TCCA-promoted solvent-free chemoselective synthesis of thiosulfonates on grinding

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Trichloroisocyanuric acid (TCCA) is an inexpensive and efficient reagent for solvent-free chemoselective synthesis of thiosulfonates by grinding, providing a metal-free new methodology for the oxidation of disulfides. The important features of this method are that it is reasonably fast, very clean, high yielding, has a simple workup and is environmentally benign.

Keywords: trichloroisocyanuric acid (TCCA), disulfides, thiosulfonates, solvent-free synthesis

Thiosulfonates, with strong sulfenylating power, have found wide industrial applications both in polymer production and in photographic processes.[1] One of the most practically and widely used routes for the synthesis of thiosulfonates involves the direct oxidation of disulfides in the presence of various promoting agents, such as benzenesulfinate/bromine,[2] sodium trifluoromethanesulfinate/[bis(trifluoroacetoxy) iodo]benzene[3] and dinitrogen tetroxide/charcoal.[4] In another method, thiosulfonates have been prepared by tandem reaction of thiols under oxidative conditions.[5] Some other methods include selective reduction of arenesulfonyl chlorides promoted by samarium metalin DMF.[6] However, these methods usually suffer from one or more limitations such as use of volatile organic solvents and strong oxidizing agents, drastic reaction conditions, expensive reagents, unsatisfactory yields, tedious workup procedures, and co-occurrence of several side reactions. Therefore, the introduction of new methods to overcome these limitations is an important experimental challenge.

In recent years, significant articles have appeared reporting solid-state reactions by grinding.[7–9] Most of these reactions were carried out at room temperature in an absolutely solvent-free environment using only a mortar and pestle, and a common merit of these processes is that they are efficient, economical, and environmentally friendly.

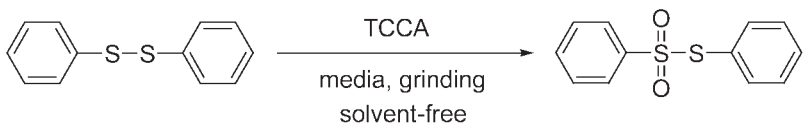
Trichloroisocyanuric acid (TCCA), an inexpensive, easily available reagent, having low toxicity, has been widely used in organic reactions,[10,11] but it has not been carefully studied as a promotor in the synthesis of thiosulfonates until now.

As a part of our continuing interest in the synthesis of sulfur-containing compounds using green chemistry,[9,12,13] we report here a new and simple TCCA-promoted solvent-free chemoselective synthesis of thiosulfonates by oxidation of disulfides under mild conditions.

To optimise the reaction conditions, initial studies were concentrated on treatment of disulfides **1a** with TCCA as a model reaction. Different reaction media were tested to find the optimised conditions. As shown in Table 1, silica gel was determined to be the more suitable medium, which afforded the desired product **2a** with excellent yield (Table 1, entry 5). Using 0.7 equiv. of TCCA the reaction gave the highest yield (99%) (Table 1, entry 13). However, when the amount of TCCA was more than 0.7 equiv. or less than 0.7 equiv., the yields were unsatisfactory (Table 1, entries 6–12). Nevertheless, a trace of product was obtained in the absence of TCCA, which also further proved that TCCA does play an important role in this reaction (Table 1, entry 14).

In the light of these results, subsequent studies were carried out under the following optimized conditions with 0.7 equiv.

Table 1 Optimisation of reaction conditions for the oxidation of PhSSPh[a]



Entry	Media	TCCA/equiv.	Time/min	Yield/%[b]
1	Acidic Al_2O_3	0.8	10	72
2	Neutral Al_2O_3	0.8	10	78
3	Basic Al_2O_3	0.8	5	79
4	Basic Al_2O_3	0.8	10	86
5	Silica gel	0.8	10	95
6	Silica gel	0.8	5	64
7	Silica gel	1.0	10	94
8	Silica gel	1.5	10	42
9	Silica gel	1.2	10	57
10	Silica gel	1.1	10	63
11	Silica gel	0.4	10	61
12	Silica gel	0.7	5	78
13	Silica gel	0.7	10	99
14	Silica gel	–	30	trace

[a]Reactions conditions: PhSSPh **1a** (0.5 mmol) and media (0.5 g) in the presence of TCCA on grinding at room temperature under solvent-free conditions.
[b]Isolated yields.

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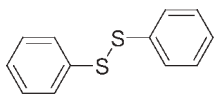
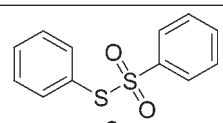
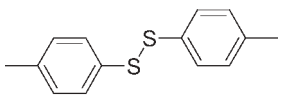
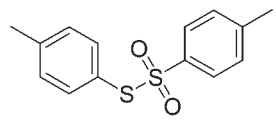
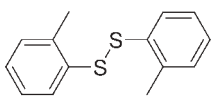
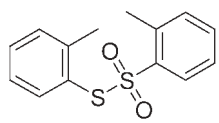
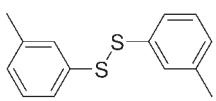
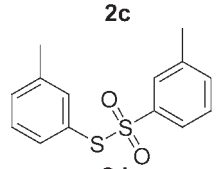
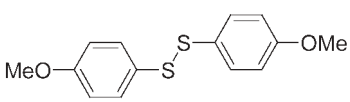
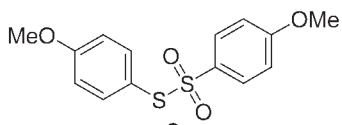
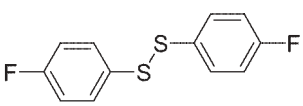
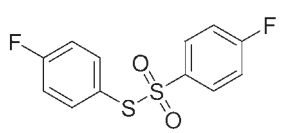
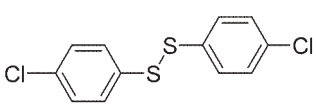
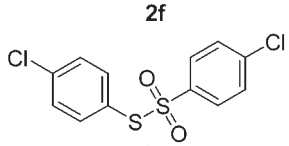
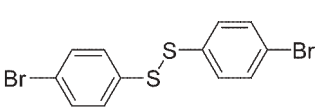
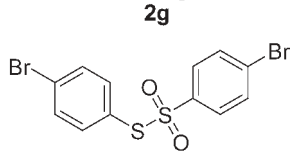
TCCA, 0.5 g silica gel, grinding, at room temperature under solvent-free conditions. Next, to extend the scope and generality of this method, a variety of aromatic disulfides were oxidised to give various thiosulfonates by grinding and the results are summarised in Table 2.

As shown in Table 2, a series of aromatic disulfides were investigated. Disulfides containing electron-donating groups, such as the dimethyl substituted diphenyldisulfides (**1b–d**) and the 4,4′-dimethoxydiphenyldisulfide (**1e**) afforded the corresponding thiolsulfonates in 92%, 98%, 92% and 89% yields, respectively (Table 2, entries 2–5). Similarly, disulfides containing electron-withdrawing groups, such as 4,4′-difluorodiphenyl disulfide (**1f**), 4,4′-dichlorodiphenyl disulfide (**1g**), 4,4′-dibromodiphenyl disulfide (**1h**) afforded the corresponding thiosulfonates in 95%, 95%, and 99% yields respectively (Table 2, entries 6–8), which showed no obvious electronic effect. Again the high yields of **2c** and **2d** from substrates with steric constraints indicate an absence of large steric effects (Table 2, entries 3 and 4).

To the best of our knowledge, it was little reported that a reaction could be conducted within 10 min; except, Iranpoor[5] reported TBAO/Im/Mn(TPP)OAc promoted synthesis of thiosulfonates. Compared to the reaction carried out by TBAO/Im/Mn(TPP)OAc, this procedure is completely free from organic solvents and does not use any additives during the reaction.

In conclusion, we have developed a highly efficient and facile method for the synthesis of thiosulfonates on grinding under solvent-free conditions. Good yields, short reaction times and neat conditions are the notable advantages of this method. We believe that this method provides improved scope in the synthesis of thiosulfonates and might be a more practical alternative to existing methods for other organic reactions. Investigations for the application of the protocol are underway in our laboratory.

Table 2 Preparation of thiosulfonates from disulfides[a]

Entry	Substrate (**1**)	Product (**2**)	Yield/%[b]
1	 **1a**	 **2a**	99
2	 **1b**	 **2b**	92
3	 **1c**	 **2c**	98
4	 **1d**	 **2d**	92
5	 **1e**	 **2e**	89
6	 **1f**	 **2f**	95
7	 **1g**	 **2g**	95
8	 **1h**	 **2h**	99

[a] Reactions were carried out on a 0.5-mmol scale with TCCA (0.7 equiv.) and silica gel (0.5 g) by grinding at room temperature under solvent-free conditions.
[b] Isolated yields.

Experimental

Chemicals were purchased and used without further purification. Melting points were recorded on Digital Melting Point Apparatus WRS-1B and are uncorrected. NMR spectroscopy was performed on a Bruker-300 spectrometer or Bruker-500 spectrometer using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS, the coupling constants *J* are given in Hz. Mass spectra (MS) were measured with a Thermo Finnigan LCQ-Advantage. Column chromatography was performed using EM Silica gel 60 (300–400 mesh).

Typical procedure for preparation of thiosulfonates

The following components were added to the glass mortar: silica gel (200–300mesh, 500 mg), diphenyldisulfide **1a** (109 mg, 0.5 mmol) and TCCA (81.4 mg, 0.35 mmol). Then the mixture was ground at room temperature with a glass pestle in the glass mortar. The reaction was monitored by TLC. After completion of the reaction, the mixture was transferred into ethyl acetate. The combined organic solvent was removed under vacuum. The pure product **2a** was obtained by silica gel column chromatography. The physical and spectra data of the compounds **2a**–**h** are as follows.

S-Phenyl benzenesulfonothioate (**2a**): Solid, m.p. 38–40 °C, (lit.[14] 41–42 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.33–7.45 (m, 7H, ArH), 7.55–7.58 (m, 3H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 127.6, 127.9, 128.8, 129.5, 131.4, 133.7, 136.6, 143.0. ESI-MS: *m/z* (%): 250 ([M+H]$^+$, 100).

S-p-Tolyl 4-methylbenzenesulfonothioate (**2b**): Solid, m.p. 69–70 °C, (lit.[14] 73–75 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.40 (s, 3H), 7.11–7.20 (m, 6H, ArH), 7.42–7.44 (m, 2H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.4, 21.5, 124.3, 127.4, 129.3, 130.1, 136.3, 140.1, 142.0, 144.5. ESI-MS: *m/z* (%): 279 ([M+H]$^+$, 100).

S-o-Tolyl 2-methylbenzenesulfonothioate (**2c**): Solid, m.p. 39–40 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.14 (s, 3H), 2.69 (s, 3H), 7.09–7.24 (m, 4H, ArH), 7.30–7.46 (m, 4H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.3, 20.4, 125.8, 126.7, 126.9, 129.9, 130.7, 131.7, 132.8, 133.7, 137.6, 138.2, 140.8, 144.0. MS (ESI): *m/z* (%) = 278 ([M+H]$^+$, 100). Anal. Calcd for $C_{14}H_{14}O_2S_2$: C, 60.40; H, 5.07. Found: C, 60.36; H, 5.12%.

S-m-Tolyl 3-methylbenzenesulfonothioate (**2d**): Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H), 2.33 (s, 3H), 7.13–7.24 (m, 2H, ArH), 7.29–7.39 (m, 6H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.02, 21.03, 124.6, 127.4, 127.9, 128.5, 129.0, 132.1, 133.5, 134.3, 137.0, 138.9, 139.3, 142.5. MS (ESI): *m/z* (%) = 278 ([M+H]$^+$, 100). Anal. Calcd for $C_{14}H_{14}O_2S_2$: C, 60.40; H, 5.07. Found: C, 60.45; H, 5.01%.

S-4-Methoxyphenyl 4-methoxybenzenesulfonothioate (**2e**): Solid, m.p. 84–85 °C, (lit.[15] 83–84 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 3H), 3.85 (s, 3H), 6.81–6.87 (m, 4H, ArH), 7.23–7.26 (m, 2H, ArH), 7.46–7.49 (m, 2H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.4, 55.6, 113.8, 114.9, 118.9, 129.8, 134.9, 138.3, 162.2, 163.5. ESI-MS: *m/z* (%): 310 ([M+H]$^+$, 100).

S-4-Fluorophenyl 4-fluorobenzenesulfonothioate (**2f**): Solid, m.p. 66–67 °C, (lit.[16] 70–71 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.01–7.13 (m, 4H, ArH), 7.32–7.36 (m, 2H, ArH), 7.54–7.59 (m, 2H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 116.1, 116.2, 116.8, 117.0, 123.1, 123.2, 130.3, 130.4, 138.65, 138.67, 138.7, 138.8, 163.8, 164.5, 165.8, 166.5. ESI-MS: *m/z* (%): 286 ([M+H]$^+$, 100).

S-4-Chlorophenyl 4-chlorobenzenesulfonothioate (**2g**): Solid, m.p. 130–131 °C, (lit.[14] 134–136 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.36 (m, 4H, ArH), 7.40–7.43 (m, 2H, ArH), 7.50–7.53 (m, 2H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 125.0, 127.9, 128.3, 128.9, 136.7, 137.5, 139.5, 140.3.

S-4-Bromophenyl 4-bromobenzenesulfonothioate (**2h**): Solid, m.p. 150–152 °C, (lit.[17] 157–158 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21–7.23 (m, 2H, ArH), 7.41–7.86 (m, 6H, ArH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 126.6, 127.1, 129.0, 129.2, 132.3, 133.0, 137.9, 141.9.

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