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A practical highly selective oxybromination of phenols with dioxygen

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Abstract—A simple, low cost and highly selective method for the synthesis of mono-bromophenols from phenol and electron-rich phenolic compounds has been developed. Bromide ions are used as halogenating agents, dioxygen as a final oxidant, and $Cu(OAc)_2$ as a catalyst.

Bromination of aromatic compounds is a fundamental reaction of organic chemistry widely involved in the manufacture of many bulk and fine chemicals.[1] Bromophenols, in particular, have been recently recognized as an important group of key flavor compounds, which cause a typical sea-like taste and flavor.[2,3] They are also commercially used as flame retardants and wood preservatives with fungicide activity.[3] Conventional methods for the synthesis of bromoaromatics involve an electrophilic aromatic halogenation using various brominating agents such as bromine,[4] *N*-bromosuccinimide,[5] and hypobromites.[6] Lewis or Brønsted acid catalysts are usually employed in these reactions, often in stoichiometric amounts.

An alternative pathway to bromophenols is the oxidative bromination, which can use bromide ions as a bromine source and a suitable oxidant. Main advantages of oxybromination compared to the classical direct bromination are atom economy, that is, a full utilization of bromine atoms with no formation of by-products, and the use of low value and easy to handle halogenating agents rather than more expensive and hazardous ones, like molecular bromine. However, the information on the oxybromination of aromatics is scarce, especially little being achieved with the use of the most attractive oxidant molecular oxygen.[7–15] Most of the reported reactions involve peroxo compounds as oxidants and result in complex mixtures of mono- and polybrominated products, from which a desired isomer has to be isolated.[7–12] Moreover, the potential oxidation of side-chains in substituted aromatics can further complicate the reactions.

Only few examples of aerobic oxybromination have appeared, all reporting low substrate conversions and/or low selectivities for individual products in spite of the use of high oxygen pressures (20–70 atm).[7,13,14] Recently, oxybromination of 2-phenylpyridine giving mono- and dibrominated products under one atmosphere of air has been reported; however, the method involves the use of stoichiometric amounts of $Cu(OAc)_2$ and $Br_2CHCHBr_2$ as a bromine source.[15]

In the present work, we report for the first time a simple, low cost, and highly selective Cu-catalyzed oxidative bromination of phenols under mild aerobic conditions, in which bromide ions are used as halogenating agents and molecular oxygen is used as the stoichiometric oxidant.

We have discovered that solutions of eugenol (**1a**) in acetic acid containing LiBr and $Cu(OAc)_2$ readily consume dioxygen, with only one product being detected by gas chromatography (GC).[16] Product characterization revealed that, under the conditions used, a selective nuclear bromination of **1a** occurred resulting in monobrominated product **1c** with bromine being exclusively in *ortho*-position (Scheme 1).

This reaction formally consists of a nucleophilic substitution of aromatic hydrogen by Br^- and a further oxidation

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Keywords: Catalytic oxybromination; Phenols; Dioxygen; Copper catalyst.

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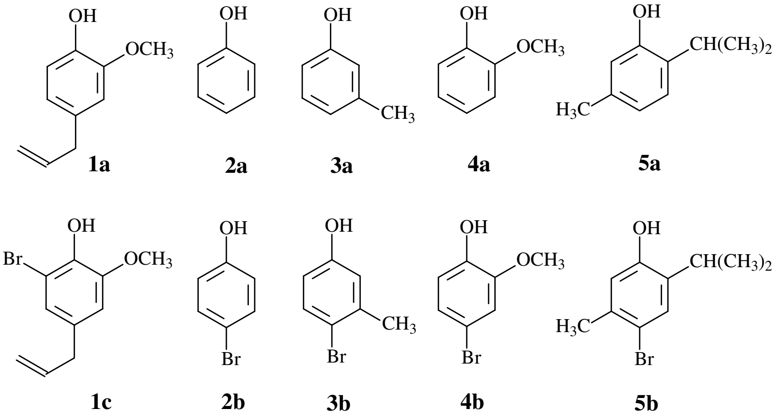
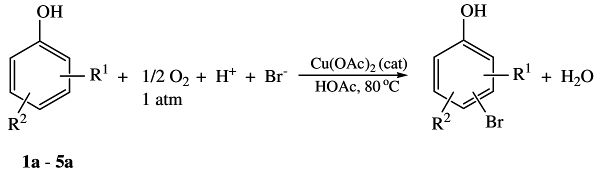


Scheme 1.



Scheme 2.

of H^- by Cu^{II} (Scheme 2) and seems to be similar to the $CuCl_2$-catalyzed oxychlorination of phenols reported in our previous work.[17,18] Dioxygen re-oxidizes the reduced Cu^{I} species; thus, catalytic on copper turnover can be achieved. Under optimized conditions, a 90% conversion of eugenol occurred for 12 h (Table 1, run 1). $Cu(OAc)_2$ was used in catalytic amounts. The reaction is remarkably *ortho*-selective: no even traces of *meta*-isomer were observed, with chemoselectivity for monobromination being as high as 99%. A GC mass balance was based on the substrate charged using dodecane as an internal standard.

The reactivity of various aromatic compounds was examined (Table 1) to evaluate a substrate scope (for product characterization data see Supplementary data). The reaction with phenol itself (**2a**) occurs slower than that with eugenol resulting in a 75% conversion for 12 h (run 2). Under non-optimized conditions, *para*-bromophenol **2b** is formed as a main product (80%), along with 17% of *ortho*-isomer **2c**. On the other hand, phenolic compounds having at least one electron donating group, such as *meta*-cresol **3a**, guaiacol **4a**, and thymol **5a**, undergo oxybromination at much higher rates, even faster than eugenol (runs 3–5). All these reactions show a dioxygen-coupled catalytic turnover, that is, catalytic amounts of $Cu(OAc)_2$ are used and dioxygen is consumed as the final oxidant. In the absence of $Cu(OAc)_2$, no bromination products are formed and no other reactions occur with phenols under the conditions shown in Table 1.

All substrates showed good to excellent *para*-selectivities. The only exception is eugenol, in which *para*-position is occupied by the allylic group; therefore, bromination occurs exclusively in *ortho*-position. Thymol **5a** and *meta*-cresol **3a** form *para*-products in more than 95% selectivity, whereas phenol **2a** and guaiacol **4a** show *para*-selectivity of near 80%, albeit the conditions for two latter substrates have not been optimized yet. In this regard, it should be mentioned that

Table 1. Copper-catalyzed oxybromination of aromatics with dioxygen[a]

Run	Substrate (0.40 M)	Time (h)	Conversion (%)	Selectivity (%)		
				para-Isomer (**2b**–**5b**)	*ortho*-Isomer (**1c**–**5c**)	S_{mono}[b]
1	Eugenol (**1a**)	12	90	—	99	99
2	Phenol (**2a**)	12	75	80	17	97
		24	95	80	17	97
3	*meta*-Cresol (**3a**)	10	95	95	4[c]	99
4	Guaiacol (**4a**)	8	92	82	17	99
5	Thymol (**5a**)	6	92	96	3	99
6[d]	Thymol (**5a**)	6	87	97	2	99
7	*para*-Nitrophenol	6	<1	—	—	—
8	Nitrobenzene	6	<1	—	—	—
9	Toluene	6	<1	—	—	—

[a] Conditions: solvent–acetic acid, $[Cu(OAc)_2] = 0.05$ M, $[LiBr] = 0.80$ M, 80 °C, O_2 (1 atm). Conversion and selectivity were determined by GC. Product and substrate structures are given in Scheme 1.

[b] Selectivity for monobrominated products.

[c] A mixture of two *ortho*-isomers.

[d] $[LiBr] = 0.60$ M.

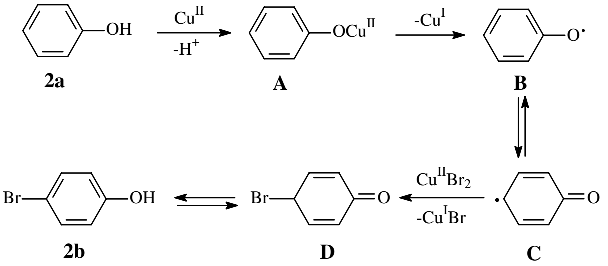
para-bromoaromatics usually have greater commercial significance.[4]

The extremely high chemoselectivity of this reaction for monobromination products is remarkable. For all substrates studied, a combined selectivity for monobromophenols was 97–99%. Although a substitution of the *ortho*-hydrogen in eugenol occurs smoothly, no further *ortho*-bromination of *para*-bromophenols **2b**–**5b**, having *ortho*-positions available, has been observed even at longer reaction times. Thus, the presence of the electron withdrawing bromine atom, attached to the aromatic nucleus in the primarily formed products, virtually suppresses their further bromination, conferring such a high monoselectivity on the process. The fact that electron-poor phenol *para*-nitrophenol shows no reactivity under similar conditions (run 7) collaborates with this explanation of the high selectivity to monobrominated products.

Non-phenolic compounds, both with electron withdrawing and with electron donating groups, that is, nitrobenzene and toluene, also undergo no transformation at all under the conditions used for the oxybromination of substrates **1a**–**5a** (runs 8 and 9). Thus, the method is highly substrate specific and could be used for the monobromination of phenols in the mixtures with other aromatics. Another practical advantage of this catalyst is its ability to promote with substituted phenols exclusively their nuclear bromination, with neither side-bromination nor oxidation products being observed.

We studied the oxybromination of thymol (**5a**) in more details and found that the reaction is approximately first order in the Cu^{II} concentration. On the other hand, amounts of bromide ions virtually have no effect on the initial reaction rates and reaction selectivity. Only when near- or sub-stoichiometric initial bromide concentrations are used, the reaction occurs slower at high substrate conversions. It suggests a pseudo-zero order of the reaction on bromide ions under these conditions. Thus, the use of LiBr can be decreased to near stoichiometric amounts (run 6). It should be remembered, however, that although the dissolved Cu^{I} species can be easily re-oxidized by dioxygen, CuBr is well soluble in acetic acid only in the presence of an excess of bromine ions. Thus, a precipitation of CuBr at the end of the reaction for the lack of bromide ions should be avoided. To keep Cu^{I} in the solution and to allow its fast re-oxidation, a sufficient excess of bromide ions ($Br/Cu \geqslant 2/1$) has to remain in the reaction solutions after a complete substrate conversion.

Kinetic data on the oxybromination of thymol obtained at different temperatures and expressed by means of the Arrhenius equation yield the activation energy of ca. $70\ kJ\ mol^{-1}$ in the range of 40–100 °C. This value is considerably higher than those found for the oxychlorination of thymol ($13\ kJ\ mol^{-1}$) and eugenol ($25\ kJ\ mol^{-1}$).[18] However, we suppose that the oxybromination of phenols can also be described as a free-radical process. A proposed mechanism is presented in Scheme 3 using for simplicity phenol itself as the substrate.



Scheme 3.

Most of the copper-catalyzed oxidations are thought to proceed via a one-electron oxidation of phenolate by Cu^{II} to the corresponding phenoxy radical.[19] Thus, we suggest the formation of phenoxy radical **B**, probably, from Cu^{II} (phenolate) complex **A** or via the direct oxidation of phenol by Cu^{II}. Tautomeric cyclohexadienyl radical **C** reacts with $CuBr_2$ resulting in CuBr and brominated product **D**, whose tautomerization gives *para*-bromophenol **2b**. Re-oxidation of Cu(I) complexes by dioxygen completes a catalytic cycle. In the absence of dioxygen under an inert atmosphere, a rapid precipitation of CuBr occurs and the reaction becomes stagnated.

In general, several concurrent transformations can occur with the tautomeric phenoxy and cyclohexadienyl radicals, such as carbon-carbon and carbon-oxygen coupling to afford diphenoquinones, dihydroxybiphenyls or polyphenylene ethers.[19] Therefore, a high chemoselectivity of the reaction described in this work is especially attractive. It seems that a rate determining step of the reaction is the formation of radicals **B** and **C**, whereas their bromination occurs faster. Indeed, the reaction is first-order in copper, but it does not depend on the concentration of bromide ions. Thus, radicals **C** are rapidly trapped by bromine atoms and have no time for other transformations.

The electron transfer from phenolate to Cu^{II} should be favored by electron donating groups attached to aromatic nucleus; therefore, eugenol, *meta*-cresol, guaiacol, and thymol are more reactive than phenol itself. On the other hand, *para*-nitrophenol as well as primarily formed monobrominated phenols, all having electron withdrawing substituents, undergo no bromination at all under similar conditions. This feature of the process seems to account for its extremely high monoselectivity. Within the proposed mechanistic scheme, it also turns understandable why non-phenolic compounds are not reactive in oxybromination.

In summary, we have developed a highly selective Cu-catalyzed process for the oxidative nuclear monobromination of phenol and electron-rich phenolic compounds under mild aerobic conditions. The use of an inexpensive copper catalyst, lithium bromide, as a source of bromine and dioxygen as a final oxidant is a significant practical advantage. This simple and low cost method provides a new attractive entry to the synthesis of high-priced low-volume bromoaromatics with remarkable atom economy and selectivity. Further studies are targeted towards developing the aerobic oxyfluorination of aromatics.

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Supplementary data

Characterization data for the products are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.093.

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16. The reactions were carried out in a stirred glass reactor and followed by measuring the dioxygen uptake and by gas chromatography using dodecane as an internal standard (Shimadzu 17 instrument, Carbowax 20 M capillary column, flame ionization detector). In a typical run, a solution of the aromatic compound, dodecane, $Cu(OAc)_2$ and LiBr in acetic acid was intensively stirred under oxygen at 80 °C for a specified time. The products were isolated by column chromatography and characterized by ^1H and ^{13}C NMR (Bruker DRX-400, tetramethylsilane, $CDCl_3$, COSY, HMQC, DEPT and NOESY experiments). For the product characterization data see Supplementary data.
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