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SELECTIVE ORTHO-HYDROXYLATION OF PHENOLS IN COPPER (I) COMPLEXES

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Summary: Several catechols are obtained by reacting excess of the corresponding phenols with the tetrahydroborato copper(I) complex (**4**) and subsequent dioxygen oxidation of the intermediate copper(I) phenoxo complex (**1**)

The usual methods employed to obtain catechols from phenols are the acid-catalysed rearrangement of O-aryl-N-benzoylhydroxylamines[1] and the hydrogen peroxide oxidation of *ortho*-hydroxyacetophenone[2], although the persulfate oxidation of phenols[3], their benzoylation with benzoyl peroxide[4] and the photodecomposition of hydrogen peroxide in the presence of phenols[5] give some catechols, the predominant products are hydroquinones In industry some simple catechols are produced through the microbiological oxidation of the corresponding phenols[6]

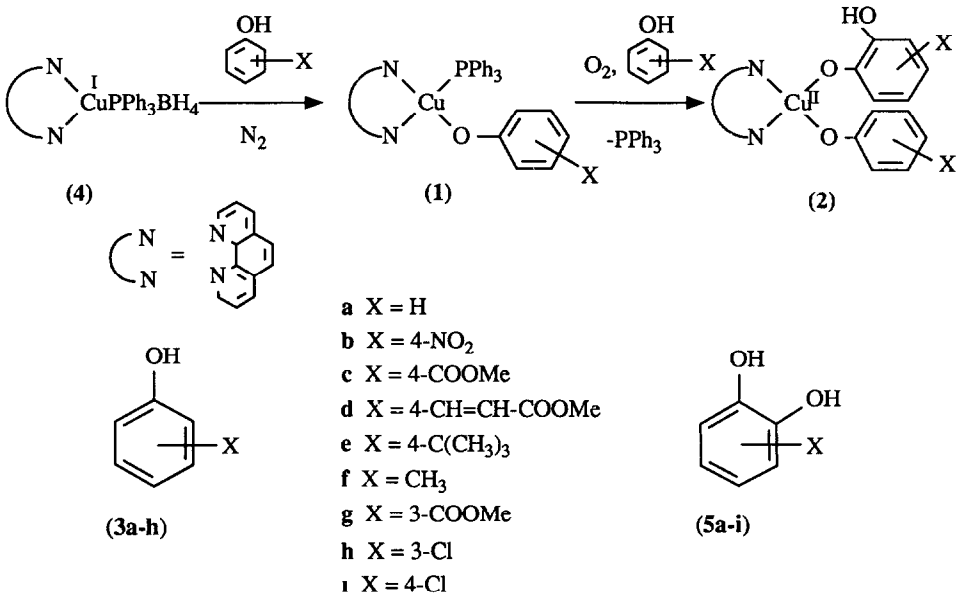
Selective *ortho* hydroxylation could take place by using reagents which would deliver oxygen into the *ortho* position because of prior reaction at the phenolate oxygen Benzeneselenic anhydride in an example of such a case[7] Moreover a metal center such as chromium can be used to direct a molybdenum oxidation[8], and the copper/dioxygen system would be suitable for the reaction as it has the ability to form copper phenolate complexes[9] and it acts in enzymes such as tyrosinase[10] The use of cuprous chloride and metallic copper[11] or a copper-amine complex[12] in the *ortho* hydroxylation of phenols have been reported

The main limitation of these methods is the lack of selectivity, since various reactions occur according to the state of the copper ion, the nature of the phenolic compound and the reaction conditions Such transformations are oxidative coupling, with the formation of various polymeric products, and oxygenation which affords diphenols and carbon-carbon bond cleavage products[13] Catechols seldom result,

since these, once formed, are further oxidized to *ortho*-benzoquinones, with final cleavage to muconic acids or their derivatives[14] Hence a mild and selective method for the *ortho* hydroxylation of phenols bearing various functional groups is needed Such a method was recently reported[15] in the presence of excess phenol the copper(I) phenoxo complex (**1**) reacts under a dioxygen atmosphere, to give the copper(II) derivative (**2**) This compound contains a phenoxo and a catecholato group as ligands Thus, the selective hydroxylation of a phenoxo unit, promoted by the copper center, produces the catechol

This result stimulated work intended to test the *ortho* hydroxylation of phenols (**3a-h** and **6**) *via* the corresponding Cu(I) phenoxo complexes (scheme 1) These complexes (**1**) were obtained by treating the tetrahydroborato copper(I) complex (**4**) in tetrahydrofuran with a large excess of the phenols (molar ratio 1 8)

Scheme 1



The formation of the copper(I) phenoxo complexes from the less acidic phenols, such as 4-t-butylphenol (**3e**) or 4-methylphenol (**3f**), required several hours and mild heating (40-50 °C) Higher temperatures led to the formation of a copper mirror due to the lability of (**4**)

After treatment with dioxygen and working up of the reaction mixture, analyses by glc-ms and hplc of the resulting products evidenced that all the phenols, except 2,6-di-tert-butylphenol (**6**), underwent selective *ortho*-hydroxylation to give the corresponding catechols (**5a-i**) The yields (table 1) were calculated according to the following stoicheiometric equation and are referred to Cu(I) added

$$\text{Phenol} + 2\text{Cu(I)} + 1/2O_2 \text{ ------ Catechol} + 2\text{ Cu (II)}$$

Yields ranged from 33% for 4-nitrophenol (**3b**) to almost quantitative for phenol (**3a**), methyl 4

-hydroxybenzoate (**3c**) and methyl 4-hydroxycinnamate (**3d**) The catechols bearing electron-releasing groups showed significantly lower yields, probably because further oxidation after the extraction with ethyl acetate could be catalyzed by even a residual trace of copper ions

Table 1. Reaction Conditions and Yields in the *O*rtho-Hydroxylation of Phenols with the Tetrahydroboratocopper(I) Complex (**4**)

Substr	Ratio S/Cu	Cu(I) phenoxo complex formation t(h)	T °C	Oxidation conditions t(h)	T °C	Reaction products (%)[a]
(**3a**)	5 1	24	40	24	25	(**5a**) (100)
(**3b**)	8 1	1	25	18	40	(**5b**) (33)
(**3c**)	8 1	1	25	20	25	(**5c**) (96)
(**3c**)	2 1	20	40	18	25	(**5c**) (76)
(**3c**)	3 1[b]	20	40	18	25	(**5c**) (30)
(**3d**)	8 1	1	25	18	25	(**5d**) (90)
(**3d**)	2 1	20	40	18	25	(**5d**) (75)
(**3e**)	8 1	24	40	12	25	(**5e**) (25)
(**3f**)	8 1	24	45	12	25	(**5f**) (28)
(**6**)	8 1	3	25	36	25	(**7**) (65)
(**3g**)	8 1	6	25	16	25	(**5c**) (34)
						(**5g**) (11)
(**3h**)	3 1	6	40	18	25	(**5h**) (50)
						(**5i**) (40)

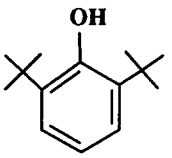
[a]Yields referred to Cu(I) added

[b]Reaction performed in two steps

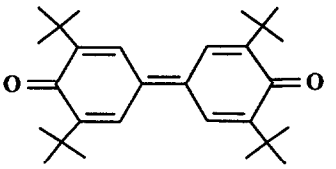
2,6-di-t-butylphenol (**6**) underwent catalytic oxidation to give mainly the dimerisation quinone product (**7**)

This behaviour evidenced that dimerization could compete with hydroxylation in this copper-centered reaction

The differences in the reaction of the intermediate complexes with dioxygen explain the slow



(6)



(7)

oxidation of phenols such as methyl-4-hydroxybenzoate (**3c**), the formation of methyl 3,4-dihydroxybenzoate (**5c**) taking place over a period of several hours On the contrary, the oxygenation of 4-t-butylphenol (**3e**) was complete within fifteen minutes (glc evidence) Thus , oxidation of the intermediate Cu(I) phenoxo complexes is favoured by electron-releasing groups

Methyl 3-hydroxybenzoate (**3g**) gave the hydroxylation products methyl 2,3-dihydroxybenzoate (**5g**) and 3,4-dihydroxybenzoate (**5c**) in a molar ratio of about 3 1 In the cuprous chloride/metallic copper system an analogous result was obtained and was ascribed to the higher electronegativity of 2-position[11] Some involvement of the carbonyl group in the coordination sphere of the copper ion could also direct the reaction toward the isomer (**5g**) In fact, 3-chlorophenol (**3i**) gave 3- and 4-chlorocatechol (**5h** and **5i** respectively) in similar amounts

A drawback of the described synthetic approach is the low conversion from the initial phenols to the catechols This is due to the large excess of phenols necessary for the formation of the corresponding phenoxo complex (**1**) in the first reaction step

Attempts were made to give a synthetic value to this reaction, either by carrying on several reaction cycles or using a lower ratio phenol/copper (I) complex (**4**)

The former procedure, using methyl 4-hydroxybenzoate (**3c**) as a substrate, gave the catechol (**5c**) in poor yields, due to the concomitant formation of oligomeric products (hplc evidence) On the contrary the latter procedure gave good results, although the formation of the complex (**1**) required prolonged heating (20/24h) at 40/45° In this case, a molar ratio phenol/Cu(I) complex (**4**) of 2, methyl 4-hydroxybenzoate (**3c**) was converted in the corresponding catechol (**5c**) in 78% yield and about 20% conversion while methyl *p*-coumarate (**3d**) afforded methyl caffeate (**5d**) in 75% yield and 18% conversion

In conclusion, this reaction allows selective *ortho*-hydroxylation of phenols in mild conditions without the concomitant formation of *ortho*-benzoquinones, furthermore it can also be used with highly oxidizable phenols like those bearing an alkyl group Nitro and carbonyl groups are not altered in the reaction The obtainment of caffeic acid methyl ester (**5d**) from 4-hydroxycinamic acid methyl ester (**3d**) mimicks a biological process related to lignin ogenesis and has no precedent in the synthetic literature

Further studies are now in progress to extend the described reaction to the conversion of complex phenols into catechols of biological interest, difficult to obtain otherwise

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EXPERIMENTAL

GENERAL PROCEDURE The appropriate phenol (1 6 m mols) and the required amount of the copper(I) complex (**4**)[16] were dissolved in tetrahydrofuran (10 ml) previously deoxygenated with a nitrogen stream and the mixture was stirred under nitrogen until the reaction was complete The proper reaction time for the individual substrates was found by adding a few drops of aqueous HCl to an aliquot of the reaction mixture taken at different times and monitoring hydrogen formation from unreacted (**4**) Dioxygen was then introduced into the reaction vassel Table 1 reports the temperature and the time for these two steps

At the end of the oxygenation, the reaction mixture was diluted with ethyl acetate (10 ml) and washed with aqueous 2M HCl The aqueous layer was extracted twice with ethyl acetate (10 ml portions) and the combined organic extracts were dried over sodium sulphate Removal of the solvent under reduced pressure afforded a residue which was fractionated over silica gel 0 05-0 2 mesh (R=100), eluting with chloroform and chloroform- methanol mixtures The crude reaction mixture was also analysed by gas chromatography and reverse phase high performance liquid chromatography in comparison with authentic samples of the expected catechols

TWO REACTION CYCLE PROCEDURE. Methyl 4-hydroxybenzoate (**3c**) was reacted with the copper(I) complex (**4**) in a molar ratio 3 1 and the resulting mixture was oxygenated as above After removal of dioxygen with a nitrogen stream, a second reaction cycle was performed adding more (**3c**) and (**4**) to obtain again a 3 1 molar ratio After phenoxo complex formation and subsequent oxidation, the usual work up and hplc analyses evidenced 10% conversion of phenol, 30% yield in catechol and concomitant formation of oligomeric products

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