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An efficient metal-free synthesis of organic disulfides from thiocyanates using poly-ionic resin hydroxide in aqueous medium

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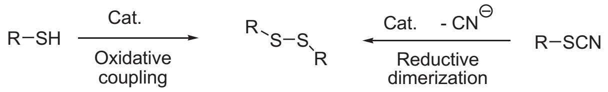
ABSTRACT

An efficient and metal-free method is described for the preparation of organic disulfides from alkyl and acyl methyl thiocyanates in the presence of poly-ionic resin hydroxide in aqueous medium. Further extension of this protocol has been tested using two different organyl thiocyanates to prepare unsymmetrical disulfides.

Organic disulfides are useful compounds of widespread occurrence possessing unique and diverse chemistry in the synthetic, biochemical, and agrochemical areas.[1] Disulfide-linked aggregates ubiquitously occur in proteins and many other bioactive molecules. Disulfide bonds play an important role in the folding and stability of some proteins.[2] Industrially, disulfides find vast applications as vulcanizing agents for rubbers and elastomers, contributing them considerable tensile strength.[3] Numerous reagents and metal catalysts have been developed to oxidize thiols to disulfides under controlled conditions.[4] Disulfides can also be prepared by electrochemical approach via a sulfenium cation under conditions of constant current.[5] Apart from thiols, organic thiocyanates are known to undergo reductive dimerization producing organic disulfides promoted by several catalysts leaving cyanide ion (Scheme 1).[6]



Scheme 1.

In laboratory preparation, either base-promoted (e.g., NaOH or NH_3),[6b] or metal-catalyzed reductive dimerization of organic thiocyanates (e.g., SmI_2, $TiCl_4$/Sm, or tetrathiomolybdate),[7a–c] remains the major choice for the synthesis of disulfides. In general, oxidative coupling of thiol to disulfide often leads to an appreciable formation of trimer and polymers. On the other hand, the use of metal catalysts for the reductive dimerization of organic thiocyanate is associated with contamination with the products and also poses a threat to the environment. Although base-promoted dimerization of thiocyanate has been successful in simple cases, there are no similar studies with acyl methyl or other base-sensitive thiocyanates except conversion of acid chlorides to acyl disulfides using elemental sulfur.[7d,e] Direct conversion of alcohol to disulfide in the presence of NH_4SCN under Mitsonobu conditions requires other reagents like heteroaromatic azo compounds, PPh_3, etc. and is associated with the formation of other products.[8] Since organic disulfides are useful compounds, it is necessary to develop mild, metal-free, and aqueous eco-friendly conditions for their preparation from organyl thiocyanates. Use of polymeric reagents offers a two-fold advantage: first, the reaction can be driven to completion using excess amounts of reagents and secondly, the reagent can be removed quantitatively after the reaction by simple filtration. In conjunction with our interest in solid-phase hetero bond-forming reactions,[9a,b] and use of poly-ionic resins in organic reactions and catalysis,[9c,d] we report herein a mild, efficient, and metal-free aqueous protocol for the preparation of organic disulfides from alkyl (or acyl methyl) thiocyanates in the presence of ion-exchange resins, Amberlyst® A-26(OH). The poly-ionic resins are recovered by simple filtration, washed, and can be recycled with appreciable conversions of thiocyanates. Moreover, a comparison with other homogeneous bases (NaOH, NH_3, K_2CO_3) clearly establishes the advantage of using poly-ionic resin hydroxide.

Initially, the organic thiocyanates were prepared from alkyl (or acyl methyl) halides by reaction of NH_4SCN in the presence

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Table 1
Optimization of disulfide formation from organic thiocyanates in water[a]

Entry	Reagent[b]	Additive[c]	Temp (°C)/time (h)	Yield[d] (%)
1	Amberlyst® A-26(OH)	Nil	rt/12	52[e]
2	**Amberlyst® A-26(OH)**	**Nil**	**60/3**	**91**
3	Amberlyst® A-26(OH)	$Na_2S_2O_3{\cdot}5H_2O$	60/20	76
4	Amberlyst® A-26(OH)	L-Cysteine	rt/2	90
5	Amberlyst® A-26(OH)	L-Cystine	60/2.5	87
6	Amberlite® IRA-900(Cl)	Nil	60/12	Nil
7	Amberlite IRA-900(HCOO)	Nil	60/6	81

[a] Reactions were performed in 2 mmol scale in water (2 mL).
[b] Different resins were used 150 mg $mmol^{-1}$.
[c] Additives were used in stoichiometric quantities.
[d] Yield refers to isolated product after column chromatography.
[e] Starting thiocyanate still remains in the reaction mixture, as indicated on TLC.

polyethylene glycol (PEG 400) following a reported procedure with minor modifications.[10] Optimization of the conversion of organic thiocyanate to symmetrical disulfide was performed using benzyl thiocyanate as the model compound (Table 1). In a typical experiment, benzyl thiocyanate (2 mmol) was stirred in water at room temperature in the presence of commercially available Amberlyst® A-26 (OH) (particle size: 0.35 mm, pH 9.4, 300 mg) (entry 1). Since the conversion was not complete even after 10 h, we increased the temperature to 60 °C and now a complete conversion was achieved within 3 h affording dibenzyl disulfide in 91% yield (entry 2). As the enzymatic (rhodanese) conversion of cyanide to thiocyanate has occurred in the presence of sulfur donors,[11] we tested the same reaction in the presence of equimolar quantity of $Na_2S_2O_3$, cystine or cysteine (entries 3–5). It is observed that while the presence of $Na_2S_2O_3$ could have an effect in lowering the rate of the conversion, the amino acid bearing –SH group (cysteine) did show an appreciable change in the rate of the conversion (rt/2 h). However, there was no significant change by using cystine (–S–S– linkage) as the additive. The same reaction was also tested in the presence of other anion exchange amberlite resins, like commercially available Amberlite® IRA(Cl) or our laboratory derived Amberlite resin formate (ARF),[9c] with varying results (entries 6 and 7).

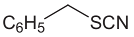
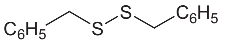
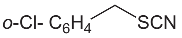
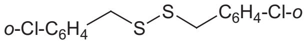
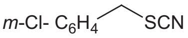
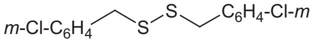
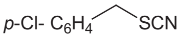
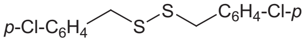
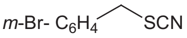
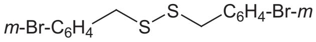
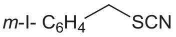
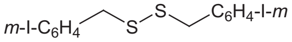
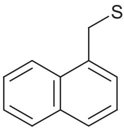
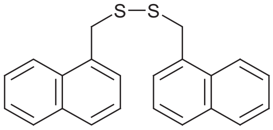
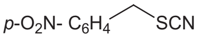
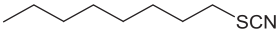
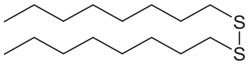
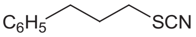
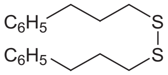
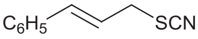
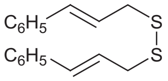
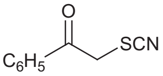
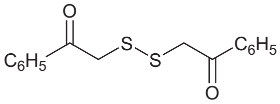
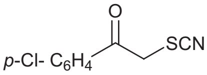
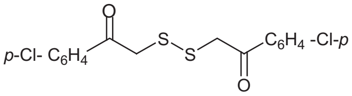
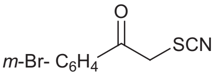
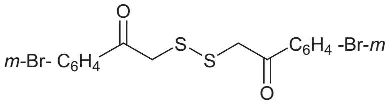
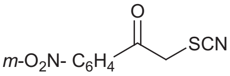
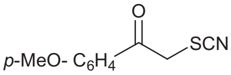
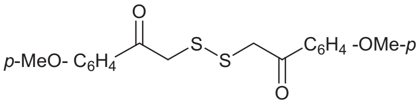
We had chosen the optimized condition as in entry 2 for the easy formation of the dibenzyl disulfide from benzyl thiocyanate. We were interested to establish this mild, efficient, and aqueous metal-free condition as a general protocol.[12] Accordingly, several substituted benzyl thiocyanates were subjected to a similar reaction. The results are presented in Table 2. It is gratifying that different halo-substituted benzyl thiocyanates and naphthyl methyl thiocyanate underwent smooth conversion to the corresponding disulfides (entries 2–7). However, the nitro benzyl thiocyanate remained unchanged under the reaction conditions (entry 8). This could possibly be attributed to the strong electron-withdrawing nature of the nitro group that reduces nucleophilic character of the benzyl carbon and electron density on the sulfur atom. Purely aliphatic thiocyanates, *n*-octyl thiocyanate, or other compounds such as 3-phenyl propyl thiocyanate or allyl thiocyanate derivative (3-phenyl-2-propenyl thiocyanate) also undergo disulfide formation in good to excellent yields (entries 9–11). In order to further generalize the reaction, acyl methyl thiocyanates were subjected to a similar reaction. Organic disulfides flanked by two carbonyl groups at the C-2 position would be the S-analogue of 1,6-diketones. Such bis(benzoylmethyl) disulfides could be easily prepared if benzoyl methyl thiocyanate undergoes similar dimerization. We had prepared different benzoyl methyl thiocyanates and carried out similar reactions using the resin hydroxide in water. As shown in Table 2 (entries 12–16), the corresponding disulfides were formed efficiently and isolated in excellent yields except the nitro-bearing benzoyl methyl thiocyanate (entry 15), possibly due to the same reason as mentioned in the case of entry 8 of this table.

In order to verify any advantage of using poly-ionic resin hydroxide base, a comparison between the heterogeneous base Amberlyst® A-26(OH) and other homogeneous bases (NaOH, NH_3, K_2CO_3) was performed. Thus, the conversion of benzyl thiocyanate to dibenzyl disulfide was carried out using homogeneous bases NaOH, NH_3, and K_2CO_3 that, respectively, afford 83%, 46%, and 25% yields, while Amberlyst® A-26(OH) can give rise to 91% yield (Table 3) under similar conditions. The variation of reactivity is even more prominent in the case of acyl methyl thiocyanates (Table 4).

Comparative studies using *p*-methoxy benzoyl methyl thiocyanate as a model case revealed that the Amberlyst® A-26(OH) can lead to the formation of the corresponding disulfide in 81% yield with a trace amount of *p*-methoxy acetophenone, while the base NaOH affords only *p*-methoxy acetophenone in 69% yield and no disulfide (Table 4, entries 1 and 2). On the other hand, use of K_2CO_3 afforded a mixture of compounds as seen on tlc (no separation was attempted), while NH_3 solution gave a mixture of the corresponding disulfide and acetophenone in 21% and 18% yield, respectively, the remaining was the starting material (60%), as analyzed by HPLC (Table 4, entries 3 and 4). These results clearly establish the advantage of the heterogeneous base Amberlyst® A-26(OH) over the existing homogeneous bases.

We then focused our attention to explore whether this mild and eco-friendly protocol could be employed for the preparation of unsymmetrical disulfides. In order to get an unsymmetrical disulfide, it is required to perform the reaction taking a mixture of two different organyl thiocyanates. This might also help us to propose a possible pathway of the reaction. Firstly, we performed one reaction using two different benzyl thiocyanates. For example, carrying out the reaction using an equimolar mixture of benzyl thiocyanate and *m*-chlorobenzyl thiocyanate indeed afforded all three possible disulfides in varying amounts (two homo-coupled products and one cross-coupled product) (Table 5, entry 1). After the reaction and work-up, HPLC analysis of the crude mixture showed three peaks of which two are from homo-coupled products (confirmed by co-injection), leaving the third peak assigned for the cross over product, that is, the unsymmetrical disulfide. Similar results are observed when a mixture of other alkyl thiocyanates is subjected to undergo the reaction (Table 5, entries 2 and 3). In all the three examples, the prominent similarity is in the formation of the unsymmetrical disulfide in larger quantity than homo-coupled disulfides. In the case of using acyl methyl thiocyanate as one of the partners, the cross product could not be distinctly analyzed by HPLC and appeared as two overlapping peaks of the total area about 26% only, which is in contrast to the observations in other cases (entry 4). As regards the mechanism of the reaction, formation of the cross- over product suggests that the S–S linkage is made in a step-wise manner and not through a concerted process. In the presence of heterogeneous base, presumably the

Table 2
Synthesis of various organic disulfides using Amberlyst® A-26(OH) in water[a]

Entry	Substrate	Temp (°C)/time (h)	Product[b]	Yield[c] (%)
1		60/3		91
2		60/5		92
3		60/5		81
4		60/6		88
5		60/2		82
6		60/3		85
7		60/8		78
8		60/10	No reaction	
9		60/5		74
10		60/8		80
11		60/24		88
12		80/16		78
13		60/12		76
14		60/5		74
15		60/16	No reaction	
16		60/12		81

[a] All reactions were carried out in 2 mmol scale using 300 mg of Amberlyst® A-26(OH).
[b] Products were characterized by NMR, HRMS, and mp.
[c] Yield refers to the pure product, isolated by column chromatography.

Table 3
Comparative study of different bases for conversion of benzyl thiocyanate to dibenzyl disulfide in water[a]

Entry	Base	Amount of base[b]	Time (h)/temp (°C)	Yield[c] (%)
1	Amberlyst® A 26(OH)	150 mg	3/60	91
2	NaOH	40 mg	3/60	83
3	K_2CO_3	138 mg	3/60	46
4	NH_3 solution	0.6 mL[d]	3/60	25

[a] Reactions were performed in 1 mmol scale in water (2 mL).
[b] Quantity of bases used $mmol^{-1}$.
[c] Yield refers to isolated product after column chromatography.
[d] Ammonia solution (about 30%) (LR grade) obtained from Thomas Baker, India.

nucleophilic thiolate anion is formed initially, which could displace the cyanide ion of another organyl thiocyanate resulting in the formation of the disulfide and the ion-exchange resins possibly could scavenge the cyanide ion (Scheme 2).

Table 4

Comparative study of different bases for conversion of *p*-methoxy benzoyl methyl thiocyanate to *p*-methoxy dibenzoyl disulfide and *p*-methoxy acetophenone in water[a]

Entry	Base	Amount of base[b]	Time (h)/temp (°C)	Yield (%)	
				Disulfide	Ketone
1	Amberlyst® A 26(OH)	150 mg	12/60	81[c]	Trace
2	NaOH	40 mg	12/60	Nil	69[c]
3	K_2CO_3	138 mg	12/60	Mixture of compounds[d]	
4	NH_3 solution	0.6 mL[e]	12/60	21[f]	18[f]

[a] Reactions were performed in 1 mmol scale in water (2 mL).

[b] Quantity of bases used $mmol^{-1}$.

[c] Yield refers to isolated product after column chromatography.

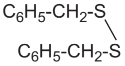
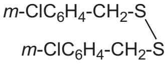
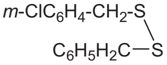
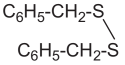
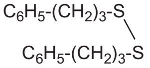
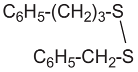
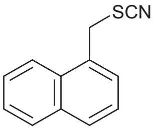
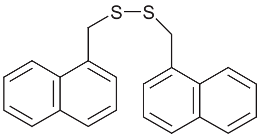
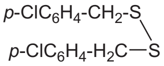
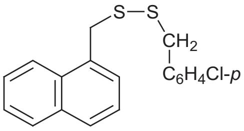
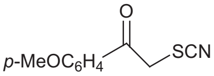
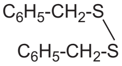
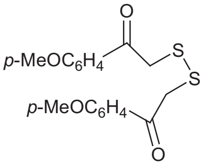
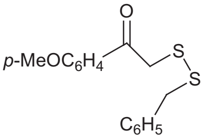
[d] As seen on TLC.

[e] Ammonia solution (about 30%) (LR grade) obtained from Thomas Baker, India.

[f] Analyzed by HPLC [Column ZORBAX Rx-SIL (4.6 × 150 mm, 5 μm); mobile phase: hexane/ethyl acetate (9:1); flow rate = 0.5 mL/min].

Table 5

Synthesis of unsymmetrical disulfides and result analysis by HPLC[a,b]

Entry	Substrate A	Substrate B	Product A–A (%)/rt[c] (min)	Product B–B (%)/rt (min)	Product A–B (%)/rt (min)
1	$C_6H_5\text{-}CH_2\text{-}SCN$	*m*-$ClC_6H_4\text{-}CH_2\text{-}SCN$	 $C_6H_5\text{-}CH_2\text{-}S\text{-}S\text{-}CH_2\text{-}C_6H_5$ (38)/4.37	 *m*-$ClC_6H_4\text{-}CH_2\text{-}S\text{-}S\text{-}CH_2\text{-}C_6H_4Cl$-*m* (15)/3.41	 *m*-$ClC_6H_4\text{-}CH_2\text{-}S\text{-}S\text{-}CH_2C_6H_5$ (47)/3.71
2	$C_6H_5\text{-}CH_2\text{-}SCN$	$C_6H_5\text{-}(CH_2)_3\text{-}SCN$	 $C_6H_5\text{-}CH_2\text{-}S\text{-}S\text{-}CH_2\text{-}C_6H_5$ (37.4)/3.36	 $C_6H_5\text{-}(CH_2)_3\text{-}S\text{-}S\text{-}(CH_2)_3\text{-}C_6H_5$ (15.5)/3.92	 $C_6H_5\text{-}(CH_2)_3\text{-}S\text{-}S\text{-}CH_2\text{-}C_6H_5$ (47.1)3.55
3		*p*-$ClC_6H_4\text{-}CH_2\text{-}SCN$	 (22.0)/9.54	 *p*-$ClC_6H_4\text{-}CH_2\text{-}S\text{-}S\text{-}CH_2\text{-}C_6H_4Cl$-*p* (25.4)/3.63	 (52.6)/5.29
4	$C_6H_5\text{-}CH_2\text{-}SCN$		 $C_6H_5\text{-}CH_2\text{-}S\text{-}S\text{-}CH_2\text{-}C_6H_5$ (27.8)/1.79[d]	 (45.7)/8.35	 2.6 & 2.9/16.7 & 9.8[e]

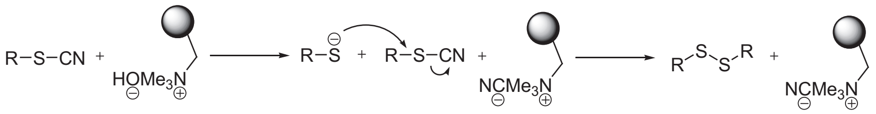
[a] Column: ZORBAX Rx-SIL (4.6 × 150 mm, 5 μm); temperature: Ambient (25 °C); mobile phase: hexane for entries (1–3), and 1% *i*-PrOH in hexane for entry 4; flow rate = 2 mL/min for all entries.

[b] Peaks were confirmed by co-injection with homo-coupled disulfides.

[c] t_R in minute for the peaks indicated by RI detector.

[d] t_R in minute for the peaks indicated by UV detector at λ = 380 nm.

[e] Unsymmetrical disulfide showed overlapping of two peaks, as indicated with t_R (min) and area, respectively.



Scheme 2.

We also checked the reusability of the poly-ionic resin hydroxide taking the model reaction with benzyl thiocyanate. It is observed that the resins can be reused after filtration from the reaction mixture, washed with water followed by acetone, and then dried under vacuum. Although, disulfide is obtained up to the fourth run requiring longer reaction time, the yield of the product showed a gradual decreasing trend (from 90% to 75%) (Table 6).

In summary, we have developed an efficient and eco-friendly protocol to form disulfide bond (S–S linkage) from alkyl and acyl methyl thiocyanates producing corresponding disulfides in good

Table 6

Recycling of Amberlyst® A-26(OH) in the dimerization of benzyl thiocyanate[a]

Run	pH[b]	Time (h)	Yield (%)
1	9.4	3	90
2	8.2	6	78
3	8.0	8	75
4	7.9	10	75

[a] Reactions were carried out using Amberlyst® A-26(OH) for 2 mmol of the substrate in water.

[b] pH of the resin-suspended water was measured before each run.

to excellent yields under complete metal-free conditions. The present protocol further establishes the advantage of using the heterogeneous base Amberlyst® A-26(OH) over some existing homogeneous bases (NaOH, NH_3, K_2CO_3). Other notable features are: (i) reaction can be carried out in water and simple filtration and removal of the water could afford the organic disulfide; (ii) the resins can be reused for three more runs tested with appreciable conversions; (iii) cross-over experiments revealed that the procedure is somewhat effective for the preparation of unsymmetrical disulfides.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.02.070.

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12. General procedure for the preparation of disulfide: To a mixture of alkyl/acyl methyl thiocyanate (2 mmol) in water (2 mL) was added Amberlyst® A-26(OH) (300 mg) (Source: Sigma–Aldrich) and the reaction mixture was stirred with a magnetic bar gently at 60–80 °C. The progress of the reaction was monitored by TLC. After the reaction continued for specific time, as mentioned in Table 2, the resin beads were separated by filtration over a piece of cotton. The reaction mixture was extracted repeatedly with diethyl ether and combined ethereal layer was dried over anhydrous Na_2SO_4 and concentrated. The crude product (almost pure) was further purified by column chromatography over silica gel. The products were identified on the basis of ^1H, ^{13}C NMR, and HRMS data, and/or by comparison with the data reported in the literature.