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Sodium Nitrite-Catalyzed Oxybromination of Aromatic Compounds and Aryl Ketones with a Combination of Hydrobromic Acid and Molecular Oxygen under Mild Conditions

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Abstract: A novel and efficient catalytic system for the oxybromination of aromatic compounds and aryl ketones utilizing a combination of aqueous hydrobromic acid and molecular oxygen in the presence of sodium nitrite under mild conditions has been developed. The newly developed catalytic system utilizes cheap and readily available reactants, exhibits high bromine atom economy and releases only innocuous water as the by-product.

Keywords: arenes; aryl ketones; atom economy; oxybromination; oxygen; sodium nitrite

The central importance of bromination reactions is a widely accepted fact in synthetic organic chemistry.[1] Bromocarbon products are useful chemical intermediates, serving as branch points in the synthesis of numerous functionalized compounds such as antitumor, antibacterial, and antioxidant agents[2] as well as specialty chemicals, agrochemicals and pharmaceuticals. For over 100 years, bromination processes using molecular bromine as the bromination reagent have been a class of the most significant and widely used synthetic methods for bromocarbon products because molecular bromine is known to be a cheap and readily available bromination reagent (Scheme 1).

However, these classical bromination methods suffer from the inherent disadvantage that the efficiency of bromine use allows for only 50% atom economy with one equivalent of HBr being produced. It is certain that such bromination processes do not advance the goal of non-toxic and waste-free chemistry. In large-scale operations this is not only an economic problem but also an environmental one. Recently, an intriguing solution, namely the oxidation and recycling of the bromination by-product, HBr, using an *in situ* oxidizing agent, is emerging as a versatile strategy to reach this goal. Typically, oxybrominations of aromatic compounds are carried out with a combination of a bromination reagent and a variety of oxidizing reagents.[3–18] Although these systems have nicely embodied the bromine atom economy, many such systems require stoichiometric oxidizing agents. The use of stoichiometric oxidizing agents to perform the transformation is not an ideal process as the concurrent formation of undesirable wastes is inherently unavoidable.[5,7–9] H_2O_2-based oxybromination systems,[10–17] however, seem to be green and many of them are synthetically useful. Even so, several drawbacks remain including the relatively higher cost of hydrogen peroxide and its undesirable decomposition during a reaction at elevated temperatures and/or in the presence of metal catalysts. In addition, most reports involve the oxybromination of aromatic compounds and only rare examples involve the oxybromination of ketones.[6a,18,19]

$$RH + Br_2 \longrightarrow RBr + HBr$$

Scheme 1.

On the other hand, molecular oxygen is the most abundant, and atom economical oxidant known today. Thus, it is surprising that oxybromination methods using molecular oxygen for the oxidation and recycling of the concurrent product, HBr, have until now been comparatively less common and underdeveloped. Only two examples involving aerobic oxybrominations of aromatic compounds have been reported. Neumann et al. have described an efficient aerobic oxybromination method for active aromatic compounds with $H_5PMo_{10}V_2O_{40}$ as the catalyst and HBr gas as the brominating reagent.[19] More recently, Raja et al. have developed a heterogeneous copper phthalocyanine catalyst for the aerobic oxybromination of aromatic compounds. Under relatively mild conditions the authors were able to achieve a

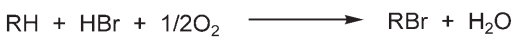
6.7% conversion for anisole and a 16.8% conversion for toluene.[20]

Development of an innovative catalytic system that uses cheap and easily available oxidants/catalysts for the mild and efficient oxybromination of a wide range of substrates, e.g., ketones and aromatics is still desired. Herein we report our preliminary results toward achieving these goals (Scheme 2).

Recently we reported a highly efficient transition metal-free catalytic system for aerobic alcohol oxidation.[21] Keys to the newly developed oxidation process are the discovery of molecular oxygen being able to oxidize HBr to Br_2 *in situ* with $NaNO_2$ as the catalyst and its suitability to an aqueous environment. Based on this observation, we reasoned that use of $NaNO_2$ as the catalyst as well as HBr and molecular oxygen as the reactants would likely lead to a green and atom-economic catalytic system for the efficient oxybromination of a wide range of target substrates.

In our initial experiments, we chose anisole as a test substrate and allowed it to react in CH_2Cl_2 with 3 mol % of sodium nitrite in the presence of hydrobromic acid solution (42%) and oxygen at 25 °C. A 30% conversion is achieved with 1.13 equivs. of hydrobromic acid solution within 1 h (entry 4, Table 1). The preliminary results suggest that our initial assumption is feasible, and it prompted us to further systematically optimize the reaction conditions.

During the screening of a variety of reaction conditions including the solvent, reaction temperature, and the amounts of catalyst, we found that a wide range of solvents such as CH_3CN, $CHCl_3$ and 1,4-dioxane could be applied for efficient conversions of anisole. In particular, when using CH_3CN as the solvent, the reaction was complete within 1 h and gives *p*-brominated product with >99% yield (entry 6, Table 1). Subsequently, different temperatures and amounts of $NaNO_2$ were tested for the oxybromination of anisole and the results are shown in Table 1. As the reaction temperature increases, the rate of anisole conversion increases correspondingly. When the temperature is decreased to 5 °C, the reaction does not go to completion even when the reaction time is prolonged to 3 h (conversion 94%, entry 11). Thus we chose 25 °C as the reaction temperature and acetonitrile as the solvent to test the influence of the amount of $NaNO_2$ on the oxybromination reaction. When the amount is decreased from 10 mol % to 3 mol % (entries 12, 13 and 6), the reaction efficiency is not significantly influenced. On further reducing the amount of $NaNO_2$ to 1.5 mol %, a significant decrease of conversion is observed so that only 67% conversion is obtained even with a reaction time of 180 minutes (entry 14).



Scheme 2.

To evaluate the scope of this catalytic system, the oxybromination of a variety of aromatic compounds was further examined with $NaNO_2$ as the catalyst and acetonitrile as the solvent. The results are summarized in Table 2. Electron-rich aromatic compounds are quantitatively converted into the corresponding brominated compounds in high isolated yield at 25 °C within 1 h (entries 1–5). It may be observed that normally non-reactive aromatic compounds, such as toluene and naphthalene, react in relatively high yields (entries 8 and 9). Benzene is somewhat reactive (entry 10), while deactivated chlorobenzene does not react at 65 °C for 24 h (entry 11).

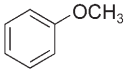
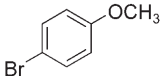
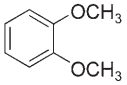
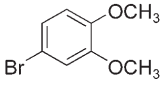
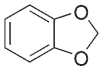
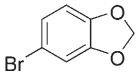
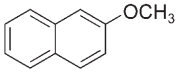
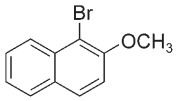
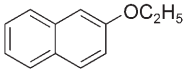
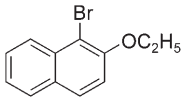
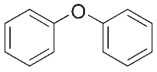
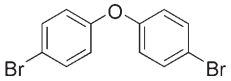
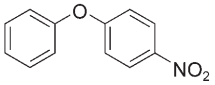
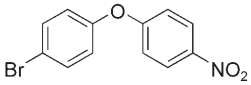
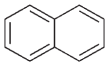
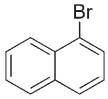
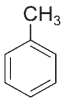
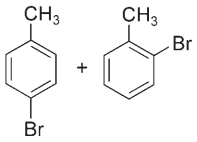
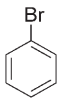
It is noteworthy that regioselective bromination, which is generally problematic in classical bromination processes, can be achieved with this method. When using anisole as a substrate the regioselectivity is more than 99% (entry 1). Moreover, dibromination of diphenyl ether, a binuclear aromatic compound, has led

Table 1. The $NaNO_2$-catalyzed oxybromination of anisole with HBr and molecular oxygen under different reaction conditions.

Entry	Solvent	Temp. [°C]	$NaNO_2$ [mol %]	Time [min]	Conversion [%][a]
1	CH_3OH	25	3	60	10
2	CCl_4	25	3	60	16
3	$CHCl_3$	25	3	60	80
4	CH_2Cl_2	25	3	60	30
5	$ClCH_2CH_2Cl$	25	3	60	45
6	CH_3CN	25	3	60	>99
7	CH_3CH_2OH	25	3	60	22
8	1,4-dioxane	25	3	60	82
9	CH_3CN	65	3	30	>99
10	CH_3CN	45	3	40	>99
11	CH_3CN	5	3	180	94
12	CH_3CN	25	10	30	>99
13	CH_3CN	25	5	40	>99
14	CH_3CN	25	1.5	180	67

[a] Determined by GC.

Table 2. The $NaNO_2$-catalyzed oxybromination of aromatic compounds with a combination of HBr and O_2.[a]

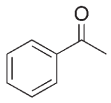
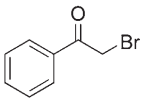
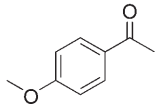
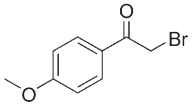
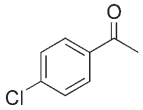
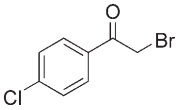
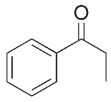
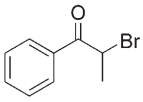
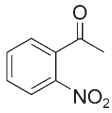
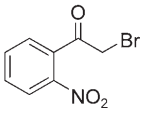
Entry	Substrate	Product[b]	Time [h]	Yield [%][c]
1			1	91
2			1	92
3			1	91
4			1	96
5			1	95
6			2	90[d, e]
7			6	90[e]
8			4	87[e, f]
9			24	76[f, g] (67 : 33)
10			24	19[f, g]
11		–	24	–

[a] Aerobic oxybromination conditions are as follows: aromatic compound (10 mmol), HBr (42%, 11.3 mmol), $NaNO_2$ (0.3 mmol), at 25 °C.
[b] Product is characterized by spectroscopic data or by comparison with authentic sample.
[c] Yield refers to isolated pure product after silica gel column chromatography.
[d] HBr (21.3 mmol).
[e] $NaNO_2$ (0.5 mmol, 5 mol %), 65 °C.
[f] Yield is based on the gas chromatography (GC) with area normalization.
[g] $NaNO_2$ (1.0 mmol, 10 mol %), 65 °C.

selectively to 4,4′-dibromodiphenyl ether on controlling the amount of hydrobromic acid used (entry 6). This regioselectivity may be of great interest in synthetic organic chemistry when two active positions may be brominated in the same molecule.

When acetophenone, a deactivated aromatic compound, was the reaction substrate, unexpectedly we found that the oxybromination reaction occurred at the side-chain carbon (entry 1, Table 3), whereas the aromatic ring largely remained unreacted. This result suggested that the current catalyst system would likely be suitable for the aerobic oxybromination of aromatic ketones. A variety of aromatic ketones were later reacted with hydrobromic acid at the presence of $NaNO_2$ and molecular oxygen and with ethanol as the solvent (Table 3). We were pleased to find that all aromatic ketones

Table 3. The $NaNO_2$-catalyzed oxybromination of ketones with a combination of HBr and O_2.[a]

Entry	Substrate	Product[b]	Time [h]	Yield [%][c]
1			5	90
2			10	87
3			10	92
4			10	82
5			24	68

[a] Aerobic oxybromination conditions are as follows: ketone (10 mmol), HBr (42%, 13 mmol), $NaNO_2$ (2 mmol), at 60 °C.
[b] Product is characterized by spectroscopic data or by comparison with authentic sample.
[c] Yield refers to isolated pure product after silica gel column chromatography.

including activated and deactivated aromatic compounds were converted into the corresponding brominated products in high isolated yields.

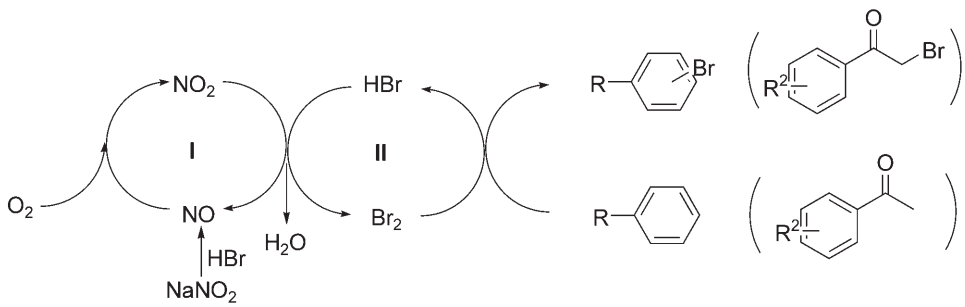
A possible mechanism of this new aerobic oxybromination of aromatic compounds and aryl ketones can be proposed as the sequential bicycle shown in Scheme 3. The newly developed oxybromination system is regarded as a sequential cascade of double-cycle redox reactions. Cycle I and cycle II have been described in our previous study.[21a]

In summary, we have shown that sodium nitrite can catalyze aerobic oxybromination of a variety of aromatic substrates and ketones. Moreover, this novel aerobic oxybromination system also exhibits fairly efficient regioselectivity for some substrates. The reaction conditions are simple and mild, and the catalyst is very cheap. The use of molecular oxygen as the terminal oxidant for the oxybromination of aromatic compounds and aryl ketones renders the reaction very attractive from both economical and environmental viewpoints.

Experimental Section

Typical Procedures

The oxybromination of anisole is described as a representative example of oxybromination of aromatic compounds: In a 250-mL Schlenk flask equipped with magnetic stirrer, filled with oxygen beforehand, was placed anisole (10 mmol) dissolved in acetonitrile (10 mL) under oxygen. Then a 42% aqueous solution of hydrobromic acid (11.3 mmol) was added to the solution. Next, the sodium nitrite (0.3 mmol) was added in one portion and system was immediately closed. The reaction mixture was stirred at 25 °C. Upon completion, as detected by GC, the



Scheme 3. Plausible catalytic mechanism for the oxybromination by oxygen.

solvent was removed under vacuum and the residue extracted with 1,2-dichloroethane. The organic extract was first washed with 5% sodium bicarbonate solution, then with water and finally dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, petroleum ether:ethyl acetate = 20:1) to afford the product, 4-bromoanisole; yield: 1.707 g (91%).

The oxybromination of acetophenone is described as a representative example of oxybromination of aryl ketones: In a 250-mL Schlenk flask equipped with magnetic stirrer, filled with oxygen beforehand, was placed acetophenone (10 mmol) dissolved in ethanol (10 mL) under oxygen. Then a 42% water solution of hydrobromic acid (13.0 mmol) was added to the solution. Next, the sodium nitrite (2.0 mmol) was added in one portion and system was immediately closed. The reaction mixture was stirred at 60 °C. Upon completion, as detected by GC, the solvent was removed under vacuum and the residue extracted with 1,2-dichloroethane. The organic extract was first washed with 5% sodium bicarbonate solution, then with water and finally dried over anhydrous sodium sulfate. The solvent was removed under vacuum and the residue was purified by column chromatography (silica gel, petroleum ether : ethyl acetate = 9:1) to afford the product, 2-bromo-1-phenylethanone; yield: 1.790 g (90%).

Acknowledgements

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