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N-Hydroxy-*o*-benzenedisulfonimide: A Misunderstood Selective Oxidizing Agent

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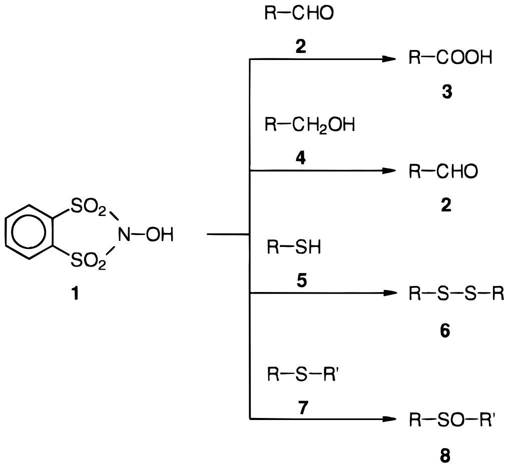
N-Hydroxy-*o*-benzenedisulfonimide (now an easily accessible reagent) is a useful selective oxidizing agent; this is contrary to what was previously believed. The oxidation reactions of aldehydes to acids, benzyl alcohols to aldehydes, thiols to disulfides, and sulfides to sulfoxides were investigated (18 examples).

N-Hydroxy-*o*-benzenedisulfonimide (NHOBS, **1**) was first prepared in 1926 by Hurtley and Smiles by reduction of *o*-benzenedisulfonyl chloride with sodium sulfite, followed by nitrosation.[1] More than 40 years later Hendrickson et al. reassessed **1**, together with quite a few other N-substituted derivatives of *o*-benzenedisulfonimide, as synthetic tools.[2] The possibility of NHOBS being a potential source of $^+$OH, like a peracid, was particularly investigated, but the results were negative, both as a Baeyar−Villiger reagent and a valid oxidizing agent to convert aldehydes to acids. It was probably these conclusions that led to no further investigations into NHOBS as an oxidizing agent. However, it was found[2] that *N*-chloro- and *N*-bromo-*o*-benzenedisulfonimide are very active sources of ionic positive halogen, Cl^+ or Br^+. Furthermore other researchers have since demonstrated that *N*-fluoro-*o*-benzenedisulfonimide acts as a selective electrophilic fluorinating agent.[3,4]

On the basis of these results, and as we had available a fairly efficient method (tiresome in the past) for the preparation of the key intermediate, *o*-benzenedisulfonyl chloride,[5] for the synthesis of *N*-hydroxy-*o*-benzenedisulfonimide and other N-substituted derivatives of *o*-benzenedisulfonimide, we thought to further investigate the explorative experiments of Hendrickson[2] on the oxidizing properties of NHOBS. We prepared this reagent by putting together known procedures, *i.e.* starting from anthranilic acid and proceeding *via* 1,3-benzodithiolium tetrafluoroborate,[6,7] resulting in *o*-benzenedisulfonyl chloride [5] that was then converted into NHOBS (**1**).[8]

Scheme 1



2,3,4	R
a	Ph
b	4-MeC$_6$H$_4$
c	4-MeOC$_6$H$_4$
d	4-ClC$_6$H$_4$
e	4-O$_2$NC$_6$H$_4$

7,8	R	R'
a	Ph	Ph
b	Ph	Me
c	4-OHCC$_6$H$_4$	Me
d	Bu	Bu
e	*s*-Bu	*s*-Bu
f	*t*-Bu	*t*-Bu

5,6	R
a	Ph
b	*n*-C$_8$H$_{17}$

We investigated the oxidation of aldehydes **2** to acids **3**, benzyl alcohols **4** to aldehydes **2**, thiols **5** to disulfides **6**, and sulfides **7** to sulfoxides **8** (Scheme 1). Hendrickson's attempts[2] to convert aldehydes to acids were focused on 4-anisaldehyde and on phenylacetaldehyde: these were reacted with **1** (molar ratio = 1:1) in THF, or in acetonitrile, in the presence of catalytic amounts of 4-toluenesulfonic acid or equimolar amounts of boron trifluoride etherate for several hours at rt or at reflux. In all cases the NHOBS (**1**) was largely consumed or completely destroyed without substantial change in the substrate to be oxidized. In fact in the case of phenylacetaldehyde no oxidation took place and 50% of the starting aldehyde was recovered whereas in the case of 4-anisaldehyde the result was 4-anisic acid, maximum yield 13%, and the amount of aldehyde recovered was 60−81%. In our experiments we first investigated the oxidation of benzaldehyde (**2a**). Under the best conditions (entry 1), to a heated solution (60 °C) of **2a** in acetic acid we added, dropwise and in two portions, a solution of **1** in acetonitrile (molar ratio **2a**:**1** = 1:1.5). The reaction lasted a total of 4 h. This led to a 75% yield of benzoic acid (**3a**), an aldehyde recovery of 19%, and also *o*-benzenedisulfonimide (**1**: OH = H) in an amount

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almost corresponding to that of the NHOBS reagent. With 4-tolualdehyde (**2b**), 4-chlorobenzaldehyde (**2d**) and 4-nitrobenzaldehyde (**2e**) almost identical results were obtained (entries 2, 4, 5). On the contrary 4-anisaldehyde (**2c**; entry 3) gave the corresponding 4-anisic acid (**3c**), maximum yield 22%, 69% of **2c** being recovered unaltered, even with an excess of NHOBS (molar ratio **2c**:**1** = 1:2.5) and extending the reaction time to 15 h. Thus on comparing our results with those previously obtained[2] it can be concluded that the choice of the target reactions was unfortunate and, as a consequence, the results were misleading.

To further evaluate the oxidizing properties of NHOBS (**1**) we investigated the oxidation of benzyl alcohols **4** (entries 6−10) carrying out the reactions at 60 °C in acetonitrile. The reactions of entries 6, 7, and 10 gave only the aldehydes **2a**, **2b**, and **2e** in fair yields, without the corresponding carboxylic acids. The reaction of entry 9 gave 4-chlorobenzaldehyde (**2d**) in excellent yield together with a small amount of 4-chlorobenzoic acid (**3d**). Attempts to oxidize 4-methoxybenzyl alcohol (**4c**) failed (entry 8) and the starting compound was completely destroyed.

Following this we investigated the oxidation of benzenethiol (**5a**) and octanethiol (**5b**), carrying out the reactions in acetic acid−acetonitrile or only acetic acid: thiol **5a** gave diphenyl disulfide (**6a**) in good yield (entries 11, 12); thiol **5b** in acetic acid−acetonitrile gave rise to dioctyl disulfide (**6b**) in moderate yield, while with only acetonitrile the disulfide yield was slightly better (entries 13, 14). In all cases the starting thiols were completely consumed.

Finally a study was made of the oxidation action of NHOBS (**1**) on several representative sulfides **7a**−**f**. The reactions were carried out at 60 °C in acetic acid−acetonitrile or only acetonitrile, working with an excess of oxidant (**7**:**1** = 1:1.1−1.6). In all the considered cases, the only exception being di-*tert*-butyl sulfide (**7f**), there was the disappearance of the starting compound and the formation of the corresponding sulfoxide **8** without sulfone. The yields in sulfoxide **8** were good for diphenyl sulfide (**7a**; entries 15, 16), thioanisole (**7b**; entries 17, 18), and dibutyl sulfide (**7d**; entries 20, 21), modest for di-*sec*-butyl sulfide (**7e**; entries 22, 23) and nil for di-*tert*-butyl sulfide (**7f**; entries 24, 25). The oxidation of *p*-(methylthio)benzaldehyde (**7c**) gave excellent yields of the corresponding sulfoxide **8c** with regioselective attack at the sulfur atom, leaving the formyl group unchanged (entry 19).

The conclusion of this research is that not only does *N*-hydroxy-*o*-benzenedisulfonimide (now an easily accessible reagent) have outstanding oxidizing properties, previously denied,[2] but it also has high selectivity, a particularly important feature for sulfide oxidation.[9] Furthermore although the knowledge acquired till now allows only a rough evaluation for or against the use of NHOBS, one point in favor of the reagent is that it does not involve metals as do most oxidizing agents.

Experimental Section

Column chromatography and TLC were performed on Merck silica gel 60 (70−230 mesh ASTM) and GF 254, respectively. Petroleum ether refers to the fraction boiling in the range 40−70 °C and is abbreviated as PE. Details for reactions 1−25 are listed in Table 1. Aldehydes **2**, benzyl alcohols **4**, thiols **5**, sulfides **7**, glacial AcOH, and MeCN were of commercial origin (Aldrich). 1,3-Benzodithiolium tetrafluoroborate,[6,7] *o*-benzenedisulfonyl chloride,[5] and *N*-hydroxy-*o*-benzenedisulfonimide (NHOBS, **1**)[8] were prepared according to the literature methods.

Oxidation of Aldehydes 2 to Acids 3: Representative Procedure. Benzoic Acid (3a). In entry 1 (Table 1) a solution of benzaldehyde (**2a**; 1.06 g, 10 mmol) in glacial AcOH (20 mL) was heated at 60 °C. A solution of NHOBS (**1**; 2.35 g, 10 mmol) in MeCN (20 mL) was added dropwise during 30 min, and the resulting mixture was stirred at the same temperature for an additional 1.5 h. Then a second portion of **1** (1.18 g, 5 mmol) in MeCN (10 mL) was added dropwise during 10 min, and heating at 60 °C was continued for a further 2 h, until TLC analysis (PE−acetone, 9.5:0.5) showed that the reaction stalled. The major product was the acid **3a**; a minor amount of the starting compound **2a** was also present. Further additions of imide **1** did not change the **3a**:**2a** ratio. After cooling, the reaction mixture was treated with H_2O−diethyl ether (1:1; 200 mL). The organic phase (A) was separated and washed with H_2O (100 mL), and the aqueous solutions were collected (B). Then the organic phase (A) was dried over Na_2SO_4 and concentrated under reduced pressure to complete the elimination of AcOH. The residue was dissolved again in diethyl ether (100 mL), which was washed with 5% aqueous NaOH (2 × 50 mL) and successively H_2O (50 mL), dried, and evaporated as above to afford the starting compound **2a** in 19% yield (0.20 g). The collected aqueous solutions were acidified with concd HCl and extracted with diethyl ether (3 × 50 mL). The extracts were dried and evaporated to afford the virtually pure (TLC, NMR) title compound **3a** in 75% yield (0.92 g). The aqueous solution (B) was evaporated under reduced pressure to eliminate AcOH. The residue was crude *o*-benzenedisulfonimide hydrate (**1**: OH = H) that was washed with pentane (20 mL) and then dissolved in H_2O (5 mL). The acid solution so obtained was neutralized by addition of 10% aqueous NaOH and then passed through a 50 g column of Dowex 50 × 8 ion-exchange resin (Fluka), eluting with H_2O (50 mL). After evaporation of water, virtually pure (NMR) *o*-benzenedisulfonimide hydrate was obtained in 92% yield (3.02 g): mp 192−194 °C (toluene) (lit.[3] 192−194 °C); ^1H and ^{13}C NMR spectra were identical to those reported.[3]

Entries 2−5 were also performed in the same way. Yields are reported in Table 1. The starting compounds **2b**−**e** were recovered in 23, 69, 16, and 21% yields, respectively, in entries 2, 3, 4, and 5.

Oxidation of Benzyl Alcohols 3 to Aldehydes 2: Representative Procedure. 4-Chlorobenzaldehyde (2d). In entry 9 a solution of NHOBS (**1**; 2.82 g, 12 mmol) in MeCN (40 mL) was added dropwise during 60 min to a stirred solution of 4-chlorobenzyl alcohol (**3d**; 1.43 g) in the same solvent (20 mL), previously heated at 60 °C. Stirring and heating was maintained for a further 1.5 h, until NMR analysis showed the disappearance of the starting compound **3d**. The obtained solution was concentrated under reduced pressure, and the residue was treated with H_2O−diethyl ether (1:2; 150 mL). The organic phase (A) was separated and washed with H_2O (50 mL), and the aqueous solutions were collected (B). Then the organic phase (A) was washed with 5% aqueous NaOH (2 × 50 mL) and successively H_2O (50 mL), dried, and evaporated under reduced pressure: the virtually pure (TLC, GC, NMR) title compound **2d** was obtained in 91% yield (1.28 g). The collected aqueous solutions were acidified with concd HCl and extracted with diethyl ether (2 × 50 mL).

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Table 1. Oxidation of Aldehydes 2 to Acids 3, Alcohols 4 to Aldehydes 2, Thiols 5 to Disulfides 6, and Sulfides 7 to Sulfoxides 8

entry	starting compd **2**, **4**, **5**, **7**	molar ratio **2**,**4**,**5**,**7**:**1**	reaction solvent	time[a] (h)	product **3**, **2**, **6**, **8**	yield[b] (%)	chromatographic solvent	mp (°C) (solvent) or bp (°C)/mmHg	lit. mp (°C) or bp (°C)/mmHg
1	**2a**	1:1.5	AcOH−MeCN	4.0	**3a**	75		122−123 (H_2O)	*c*
2	**2b**	1:1.5	AcOH−MeCN	4.5	**3b**	75		180−181 (EtOH−H_2O)	*c*
3	**2c**	1:2.5	AcOH−MeCN	15.0	**3c**	22		183−184 (EtOH−H_2O)	*c*
4	**2d**	1:2.0	AcOH−MeCN	5.5	**3d**	68		242−243 (EtOH−H_2O)	*c*
5	**2e**	1:2.0	AcOH−MeCN	8.0	**3e**	64		240−241 (EtOH−H_2O)	*c*
6	**4a**	1:1.5	MeCN	5.0	**2a**	52[d]		236−237 ($PhNO_2$)	*e*
7	**4b**	1:1.25	MeCN	5.0	**2b**	57[f]		233−234 ($PhNO_2$)	*e*
8	**4c**	1:1.2	MeCN	6.0	**2c**	6	PE−MeCOMe (9:1)	*g*	*c*
9	**4d**	1:1.2	MeCN	2.5	**2d**	91		47−48 (PE)	*c*
10	**4e**	1:2.0	MeCN	7.0	**2e**	45	PE−Et_2O (9:1)	106−107 (C_6H_6−PE)	*c*
11	**5a**	1:0.5	AcOH−MeCN	1.0	**6a**	89	PE	60−61 (PE)	61[10]
12		1:0.5	AcOH	1.5		87			
13	**5b**	1:0.9	AcOH−MeCN	8.0	**6b**	40	PE	170−171/0.5	178−183/5[11]
14		1:0.75	MeCN	7.5		59			
15	**7a**	1:1.5	AcOH−MeCN	3.0	**8a**	80	PE−Et_2O (3:2)	71−72 (C_6H_6−PE)	69−71[12]
16		1:1.5	MeCN	4.0		84			
17	**7b**	1:1.2	AcOH−MeCN	0.5	**8b**	87	$CHCl_3$	110−111/1	115/2[12]
18		1:1.2	MeCN	1.0		76			
19	**7c**	1:1.1	AcOH−MeCN	4.5	**8c**	87		90−91 ($CHCl_3$−PE)	92−93[13]
20	**7d**	1:1.6	AcOH−MeCN	6.0	**8d**	70	$CHCl_3$	109/1	32[12]
21		1:1.6	MeCN	9.0		70			
22	**7e**	1:1.5	AcOH−MeCN	6.0	**8e**	48	$CHCl_3$	80−81/0.5	72−74/1[14]
23		1:1.5	MeCN	7.0		31			
24	**7f**	1:1.5	AcOH−MeCN	7.0	**8f**	*h*			
25		1:1.5	MeCN	7.0		*h*			

[a] Reaction time at 60 °C includes the dropping time of NHOBS. [b] Yields of pure isolated products. [c] Identical to that of an authentic sample of commercial origin (Aldrich) and analytical purity. [d] Yield of benzaldehyde 2,4-dinitrophenylhydrazone. [e] Identical to that of an authentic sample. [f] Yield of 4-tolualdehyde 2,4-dinitrophenylhydrazone. [g] MS: *m/z* 136 (M^+); structure was confirmed by comparison of ^1H NMR spectrum with that of an authentic sample. [h] The reaction failed.

After evaporation, virtually pure (TLC, NMR) 4-chlorobenzoic acid (**3d**) was obtained in 8.2% yield (0.13 g). According to the procedure described above in entry 1, virtually pure (NMR) *o*-benzenedisulfonimide hydrate was obtained in 91% yield (2.39 g) from aqueous solution (B).

Entries 6−8 and 10 were performed in the same way: in all cases the only reaction products were the aldehydes **2**. In entries 6 and 7, pentane was used as solvent for the extraction and was then evaporated at atmospheric pressure. From the crude reaction residues, aldehydes **2a** and **2b** were isolated as 2,4-dinitrophenylhydrazones.

Oxidation of Thiols 5 to Disulfides 6: Representative Procedure. Diphenyl Disulfide (6a). In entry 11 a solution of NHOBS (**1**; 1.18 g, 5 mmol) in MeCN (10 mL) was added dropwise during 10 min to a stirred solution of benzenethiol (**5a**; 1.10 g, 10 mmol) in AcOH (10 mL), previously heated at 60 °C. Stirring and heating was maintained for a further 50 min, until TLC (PE) and GC analyses showed the disappearance of the starting compound **5a**. After being cooled, the reaction mixture was treated with H_2O−diethyl ether (1:2; 150 mL). The organic phase (A) was separated and washed with H_2O (2 × 50 mL), and the aqueous solutions were collected (B). Then the organic phase (A) was washed with 5% aqueous NaOH (4 × 50 mL) and successively H_2O (2 × 50 mL). The crude residue obtained after the usual workup was chromatographed on a short column with PE as eluent, to afford the title compound **6a** in 89% yield (0.97 g). As above, virtually pure (NMR) *o*-benzenedisulfonimide hydrate was obtained in 84% yield (0.92 g) from aqueous solution (B).

Entry 12 was performed in the same way carrying out the reaction at 40 °C in AcOH as only solvent; in entry 14 AcOH was replaced with the same amount of MeCN. In entries 13 and 14 the above procedure was slightly modified as follows: NHOBS (**1**) was added in three portions, *i.e.* 5 mmol (1.18 g) at the beginning, 1.5 mmol (0.35 g) after 2 h, and 2.5 (0.59 g) or 1 mmol (0.23 g), respectively, in entry 13 or in entry 14, after another 2 h.

Oxidation of Sulfides 7 to Sulfoxides 8: Representative Procedures. Diphenyl Sulfoxide (8a). According to the procedure described in entry 1 for the oxidation of benzaldehyde, in entry 15 NHOBS (**1**) was added in two portions to the solution of diphenyl sulfide (**7a**; 1.86 g, 10 mmol) in AcOH (20 mL), previously heated at 60 °C. The first portion (2.82 g, 12 mmol, in 25 mL of MeCN) was added during 25−30 min and the second portion (0.7 g, 3 mmol) was added in 10 min, after 2 h. Heating at 60 °C was continued for 30 min, until disappearance of the starting sulfide **7a** (GC; TLC: PE−diethyl ether, 3:2). The reaction mixture was worked up as described above for diphenyl disulfide. The crude residue was purified by chromatography on a short column, using PE−diethyl ether (3:2), as eluent to afford the title compound **8a** in 80% yield (1.62 g). Virtually pure (NMR) *o*-benzenedisulfonimide hydrate was isolated in 100% yield (3.28 g).

Entries 16−18, 20−25 were also performed in the same way. In entries 17 and 18 the first portion of NHOBS was enough to complete the reaction. Entries 16, 18, 21, 23, and 25 were carried out in MeCN. Entries 24 and 25 failed.

4-(Methylsulfinyl)benzaldehyde (8c). In entry 19 a solution of NHOBS (**1**; 2.59 g, 11 mmol) in MeCN (40 mL) was added dropwise during 2.5 h to a stirred solution of 4-(methylthio)benzaldehyde (**7c**; 1.52 g, 10 mmol) in glacial AcOH (14 mL), previously heated at 60 °C. After an additional 2 h the reaction was complete (TLC: $CHCl_3$). After cooling, the reaction mixture was treated with saturated aqueous NaCl (50 mL) and extracted with CH_2Cl_2 (3 × 100 mL). The collected organic extracts were worked up as described for the oxidation of benzaldehyde. Pure title compound **8c** was obtained in 87% yield (1.47 g); no traces of 4-(methylthio)-benzoic acid were isolated.

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