Communications to the Editor

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O_2-Cu^{2+}-ASCORBIC ACID: A NOVEL OXIDATION SYSTEM FOR THE HIGHLY SELECTIVE O-DEALKYLATION OF 2-ALKOXYPHENOLS

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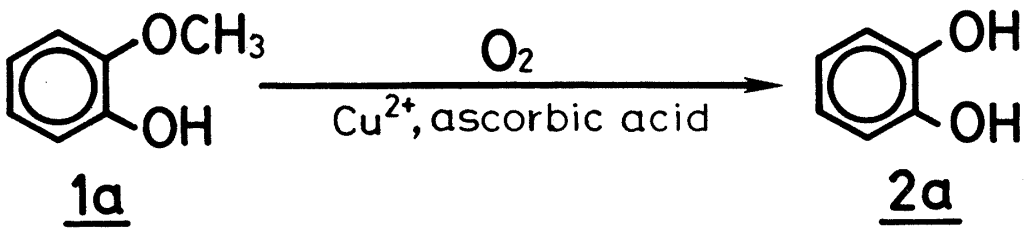
The novel oxidation system "O_2-Cu^{2+}-ascorbic acid" is a selective reagent for the oxidative O-dealkylation of 2-alkoxyphenols and affords catechols in good yield.

KEYWORDS —— O-dealkylation; oxygen; ascorbic acid; copper ion; oxidation; 2-alkoxyphenol; vanillin; dopamine; guaiacol; catechol

Cytochrome P-450 mediates a wide variety of oxidations such as hydroxylation of hydrocarbons, epoxidation of olefins, oxidative N-dealkylation of amines and O-dealkylation of ethers by activation of molecular oxygen.[1] The diverse functions of the enzyme are of great importance from the viewpoint of catalytic chemistry and biochemistry. The oxidative cleavage reaction of etheral C-O bonds, which cytochrome P-450 catalyzes efficiently, cannot be easily reproduced in purely chemical systems.[2-4] Nevertheless, the utility of this type of reaction for synthesis and our interest in the function of cytochrome P-450 prompted us to investigate biomimetic O-dealkylation by the use of molecular oxygen, metal ions and reductants as an analog of the cytochrome P-450 system. We now wish to report a new oxidation system using O_2-Cu^{2+}-ascorbic acid in aqueous solution, which is effective in cleaving the etheral C-O bond of 2-alkoxyphenols. This system is known to degrade proteins,[5,6] DNA[7] and other biomolecules[8] in vitro by generating hydroxyl radicals, though as far as we know, it has not been reported as a synthesis tool. By using a reagent couple, guaiacol (1a) was demethylated to give catechol (2a) with high selectivity (up to 100% yield based on the substrate consumed, Table I). Moreover the catechol (2a) given was quite stable under the conditions.



1a 2a

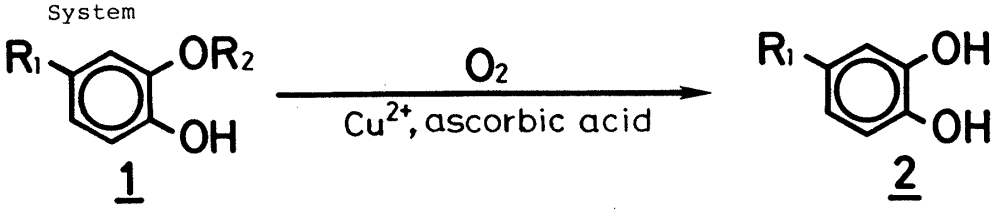
Table I. Demethylation of 1a by the O_2-Cu^{2+}-Ascorbic Acid System or Other System

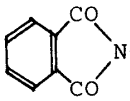
Run	Metal[a]		Ascorbic acid[a]	Time	Temperature	Yield[b]
1	$Cu(ClO_4)_2$	1 eq	10 eq	16 h	60 °C	96% (26%)
2		1	5	8 (2[c])	r.t.	96 (19)
3		2	100	24 (21[c])	r.t.	100 (28)
4		5	100	24 (19[c])	r.t.	71 (45)
5		3[d]	30[d]	24	40	99 (33)
6		0	10	17	r.t.	- (0)
7		1	0	17	r.t.	- (0)
8[e]		1	10	20	r.t.	- (0)
9[f]		1	0	15	r.t.	- (<0.1)
10	$Fe(ClO_4)_2$	1	10	20	28	- (4)
11	$Co(OAc)_2$	1	10	20	28	- (<0.1)
12	$Ni(OAc)_2$	1	10	20	28	- (<0.1)
13	CuBr	1[g]	10	20	28	- (2)

Condition: An aqueous solution of guaiacol 1a (1 mmol), metal salt and ascorbic acid was stirred under O_2 (1 atm). a) The numbers of equivalents were based on the substrate used. b) Yields of catechol were based on substrate consumed and yields in parentheses on total substrate. c) Duration time for the addition of an aqueous solution of ascorbic acid from the beginning of the reaction. d) Added three times by one third portions at every 4 h. e) Under Ar. f) Hydrogen peroxide (10 eq 30% aqueous) was added under Ar to an aqueous solution of 1a and $Cu(OAc)_2 \cdot H_2O$. g) CuBr is only slightly soluble in water.

Addition of ascorbic acid to 1a and $Cu(ClO_4)_2$ in water and stirring under a pure oxygen atmosphere afforded 2a selectively (run 1). The time-course experiment showed that the reaction was finished at 6 h at room temperature and neither 1a nor 2a decomposed during a further 24 h. Slow addition of an aqueous solution of ascorbic acid to the mixture of the substrate and cupric perchlorate in water increased the yield (runs 2 and 3). The use of a large excess of cupric ion raised the yield of 2a based on the substrate while it reduced the selectivity (run 4). Moreover, portionwise addition of ascorbic acid and cupric perchlorate to the reaction mixture in water gave a moderate yield of 2a with high selectivity (run 5). All of the components were shown to be essential for the reaction since no catechol was obtained when one of them was omitted (runs 6, 7 and 8). Apparently, ascorbic acid serves as both reductant of cupric ion and scavenger of excess active oxygens. Other cupric salts such as $CuCl_2$, $CuSO_4$, $Cu(OAc)_2$, $Cu_3(PO_4)_2$ and $Cu_2P_2O_7$ were almost as effective for the O-demethylation as $Cu(ClO_4)_2$ itself. The aqueous H_2O_2 -Cu^{2+} system[9] gave 2a in very low yield (run 9). Other metal ions, such as Fe^{2+}, Co^{2+} and Ni^{2+}, were less effective than Cu^{2+} (runs 10, 11 and 12). Cuprous bromide did not catalyze the demethylation of 1a well because of its low solubility in water (run 13). Catechol was much more stable under the reaction conditions than hydroquinone. We therefore assume that Cu^{2+} protects catechol from oxidation by chelation.

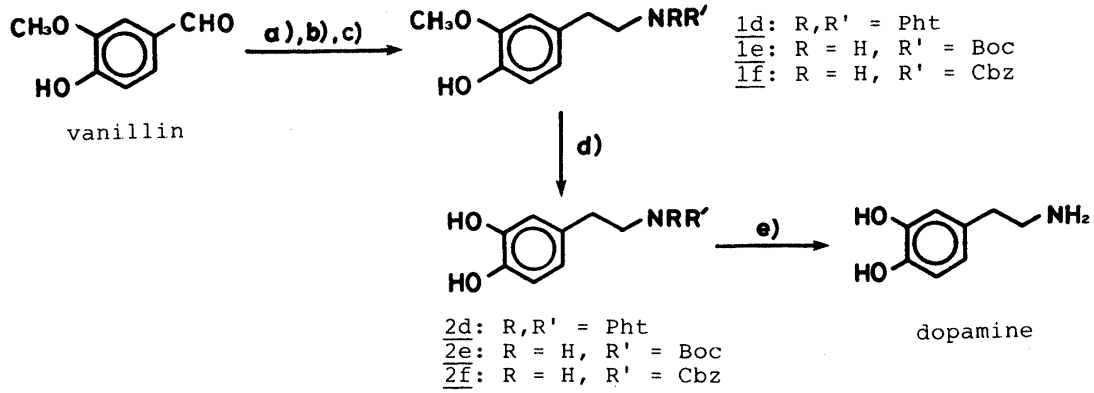
Table II. Dealkylation of Various 2-Alkoxyphenols by the O_2-Cu^{2+}-Ascorbic Acid System



R_1	R_2		Time	Temp.	Isolated yield of 2[a]	
H-	CH_3CH_2-	(1b)	20 h	60 °C	(2b)	96% (25%)
CH_3OCO-	CH_3-	(1c)	50[b]	40	(2c)	61 (25)
	CH_3-	(1d)	24	60	(2d)	49 (14)
t-$BuOCONHCH_2CH_2$-	CH_3-	(1e)	27[c]	20	(2e)	42 (28)
$PhCH_2OCONHCH_2CH_2$-	CH_3-	(1f)	43[d]	40	(2f)	39 (21)

These reactions were carried out under the following conditions. A mixture of a substrate, $Cu(ClO_4)_2$ (1 eq) and ascorbic acid (10 eq) in acetone-water was stirred under an oxygen atmosphere.

a) Yields are based on the substrate consumed and yields in parentheses are based on the substrate added. b) Ten more eq. of ascorbic acid were added at 6.5 h from the beginning of the reaction. c) To the clear solution of 1e and $Cu(ClO_4)_2$ (5 eq of 1e) in acetone-water an aqueous solution (pH 5.0) of ascorbic acid (62.5 eq of 1e) and monosodium ascorbate (187.5 eq of 1e) in water was added dropwise over 26 h with vigorous stirring, and then the reaction mixture was stirred for another 1 h. d) More ascorbic acid (10 eq) and $Cu(ClO_4)_2$ (1 eq) were added at 12 h from the beginning of the reaction.



a) CH_3NO_2, CH_3NH_2. b) H_2(60 atm), 10% Pd-C, 60 °C. c) i. EtOCOPht(1d), ii. Boc_2O(1e), iii. CbzCl(1f). d) $Cu(ClO_4)_2$, ascorbic acid, O_2. e) i. NH_2NH_2(2d), ii. TFA, PhOMe(2e), iii. H_2, 10% Pd-C(2f).

Chart. Preparation of Dopamine from Vanillin

Next, several 2-alkoxyphenols were dealkylated using the new oxidation system (Table II). Acetone or acetic acid was useful as a cosolvent in cases where the substrate solubility in water was low. The ethyl group of 1b was removed as easily as the methyl group of 1a. The methoxycarbonyl moiety of 1c remained unaffected under the reaction conditions. The 3-O-methyldopamine derivatives 1d, 1e and 1f were readily prepared from vanillin. Demethylation of 1d, 1e and 1f afforded 2d, 2e and 2f respectively, which were directly converted into dopamine upon deprotection (Chart). The acid-labile tert-butoxycarbonyl group (1e) and benzyloxycarbonyl group (1f) were almost unaffected under the reaction conditions. In the dealkylation of 2-alkoxyphenols the present system may therefore be superior to reagents previously developed in terms of selectivity and mildness of conditions. However, mechanistic details require further investigation.

The preparation of N-tert-butoxycarbonyldopamine (2e) will be described as an example: To a clear blue solution of N-tert-butoxycarbonyl-3-O-methyldopamine (1e, 0.11 g, 0.40 mmol) and cupric perchlorate hexahydrate (0.74 g, 2.0 mmol) in water (5 ml) and acetone (5 ml) an aqueous solution (pH 5) of ascorbic acid (4.40 g, 25 mmol) and monosodium ascorbate (14.9 g, 75 mmol) in water (100 ml) was added dropwise over 26 h with vigorous stirring under oxygen atomosphere at room temperature. After further stirring for 1 h, the pH value of the reaction mixture was adjusted to about pH 4, and the mixture was extracted with ethyl acetate. The combined organic layer was washed with 5% $NaHCO_3$ aq. and brine, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residue was chromatographed to afford N-t-butoxycarbonyldopamine (2e, 0.028 g, 28%) and recovered starting material (1e, 0.025 g, 23%).

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9) Guaiacol (1a) was demethylated to give 2a in 10% yield in the H_2O_2-Cu^{2+} system in acetic acid instead of water.

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