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3-Oxo 3*H*-Indole from Dioxygen Copper-Catalyzed Oxidation of Indole: One-Flask Synthesis of 2-Dialkylamino 3-Oxo 3*H*-Indoles.

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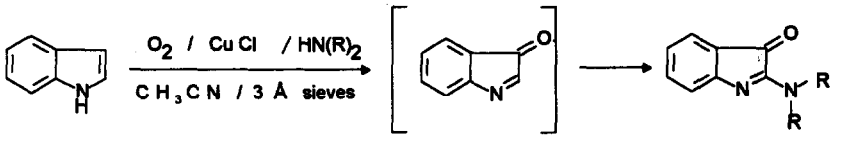
Key Words: Copper-catalyzed oxidation; dioxygen; indole; 2- dialkylamino 3- oxo 3H- indoles.

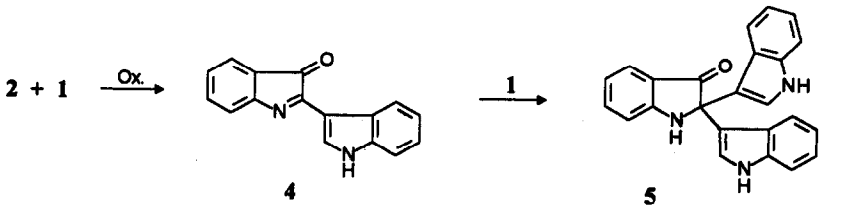
Abstract : *Cu(I)Cl-catalyzed oxidation of indole* **1** *by dioxygen in anhydrous acetonitrile leads to highly reactive 3-oxo 3H- indole* **2**, *which provides directly 2- dialkylamino 3- oxo 3H- indoles* **3** *in presence of dialkylamines. Amidines* **3**, *previously difficult to prepare, are potentially useful synthons in the field of heterocyclic chemistry.*

Reactions of various substituted indoles with dioxygen, catalyzed by Cu(I)Cl / pyridine system[1,2] or Schiff base cobalt complexes,[3,4] have been reported to afford 2,3-dioxygenated cleavage products, and therefore to constitute an approximate model for tryptophane-2,3 dioxygenase. We report here an original reaction of unsubstituted indole **1** with dioxygen, catalyzed by Cu(I)Cl in dry acetonitrile in the presence of molecular sieves: the intermediate 3-oxo 3*H*- indole **2** does not add H_2O to give subsequent 2,3- oxidative cleavage, but becomes an useful synthetic intermediate, due to the high reactivity of its C-2 position toward nucleophiles. Reacting *in situ* with a secondary amine (piperidine or diethylamine), it yields[5] the amidine derivatives **3** or **3'** (> 50 %) through an addition / oxidation sequence. Compound **3** has been previously obtained - but not characterized - in the autoxidation of 2- piperidino indole[6], and **3'** prepared through perbromide oxidation of 3- oxo 1- tosyl indole in presence of diethylamine.[7]

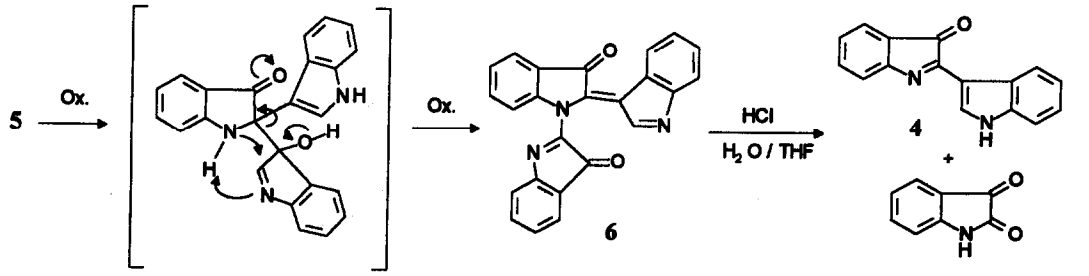


1 **2** **3** R, R = - (CH_2)$_5$ -
3' R = C_2H_5

In the absence of secondary amines, intermediate **2** reacts with indole **1** itself, leading first to "indoxyl red" **4**[8,9] then to 2,2-bis[3-indolyl] indoxyl **5**[8,10], each of them isolable during the course of the reaction and identical with authentic samples[9,10].

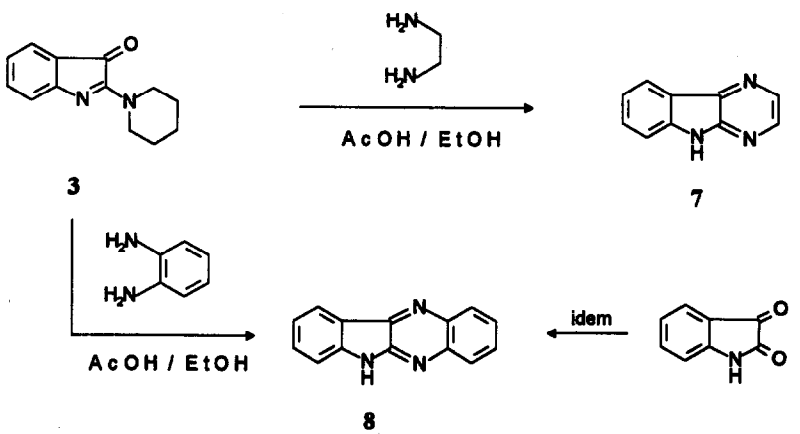


Trinuclear compound **5** is oxidized in his turn, likely involving a retro-aldol cleavage-based rearrangement, into final product **6**[11], previously unknown. Structure **6** is established by subsequent hydrolytic cleavage into indoxyl red **4** and isatine. It has been checked independently that **5** is effectively oxidized into **6** when submitted alone to our Cu(I)Cl / O_2 system.

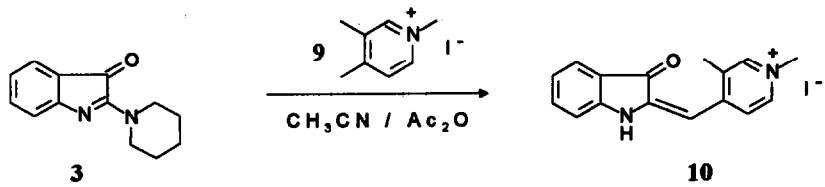


3-keto amidine compounds **3**, **3'** undergo facile displacement of the 2-amino group in presence of nucleophilic reagents: reactions with amines occur under acid catalysis, whereas their own basicity allows **3** and **3'** to react directly with methylene-active compounds.

For instance, **3** and ethylenediamine in presence of AcOH afford 5*H*-pyrazino [2,3-b] indole[12] **7** (50%) *via* cyclization, then spontaneous aromatization in air. Such condensations of 1,2 diamines are generally not obtained with isatine, apart from *o*-phenylene diamine, which yields the same indolo [2,3-b] quinoxaline[13] **8** than **3** (55%).

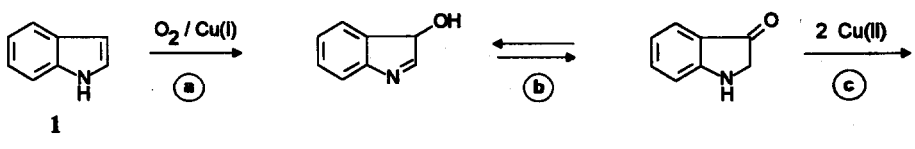


As an example of C-C bond formation involving carbon nucleophiles, **3** reacts spontaneously with 3,4-dimethyl-*N*-methyl-pyridinium iodide **9** (released piperidine is trapped by Ac_2O) to yield (80%) condensation product **10**[14], whose skeleton is related to the *ellipticine* series. This reaction suggests a new synthetic route to obtain these antitumoral molecules, once conditions for the final cyclisation will have been attained (by the mean of an appropriate functionalization of 3-methyl group in **9**).

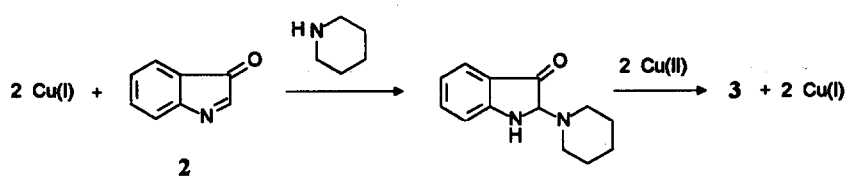


3 **10**

Global transformation **1** → **3** is clearly copper-catalyzed, since 6 electrons are involved, to be compared with c. a. 0.6 equivalent Cu(I)Cl present in our experimental conditions[5]. On the other hand, cupric complex Cl-Cu(II)-O-Cu(II)-Cl (previously obtained[15] from reaction of O_2 and Cu(I)Cl in CH_3CN) does not oxidize **1** in absence of dioxygen. Reaction requires therefore the activation of dioxygen by Cu(I) catalyst (step **a**), and is quite reminiscent of the oxidation of aniline into transient *ortho*- quinone-imine, leading to a phenylamino-substituted quinone-imine[16] through similar addition-oxidation process. Here, regeneration of catalyst is clearly due to Cu(II) oxidation (step **c**) of indoxyl intermediate, present in two tautomeric forms (equilibrium **b**), as α-amino ketones are well known to be oxidized into α- keto imines in such conditions.[17]



1



2

Intermediate 3-oxo 3*H*- indole **2** adds piperidine and leads to **3** through another c- type dehydrogenation of a 2-amino indoxyl intermediate. Classical autoxidation of indoxyl by dioxygen alone would have led to indigo through 2- centred radical dimerization [18]; this process is totally absent here.

References and Notes

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5. Piperidine (15 ml) then indole **1** (10 g) are added within 15 mn each to a solution of CuCl (6 g) in CH_3CN (300 ml) stirred under O_2 (1 atm.) with 3 Å molecular sieves (10 g); after 24 h, the mixture is repeatedly extracted with 150 ml hexane portions until deep violet colour faint. Basic compound **3** is separated from unreacted indole (2,6 g) by extraction from hexane solutions with 1N aqueous HCl, then recovered in Et_2O after addition of Na_2CO_3 up to pH 8; ethereal solution is dried over $MgSO_4$, evaporated, and residual piperidine trapped *in vacuum* over P_4O_{10}. Residue is recrystallized from pentane to yield pure **3** (9.5 g), black-violet crystals (λ_{max} = 530 nm), m.p. = 52°C.
   60 MHz ^1H NMR ($CDCl_3$ / TMS) δ (ppm): 1.5-1.8 (broad, 6H); 3.6-4.2 (broad, 4H); 6.6-6.9 (m, 2H); 7.1-7.5 (m, 2H). IR (KBr): ν = 1720 cm^{-1}.
   In the same conditions, diethylamine yields **3'**, whose properties are consistent with literature data[7].
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11. The precipitate obtained from reaction of indole (3 g), CuCl (0.8 g) and O_2 in CH_3CN for 3 days is continuously extracted with hot AcOEt to afford **6**, red crystals, 1.1 g, m.p.= 262°C (dec.).
    MS : 375 ($M^{+\cdot}$); 347 (M - CO); 319 (M - 2 CO); IR (KBr): ν = 1720 cm^{-1}.
    6 is too much insoluble to allow satisfactory NMR analysis.
    Di- and trinuclear compounds **4** and **5** are recovered (preparative TLC) from mother liquors.
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14. 2-piperidino 3-oxo 3*H*-indole **3** (0.5 g), N-methyl 3,4-dimethyl pyridinium iodide **9** (0.7 g) and Ac_2O (0.4 ml) are reacted in CH_3CN for 24 h. Insoluble condensation product **10** is collected and rinsed twice with CH_3CN: 0.7 g, brick-red crystals, m.p.= 304°C.
    60 MHz ^1H NMR (DMSO-d_6 / TMS) δ (ppm): 2.45 (s, 3H); 4.25 (s, 3H), 6.4 (s, 1H); 6.9-7.3 (m, 2H); 7.5-7.8 (m, 2H); 8.1-8.3 (m, 1H); 8.8-8.9 (m, 2H); 10.7 (broad s, 1H).
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