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Oxidative Cleavage Reaction of 3-Substituted Indoles Catalyzed by CuCl–Pyridine Complex under Oxygen

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Oxidative cleavage of 3-methylindole using a catalytic amount of copper(II) salts with added pyridine under an oxygen atmosphere was studied. Smooth cleavage of 3-methylindole took place to give 2-formamidoacetophenone in 73—80% yield, whereas exclusive formation of a hydrate compound derived from 3,3′-dimethyl-3,3′-bi-3*H*-indole resulted under anaerobic conditions. Clean oxidative cleavage of *N*-acetyltryptamine, methyl 3-indolylacetate, and methyl 2-acetamido-3-(3-indolyl)propionate was also achieved, constituting a mimic of tryptophan-2,3-dioxygenase.

We have reported the oxidative cleavage reaction of catechol and phenol using CuCl–pyridine complex under oxygen to give methyl *cis,cis*-muconate in high yields as a non-enzymic model for pyrocatechase.[1)]

As an extension of our studies on the metal salt-catalyzed liquid-phase oxidation, which includes oxidative cleavage of *o*-phenylenediamine to *cis,cis*-mucononitrile,[2)] oxidation of various olefins to carbonyl compounds,[3)] and facile oxidative conversion of acid hydrazides to the corresponding acids,[4)] we attempted an oxidative cleavage of an indole ring as a non-enzymic model for tryptophan-2,3-dioxygenase. Although indole derivatives related to tryptophan are fairly sensitive to oxidation, controlled oxidation to give rise to the cleavage of the indole ring is rather limited.[5)] We have recently disclosed clean oxidative cleavage of 3-methylindole catalyzed by CuCl–pyridine complex under oxygen.[6)] There has been reported an independent study on the oxidative cleavage of 2- and 3-substituted indoles using a CuCl–pyridine–O_2 system.[7)]

Tryptophandioxygenase is an important enzyme which selectively cleaves the indole ring of tryptophan and several studies on its model reaction have been reported. Photosensitized oxygenation of tryptophan and related indole derivatives gave the cleaved product.[8,9)] Nishinaga reported a successful oxidative cleavage of various indole derivatives using cobalt-Schiff base complexes as catalyst to give 2-formamidoacetophenone derivatives in high yields.[10)] Manganese phthalocyanine-catalyzed oxidative cleavage of 3-methylindole gave similar results.[11)] More recently, copper-Schiff base complex-catalyzed oxidation of tryptophan has been reported.[12)]

In this paper we describe the oxidative cleavage reaction of several 3-substituted indoles under the optimum conditions so far examined using CuCl–pyridine complex under oxygen.

Results and Discussion

Catalytic Oxidation Using Copper(II) Salts. 3-Methylindole: Oxidative cleavage reaction of 3-methylindole using various copper(II) salts as a catalyst under an oxygen atmosphere was studied. Although copper(II) salts such as copper(II) acetate and methoxide did act as a catalyst effectively in the presence of oxygen, copper(I) chloride was principally used in order to compare the catalytic behavior for the oxidative cleavage of 3-methylindole with that for catechol oxidation.

Prior to the reaction, copper(I) chloride dissolved in pyridine–dichloromethane was oxidized until oxygen absorption ceased. Usually about one-fourth mole of oxygen per mole copper(I) used was found to be absorbed, substantiating the equation:[1d)]

$$2\,CuCl + 1/2\,O_2 \xrightarrow{\text{pyridine}} CuCl_2 \cdot CuO.$$

Results of screening of the reaction conditions indicated that an added pyridine is crucial and that the choice of solvent has a considerable effect on the reaction rate and the yield of the cleaved product, dichloromethane being satisfactory. Also relative amounts of pyridine to the solvent seem to be important.

The reaction proceeded smoothly at ambient temperature (15—20 °C) with absorption of additional oxygen during the course of 3—6 h. Under the best conditions so far examined, 2-formamidoacetophenone was obtained in 73—80% yield. Results are summarized in Table 1.

It is of interest to note that overall oxygen uptake roughly parallels yields of the cleaved product, except for entries **1a** and **1b**, regardless of the molar ratios of the substrate to catalyst in the range of 3.3 to 0.5.

Under the same conditions as entry **1f** 2,3-dimethylindole underwent oxidative cleavage to form 2-acetamidoacetophenone in 50% yield.

As is discussed below, intervention of a 3*H*-indol-3-yl radical, which is formed by facile one electron transfer from 3-methylindole to Cu(II) species followed by deprotonation, is likely responsible for the subsequent oxygenation to result in the cleavage of the indole ring. Thus, the most effective species for the oxidative cleavage of 3-methylindole would be Cu(II) ion coordinated with pyridine, which is, in turn, able to transfer molecular oxygen effectively to the intermediate 3*H*-indol-3-yl radical.

3-Substituted Indoles. Oxidative cleavage of *N*-acetyltryptamine, methyl 3-indolylacetate, and methyl 2-acetamido-3-(3-indolyl)propionate was carried out under the conditions aforementioned.

These reactions were found to be rather sluggish and the latter two substrates underwent cleavage with relatively low conversions as compared with 3-methylindole even after 24 h of reaction period. All results obtained are summarized in Table 2.

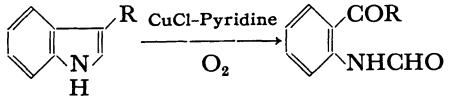
A few points deserve comments. Steric demand of R

Table 1. Copper(II)-catalyzed oxidation of 3-methylindole to 2-formamidoacetophenone under oxygen[a)]

Entry	Cu(II) salt (mmol)	Pyridine (ml)	Solvent (ml)	O_2 Uptake[b)] (mmol)	Yield[c)] %
1a	CuCl, 0.3	20	—	(1.5)	13
1b	0.5	0 (DBU, 1.0)	CH_2Cl_2(20)	(2.9)	8
1c	0.3	0 (DMF, 1.0)	CH_2Cl_2(15)	0.6	32
1d	0.3	0.5	PhMe(20)	0.84	45
1e	0.5	0.5	$CHCl_3$(20)	1.2	56
1f	0.5	0.5	CH_2Cl_2(20)	1.6	73
1g	2.0	2.0	CH_2Cl_2(20)	1.4	72
2	$Cu(OAc)_2$, 0.5	0.5	CH_2Cl_2(20)	1.6	81
3	$Cu(OMe)_2$,0.5	0.5	CH_2Cl_2(20)	—	55

a) 3-Methylindole (1.0 mmol) dissolved in a given solvent (10 ml) was added to the copper(II) catalyst solution (*ca.* 10 ml) under oxygen, and oxidized at ambient temperature in 3—6 h. b) Overall oxygen uptake. c) Isolated by column chromatography.

Table 2. Oxidative cleavage of 3-substituted indoles catalyzed by CuCl–pyridine complex under oxygen[a)]



R	O_2 Uptake (mmol)	Conversion %	Yield[b)] %	Mp °C
CH_2CH_2NHAc	1.6	100	68	117—118 (117—119)[10)]
CH_2CO_2Me	—	79	48	40 (44)[7)]
CH_2CHCO_2Me NHAc	1.2	68	57	160—162 (syrup)[7,10)]

a) Substrate (1.0 mmol) and copper(I) chloride (0.5 mmol) in pyridine (0.5 ml) and dichloromethane (20 ml) were used. b) Based on the conversion.

Table 3. Oxidative cleavage of 3-methylindole to 2-formamidoacetophenone under anaerobic conditions[a)]

Cu(II) salt	Pyridine (ml)	Yield %	Recovery %
$CuCl_2$	4.0	34	14
$Cu(OAc)_2 \cdot H_2O$	4.0	48	29
$Cu(OAc)_2$	4.0	67	9
$Cu(OAc)_2$	0.65	63	12
$Cu(OMe)_2$[b)]	2.0	0 (dimer,[c)] 80)	19
$[CuCl_2 \cdot CuO]$[d)]	2.0	0 (dimer,[c)] 59)	16

a) 3-Methylindole (1.0 mmol), Cu(II) salt (4.0 mmol) in dichloromethane (25 ml) with added pyridine under argon. Stirred at room temperature for 4 d. b) Prepared *in situ* from anhydrous MeOLi and $CuCl_2$ in dry THF. c) Hydrate compound (II) (R=Me) derived from 3,3′-dimethyl-3,3′-bi-3*H*-indole (III) (R=Me). Duplicated results. d) Pretreated CuCl with requisite amounts of oxygen:

$$2CuCl + 1/2O_2 \xrightarrow{py} CuCl_2 \cdot CuO \quad (cf.\ \text{Ref. 1}).$$

groups at the 3-position apparently affects the reaction rate, reflecting low conversions of the cleavage. The same is true for cobalt–salen complex-catalyzed oxidative cleavage of these 3-substituted indoles.[10)] Cobalt complex-catalyzed oxidation of methyl 3-indolylacetate in methanol resulted in a side chain oxidation rather than a ring cleavage, whereas the present copper complex-catalyzed reaction afforded methyl 2-formamidobenzoylacetate in 48% yield.

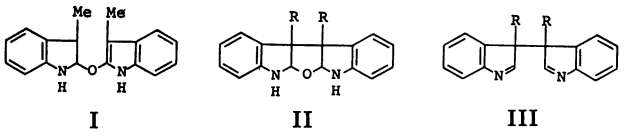
Generally, yields of the cleaved products attained under the present reaction conditions are much superior to those reported,[7)] using CuCl–pyridine–O_2 system without dichloromethane. Selecting simply a solvent, one can improve significantly the yield of oxidative cleavage of 3-substituted indoles, as is seen from Table 1 with respect to 3-methylindole.

Cu(II) as an Oxidant. 3-Methylindole was treated with excess copper(II) salts (4 equiv.) with added pyridine in dichloromethane solution at room temperature under an argon atmosphere. TLC monitoring of the reaction mixture revealed that very slow cleavage took place to give 2-formamidoacetophenone as a sole product in moderate yields with recovery of appreciable amounts of the starting 3-methylindole even after four days. Results obtained are given in Table 3. Although the reaction rate was found to be much slower than that found under oxygen as mentioned above, it is obvious that both copper(II) chloride and acetate are capable of initiating selective cleavage of 3-methylindole.

The most striking, however, is the fact that no cleaved product was obtained when copper(II) methoxide, prepared *in situ* from copper(II) chloride and two equivalents of anhydrous lithium methoxide in tetrahydrofuran (THF), was used as an oxidant. The results are confirmed by duplicated runs. Similar results were also obtained with a dichloromethane solution of copper(I) chloride with added pyridine, which was allowed to absorb a requisite amount of oxygen, followed by purging excess oxygen thoroughly with argon (see Experimental).

The sole product obtained in these two sets of reactions was white crystalline material which had exactly the same melting point after recrystallization from chloroform as well as analytical data as one previously obtained by Dobeneck[13)] in the oxidation of 3-methylindole with iron(III) chloride, and characterized as an ether (I). Acid catalyzed dimerization of 3-methylindole occurs readily, but the resulting dimer has indoline-

indole moieties joined at their 2-positions,[14] while radical dimerization of 3-substituted indoles has been suggested without any structure characterization.[15]



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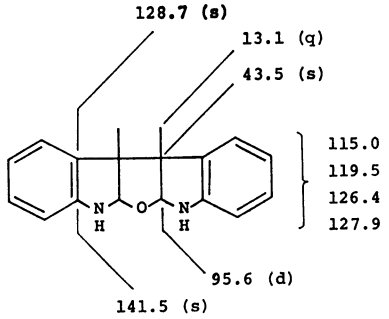
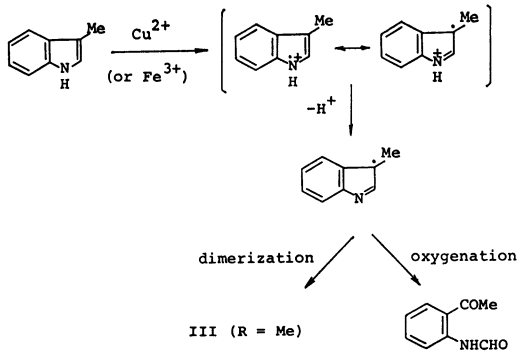


Fig. 1. ^{13}C NMR Data for II (R=Me), δ/ppm (OFR splitting are given in parentheses).

However, the structure (I) assigned by Dobeneck[13] was now found to be erroneous. ^1H and ^{13}C NMR (Data given in Fig. 1) as well as MS data of the products prepared by using either Cu(II) or Fe(III) salt indicate a symmetric structure of compound (II) (R=Me), which is obtained as one diastereomer and is most probably derived from addition of water to a rather unstable 3,3'-dimethyl-3,3'-bi-3*H*-indole III (R=Me). III is a 3*H*-indole-3*H*-indole dimer, the dimeric bond being formed at 3-position in the 3*H*-indole moiety.

It has been reported that such oxidants as potassium hexacyanoferrate(III) and manganese oxide are insufficient for radical generation from indolic nitrogen. Successful oxidative dimerization of indolylmagnesium halides with iron(III) chloride has already been described[16] to form intermediate III ($R=CH_2CH_2NHMe$).

It appears to be difficult to account for exactly why the two reaction paths were observed in the course of oxidation of 3-methylindole using four different copper(II) salts under apparent anaerobic conditions. However, the exclusive formation of a dimer (III) (R=Me), which is trapped as compound (II) (R=Me),



from 3-methylindole in certain cases may now be rationalized by the following scheme.

Facile one electron transfer from 3-methylindole at the nitrogen atom to copper(II) (as well as to iron(III)) followed by deprotonation gives an intermediate 3*H*-indol-3-yl radical, which may or may not coordinate to the copper species. The radical undergoes either dimerization under rigorous anaerobic conditions, if any, to give III or oxygenation with oxygen presumably adsorbed on certain copper salts present in the reaction mixture to afford selectively 2-formamidoacetophenone.[17] The scheme is consonant with the fact that attempted reaction of 1,3-dimethylindole under oxygen resulted in complete recovery of the starting material. It is confirmed that 3-ethylindole also formed the corresponding dimeric compound (II) (R=Et). However, the significant role of the anionic ligands of copper(II) species is still unclear at present.

Experimental

Apparatus. For the present oxidative cleavage reactions was throughout used a three-neck, round-bottomed 50 ml flask equipped with a magnetic stirrer, a Hershberg dropping funnel, a serum cap, and a three-way stopcock which was connected either with an oxygen gas buret or with an argon balloon.

Copper(II) Salts. $CuCl_2$ and $Cu(OAc)_2 \cdot H_2O$ were used as received. Anhydrous $Cu(OAc)_2$ commercially available was dried *in vacuo* prior to use. $Cu(OMe)_2$ was prepared *in situ* by the following procedure. A brown suspension of $CuCl_2$ (0.588 g, 4.2 mmol) and LiOMe (0.34 g, 8.6 mmol) in THF (20 ml) was stirred for 1 h under argon. The reaction mixture turned green was evaporated to dryness *in vacuo* and used in dichloromethane for the oxidation immediately. For "Cu reagent," CuCl–pyridine–O_2 system, a typical run is as follows. A clear green solution of CuCl (0.398 g, 4.0 mmol) dissolved under argon in dichloromethane (20 ml) and pyridine (2 ml) was exposed to oxygen with stirring. Oxygen uptake (about 1 mmol) ceased within 1 h, during which time the solution turned to a dark green suspension. The "Cu reagent" thus prepared was used either under oxygen for cleavage reactions or after purging excess oxygen with argon for anaerobic reactions.

Catalytic Oxidative Cleavage of 3-Methylindole. Using "Cu reagent," the following is the best procedure; "Cu reagent" was prepared as above using CuCl (0.050 g, 0.5 mmol), dichloromethane (10 ml), and pyridine (0.5 ml). Into the dropping funnel was placed a solution of 3-methylindole (0.131 g, 1 mmol) in dichloromethane (10 ml). The solution was added dropwise to the "Cu reagent" under oxygen over 1 h. After additional 1.48 mmol of oxygen was absorbed within 4 h, the reaction mixture was hydrolyzed with 40 ml of 3 mol dm^{-3} HCl. The organic layer was separated and aqueous layer was extracted with dichloromethane. The combined organic layer was washed with brine three times and dried over $MgSO_4$. The dichloromethane was removed by evaporation and the residue was purified by column chromatography (silica gel, dichloromethane as eluent) to give 2-formamidoacetophenone in 73% yield: mp 77—78 °C (lit,[10] mp 79—80 °C); ^1H NMR ($CDCl_3$) δ 2.64 (s, 3H), 6.94—8.01 (m, 3H), 8.35—8.87 (m, 2H), and 11.51 (s, broad, 1H); IR (KBr) 3250, 2890, 1690, and 1660 cm^{-1}.

Similarly, a solution of 2,3-dimethylindole (0.022 g, 0.15 mmol) in dichloromethane (2.0 ml) was added dropwise to

the "Cu reagent" prepared from CuCl (0.009 g, 0.09 mmol) and pyridine (0.8 ml) dissolved in dichloromethane (2.0 ml) under oxygen atmosphere. Oxygen uptake ceased within 4 h, and the reaction mixture was worked up as above. Purification of the product by column chromatography gave 2-acetamidoacetophenone in 50% yield: mp 73—75 °C (lit,[18] mp 74—75 °C); ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3H), 2.63 (s, 3H), 6.85—7.94 (m, 3H), 8.56—8.78 (m, 1H), and 11.61 (s, broad, 1H); IR (KBr) 3250, 1690, and 1655 cm^{-1}.

$Cu(OAc)_2$ (0.09 g, 0.5 mmol) was dissolved in a solution of dichloromethane (10 ml) and pyridine (0.5 ml) under oxygen. In a similar manner as above, the solution of 3-methylindole (0.131 g, 1 mmol) in dichloromethane (10 ml) was added for 1 h. The mixture was stirred for 6 h, during which time slow absorption of oxygen (1.6 mmol) was observed. The reaction mixture was worked up as usual and 2-formamidoacetophenone was obtained in 81% yield.

$Cu(OMe)_2$ was prepared as above using $CuCl_2$ (0.060 g, 0.44 mmol) and LiOMe (0.033 g, 0.87 mmol). The oxidative cleavage of 3-methylindole (0.117 g, 0.89 mmol) under oxygen provided 2-formamidoacetophenone in 55% yield.

Oxidative Cleavage of 3-Substituted Indoles. Oxidation of *N*-acetyltryptamine (0.218 g, 1 mmol) with the "Cu reagent" was carried out under oxygen atmosphere. Stirring was continued for 22 h. Usual workup provided 2-(3-acetamidopropionyl)formanilide in 68% yield: mp 117—118 °C; NMR ($CDCl_3$) δ 1.94 (s, 3H), 2.96—3.78 (m, 4H), 6.38—6.78 (m, 1H), 6.88—7.93 (m, 3H), 8.26—8.79 (m, 2H), and 11.32 (s, broad, 1H); IR (KBr) 3330, 2920, 1675, and 1645 cm^{-1}.

Oxidation of methyl 2-acetamido-3-(3-indolyl)propionate (0.260 g, 1 mmol) with the "Cu reagent" under oxygen provided methyl 2-acetamido-3-(2-formamidobenzoyl)propionate in 57% yield (based on 68% conversion): mp 160—162 °C (hexane–CH_2Cl_2); NMR ($CDCl_3$) δ 2.01 (s, 3H), 3.74 (s, 3H), 4.74—5.09 (m, 1H), 6.42—6.78 (m, 1H), 6.98—8.01 (m, 3H), 8.34—8.90 (m, 2H), and 11.36 (s, broad, 1H); IR (KBr) 3260, 2950, 1755, 1695, and 1655 cm^{-1}. Found: C, 57.78; H, 5.58; N, 8.94%; Calcd for $C_{14}H_{16}N_2O_4$: C, 57.53; H, 5.52; N, 9.58%. MS *m/e* (rel intensity) 292 (3) (M^+); 167 (37), 149 (100), 148 (42), 71 (40), 57 (70), 43 (52), 41 (41).

Oxidation of methyl 3-indolylacetate (0.175 g, 1 mmol) as above with the "Cu reagent" gave methyl (2-formamidobenzoyl)acetate in 48% yield (based on the 79% conversion): mp 40 °C; NMR ($CDCl_3$) δ 3.76 (s, 3H), 4.06 (s, 2H), 7.01—7.99 (m, 3H), 8.47—8.98 (m, 2H), and 11.37 (s, broad, 1H); IR (KBr) 3280, 1725, 1690, and 1600 cm^{-1}.

Cu as an Oxidant. $CuCl_2$ (0.538 g, 4 mmol) was dessolved in a solution of dichloromethane (20 ml) and pyridine (2 ml). As in the case of catalytic oxidative reaction but under argon atmosphere, the solution of 3-methylindole (0.131 g, 1 mmol) in dichloromethane (5 ml) was added dropwise for 1 h. Stirring was continued for 4 d. Work up of the reaction mixture as usual, afforded 2-formamidoacetophenone in 34% yield.

Oxidation of 3-methylindole (0.131 g, 1 mmol) as above with $Cu(OAc)_2 \cdot H_2O$ (0.799 g, 4 mmol) or anhydrous $Cu(OAc)_2$ (0.727 g, 4 mmol) after 4 d afforded 2-formamidoacetophenone in 48 and 67% yields, respectively.

Oxidation of 3-methylindole was carried out under argon for 4 d with $Cu(OMe)_2$ prepared *in situ* described as above. Purification of the product by column chromatography (silica gel, dichloromethane as eluent) gave compound (II) (R=Me) which was thought to consist of two diastereomers: mp 165—167 °C. Recrystallization from chloroform afforded one diastereomer as white crystals: mp 202—204 °C; ^{1}H NMR ($CDCl_3$) δ 1.32 (s, 6H), 4.94 (s, 2H), and 6.45—7.35 (m, 10H); ^{13}C NMR ($CDCl_3$) data are given in Fig. 1; IR (KBr) 3400, 3350, 2960, 1605, 1475, 1295, 1265, 1090, 1050, 885, 805, 755, and 745 cm^{-1}. Found: C, 77.40; H, 6.41; N, 10.06%. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06%; MS *m/e* (rel intensity) 278 (6) (M^+), 263 (19), 261 (19), 260 (84), 259 (28), 246 (21), 245 (100), 232 (41), 217 (15), and 130 (16).

Compound (II) (R=Me) was dissolved in MeOH containing HCl. After the solution was warmed for 10 min, 3-methylindole and 3-methyl-2-indolinone were obtained. *N,N'*-Dimethyl derivative of II (R=Me) is known to undergo similar cleavage reaction.[19]

Oxidation of 3-Methylindole with $FeCl_3$ and Et_2NH. Oxidation of 3-methylindole (0.508 g, 3.9 mmol) with $FeCl_3$ (1.32 g, 8 mmol), Et_2NH (2.1 ml, 20 mmol), and Et_2O (26 ml) according to Dobeneck's[13] procedure afforded the same product which was obtained by the oxidation with $Cu(OMe)_2$ or "Cu reagent" as an oxidant. Yield 32%.

Oxidation of 3-Ethylindole with $Cu(OMe)_2$. Oxidation of 3-ethylindole (0.145 g, 1 mmol) with $Cu(OMe)_2$ under argon provided compound (II) (R=Et) in 50% yield which was also found to be a mixture of two diastereomeric isomers mp 41—54 °C; ^{1}H NMR ($CDCl_3$) δ 0.68 (t, J=7 Hz, 3H), 1.79 (q, J=7 Hz, 2H), 5.31 (5.02) (s, 1H), and 6.42—7.50 (m, 5H); ^{13}C NMR ($CDCl_3$) Compound (IIa) (R=Et): δ 9.5, 22.1, 47.4, 98.3, 109.5, 118.5, 127.4, 128.0, 129.5, and 149.4; Compound (IIb) (R=Et): δ 8.8, 23.8, 43.5, 95.4, 115.2, 119.0, 126.4, 127.8, 128.1, and 142.6; IR (KBr) 3380, 2960, 1605, 1480, 1260, and 740 cm^{-1}; MS *m/e* (rel intensity) 306 (5) (M^+), 277 (30), 259 (17), 162 (20), 161 (18), 146 (36), 145 (26), 132 (19), and 130 (100).

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