N-Bromophthalimide [NBPI] as a powerful oxidizing agent for the facile and chemoselective oxidation of thiols to symmetrical disulfides

Ardeshir Khazaei*, Abbas Amini Manesh and Amin Rostami

Department of Chemistry, Faculty of Science, Bu-Ali Sina University P.O. Box: 65174-4119, Hamadan, Iran

A new application of *N*-bromophthalimide for the facile oxidation of thiols to their corresponding symmetrical disulfides is described. A wide variety of thiols (aromatic, aliphatic and heterocyclic) were selectively oxidised to their corresponding disulfides with [NBPI] in a mixture of acetone and water under microwave irradiation in a microwave oven at a power output of 650W.

Keyword: *N*-bromophthalimide, oxidation, thiol, disulfides

Disulfides are important compounds from both synthetic and biological viewpoints.[1] Disulfides are also important intermediates with many applications in organic synthesis.[2] The transformation of thiols to disulfides has been studied employing various oxidants (metal-assisted methods[3] and non-metal containing oxidants).[4] However, some of these reagents suffer from disadvantages such as long reaction times, availability, difficulty to work-up and preparation and instability. Also most of the reagents involve toxic metal ions and solvents in protocols that lack general applicability to thiol substrates bearing alkyl, aryl and heterocyclic moieties and are not eco-friendly. Recently, there has been a growing interest in the application of microwave irradiation to chemical reaction due to high reaction rates and the formation of cleaner products.[5]

Thus there is need for the development of protocols using readily available reagents to overcome the above limitations.

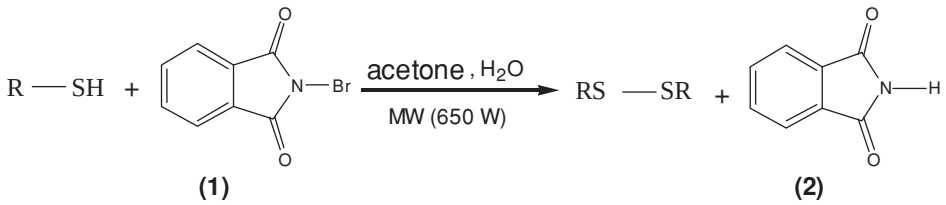
During the course of our systematic study on the oxidation of organic compounds with *N*-halo reagents,[6] we report a convenient method for the effective conversion of thiols into their corresponding symmetrical disulfides by using *N*-Bromophthalimide (NBPI) under microwave irradiation as displayed in Scheme 1.

On the basis of previously reported mechanisms for the mode of action of NCS/Me_2S[7] or NBS/Ph_3P[8] and our observation of bromine generation plus phthalimide production, the following mechanism is proposed for the coupling of thiols (Scheme 2**).**

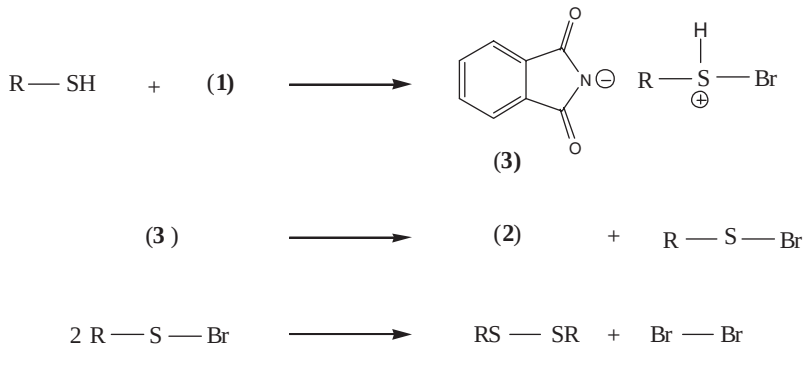
The results of this study are summarised in Table 1. A wide variety of thiols (aromatic, aliphatic and heterocyclic) were selectively oxidised to their corresponding disulfides in high yields without any evidence for the formation of the corresponding sulfonic acid. Thiosalicylic acid (Entry 4) and 2-benzimidazoyl thiol (Entry 6), which are very difficult to oxidise with other reagents, were easily oxidised with *N*-bromophthalimide (NBPI).

Three main advantages of this method are the oxidation of thiols to disulfides without over-oxidation of disulfides, (Scheme 3), the oxidation of the SH functional group in the presence of a hydroxy group (Entry 12 Table 1, Scheme 4) and the oxidation of aromatic thiols to their corresponding disulfides without bromination of aromatic rings (Entries 1–7 Table 1, Scheme 5).

In conclusion, the method offers several advantages including high yields of the products, short reaction times, easy work-up, and a stable, inexpensive and non-toxic reagent, all of which make the reaction process convenient and environmentally benign. The recovered starting material **2** as rebrominated and reused many times without reducing the yield.

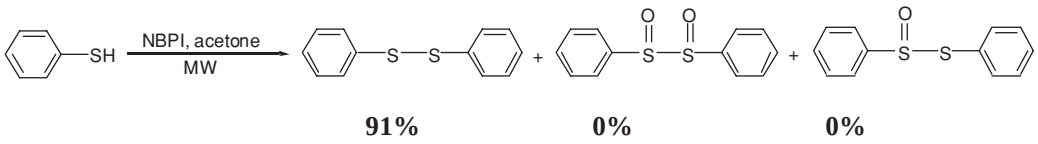


Scheme 1

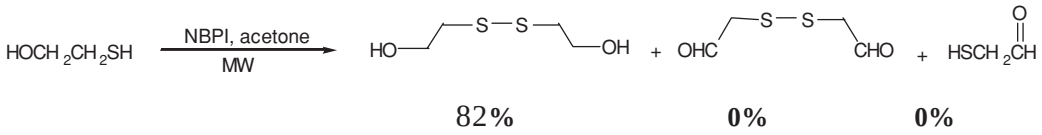


Scheme 2

* Correspondent. E-mail: khazaei_1326@yahoo.com



Scheme 3 Chemoselective coupling of thiophenol without over-oxidation products.



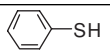
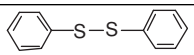
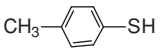
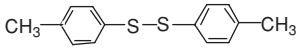
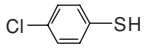
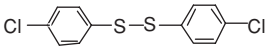
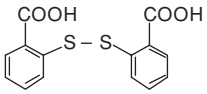
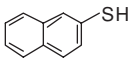
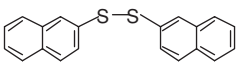
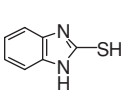
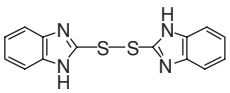
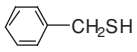
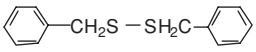
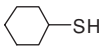
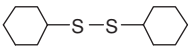
Scheme 4 Chemoselective coupling of 2-mercaptoethanol without oxidation of an OH group.

Experimental

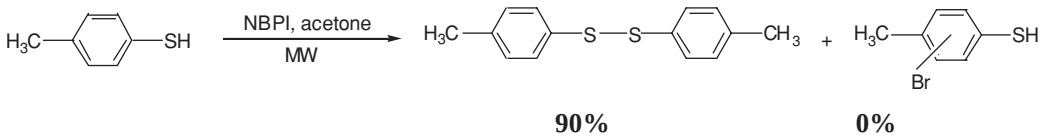
General procedure for oxidation of thiol with NBPI

A mixture of the thiol (1 mmol) and NBPI (1.5 mmol) in acetone (10 ml) and water (1 ml), was introduced into a flask and was irradiated in a microwave oven at a power output of 650W for the appropriate time as indicated in Table 1. After the reaction was completed (TLC), the solvent was removed under reduced pressure, and 20 ml of diethyl ether was added to the mixture. [Every 30 s the microwave oven was turned off and progress the reaction was monitored by TLC (hexane: ethyl acetate 10:1).] It was stirred for 10 min and then the phthalimide (**2**) was removed by filtration. Final evaporation of solvent gave the corresponding disulfides in 82–94% yields. The liquid products were further purified by column chromatography (*n*-hexane: ethyl acetate 10:1) and the solid products by recrystallisation from methanol. The spectroscopic data (^{1}H NMR and IR) of disulfides are shown in Table 2.

Table 1 Oxidation of thiols to disulfides with *N*-bromophthalimide [NBPI] under microwave irradiation

Entry	Substrate	Product[b]	Time/ min	Molar ratio oxid/sub	Yield[a]/ %	M.p./ °C	Lit. M.p./°C
1			2	1.5	91	60–61	58–60[4h]
2			2	1.5	90	44–45	45–46[4h]
3			3	1.5	92	69–71	72–74[3h]
4			12	1.5	90	287–289	286[4h]
5			6	1.5	94	143–145	144–145[3e]
6			10	1.5	90	198–200	200–201[4h]
7			4	1.5	88	70–72	69–70[4d]
8			10	1.5	89	126–128	124–129[3e]
9	$CH_3(CH_2)_6CH_2SH$	$CH_3(CH_2)_6CH_2S - SCH_2(CH_2)_6CH_3$	7	1.5	86	oil	oil[3h]
10	$CH_3(CH_2)_2CH_2SH$	$CH_3(CH_2)_2CH_2S - SCH_2(CH_2)_2CH_3$	7	1.5	87	oil	oil[3h]
11	$HOOCCH_2CH_2SH$	$HOOCCH_2CH_2S - SCH_2CH_2COOH$	10	1.5	89	156–158	157–15[9]
12	$HOCH_2CH_2SH$	$OHCH_2CH_2S - SCH_2CH_2OH$	8	1.5	82	oil	oil[3h]

[a]Yield refers to material isolated directly from the reaction mixture. [b]All products were characterised by comparison of their spectroscopic data (^{1}H NMR and IR) and physical properties with those of authentic samples.



Scheme 5 Coupling of 4-methylthiophenol without bromination of an aromatic ring.

Table 2 Spectroscopic data (1H NMR IR spectra) of products (disulfides)

Entry	Spectroscopic data IR(w:weak, m:medium, s:strang)	Spectroscopic data ^{1}H NMR
1	IR (KBr), ν (cm^{-1}): 3050(w), 2900(w), 1570(m), 1470(m), 1430(m), 1140(w), 1060(w), 1020(m), 980(w), 780(s)	^{1}H NMR ($CDCl_3$), δ (ppm): 7.2–7.6(10H, m)
2	IR(KBr), ν (cm^{-1}): 3019(w), 2974(w), 1633(w), 1580(m), 1489(s), 1390(m), 1180 (m), 1110 (m), 1070 (m), 1030(w), 1005(m), 802(s), 490(s), 790(s)	^{1}H NMR ($CDCl_3$), δ (ppm): 2.2(6H, s), 7(4H, d), 7.4 (4H, d)
3	IR(KBr), ν (cm^{-1}): 3050(W), 1560(m), 1450(s), 1370(s), 1080(s), 1000(s), 810(s), 770(m), 730(s)	^{1}H NMR ($CDCl_3$), δ (ppm): 7.4 (8H, m)
4	IR(KBr), ν (cm^{-1}): 3419(W), 3067(m), 3000(m), 2989(m), 2876(m), 2661(m), 1678(s), 1606(m), 1565(m), 1316 (s), 1293 (s), 1276 (s), 1261(s), 1039(m), 754(s)	^{1}H NMR ($CDCl_3$), δ (ppm): 7.08–8.2 (8H, m), 9.4(2H, s)
5	IR (KBr), ν (cm^{-1}): 3070(W), 1590(m), 1490(m), 1450(m), 1170(w), 1080(w), 1040(m), 980(w), 790(s)	^{1}H NMR ($CDCl_3$), δ (ppm): 7.3–7.9(14H, m)
6	IR(KBr), ν (cm^{-1}): 3066(w), 2959(w), 1600(w), 1451(s), 1398(m), 1352(m), 1274 (w), 977(m), 804(w), 741(s)	^{1}H NMR ($CDCl_3$), δ (ppm): 7.26–7.70 (8H, m)
7	IR(KBr), ν (cm^{-1}): 3050(w), 2955(w), 2580(w), 1590(w), 1485(s), 1450(s), 1405(m), 1220 (m), 1190 (m), 1160(m), 1050(w), 880(m), 755(s)	^{1}H NMR($CDCl_3$), δ (ppm): 3.5(4H, s), 7.3 (10H, s)
8	IR(KBr), ν (cm^{-1}): 2900(s), 2840(s), 1445(s), 1310(m), 1260 (m), 1190 (w), 1170(w), 1130(s), 990(m), 885(w), 780(s)	^{1}H NMR ($CDCl_3$) δ 1.45(12H , m) 1.70(8H, q), 2.5(2H , m)
9	IR(liquid film), ν (cm^{-1}): 2950(s), 2900(s), 2850(s), 1460(s), 1375(m), 1260(m), 720(m)	^{1}H NMR ($CDCl_3$), δ (ppm):1–2(22H, m), 3(4H, t)
10	IR(liquid film), ν (cm^{-1}): 2950(s), 2870(s), 1465(s), 1439(m), 1300(m), 1120 (w), 1050(w)	^{1}H NMR ($CDCl_3$) δ 0.95(6H, t), 1.425(4H, m), 1.67(4H, m), 2.69(4H, t).
11	IR(KBr), ν (cm^{-1}): 3027(W), 2967(w), 1699(s), 1424(m), 1400(m), 13415(w), 1450(s), 1243 (s), 939(m), 755(w)	^{1}H NMR (DMSO-d_6) δ 2.53(4H, t), 2.83(4H, t), 9.5(2H, s)
12	IR(liquid film), ν (cm^{-1}): 3300(m), 2900(m), 1250(m), 980(m)	^{1}H NMR(CD_3OD), δ (ppm): 3 (4H, t), 3.9(7H, t), 4.8 (2H, s)

We are thankful to the Bu-Ali Sina University Research Councils for partial support of this work.

Received 4 November 2004; accpeted 8 March 2005
Paper 04/2846

References

1 G. Capozzi, G. Modena and S. Patai, *The Chemistry of Thiol Group*; Part 2; Patai, S., Ed., Wiley: New York, 1974; pp 785; (b) D.C. Jocelyn, *Biochemistry of the Thiol Group*, Academic Press: New York, 1992, pp 1.

2 (a) J. Lam, H. Bilddose, L.P. Christensen and T. Thomsen, *Acta. Chem. Scand. Ser. B.*, 1989, **43**, 799; (b) V. Srivastav, R. Gupta and R.R. Guptam, *Ind. J. Chem*., 2000, **39B**, 223; (c) P. Metzner, *Synthesis*, 1992, 1185.

3 (a) H. Firouzabadi and I. Mohammadpoor-Baltork, *Bull. Chem. Soc. Jpn*, 1992, **65**, 1485; (b) N. Iranpoor, H. Firouzabadi and M.A. Zolfigol, *Synth. Commun.*, 1998, **28**, 367; (c) N. Iranpoor and B. Zeynizadeh., *Synthesis*, 1999, **49**; (d) Y.-H. Sun, and K.-Y. Ko, *Bull. Korean Chem. Soc.*, 2000, **21**, 669; (e) S. Raghavan, A. Rajender, S.C. Joseph and M.A. Rasheed, *Synth. Commun.*, 2001, **31**, 1477; (f) P. Salehi, A. Farrokhi and M. Gholizadeh, *Synth. Commun.*, 2001, **31**, 2777; (g) O.M. Lezina, S.A. Rubtsova and A.V. Kuchin, *Russ. Chem. Bull.*, 2003**, 52**, 1878; (h) M.M. Khodaei, I. Mohammadpoor-Baltork and K. Nikoofar, *Bull. Korean Chem. Soc*., 2003, **24**, 885; (i) B. Zeynizadeh and N. Iranpoor, *J. Chin. Soc-Taip*., 2003, **50**, 849; (j) F.J. Arnaiz, R. Aguado and M.R. Pedrosa, *Synthesis.*, 2002, **7**, 856; (k) S.M.S. Chauhan, A. Kumar and K.A. Srinivas, *Chem. Commun.*, 2003**, 21**, 2348; (l) M. Tajbakhsh, R. Hosseinzadeh and A. Shakoori, *Tetrahedron Lett.*, 2004, **45**, 1889; (m) M.M. Hashemi and Z. Karimi-Jaberi, *Montash Chem.*, 2004, **135**, 41.

4 (a) J. Drabowicz and M. Mikolajczyk, *Synthesis*, 1980, **32**; (b) B. Movassagh, M.M. Lakouraj and K. Ghodrati, *Synth. Commun.*, 1999, ***29***, 3597; (c) V. Kesavan, D. Bonnet-Delpon and J.-P. Begue,. *Synthesis*, 2000, 223; (d) M.A. Zolfigol, *Synth. Commun.*, 2000, **30**, 1593; (e) R.S. Varma, H.M. Meshram and R. Dahiya, *Synth. Commun.*, 2000**, 30**, 1249; (f) M.A. Zolfigol, *Tetrahedron*, 2001, **57**, 9509; (h) F.-E. Chen, Y.-W. Lu, Y.-P. He, Y.-F. Luo and M.-G. Yan,. *Synth. Commun.*, 2002, **32**, 3487; (i) M.A. Zolfigol, F. Shirini, A. Ghorbani-Choghamarani and E.Ghofrani, *Phosphorus, Sulfur and Silic*a, 2003, **178**, 1477, (j) M.H. Ali and M.Mc-Dermott, *Tetrahedron Lett.*, 2002, **43**, 6271;

5 S. Caddick, *Tetrahedron* 1995, **51**, 10403.

6 (a) A. Khazaei and R.G. Vaghei, *Tetrahedron Lett.*, 2002, **43**, 30733; (b) A. Khazaei, R.G. Vaghei and M. Tajbakhsh, *Tetrahedron Lett*., 2001, **42**, 59; (c) A. Khazaei and A. Shirdarreh, *Synth. Commun.*, 1999, **29**, 4079; (d) A. Khazaei, K. Bridson and R.G. Pitchard, *Cryst. Str. Commun*., *C5*. 2001, 970; (e) A. Khazaei, E. Mehdipour and B. Roodpeyma, *Iran. J. Chem. Chem. Eng.* 1995, **14**, 77; (f) A. Khazaei and A.A. Manesh, *Synthesis*, 2004, **11**, 1739.

7 E.J. Corey and C.U. Kim, *J. Am. Chem. Soc*., 1972, **94**, 7586.

8 P. Frøyen, *Synth. Commun*., 1995, **25**, 959.

9 J. Charles Poucher. *The Aldrich Library of NMR Spectra* Edition II. 1983**,** Vol 1, 1,465B.