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Nucleophilic dimerization of indoline under oxidative conditions

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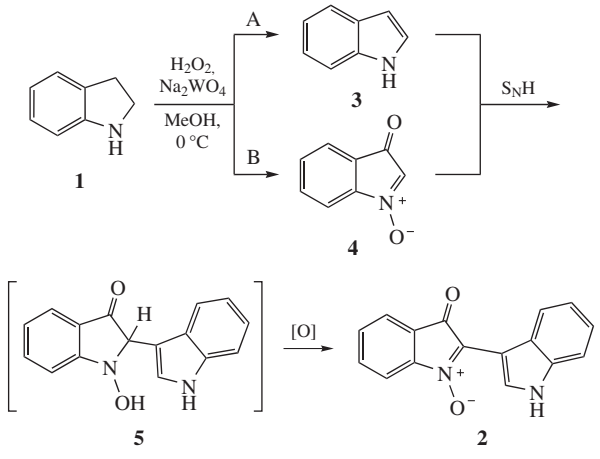
Oxidation of indoline with 30% hydrogen peroxide in methanol in the presence of sodium tungstate affords the dimeric 3-oxo-1′*H*,3*H*-2,3′-biindole-1-oxide.

The synthetic potential of S_NH reactions is based on the fundamental ability of C–H bonds of π-deficient (het)arenes to be cleaved with the subsequent formation of C–X bond (X = C_{sp^3}, C_{sp^2}, C_{sp}, O, N, S, P, *etc*.) in interaction with various nucleophiles. For instance, azines readily form σ^H-adducts and S_NH substitution products. Meantime, only few cases are known for the dimerization of 6-membered π-deficient heterocycles, in particular mono- or diazines, such as pyrimidine,[1] pyridine, quinolone and isoquinoline,[2] on treating with non-nucleophilic lithiating superbases. Nucleophilic addition of two molecules of 3-methyl-1-phenylpyrazol-5-one to 3-phenyl-1,2,4-triazine through the dimerization step gives finally a 1,1,2,2-tetrakispyrazolylethane derivative.[3]

Among azoles, reactions of nucleophilic addition are scarce. Isatogens react easily with various nucleophiles[4] and act as traps for hydroxyl and superoxide radicals.[5] The practical usefulness of isatogens is confirmed by their antimicotic activity,[6] as well as moderate antibacterial activity *in vitro*.[7] Therefore, search for new isatogens is of current interest.

Isatogens can be obtained in yields from good to excellent by condensation of *o*-ethynylnitrobenzenes catalyzed by gold(III) bromide,[8] however, benzooxazoles would sometimes form as by-products. Oxidation of 2-R-2,3-dihydro-1*H*-indoles derived from the corresponding indoles,[9] is another access to isatogens.

Herein, we describe a simple one-pot synthesis of isatogen starting from 2,3-dihydroindole (Scheme 1). Oxidation of indoline **1** with 30% hydrogen peroxide in methanol in the presence of sodium tangstate unexpectedly afforded the dimeric compound, *i.e*., 3-oxo-1′*H*,3*H*-2,3′-biindole-1-oxide **2** that is composed by two intermediates of indoline oxidation.† The formation of product **2** can be caused by the indoline oxidation directed in two parallel pathways. Pathway A leads to indole **3**;[10] while pathway B affords 3-oxo-3*H*-indole 1-oxide **4**.[9] The subsequent nucleophilic attack of indole **3** at the position C-2 of intermediate **4** gives dimer **5**. Finally, oxidation of adduct **5** results in the biindole **2**.



Scheme 1

The spectral data fully correspond to the proposed structure of **2**. ^{1}H NMR spectra contain the characteristic resonance of NH proton of indole as a broad singlet at 11.95 ppm, whereas signals of aliphatic protons of starting indoline **1** are absent. In the ^{13}C NMR spectra the resonance of carbonyl carbon at 187.1 ppm, as well as resonances of other aromatic carbons are observed. ESI-MS spectra contain clear peak of molecular ion $[M+H]^+$ with *m*/*z* 263.0793 (calc. for $C_{16}H_{11}N_2O_2$, 263.0815). The study of CID fragmentation in mass spectra of molecular ion of product **2** $[M+H]^+$ revealed the appearance of the characteristic ions: 246.0772 $[M+H-OH]^+$; 146.0202 $[M+H-Indole]^+$; 235.0849 $[M+H-CO]^+$. IR spectra manifest the valence absorption band of carbonyl group at 1716 cm^{-1}. EPR-spectroscopic study did not reveal the presence of uncoupled electrons in product **2**, so compound **2** does not contain any oxylic fragments in its structure.

In summary, we have developed the efficient one-pot synthesis of isatogen **2** by nucleophilic oxidative dimerization of indoline.

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† *3-Oxo-1′*H,*3*H-*2,3′-biindole-1-oxide* **2**. To a magnetically stirred suspension of sodium tungstate dihydrate (5 mg, 0.015 mmol) in MeOH (5 ml) compound **1** (1 g, 8.4 mmol) was added, then H_2O_2 (30%, 2.8 ml) was added dropwise at 0 °C. The resulting mixture was gradually warmed to room temperature and stirred for 3 h. The precipitate formed was filtered off, washed with ethanol and chromatographed on SiO_2 using 10% AcOEt in toluene as an eluent to afford the product (R_f = 0.5) as violet crystals in 39% yield (0.430 g, 1.64 mmol); mp > 250 °C (decomp.). ^{1}H NMR (400 MHz, DMSO-d_6–CCl_4) δ: 7.13 (td, 1H, *J* 7.5 and 1.3 Hz), 7.19 (td, 1H, *J* 7.5 and 1.1 Hz), 7.47 (d, 1H, *J* 7.8 Hz), 7.52 (d, 1H, *J* 7.8 Hz), 7.56 (d, 1H, *J* 7.5 Hz), 7.61 (d, 1H, *J* 7.0 Hz), 7.73 (td, 1H, *J* 7.7 and 1.0 Hz), 8.56 (d, 1H, *J* 8.0 Hz), 8.93 (d, 1H, *J* 3.0 Hz), 11.95 (br.s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 100.2, 104.6, 111.5, 113.5, 121.8, 122.0, 123.2, 124.0, 124.5, 124.6, 130.1, 130.2, 135.1, 136.1, 148.6, 187.1 (CO). IR (ν/cm^{-1}): 573, 749, 862, 1037, 1167, 1434, 1455, 1593, 1621, 1716 (CO), 3063, 3218. ESI-MS (CID), *m*/*z* (%): 263.0793 (15.5), 246.0772 (100), 235.0849 (32.8), 218.0823 (26.3), 146.0228 (10.2), 144.0434 (38.6), 120.0434 (2.6). Found (%): C, 73.35; H, 3.74; N, 10.56. Calc. for $C_{16}H_{10}N_2O_2$ (%): C, 73.27; H, 3.84; N, 10.68. For additional details, see Online Supplementary Materials.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2013.12.013.

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