An efficient one-pot approach to the synthesis of symmetric trithiocarbonates from carbon disulfide and alkyl halides using imidazole

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A novel method is reported for the synthesis of symmetric dialkyl and cyclic (5, 6 and 7 member) trithiocarbonates from alkyl halides and carbon disulfide in the presence of imidazole and water in DMSO under mild reaction conditions. Imidazole is used as an inexpensive, non-toxic and readily available catalyst in this procedure.

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\text{R-X + CS}_2 \xrightarrow{\text{Imidazole}} \text{DMSO/H}_2\text{O, 45 °C} \xrightarrow{} \text{R-S-S-R}
\]

\[
\text{X-(CH}_2\text{n-X + CS}_2 \xrightarrow{\text{Imidazole}} \text{DMSO/H}_2\text{O, 45 °C} \xrightarrow{} \text{S}_{(\text{CH}_2\text{m})}\text{S}
\]

**Keywords:** trithiocarbonate; carbon disulfide; imidazole; alkyl halide; one-pot reaction

1. Introduction

Dialkyl trithiocarbonates are of importance in synthetic chemistry, biochemistry and industry.[1–5] They are especially used as pesticides in agriculture,[6,7] lubricating additive,[8,9] reversible addition fragmentation chain transfer agent in the free radical polymerization reactions,[10,11] pharmaceuticals,[12,13] agrochemical[14,15] and intermediate in organic synthesis.[16–20] The most convenient method for the synthesis of symmetrical trithiocarbonates is alkylation (arylation) of \text{CS}_3^- with alkyl (aryl) halides. The trithiocarbonate anion \[21,22\] is generally prepared by \textit{in situ} one-pot reaction of carbon disulfide with alkali metal or ammonium sulfide, \[23–25\] ammonium hydroxide,\[21\] KF/alumina or alumina,\[26,27\] anion-exchange resin\[28\] and hydroxide,\[29,30\] carbonate \[29\] and the phosphate\[31\] of the alkali metal group. In our previous studies, we used KF/Al\textsubscript{2}O\textsubscript{3} \[26\] as a recyclable catalyst and tetra-\textit{n}-butyl ammonium hydroxide \[32\] as a neat
aqueous medium for the one-pot synthesis of symmetrical dialkyl trithiocarbonate. This was an effective method and suitable from the novelty and green chemistry viewpoint,[33] but like all other reported methods, the catalysts were inorganic. The use of inorganic and metal bases has several disadvantages such as their expense, their toxic and corrosive behavior, the strongly basic reaction conditions that are employed, and the difficulty in work-up encountered in these reactions. Herein, we describe a new alternative approach to one-pot synthesis of symmetrical dialkyl trithiocarbonate from carbon disulfide and alkyl halides using imidazole as a highly stable, readily available, low-cost, low toxicity and mild organic compound.

2. Results and discussion

As a model, the reaction of benzyl chloride (2.0 mmol) 1 and carbon disulfide (6.0 mmol) 2 in the presence of imidazole (6.0 mmol) was studied under normal atmospheric conditions in order to optimize the reaction conditions with respect to the solvent and temperature (Scheme 1). Several solvents were examined at room temperature and at 45 °C.

According to the results given in Table 1, it was found that the reaction solvent and temperature significantly affected the rate of reaction and the type and amount of product formed. In aqueous DMSO and DMF, product 3 was the main product, whereas by-product 4 was the major product in the absence of water (0.2 ml). The presence of water is often beneficial to the rate and selectivity of the reaction. Furthermore, the yield and rate of reaction also increased with temperature, whereas the formation of by-product 4 was reduced. In aqueous DMSO and DMF at 45 °C, dibenzyl trithiocarbonate 3 was obtained as the sole product, while at room temperature 15–23% of by-product 4 was also isolated. Despite the fact that DMF and DMSO promoted the reaction, no reaction was observed in THF or 1,4-dioxane. Furthermore, during our optimization studies we discovered that decreasing the imidazole from 6 to 4 or 5 mmol decreased the efficiency of the reaction and lowered the yields to 53% and 78%, respectively.

Eventually, a large number of symmetrical dialkyl trithiocarbonate 6a–6m were synthesized under the optimized conditions by the reaction of alkyl halides 5 with carbon disulfide in the presence of imidazole at 45 °C under normal atmospheric conditions (Scheme 2, Table 2).

The procedure worked well with primary, secondary, and tertiary alkyl, benzyl and alkyl halides, to give the corresponding dialkyl trithiocarbonates as the sole product in high to excellent yields (Table 2). However, the attempted reactions of aryl halides failed under the same conditions, even after long reaction times (Table 2, Entry 13). More interestingly, the base-sensitive functional groups such as carboxylic ester and carboxylic acid remained unchanged in the synthesis of corresponding symmetric trithiocarbonates (6j and 6k) from α-bromoethyl acetate 5j and α-chloroacetic acid 5k (Table 2, Entries 10, 11).
Table 1. Optimization study: screening of solvent of reactions, optimize of the reaction temperature, and water amounta.

| Entry | Solvent (5 ml) | Temp. (°C) | Time (h) | Isolated yield (%) |
|-------|----------------|------------|----------|--------------------|
| 1     | THF            | 45         | 15       | –                  |
| 2     | 1,4-dioxane    | 45         | 15       | –                  |
| 3     | CH₃CN          | 45         | 15       | –                  |
| 4     | DMF            | 45         | 10       | 15                 |
| 5     | H₂O            | 45         | 8        | –                  |
| 6     | H₂Oᵇ          | 45         | 8        | 25                 |
| 7     | DMSO           | 45         | 4.5      | 10                 |
| 8     | DMF            | 25         | 10       | Trace              |
| 9     | H₂O            | 25         | 15       | –                  |
| 10    | DMSO/H₂O (4.8/0.2) | 25     | 10.5     | 73                 |
| 11    | DMF/H₂O (4.8/0.2) | 25     | 11       | 60                 |
| 12    | DMSO/H₂O (4.8/0.2) | 45     | 4.5      | 92                 |
| 13    | DMSO/H₂O (4.5/0.5) | 45     | 10       | 37                 |
| 14    | DMSO/H₂O (4/1)  | 45         | 10       | 25                 |
| 15    | DMF/H₂O (4.8/0.2) | 45     | 7        | 82                 |
| 16    | CH₃CN/H₂O (4.8/0.2) | 45     | 10       | 13                 |

a Model reaction conditions: carbon disulfide (6.0 mmol), benzyl chloride (2.0 mmol), imidazole (6.0 mmol), solvent (5.0 ml) under air atmosphere.
bIn 0.2 ml solvent.

Scheme 2. Synthesis of symmetric trithiocarbonates.

Table 2. Imidazole mediated symmetrical dialkyl trithiocarbonates synthesis.

| Entry | R-X, 5      | Product | Time (h) | Yielda (%) |
|-------|-------------|---------|----------|------------|
| 1     | CH₃CH₂I, 5a | 6a      | 8        | 70         |
| 2     | PhCH₂Cl, 5b | 6b      | 4.5      | 92         |
| 3     | PhCH₂Br, 5c | 6c      | 3.5      | 91         |
| 4     | CH₃CH₂CH₂Br, 5d | 6d | 9.5 | 72     |
| 5     | s-BuBr, 5e  | 6e      | 8        | 90         |
| 6     | i-BuBr, 5f  | 6f      | 7.5      | 86         |
| 7     | t-BuBr, 5g  | 6g      | 14       | 65         |
| 8     | PhCH₂CH₂Br, 5h | 6h | 7.5 | 85     |
| 9     | Ph(C₂H₅)₁CH₂Br, 5i | 6i | 8.5 | 80     |
| 10    | EtO₂CCH₂Br, 5j | 6j | 9       | 78         |
| 11    | HO₂CCH₂Cl, 5k | 6k | 10.5    | 75         |
| 12    | CH₂=CHCH₂Br, 5l | 6l | 9.5 | 75     |
| 13    | PhI, 5m     | 6m      | 15       | –          |

a Isolated yield by preparative chromatography.

Furthermore, the procedure’s efficiency for the synthesis of cyclic trithiocarbonates (1, 3-dithiolane-2-thione) from dihalides 7 was examined (Scheme 3). Five- (8a), six- (8b) and seven-membered cyclic trithiocarbonates (8c) were successfully prepared with moderate yields without any by-product (Table 3).
Scheme 3. Synthesis of cyclic trithiocarbonates.

Table 3. Symmetrical cyclic trithiocarbonates from alkyl halides and CS$_2$ under optimized conditions.

| Entry | X-(CH$_2$)$_n$-X, 7 | Product$^a$ | Time (h) | Yield$^b$ (%) |
|-------|-------------------|-------------|----------|--------------|
| 1     | ICH$_2$CH$_2$I     | 8a, m = 1   | 8        | 91           |
| 2     | BrCH$_2$CH$_2$CH$_2$Br | 8b, m = 2   | 8.5      | 82           |
| 3     | BrCH$_2$(CH$_2$)$_2$CH$_2$Br | 8c, m = 3   | 9.5      | 70           |

$^a$Known products compounds were characterized by comparison of NMR spectral data with those reported in the literature.

$^b$ Isolated yield.

In order to establish the general applicability of the procedure for the synthesis of unsymmetrical dialkyl trithiocarbonate from two different alkyl halides under optimal reaction conditions, $\alpha$-bromo ethyl acetate 5j and ethyl iodide 5a were treated with carbon disulfide and imidazole (Scheme 4). The unsymmetrical trithiocarbonate product 9 was obtained as the major product (60%) with good chemoselectivity. The symmetrical products 10 (25%) and 11 (10%) were isolated as the minor products.

Scheme 4. Synthesis of unsymmetrical trithiocarbonates.

We also propose a possible reaction mechanism in which intermediate I is generated in the first step by the reaction of imidazole with carbon disulfide and alkyl halides and is hydrolyzed in situ to produce of thiol moiety (intermediate II), COS and imidazole. In the final step, the generated thiol (II) attacks the thiocarbonyl carbon of the intermediate I to readily yield a trithiocarbonate III and regenerate imidazole. It is presumed that water is necessary, especially, in the hydrolysis of the intermediate I. The proposed mechanism is a fairly accurate presentation of what may happen due to common considerations during the course of the reaction. In the model reaction, benzyl mercaptan and the intermediate I were in fact isolated and fully characterized by spectroscopy techniques. The proposed pathway is shown in Scheme 5.
3. Conclusion

To conclude, this strategy provides a new and alternative procedure for the one-pot synthesis of symmetrical dialkyl trithiocarbonates from alkyl halides and carbon disulfide. It is more economic, more general and more environmentally friendly than previous methods. The use of imidazole as an inexpensive, non-toxic and readily available catalyst is another significant advantage of this process. In addition, other advantages of this process are the ease of performing and controlling the reaction as well as purification of the product, and the avoidance of expensive and/or dangerous reagents.

4. Experimental

General procedures: Symmetrical trithiocarbonates synthesis from alkyl halides and carbon disulfide: Alkyl halides (2.0 mmol) (or alkyl dihalides (1.0 mmol)) were added in one portion to a solution of imidazole (6.0 mmol) and CS₂ (6.0 mmol) in 5 ml DMSO/H₂O (4.8/0.2). The color of the resulting reaction solution immediately changed from light red to yellow. Then, the solution was allowed to stir for the appropriate time (Table 2) at 45 °C in an air atmosphere. The progress of the reaction was monitored by TLC. After completion of the reaction, 20 ml CH₂Cl₂ was added to the mixture, and the mixture was then washed with water (2 × 20 ml). The organic layer was separated and then dried over anhydrous Na₂SO₄. The solvent was evaporated under reduced pressure. The residue was purified by preparative TLC silica gel, eluent n-hexane: EtOAc; 30:1) to afford pure product (symmetric dialkyl trithiocarbonate). In the case of Entries 10 and 11, Table 2 (6j and 6k), the TLC eluent was n-hexane: EtOAc 4:1.

Selected spectral data for representative trithiocarbonate: Table 2, Entry 5 (6e): pale yellow oil; ¹H NMR (400 MHz, CDCl₃): δ = 1.01 (t, J = 7.2 Hz, 6H), 1.4 (d, J = 6.8 Hz, 6H), 1.65–1.83 (m, 4H.), 4.21 (sext, J = 6.8 Hz, 2H). ¹³C NMR (100 MHz, CDCl₃): δ = 11.41, 19.57, 28.81, 47.98, 224.04.
Entry 8 (6h): yellow oil $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 3.05$ (t, $J = 7.8$ Hz, 4H), 3.67 (t, $J = 7.8$ Hz, 4H), 7.26–7.37 (m, 10H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 34.47, 37.91, 126.73, 128.61, 128.65, 139.59, 223.74$.

Table 2, Entry 9 (6i): yellow oil $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 2.1$ (quin, $J = 7.4$ Hz, 4H), 2.79 (t, $J = 7.6$ Hz, 4H), 3.4 (t, $J = 7.4$ Hz, 4H), 7.26–7.38 (m, 10H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 29.73, 34.93, 36.14, 126.16, 128.51, 140.91, 224.08$. MS (EI, 70 eV): $m/z = 65.1, 91.1, 117.2, 151.1, 195.1, 313.2, 347.3$.

Table 2, Entry 10 (6j): Pale yellow oil $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.32$ (t, $J = 7.2$ Hz, 6H), 4.20 (s, 4H), 4.26 (q, $J = 7.0$ Hz, 4H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 14.11, 38.39, 62.07, 167.14, 220.33$. MS (EI, 70 eV): $m/z = 59.1, 87.1, 107, 119, 135, 140.1, 168, 195, 206, 237.1, 282.1$.

Table 3, Entry 3 (8c): yellow oil $^1$H NMR (400 MHz, CDCl$_3$): yellow oil $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 2.51$ (m, 4H), 3.29 (m, 4H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 29.72, 38.69, 223.32$. MS (EI, 70 eV): $m/z = 54.1, 60.1, 76, 88.1, 120.1, 164.1$.

9: pale yellow oil $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 1.3$ (t, $J = 7.2$ Hz, 3H), 1.41 (t, $J = 7.2$ Hz, 3H), 3.4 (q, $J = 7.4$ Hz, 2H), 4.20 (s, 2H), 4.26 (q, $J = 7.2$ Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 12.95, 14.12, 31.78, 38.39, 62.07, 167.53, 222.20$. MS (EI, 70 eV): $m/z = 61, 77, 106, 120, 135, 163, 179, 195, 224.1$.

Intermediate I (R = PhCH$_2$): pale yellow $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 4.64$ (s, 2H), 7.14 (s, 1H), 7.29–7.43 (m, 5H), 7.8 (s, 1H), 8.52 (s, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 41.80, 117.73, 128.33, 128.95, 129.44, 131.50, 133.50, 135.67, 197.31$. MS (EI, 70 eV): $m/z = 50, 57.1, 65.2, 76.1, 83.1, 91.2, 111.2, 123.2, 158.2, 168.1, 234.1$.

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Supplemental data

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