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Cupric Oxide as an Efficient Catalyst in Methylenation of Catechols¹⁾MASAO TOMITA^{2a)} and YOSHIKI Aoyagi²⁾Faculty of Pharmaceutical Sciences, Kyoto University²⁾

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Methylenation of catechols with methylene halides was found to be catalyzed more effectively by cupric oxide in dimethylformamide.

Preparations of 1,3-benzodioxoles (methyleneedioxybenzene derivatives) by methylenation of catechols have been carried out in aqueous alkaline alcoholic solvent with methylene halide or methylene sulfate as reagent, and copper powder has been employed as catalyst in some reactions.^{3,4)} However, the yield of product was usually poor, and the reaction required to be undertaken in sealed tube under nitrogen atmosphere to avoid a ready oxidation of catechols.

Campbell, *et al.*⁴⁾ reported an efficiency of bronze catalyst consisted mainly of copper, zinc, and aluminum (Tobin bronze) in the above mentioned reactions.

This paper concerns with the cupric oxide-catalyzed methylenation of catechols with methylene halides in dimethylformamide (DMF), by which 1,3-benzodioxoles are afforded in improved yield in a short reaction time.

Methylenation of 3-bromo-4,5-dihydroxybenzaldehyde (I) with methylene sulfate was reported by Erne and Ramirez.⁵⁾ The product, 5-bromopiperonal (II), was obtained in total yield of 30% with repetition of the reaction using the recovered starting material.

TABLE I. Methylenation of 5-Bromoprotocatechuic Aldehyde (I)



I (g)	Reagent (g)	Catalyst (g)	Solvent (ml)	K ₂ CO ₃ (g)	Bath temperature (°C)	Reaction time (hr)	Yield of II (%)
10.0	CH ₂ Br ₂ 10.0	CuO 1.0	DMF 100	20	130—140	4	40
10.0	CH ₂ Br ₂ 10.0	Cu 1.0	DMF 100	20	130—140	4	27
10.0	CH ₂ Br ₂ 10.0	none	DMF 100	20	130—140	4	16
5.0	CH ₂ Br ₂ 5.0	CuO 1.0	pyridine 50	10	(reflux)	4	13.3
5.0	CH ₂ Br ₂ 5.0	Cu 1.0	pyridine 50	10	(reflux)	4	9.9
50.0	CH ₂ Br ₂ 50.0	CuO 5.0	DMF 500	100	130—140	4	42
10.0	CH ₂ I ₂ 20.0	CuO 1.0	DMF 60	20	130—140	4	64
10.0	CH ₂ I ₂ 20.0	Cu ₂ O 1.0	DMF 60	20	130—140	4	12
5.0	CH ₂ Br ₂ 5.0	CuO 0.5	DMSO 50	10	130—140	4	poor
5.0	CH ₂ Br ₂ 5.0	CuO 0.5	acetone 50	10	(reflux)	4	poor
5.0	CH ₂ Br ₂ 5.0	CuO 0.5	MeOH 50	10	(reflux)	4	poor
5.0	CH ₂ Br ₂ 5.0	Cu 0.5	MeOH 50	10	(reflux)	4	poor

- 1) Part of this work was presented at the monthly meeting of the Kinki Branch, the Pharmaceutical Society of Japan (Jan. 21, 1967).
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- 3) W. Bradley, R. Robinson, and G. Schwarzenbach, *J. Chem. Soc.*, 1930, 793.
- 4) K.N. Campbell, P.F. Hopper, and B.K. Campbell, *J. Org. Chem.*, 16, 1736 (1951).
- 5) M. Erne and F. Ramirez, *Helv. Chim. Acta*, 33, 912 (1950).

The present authors examined the above reaction in various conditions, and found that the reaction proceeded most smoothly in the presence of cupric oxide in dimethylformamide. A brief summary of the many runs is given in Table I.

The product, 5-bromopiperonal, was used as a starting material for the synthetic work of *dl*-cepharanthine by the authors.⁶⁾

It was reported by Campbell⁴⁾ that 3-methoxy-4,5-methylenedioxybenzaldehyde (myristicin aldehyde) (IV) was obtained in 35% yield by methylenation of the corresponding catechol (III) catalyzed by Tobin bronze using methylene bromide as reagent.

In the same reaction catalyzed by cupric oxide in DMF, the yield of myristicin aldehyde was improved up to 72%.

On the one hand, in the reaction using metallic copper (Gattermann's copper powder) as catalyst, the yield of the product was 34%.

Conditions and results are shown in Table II.

TABLE II. Methylenation of 3,4-Dihydroxy-5-methoxybenzaldehyde (III)



II (g)	Reagent (g)	Catalyst (mg)	Solvent (ml)	K ₂ CO ₃ (g)	Bath temperature (°C)	Reaction time (hr)	Yield of IV (%)
2.0	CH ₂ Br ₂ 2.5	CuO 250	DMF 25	3.5	135-145	4	72
2.0	CH ₂ Br ₂ 2.5	Cu 250	DMF 25	3.5	135-145	4	34

In methylenation reaction of protocatechuic aldehyde (V) catalyzed by both cupric oxide and copper powder, the yield of piperonal (VI) was 68 and 54%, respectively.

The reaction conditions are summarized in Table III.

TABLE III. Methylenation of Protocatechuic Aldehyde (V)



V (g)	CH ₂ Br ₂ (g)	Catalyst (mg)	DMF (ml)	K ₂ CO ₃ (g)	Bath temperature (°C)	Reagent time (hr)	Atmosphere	Yield of VI (%)
5.0	10.0	CuO 300	70	20	100-110	3	N ₂	68
5.0	10.0	Cu 300	70	20	100-110	3	N ₂	54

Although 3,4-dihydroxy-5-methoxybenzaldehyde (III) and pyrogallol 1-methyl ether⁷⁾ were shown to be readily methylenated into corresponding 1,3-benzodioxoles, any successful example of methylenation of pyrogallol has not yet been reported. From this point of view, it appeared of interest to investigate the product of the same reaction using cupric oxide as catalyst in DMF.

A neutral crystalline product which showed positive Labat test was obtained in 41% yield by the reaction, though any phenolic product was not isolated.

6) M. Tomita, K. Fujitani, and Y. Aoyagi, *Tetrahedron Letters*, 1967 (No. 13), 1201; *Chem. Pharm. Bull.* (Tokyo), 16, 217 (1968).

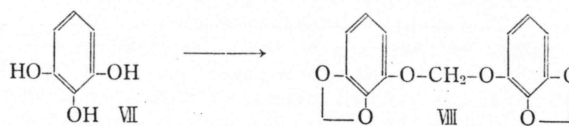
7) W. Baker, L.V. Montgomery, and H.A. Smith, *J. Chem. Soc.*, 1932, 1281.

Characterization of this product was effected by NMR spectrometry and elemental analysis. These data were in accord with the structure VIII.

An attempted cleaving of methylenedioxy bridge between two 1,3-benzodioxole nuclei with methanolic hydrochloric acid was unsuccessful.

The reaction conditions are given in Table IV.

TABLE IV. Methylenation of Pyrogallol (VII)



VII (g)	CH ₂ I ₂ (g)	Catalyst (mg)	DMF (ml)	K ₂ CO ₃ (g)	Bath temperature (°C)	Reaction time (hr)	Atmosphere	Yield of VIII (%)
3.0	10.0	CuO 250	30	20	100—110	3	N ₂	41

From the data stated above, it might be concluded that methylenation of catechols with methylene halides is more effectively catalyzed by cupric oxide, and that the reaction proceeds smoothly in dimethylformamide.

However, in case of the methylenation of simple pyrocatechol, the yield of 1,3-benzodioxole was not improved by the use of catalysts involving cupric oxide or copper powder.

The reaction conditions are summarized in Table V.

TABLE V. Methylenation of Pyrocatechol



K (g)	CH ₂ Br ₂ (g)	Catalyst (g)	DMF (ml)	K ₂ CO ₃ (g)	Bath temperature (°C)	Reaction time (hr)	Atmosphere	Yield of X (%)
10.0	20.0	CuO 1.0	100	25	100—110	3	N ₂	52
10.0	20.0	Cu 1.0	100	25	100—110	3	N ₂	50
10.0	20.0	none	100	25	100—110	3	N ₂	51

Experimental⁸⁾

General Procedure of the Reactions—Catechols, methylene halides, potassium carbonate, and catalyst were added into solvent; then the mixture was heated on an oil bath with stirring. After the reaction ended, the product was isolated and characterized as stated below.

Cupric oxide catalyst was prepared from CuSO₄ and NaOH,⁹⁾ and copper powder from CuSO₄ and Zn powder.

3-Bromo-4,5-methylenedioxybenzaldehyde (5-Bromopiperonal) (II)—The reaction mixture was poured into water, and the product was extracted with ether. The ethereal extract was washed successively with 2% HCl, 2% NaOH, and water. Evaporation of the solvent after drying over anhyd. K₂CO₃ gave light-brown crystalline mass, which, on recrystallization from MeOH, afforded pure 5-bromopiperonal (II). Colorless pillars, mp 121—123° (lit.⁵⁾ mp 124—125°).

3-Methoxy-4,5-methylenedioxybenzaldehyde (Myristicin aldehyde) (IV)—Recrystallization from MeOH of the crude product obtained by the same work-up method as that in 5-bromopiperonal (II) gave pure myristicin aldehyde (IV). Colorless pillars, mp 129—130° (lit.¹⁰⁾ mp 130—131°).

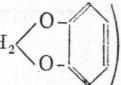
8) Melting points were measured on Yanagimoto's Micro Melting Point Apparatus and not corrected. The NMR spectra were taken on Varian A-60 spectrometer with tetramethylsilane as an internal standard.

9) M. Tomita, K. Fujitani, and Y. Aoyagi, *Chem. Pharm. Bull.* (Tokyo), **13**, 1341 (1965).

10) W. Baker, L.V. Montgomery, and H.A. Smith, *J. Chem. Soc.*, **1930**, 793.

3,4-Methylenedioxybenzaldehyde (Piperonal) (VI)—The crude product obtained by the same treatment as above was recrystallized from hexane-ether after decolorizing charcoal treatment in MeOH. Pale-yellow pillars, mp 34–34.5° (lit.¹¹⁾ mp 37°).

Methylenation of pyrogallol (VII)—Recrystallization from MeOH of the crude product obtained by the same way as above gave the pure product. Colorless pillars, mp 118–120°. Labat test: Positive.

NMR (CDCl₃) τ : 3.15–3.50 (6H, multiplet, aromatic protons); 4.07 (4H, singlet, $2 \times \text{CH}_2$ ); 4.20

(2H, singlet, ArO-CH₂-OAr). Bis(2,3-methylenedioxyphenoxy)methane (VIII): *Anal.* Calcd. for C₁₃H₁₂O₆: C, 62.50; H, 4.20. Found: C, 62.42; H, 4.11.

1,3-Benzodioxole (X)—The reaction mixture was poured into water (500 ml); then the product was distilled with steam. The distillate was extracted with ether, and the ethereal layer was washed successively with 2% HCl, 2% NaOH, and water. Drying over anhyd. K₂CO₃ and evaporation of the solvent gave colorless liquid. Beilstein test: Negative. 1,3-Benzodioxole (X): NMR (CDCl₃) τ : 3.20 (4H, singlet, aromatic protons); 4.11 (2H, singlet, O-CH₂-O).

Acknowledgement The authors are indebted to Dr. T. Shingu of this Faculty for measurements of NMR spectra. Thanks are also due to the members of the Microanalytical Center of this University for elemental analysis.

11) J. McLang, *Chem. Trade J.*, 79, 359 (1926) [*C.A.*, 21, 77 (1927)].