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Aerobic oxidative iodination of organic molecules activated by sodium nitrite

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Abstract

Aerobic oxidative iodination activated by sodium nitrite occurs effectively and selectively with 100% iodine atom economy with air as the oxidant. Silica-supported sulfuric acid was used for the activation of the catalyst and iodination. Thus, $I_2/NaNO_2$/air/silica-supported H_2SO_4 in acetonitrile iodinated aromatics, ketones and aldehydes effectively at ambient temperature.

Keywords: Iodination; Halogenation; Haloperoxidation; Hydrogen peroxide; Green chemistry; Aerobic halogenation; Organo-halogen compounds

Iodinated organic molecules are important compounds in synthetic chemistry, and are used widely in the pharmaceutical and chemical industries creating high demand for efficient and economical methods for their production.[1] Due to the negative impacts that chemicals can have on the environment, for example, chlorinated hydrocarbons and VOCs, scientists are trying to adapt existing chemical processes into more environmentally benign methods.[2] In the field of halogenation, this necessity reflects the revival of the oxidative halogenation reaction first reported in 1924 by Leulier and Speyer.[3] This is because of the atom economy of the halogen atoms during oxidative halogenation, which is 100% due to the regeneration of the residual halogenide ion by oxidation into a reactive molecular halogen. The most environmentally benign oxidants are hydrogen peroxide and oxygen.[4] While H_2O_2 is often used in oxidative halogenations,[5] especially in metal-catalyzed examples,[6] oxygen is seldom used and only arenes were iodinated in an oxygen atmosphere by metal-catalyzed iodination with polyoxometalate and bismuth salts as catalysts or lower nitrogen oxide species in $AcOH/CF_3COOH/Ac_2O$.[7] Recently, Liang and Hu's group reported the transition-metal free aerobic oxidation of alcohols and oxidative bromination of arenes and aryl ketones with $NaNO_2$/HBr/TEMPO under an oxygen atmosphere.[8] It might be possible to use $NaNO_2$ for iodination reactions, however, HI is unstable and I_2 is the preferred iodinating reagent, while air would be a safer alternative to hazardous oxygen gas. The presence of acid, however, is obligatory because it converts $NaNO_2$ into nitrogen oxides, which are the true catalysts in the oxidation reactions. The acid is also an excellent activator of iodine for the iodination of less reactive substrates.

As part of our continued interest in developing 'greener' methods for halogenation, we studied the air/$I_2/NaNO_2$/acid system for the aerobic oxidative iodination of organic molecules. First, we performed the iodination of anisole **1** (as a model substrate) using an air/$I_2/NaNO_2$ system in the presence of 0.1 M equiv of H_2SO_4 and obtained 4-iodoanisole **2**, quantitatively (Scheme 1). We also found that a Lewis acid (ethereal solution of BF_3) was an effective activator of the aerobic $NaNO_2$-catalyzed iodination. Also, because less reactive substrates require a higher amount of acid, we investigated solid acids that have the potential to be recycled. Using strongly acidic ion-exchange resins

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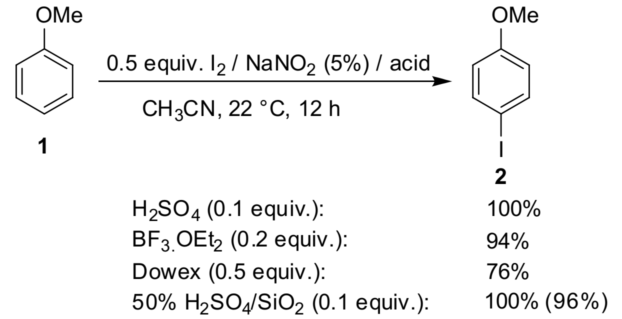


Scheme 1.

(sulfonated polystyrene/DVB matrix, Dowex 50W) the reaction of **1** took place with only 76% conversion with 0.5 equiv of acid. Next, 50% sulfuric acid supported on silica was prepared and used as reported in the literature.[9] Iodination of **1** was effective with silica-supported acid (0.1 M equiv) and **2** was formed selectively and quantitatively. Different solvents (EtOAc, *tert*-butylmethyl ether, water and EtOH) were also tested; however, acetonitrile was by far the best.

Further, we investigated the effect of silica-supported acid on the aerobic $NaNO_2$-catalyzed oxyiodination (Fig. 1). Although a blank experiment without the presence of acid yielded only trace amounts of 4-iodoanisole, conversion, gradually increased as the quantity of acid was increased reaching a maximum at 7.5 mol % of sulfuric acid in the reaction mixture.

Finally, we investigated the aerobic iodination of various aromatic and carbonyl compounds using the air/I_2/$NaNO_2$/acid system (Table 1). In a typical preparative experiment we dissolved 1 mmol of anisole **1** in 2 mL of acetonitrile, added 0.5 mmol of I_2, 0.03 mmol of $NaNO_2$ and 21 mg of silica-supported 50% H_2SO_4 (0.075 mmol of H_2SO_4, 3.62 mmol H_2SO_4/g), covered the flask with a balloon filled with air and stirred the contents at 22 °C for 6 h. At the end of the reaction, the mixture was diluted with hexane–EtOAc (9:1) and the solid acid filtered off. The organic phase was firstly discoloured by adding a few drops of 37% $NaHSO_3$, neutralized by the addition of $NaHCO_3$, dried over Na_2SO_4 and the inorganic salts filtered off. After the removal of the solvents we obtained pure 4-iodoanisole **2** as determined by NMR spectroscopy, while further purification on a short silica column gave **2** in 96% yield (Scheme 1). Various aromatic derivatives were selectively iodinated including *p*-*tert*-butylphenol **5**, which usually gives a mixture of mono- and diiodo products, while the reactivity of the system was manipulated by varying the amount of acid. The method was also applicable for the iodination of ketones. Various ketones (dialkyl **15**, arylalkyl **17**, β-ketoester **19** and cyclic ketone **21**) were iodinated by tuning the reactivity by adjusting the amount of acid; no formation of diiodo products was observed (Scheme 2). Aldehydes **23** and **25** were also iodinated using this method, albeit α-iodo aldehydes **24** and **26** are less stable and begin to decompose during isolation.

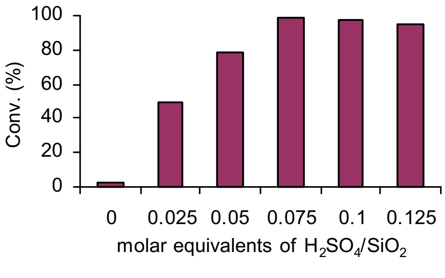
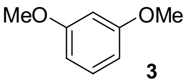
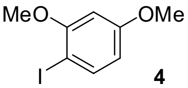
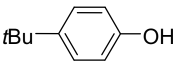
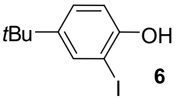
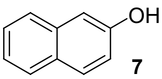
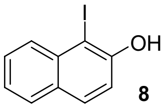
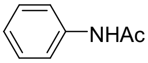
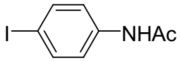
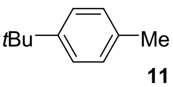
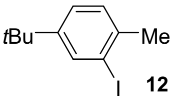
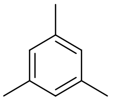
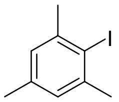


Fig. 1. The effect of silica-supported H_2SO_4 on the conversion of anisole **1** (0.5 equiv I_2/air/0.03% $NaNO_2$, MeCN (0.5 M), 3 h, 22 °C).

Table 1
Aerobic iodination of arenes with iodine activated by $NaNO_2$ and silica-supported acid

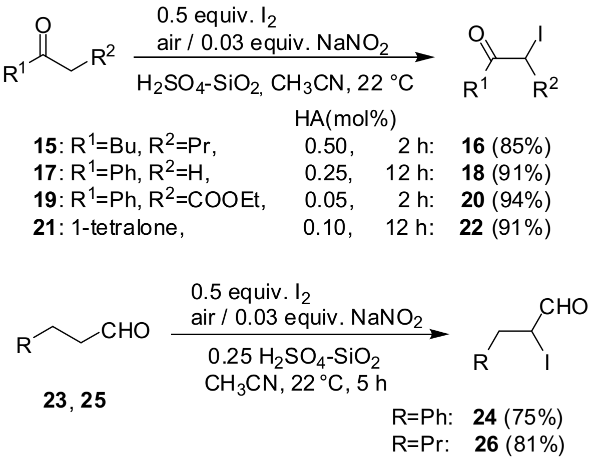
Substrate	Acid (mmol)	Time (h)	Product	Yield[a] (%)
 **3**	0.05	1[b]	 **4**	98
 **5**	0.25	12	 **6**	85
 **7**	0.25	20	 **8**	87
 **9**	1	24	 **10**	97
 **11**	1	24	 **12**	95
 **13**	0.25	5	 **14**	94

[a] Reaction conditions: 1 mmol of substrate, 127 mg I_2 (0.5 mmol), 2 mg $NaNO_2$ (0.03 mmol), 50% H_2SO_4/SiO_2 (3.62 mmol H_2SO_4/g), 2 mL MeCN.

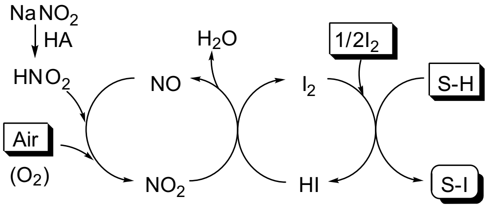
[b] 0 °C.

Importantly, the aerobic iodination procedure produced no organic waste and as the iodination of anisole **1** required only 10 mol % of H_2SO_4 for quantitative iodination, we performed an experiment on a 1 g scale (**1**/0.5 equiv. I_2/0.03 equiv $NaNO_2$/0.1 equiv $H_2SO_{4conc.}$/MeCN, 0.5 M). After stirring for 3 h at 22 °C, the reaction mixture was poured over crushed ice and the resulting white precipitate filtered off. From this we obtained a 93% yield of pure 4-iodoanisole.

In conclusion, $NaNO_2$-activated aerobic oxidative iodination presents a rare system, where air is used as the oxidant for the regeneration of I_2 from eluted HI and thus



Scheme 2.



Scheme 3.

enables 100% iodine atom economy (Scheme 3). Acidic conditions are a requisite for both $NaNO_2$-catalysis and iodination reactions where the amount of acid employed is used to tune the reactivity of the system. The method offers an effective system for metal-free iodination of aromatics, ketones and aldehydes. Furthermore, there is no organic waste from the reaction and the isolation procedure is straightforward requiring only the separation of the organic product from the inorganic salts.

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