Oxidation of thiols with 1-butyl-4-aza-1-azoniabicyclo[2.2.2]octane dichromate (BABOD) under non-aqueous conditions

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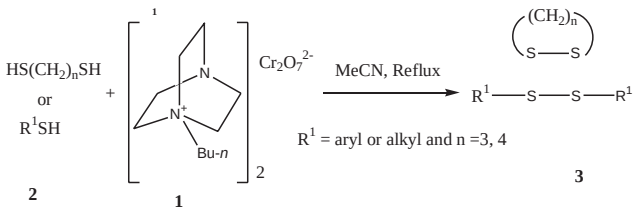
The preparation of 1-butyl-4-aza-1-azoniabicyclo[2.2.2]octane dichromate and the use of this reagent for selective oxidation of aromatic and aliphatic thiols to their corresponding disulfides under non-aqueous conditions is reported

Keywords: thiols, 1-butyl-4-aza-1-azoniabicyclo[2.2.2]octane dichromate

The oxidative coupling of thiols to their corresponding disulfides under mild conditions is of significant importance from a biological and practical point of view.[1-3] Since thiols are among functional groups, which can be over-oxidised, extensive research has been performed to control their oxidation.[4-10] The oxidation of thiols to disulfides is a characteristic reaction, and further oxidation to disulfide S-oxides (thiosulfinates), 1,1-dioxides (thiosulfonates), and sulfonic acids is possible. The weak S–S bonds in these compounds impart high reactivity,[11] and in natural products, these moieties and related cyclic analogues are associated with interesting biological activity and DNA-cleaving properties.[12-15]

Cr(VI) oxide is an inexpensive, water-soluble and stable oxidising reagent that is commercially available. This reagent is insoluble in non-aqueous solvents; however, the requirement of aqueous conditions had to be overcome. As part of our continued effort to develop new reagents for the oxidation of organic compounds,[16-17] we now wish to report the synthesis of 1-butyl-4-aza-1-azoniabicyclo[2.2.2]octane dichromate **1**, as a mild, efficient, stable and inexpensive reagent for oxidation of thiols to the corresponding disulfides. This reagent is an orange powder, which is quite soluble in dichloromethane, chloroform, acetone and acetonitrile and insoluble in non-polar solvents such as carbon tetrachloride, *n*-hexane and diethyl ether. This reagent is readily prepared by the dropwise addition of an aqueous solution of CrO_3 in HCl 3 M to an aqueous solution of 1-butyl-4-aza-1-azoniabicyclo[2.2.2]octane bromide in quantitative yield at room temperature and could be stored for months without losing its potency.



Scheme 1

At first, the oxidation of thioanisole as the model compound in various solvents was examined. The solvents examined were dichloromethane, chloroform and acetonitrile. The reactions were carried out by stirring the model compound with one molar amount of **1** under reflux conditions. Dichloromethane and chloroform were inferior solvents to acetonitrile, because the reaction stopped at lower conversions in these solvents than in acetonitrile (Table 1 and Scheme 1). A variety of aromatic and aliphatic thiols **2** were converted into symmetrical

Table 1 Oxidative coupling of thiols **4** to disulfides **5** with reagent **1** in refluxing acetonitrile

Thiols (**4**)	Product (**5**)[a,b]	Reaction time/h	Yields/%[e]	M.p. or B.p./mmHg/°C (Lit.)[13-18]
C_6H_5SH	$C_6H_5SSC_6H_5$	0.5	92	56–60 (59–60)
4-MeC_6H_4SH	4-$MeC_6H_4SSC_6H_4Me$-4	0.8	98	47–48 (46–48)
4-$MeOC_6H_4SH$	4-$MeOC_6H_4SSC_6H_4OMe$-4	0.9	93	44–45 (43.8)
4-$NH_2C_6H_4SH$	4- $NH_2C_6H_4SSC_6H_4$ NH_2-4	1.1	95	75–77 (76–77)
3-MeC_6H_4SH	3-$MeC_6H_4SSC_6H_4Me$-3	0.8	98	–21 (–21)
4-ClC_6H_4SH	4-$ClC_6H_4SSC_6H_4Cl$-4	0.9	98	72–73 (72–73)
2-$MeOOCC_6H_4SH$	2-$MeOOCC_6H_4SSC_6H_4COOMe$-2	0.8	96	198–191 (193)
$C_6H_5CH_2SH$	C_6H_5 CH_2SS $CH_2C_6H_5$	1.1	95	69–70 (69–70)
4-$NO_2C_6H_4SH$	4- $NO_2C_6H_4SSC_6H_4$ NO_2-4	0.75	88	182–184 (182)
2-PyridylSH	2-PyridylSS-Pyridyl-2	0.8	92	52–53 (52–53)
4-PyridylSH	4-PyridylSS-Pyridyl-4	1.1	91	76–77 (76–77)
CyclopentylSH	CyclopentylSSCyclopentyl	1.0	93	105–106 (107–108)
CyclohexylSH	CyclohexylSSCyclohexyl	1.2	87	124 129 (125–130)
HO-CH_2CH_2SH	HO-$CH_2CH_2SSCH_2CH_2OH$	1.2	80	156–148/2(158–163/3.5)
$HOOCCH_2CH_2SH$	$HOOCCH_2CH_2SSCH_2CH_2COOH$	1.0	86	157–159 (1157–159)
$HOOCCH_2SH$	$HOOCCH_2SSCH_2COOH$	1.1	91	138–139 (140)
$CH_3(CH_2)_3SH$	$CH_3(CH_2)_3SS(CH_2)_3CH_3$	1.2	92	94–96/6 (86/3.5)
$CH_3(CH_2)_4SH$	$CH_3(CH_2)_4SS(CH_2)_4CH_3$	1.1	87	117–119/6 (90–92/1)
$CH_3(CH_2)_6SH$	$CH_3(CH_2)_6SS(CH_2)_6CH_3$	1.2	90	152–154/6 (143–147/5)
$CH_3(CH_2)_7SH$	$CH_3(CH_2)_7SS(CH_2)_7CH_3$	1.0	96	152–154/6 (143–147/5)
1-$HSCH_2C_6H_4CH_2SH$-4	Linear polymer[c]	1.2	98	–
$SH(CH_2)_3SH$	1,5-Cyclopentanedisulfide + (-S $(CH_2)_3$S-)$_n$[d]	2.0	70 (30 Polymer)	45–47/6 (-) 65–70 (71–73)
$SH(CH_2)_4SH$	1,6-Cyclohexanedisulfide	1.2	98	30–32 (32-33)

[a]Confirmed by comparison with authentic samples (IR, TLC,and NMR). [b]Oxidant/Thiol (1.0:1.0).

[c]$HSCH_2C_6H_4CH_2S$—(—$SCH_2C_6H_4CH_2S$—)$_n$—$SCH_2C_6H_4CH_2SH$, [d]$HS(CH_2)_3S$—(—$SCH_2CH_{24}CH_2S$—)$_n$—$S(CH_2)_3SH$,

[e]Yield of isolated pure product after chromatography or distillation.

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disulfides **3** upon simple admixing with the reagent **1**. The optimum mole ratio between the thiol and the oxidant is found to be 1:1, which produces pure disulfides **3** in high yields (Table 1 and Scheme 1). This method is a remarkably effective methodology for oxidising aliphatic and aromatic thiols to disulfides. This reagent also exhibits a synthetically valuable method for producing cyclic disulfides from dithiols.

The oxidation of dithiols results in the formation of cyclic and/or polymers disulfides. The polymers result from intermolecular oxidation, while the cyclic disulfides arise from intramolecular oxidative coupling of dithiols. For example, oxidative coupling of 1,4-benzenedimethanethiol gives only a polymeric product (Table 1), while propane1,3-dithiol gives 70% cyclic disulfides and 30% polymeric products. The butane-1,4-dithiol gives only cyclic disulfides in 98% yields. It was found that further oxidation of disulfide to S-oxides (thiosulfinates), 1,1-dioxides (thiosulfonates), and sulfonic acid did not occur. A series of thiols were oxidised to disulfides rapidly by this reagent (Table 1). Primary alcohol, amine, carboxylic acid, ester, and methoxy functional groups were unaffected during the oxidation of the thiols. The dithiols were oxidised to the corresponding cyclic disulfides in good yields.

In conclusion, this new method for converting of thiols into their corresponding disulfides offers the following advantages: (a) the reagent **1** is an inexpensive and selective oxidant, (b) the procedure is simple and occurs in aprotic solvent, (c) the yield of disulfide is high.

Experimental

General

Yields refer to isolated pure products. The oxidation products were characterised by comparison of their spectral (IR, ^{1}H NMR) and physical data with authentic samples.[18] All ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ relative to TMS and IR spectra were recorded on Shimadzu 435 IR spectrometer. All reactions were carried out in refluxing acetonitrile.

CAUTION: Chromium compounds can cause pimary irritation, ulceration and allergic eczema when directly contacted with the skin and nasal and pulmonary irritation, with possible bronchogenic carcinoma upon breathing of chromate dust. Oral ingestion produces violent gastrointestinal irritation with vomiting and diarrhea.

Preparation of 1-Butyl-4-aza-1-azoniabicyclo[2.2.2]octane Dichromate (BABOD) **(1):** To a solution of 1-butyl-4-aza-1-azoniabicyclo[2.2.2] octane bromide (24.90 g, 100 mmol) in water (100 ml) was added dropwise a solution of CrO_3 (10 g, 100 mmol) in aqueous HCl (100 ml, 3 M). The above solution was stirred for 20 min. at room temperature. The resulting orange precipitate was removed by filtration and washed with cooled distilled water (2×50 ml), and dried in a desiccator under vacuum over calcium chloride to afford an orange powder (26.3 g, 95% yield), which decomposed at 117–118 ºC to a dark-brown material. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 3.66 (m, 12 H), 1.48 (m, 5 H), 0.92 (m, 4 H). ^{13}C NMR (d_6-DMSO, 75 MHz) δ = 64.74, 51.86, 44.93, 41.45, 40.95, 40.79, 24.69, 20.42, 14.83; Anal calcd for $C_{20}H_{42}N_2Cr_2O_7$: C, 39.41; H, 6.95; N, 9.19 %. Found: C, 39.56; H, 6.73; N, 9.25 %.

Typical procedure for oxidative coupling of thiols 4 to disulfides 5 with reagent **1**: In a round-bottomed flask (250 ml) equipped with a condenser and a magnetic stirrer, a solution of thiophenol (10 mmol, 1.1 g) in acetonitrile (50 ml) was prepared. Reagent **1** (10 mmol, 4.6 g) was added to the solution and the resulting mixture was stirred magnetically under reflux conditions for 0.5 h. After completion of the reaction, monitored by TLC using EtOAc/hexane (1:9), the reaction mixture was filtered and the solid material was washed with acetonitrile (2×50 ml). The solvent was removed under reduced pressure. The residue was purified by column chromatography using silica gel (EtOAc/cyclohexane, 2:8) to afford diphenyl disulfide in 92% yield, m.p. 59–61 ºC. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.62–7.48 (m, 4H), 7.42–7.20 (m, 6H). IR (KBr): ν = 459, 470, 687, 734, 1435, 1474, 1572, 3050 cm^{-1}.

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References

1 J.R. Johnson, W.F. Bruce and J.D. Dutcher, *J. Am. Chem. Soc.*, 1943, **65**, 2005.
2 P.C. Jocelyn, *Biochemistry of the Thiol Group*, Academic Press: New York, **1977.**
3 (a) S.J. Behroozi, W. Kim and K.S. Gates, *J. Org. Chem.*, 1995, **60**, 3964; (b) S.J. Behroozi, W. Kim, J. Dannaldson and K.S. Gates, *Biochemistry*, 1996, **35**, 1768.
4 A.R. Hajipour and S.E. Mallakpour, *J. Chem. Res. (S)*, **2000**, 32.
5 A.R. Hajipour, I.M Baltork and G. Kianfar, *Ind. J. Chem.*, 1999, **37B**, 607.
6 I.M. Baltork, A.R. Hajipour and H. Mohammadi, *Bull. Chem. Soc. Jpn.*, 1998, **71,** 1649.
7 E. Santaniello, F. Milani and R. Casati, *Synthesis*, **1983**, 749.
8 C. Lopez, A. Gonzalez, E.P. Cossio and C. Palomo, *Synth. Common.*, 85, **15,** 1197.
9 S.V. Ley, C.A. Meerholz and D.H.R. Barton, *Tetrahedron*, 1981, **37**, Suppl.9, 213.
10 A.R. Hajipour and I.M. Baltork, *Phosphorus, Sulfur Silicon*, 2000, **164**, 145.
11 A.R. Hajipour and S.E. Mallakpour, *Mol. Cryst. Liq. Cryst.*, 2001, **356**,: 371.
12 E. Block, and J. O'Connor, *J. Am. Chem. Soc.*, 1974, **96**, 1135.
13 E. Block, *Angew, Chem., Int. Ed. Engl.*, 1992, **31**, 1135.
14 L. Teuber, *Sulfur, Rep.*, 1992, **31**, 257
15 (a) Y. Kanda and T. Fukuyama, *J. Am. Chem. Soc.*, 1993, **115**, 8451; (b) G. Pattenden, A.J. Shuker, *J. Chem. Soc., Perkin Trans. 1*, **1992**, 1215.
16 (a) A.R. Hajipour, S.E. Mallakpour and H. Adibi, *Chem. Lett.*, **2000**, 460; (b) A.R. Hajipour, S.E. Mallakpour and S. Khoee, *Chem. Lett.*, **2000**, 120; (c) A.R. Hajipour, S.E. Mallakpour and S. Khoee, *Synlett*, **2000**, 740.
17 (a) A.R. Hajipour and N. Mahboobkhah, *Synth. Commun.*, 1998, **28,** 3143; (b) A.R. Hajipour and N. Mahboobkhah, *J. Chem. Res. (S)*, **1998**, 122; (c) A.R. Hajipour, I.M Baltork and G. Kianfar, *Bull. Chem. Soc. Jpn.*, 1998, **71,** 2655; (d) A.R. Hajipour and N. Mahboobkhah, *Org. Prep. Proc. Int.*, 1999, **31**, 112; (e) A.R. Hajipour, I.M Baltork and K. Niknam, *Org. Prep. Proced. Int.*, 1999, **31**, 335; (f) I.M. Baltork, A.R. Hajipour and R. Haddadi, *J. Chem. Res. (S)*, **1999**, 102.
18 A.R. Hajipour and A.E. Ruoho, *Phosphorus, Sulfur Silicon*, 2003**, 178**, 1277.