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 bisthioalicyclic 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 bisthioalicyclic acid derivatives.

Our literature survey at this stage revealed that there are no reports on the synthesis of bisthioalicyclic 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 bisthioalicyclic 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 bisthioalicyclic 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 NO2, and the desired compounds were obtained in high-to-excellent

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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), 1H nuclear magnetic resonance (NMR), 13C 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

![Scheme 1. Synthesis of various symmetrical bisthioglycolic acid derivatives.](image)

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-Naphthaldehyde         | 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: aReaction conditions: aldehyde (2 mmol), thioglycolic acid (2 mmol), 80°C.
bIsolated yield.
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\(_{254}\) precoated sheets 20–20 cm, layer thickness 0.2 mm (E-Merck), and were visualized by ultraviolet (UV) lamp at wavelength (\(\lambda\)) 254 nm. The elemental analysis was performed with an Elemental Analyses system GmbH VarioEL CHNS mode.

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

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, ¹H NMR, ¹³C NMR) and analytical data of selected compounds are given below:

Compound 3f (Entry 6): IR (KBr) (νmax/cm⁻¹): 3430–2681 (br), 1715 (s), 1203 (m), 1170 (m). ¹H NMR (250 MHz, CDCl₃): 3.24 (d, 2H, J = 15.75 Hz, CH₂), 3.62 (d, 2H, J = 15.75 Hz, CH₂), 6.05 (S, 1H, CH), 7.70 (m, 4H, ArH), 11.0 (s, 2H, 2OH) ppm; ¹3C NMR (62.5 MHz, CDCl₃): 33.2, 51.9, 127.7, 127.9, 138.3, and 177.7 ppm. Anal. Calcd. For C₁₁H₁₁BrO₄S₂: 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); ¹H NMR (250 MHz, CDCl₃): 3.25 (d, 2H, J = 15.75 Hz, CH₂), 3.64 (d, 2H, J = 15.75 Hz, CH₂), 6.10 (S, 1H, CH), 7.24–7.71 (m, 3H, ArH), 10.92 (s, 2H, 2OH) ppm; ¹³C NMR (62.5 MHz, CDCl₃): 33.7, 50.8, 127.7, 127.9, 130.5, 131.5, 133.6, 138.3, and 176.8 ppm. Anal. Calcd. For C₁₁H₁₁BrO₄S₂: C, 41.63; H, 3.49; S, 18.79; Found: C, 38.63; H, 2.87; S, 18.70.

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