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OXIDATIVE CLEAVAGE REACTION OF 3-METHYLINDOLE CATALYZED BY CuCl-PYRIDINE COMPLEX UNDER OXYGEN

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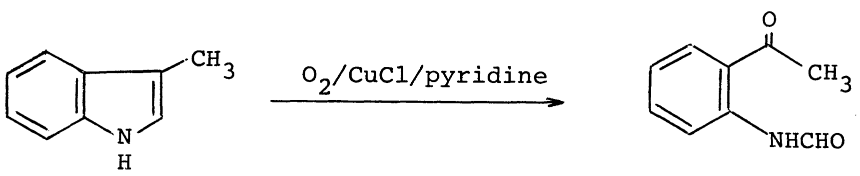
Oxidative cleavage reaction of 3-methylindole to give 2-formylaminoacetophenone in 70% yield was achieved by using CuCl-pyridine complex as a catalyst under oxygen.

We have reported the oxidative cleavage reaction of catechol using CuCl-pyridine complex under oxygen to give methyl *cis,cis*-muconate in high yields as a non-enzymic model reaction of pyrocatechase.¹⁾ As an extension of our studies on metal salt-catalyzed liquid phase oxidation, we attempted the oxidative cleavage of an indole ring as a non-enzymic model for tryptophan-2,3-dioxygenase. 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 products.2,3) Nishinaga reported the successful oxidative cleavage reaction of various indole derivatives using cobalt Schiff base complexes as a catalyst to give 2-formylaminoacetophenone derivatives in high yields.4) Also manganese phthalocyanine-catalyzed oxidative cleavage of 3-methylindole afforded formylaminoacetophenone in somewhat lower yield.5) Recent report on the same reaction catalyzed by copper complexes of Schiff base composed of L-amino acids and hydroxymethylenecamphor6) has prompted us to report our results of copper-catalyzed oxidation.

We now wish to report oxidative cleavage reaction of 3-methylindole using CuCl-pyridine as a catalyst under oxygen atmosphere. At first we tried the oxidation with CuCl in pyridine, but 2-formylaminoacetophenone was isolated in a low yield. The addition of solvents showed favorable effect. Toluene and chloroform are good solvents. The best results were obtained in dichloromethane. Also relative amounts of pyridine to the solvents were found to be important. The reaction proceeded rapidly at 0°C with absorption of oxygen. Results of screening of the reaction conditions are shown in the table. Under the best conditions, 2-formylaminoacetophenone was isolated as crystals in 70% yield.



The typical reaction was carried out in the following way. In a three-necked flask, was placed a mixture of dichloromethane (10 ml), pyridine (0.5 ml, 6.3 mmol), and CuCl (40 mg, 0.4 mmol) under oxygen. Then 3-methylindole (113 mg, 1 mmol), dissolved in dichloromethane (10 ml), was added dropwise in 1.5 h, and the reaction mixture was stirred for another 1.5 h. During the reaction, absorption of oxygen (total 30 ml, 1.2 mmol) was observed. The solution was acidified with hydrochloric acid and extracted with dichloromethane. From the organic layer, 2-formylaminoacetophenone was obtained as crystals (114 mg, 70%, mp 78-79°C, lit. 79°C$^{4)}$). Its NMR spectrum fully supports the structure: NMR ($CDCl_3$) δ 2.68 (s, 3H), 7.00-7.98 (m, 3H), 8.47-8.78 (m, 2H), and 11.60 (s, broad, 1H).

Table. Oxidation of 3-Methylindole to 2-Formylaminoacetophenone

CuCl (mmol)	Solvent	(ml)	Pyridine (ml)	O_2 uptake (mmol)	Yield (%)
0.3		0	20	1.5	13
0.3	CH_2Cl_2	20	0.5	1.0	53
0.3	toluene	20	0.5	0.84	45
0.3	CH_2Cl_2	15	0 (DMF 1)	0.6	32
0.5	$CHCl_3$	20	0.5	1.2	56
0.4	CH_2Cl_2	20	0.5	1.2	70
2.0	CH_2Cl_2	20	2.0	1.4	72

1.0 mmol of 3-methylindole dissolved in 10 ml of CH_2Cl_2, was oxidized at 0°C in 1-3 h.

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