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172. **Masao Tomita, Kazuyoshi Fujitani, and Yoshiaki Aoyagi :**
Cupric Oxide as an Efficient Catalyst in Ullmann Condensation Reaction.

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A condensation reaction between aryl halide and nucleophilic reagent in the presence of metal catalyst, such as copper, has been known as Ullmann condensation reaction,[*2] and has been used widely for the syntheses of diaryl ethers and diaryl amines.

Recently, several reports concerning the modification of the reaction using solvents,[1] and on the catalytic powers of some copper compounds[2~4] and the effect of an addition of alkali in the reaction media were seen,[1,5] and also studies on reaction mechanism[4,6] were presented.

On the other hand, attempts to synthesize biscoclaurine alkaloids having diphenyl ether linkage have been reported in the literature, and hitherto known successful syntheses have been achieved through the Ullmann condensation reaction. However, the yield of the condensation product is usually not so high, and this has formed a bottleneck in the full synthetic route.

The authors wish to report on the efficiency of cupric oxide as a catalyst in Ullmann condensation reactions affording diaryl ether derivatives, which were undertaken in order to obtain a fundamental information for the synthetic study of biscoclaurine alkaloids.

The reactions were carried out between 5-bromo-3,4-dimethoxybenzaldehyde diethyl acetal (I) and phenolic component (phenol (Ⅲ) and methyl *p*-hydroxyphenylacetate (Ⅳ)) (Reaction A and B), and between bromobenzene (Ⅱ) and methyl *p*-hydroxyphenylacetate (Ⅳ) (Reaction C). In reaction B, the product (Ⅵ) is a key intermediate for the syntheses of some biscoclaurine alkaloids.

Table I summarizes conditions and results of the reactions. A minor deviation of the amount of catalyst did not affect the yield of the diaryl ethers.

The results of the above experiments show that copper oxide gave better yields than metallic copper in every case, though any remarkable difference between cuprous and cupric oxide could not be detected.

Bacon and Hill[3] stated that cuprous oxide readily replaces halogen in unactivated aryl halides in polar solvents, though any mention on cupric oxide was not made. Therefore, the results obtained above led us to try an additional experiments to compare the yield more rigorously between the reactions promoted by cuprous and cupric oxide, using the same reaction described by Bacon and Hill as cuprous oxide was effective.

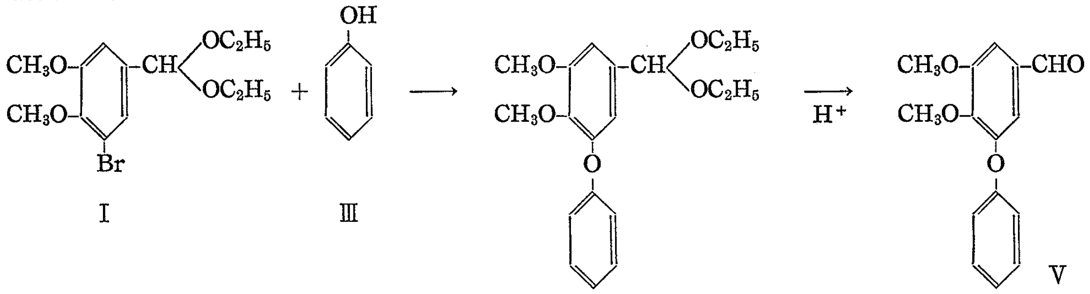
[*1] Yoshida-shimoadachi-cho, Sakyo-ku, Kyoto (富田真雄, 冨士谷憲徳, 青柳良明).

[*2] Should be distinguished from Ullmann synthesis of biaryls; (See J.E. Gowan, T.S. Wheeler : "Name Index of Organic Reactions" (1962). Williams Clowes and Sons, Ltd., London)
K. Fujimoto, *et al.* reported on the catalytic activities of copper powder and copper oxide in Ullmann synthesis of biaryls; K. Fujimoto, S. Arita, K. Takeshita: Yuki Gosei Kagaku Kyokai Shi, **22**, 390 (1964).

1) Y.K. Sawa, N. Tsuji, S. Maeda : Tetrahedron, **15**, 144 (1961).
2) P.E. Weston, H. Adkins : J. Am. Chem. Soc., **50**, 859 (1928).
3) R.G.R. Bacon, H.A.O. Hill : J. Chem. Soc., **1964**, 1108.
4) H. Weingarten : J. Org. Chem., **29**, 977, 3624 (1964).
5) Y.K. Sawa, N. Tsuji, S. Maeda : Tetrahedron, **20**, 2255 (1964).
6) W. Mayer, R. Fikentscher : Chem. Ber., **91**, 1536 (1958).

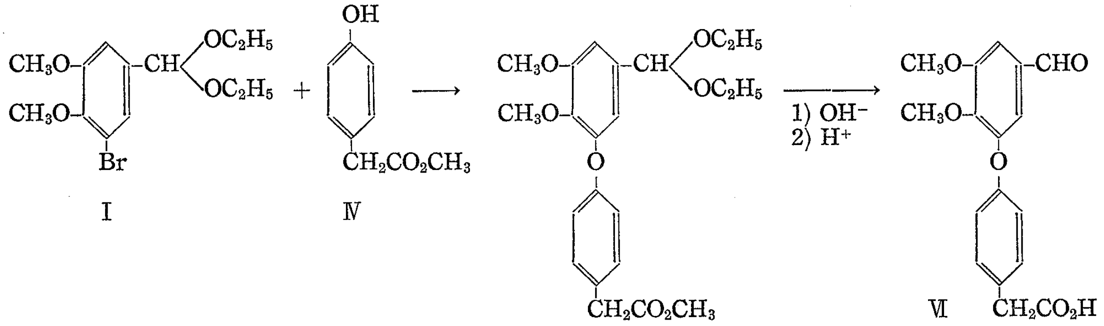
Table I. Conditions and Results of the Ullmann Condensation Reactions

Reaction A.



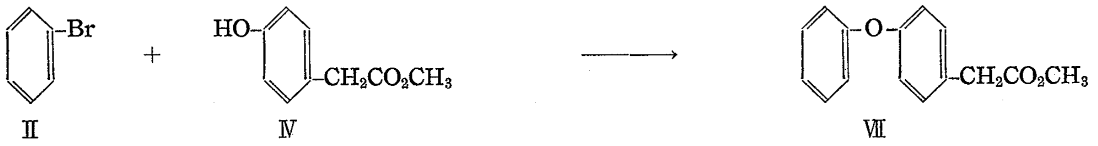
I (g.)	III (g.)	Alkali (K_2CO_3 : g.)	Catalyst (mg.)	Solvent	Reaction time (hr.)	Yield based on I, (%)
2.0	2.0	1.6	Cu : 100	pyridine	5	10
2.0	2.0	1.6	CuO : 300	〃	5	57

Reaction B.



I (g.)	IV (g.)	Alkali (K_2CO_3 : g.)	Catalyst (mg.)	Solvent	Reaction time (hr.)	Yield based on I, (%)
3.0	3.0	1.0	Cu : 600	pyridine	30	8
2.0	2.0	1.0	Cu : 200	〃	15	10
1.0	1.0	1.0	Cu : 100	dimethylformamide	15	10
3.0	2.0	1.5	Cu_2O : 600	pyridine	10	30
3.0	3.0	1.5	CuO : 300	〃	9	35
3.0	3.0	none	CuO : 400	〃	6	20

Reaction C.



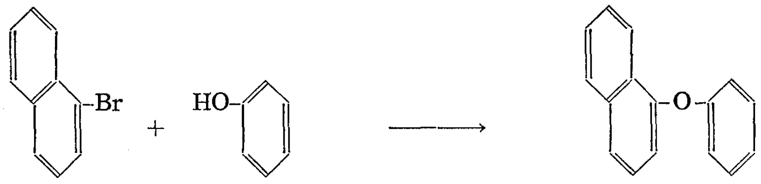
II (g.)	IV (g.)	Alkali (K_2CO_3 : g.)	Catalyst (mg.)	Solvent	Reaction time (hr.)	Yield based on IV, (%)
2.0	2.0	1.0	Cu : 300	pyridine	6	7
2.0	2.0	1.0	CuO : 300	〃	6	60

The reaction affording 1-phenoxynaphthalene (Ⅸ) from 1-bromonaphthalene (Ⅷ) and phenol (Ⅲ) was carried out (Reaction D) and the effect of alkali added to the reaction media was also examined.

The conditions and yields are listed in Table Ⅱ.

TABLE Ⅱ. Ullmann Condensation Reactions of 1-Bromonaphthalene and Phenol

Reaction D.



Ⅷ Ⅲ Ⅸ

Ⅷ (mol.)	Ⅲ (mol.)	Alkali (mol.)	Catalyst (g.)	Solvent	Bath temperature (℃)	Reaction time (hr.)	Yield based on Ⅷ, (%)
1/100	3/100	K_2CO_3 : 3/200	CuO : 1.0	pyridine	150±5	3	78
1/100	3/100	KOH : 3/200	CuO : 1.0	〃	150±5	3	76
1/100	3/100	none	Cu_2O : 1.0	〃	150±5	3	61
1/100	3/100	〃	CuO : 1.0	〃	150±5	3	80
1/100	3/100	〃	CuO : 1.0	piperidine	150±5	3	68
1/100	3/100	〃	CuO : 1.0	dimethylformamide	165±5	3	32
1/100	3/100[a]	KOH[a] : 3/100	CuO : 1.0	〃	165±5	3	85
1/100	3/100[a]	KOH[a] : 3/100	Cu_2O : 1.0	〃	165±5	3	13

a) Used in the form of potassium phenolate.

In case of the reaction carried out in basic solvent, no significant difference was found in the yield of the product between the reactions promoted by cuprous and cupric oxide. In dimethylformamide, however, cupric oxide gave better yield than cuprous oxide. An addition of alkali improved the yield in dimethylformamide, but no remarkable effect was found in pyridine.

Furthermore, in order to get an additional data in case of the reaction involving the compound having unprotected reactive functional group, following experiments were undertaken.

The reactions were carried out between bromobenzene (Ⅱ) and hydroxybenzaldehyde derivatives (vanillin (Ⅹ) and isovanillin (Ⅺ)) (Reaction E and F).

Table Ⅲ shows the results of the reactions.

The results of the above experiments show that, although cupric oxide is still active, there is no significant difference in the yield of the product between the reactions promoted by metallic copper and cupric oxide. In reaction E, the corresponding benzylalcohol was obtained together with phenoxybenzaldehyde derivative.

In every case of the reaction when cuprous oxide in pyridine was employed, an orange-yellow color of cuprous oxide was discolored immediately to dark brown and a small amount of metallic copper and cupric copper were noticed after the reaction was completed, and cupric copper was also noticed in the reaction promoted by metallic copper. Further, in the reaction promoted by cupric oxide both in pyridine and in dimethylformamide, metallic copper and a small amount of orange-yellow powder which must presumably be cuprous oxide were formed during the reactions.

In Ullmann condensation reaction, it has been known[7] that a dehalogenation product from aryl halide and resinous substances which may be consisted of oxidation

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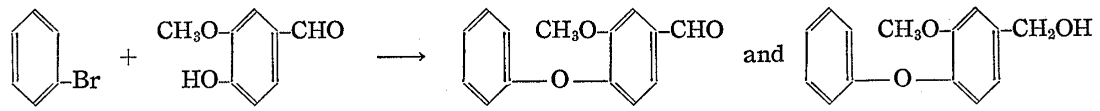
[7] R.G.R. Bacon, S.C. Rennison, O.J. Stewart: Proc. Chem. Soc., **1964**, 409.

Table III. Conditions and Results of the Ullmann Condensation Reaction of Hydroxybenzaldehyde Derivatives

Reaction E.



II X XII XIII

II (g.)	X (g.)	Alkali (K_2CO_3 : g.)	Catalyst (mg.)	Solvent	Reaction time (hr.)	Yield based on X, (%)	
						XII	XIII
3.0	2.0	1.0	Cu : 200	dimethylformamide[b)]	6	7	5
3.0	2.0	1.0	CuO : 400	〃 [b)]	6	12	3

b) The reaction did not proceed in pyridine, owing probably to the small solubility of potassium salt of vanillin in the media.

Reaction F.

II XI XIV

II (g.)	XI (g.)	Alkali (K_2CO_3 : g.)	Catalyst (mg.)	Solvent	Reaction time (hr.)	Yield based on XI, (%)
2.0	2.0	1.0	Cu : 300	pyridine	6	51
2.0	2.0	1.0	CuO : 500	〃	6	42

product of the phenolic materials are obtained together with diaryl ethers. The authors observed qualitatively on thin-layer chromatogram that, when cupric oxide was employed, this dehalogenation occurred in much smaller extent and the oxidation in rather large extent.

From these observations stated above, it seems reasonable to assume that some redox processes are taking place in the system of Ullmann condensation reaction. From these facts, and now that the reaction mechanism has not been fully established, it can hardly be concluded that cupric oxide is the true catalytic species working in Ullmann condensation reaction.

However, from the practical point of view, the obtained results suggest that cupric oxide is an efficient catalyst in Ullmann condensation reaction affording diaryl ether derivatives.

Experimental[*3,4]

Metallic Copper——Commercial copper powder (Nakarai Chemicals).

Cuprous Oxide——To a boiling solution of $CuSO_4 \cdot 5H_2O$ (25 g.) and anhydrous glucose (20 g.) in 300 ml. of water, a hot solution of NaOH (10 g.) in 50 ml. of water was added slowly under vigorous stirring. After cooling, orange-yellow precipitate of cuprous oxide was collected by filtration, washed with distilled water, dried at 100° for 10 hr. in vacuum, then powdered finely (100～200 mesh).

Cupric Oxide——To a boiling solution of $CuSO_4 \cdot 5H_2O$ (50 g.) in 300 ml. of water, a hot solution of NaOH (18 g.) in 50 ml. of water was added slowly under vigorous stirring. After cooling, dark brown

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[*3] All melting points were not corrected.

[*4] The purities of the products were all examined by thin-layer chromatography and NMR spectra.

precipitate of cupric oxide was collected by filtration, washed with distilled water, dried for 10 hr. at 110°, then powdered finely (100~200 mesh).

General Procedure for the Ullmann Condensation Reaction A, B, C, E, and F——To a solution of starting materials in 7 ml. of anhydrous solvent, finely powdered anhydrous K_2CO_3 was added with stirring, then the mixture was heated on an oil bath under N_2 atmosphere. When the temperature of the bath was raised to 150°, catalyst was added. The temperature of the bath was kept at $150 \pm 5°$ during the reaction. After the reaction ended, the mixture was taken up in a small amount of MeOH, then poured into ether. Ethereal solution was washed successively with 3% NaOH, 5% citric acid solution and water, dried over anhyd. $MgSO_4$, then the solvent was evaporated off. Residual neutral substance was purified on alumina column chromatography.

5-Phenoxy-3,4-dimethoxybenzaldehyde (V)——The neutral substance obtained was dissolved in *n*-hexane-benzene, and chromatographed carefully on alumina. Eluted 5-phenoxy-3,4-dimethoxybenzaldehyde diethyl acetal was treated with 10% HCl in MeOH at room temperature. The solvent was evaporated, and the free aldehyde remained was extracted with ether. The ethereal solution was dried over anhyd. $MgSO_4$, and evaporation of the solvent gave colorless oily substance; 2,4-dinitrophenylhydrazone: recrystallization from EtOH-AcOEt gave deep red plates of m.p. 186°. *Anal.* Calcd. for $C_{21}H_{18}O_7N_4$: C, 57.53; H, 4.14. Found: C, 57.41; H, 4.37.

5-(*p*-Carboxymethylphenoxy)-3,4-dimethoxybenzaldehyde (VI)——The neutral reaction product was chromatographed on alumina with benzene. Eluted pale yellow oily substance was dissolved in 30 ml. of MeOH. To this solution, 30 ml. of 10% $NaHCO_3$ solution was added and refluxed for 4 hr. with stirring. After cooling, the reaction mixture was acidified with conc. HCl and left at room temperature for 30 min., then made alkaline with NH_4OH, washed thoroughly with ether, acidified again with conc. HCl, and extracted with ether. Ethereal extract was dried over anhyd. $MgSO_4$. Removal of the solvent gave pale yellow crystalline mass. Recrystallization from CCl_4 or benzene gave colorless prisms, m.p. 116°. *Anal.* Calcd. for $C_{17}H_{16}O_6$: C, 64.55; H, 5.10. Found: C, 65.03; H, 5.02.

Methyl *p*-Phenoxyphenylacetate (VII)——The neutral product was taken up in benzene and chromatographed on alumina, providing colorless oily substance.

***p*-Phenoxyphenylacetic Acid**——To a solution of 1.7 g. of the methyl ester (Ⅶ) in 20 ml. of MeOH, 15 ml. of 10% NaOH solution was added and refluxed for 1 hr. After cooling, the acidic substance was extracted with AcOEt. Evaporation of the solvent after drying over anhyd. $MgSO_4$ gave 1.5 g. of pale yellow crystalline mass. Recrystallized from *n*-hexane. Colorless prisms, m.p. 79°. *Anal.* Calcd. for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30. Found: C, 73.84; H, 5.50.

O-Phenylvanillin (XII) and 3-Methoxy-4-phenoxybenzylalcohol (XIII)——The neutral product obtained was dissolved in benzene and purified on alumina chromatography. The fractions eluted with benzene gave O-phenylvanillin as colorless oily substance. 2,4-Dinitrophenylhydrazone: recrystallized from EtOH-AcOEt. Orange-red prisms, m.p. 204~206°. *Anal.* Calcd. for $C_{20}H_{16}O_6N_4$: C, 58.82; H, 3.95. Found: C, 59.12; H, 4.20.

The fractions eluted with benzene-$CHCl_3$ (1:1) gave 3-methoxy-4-phenoxybenzylalcohol. Recrystallization from ligroin afforded colorless needles, m.p. 83°. *Anal.* Calcd. for $C_{14}H_{14}O_3$: C, 73.02; H, 6.13. Found: C, 72.96; H, 6.33.

O-Phenylisovanillin (XIV)——The neutral substance was dissolved in benzene and purified on alumina chromatography, then recrystallized from ligroin. Colorless plates, m.p. 48°. *Anal.* Calcd. for $C_1H_{12}O_{34}$: C, 73.67; H, 5.30. Found: C, 73.73; H, 5.58.

Ullmann Condensation Reaction of 1-Bromonaphthalene and Phenol (Reaction D)——Starting materials and finely powdered alkali were added in 7 ml. of anhydrous solvent, then heated on an oil bath under N_2 atmosphere with stirring. When the solvent began to reflux, catalyst was added. After the reaction was completed, reaction mixture was poured into ether, washed successively with 3% NaOH, 2% HCl and water, dried over anhyd. $MgSO_4$, then the solvent was evaporated off. Residual neutral substance was taken up in petr. ether, and purified on alumina chromatography. 1-Phenoxynaphthalene: recrystallization from MeOH afforded colorless pillars, m.p. 54~55° (lit.[3] m.p. 55°).

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Summary

Cupric oxide catalyst improved the yield in some Ullmann condensation reactions affording diaryl ether derivatives. Though it was not concluded whether cupric oxide was the true catalytic species or not, its efficiency was proved.

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