, via the dichloroindolenine derivative **8**. In the case of substrates **3f–j** bearing an additional chlorine substituent at C4, the effect of the presence of the substituent on C3 seems to fade out, probably also due to the lost of coplanarity imposed by steric hindrance of the chlorine at C4. As a consequence, the competitive C3 electrophilic attack takes place all along, affording directly oxindoles **5**, together with 3-chlorooxindoles **6**. In these cases, slight differences in the ratio between yields of compounds **5** and **6** could be addressed to further less predictable stereoelectronic effects.



Scheme 2 Proposed mechanism for the reaction of 3-heteroarylindoles **3a–j** with *t*-BuOCl

In summary, by means of a careful adjustment of the reaction conditions, the synthesis of 3-heteroaryloxindoles by *t*-BuOCl-mediated oxidation of 3-heteroarylindoles was found to be general. It can be applied to a variety of functionalized indoles yielding products, which are at this time hardly achievable by other methods. It should be highlighted that both oxindoles **5** and 3-chlorooxindoles **6** proved to be well suited for subsequent transformation towards 3-amino-3′-heteroaryloxindoles.

All solvents were distilled and properly dried, when necessary, prior to use. All chemicals were purchased from commercial sources and used directly, unless indicated otherwise. All reactions were run un-

der N_2, unless otherwise indicated. All reactions were monitored by TLC on precoated silica gel 60 F254; spots were visualized with UV light or by treatment with 1% aq $KMnO_4$. Products were purified by flash chromatography (FC) on silica gel 60 (230–400 mesh). ^1H and ^{13}C NMR spectra were recorded using 300 and 400 MHz spectrometers. Chemical shifts (δ) are expressed in ppm relative to TMS at δ = 0 for ^1H NMR and to $CDCl_3$ at δ = 77.16 for ^{13}C NMR spectroscopy. High-resolution MS spectra were recorded using an FT-ICR (Fourier Transform Ion Cyclotron Resonance) instrument, equipped with ESI source, or a standard MS instrument, equipped with EI source. IR spectra were recorded using an FTIR instrument.

3-Heteroarylindoles 3; 6-Chloro-3-(5-methylpyridin-2-yl)-1*H*-indole (3a); Typical Procedure

To a solution of 2-bromo-5-methylpyridine (172 g/mol, 2 g, 11.6 mmol, 1 equiv) and [6-chloro-1-(triisopropylsilyl)-1*H*-indol-3-yl]boronic acid (**2a**; 351 g/mol, 4 g, 11.6 mmol, 1 equiv) in a toluene–MeOH (4:1) solution (50 mL) were added aq 2 M Na_2CO_3 (9 mL), and $Pd(PPh_3)_4$ (1155.5 g/mol, 670 mg, 0.6 mmol, 0.05 equiv). The mixture was heated at reflux under stirring for 4 h, cooled, and then partitioned between EtOAc (50 mL) and H_2O (50 mL). After extraction, the organic phase was washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated. The residue was dissolved in THF (30 mL) at 0 °C and a 1 M solution of $Bu_4N^+F^-$ in THF (2 equiv) was added. After stirring for 2 h, the reaction mixture was diluted with CH_2Cl_2 (30 mL) and the CH_2Cl_2 was washed with H_2O (30 mL). The organic phase was dried ($MgSO_4$), filtered, and concentrated; the residue was purified by FC (*n*-hexane–EtOAc, 98:2) to give **3a** (1.83 g, 65%) as a foam.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.76 (br s, 1 H), 8.44 (br s, 1 H), 8.20 (d, *J* = 8.8 Hz, 1 H), 7.65 (d, *J* = 1.9 Hz, 1 H), 7.59–7.51 (m, 2 H), 7.36 (d, *J* = 1.4 Hz, 1 H), 7.17 (dd, *J* = 8.8, 1.4 Hz, 1 H), 2.35 (s, 3 H).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{11}ClN_2$: 242.0611; found: 242.0622.

Anal. Calcd for $C_{14}H_{11}ClN_2$: C, 69.28; H, 4.57; N, 11.54; Cl, 14.61. Found: C, 69.33; H, 4.47; N, 11.61; Cl, 14.64.

6-(6-Chloro-1*H*-indol-3-yl)quinoline (3b)

Compound **3b** (69% yield, foam) was prepared starting from **2a** and from the proper heteroaryl bromide, according to the procedure described for **3a** and purified by FC (*n*-hexane–EtOAc, 98:2).

^1H NMR (400 MHz, DMSO-d_6): δ = 12.20 (s, 1 H), 8.89 (dd, *J* = 5.2, 1.5 Hz, 1 H), 8.33 (dd, *J* = 7.8, 1.5 Hz, 1 H), 8.04 (br d, *J* = 8.7 Hz, 1 H), 8.00 (br s, 1 H), 7.99 (dd, *J* = 8.7, 1.9 Hz, 1 H), 7.59 (d, *J* = 1.6 Hz, 1 H), 7.57 (dd, *J* = 7.8, 5.2 Hz, 1 H), 8.22 (d, *J* = 7.5 Hz, 1 H), 7.19 (dd, *J* = 7.5, 1.4 Hz, 1 H), 7.39 (br s, 1 H).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{11}ClN_2$: 278.0611; found: 278.0622.

Anal. Calcd for $C_{17}H_{11}ClN_2$: C, 73.25; H, 3.98; N, 10.05; Cl, 12.72. Found: C, 73.28; H, 3.88; N, 9.94; Cl, 12.69.

6-Chloro-3-[4-(furan-2-yl)phenyl]-1*H*-indole (3c)

Compound **3c** (87% yield, foam) was prepared starting from **2a** and from the proper heteroaryl bromide, according to the procedure described for **3a** and purified by FC (cyclohexane).

^1H NMR (400 MHz, DMSO-d_6): δ = 11.6 (s, 1 H), 7.89 (d, *J* = 8.5 Hz, 1 H), 7.79 (d, *J* = 2.2 Hz, 1 H), 7.76–7.71 (m, 5 H), 7.53 (br d, *J* = 1.3 Hz, 1 H), 7.12 (dd, *J* = 8.5, 1.3 Hz, 1 H), 6.91 (d, *J* = 3.5 Hz, 1 H), 6.61–6.59 (m, 1 H).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{12}ClNO$: 293.0607; found: 293.0616.

Anal. Calcd for $C_{18}H_{12}ClNO$: C, 73.60; H, 4.12; N, 4.77; Cl, 12.07. Found: C, 73.67; H, 4.01; N, 4.67; Cl, 12.09.

6-Chloro-3-(6,7,8,9-tetrahydrodibenzo[*b*,*d*]furan-2-yl)-1*H*-indole (3d)

Compound **3d** (67% yield, foam) was prepared starting from **2a** and from the proper heteroaryl bromide, according to the procedure described for **3a** and purified by FC (*n*-hexane–EtOAc, 98:2).

^1H NMR (400 MHz, DMSO-d_6): δ = 11.40 (br s, 1 H), 7.85 (d, *J* = 8.5 Hz, 1 H), 7.67 (s, 1 H), 7.66 (s, 1 H), 7.51 (br s, 1 H), 7.51–7.47 (m, 2 H), 7.10 (dd, *J* = 8.5, 1.9 Hz, 1 H), 2.75 (br t, *J* = 5.8 Hz, 2 H), 2.65 (br t, *J* = 5.8 Hz, 2 H), 1.94–1.89 (m, 2 H), 1.86–1.79 (m, 2 H).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{16}ClNO$: 321.0920; found: 321.0931.

Anal. Calcd for $C_{20}H_{16}ClNO$: C, 74.65; H, 5.01; N, 4.35; Cl, 11.02. Found: C, 74.71; H, 5.09; N, 4.25; Cl, 11.09.

3-(Benzofuran-5-yl)-6-chloro-1*H*-indole (3e)

Compound **3e** (79% yield, foam) was prepared starting from **2a** and from the proper heteroaryl bromide, according to the procedure described for **3a** and purified by FC (*n*-hexane–EtOAc, 98:2).

^1H NMR (400 MHz, DMSO-d_6): δ = 11.40 (br s, 1 H), 7.99 (d, *J* = 2.0 Hz, 1 H), 7.91 (d, *J* = 1.3 Hz, 1 H), 7.87 (d, *J* = 8.3 Hz, 1 H), 7.70 (d, *J* = 2.3 Hz, 1 H), 7.65 (d, *J* = 8.2 Hz, 1 H), 7.59 (dd, *J* = 8.3, 1.3 Hz, 1 H), 7.50 (d, *J* = 1.8 Hz, 1 H), 7.11 (dd, *J* = 8.3, 1.8 Hz, 1 H), 6.99 (dd, *J* = 2.0, 0.7 Hz, 1 H).

HRMS (EI): *m*/*z* calcd for $C_{16}H_{10}ClNO$: 267.0451; found: 267.0444.

Anal. Calcd for $C_{16}H_{10}ClNO$: C, 71.78; H, 3.77; N, 5.23; Cl, 13.24. Found: C, 71.68; H, 3.65; N, 5.31; Cl, 13.28.

4,6-Dichloro-3-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-indole (3f)

Compound **3f** (95% yield, foam) was prepared starting from **2b** and from the proper heteroaryl bromide, according to the procedure described for **3a** and purified by FC (*n*-hexane–EtOAc, 9:1).

^1H NMR (300 MHz, $CDCl_3$): δ = 8.85 (br s, 1 H), 8.72 (br s, 1 H), 8.01 (br d, *J* = 7.5 Hz, 1 H), 7.71 (d, *J* = 7.5 Hz, 1 H), 7.39 (br s, 1 H), 7.29 (d, *J* = 2.1 Hz, 1 H), 7.19 (br s, 1 H).

HRMS (EI): *m*/*z* calcd for $C_{14}H_7Cl_2F_3N_2$: 329.9938; found: 329.9951.

Anal. Calcd for $C_{14}H_7Cl_2F_3N_2$: C, 50.78; H, 2.13; N, 8.46; Cl, 21.41. Found: C, 50.61; H, 2.15; N, 8.52; Cl, 21.49.

6-(4,6-Dichloro-1*H*-indol-3-yl)quinoline (3g)

Compound **3g** (72% yield, foam) was prepared starting from **2b** and from the proper heteroaryl bromide, according to the procedure described for **3a** and purified by FC (*n*-hexane–EtOAc, 98:2).

^1H NMR (300 MHz, DMSO-d_6): δ = 11.87 (br s, 1 H), 8.90 (dd, *J* = 4.1, 1.9 Hz, 1 H), 8.37 (dd, *J* = 8.2, 1.6 Hz, 1 H), 8.02 (d, *J* = 7.5 Hz, 1 H), 8.01 (s, 1 H), 7.89 (dd, *J* = 7.5, 1.9 Hz, 1 H), 7.67 (d, *J* = 1.9 Hz, 1 H), 7.56 (d, *J* = 1.6 Hz, 1 H), 7.55 (dd, *J* = 8.2, 5.2 Hz, 1 H), 7.17 (d, *J* = 1.6 Hz, 1 H).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{10}Cl_2N_2$: 312.0221; found: 312.0226.

Anal. Calcd for $C_{17}H_{10}Cl_2N_2$: C, 65.20; H, 3.22; N, 8.94; Cl, 22.64. Found: C, 65.28; H, 3.31; N, 8.83; Cl, 22.54.

3-(4,6-Dichloro-1*H*-indol-3-yl)quinoline (3h)

Compound **3h** (96% yield, foam) was prepared starting from **2b** and from the proper heteroaryl bromide, according to the procedure described for **3a** and purified by FC (*n*-hexane–EtOAc, 98:2).

^1H NMR (300 MHz, DMSO-d_6): δ = 12.01 (br s, 1 H), 9.19 (d, *J* = 1.6 Hz, 1 H), 8.40 (br s, 1 H), 8.09 (d, *J* = 8.1 Hz, 1 H), 8.03 (d,

J = 8.1 Hz, 1 H), 7.80 (m, 2 H), 7.64 (t, *J* = 8.1 Hz, 1 H), 7.58 (d, *J* = 1.4 Hz, 1 H), 7.25 (br s, 1 H).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{10}Cl_2N_2$: 312.0221; found: 312.0218.

Anal. Calcd for $C_{17}H_{10}Cl_2N_2$: C, 65.20; H, 3.22; N, 8.94; Cl, 22.64. Found: C, 65.18; H, 3.26; N, 8.88; Cl, 22.55.

6-(4,6-Dichloro-1*H*-indol-3-yl)quinoxaline (3i)
Compound **3i** (50% yield, foam) was prepared starting from **2b** and from the proper heteroaryl bromide, according to the procedure described for **3a** and purified by FC (*n*-hexane–EtOAc, 98:2).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 12.01 (s, 1 H), 9.00–8.94 (m, 2 H), 8.13 (d, *J* = 2.9 Hz, 1 H), 8.13 (d, *J* = 8.0 Hz, 1H), 8.02 (dd, *J* = 8.0, 2.9 Hz, 1 H), 7.80 (s, 1 H), 7.58 (d, *J* = 1.8 Hz, 1 H), 7.24 (d, *J* = 1.8 Hz, 1 H).

HRMS (EI): *m*/*z* calcd for $C_{16}H_9Cl_2N_3$: 313.0174; found: 313.0153.

Anal. Calcd for $C_{16}H_9Cl_2N_3$: C, 61.17; H, 2.89; N, 13.38; Cl, 22.57. Found: C, 61.08; H, 2.95; N, 13.27; Cl, 22.50.

1-[5-(4,6-Dichloro-1*H*-indol-3-yl)benzofuran-2-yl]ethanone (3j)
Compound **3j** (63% yield, foam) was prepared starting from **2b** and from the proper heteroaryl bromide, according to the procedure described for **3a** and purified by FC (*n*-hexane–EtOAc, 98:2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.76 (s, 1 H), 7.91 (br s, 1 H), 7.85 (br d, *J* = 1.3 Hz, 1 H), 7.71 (br d, *J* = 8.5 Hz, 1 H), 7.61 (dd, *J* = 8.5, 1.9 Hz, 1 H), 7.56 (s, 1 H), 7.53 (d, *J* = 1.9 Hz, 1 H), 7.14 (d, *J* = 1.9 Hz, 1 H), 2.59 (s, 3 H).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{11}Cl_2NO_2$: 343.0167; found: 343.0176.

Anal. Calcd for $C_{18}H_{11}Cl_2NO_2$: C, 62.81; H, 3.22; N, 4.07; Cl, 20.60. Found: C, 62.99; H, 3.31; N, 4.00; Cl, 20.55.

Preparation of *t*-BuOCl
In a flask containing commercial bleach (50 mL) cooled at 10 °C were quickly added *t*-BuOH (74.1 g/mol, 3.7 mL, 39 mmol, 0.79 g/mL, 1 equiv) and glacial AcOH (60.0 g/mol, 2.45 mL, 43 mmol, 1.05 g/mL, 1.1 equiv). This mixture was stirred for 5 min, then the organic layer was separated and washed with 10% aq $NaHCO_3$ (5 mL) and then with H_2O (5 mL). The organic phase (yellow oil, *t*-BuOCl, 3 g) was dried with $CaCl_2$ and conserved in freezer. **CAUTION**: avoid exposure to light and contact with plastic material and metallic needles.

Oxidation of 3-Heteroarylindoles 3 with *t*-BuOCl; General Procedure
To a solution of *t*-BuOCl (108.4 g/mol, 0.24 mL, 2.0 mmol, 2.0 equiv, 0.91 g/mL) in anhyd CH_2Cl_2 (3 mL) was added a solution of indole **3** (1.0 mmol) in anhyd CH_2Cl_2 (3 mL) and the reaction mixture was stirred at r.t. for 1 h. Then, the solvent was evaporated under a N_2 stream and the residue was treated with 3 N aq 1,4-dioxane–H_2SO_4 (2:1, 3 mL) and stirred for 1 h. Sat. aq $NaHCO_3$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (2 × 2 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was purified by FC on silica gel (see below) to give the products as foams.

2,6-Dichloro-3-(5-methylpyridin-2-yl)-1*H*-indole (4a)
FC (hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.81 (br s, 1 H), 8.56 (br s, 1 H), 8.02 (d, *J* = 8.9 Hz, 1 H), 7.66–7.63 (m, 1 H), 7.58–7.55 (m, 1 H), 7.19 (br s, 1 H), 7.11 (dd, *J* = 8.9, 2.3 Hz, 1 H), 2.32 (s, 3 H).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{10}Cl_2N_2$: 276.0221; found: 276.0231.

Anal. Calcd for $C_{14}H_{10}Cl_2N_2$: C, 60.67; H, 3.64; N, 10.11; Cl, 25.58. Found: C, 60.58; H, 3.54; N, 10.26; Cl, 25.52.

3,6-Dichloro-3-(5-methylpyridin-2-yl)indolin-2-one (6a)
FC (hexane–EtOAc, 1:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.78 (br s, 1 H), 8.32 (d, *J* = 1.1 Hz, 1 H), 7.87 (d, *J* = 9.8 Hz, 1 H), 7.58 (dd, *J* = 9.8, 1.1 Hz, 1 H), 7.21 (d, *J* = 8.9 Hz, 1 H), 7.01 (dd, *J* = 8.9, 2.8 Hz, 1 H), 6.89 (d, *J* = 2.8 Hz, 1 H), 2.33 (s, 3 H).

HRMS (EI): *m*/*z* calcd for $C_{14}H_{10}Cl_2N_2O$: 292.0170; found: 292.0155.

Anal. Calcd for $C_{14}H_{10}Cl_2N_2O$: C, 57.36; H, 3.44; N, 9.56; Cl, 24.19. Found: C, 57.39; H, 3.34; N, 9.65; Cl, 24.16.

3,6-Dichloro-3-(quinolin-6-yl)indolin-2-one (6b)
FC (hexane–EtOAc, 8:2).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.80 (s, 1 H), 8.90 (dd, *J* = 4.0, 1.9 Hz, 1 H), 8.35 (d, *J* = 8.5 Hz, 1 H), 7.93 (d, *J* = 8.7 Hz, 1 H), 7.77 (d, *J* = 1.7 Hz, 1 H), 7.55 (dd, *J* = 8.5, 4.0 Hz, 1 H), 7.42 (dd, *J* = 8.7, 1.8 Hz, 1 H), 7.23 (d, *J* = 1.7 Hz, 1 H), 7.13–7.00 (m, 2 H).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{10}Cl_2N_2O$: 328.0170; found: 328.0187.

Anal. Calcd for $C_{17}H_{10}Cl_2N_2O$: C, 62.03; H, 3.06; N, 8.51; Cl, 21.54. Found: C, 62.23; H, 3.15; N, 8.47; Cl, 21.45.

3,6-Dichloro-3-[4-(furan-2-yl)phenyl]indolin-2-one (6c)
FC (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.14 (br s, 1 H), 7.86 (d, *J* = 2.0 Hz, 1 H), 7.72–7.70 (m, 2 H), 7.53–7.51 (m, 3 H), 7.44 (d, *J* = 8.2 Hz, 1 H), 7.18 (dd, *J* = 8.2, 1.9 Hz, 1 H), 7.04 (d, *J* = 3.5 Hz, 1 H), 6.62–6.64 (m, 1 H).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{11}Cl_2NO_2$: 343.0167; found: 343.0176.

Anal. Calcd for $C_{18}H_{11}Cl_2NO_2$: C, 62.81; H, 3.22; N, 4.07; Cl, 20.60. Found: C, 62.88; H, 3.26; N, 4.00; Cl, 20.62.

3,6-Dichloro-3-(6,7,8,9-tetrahydrodibenzo[*b*,*d*]furan-2-yl)indolin-2-one (6d)
FC (hexane–EtOAc, 95:5).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.50 (s, 1 H), 7.45 (d, *J* = 1.8 Hz, 1 H), 7.37 (d, *J* = 8.6 Hz, 1 H), 7.12–7.10 (m, 1 H), 7.05–6.99 (m, 2 H), 6.93 (d, *J* = 1.7 Hz, 1 H), 2.73–2.70 (m, 2 H), 2.57–2.54 (m, 2 H), 1.90–1.87 (m, 2 H), 1.81–1.78 (m, 2 H).

HRMS (EI): *m*/*z* calcd for $C_{20}H_{15}Cl_2NO_2$: 371.0480; found: 371.0489.

Anal. Calcd for $C_{20}H_{15}Cl_2NO_2$: C, 64.53; H, 4.06; N, 3.76; Cl, 19.05. Found: C, 64.64; H, 4.12; N, 3.66; Cl, 19.10.

3-(Benzofuran-5-yl)-3,6-dichloroindolin-2-one (6e)
FC (hexane–EtOAc, 97:3).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.50 (s, 1 H), 7.96 (d, *J* = 2.2 Hz, 1 H), 7.58 (d, *J* = 1.8 Hz, 1 H), 7.52 (d, *J* = 8.6 Hz, 1 H), 7.23 (dd, *J* = 8.7, 1.9 Hz, 1 H), 7.14 (d, *J* = 8.1 Hz, 1 H), 7.04–7.02 (m, 1 H), 6.96–6.94 (m, 2 H).

HRMS (EI): *m*/*z* calcd for $C_{16}H_9Cl_2NO_2$: 317.0010; found: 317.0019.

Anal. Calcd for $C_{16}H_9Cl_2NO_2$: C, 60.40; H, 2.85; N, 4.40; Cl, 22.29. Found: C, 60.30; H, 2.79; N, 4.35; Cl, 22.22.

2,4,6-Trichloro-3-[5-(trifluoromethyl)pyridin-2-yl]-1*H*-indole (4f)
FC (hexane–EtOAc, 9:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.09 (br s, 1 H), 8.82 (d, *J* = 1.4 Hz, 1 H), 7.97 (dd, *J* = 8.2, 1.4 Hz, 1 H), 7.77 (d, *J* = 8.2 Hz, 1 H), 7.32 (d, *J* = 2.8 Hz, 1 H), 7.17 (d, *J* = 2.8 Hz, 1 H).

HRMS (EI): *m*/*z* calcd for $C_{14}H_6Cl_3F_3N_2$: 363.9549; found: 363.9557.

Anal. Calcd for $C_{14}H_6Cl_3F_3N_2$: C, 46.00; H, 1.65; N, 7.66; Cl, 29.09. Found: C, 45.88; H, 1.54; N, 7.75; Cl, 29.01.

4,6-Dichloro-3-[5-(trifluoromethyl)pyridin-2-yl]indolin-2-one (5f)
FC (hexane–EtOAc, 9:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.62 (s, 1 H), 8.48 (br s, 1 H), 7.64 (s, 2 H), 7.09 (d, *J* = 1.3 Hz, 1 H), 6.92 (d, *J* = 1.3 Hz, 1 H), 4.68 (s, 1 H).

HRMS (EI): *m*/*z* calcd for $C_{14}H_7Cl_2F_3N_2O$: 345.9888; found: 345.9903.

Anal. Calcd for $C_{14}H_7Cl_2F_3N_2O$: C, 48.44; H, 2.03; N, 8.07; Cl, 20.43. Found: C, 48.52; H, 2.11; N, 8.01; Cl, 20.39.

3,4,6-Trichloro-3-[5-(trifluoromethyl)pyridin-2-yl]indolin-2-one (6f)
FC (hexane–EtOAc, 9:1).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.66 (br s, 1 H), 8.33 (br s, 1 H), 8.13 (dd, *J* = 8.9, 1.3 Hz, 1 H), 7.75 (d, *J* = 8.9 Hz, 1 H), 7.17 (s, 1 H), 6.97 (br s, 1 H).

HRMS (EI): *m*/*z* calcd for $C_{14}H_6Cl_3F_3N_2O$: 379.9498; found: 379.9507.

Anal. Calcd for $C_{14}H_6Cl_3F_3N_2O$: C, 44.07; H, 1.58; N, 7.34; Cl, 27.87. Found: C, 44.00; H, 1.71; N, 7.39; Cl, 27.81.

4,6-Dichloro-3-(quinolin-6-yl)indolin-2-one (5g)
FC (hexane–EtOAc, 8:2).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.90 (s, 1 H), 8.90 (dd, *J* = 4.1, 1.9 Hz, 1 H), 8.37 (d, *J* = 8.5 Hz, 1 H), 7.98 (d, *J* = 8.8 Hz, 1 H), 7.78 (d, *J* = 1.8 Hz, 1 H), 7.55 (dd, *J* = 8.2, 4.0 Hz, 1 H), 7.46 (dd, *J* = 8.8, 1.8 Hz, 1 H), 7.16 (d, *J* = 1.7 Hz, 1 H), 6.98 (d, *J* = 1.7 Hz, 1 H), 5.08 (s, 1 H).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{10}Cl_2N_2O$: 328.0170; found: 328.0175.

Anal. Calcd for $C_{17}H_{10}Cl_2N_2O$: C, 62.03; H, 3.06; N, 8.51; Cl, 21.54. Found: C, 62.13; H, 3.09; N, 8.48; Cl, 21.50.

3,4,6-Trichloro-3-(quinolin-6-yl)indolin-2-one (6g)
FC (hexane–EtOAc, 8:2).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 10.87 (s, 1 H), 8.88 (dd, *J* = 4.1, 1.8 Hz, 1 H), 8.35 (d, *J* = 8.5 Hz, 1 H), 7.95 (d, *J* = 8.8 Hz, 1 H), 7.76 (d, *J* = 1.8 Hz, 1 H), 7.52 (dd, *J* = 8.2, 4.0 Hz, 1 H), 7.44 (dd, *J* = 8.7, 1.8 Hz, 1 H), 7.23 (d, *J* = 1.7 Hz, 1 H), 7.03 (d, *J* = 1.7 Hz, 1 H).

HRMS (EI): *m*/*z* calcd for $C_{17}H_9Cl_3N_2O$: 361.9780; found: 361.9787.

Anal. Calcd for $C_{17}H_9Cl_3N_2O$: C, 56.15; H, 2.49; N, 7.70; Cl, 29.25. Found: C, 56.21; H, 2.57; N, 7.67; Cl, 29.23.

4,6-Dichloro-3-(quinolin-3-yl)indolin-2-one (5h)
FC (hexane–EtOAc, 9:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.12 (s, 1 H), 8.78 (d, *J* = 2.1 Hz, 1 H), 8.10 (d, *J* = 1.4 Hz, 1 H), 8.05 (d, *J* = 9.2 Hz, 1 H), 8.01 (d, *J* = 9.2 Hz, 1 H), 7.78 (t, *J* = 8.2 Hz, 1 H), 7.63 (t, *J* = 8.2 Hz, 1 H), 7.23 (br s, 1 H), 7.02 (br s, 1 H), 5.05 (s, 1 H).

HRMS (EI): *m*/*z* calcd for $C_{17}H_{10}Cl_2N_2O$: 328.0170; found: 328.0179.

Anal. Calcd for $C_{17}H_{10}Cl_2N_2O$: C, 62.03; H, 3.06; N, 8.51; Cl, 21.54. Found: C, 62.12; H, 3.17; N, 8.45; Cl, 21.50.

3,4,6-Trichloro-3-(quinolin-3-yl)indolin-2-one (6h)
FC (hexane–EtOAc, 9:1).

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.58 (s, 1 H), 8.88 (d, *J* = 1.1 Hz, 1 H), 8.46 (d, *J* = 1.1 Hz, 1 H), 8.14 (d, *J* = 8.9 Hz, 1 H), 8.09 (d, *J* = 8.9 Hz, 1 H), 7.86 (t, *J* = 7.5 Hz, 1 H), 7.7 (t, *J* = 7.5 Hz, 1 H), 7.44 (s, 1 H), 7.15 (s, 1 H).

HRMS (EI): *m*/*z* calcd for $C_{17}H_9Cl_3N_2O$: 361.9780; found: 361.9787.

Anal. Calcd for $C_{17}H_9Cl_3N_2O$: C, 56.15; H, 2.49; N, 7.70; Cl, 29.25. Found: C, 56.23; H, 2.42; N, 7.60; Cl, 29.21.

4,6-Dichloro-3-(quinoxalin-6-yl)indolin-2-one (5i)
FC (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.08 (s, 1 H), 8.98 (br s, 2 H), 8.08 (d, *J* = 8.5 Hz, 1 H), 7.93 (d, *J* = 1.5 Hz, 1 H), 7.54 (dd, *J* = 8.6, 1.5 Hz, 1 H), 7.18 (d, *J* = 1.7 Hz, 1 H), 7.02 (d, *J* = 1.7 Hz, 1 H), 5.23 (s, 1 H).

HRMS (EI): *m*/*z* calcd for $C_{16}H_9Cl_2N_3O$: 329.0123; found: 329.0115.

Anal. Calcd for $C_{16}H_9Cl_2N_3O$: C, 58.20; H, 2.75; N, 12.73; Cl, 21.48. Found: C, 58.25; H, 2.68; N, 12.69; Cl, 21.58.

3,4,6-Trichloro-3-(quinoxalin-6-yl)indolin-2-one (6i)
FC (hexane–EtOAc, 9:1).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.97 (s, 1 H), 9.11 (br s, 2 H), 8,24 (d, *J* = 8.4 Hz, 1 H), 7.95 (d, *J* = 1.6 Hz, 1 H), 7.82 (dd, *J* = 8.5, 1.5 Hz, 1 H), 7.43 (d, *J* = 1.6 Hz, 1 H), 7.14 (d, *J* = 1.6 Hz, 1 H).

HRMS (EI): *m*/*z* calcd for $C_{16}H_8Cl_3N_3O$: 362.9733; found: 362.9726.

Anal. Calcd for $C_{16}H_8Cl_3N_3O$: C, 52.71; H, 2.21; N, 11.52; Cl, 29.17. Found: C, 52.80; H, 2.25; N, 11.48; Cl, 29.12.

3-(2-Acetylbenzofuran-5-yl)-4,6-dichloroindolin-2-one (5j)
FC (hexane–EtOAc, 8:2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 10.85 (s, 1 H), 7.84 (s, 1 H), 7.67 (d, *J* = 8.8 Hz, 1 H), 7.59 (d, *J* = 1.3 Hz, 1 H), 7.26 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.15 (d, *J* = 1.5 Hz, 1 H), 6.97 (d, *J* = 1.5 Hz, 1 H), 5.0 (s, 1 H), 2.56 (s, 3 H).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{11}Cl_2NO_3$: 359.0116; found: 359.0131.

Anal. Calcd for $C_{18}H_{11}Cl_2NO_3$: C, 60.02; H, 3.08; N, 3.89; Cl, 19.69. Found: C, 60.12; H, 3.15; N, 3.82; Cl, 19.63.

3-(2-Acetylbenzofuran-5-yl)-3,4,6-trichloroindolin-2-one (6j)
FC (hexane–EtOAc, 8:2).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.38 (s, 1 H), 7.90 (m, 2 H), 7.76 (d, *J* = 8.8 Hz, 1 H), 7.51 (dd, *J* = 8.8, 2.0 Hz, 1 H), 7.35 (d, *J* = 1.5 Hz, 1 H), 7.08 (d, *J* = 1.5 Hz, 1 H), 2.57 (s, 3 H).

HRMS (EI): *m*/*z* calcd for $C_{18}H_{10}Cl_3NO_3$: 392.9726; found: 392.9732.

Anal. Calcd for $C_{18}H_{10}Cl_3NO_3$: C, 54.78; H, 2.55; N, 3.55; Cl, 26.95. Found: C, 54.85; H, 2.60; N, 3.51; Cl, 26.94.

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