Cleavage of C=N derivatives and oxidation of thiols in water under neutral conditions with 1,4-dichloro-1,4-diazoniabicyclo[2,2,2]octane bischloride

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1,4-Diazabicyclo[2,2,2]octane (DABCO) is easily chlorinated and gives a complex which efficiently converts aliphatic and aromatic oximes, phenylhydrazones and semicarbazones to their corresponding carbonyl compounds in water at 50°C in high yield. This reagent can also be used for conversion of thiols to their compounding disulfide under the same reaction conditions. DABCO is quantitatively recovered which can be rechlorinated and reused several times.

Keywords: 1,4-dichloro-1,4-diazoniabicyclo[2,2,2]octane bischloride, oximes, phenylhydrazones, semicarbazones, deprotection, thiols, oxidation

Oximes, phenylhydrazones and semicarbazones are utilised for the purification and characterisation of carbonyl compounds and as protecting groups for carbonyl compounds.[1] Their synthesis from noncarbonyl compounds provides an alternative pathway to aldehydes and ketones. Therefore, the regeneration of carbonyl compounds from their C=N analogues has received much attention.[2-4] Although some of the known methods are very efficient,[5-10] most of them require drastic conditions. Disulfides play important roles in the biological and chemical processes.[11] Oxidation of thiols is the common method for disulfide synthesis mainly because a large number of thiols are commercially available and are easily synthesised.[12,13] Organic reactions in water, are of current interest, because water is an easily available, economical, safe, and environmentally benign solvent.[14]

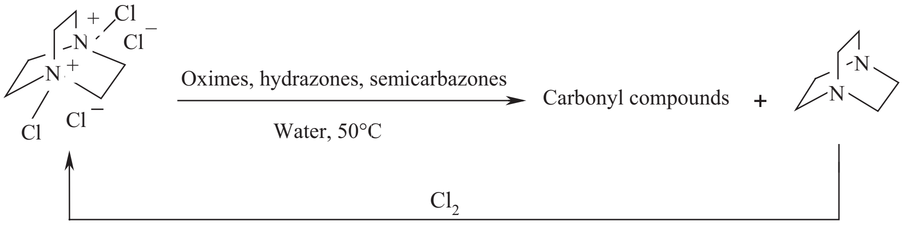
Results and discussion

In our ongoing program to find new oxidising reagents,[15-16] we now report the preparation of complex 1,4-dichloro-1,4-diazoniabicyclo[2,2,2]octane bischloride[17] as a new efficient and reusable reagent for the cleavage of oximes, phenylhydrazones, and semicarbazones in water and the oxidation of thiols (Scheme 1).

Very recently we have used this reagent for oxidation of alcohols under microwave irradiations and the oxidative deprotection of tetrahydropyranyl and trimethylsilyl ethers in water.[17]

We have studied different substrate/reagent ratio and found that 1 : 0.5 is suitable for these transformations. Several oximes were deoximated to their corresponding aldehydes and ketones in a good to excellent yield in water. Overoxidation of the aldehydes to their carboxylic acids was not observed. The results are shown in Table 1.

As indicated, aromatic oximes bearing both electron withdrawing and electron releasing groups on the ring were deoximated with this reagent within 15–45 minute in water (Table 1, entries 1–7). Aliphatic oximes (Table 1, entries 8–10) were also deoximated in high yield. The α,β-unsaturated acroleinoxime was converted to acrolein without affecting



Scheme 1

Table 1 Regeneration of carbonyl compounds from their corresponding oximes, semicarbazones and phenylhydrazones in water

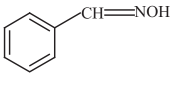
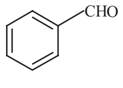
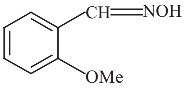
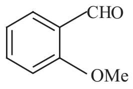
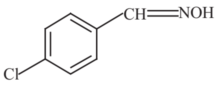
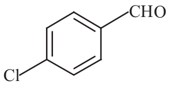
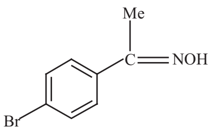
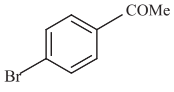
Entry	Substrate	Product[a]	Time/min	Yield/%	M.p./°C or b.p./°C Torr	
					Found	Reported[18]
1			20	95	174–177	176–179/760
2			20	90	35–38	35–37
3			15	88	46–48	45–47
4			25	85	48	49–51

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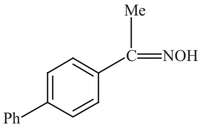
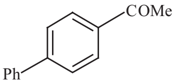
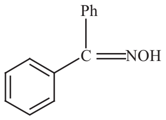
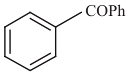
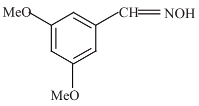
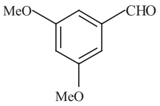
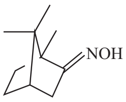
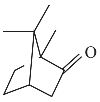
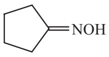
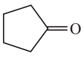
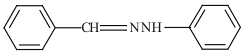
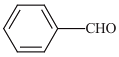
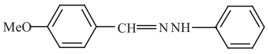
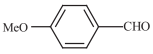
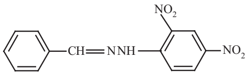
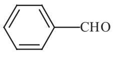
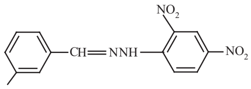
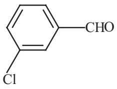
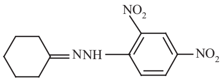
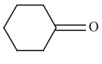
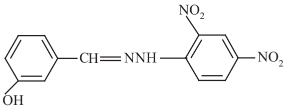
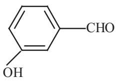
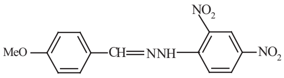
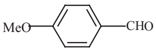
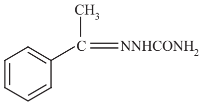
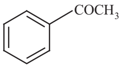
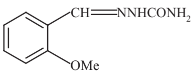
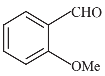
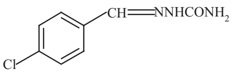
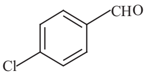
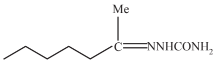
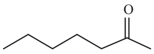
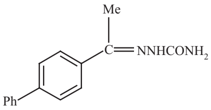
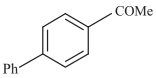
Table 1 *Continued*

Entry	Substrate	Product[a]	Time/min	Yield/%	M.p./°C or b.p./°C Torr	
					Found	Reported[18]
5			15	90	116–117	117–119
6			45	89	50	49–50
7			20	85	45–47	44–48
8			40	83	176	175–177
9	$CH_3CH_2CH_2CH_2CH{=}NOH$	$CH_3CH_2CH_2CH_2CHO$	15	90	101–104/760	100–103/760
10			15	92	126–131/760	127–131/760
11	$PhCH{=}CHCH{=}NOH$	$PhCH{=}CHCHO$	15	89	124–128/11	125–128/11
12			20	91	178/760	178–179/760
13			18	90	118–122/12	118–121/12
14			20	87	177–179/760	178–179/760
15			25	86	211–214/760	213–215/760
16			25	92	155/760	154–156/760
17			15	86	101	100–103
18			15	95	116–120/12	118–121/12
19			10	85	202–203/760	202/760
20			10	90	35	35–37
21			15	89	44–46	45–47
22			15	87	147–150/760	149–152/760
23			20	93	117	117–119

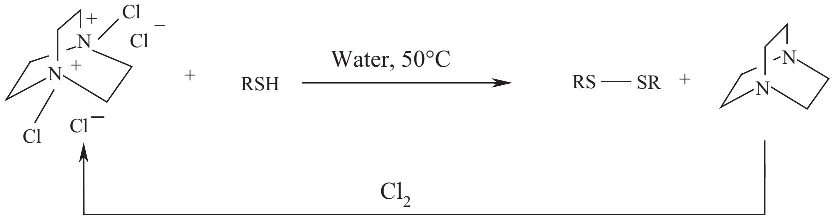
[a] All products were characterised spectroscopically (^{1}H NMR, IR) and showed physical and spectral data in accordance with their expected structure and by comparison with authentic sample.

[b] The yields refer to isolated products.

the carbon–carbon double bond (Table 1, entry 11). Even the sterically-hindered benzophenone oxime and camphor oxime were converted to their corresponding carbonyl compounds with a longer reaction time. Similarly aromatic and aliphatic phenylhydrazones and semicarbazones were deprotected in high yield in water within 10–25 minute (Table 1, entries 12–23).

Several thiols were also oxidised to their corresponding disulfides in a good to excellent yield in water (Scheme 2).

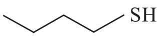
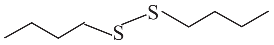
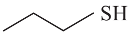
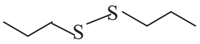
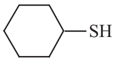
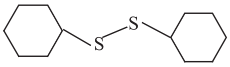
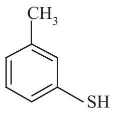
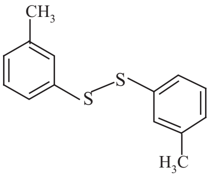
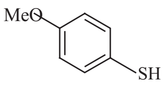
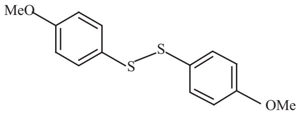
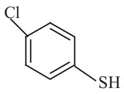
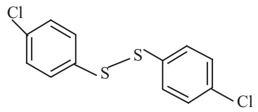
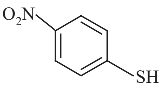
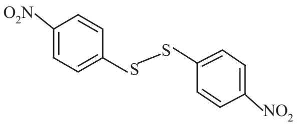
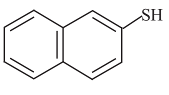
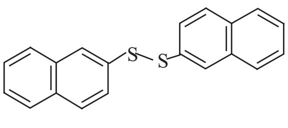
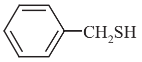
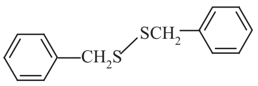
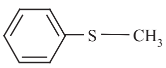
As shown in the Table 2 aliphatic and aromatic thiols were oxidised in water in excellent yield (Table 2, entries 1–9). Aliphatic thiols (Table 2, entries 1–3), aromatic thiols (Table 2, entries 4–8) and benzylthiol (Table 2, entry 9) underwent oxidation with 1,4-dichloro-1,4-diazoniabicyclo[2,2,2]octane bischloride in water to afford the corresponding disulfides in high yields within very short reaction times. These mild conditions without any catalysts and any co-solvent allow the oxidation of thiols to disulfide. Under these reaction conditions sulfides are not oxidised. Thus phenyl methyl sulfide did not give any oxidised product even after 4 hours (Table 2, entry 10).



R= Aliphatic or aromatic

Scheme 2

Table 2 Oxidation of thiols to disulfides with the 1,4-dichloro-1,4-diazoniabicyclo[2,2,2]octane bischloride

Entry	Substrate	Product[a]	Time/min	Yield/%	M.p./°C or b.p./°C Torr	
					Found	Reported[18]
1			25	98	113/19	114–115/19[19a]
2			25	96	91–92/760	92/760[19b]
3			55	90	143–144	144–145[19b]
4			45	96	44–45	45[19b]
5			18	90	44	43–44[19c]
6			35	92	73	72–75[19d]
7			45	93	176–177	177–178[19e]
8			30	93	143	142–145[19f]
9			40	91	70–71	71–72[19c]
10			N.R.	240	N.R.	

[a]All products were characterised spectroscopically (^{1}H NMR, IR) and showed physical and spectral data in accordance with their expected structure and by comparison with authentic sample.

[b]The yields refer to isolated products.

The 1,4-diazabicyclo[2,2,2]octane which is formed in this reactions, is recovered almost quantitatively and can be rechlorinated and reused several times. Moreover, since there is the possibility of recovering and reusing the DABCO and water as a solvent, this method might be useful in large-scale synthesis. We have carried out the oxidation of an oxime, phenylhydrazone, semicarbazone and thiol under our optimum reaction conditions on a larger scale and obtained almost the same yields as in the small-scale reaction.

In conclusion, this paper describes the use of 1,4-dichloro-1,4-diazoniabicyclo[2,2,2]octane bischloride for the deprotection of oximes, phenylhydrazones semicarbazones and oxidation of thiols in water. The advantages of this method are the use of water as a solvent, the ease of work up, short reaction time, high yield, and the use of a reagent that is easy to handle and inexpensive.

Experimental

All the starting materials were purchased from Fluka and Merck. The reaction was monitored by TLC using silica gel plate and the products were identified by comparison of their spectra and physical data with those of the authentic samples. ^{1}H NMR spectra were recorded at 300 MHz on a JEOL spectrometer with tetramethylsilane (Me_4Si) as an internal reference and $CDCl_3$ as the solvent for aldehydes, ketones and disulfides. IR spectra were recorded on Pye-Unicam SP 1100 spectrophotometer. Elemental analysis was performed on a LECO 250 instrument. All yields refer to isolated products.

Preparation of 1,4-dichloro-1,4-diazoniabicyclo[2,2,2]octane bischloride
Chlorine gas was bubbled for 10 min at room temperature through a solution of 1,4-diazabicyclo[2,2,2]octane (DABCO) (6.72 g, 60 mmol) in chloroform (100 ml). The solvent was evaporated under reduced pressure to afford almost pure product (14.94 g, 98%), m.p. decomp. 125–130°C. Anal. Calcd for $C_6H_{12}N_2Cl_4$: C, 28.3; H, 4.7; N, 11.0; Cl, 55.9. Found: C, 27.9; H, 4.6; N, 11.2; Cl, 55.6. ^{1}H NMR (D_2O) δ 3.2 (s, 12H, $6CH_2$). ^{13}C NMR (D_2O) δ 91.3. IR 2800, 1500, 1380, 1000 and 750 cm^{-1}.

General procedure for the cleavage of C=N bonds and the oxidation of thiols
An appropriate substrate (4 mmol) and 1,4-dichloro-1,4-diazoniabicyclo[2,2,2]octane bischloride (0.51 g, 2.0 mmol) was added to H_2O (12 ml) in a flask. The reaction mixture (pH = 7) was warmed to 50°C. After completion of the reaction (TLC), ether was added to the reaction mixture and the extract was washed with a solution of 1% HCl (1 × 10 ml). The aqueous layer (**1**) was separated and the organic layer was washed with 3% sodium bicarbonate (2 × 10 ml) and water (1 × 10 ml) respectively. The organic solution was dried over $MgSO_4$, filtered and evaporated to dryness under reduced pressure to afford the corresponding carbonyl compound or disulfide.

Regeneration of 1,4-diazabicyclo [2,2,2] octane(DABCO)
The aqueous layer (**1**) from above procedure was further treated with 10% sodium bicarbonate solution (2 × 10 ml) and 1,4-diazabicyclo [2,2,2] octane (DABCO) was extracted with ether (2 × 10 ml). The ether layer was dried over $MgSO_4$, and evaporated to give pure 1,4-diazabicyclo [2,2,2] octane (0.21 g, 95%), which can be chlorinated and reused several times.

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