Introduction of efficient catalytic system for the regioselective aerobic bromination of aromatic compounds

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ABSTRACT
A highly regioselective aerobic bromination of aromatic compounds has been achieved using Fe3O4@SiO2/CuO nanocatalyst and O2 as a green oxidant. In this procedure, the reactions gave high yields and para-selectivity for the various aromatic compounds. Mechanistic studies are described, and the possible mechanisms are proposed. Recyclability of the Fe3O4@SiO2/CuO nanocatalyst has also been explored upon aerobic bromination of aromatic compounds. The nanocatalyst can be reused five times without any significant decrease in the catalytic activity and selectivity.

GRAPHICAL ABSTRACT

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Introduction

The bromoarenes have been widely used as starting materials for the synthesis of biologically active compounds, pharmaceuticals, agrochemicals, and many functional chemicals.\(^1,2\) They can be utilized in the C–C and C–heteroatom bond formation reactions, transition metal-mediated coupling reactions such as Stille, Suzuki, Heck, Sonogashira, and Wurtz reactions.\(^3–5\) Moreover, bromoarenes have been applied as classical precursors to Grignard and organolithium reagents, nucleophilic aromatic substitution, and benzyn generation.\(^6,7\) In this regard, many brominating reagents and methodologies for the synthesis of these compounds have been developed.\(^8–22\) Although bromine...
molecules have been used extensively to bromination of aromatic compounds, however, due to its low reactivity, the use of additive substances such as oxidizing reagents and Lewis acids is mandatory. Moreover, these procedures have some drawbacks such as use of toxic and corrosive reagents, expensive oxidizing or Lewis acids generate hydrogen bromide as hazardous compound, and difficult work-up. Furthermore, regioselective synthesis of mono-bromide compounds is one of the issues that is receiving a lot of attention, and efforts to report a new and efficient method in this field continue. Therefore, from the view of green and sustainable chemistry, there is ever increasing need to synthesize bromoarenes under environmentally more acceptable green while at the same time achieving atom economy, selectivity, and high yields.

Because of the availability of oxygen in the air, and the point that by-product of the oxidation in an atmosphere of oxygen is water, aerobic bromination of aromatic compounds is a suitable procedure that can be considered for the synthesis of aryl bromides. Though some valuable procedures have been reported aerobic bromination of aromatic compounds, but they have main disadvantages such as low selectivity, non-recyclable oxidizing reagents and work-up of reaction mixture are difficult.

In the last two decades, transition-metal-catalyzed C–H bond functionalization has been attracted increasing attention and gradually become a modern and benign tool in organic synthesis. The copper-based metal oxides are more stable, less hazardous, and easier to handle than metals and metal halides. Moreover, they can easily remove from the reaction medium by an external magnetic field when combined with magnetic material.[23] Based on literature, the performance of some copper-based reagents for the halogenation are reported.[24–27] These methods are limited mainly by employing toxic halogen sources such as CuBr2, Br2CHCHBr2, or by the scope of electron-rich substrates.

In the previous researches, we have reported the catalytic activity of various nanocatalysts on the aerobic oxidation reactions.[28–31] Regarding the significant role of aryl bromides, and in continuation of our interest on the synthesis of halogenated aromatic compounds,[32,33] we wish to report an efficient regioselective procedure for the aerobic bromination of various aromatic compounds in the presence of Fe3O4@SiO2/CuO with potassium bromide under O2 atmosphere.

**Result and discussion**

In this research, our main goal is to present a new and efficient catalytic system for the synthesis of aromatic compounds in the presence of Fe3O4@SiO2/CuO nanocatalyst under mild aerobic conditions.

Initially, the possibility of aerobic bromination of anisole with KBr as a bromine source in the presence of Fe3O4@SiO2/CuO was investigated. It should be noted that the reaction did not progress much at room temperature, so all reactions were examined at 70 °C. The effect of different solvents and various amounts of the catalyst were examined (Table 1). In solvents such as water and ethanol, the desired product was obtained with a very low yield after 24 hours (Table 1, entries 1–2). Also, in DMSO the reactions were investigated. The results in DMSO were improved. However, increasing the amount of catalyst did not significantly alter the reaction conditions. (Table 1, entries 3–5). Studies have shown that the best results are obtained in acetonitrile in the
presence of 0.02 g Fe$_3$O$_4$@SiO$_2$/CuO nanocatalyst at 70 °C. Moreover, in the absence of Fe$_3$O$_4$@SiO$_2$/CuO nanocatalyst in acetonitrile, no product was obtained even after 10 h. (Table 1, entry 6). In the next step, we studied the competence of the reaction under air. It was found that the corresponding brominated product under air was completed for a long time and the yield of the product was not satisfactory (Table 1, entry 12).

Therefore, O$_2$ atmosphere was essential for achievement to the best results. It was found that under the oxygen atmosphere and in the presence of Fe$_3$O$_4$@SiO$_2$/CuO nanocatalyst (0.02 g), p-bromoanisole was obtained in 90% yield at at 70 °C (Table 1, entry 8).

In continuous, the reaction of anisole in the presence of the various amounts of KBr was optimized while the other conditions remained without any change. In the presence of 0.5, 1, and 1.5 mmol of KBr, the reactions were not completed, and p-bromoanisole was obtained in low to good yields (Table 2, entries 1–3). As a result, the molar ratio of 1:1.75, for the aromatic substrate and KBr was selected as optimized reaction conditions.

To examine the generality of this method, various aromatic substrates were subjected to bromination. Concerning the results of Table 3, it is noteworthy that the present catalytic system is highly efficient in para selectivity and monobromination of the

| Table 1. Optimization of the reaction conditions in the model reaction.$^a$
|---|---|---|---|
| Entry | Solvent | Catalyst amount (g) | Time (h) | Yield (%)$^b$
| 1 | H$_2$O | 0.02 | 10 | Trace |
| 2 | EtOH | 0.02 | 10 | Trace |
| 3 | DMSO | 0.02 | 10 | 70 |
| 4 | DMSO | 0.04 | 10 | 72 |
| 5 | DMSO | 0.06 | 10 | 70 |
| 6 | CH$_3$CN | 0 | 10 | – |
| 7 | CH$_3$CN | 0.01 | 10 | 80 |
| 8 | CH$_3$CN | 0.02 | 7 | 90 |
| 9 | CH$_3$CN | 0.03 | 7 | 90 |
| 10 | CH$_3$CN | 0.02 | 10 | 30$^c$ |

$^a$Reaction conditions: Anisole (1 mmol, 0.12 ml), KBr (1.75 mmol), Fe$_3$O$_4$@SiO$_2$/CuO (0.02 g), at heat condition under an O$_2$ atmosphere. $^b$Isolated pure products. $^c$Under air atmosphere.

| Table 2. Optimization of the KBr amounts in the model reaction.$^a$
|---|---|---|---|
| Entry | KBr (mmol) | Time (h) | Yield (%)$^b$
| 1 | 0.5 | 7 | 31 |
| 2 | 1 | 7 | 64 |
| 3 | 1.5 | 7 | 79 |
| 4 | 1.75 | 7 | 90 |
| 5 | 2 | 7 | 90 |
| 6 | 3.5 | 7 | 85 |

$^a$Reaction conditions: Anisole (1 mmol), Fe$_3$O$_4$@SiO$_2$/CuO (0.02 g), in CH$_3$CN at 70 °C under O$_2$ atmosphere. $^b$Isolated pure products.
Table 3. Bromination of aromatic compounds using Fe₃O₄@SiO₂/CuO nanocatalyst.a

| Entry | Substrate | Product | Time (h) | Yield (%) b |
|-------|-----------|---------|----------|-------------|
| 1     | ![苯甲醚](image) | ![卤代苯甲醚](image) | 7        | 90          |
| 2     | ![氯苯甲醚](image) | ![卤代氯苯甲醚](image) | 8        | 91          |
| 3     | ![二氯苯甲醚](image) | ![卤代二氯苯甲醚](image) | 8.5      | 87          |
| 4     | ![苯并环己酮](image) | ![卤代苯并环己酮](image) | 9        | 90          |
| 5     | ![苯酚](image) | ![卤代苯酚](image) | 9        | 64          |
| 6     | ![苯胺碘代](image) | ![卤代苯胺碘代](image) | 5.5      | 89          |
| 7     | ![苯酚甲醇](image) | ![卤代苯酚甲醇](image) | 4        | 93          |
| 8     | ![苯甲基甲醇](image) | ![卤代苯甲基甲醇](image) | 8.5      | 69          |
| 9     | ![苯并环己醇](image) | ![卤代苯并环己醇](image) | 7.5      | 68          |
| 10    | ![苯并环己硫甲基](image) | ![卤代苯并环己硫甲基](image) | 8        | 73          |
| 11    | ![苯并环己氮代](image) | ![卤代苯并环己氮代](image) | 4        | 95          |
| 12    | ![苯并环己酰胺](image) | ![卤代苯并环己酰胺](image) | 6.5      | 73          |
| 13    | ![苯并环己二甲基](image) | ![卤代苯并环己二甲基](image) | 12       | 74          |
| 14    | ![苯并环己溴代](image) | ![卤代苯并环己溴代](image) | 14       | 73          |
| 15    | ![苯并环己硫甲基](image) | ![卤代苯并环己硫甲基](image) | 8        | 81          |
| 16    | ![苯并环己氮代](image) | ![卤代苯并环己氮代](image) | 9        | 77          |

aReaction conditions: Anisole (1 mmol), KBr (1.75 mmol), Fe₃O₄@SiO₂/CuO (0.02 g), in CH₃CN at 70 °C under an O₂ atmosphere. bIsolated pure products.
aromatic compounds. Complete regioselectivity in substrates followed at the more active and less sterically hindered position. In compounds that can be substituted in both ortho- and para region, the para-substituted product was the only isomer. Electron-rich arenes gave regioselective monobrominated products in high yields (Table 3, entries 1, 2–4, 6, 7, 9–11, and 13).

However, introducing an electron-withdrawing group to the aromatic ring or blocking of the para position substantially decreased the rate and yield of bromination (Table 3, entries 3, 5, and 8). Moreover, N-phenylacetamide, 1,2,4,5-tetramethyl benzene, 9-bromoanthracene and aromatic heterocyclic compounds, gave the corresponding products in good to high yields (Table 3, entries 12, 13, 15, 16). To investigate the recyclability of the catalyst, the model reaction was studied under the optimized reaction conditions. After the reaction was completed, the catalyst was separated by an external magnet, washed with hot acetonitrile, dried, and stored for the next run. The recovered catalyst showed high catalytic activity and selectivity in successive runs (Figure 1). The catalyst recycling property was investigated up to ten times. The results were satisfactory up to 7 times. After 7 times, the reaction was not finished and the yield of the corresponding product was low. The possible reason for the decrease in the activity of the catalyst can be the aggregation of particles until the size of the particles increases and the catalyst becomes lumpy. In addition, to determine whether copper was being leaching out from the catalyst surface to the solution, the copper content was evaluated by ICP–OES analysis. The results displayed a negligible amount of copper leaching in the filtrate (2.47 wt % after seven run). Moreover, the filtrate mixture did not show catalytic activity toward further bromination. These results confirmed that the catalyst is highly stable and heterogeneous in nature, which offers several advantages over the homogeneous counterpart.

**Mechanistic studies**

It was well understood that some metal ions have low solvation energies in the relatively weak base acetonitrile than the much stronger base water. Indeed, these metal
ions have higher positive standard potential in acetonitrile than in protic solvents like water. Copper ions are exceptional in that they coordinate strongly with acetonitrile, and therefore they can be used as a strong oxidizing agent in this solvent.\cite{34}

The reduction potential of Cu(II)/Cu(I) couple in acetonitrile is equal to \( E^0_{\text{Cu(II)/Cu(I)}} = 1.0 \text{ vs SCE} \), which is extremely positive as opposed to that in water \( E^0_{\text{Cu(II)/Cu(I)}} \approx 0.0 \text{ vs SCE} \). Consequently, the copper-based nanocatalysts can be operated as a strong oxidizing agent in acetonitrile to regioselectively aromatic carbons to carbocation or convert either Br\(^-\) to Br\(_2\) reagent.\cite{29} Thus, the two possible mechanisms proposed below for the bromination of aromatic compounds in this work (Scheme 1).

**Experimental**

**General**

All chemicals were purchased from the Merck chemical company. All the synthesized compounds were characterized by comparing their spectroscopic data and physical
properties with those reported in the known samples. The reaction progress was controlled by TLC on silica-gel Polygram SIL G UV 254 and 312 plates. The Fe₃O₄@SiO₂/CuO nanocatalyst was prepared according to our previously reported research.

**General procedure**

A mixture of aromatic compound (1 mmol), KBr (1.75 mmol), and Fe₃O₄@SiO₂/CuO nanocatalyst (0.02 g) in acetonitrile (8 mL) was stirred under an oxygen atmosphere at 70 °C. After reaction completing (monitored by TLC), the catalyst was removed using an external magnet, washed with hot acetonitrile (2 × 5 mL), and dried for the following reaction runs. Evaporation of the solvent followed by recrystallization or column chromatography on silica gel gave the corresponding pure product (Table 3). Products were characterized by comparison of their spectroscopic data (NMR data) and melting points with those reported in the literature (supplementary file).

**Conclusion**

In conclusion, we report an efficient and new catalytic system for the regioselective aerobic bromination of various aromatic compounds in the presence of Fe₃O₄@SiO₂/CuO nanocatalyst under O₂ atmosphere. The catalyst could be easily recovered by an external magnetic field and reused without significant loss of catalytic activity and selectivity after five consecutive runs. Leaching analysis showed that the catalytic reaction is mainly heterogeneous in nature. High selectivity, high yields of products and simple work-up make this procedure a valuable addition to the available methods.

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