



## Cobalt Assisted Cleavage of S-S Bonds and a Base-free Synthesis of Mercapturic Acids

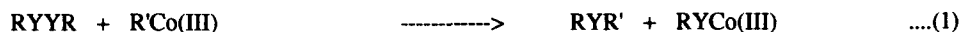
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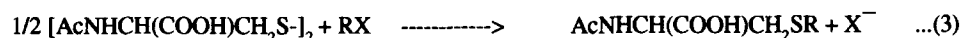
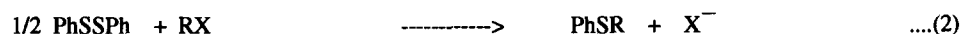
**ABSTRACT:** Base free transformation of PhSSPh to sulfides, PhSR (R= alkyl, benzyl, allyl, acyl) and N-acetyl-L-cystine to mercapturic acids [AcNHCH(COOH)CH<sub>2</sub>SR, R= alkyl, benzyl, allyl, acyl] have been achieved using Zn / cat. CoCl<sub>2</sub> / organic halide in MeCN at room temperature.

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Cleavage of -S-S- bond in disulfides can be achieved by three major routes<sup>1</sup>: oxidative cleavage,<sup>2</sup> nucleophile assisted cleavage<sup>3</sup> and radical assisted cleavage.<sup>4</sup> We became interested in the last route and along with others have demonstrated the utility of radical trapping in the reaction of preformed organocobalt(III) complexes with dichalcogenides [Eqn. 1].<sup>5,6</sup> From a synthetic point of view, two major limitations of this reaction are: (i) the necessity to synthesize the organometallic complex and (ii) loss of half-unit of disulfide as thiometal complex. Close to the above mentioned effort, we have recently speculated<sup>7</sup> that transient organocobalt(III) species bearing weak-field ligand(s) can be generated in-situ. This prompted us to explore and devise an one-pot and base-free conversion of disulfides to sulfides [Eqn.2] using an in-situ generated organocobalt(III) reagent and further utilize the methodology for the synthesis of mercapturic acids<sup>8</sup> [Eqn. 3]. This communication illustrates our results in this direction.



Co = Co(dmgh)<sub>2</sub>Py, Y = S, Se, Te



The strategy delineated here includes three distinct chemical reactions: (a) one electron reduction of cobalt(II) to cobalt(I) by zinc metal,<sup>9</sup> (b) oxidative alkylation of cobalt(I) by alkyl halides (RX) to R-Co(III) and (c) reaction of R-Co(III) with disulfide liberating Co(II) and product sulfide. In other words, the strategy invokes a tandem process involving Co(II), Co(I) and Co(III) intermediates and is also catalytic with respect to cobalt (Scheme 1). Thus reaction of diphenyldisulfide **1** (2.3mM) with MeI (5mM) in the presence of zinc dust (2.8mM), cobalt(II)chloride (0.23mM) in degassed MeCN at ambient temperature and under an inert atmosphere furnishes, after 0.5 h, phenylmethylsulfide in 90% isolated yield [Table 1].<sup>10</sup> Similar reactions of **1** with alkyl, allyl, benzyl, vinyl and acyl halides afford the corresponding sulfides in moderate to excellent

yields.<sup>11</sup> Attempted reactions of **1** with arylhalides and cyclohexylbromide met with failure, the disulfide being recovered quantitatively. Control experiments further reveal that PhSSPh alone cannot be activated (via oxidative-addition mode or reduction to PhS<sup>-</sup>) by Zn or Co(II) or Zn/Co(II) combination.<sup>12</sup>

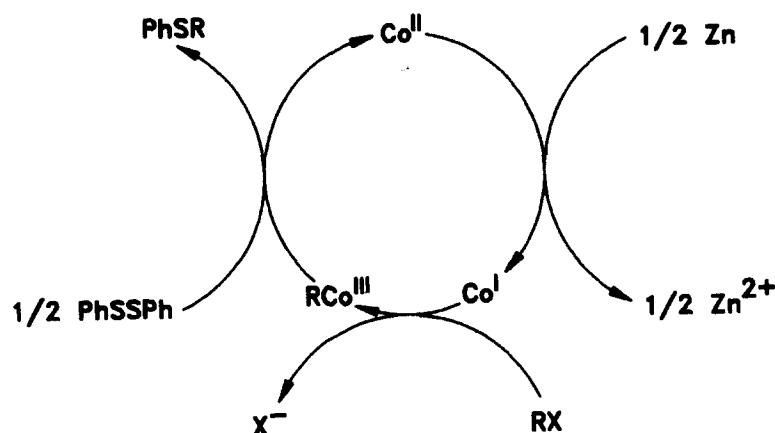
**Table 1:** Conversion of Diphenyldisulfide to Phenylsulfides with zinc and CoCl<sub>2</sub> in MeCN (ref. 10).

$$\text{PhSSPh} + 2\text{RX} \longrightarrow 2\text{PhSR}$$

R	X	Time(h)	Isolated yield (%)
CH <sub>3</sub>	I	0.5	90
PhCH <sub>2</sub>	Br	1	92 <sup>a</sup>
	Cl	12	95
CH <sub>2</sub> CH=CH <sub>2</sub>	Br	1	90
PhCH=CHCH <sub>2</sub>	Cl	8	70
PhCH=CH	Br	6 <sup>b</sup>	35 <sup>c</sup>
Ph <sub>3</sub> C	Cl	4	72
PhCO	Cl	8	65
Ph <sub>2</sub> CH	I	2	70

<sup>a</sup> 4% PhCH<sub>2</sub>CH<sub>2</sub>Ph was obtained ; <sup>b</sup> refluxing MeCN ; <sup>c</sup> recovered PhSSPh (50%)

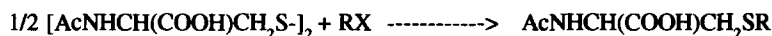
**Scheme 1**



Having achieved the alkylation of disulfide we desired to extend the methodology for the synthesis of S-alkylated-N-acetyl-L-cysteines, trivially known as mercapturic acids, from in situ generated N-acetyl-L-cysteine. Synthetic methods for S-alkyl mercapturic acid derivatives heretofore have relied on the nucleophilic attack of the cysteine sulfur on an electrophilic centre assisted by bases.<sup>13</sup> S-aryl conjugates have been synthesised by various methods.<sup>14</sup> A palladium catalysed synthesis of S-aryl mercapturic acid methyl esters has been

reported recently.<sup>15</sup> In our methodology, N-acetyl-L-cystine is directly converted to the corresponding mercapturic acids using zinc and catalytic cobalt(II)chloride and various halides [allyl, benzyl and acyl] in degassed MeCN at ambient temperature [Table 2].<sup>16</sup> In the reaction of chloroacetylchloride exclusive S-acylation is observed. This procedure being base free and operating under ambient conditions is expected to be synthetically attractive, in particular for halides bearing base sensitive functionalities.

**Table 2 :** Formation of S-conjugates of N-acetyl-L-cysteine in MeCN (ref. 16).



R	X	Isolated yield (%)
CH <sub>3</sub>	I	52
PhCH <sub>2</sub>	Br	70
CH <sub>2</sub> =CHCH <sub>2</sub>	Br	60
PhCO	Cl	75
Ph <sub>3</sub> C	Cl	66
ClCH <sub>2</sub> CO	Cl	59 <sup>a</sup>
Ph <sub>2</sub> CH	I	62

<sup>a</sup> S-acyl-substituted product obtained exclusively

In conclusion, we have demonstrated a new route for the synthesis of sulfides from disulfides via in-situ generated organocobalt(III) intermediate. Efforts are underway to trap such intermediate to conclusively prove the catalytic cycle.

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#### References and notes

- For recent reviews, see: (a) Rayner, C.M. *Contemp. Org. Synth.* **1995**, *2*, 409-440. (b) Rayner, C.M. *Contemp. Org. Synth.* **1994**, *1*, 191-203. (c) Solladie, G. *Comprehensive Org. Synth.* Trost, B.M.; Fleming, I. Eds.; Pergamon: Oxford, **1991**, Vol.6, 133-170.
- (a) Kumar, R.; Mabrouk, H.E.; Tuck, D.G. *Dalton Trans.* **1988**, *4*, 1045. (b) Taniguchi, Y.; Maruo, M.; Takaki, K.; Fujiwara, Y. *Tetrahedron Lett.* **1994**, *35*, 7789.
- Kobanyane, S.T.; Majee, D.I. *Can. J. Chem.* **1992**, *70*, 2758.
- Pryor, W.A.; Kennedy, S. *J. Am. Chem. Soc.* **1970**, 2731. (b) Haszeldine, R.N.; Rigby, R.B.; Tipping, A.E. *Perkin Trans. 1.* **1972**, 159.
- (a) Das, I.; Roy, S. *J. Organomet. Chem.* **1994**, *467*, 223. (b) Das, I.; Chowdhury, S.; Ravikumar, K.; Roy, S.; Gupta, B.D. *J. Organomet. Chem.*, (in press).
- (a) Deniau, J.; Duong, K.N.V.; Gaudemer, P.; Johnson, M.D. *Perkin Trans. 2.* **1981**, 393. (b) Kijima, M.; Miyamori, M.; Sata, T. *J. Org. Chem.* **1988**, *53*, 4147. (c) Tada, M.; Sugano, K.; Yoshiara, T. *Bull. Chem. Soc. Japan* **1995**, *68*, 2969. (d) Beak, P.; Sullivan, T.A. *J. Am. Chem. Soc.* **1982**, *104*, 4450. (e) Baldwin, J.E.; Addington, R.M.; Bohman, M.J. *Chem. Commun.*

- 1985, 357. (f) Patel, V.F.; Pattenden, G. *Tetrahedron Lett.*, **1987**, *28*, 1451. (g) Branchaud, B.P.; Meier, M.S.; Malekzadeh, N.M. *J. Org. Chem.*, **1987**, *52*, 212.
7. Chowdhury, S.; Samuel, P.M.; Das, I.; Roy, S. *Chem. Commun.* **1994**, 1993.
  8. Mercapturic acids are S-alkylated derivatives of N-acetyl-L-cysteine. The biosynthesis of mercapturic acids involves reaction of an electrophile with the sulfhydryl group of glutathione (...Glu-Cys-Gly) followed by enzymatic hydrolysis of the Glu-Cys and Cys-Gly bonds and N-acetylation. Contemporary interests in mercapturic acids derives largely from the fact that their excretion implies the previous presence in the animal of an electrophile, many of which have been associated with toxic effects on living cells. Since these acids are not readily available general methods for their preparation, as authentic standards, is of interest, please see: (a) Mannervick, B. *Adv. Enzymol. Relat. Areas Mol. Biol.* **1985**, *57*, 357-406. (b) Jakoby, W.B.; Stevens, J.; Duffel, M.W.; Weisiger, R.A. *Rev. Biochem. Toxicol.* **1980**, *15*, 97-115.
  9. For example, see: Schrauzer, G.N.; Holland, R.J. *J. Am. Chem. Soc.* **1971**, *93*, 4060.
  10. Zinc dust (3mM) was added to a degassed solution of PhSSPh (2mM) and cobalt(II)chloride (0.2mM) dissolved in MeCN (5mL) and the system flushed with nitrogen. Halide (4.2mM) in degassed MeCN (5mL) was administered dropwise and the mixture stirred at room temperature. On completion (0.5-8h; TLC inf.) MeCN was removed under reduced pressure and the mixture purified by column chromatography (silica-gel 60-120, eluent : hexane-EtOAc, 95:5) to obtain pure sulfides.
  11. In blank experiments the effect of various parameters were studied, the results of which are summarised below. (i) No significant reaction was observed when benzylbromide and **1** were stirred for 24 hrs in the absence of zinc. (ii) Reaction in absence of CoCl<sub>2</sub>, after 24 hrs, furnished a complicated mixture comprising of unreacted PhSSPh, sulfide PhSCH<sub>2</sub>Ph, PhSH, PhCH<sub>2</sub>CH<sub>2</sub>Ph and PhCH<sub>2</sub>Br in 25%, 43%, 14%, 10% and 8% yields respectively vide NMR. (iii) When benzylbromide was stirred in the presence of zinc and CoCl<sub>2</sub> for 24 hrs bibenzyl (52%) was obtained alongwith unreacted PhCH<sub>2</sub>Br.
  12. It is interesting to note that while In, Sn, Sm can cleave disulfide bond, Zn, Tl, Ga cannot, see ref. 2a.
  13. van Bladderren, P.J.; Buys, W.; Breimer, D.D.; van der Gen, A. *Eur. J. Med. Chem.* **1980**, *15*, 495. (b) McKinney, L.L.; Picken, J.C.; Weakely, R.B.; Eldridge, A.D.; Campbell, R.E.; Cowan, J.C.; Beiler, H.E. *J. Am. Chem. Soc.* **1959**, *81*, 909.
  14. (a) Parke, D.V.; Williams, R.T. *Biochem. J.* **1951**, *48*, 624. (b) Hickman, R.J.S.; Christie, B.J.; Guy, R.W.; White, T.J. *Aust. J. Chem.* **1985**, *38*, 899.
  15. Ciattini, P.J.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1995**, *36*, 4133.
  16. N-acetyl-L-cystine was generated in-situ from N-acetyl-L-cysteine (2mM) and cobalt(II)chloride (0.2mM) in MeCN (10mL) [2 hrs, ref. 7]. The solution was degassed and zinc dust (3mM) was added and the mixture flushed with nitrogen. Halide (2.2mM) in degassed MeCN (5mL) was added dropwise and the mixture stirred for 2 hrs at room temperature under an inert atmosphere. MeCN was removed under reduced pressure, the residue dissolved in minimum volume of water, acidified with 2N HCl and H<sub>2</sub>S was bubbled through the solution whence a black precipitate was obtained. This precipitate was filtered, filtrate saturated with sodiumchloride and extracted with ethylacetate at 50°C. The organic layer was dried with magnesium sulfate, concentrated and the residue purified by column chromatography [silica-gel 60-120, eluent : benzene:methanol: aceticacid - 7:2:1] to obtain the desired mercapturic acid. For benzoyl chloride reaction was worked up after 4 hrs.

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