

Note

Oxidative coupling of thiols to disulphides

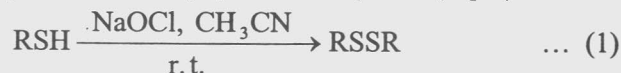
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Two rapid and inexpensive procedures have been reported for the oxidative coupling of thiols to disulphides namely, sodium hypochlorite in acetonitrile and with *t*-butyl chloride/K₂CO₃ in DMF at ambient temperature.

Formation and cleavage of disulphide bond is a biologically important process in connection with enzymatic oxidation-reduction reactions. The cystein-cystine interconversion has a significant role in biochemistry. The conversion of thiols to disulphides is thus of importance in chemical and biological redox reactions. Many reagents are known to bring about the oxidation of thiols to disulphides¹. We have been working on the oxidations of a variety of substrates using inexpensive sodium hypochlorite².

In this note we report that thiols undergo very rapid oxidative coupling with aqueous sodium hypochlorite (0.5 M), a very inexpensive reagent, in acetonitrile at room temperature to give disulphides in nearly quantitative yields (Eq. 1).

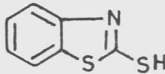


R=aryl, aralkyl, heteroaryl and fatty

The starting material disappeared in 5 min. as monitored by TLC and reactions were worked-up immediately. But if reactions were allowed to continue for longer time other products also appeared probably due to subsequent oxidations. A variety of thiols e.g., aryl, aralkyl, heteroaryl and fatty thiols were oxidatively coupled to symmetrical disulphides in quantitative yields in a very fast reaction. The oxidations carried out in methanol and dioxane were not clean. These results are listed in Table I.

We also report herein that the oxidative coupling of thiols to disulphides can be achieved un-

Table I—Oxidative coupling of thiols with NaOCl in CH₃CN
{Molar ratio of RSH:NaOCl=1:2; Reaction time^a=5 min}

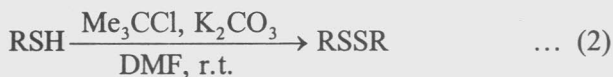
Substrate RSH	% yield (RSSR) ^b	m.p., (lit. ⁴ m.p.) (°C)
C ₆ H ₅ SH	92	57-59 (60)
C ₆ H ₅ CH ₂ SH	81	68-70 (71-72)
<i>p</i> -ClC ₆ H ₄ SH	98	68-69 (70-71)
<i>p</i> -MeOC ₆ H ₄ SH	92	41-43 (44-45)
CH ₃ (CH ₂) ₁₁ SH	90	- ^c (30-31)
CH ₃ (CH ₂) ₁₃ SH	93	47-48 (48-50)
	75	177-80 (186)
<i>p</i> -BrC ₆ H ₄ SH	55	90-92 (93-95)
HOCH ₂ CH ₂ SH	57	- ^c (17)

^aMonitored by complete disappearance of starting material on TLC and Ellman's reagent.

^bProducts were identified by m.p. and ¹H NMR.

^cLiquid at room temperature.

der very mild conditions by treatment with *t*-butyl chloride and freshly ignited K₂CO₃ in dry DMF at ambient temperature. The oxidative coupling of alkyl, aryl, aralkyl and fatty thiols to disulphides has been carried out under these conditions (Eq. 2).



R=aryl, aralkyl, heteroaryl and fatty

The molar ratio of substrate to *t*-butyl chloride varies with the thiol. These results are listed in Table II. The reactions are chemoselective as methoxy, chloro and bromo groups are not affected and no over oxidized products were obtained. This is a very useful procedure for oxidative coupling of thiols as most other groups are unaffected by this reagent. Therefore thiols sensitive to acidic or basic reagents can be easily coupled with this reagent. Treatment of thiols with primary and secondary halides in the presence of K₂CO₃/DMF leads to the formation of sulphides³.

Experimental Section

Melting points were measured on a Tropical Labequip apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Model 621 and

Table II—Oxidative coupling of thiols with *t*-butyl chloride/K₂CO₃ in DMF

Substrate (RSH)	Molar ratio ^a RSH: <i>t</i> -BuCl	Reaction time (hr) ^b	(RSSR) ^c yield (%)	m.p. (lit. ⁴ m.p.) (°C)
C ₆ H ₅ SH	1:3	4	92	57-59 (60)
C ₆ H ₅ CH ₂ SH	1:2	1	88	69-71 (71-72)
<i>p</i> -ClC ₆ H ₄ SH	1:4	4	83	68-70 (70-71)
<i>p</i> -BrC ₆ H ₄ SH	1:4	4	87	88-91 (93-95)
<i>p</i> -MeOC ₆ H ₄ SH	1:6	5	88	40-42 (44-45)
<i>p</i> -ClC ₆ H ₄ CH ₂ SH	1:6	7	77	53-56 (59)
<i>o</i> -HOOC ₆ H ₄ SH	1:4	5	88	284-87 (287-89)
CH ₃ (CH ₂) ₁₁ SH	1:3	4	85	- ^d (30-31)
CH ₃ (CH ₂) ₁₅ SH	1:3	6	85	47-48 (48-50)
CH ₂ =CHCH ₂ SH	1:10	17	59	- ^d
HOCH ₂ CH ₂ SH	1:4	7	51	- ^d (17)

^aAll the reactions were carried out in the presence of freshly ignited K₂CO₃ (1.5 molar excess of to substrate).

^bMonitored by complete disappearance of starting material by TLC and Ellman's reagent.

^cProducts were identified by m.p. and ¹H NMR.

^dLiquid at room temperature.

Shimadzu model 435 spectrophotometers; ¹H NMR spectra on a Perkin-Elmer model R-32 at 90 MHz and on Hitachi FT-NMR at 60 MHz (chemical shifts in δ , ppm) with TMS as the internal standard. Sodium hypochlorite (Aldrich), DMF and acetonitrile (E. Merck) were used in all the reactions; the concentration of sodium hypochlorite was estimated by iodometry⁵. The thiols were obtained commercially or prepared by known methods.

General procedure for oxidations with sodium hypochlorite. To the mixture of thiol (10 mmoles) and acetonitrile (5 mL) placed in a 50 mL RB flask, 40 mL of 0.5 M sodium hypochlorite solution (20 mmoles) was added and the contents were stirred at ambient temperature. Almost immediately some solid precipitated out. The reaction mixture was worked-up by acidifying with 6N HCl. The solid was filtered under pressure. The filtrate was extracted with CH₂Cl₂ (3×10 mL). The combined extract was dried over anhyd. MgSO₄ and concentrated using vacuum rotary evaporator to give more of the disulphide. A portion of the solid was recrystallized and analyzed by m.p. and ¹H NMR spectra.

General procedure for oxidations with *t*-butyl chloride/K₂CO₃. To the mixture of thiol (10 mmoles) and dry DMF (4 mL) placed in a 50 mL RB flask, *t*-butyl chloride and freshly ignited K₂CO₃ (see Table II for molar ratios) were added.

The system was sealed with a mercury trap and the contents were stirred at ambient temperature. The progress of the reaction was monitored by thin layer chromatography. After complete disappearance of the starting material, the contents of the reaction flask were poured into water (~100 mL) and extracted with ether (3×10 mL). The combined extract was dried over anhyd. MgSO₄ and concentrated on a vacuum rotavapour to yield the crude disulphide. A portion of the solid was recrystallized and analyzed by m.p. and ¹H NMR spectra.

Acknowledgement

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