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Catalyst-free and solvent-free synthesis of novel symmetrical bisthioglycolic acid derivatives

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A simple, efficient, eco-friendly, and cost-effective method has been developed for the synthesis of symmetrical bisthioglycolic acid derivatives by a one-pot reaction of aldehydes or ketones with thioglycolic acid under solvent- and catalyst-free conditions in excellent yields (87–97%). The advantages of this novel protocol include the excellent yields, operational simplicity, short reaction times, and the avoidance of the use of organic solvents and catalysts.

Keywords: thioglycolic acid; catalyst-free; solvent-free; thioethers; aldehydes

Introduction

With increasing global environmental concerns, the design of 'solvent-free' green processes has gained significant attention from synthetic organic chemists (*1, 2*). As a result, many reactions are designed to proceed cleanly and efficiently in the solid state or under solvent-free conditions (*3–7*). Less chemical pollution, lower cost, and an easier workup procedure are the main reasons for the recent increase in the popularity of solvent-free reactions.

Sulfur-containing compounds are found in a number of natural products and are of particular importance regarding pharmaceutically active substances (*8*). Thioethers have been widely employed as perfume additives (*9*). Furthermore, aromatic thioethers often feature as important synthetic intermediates and biologically interesting compounds, including several therapeutic drugs (*10*, *11*).

Synthesis of bisthioglycolic acid derivatives is important in the realm of natural and synthetic organic chemistry as these compounds can be used as precursors for the synthesis of important heterocyclic compounds. Several methods have been reported for the synthesis of 1,3-oxathiolan-5-one through the reaction of thioglycolic acid with carbonyl compounds (*12–14*). However in this paper, the reaction of thioglycolic acid with carbonyl compounds afforded bisthioglycolic acid derivatives.

Our literature survey at this stage revealed that there are no reports on the synthesis of bisthioglycolic acid derivatives under solvent- and catalyst-free conditions. Our main strategy is to develop a green organic reaction enhancement methodology, which is relatively faster and cleaner than conventional reactions. As part of our ongoing research program on the development of clean protocols under solvent-free conditions (*15–17*) herein, we report a facile one-pot synthesis of symmetrical bisthioglycolic acid derivatives **3** via coupling of aldehydes/ketone **1** and thioglycolic acid **2** under solvent- and catalyst-free conditions at 80°C (Scheme 1).

Results and discussion

Treatment of aromatic aldehyde/cyclohexanone **1** and thioglycolic acid **2** afforded the corresponding bisthioglycolic acid derivatives **3** under catalyst free and solvent free at 80°C in short reaction times with good yields (Scheme 1).

In order to standardize the reaction, 4-chlorobenzaldehyde (2 mmol) and thioglycolic acid (2 mmol) to give **3e** were explored first. The mixture was heated in an oil bath at 80°C. Compound **3e** has been obtained after 3 min without using any solvent or catalyst (Table 1, Entry 5).

To establish the generality of the method, these conditions were employed for other aldehydes. The results are summarized in Table 1. The experimental procedure is very simple and proceeds smoothly under these solvent- and catalyst-free conditions and gives the title compounds **3a-s** in excellent yields.

Our research shows that this method has many dramatic advantages such as the short reaction time (3–5 min), high yields (87–97%) and environmental benign, as well as convenient to operate.

As shown in Table 1, the direct reaction worked well with a variety of aryl aldehydes including those bearing electron-donating and electron-withdrawing groups such as Me, OMe, Cl, Br, CN, F, and NO_2, and the desired compounds were obtained in high-to-excellent

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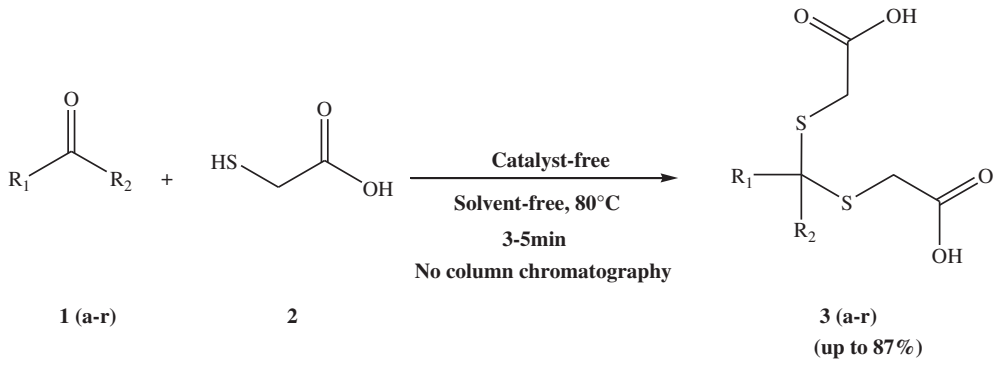


Scheme 1. Synthesis of various symmetrical bisthioglycolic acid derivatives.

yields. In general, the use of 4-methoxybenzaldehyde and 4-methylbenzaldehyde gave low yields of the desired products. Furthermore, cyclohexanone gave the corresponding product under the above reaction conditions (Table 1, Entry 17). The present protocol was also found to be effective for the aliphatic aldehydes. Thus, butyraldehyde reacted cleanly with thioglycolic acid to give product **3r** in 90% yield (Table 1, Entry 18).

The practical synthetic efficiency of this reaction was highlighted by the reaction of terephthaldehyde with thioglycolic acid to give the corresponding product **3s** (Scheme 2).

Products were characterized by infrared (IR), ^{1}H nuclear magnetic resonance (NMR), ^{13}C NMR, and physical constant. A plausible reaction mechanism for the synthesis of symmetrical bisthioglycolic acid under solvent- and catalyst-free conditions is shown in Scheme 3.

In summary, we have described a convenient and environmentally green methodology for the synthesis of novel symmetrical bisthioglycolic acid derivatives in the absence of catalyst under solvent-free conditions in excellent yields. The advantages of the present procedure are experimental simplicity, easy work-up, and high yields of products. Furthermore, product isolation does not require purification by column chromatography.

Experimental

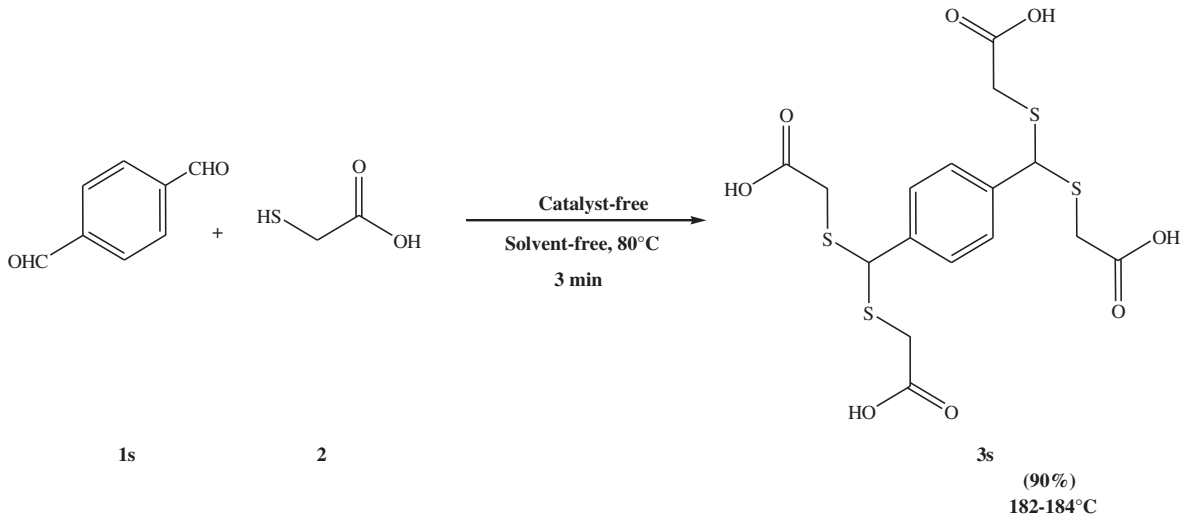
General remarks

Chemicals were purchased from Merck and Aldrich. Melting points were determined in open capillary tubes and are uncorrected. IR measurements were

Table 1. Catalyst-free and solvent-free synthesis of bisthioglycolic acid derivatives.[a]

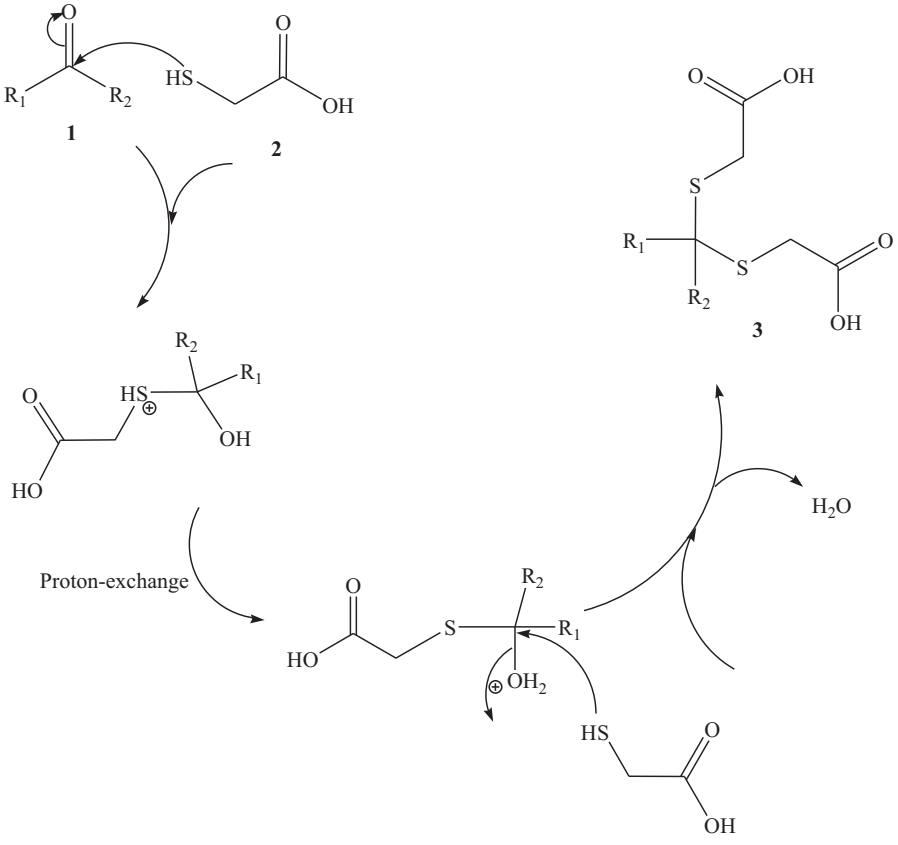
Entry	Aldehyde/ketone	Product	Time (min)	Yield (%)[b]	M.p (°C)
1	Benzaldehyde	**3a**	5	90	96–98
2	4-Methylbenzaldehyde	**3b**	5	87	94–96
3	4-Methoxybenzaldehyde	**3c**	5	87	111–112
4	4-(*N,N*-dimethyl)benzaldehyde	**3d**	5	90	oil
5	4-Chlorobenzaldehyde	**3e**	3	97	150–151
6	2-Chlorobenzaldehyde	**3f**	3	90	141–142
7	4-Cyanobenzaldehyde	**3g**	3	90	130–132
8	4-Bromobenzaldehyde	**3h**	5	90	115–116
9	4-Fluorobenzaldehyde	**3i**	3	95	157–160
10	4-Nitrobenzaldehyde	**3j**	5	93	160–162
11	3-Nitrobenzaldehyde	**3k**	5	95	103–104
12	2-Nitrobenzaldehyde	**3l**	5	92	115–117
13	2,3-Dichlorobenzaldehyde	**3m**	5	95	122–125
14	2,4-Dichlorobenzaldehyde	**3n**	5	97	140–142
15	2-Naphtaldehye	**3o**	5	90	127–129
16	Furfuraldehyde	**3p**	3	87	oil
17	Cyclohexanone	**3q**	5	90	123–125
18	Butyraldehyde	**3r**	5	90	oil

Note: [a]Reaction conditions: aldehyde (2 mmol), thioglycolic acid (2 mmol), 80°C.
[b]Isolated yield.



Scheme 2. The condensation of terephthaldehyde with thioglycolic acid under solvent- and catalyst-free conditions.

carried out using KBr pellets in Bruker Tensor A27 FTIR spectrometer. ^{1}H (250 MHz) and ^{13}C (62.5 MHz) NMR spectra were recorded on a Bruker Avance 250 spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as internal reference. All reactions were monitored by thin-layer chromatography (TLC) using silica gel 60 GF_{245} precoated sheets 20–20 cm, layer thickness 0.2 mm (E-Merck), and were visualized by ultraviolet (UV) lamp at wavelength (l) 254 nm. The elemental analysis was performed with an Elemental Analyses system GmbH VarioEL CHNS mode.



Scheme 3. A plausible reaction mechanism for the synthesis of symmetrical bisthioglycolic acid 3.

General procedure for the synthesis of bisthioglycolic acid derivatives (3a-s)

A mixture of aldehydes/ketones **1** (1 mmol) and thioglycolic acid **2** (2 mmol) was stirred at 80°C for 3–5 min. The progress of reactions was monitored by TLC (ethyl acetate/*n*-hexane). After completion of the reaction, the reaction mixture was cooled to room temperature and the product was purified by crystallization from chloroform/petroleum ether to give the pure product **3a-s**.

The spectral (IR, ^{1}H NMR, ^{13}C NMR) and analytical data of selected compounds are given below:

Compound **3f** (Entry 6): IR (KBr) (νmax/cm^{-1}): 3430–2568 (br), 1705 (s), 1429 (m), 1302 (m), 752 (m); ^{1}H NMR (250 MHz, $CDCl_3$): 3.24 (d, 2H, J = 15.75 Hz, CH_2), 3.63 (d, 2H, J = 15.75 Hz, CH_2), 6.05 (S, 1H, CH), 7.23–7.74 (m, 4H, ArH), 11.0 (s, 2H, 2OH) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): 33.6, 48.4, 127.5, 129.5, 129.7, 133.4, 135.9, 138.3, and 176.9 ppm. Anal. Calcd. For $C_{11}H_{10}Cl_2O_4S_2$: C, 43.07; H, 3.61; S, 20.90; Found: C, 43.0; H, 3.58; S, 20.83.

Compound **3h** (Entry 8): IR (KBr) (νmax/cm^{-1}): 3400–2660 (br), 1735 (s), 1669 (s), 1489 (w), 1289 (m), 1151 (s), 767 (w); ^{1}H NMR (250 MHz, $CDCl_3$): 3.15 (d, 2H, J = 15.5 Hz, CH_2), 3.62 (d, 2H, J = 15.5 Hz, CH_2), 5.52 (S, 1H, CH), 7.26–7.83 (m, 4H, ArH), 10.98 (s, 2H, 2OH) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): 33.6, 50.5, 130.5, 129.8, 132.0, 138.3, and 176.8 ppm. Anal.CalcdFor$C_{11}H_{11}BrO_4S_2$: C, 37.62; H, 3.16; S, 18.26; Found: C, 37.60; H, 3.11; S, 18.23.

Compound **3k** (Entry 11): IR (KBr) (νmax/cm^{-1}): 3432–2669 (br), 1705 (s), 1519 (s), 1348 (s), 1299 (m), 723 (w); ^{1}H NMR (250 MHz, $CDCl_3$): 3.35 (d, 2H, J = 15.65 Hz, CH_2), 3.65 (d, 2H, J = 15.65 Hz, CH_2), 5.45 (S, 1H, CH), 7.63–8.21 (m, 4H, ArH), 10.93 (s, 2H, 2OH) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): 33.7, 51.91, 127.5 127.7, 130.5, 131.5, 133.6, 138.3, and 176.8 ppm. Anal.Calcd. For $C_{11}H_{11}NO_6S_2$: C, 41.63; H, 3.49; N, 4.41; S, 20.21; Found: C, 41.58; H, 3.46; N, 4.37; S, 20.16.

Compound **3m** (Entry 13): IR (KBr) (νmax/cm^{-1}): 3425–2565 (br), 1704 (s), 1420 (m), 1310 (m), 937 (w), 756 (w); ^{1}H NMR (250 MHz, $CDCl_3$): 3.25 (d, 2H, J = 15.75 Hz, CH_2), 3.64 (d, 2H, J = 15.75 Hz, CH_2), 6.10 (S, 1H, CH), 7.24–7.71 (m, 3H, ArH), 10.92 (s, 2H, 2OH) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): 33.7, 50.8, 127.7 127.9, 130.5, 131.5, 133.6, 138.3, and 176.8 ppm. Anal. Calcd. For $C_{11}H_{10}Cl_2O_4S_2$: C, 38.72; H, 2.95; S, 18.79; Found: C, 38.63; H, 2.87; S, 18.70.

Compound **3o** (Entry 15): IR (KBr) (νmax/cm^{-1}): 3436–2681 (br), 1725 (s), 1284 (m), 1196 (m), 758 (m); ^{1}H NMR (250 MHz, $CDCl_3$): 3.21 (d, 2H, J = 15.5 Hz, CH_2), 3.65 (d, 2H, J = 15.5 Hz, CH_2), 5.75 (S, 1H, CH), 7.26–7.99 (m, 7H, ArH), 11.56 (s, 2H, 2OH) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): 33.2, 51.9, 127.7, 128.1, 129.1, 132.8, 133.4, 134.9, and 177.4 ppm. Anal. Calcd. For $C_{15}H_{14}O_4S_2$: C, 55.88; H, 4.38; S, 19.89; Found: C, 55.75; H, 4.30; S, 19.81.

Compound **3q** (Entry 17): IR (KBr) (νmax/cm^{-1}): 3436–2681 (br), 1715 (s), 1203 (m); ^{1}H NMR (250 MHz, $CDCl_3$): 1.46–1.48 (m, 2H, CH_2), 1.62–1.64 (m, 4H, $2CH_2$), 1.83–1.85 (m, 4H, $2CH_2$), 3.48 (s, 4H, CH_2-S) 12.17 (s, 2H, 2OH) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): 22.1, 24.5, 25.4, 31.7, 37.0, 62.0, and 177.7 ppm. Anal. Calcd. For $C_{11}H_{18}O_4S_2$: C, 47.46; H, 6.52; S, 23.04; Found: C, 47.51; H, 6.50; S, 23.0.

Compound **3s** (Scheme 2): IR (KBr) (νmax/cm^{-1}): 3430–2695 (br), 1720 (s), 2110 (m); ^{1}H NMR (250 MHz, $CDCl_3$): 3.15–3.76 (m, 8H, $4CH_2$), 5.60 (S, 2H, 2CH), 7.70–7.93 (m, 4H, ArH), 10.03 (s, 4H, 4OH) ppm; ^{13}C NMR (62.5 MHz, $CDCl_3$): 41.1, 53.1, 128.8, 137.4, and 178.4 ppm. Anal. Calcd. For $C_{16}H_{18}O_8S_4$: C, 41.19; H, 3.89; S, 27.49; Found: C, 41.01; H, 4.0; S, 27.57.

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