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Efficient Oxidative Coupling of Thiols into Disulfides Using *N-tert*-Butyl-*N*-chlorocyanamide

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Reaction of aliphatic/aromatic/heterocyclic thiols with *N-tert*-butyl-*N*-chlorocyanamide in presence of sodium bromide is described. The reaction was very rapid and resulted in the formation of disulfides in excellent yields under mild conditions.

The synthesis of the disulfides has attracted enormous amount of interest owing to their great significance in organosulfur chemistry and have played an important role in biological and chemical processes.[1] Disulfides have also been used in the sulphenylation of enolates and other anions.[2] Selective oxidative coupling of thiols into the corresponding disulfides is the most studied transformation in this class. This transformation can be achieved even using atmospheric oxygen,[3] which is the most convenient and inexpensive source, and water is the only by-product. However, air-oxidation of thiols requires considerable time and the conditions vary for each thiol. Therefore, work has been focused on the development of reagents/catalyst with high activity, selectivity, control oxidation rate, and broad substrate generality, which lead to practical, efficient, and environmentally friendly chemical synthesis of the disulfides. To achieve this goal, a plethora of reagents/methods, such as DMSO,[4] halogens,[5] metal ions,[6] $FeCl_3$,[7] nitrogen(V) oxide,[8] hypochlorites,[9] sodium perborate,[10] H_2O_2,[11] transition-metal-salt-catalyzed air oxidation,[12] morpholine–iodine complex,[13] PCC,[14] $KMnO_4$-mediated reactions,[15] and CsF–Celite,[16] have been investigated. Enzymatic[17] and electrochemical[18] methods are also known to be useful for this oxidative transformation. Recently, new reagents[19] have also been reported to bring about the same transformation. None of these methods completely meet the requirements and suffer from several disadvantages, such as use of expensive and toxic reagents, metal oxidants, low yields, long reaction times, and require high/low reaction temperatures. Moreover, under the conditions described, thiols are not selectively formed and also are susceptible to over oxidation that leads to over oxidized byproducts, such as sulfoxides and sulfonic acids.[20] Furthermore, the reported methods are also capable of reacting with other oxidizable sites, such as hydroxy and nitro groups. Therefore, it is still desirable to develop an efficient oxidant with high stability, selectivity, low toxicity, and ready availability.

In continuation of our on-going research program on the development of new regents/methods, we explored the versatility of *N-tert*-butyl-*N*-chlorocyanamide in organic synthesis,[21] and herein, we report a facile, cheap, extremely rapid, and high yielding procedure for the synthesis of disulfides from thiols using reagent **2**. The reaction takes place in less than 5 min in a solution of sodium bromide and acetone at room temperature with excellent yields (Scheme 1).

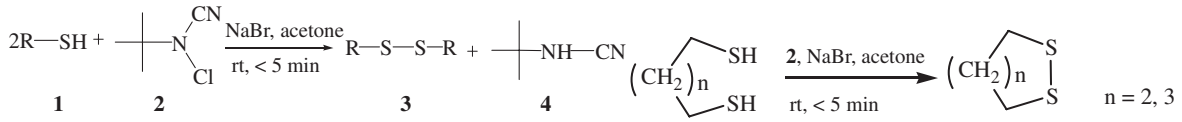
Under the same conditions, wide varieties of aliphatic, aromatic, and heterocyclic thiols were efficiently converted into the corresponding disulfides in excellent yields and gave similar results. (Table 1)

In general, aromatic/heterocyclic thiols need slightly longer times to complete the reaction as compared to aliphatic thiols. The great advantage of this method is that aromatic/heterocyclic motifs attached to the thiols have no effect on the progress of the reaction and the reaction takes place immediately upon the addition of the oxidant. Furthermore, functionalities, like hydroxy, carboxyl, nitro, and benzyl groups do not interfere and are not oxidized. Sterically hindered thiols, such as *tert*-butyl thiol (Table 1, Entry 6) and 2,6-dimethylbenzenethiol (Table 1, Entry 14), were successfully converted into the corresponding disulfides in excellent yield in less than 5 min. Hindered thiols were found to react at the same rate as to unhindered thiols.

In other words, for the synthetic transformation of thiols to disulfides, it is evident that this method is very rapid, selective, safe, and does not require expensive reagents. Furthermore, reactions also take place at room temperature with excellent yields which is an added advantage over other methods. Large ring disulfides are difficult to synthesize due to competing inter molecular reactions. Intramolecular reactions produce cyclic disulfides (Table 1, Entries 17 and 18), whereas the intermolecular reactions yield oligomers. Using this method, we also carried out the oxidation of dithiols to cyclic disulfides successfully in good yield (Scheme 1).

Toxicological properties of reagent **2** and its dechlorinated product i.e. *tert*-butylcyanamide **4** were carried out on male mice using 1% hydroxypropyl cellulose. Mice were kept on observation for 14 days with one time dose. Toxicological properties of **2** and **4** were determined in terms of LD_{50} and found to be 283 and 336 mg kg^{-1} respectively which are in acceptable limits.

Stability of reagent **2** was also examined by keeping at 25–35 °C over a period of two years and found that there was no change in its IR spectrum as well as on TLC. Chlorine content of **2** was also determined periodically by iodometric method[22] and the available chlorine was found between 25.0 to 26.5% (Calcd. 26.6%).



Scheme 1. Oxidation of thiols to disulfides by **2**.

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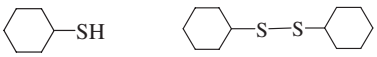
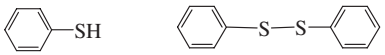
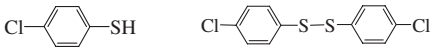
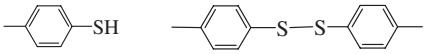
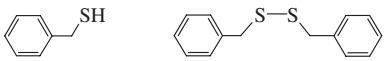
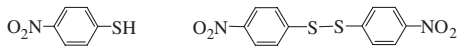
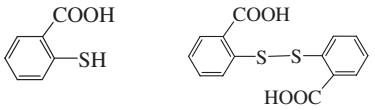
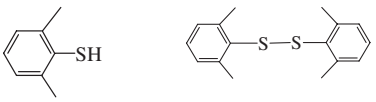
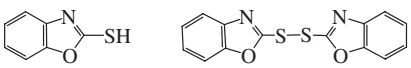
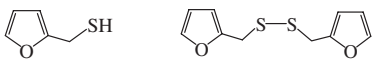
Table 1. Oxidation of Thiols into Disulfides Using **2**

Entry	Thiols	Disulfides	Yield[a)]/%
1	C_2H_5SH	$C_2H_5S–SC_2H_5$	95
2	$(CH_3)_2CHSH$	$(CH_3)_2CHS–SCH(CH_3)_2$	94
3	C_4H_9SH	$C_4H_9S–SC_4H_9$	96
4	$C_5H_{11}SH$	$C_5H_{11}S–SC_5H_{11}$	93
5	$HOCH_2CH_2SH$	$HOCH_2CH_2S–SCH_2CH_2OH$	92
6			90
7			96
8			98
9			93
10			95
11			95
12			92
13			90
14			94
15			92
16			95
17[b)]	$HS(CH_2)_4SH$		65
18[b)]	$HS(CH_2)_5SH$		72

a) Yields refer to isolated products. b) Reaction was carried out in excess of acetone (dilution effect).

In summary, we demonstrated that *N-tert*-butyl-*N*-chlorocyanamide is a highly efficient and inexpensive reagent for the oxidation of aliphatic/aromatic/heterocyclic thiols to the corresponding disulfides. This reagent oxidizes thiols into the disulfides under very mild conditions in almost quantitative yields and irrespective of the presence of other functional groups attached to thiols. In addition, it was found that cyclic disulfides could be synthesized from dithiols in good yield. We consider that this method is a useful addition to the array of procedures for the oxidation of thiols into disulfides.

Experimental

General. Melting points were determined with capillary and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker (400 and 100 MHz respectively) spectrometer (chemical shifts in δ, ppm) against TMS as internal standard; IR spectra as KBr pellet on a Perkin-Elmer model BXII FT-IR spectrophotometer (ν, cm^{-1}).

General Procedure for the Synthesis of Disulfides from Thiols. In a typical reaction, a solution of *N-tert*-butyl-*N*-chlorocyanamide[23] (1.0 g, 7.54 mmol) and sodium bromide (1 equiv) in acetone (20 mL) was stirred for 2 min at room temperature, and then the thiol (2 equiv) was added to the reaction mixture. The color of reaction became yellow or brown, which disappears immediately, indicating the completion of the reaction. Gas chromatographic analysis of the reaction mixture showed complete conversion of the thiols to disulfides. *tert*-Butylcyanamide formed as a side product due to the dechlorination of the reagent. The reaction mixture was filtered and diluted with dichloromethane (20 mL). The combined layer was washed with water (2×20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent on a rotary evaporator gave a mixture of disulfides and *tert*-butylcyanamide (bp 114–115 °C/14 mmHg). Pure disulfides were obtained either by distillation under vacuum (in case of liquid products) or recrystallization in DCM/Pet. ether (40–60 °C) (in case of solid products). All the products were compared with authentic samples and gave satisfactory IR and NMR data. Some of representative spectra data of the disulfides are included here.

Dibutyl Disulfide:[19b] Bp 228–232 °C, IR (KBr) 2959, 2927, 2874, 1465, 1411, 1380, 1270, 1217, 1133, 1090, 911 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 0.87–0.97 (m, 6H), 1.31–1.52 (m, 4H), 1.55–1.73 (m, 4H), 2.65 (t, 4H, $J = 7$ Hz). ^{13}C NMR ($CDCl_3$) δ 13.92, 21.62, 31.25, 38.96.

Di-*tert*-butyl Disulfide:[5b] Bp 199–202 °C, IR (KBr) 2960, 2922, 2895, 2864, 1455, 1388, 1360, 1217, 1160, ^{1}H NMR ($CDCl_3$) 1.31 (s, 9H), ^{13}C NMR ($CDCl_3$) 30.44, 45.97.

Dicyclohexyl Disulfide:[19b] Bp 163–164 °C, IR (KBr) 2925, 2850, 1449, 1261, 998 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.14–1.34 (m, 10H), 1.52–1.62 (m, 2H), 1.73–1.81 (m, 4H), 1.96–2.03 (m, 4H), 2.61–2.69 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 25.64, 26.00, 32.80, 49.93.

Diphenyl Disulfide:[16] Mp 59–60 °C, IR (KBr) 3071, 1575, 1472, 741, 687 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 7.27–7.30 (m, 2H), 7.34–7.41 (m, 4H), 7.51–7.54 (m, 4H). ^{13}C NMR (DMSO-d_6) δ 127.17, 127.57, 129.46, 135.75.

***p*-Tolyl Disulfide:** Mp 43–44 °C, IR (KBr) 3021, 2972, 2917, 2864, 1890, 1633, 1564, 1594, 1488, 1448. ^{1}H NMR ($CDCl_3$) δ 2.28 (s, 6H), 7.05–7.60 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 21.55, 128.51, 129.70, 135.42, 137.37.

Dibenzyl Disulfide:[19b] Mp 69–72 °C, IR (KBr) 3051, 3030, 1494, 1453, 758, 696 cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 3.71 (s, 4H), 7.24–7.29 (m, 4H), 7.30–7.37 (m, 6H). ^{13}C NMR (DMSO-d_6) δ 41.61, 127.27, 128.39, 129.36, 137.27.

Di-*p*-nitrophenyl Disulfide:[16] Mp 178–180, °C, IR (KBr) 3032, 2931, 1610, 1535, 1349, 860. ^{1}H NMR ($CDCl_3$) δ 7.64–8.19 (m, 8H). ^{13}C NMR ($CDCl_3$) δ 124.49, 126.30, 144.16, 146.98.

1,2-Dithiane:[5b] Mp 33–34 °C, IR (KBr) 2924, 2846, 1432, 1407, 1323, 1302, 1279, 1225, 1131, ^{1}H NMR ($CDCl_3$) δ 1.71–2.00 (4H, m), 2.62–2.90 (4H, m), ^{13}C NMR ($CDCl_3$) δ 27.80, 33.35.

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23 For the synthesis of *N*-*tert*-butyl-*N*-chlorocyanamide, see the Ref. 21c.