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Mendeleev Commun., 2017, **27**, 498–499

Mendeleev Communications

The C-3 chlorination of 2-aryl-1-hydroxyindoles

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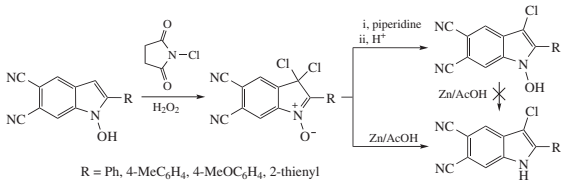
DOI: 10.1016/j.mencom.2017.09.023

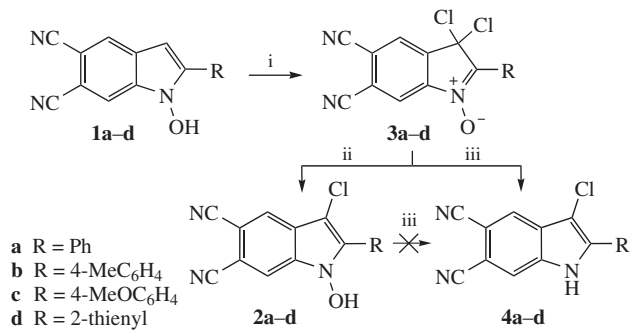
Chlorination of 2-aryl-1-hydroxyindole-5,6-dicarbonitriles with *N*-chlorosuccinimide affords previously unknown 3,3-dichloro-3*H*-indole 1-oxides instead of the expected 1-hydroxy-3-chloroindoles. The latter can be prepared in good yields by treatment of the above 3,3-dichloro-3*H*-indole 1-oxides with piperidine in ethanol.



Substituted 3-haloindoles are of interest as both biologically active compounds (in particular, recently we showed 2-substituted 3-halo-1-hydroxyindole-5,6-dicarbonitriles to be monoamine oxidaze inhibitors)[1] and starting reactants in the preparation of more complicated 3-C-substituted compounds (by arylation[2] and cyanation[3]). Various chlorinating agents are used for the chlorination of indoles, such as 1,3-dichloro-5,5-dimethylhydantoin,[4] sulfuryl chloride,[5] or trichloroisocyanuric acid.[6] In preparative synthesis, *N*-chlorosuccinimide is used most frequently.[7]

At the same time, C-3 halogenation of 1-hydroxyindoles is not a trivial task, whereas 3-chloro-1-hydroxyindoles are unknown. A treatment of 1-hydroxyindoles with chlorinating agents results in either OH group elimination yielding 3-chloro-substituted NH-indoles[2(*b*),8] or oxidation affording isatogens (3-oxo-3*H*-indole 1-oxides).[9] Meanwhile, recently we reported the reaction between 2-aryl-5,6-dicyano-1-hydroxyindoles **1** and NBS to produce corresponding 3-bromo-1-hydroxyindoles.[1(*a*)] These results prompted us to verify this method for a synthesis of their 3-chloro-substituted analogues **2** (Scheme 1).

For this purpose, we applied a procedure previously used for the preparation of 3-bromo-1-hydroxyindoles, namely, heating in glacial AcOH in the presence of 3-fold excess of *N*-halosuccinimide with a catalytic amount of H_2O_2. However, instead of expected 3-chloro-1-hydroxyindoles **2**, deeply-coloured (orange-red) 3,3-dichloro-3*H*-indole 1-oxides **3a–d** were isolated in yields up to 83%.† Reaction time was 2–2.5 h (TLC monitoring), except for R = 2-thienyl (15 min).



Scheme 1 *Reagents and conditions:* i, *N*-chlorosuccinimide, H_2O_2; ii, piperidine, EtOH, 60 °C, then HCl; iii, Zn/AcOH, room temperature.

Formation of these compounds was confirmed by mass spectrometry data, which showed molecular ions corresponding to 3,3-dichloro-3*H*-indole 1-oxides **3a–d**, the most abundant fragment being $[M-Cl]^+$. ^{1}H NMR spectra of *N*-oxides **3a–d** lack the signals for the N–H or N–OH indole protons; only low field singlets at 9.05–9.10 and 8.61–8.68 ppm attributed to protons H-7 and H-4 and signals of the protons of the 2-positioned R fragment are observed. Worthy of note is a significant downfield

† IR spectra were measured on a Perkin-Elmer RX-1 spectrometer in the range of 700–4000 cm^{-1} using suspensions in Vaseline oil. Mass spectra were obtained using a Finnigan Mat Incos 50 mass spectrometer, the ionization energy was 70 eV. NMR spectra were recorded on Bruker DRX-500 and DRX-300 instruments at 30 °C. Signals of residual protons of the solvent in ^{1}H NMR spectra (δ_H 2.50) or the signal of DMSO-d_6 in ^{13}C NMR spectra (δ_C 39.5) were used as references. Elemental analysis was performed on Perkin Elmer 2400 instrument.

*3,3-Dichloro-5,6-dicyano-3*H*-indole 1-oxides* **3a–d** (*general procedure*). A mixture of hydroxyindole **1a–d** (1 mmol), *N*-chlorosuccinimide (0.40 g, 3 mmol), AcOH (5 ml) and H_2O_2 (0.036 ml) was stirred at 40 °C for 2–2.5 h (TLC control), then cooled and diluted with water (5-fold excess). The resulting precipitate was filtered off and washed with water.

*3,3-Dichloro-5,6-dicyano-2-phenyl-3*H*-indole 1-oxide* **3a**. Yield 258 mg (79%), mp 208–209 °C. ^{1}H NMR (DMSO-d_6) δ: 7.66–7.75 (m, 3H, H-3′, H-4′, H-5′), 8.68 (s, 1H, H-7), 8.81 (d, 2H, H-2′, H-6′, *J* 7.6 Hz), 9.10 (s, 1H, H-4). IR (ν/cm^{-1}): 2236, 2231 (C≡N), 1602 (C=C). MS, *m*/*z* (%): 329 $[M]^+$ (15), 327 $[M]^+$ (24), 294 $[M-Cl]^+$ (35), 292 $[M-Cl]^+$ (100), 277 (19), 264 (18), 229 (21), 202 (12). Found (%): C, 58.31; H, 2.17; N, 12.77. Calc. for $C_{16}H_7Cl_2N_3O$ (%): C, 58.56; H, 2.15; N, 12.81.

*3,3-Dichloro-5,6-dicyano-2-(*p*-tolyl)-3*H*-indole 1-oxide* **3b**. Yield 240 mg (71%), mp 198–200 °C. ^{1}H NMR (DMSO-d_6) δ: 2.45 (s, 3H, Me), 7.53 (d, 2H, H-3′, H-5′, *J* 8.5 Hz), 8.64 (s, 1H, H-7), 8.73 (d, 2H, H-2′, H-6′, *J* 8.5 Hz,), 9.08 (s, 1H, H-7). IR (ν/cm^{-1}): 2246, 2235 (C≡N), 1600, 1515 (C=C). MS, *m*/*z* (%): 343 $[M]^+$ (12), 341 $[M]^+$ (18), 308 $[M-Cl]^+$ (34), 306 $[M-Cl]^+$ (100), 291 (26), 243 (42), 215 (20), 119 (12), 91 (22). Found (%): C, 59.41; H, 2.68; N, 12.34. Calc. for $C_{17}H_9Cl_2N_3O$ (%): C, 59.67; H, 2.65; N, 12.28.

*3,3-Dichloro-5,6-dicyano-2-(4-methoxyphenyl)-3*H*-indole 1-oxide* **3c**. Yield 297 mg (83%), mp 172–173 °C. ^{1}H NMR (DMSO-d_6) δ: 3.91 (s, 3H, OMe), 7.29 (d, 2H, H-3′, H-5′, *J* 8.8 Hz), 8.61 (s, 1H, H-7), 8.85 (d, 2H, H-2′, H-6′, *J* 8.8 Hz), 9.05 (s, 1H, H-4). IR (ν/cm^{-1}): 2240 (C≡N), 1615 (C=C). MS, *m*/*z* (%): 359 $[M]^+$ (17), 357 $[M]^+$ (29), 324 $[M-Cl]^+$ (35), 322 $[M-Cl]^+$ (100), 307 (20), 287 (12), 279 (16), 259 (30), 228 (19), 216 (28), 213 (21), 189 (15), 135 (16). Found (%): C, 56.76; H, 2.55; N, 11.69. Calc. for $C_{17}H_9Cl_2N_3O_2$ (%): C, 57.01; H, 2.53; N, 11.73.

shift of H-2′ and H-6′ protons of aryl substituent R in the ^{1}H NMR spectra of compounds **3a–c** (8.73–8.85 ppm) due to the influence of an *ortho*-located C=N$^+$ fragment of the indole ring (the same effect was observed in the spectra of 2-arylisatogens[10]). Some examples of the formation of 3,3-dihalo 3*H*-indoles (indolenines) in the course of halogenation of indoles are known;[11,12] however, 3-halo-substituted 3*H*-indole 1-oxides were not described previously.

Compounds **3** are rather labile, therefore, prolongation in chlorination drops their yields due to partial decomposition (in particular, formation of **2** was observed). The decomposition occurred even to a greater extent when compounds **3** were kept in DMSO solution. For this reason their ^{13}C NMR spectra could not be recorded (in contrast to the ^{1}H NMR spectra whose registration requires shorter time).

The target 3-chloro-1-hydroxy-1*H*-indole-5,6-dicarbonitriles **2a–d** were prepared in good yields up to 78% by treatment of *N*-oxides **3a–d** with piperidine in EtOH.‡ The structure of compounds **2a–d** was confirmed by spectral data. Thus, IR spectra of **2a–d** include a strong band of OH group at 3460–3550 cm^{-1}, in contrast to those of **3a–d**. ^{1}H NMR spectra of **2a–d** contain closely located singlets of H-4 and H-7 protons at ~8.4 ppm and a signal of N–OH proton at ~12.5 ppm. Noteworthy, the signals of H-2′ and H-6′ protons of aryl substituent R in ^{1}H NMR spectra of 1-hydroxyindoles **2a–c** (7.69–7.80 ppm) suffer a strong upfield shift (~1 ppm) compared to those in ^{1}H NMR spectra of *N*-oxides **3a–c** (8.73–8.85 ppm, see above). Mass spectra of **2a–d** demonstrate an abundant peak of a fragment ion [M – O] (such fragmentation is typical of 1-hydroxyindoles[13,14]).

Meanwhile, we found that reduction of 3,3-dichloro *N*-oxides **3a–d** with zinc in AcOH at room temperature afforded 3-chloro-1*H*-indole-5,6-dicarbonitriles **4a–d** (yields up to 79%).§ According to the spectral data, the latter were identical to those previously prepared by treatment of 1-hydroxyindoles **1** with the Vilsmeyer reagent (in particular, their ^{1}H NMR spectra contained a characteristic signal of indole N–H proton at ~13.0 ppm).[2] Interestingly, the reduction of 1-hydroxyindoles **2a–d** with Zn in AcOH failed to yield deoxygenation products **4a–d** even at the prolonged heating, this indicating higher lability of the C–Cl bond in a *gem*-dichloro fragment of compounds **3**.

In conclusion, 2-aryl-1-hydroxy-3-chloroindole-5,6-dicarbonitriles were prepared from the corresponding 3-unsubstituted indoles in two steps *via* the previously unknown intermediate 3,3-dichloro-3*H*-indole 1-oxides. The scope of this transformation (and the role of substituents in the indole ring, in particular) requires further investigation.

*3,3-Dichloro-5,6-dicyano-2-(thiophen-2-yl)-3*H*-indole 1-oxide* **3d**. Yield 230 mg (69%), mp 160–161 °C. ^{1}H NMR (DMSO-d_6) δ: 7.54 (dd, 1H, H-4′, *J* 5.0 Hz, *J* 3.8 Hz), 8.18 (dd, 1H, H-5′, *J* 5.0 Hz, *J* 1.0 Hz), 8.22 (dd, 1H, H-3′, *J* 3.8 Hz, *J* 1.0 Hz), 8.63 (s, 1H, H-4), 9.09 (s, 1H, H-7). IR (ν/cm^{-1}): 3454 (OH), 2242, 2230 (C≡N), 1594, 1534 (C=C). MS, *m*/*z* (%): 334 [M]$^+$ (20), 332 [M]$^+$ (31), 299 [M–Cl]$^+$ (39), 297 [M–Cl]$^+$ (100), 284 (16), 282 (19), 235 (31), 189 (18), 111 (18). Found (%): C, 50.08; H, 1.53; N, 12.52. Calc. for $C_{14}H_5Cl_2N_3OS$ (%): C, 50.32; H, 1.51; N, 12.57.

‡ *3-Chloro-1-hydroxyindole-5,6-dicarbonitriles* **2a–d** (*general procedure*). A solution of indole 1-oxide **3a–d** (1 mmol) in EtOH (5 ml), containing piperidine (0.5 ml), was heated at 60 °C for 30 min, cooled to room temperature, poured into water (25 ml) and acidified with 5% HCl to pH 2. The resulting precipitate was filtered, crystallized from EtOH and dried.

*3-Chloro-1-hydroxy-2-phenyl-1*H*-indole-5,6-dicarbonitrile* **2a**. Yield 225 mg (76%), mp 285–286 °C (EtOH). ^{1}H NMR (DMSO-d_6) δ: 7.48–7.68 (m, 3H, H-3′, H-4′, H-5′), 7.80 (d, 2H, H-2′, H-6′, *J* 7.8 Hz), 8.40 (s, 1H, H-4), 8.41 (s, 1H, H-7), 12.37 (br. s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ: 99.90, 104.8, 106.5, 116.6, 117.0, 117.1, 122.4, 125.4, 126.1, 127.9, 128.7 (2C), 130.1 (2C) 132.3, 138.3. IR (ν/cm^{-1}): 3473 (OH), 2240 (C≡N), 1678 (C=O), 1615 (C=C). MS, *m*/*z* (%): 295 [M]$^+$ (3), 293 [M]$^+$ (10), 279 [M – O]$^+$ (34), 277 [M – O]$^+$ (100), 273 (20), 256 (12), 249 (14), 241 (15), 229 (18), 215 (15). Found (%): C, 65.14 (65.15); H, 2.71 (2.73); N, 14.29 (14.25). Calc. for $C_{16}H_8ClN_3O$ (%): C, 65.43; H, 2.75; N, 14.31.

3-Chloro-1-hydroxy-2-(p-*tolyl)-1*H*-indole-5,6-dicarbonitrile* **2b**. Yield 240 mg (78%), mp 330 °C (decomp.). ^{1}H NMR (DMSO-d_6) δ: 2.42 (s, 3H, Me), 7.43 (d, 2H, H-2′, H-6′, *J* 8.0 Hz), 7.69 (d, 2H, H-3′, H-5′, *J* 8.0 Hz), 8.41 (s, 1H, H-7), 8.41 (s, 1H, H-4), 12.31 (s, 1H, OH). ^{13}C NMR (DMSO-d_6) δ: 21.2, 99.9, 105.0, 106.6, 116.9, 117.4, 117.5, 122.7, 123.6, 125.5, 129.6 (2C), 130.2 (2C) 132.6, 138.8, 140.1. IR (ν/cm^{-1}): 3563 (OH), 2242, 2232 (C≡N), 1616 (C=C), 813. MS, *m*/*z* (%): 309 [M]$^+$ (30), 307 [M]$^+$ (89), 293 [M – O]$^+$ (30), 291 [M – O]$^+$ (100), 263 (12), 254 (28). Found (%): C, 66.06; H, 3.24; N, 13.61. Calc. for $C_{17}H_{10}ClN_3O$ (%): C, 66.35; H, 3.28; N, 13.65.

*3-Chloro-1-hydroxy-2-(4-methoxyphenyl)-1*H*-indole-5,6-dicarbonitrile* **2c**. Yield 220 mg (68%), mp 313–315 °C (decomp.). ^{1}H NMR (DMSO-d_6) δ: 3.87 (s, 3H, OMe), 7.19 (d, 2H, H-3′, H-5′, *J* 8.5 Hz), 7.76 (d, 2H, H-2′, H-6′, *J* 8.5 Hz), 8.40 (s, 1H, H-4), 8.41 (s, 1H, H-7), 12.30 (s, 1H, OH). IR (ν/cm^{-1}): 3468 (OH), 2239, 2228 (C≡N), 1613 (C=C), 1253 (C–O), 823. MS, *m*/*z* (%): 325 [M]$^+$ (26), 323 [M]$^+$ (73), 309 [M–O]$^+$ (29), 307 [M – O]$^+$ (100), 292 (21), 271 (12). Found (%): 62.84; H, 3.08; N, 12.95. Calc. for $C_{17}H_{10}ClN_3O_2$ (%): C, 63.07; H, 3.11; N, 12.98.

*3-Chloro-1-hydroxy-2-(thiophen-2-yl)-1*H*-indole-5,6-dicarbonitrile* **2d**. Yield 213 mg (71%), mp 298–300 °C (decomp.). ^{1}H NMR (DMSO-d_6) δ: 7.34 (dd, 1H, H-4′, *J* 5.0 Hz, *J* 3.8 Hz), 7.95 (dd, 1H, H-5′, *J* 5.0 Hz, *J* 1.0 Hz), 8.07 (dd, 1H, H-3′, *J* 3.8 Hz, *J* 1.0 Hz). 8.33 (s, 1H, H-4), 8.34 (s, 1H, H-7), 12.69 (br. s., 1H, OH). ^{13}C NMR (DMSO-d_6) δ: 98.6, 105.0, 106.5, 116.0, 117.0, 122.5, 124.9, 126.6, 127.8, 130.1, 130.3, 132.2, 132.5. 133.6. Found (%): C, 55.87; H, 1.99; N, 13.98. Calc. for $C_{14}H_6ClN_3OS$ (%): C, 56.10; H, 2.02; N, 14.02.

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Received: 27th February 2017; Com. 17/5186

§ *3-Chloroindole-5,6-dicarbonitriles* **4a–d** (*general procedure*). Zinc powder (0.96 g, 0.015 mol) was added portionwise for 2–2.5 h to a stirred solution of indole 1-oxide **3a–d** (1 mmol) in AcOH (5 ml) at room temperature until zinc completely dissolved (TLC control). Water (15 ml) was added, the resulting white precipitate was filtered and crystallized from EtOH. According to ^{1}H NMR spectra and mp, products **4a–d** were identical to those described earlier.[1(b)] Yields: 79% (**4a**), 71% (**4b**), 76% (**4c**) and 68% (**4d**).