Aerobic Oxybromination of Phenols Catalyzed by Sodium Nitrite under Mild Conditions

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Abstract: An efficient catalytic system for oxybromination of phenols under mild conditions has been developed, which utilizes sodium nitrite as the catalyst, dioxygen or air as the terminal oxidant, aqueous hydrobromic acid or molecular bromine as the bromine resource. From both the atom-economic and environmental points of view, the developed protocol is expected to provide a valuable synthetic method for practical applications in laboratory or industry.

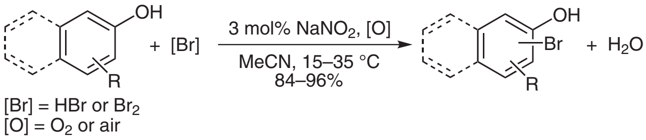
Key words: oxybromination, phenols, atom economy, oxygen, sodium nitrite

Bromination of aromatic compounds is an important and fundamental reaction in organic chemistry.[1] Aromatic bromides, in particular bromophenols, are widely used in the synthesis of pharmaceuticals, dyes, flame retardants, agrochemicals, as well as specialty chemicals.[2] Traditional methods for the synthesis of bromoarenes involve aromatic halogenations using various brominating agents such as bromine,[3] NBS,[4] hypobromite,[5] or organic perbromide,[6] which often suffer from an inherent disadvantage that the atom economy of Br is less than 50%.

Recently, to maximize the utilization of brominating reagents, an intriguing protocol, better known as oxybromination, has emerged as a versatile strategy to reach this goal. The oxybromination can in situ convert the byproduct (HBr) into molecular bromine by a variety of suitable oxidants, such as HNO_3,[7] TBHP,[8] Oxone®,[9] among others,[10] and all of these systems require stoichiometric oxidants, which lead to environmental problems due to the undesirable byproducts. So from the perspective of green chemistry, the best candidates for oxidants would be either hydrogen peroxide or oxygen, since water would be the only side product.[11]

Compared with hydrogen peroxide, aerobic oxybromination protocol has attracted much more attention because oxygen is the most abundant, cheapest, and stable oxidant. However, reports on this particular object are rare. Neumann et al.[12] described an efficient method for the aerobic oxybromination of phenol with $H_5PMo_{10}V_2O_{40}$ as the catalyst and HBr gas as the brominating agent. Raja et al.[13] have developed a heterogeneous copper phthalocyanine catalyst for the aerobic oxybromination of phenol. Under relatively mild conditions, the authors were able to achieve an 8.8% conversion of phenol. Gusevskaya et al.[14] have shown that $Cu(OAc)_2$ could be used as an effective catalyst for the selective oxybromination of phenol and electron-rich phenol compounds with bromide ions. More recently, Hirao et al.[15] have presented a new catalytic oxidative bromination system for phenols, which use a ligand-free vanadium catalyst under atmospheric oxygen or air.

Previously, we have developed a novel aerobic oxybromination method in which aromatics and ketones were converted to the desired monobrominated products under mild conditions in the presence of dioxygen, $NaNO_2$, and HBr.[16] However, oxybromination of phenols was less investigated, and we believe that the systematic study of the aerobic oxybromination of phenols with $NaNO_2$ is still valuable because of their industrially and synthetically importance. Herein, we wish to present our recent research on the oxybromination reaction of various phenols under air or dioxygen (Scheme 1). This simple and green method can provide a promising alternative for manufacturing brominated phenols from the economic and environmental points of view.



Scheme 1

Our initial investigations were focused on the solvents screening for the oxybromination of phenol in the presence of 3 mol% sodium nitrite, hydrobromic acid solution (42%), and dioxygen at room temperature. From the results listed in Table 1, most solvents such as methanol, ethanol, dichloromethane, chloroform, and carbon tetrachloride were unable to promote the desired oxybromative transformation (Table 1, entries 1–5). However, when the reaction was conducted in acetonitrile, almost quantitative conversion was obtained in 20 minutes (Table 1, entry 6). Other solvents like dichloroethane and 1,4-dioxane only gave a conversion of 12% and 7%, respectively (Table 1, entries 7 and 8). It was noteworthy to mention that these results were different from our previ-

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ous investigation on the oxybromination of anisole,[16] in which the solvents of $CHCl_3$ and 1,4-dioxane were also efficient for the conversion of anisoles to the desired products. Furthermore, considering the economic as well as practical issues, we also optimized the amounts of sodium nitrite in the oxybromination of phenol. The results indicated that 3 mol% sodium nitrite was good enough to lead to a complete transformation of the substrate in 20 minutes at room temperature (Table 1, entry 6). While reducing the amount of sodium nitrite to 1 mol%, the reaction did not complete even with a prolonged reaction time (Table 1, entry 10). Notably, the oxybromination reaction could also be carried out under air. When air was used instead of dioxygen, the reaction could also complete within 60 minutes under similar conditions (Table 1, entry 12). Moreover, the presence of $NaNO_2$ was proven to be crucial for this transformation (Table 1, entry 11).

Table 1 Optimization of Reaction Conditions for Oxybromination of Phenol Using Dioxygen as the Terminal Oxidant[a]

Entry	Solvent	$NaNO_2$ (mol%)	Time (min)	Conv. (%)[b]
1	MeOH	3	60	trace
2	EtOH	3	60	trace
3	CH_2Cl_2	3	60	trace
4	$CHCl_3$	3	60	trace
5	CCl_4	3	60	trace
6	MeCN	3	20	>99
7	DCE	3	60	12
8	1,4-dioxane	3	60	7
9	MeCN	5	15	>99
10	MeCN	1	120	94
11	MeCN	–	150	trace
12	MeCN	3	60	>99[c]

[a] Reaction conditions: phenol (5.00 mmol), HBr (5.25 mmol), solvent (10.0 mL), $NaNO_2$ (0.15 mmol, 3 mol%), 0.1 MPa oxygen pressure, r.t.

[b] Conversions were based on GC.

[c] Air was used instead of O_2.

Encouraged by the good preliminary results, we next investigated the impact of the concentration of hydrobromic acid solution on the sodium nitrite-catalyzed aerobic oxybromination of phenol. Three different concentrations of hydrobromic acid solution (42%, 30%, and 20%) were chosen as the bromine resource and their time-dependence curves for the oxybromination of phenol are shown in Figure 1. It was found that the reaction rate reduced dramatically when the concentration of hydrobromic acid was decreased from 42% to 20%. When 20% hydrobromic acid was used, the conversion of reaction was only 87% even when the reaction time was prolonged to 10 hours. In addition, a certain percentage of the starting material did not transform when the acid of 30% was used. Therefore, 42% was the ideal concentration of hydrobromic acid solution for the oxybromination of phenol. In additional, 42% HBr was readily available on the market, which might be of significant interest for the industrial community.

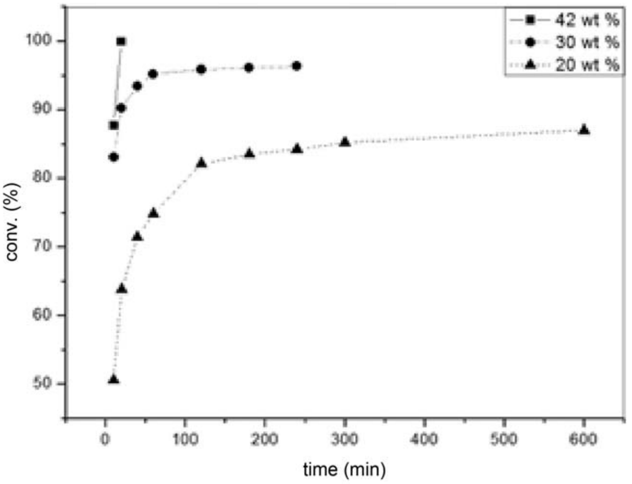
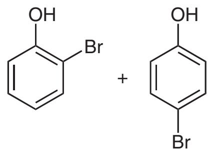
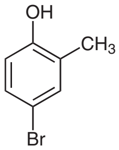
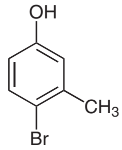
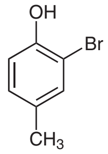
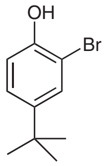
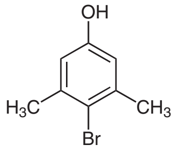
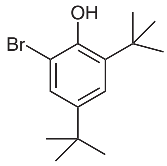
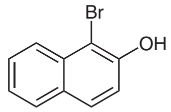
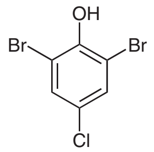
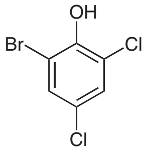


Figure 1 The effect of the concentration of hydrobromic acid on the oxybromination of phenol

With the optimized conditions in hand, we next explored the scope of this methodology to different substituted phenols, and the results are summarized in Table 2. It was gratifying to observe that electron-rich phenolic compounds were quantitatively converted into the corresponding brominated compounds in high isolated yields at room temperature within 20–60 minutes (Table 2, entries 1–8). In addition, when 4-chlorophenol and 2,4-dichlorophenol, which have an electron-withdrawing group on the arene ring, were subjected to the reaction conditions, the desired products were still obtained in excellent yields (Table 2, entries 9 and 10) at 35 °C in one hour. To our delight, dibromination of 4-chlorophenol to 2,6-dibromo-4-chlorophenol could also be achieved when the relative amount of hydrobromic acid was used (Table 2, entry 9). Notably, when air was used instead of dioxygen, the desired products were also obtained in competitive yields although the reaction time was relatively longer (Table 2, entries 1–10, method B).

Since molecular bromine was known to be cheaper and a readily available brominating source, we also investigated the possibility of directly using molecular bromine as the agent for the oxybromination of phenolic compounds. From the results summarized in Table 3, we were pleased to find that the reaction gave 88–96% yields, which were similar to those when using hydrobromic acid as brominating agent and dioxygen as the oxidant. Interestingly, when the reaction was conducted at a lower temperature, a higher regioselectivity of *para* position of the phenol could be achieved than that of hydrobromic acid (Table 3, entry 1 and Table 2, entry 1, respectively). In addition, the reaction was also smoothly performed when air was used (Table 3, entries 1–10, method B).

Table 2 $NaNO_2$-Catalyzed Aerobic Oxybromination of Various Phenols Using HBr as the Bromine Source[a]

Entry	Product	Temp (°C)	Method	Time (min)	Yield (%)[b]
1		25	A B	20 60	92 (15:85) 92 (15:85)
2		25	A B	40 120	89 87
3		25	A B	40 120	88 88
4		25	A B	40 120	88 87
5		25	A B	60 180	84 85
6		25	A B	60 180	90 89
7		25	A B	60 180	95 92
8		25	A B	60 180	96 96
9		35	A B	60 300	94 88[c]
10		35	A B	60 300	95 92

[a] Reaction conditions: phenol (5.00 mmol), HBr (42%, 5.25 mmol), $NaNO_2$ (0.15 mmol), MeCN (10.0 mL). Method A: 0.1 MPa oxygen pressure (oxygen balloon); Method B: 0.1 MPa air pressure (air balloon).

[b] Isolated yield.

[c] Phenol (1.00 mmol), HBr (42%, 2.1 mmol), $NaNO_2$ (0.03 mmol), MeCN (3.0 mL).

Table 3 $NaNO_2$-Catalyzed Aerobic Oxybromination of Various Phenols Using Br_2 as the Bromine Source[a]

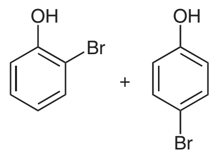
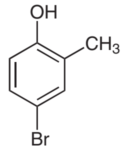
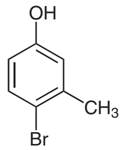
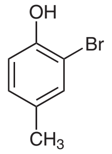
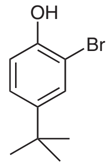
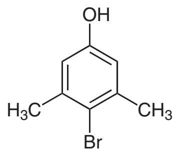
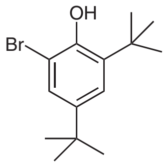
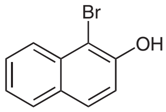
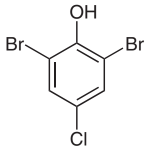
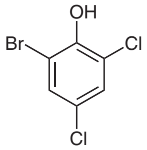
Entry	Product	Temp (°C)	Method	Time (min)	Yield (%)[b]
1		15	A B	20 60	92 (5:95) 92 (5:95)
2		15	A B	40 120	88 85
3		15	A B	40 120	92 90
4		15	A B	40 120	88 87
5		15	A B	40 120	92 92
6		15	A B	40 120	89 85

Table 3 $NaNO_2$-Catalyzed Aerobic Oxybromination of Various Phenols Using Br_2 as the Bromine Source[a] (continued)

Entry	Product	Temp (°C)	Method	Time (min)	Yield (%)[b]
7		15	A	40	92
			B	120	92
8		15	A	60	96
			B	180	95
9		35	A	60	94
			B	300	90[c]
10		35	A	60	94
			B	300	91

[a] Reaction conditions: phenol (5.00 mmol), Br_2 (2.63 mmol), $NaNO_2$ (0.15 mmol), MeCN (10.0 mL). Method A: 0.1 MPa oxygen pressure (oxygen balloon); Method B: 0.1 MPa air pressure (air balloon).

[b] Isolated yield.

[c] Phenol (1.00 mmol), Br_2 (1.05 mmol), $NaNO_2$ (0.03 mmol), MeCN (3.0 mL).

In summary, we have developed an efficient method for the aerobic oxybromination of a variety of phenols using sodium nitrite as the catalyst and dioxygen or air as terminal oxidant under mild conditions. Both aqueous solution of hydrobromic acid and molecular bromine can be used as the brominating reagents.[17] The excellent performance of the newly developed oxybromination protocol was expected to provide a valuable synthetic method for practical applications in laboratory or industry.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(17) **Representative Procedure**
In a 250 mL Schlenk flask equipped with magnetic stirrer, filled with dioxygen beforehand, was placed phenol (0.4706 g, 5.00 mmol) dissolved in MeCN (10.0 mL) under O_2. Then a 42% aq solution of HBr (1.0125 g, 5.25 mmol) was added to the solution. Next, the $NaNO_2$ (0.0103 g, 0.15 mmol) was added in one portion, and the system was immediately sealed. The reaction mixture was stirred at 25 °C. After the reaction, the solvent was removed under vacuum, and the

residue was washed with sat. $NaHCO_3$ solution and extracted with Et_2O. The organic extract was dried over with anhyd Na_2SO_4. After removing the solvent under vacuum, the residue was purified by column chromatography to afford the desired products, 2- and 4-bromophenol. The yield was 0.7962 g (92%).

4-Bromophenol

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.70–6.72 (m, 2 H, ArH), 7.31–7.33 (m, 2 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 113.0, 117.1, 132.5, 154.2 ppm.

2-Bromophenol

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.51 (s, 1 H, OH), 6.78–6.83 (m, 1 H, ArH), 7.00–7.04 (m, 1 H, ArH), 7.19–7.25 (m, 1 H, ArH), 7.44–7.47 (m, 1 H, ArH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 110.1, 116.1, 121.7, 129.0, 132.0, 152.0 ppm.