Transition-Metal-Free, Chemoselective Aerobic Oxidations of Sulfides and Alcohols with Potassium Nitrate and Pyridinium Tribromide or Bromine

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Abstract: An efficient oxidation of sulfides with air catalyzed by the combination of potassium nitrate with pyridinium tribromide under transition-metal-free conditions was reported. By replacing pyridinium tribromide with bromine, the reaction system was also useful in the oxidation of alcohols. All reactions afforded the corresponding products in good to excellent yields with high chemoselectivities.

Key words: aerobic oxidation, sulfide, alcohol, chemoselectivity, transition-metal-free

The selective oxidation of sulfides or alcohols is one of the most important and fundamental transformations in organic synthesis.[1] As one aspect of the ideology of green chemistry, catalyzed oxidations with ‘clean’ oxidants are extremely valuable.[2] Many kinds of catalytic systems have been reported on the selective oxidations of sulfides[3] and alcohols[4] with hydrogen peroxide. However, the low concentration (ca. 30%) of hydrogen peroxide limited its utilization in some industrial processes. Recently, some transition-metal- and acid-catalyzed selective oxidation reactions with air or oxygen as the oxidant have been developed.[5] Among these research, the binary system $FeBr_3$/$Fe(NO_3)_3$ is a very efficient catalyst for the selective air oxidation of sulfides[5a] and alcohols[5k] and the corresponding desired products could be obtained in high yields.[5l] However, transition metals and acids are somehow toxic, unstable, and expensive. For this reason, a variety of studies on transition-metal-free catalyst system for aerobic sulfides and alcohols oxidations have been reported which employed molecular oxygen as terminal oxidant for both economical and environmental benefits.[6] Herein, we report an efficient oxidation of sulfides and alcohols with air at room temperature with a transition-metal-free binary catalyst system (potassium nitrate/pyridinium tribromide or potassium nitrate/bromine).

Initially, methyl phenyl sulfide was treated with a catalytic amount of potassium nitrate (10 mol%) and bromine (15 mol%) in acetonitrile in an air open system at room temperature. After three hours, a moderate yield of methyl phenyl sulfoxide[13] was obtained, and the ratio of sulfoxide and sulfone was 94:6 (Table 1, entry 1). Some unexpected bromination products were isolated because of the high reactivity of bromine. It is well known that pyridinium tribromide is an alternative reagent to bromine in many reactions. The reactivity of pyridinium tribromide is lower than bromine due to the ‘slow release’ of bromine.[7] When the combination of KNO_3–Br_2 was replaced by KNO_3–$PyHBr_3$, methyl phenyl sulfide was completely converted to the corresponding sulfoxide and sulfone with a high chemoselectivity (99:1) within seven hours (Table 1, entry 2). It was found that both KNO_3 and $PyHBr_3$ (Br_2) were necessary for the oxidation. Control experiments indicated that, when each of them was employed in catalytic amount, no oxidation reaction occurred under the same conditions (Table 1, entries 3–5). While the oxidation reaction was carried out in argon, sulfoxide was only obtained in 10% yield (Table 1, entry 6). It was shown that the reaction could proceed smoothly with good conversions and high chemoselectivities in various solvents, except water and methanol (Table 1, entries 7–12). The reaction in a mixed solvent of water and acetonitrile failed to give a good conversion (Table 1, entry 12).

With the good results in hand, various sulfides were tested under the optimal conditions. As shown in Table 2, most of the reactions proceeded smoothly and afforded the corresponding sulfoxides in good to excellent yields and high chemoselectivities. A moderate electronic substrate effect was observed. While sulfides with an electron-donating group at the aromatic ring were good substrates, the reactions of those with an electron-withdrawing group afforded the corresponding products in moderate yields (Table 2, entries 2–7). It was supposed that pyridinium hydrobromide would decrease the reactivity of $PyHBr_3$ in the oxidation since there is a rapid equilibrium between pyridinium hydrobromide and bromine.[8] With the replacement of the binary catalyst KNO_3–$PyHBr_3$ by KNO_3–Br_2, the yields of those products with the electron-withdrawing groups increased to 90% (Table 2, entries 11–14). It was supposed that the electron-withdrawing groups deactivated the aryl ring and prevented bromine to react with organosulfur compounds. When the alkyl group in sulfide was altered, the reaction results did not change significantly in yields and chemoselectivities (Table 2, entries 8–10). While chlorine atom existing in alkyl group resulted in the low yield with KNO_3–$PyHBr_3$ as the catalyst, the reaction with KNO_3–Br_2 gave rise to a good yield and was obtained albeit in a lower chemoselectivity (Table 2, entry 15).

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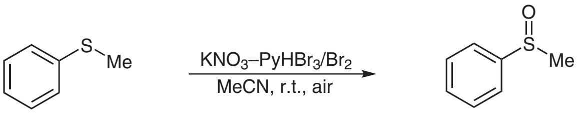
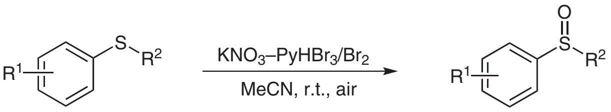
Table 1 Air Oxidation of Methyl Phenyl Sulfide Catalyzed by KNO_3–$PyHBr_3$/Br_2[a]



Entry	Catalyst	Solvent	Time (h)	Conditions	Conversion (%)[b]	SO/SO_2[b]
1	KNO_3–Br_2	MeCN	3	air	65	94:6
2	KNO_3–$PyHBr_3$	MeCN	7	air	98	99:1
3	Br_2	MeCN	24	air	5	–
4	$PyHBr_3$	MeCN	24	air	5	–
5	KNO_3	MeCN	24	air	n.r.[c]	–
6	KNO_3–$PyHBr_3$	MeCN	7	Ar[d]	10	–
7	KNO_3–$PyHBr_3$	MeOH	24	air	8	–
8	KNO_3–$PyHBr_3$	H_2O	24	air	9	–
9	KNO_3–$PyHBr_3$	THF	7	air	85	98:2
10	KNO_3–$PyHBr_3$	1,4-dioxane	7	air	90	96:4
11	KNO_3–$PyHBr_3$	EtOAc	7	air	73	100:0
12	KNO_3–$PyHBr_3$	MeCN–H_2O[e]	24	air	10	–

[a] Reactions were carried out in an air open system at r.t., with a molar ratio of substrates/KNO_3/$PyHBr_3$/Br_2 = 1:0.1:0.15 mmol in MeCN (2 mL).
[b] Determined by GC.
[c] n.r.: reaction did not occur.
[d] Under an Ar atmosphere (1 atm).
[e] Ratio of 9:1 for MeCN–H_2O.

Table 2 Air Oxidation of Sulfides to Sulfoxides Catalyzed by KNO_3–$PyHBr_3$/Br_2[a]



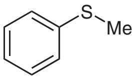
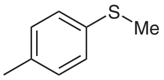
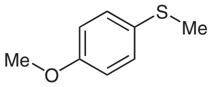
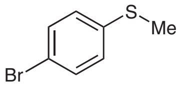
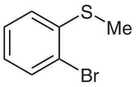
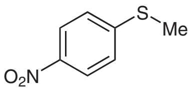
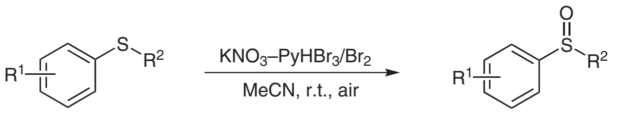
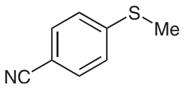
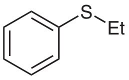
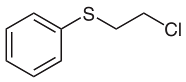
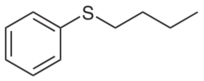
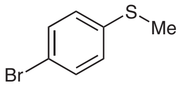
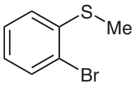
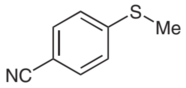
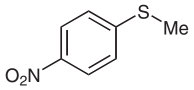
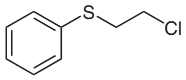
Entry	Substrate	Time (h)	Catalyst	Yield (%)[b]	SO/SO_2[c]
1		7	KNO_3–$PyHBr_3$	90	99:1
2		3.5	KNO_3–$PyHBr_3$	92	98:2
3		4	KNO_3–$PyHBr_3$	95	100:0
4		24	KNO_3–$PyHBr_3$	90	99:1
5		48	KNO_3–$PyHBr_3$	42	100:0
6		48	KNO_3–$PyHBr_3$	60	98:2

Table 2 Air Oxidation of Sulfides to Sulfoxides Catalyzed by KNO_3–$PyHBr_3$/Br_2[a] (continued)



Entry	Substrate	Time (h)	Catalyst	Yield (%)[b]	SO/SO_2[c]
7		24	KNO_3–$PyHBr_3$	76	99:1
8		6	KNO_3–$PyHBr_3$	92	100:0
9		48	KNO_3–$PyHBr_3$	32	98:2
10		8	KNO_3–$PyHBr_3$	85	93:7
11		3	KNO_3–Br_2	91	98:2
12		7	KNO_3–Br_2	93	99:1
13		4	KNO_3–Br_2	92	96:4
14		10	KNO_3–Br_2	95	96:4
15		7	KNO_3–Br_2	83	94:6

[a] Reactions were carried out in an open system at r.t., with a molar ratio of substrate/KNO_3/$PyHBr_3$/Br_2 = 1:0.1:0.15 mmol in MeCN (2 mL).

[b] Isolated after chromatography.

[c] Determined by GC.

A mechanism for the selective oxidation of sulfides to sulfoxides with air catalyzed by KNO_3–$PyHBr_3$/Br_2 was investigated. Some literature reports have pointed to Br species as being the real catalyst for the aerobic oxidation of sulfides in the presence of water.[5k,9] However, bromine could not catalyze the sulfide oxidation in air alone (Table 1, entry 3) and water prevented this oxidation reaction in this binary catalytic system (Table 1, entry 8). In comparison to the catalytic mechanism by Br species catalysis, it was believed that both KNO_3 and Br_2 were very important for the oxidation reaction of sulfide with air at room temperature.

Kochi reported that NO_2 was a good catalyst in sulfide oxidation reaction with oxygen at low temperature.[10] When 10 mol% NO_2 was used as catalyst in the oxidation of 4-(methylthio)benzonitrile with air in acetonitrile, 92% yield of product and 99:1 of chemoselectivity were observed, which was similar with the one used KNO_3–Br_2 as the catalyst (Table 2, entry 13). This result was suggested that the real catalytic species was NO_2 in the binary catalytic system.

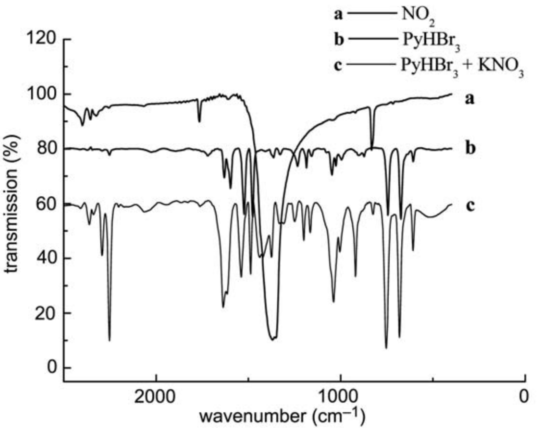


Figure 1 IR spectra of NO_2, $PyHBr_3$, and KNO_3–$PyHBr_3$ in MeCN

In order to confirm the mechanism of the sulfide oxidation catalyzed by in situ NO_2, IR spectrum was used to detect NO_2 in the reaction system. It was found that NO_2 did exist in the system when pyridinium tribromide (bromine) and potassium nitrate were mixed in acetonitrile (Figure 1 and Figure 2).[11] Meanwhile, orange-brown gas was released from the mixture of pyridinium tribromide (bromine) and potassium nitrate when the mixture was heated. NO_2 was identified from the gas because when the gas dissolved in water, NO_3^- could be detected by normal analytical methods. However, if the solvent acetonitrile was changed to water or a mixture of acetonitrile and water, NO_2 would react with water immediately to form nitric acid and lost the catalytic activity.[12]

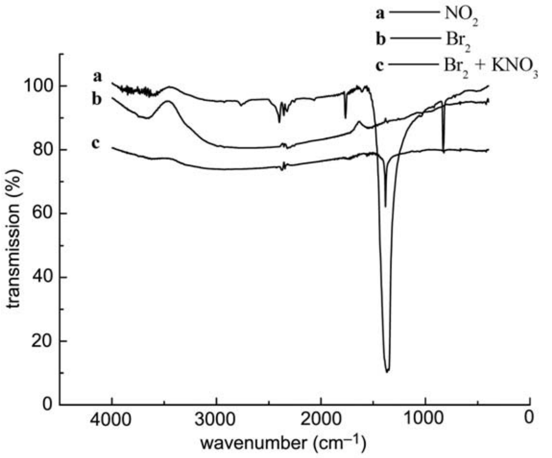
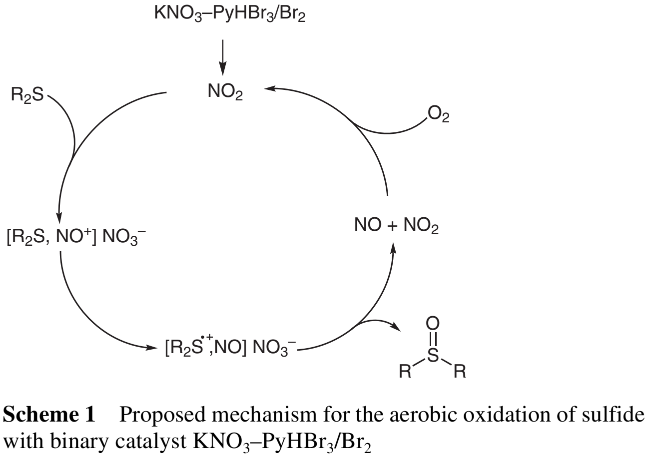


Figure 2 IR spectra of NO_2, Br_2, and KNO_3–Br_2 in MeCN

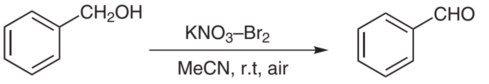
On the basis of the literature mentioned above[10] and our experimental results, we suggest the mechanism presented in Scheme 1. The mixture of KNO_3 and Br_2 was easily generated NO_2 at room temperature in acetonitrile. The in situ NO_2 reacted with sulfide immediately to form the corresponding sulfoxide and NO. Nitrogen dioxide was regenerated by transfer from NO in air readily to complete the catalytic cycle.



Scheme 1 Proposed mechanism for the aerobic oxidation of sulfide with binary catalyst KNO_3–$PyHBr_3$/Br_2

To further explore the oxidative reaction with this binary catalyst of KNO_3–$PyHBr_3$ (KNO_3–Br_2), the selective aerobic oxidation of alcohols was also studied. It was found that the combination of KNO_3–$PyHBr_3$ did not work well (17% yield), but KNO_3–Br_2 was very effective for the selective oxidation of benzylic alcohol under similar conditions. The results of solvent screening are shown in Table 3. Acetonitrile was still the best solvent. When the temperature was increased to 50 °C, benzaldehyde was formed in 94% yield.

Table 3 Solvent Screening for the Oxidation of Benzaldehyde with KNO_3–Br_2 in Air[a]



Entry	Solvent	Temp (°C)	Conversion (%)[b]
1	MeCN	25	86
2	MeOH	25	20
3	H_2O	25	23
4	THF	25	17
5	1,4-dioxane	25	27
6	CH_2Cl_2	25	77
7	EtOAc	25	59
8	MeCN–H_2O[c]	25	32
9	MeCN	50	94

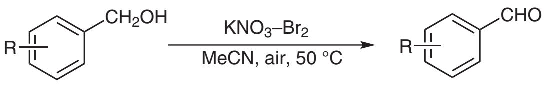
[a] Reactions were carried out in an open system at r.t., with a molar ratio of substrates/KNO_3/Br_2 =1:0.2:0.3 mmol in MeCN (2 mL).
[b] Determined by GC.
[c] Ratio of 9:1 for MeCN–H_2O.

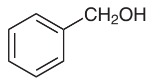
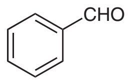
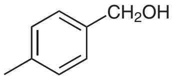
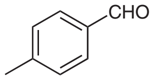
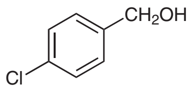
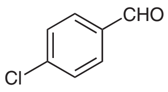
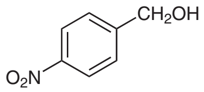
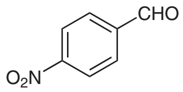
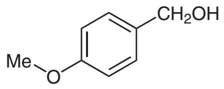
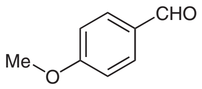
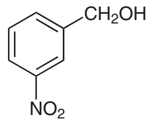
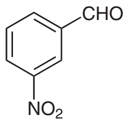
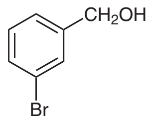
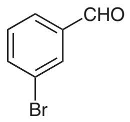
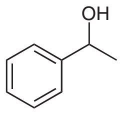
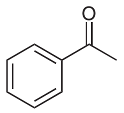
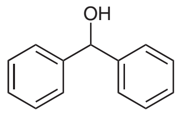
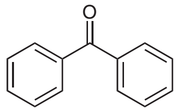
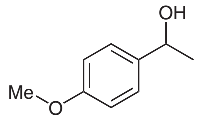
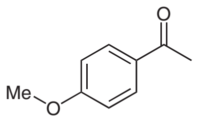
A variety of benzylic alcohols were tested (Table 4). Most reactions proceeded smoothly and afforded the corresponding aldehydes or ketones in good to excellent yields. Chloro-, bromo-, or methyl-substituted benzylic alcohols were better substrates to those with a nitro or methoxy substitution. Meanwhile, secondary alcohols could be easily converted into ketones with high yields.

In conclusion, we have developed a selective oxidation of sulfides and alcohols with air with the combination of potassium nitrate with pyridinium tribromide or bromine under the transition-metal-free conditions. Besides optimization for a 'greener' procedure, currently dedication has also been made to extend its scope and to explore its reaction mechanism and possible synthetic applications.

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

Table 4 Oxidation of Benzaldehydes and Acetophenones Using $KNO_3–Br_2/PyHBr_3$ as Catalyst[a]



Entry	Substrate	Product	Time (h)	Yield (%)[b]
1			24	90
2			24	92
3			48	91
4			48	70
5[c]			24	62
6			48	65
7			36	82
8			24	94
9			24	96
10			24	75

[a] Reactions were carried out in an open system at r.t., with a molar ratio of substrate/KNO_3/Br_2 = 1:0.2: 0.3 mmol in MeCN (2 mL).
[b] Isolated after chromatography.
[c] Pyridinium tribromide (0.3 mmol) instead of bromine.

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(13) **General Methods**

^{1}H NMR and ^{13}C NMR spectra were obtained with a Bruker AVANCE 600 spectrometer in $CDCl_3$ with TMS as an internal standard. Infrared spectra were recorded with a Bruker Tensor 27 FT-IR spectrometer using KBr pellets. GC-MS was performed on a FINNIGAN Trace DSQ chromatograph.

Procedure for Oxidation of Sulfide Using KNO_3–$PyHBr_3$/Br_2 as Catalyst

A typical experiment was carried out in an open reaction tube. Sulfide (1 mmol) was added to the mixture of KNO_3 (0.1 mmol) and $PyHBr_3$ (or bromine; 0.15 mmol) in MeCN (2 mL). The reaction mixture was stirred under aerial conditions at r.t. The reaction progress was detected by GC and TLC. After the starting material had disappeared, $Na_2S_2O_3$ aq solution was used to quench the reaction. CH_2Cl_2 was added to the reaction mixture, and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by chromatography.

Representative Spectral Data of Sulfoxide – Methyl Phenyl Sulfoxide

IR (KBr): ν_{max} = 3265, 1477, 1038, 749, 692 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 2.73 (s, 3 H), 7.48–7.54 (m, 3 H), 7.64–7.65 (d, 2 H, *J* = 7.44 Hz). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 44.13, 123.6, 129.5, 131.2, 145.7. MS (EI, 70 eV): *m/z* (%) = 140 [M$^+$].[3h]

Procedure for Oxidation of Benzaldehydes and Acetophenones Using KNO_3–Br_2/$PyHBr_3$ as Catalyst

A typical experiment was carried out in an open reaction tube. Benzaldehyde or acetophenone (1 mmol) was added to the mixture of KNO_3 (0.2 mmol) and bromine (0.3 mmol) in MeCN (2 mL). The reaction mixture was stirred under aerial conditions at 50 °C. The reaction progress was detected by GC and TLC. After the starting material had disappeared, $Na_2S_2O_3$ aq solution was used to quench the reaction. CH_2Cl_2 was added to the reaction mixture, and the two phases were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with H_2O and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by chromatography.

Representative Spectral Data of Aldehyde – Benzaldehyde

IR (KBr): ν_{max} = 3064, 2819, 1701, 1311, 1203, 746 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.51–7.54 (t, 2 H, *J* = 7.54 Hz), 7.61–7.64 (t, 1 H, *J* = 7.43 Hz), 7.87–7.88 (d, 2 H, *J* = 7.69 Hz), 10.00 (s, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$): δ = 129.0, 129.7, 134.4, 136.4, 192.4. MS (EI, 70 eV): *m/z* (%) = 106 [M$^+$].[2c]