New synthetic pathways for Thiocarbohydrazide and Salicylaldehyde azine compounds

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Abstract

Thiocarbohydrazide synthesis is an important intermediate step for many hydrazine organic synthetic reactions. Synthesis of thiocarbohydrazide can be done by reaction of carbon disulfide with hydrazine (hydrazinolysis) in water at 0 ^{o}C giving 25% yield (based on [hydrazine]). However, in this article, we achieve a 96% yield (based on [hydrazine]) by carrying out the reaction in methanol at 24 ^{o}C. The thiocarbohydrazide is then used to synthesize 1,5-bis(2-hydroxybenzaldehyde)dithiocarbohydrazone. By refluxing the latter compound in pyridine at 80 ^{o}C, it decomposes and rearranges to give salicylaldehyde azine.

Key words: Thiocarbohydrazide; salicylaldehyde azine; hydrazinolysis

1. Introduction

The chemistry and applications of thiocarbohydrazide in synthetic organic chemistry and biological sciences have recently been reviewed [1]. The applications of this compound include assessment process of the three-dimensional ultrastructure examination techniques of interphase nuclei and tissues; use as fogging agent; use in cool-burning pyrotechnic compounds for dissemination of smoke; use in chemical warfare and as therapeutic agents; use in performing a highly selective heavy metal ion adsorbent and as complexing agents in solvent extraction separation methods *etc*. As such, laboratory synthesis of thiocarbohydrazide by many chemists is unavoidable. Green chemistry practice would then suggest a synthetic pathway that produces less solvent waste with very high-quality product yields. Currently, thiocarbohydrazide can be synthesized using hydrazinolysis pathway that was patented 62 years ago [2]. However, this method gives a 25% product yield based on hydrazine concentration. Consequently, there is a high waste solvent generation. This research article reports a new pathway that allows a 96% high-quality product yield with minimal waste solvent generation.

The thiocarbohydrazide is then used to synthesize 1,5-bis(2-hydroxybenzaldehyde)dithiocarbohydrazone. Attempts to silylate the 1,5-bis(2-hydroxybenzaldehyde)dithiocarbohydrazone by 3-(triethoxysilyl)propyl isocyanate using literature method [3] results into a mixture of compounds. Column separation of the mixture yields yellow crystals. These crystals are herein characterized and their synthetic pathway proposed. The new pathway is then used in the synthesis of salicylaldehyde azine.

2. Methodology

2.1. Chemicals

All the chemical materials were purchased from Alpha Aesar and used as received without further purification, although tetraethoxysilane (TEOS, Aldrich) was distilled and stored under nitrogen atmosphere.

2.2. Synthesis of thiocarbohydrazide according to literature [2]

A 500 mL two neck round bottomed flask was connected to a reflux apparatus and dipped in a water bath. Ice cubes were placed in the water bath and the temperature allowed to acclimatize at about 0 °C. Then 0.4 moles of 85% hydrazine hydrate was added to the flask and stirred using a magnetic stirrer. After about 2 minutes, 0.08 moles of carbon disulfide was added slowly while the hydrazine solution was vigorously agitated for about 60 minutes. Then 120 mL of water was added. The reaction mixture was then refluxed at 95 °C for 8 hours. Finally, the solution was permitted to cool to room temperature and the resultant precipitate, thiocarbohydrazide, was separated by filtration. The precipitate was washed with water and dried in vacuum. The crude product was purified by recrystallization from water and finally obtained as white needles, yield 0.1 moles (25%). M.p. 171–172 °C [2]; 1H-NMR (DMSO): δ 4.48 (s, 4H, NH_2), 8.79 (m, 2H, NH).

2.3. Synthesis of thiocarbohydrazide (New method)

A 500 mL two neck round bottomed flask was connected to a reflux apparatus and 0.4 moles of 85% hydrazine hydrate added to the flask and stirred using a magnetic stirrer at 24 °C. Then 0.08 moles of carbon disulfide was added slowly while the hydrazine solution was vigorously agitated for about 60 minutes. Then 120 mL of methanol was added. The reaction mixture was then refluxed at 60 °C for 8 hours. Finally, the solution was permitted to cool to room temperature and the resultant precipitate, thiocarbohydrazide, was separated by filtration. The precipitate was washed with methanol and dried. The crude product was purified by dissolving in water at 40 °C and cooling to room temperature first before refrigeration at 0 °C for 12 hrs. The white needle crystals finally obtained were washed with methanol and dried in vacuum. The actual yield was 0.38 moles (96%). M.P. 171–172 °C [2], 1H-NMR (DMSO): δ 4.47 (s, 4H, NH_2), 8.68 (d, 2H, NH).

2.4. Synthesis of 1,5-bis(2-hydroxybenzaldehyde)dithiocarbohydrazone [4]

Salicylaldehyde (4.4 mmol) was dissolved in 20 mL of absolute ethanol, and then 2 mmol of thiocarbohydrazide dissolved in 10 mL of absolute ethanol was added dropwise. The resulting mixture was warmed at 80 °C under reflux for about 3 hours. After cooling, the precipitate was filtered off. The crude product was purified by recrystallization from absolute ethanol and finally obtained as yellow crystals, yield 1.72 mmol (85.3%). M.P. 190-191 °C [4], 1H-NMR: δ 4.35 (s, 2H, NH, NH); 6.69 (d, 2 H, Ar); 7.30 (t, 2 H, Ar); 7.42 (d, 1 H, Ar); 8.02 (s, 1 H, Ar); 8.52 (d, 1 H, Ar); 8.77 (s, 1 H, Ar); 10.03 (s, 1 H, OH); 11.6 (s, 1 H, OH); 12 (m, 2 H, ArCH). 13C-NMR ($CDCl_3$): 119, 120, 121, 129, 134 (10 C, Ar); 143 (2 C, ArCH); 152 (1 C, C-OH); 160 (1 C, C-OH); 177 (1 C, C=S).

2.5. Synthesis of Benzaldehyde,2-hydroxy-,2-[(2-hydroxyphenyl)methylene]hydrazine (also called salicylaldehyde azine) (New Method)

In a 100 mL three neck round bottomed flask 1,5-bis(2-hydroxybenzaldehyde)dithiocarbohydrazone (1 mmol) was first dissolved in 20 mL of pyridine. Thereafter, 3-(Triethoxysilyl)-propyl isocyanate (TESPIC) (2.0 mmol) dissolved in 10 mL of pyridine was added dropwise with stirring, the mixture was warmed at 80 °C for approximately 12 h in a covered flask at the nitrogen atmosphere. After isolation and purification, a yellow oil sample was obtained. The oil sample showed a mixture of compounds on a TLC plate. As such, it was treated to column purification EtOAc: PetroEther 2:1. Salicylaldehyde azine easily separated from the oil product forming shiny yellow needle crystals in the fractions. A similar result was also obtained by washing the air dried oil product with cold hexane. In addition, similar results were obtained when 1,5-bis(2-hydroxybenzaldehyde)dithiocarbohydrazone (1 mmol) was refluxed at 80 °C in 20 mL pyridine for 24 hours. M.P. 190-191 ^{o}C [5, 6]; 1H-NMR ($CDCl_3$): δ 6.69 (s, 4H, Ar); 7.42 (m, 2H, Ar); 7.70 (m, 2H, Ar); 9.00 (s, 2H, ArCH); 11.12 (s, 2H, OH). 13C-NMR ($CDCl_3$): 116.50 (2 C, Ar); 118.17 (2 C, Ar); 119.57 (2 C, Ar); 130.80 (2 C, Ar); 133.20 (2 C, Ar); 158.61 (2 C ArCH); 162.75 (2 C, Ar).

2.6. Measurements

The data for 1H-NMR, and 13C-NMR, spectra were obtained on a Bruker AV400 NMR spectrometer at the resonance frequency of 400 MHz. Fourier transform infrared (FT-IR) spectra were carried out on a Bruker Vector 22 infrared spectrometer using KBr pellet method. Electrospray ionization mass spectra (ESI-MS) were recorded using a Xevo G2 QT ESI-MS. Surface morphology was observed using a scanning electron microscope (SEM) (Zeiss Supra 55) machine.

3. Results and Discussion

In the laboratory, researchers encounter different challenges that include non-intended results. In this work, synthesis of thiocarbohydrazide [2] in large amounts was desired so as to synthesize 1,5-bis(2-hydroxybenzaldehyde)dithiocarbohydrazone and finally Silylate it using 3-(triethoxysilyl)-propyl isocyanate [3]. However, carbon disulfide (CS_2) partially dissolved in water at 0 ^{o}C. This resulted in a reduction in yields of the resultant thiocarbohydrazide (25%). As such, ways were sought to improve on yields and loss of CS_2 that is relatively expensive. Since CS_2 is a non-polar compound, hence less soluble in water, methanol was tried as a solvent instead of water. The result was amazing with the formation of white crystals that were characterized as thiocarbohydrazide (96% yield based on [hydrazine] as the limiting reagent).

Characterization of both products obtained in water and methanol as reaction solvents using 1H NMR and FTIR (see **Fig. 1**) show the products to be similar. The FTIR shows thiocarbonyl groups (R^1CSR^2) with a stretch at 1286 cm^{-1}, while primary amines (R^1NH_2) record two peaks at 3306 and 3273 cm^{-1}. The secondary amines have a peak at 3204 cm^{-1}. It was also noted that direct transfer of the recrystallization sample to refrigeration without cooling to room temperature results into poor yields (35%).

The methanol product has an advantage over the water product. The latter takes place at 0 ^{o}C while methanol product takes place at room temperature (24 ^{o}C) with increased yields 96%. The morphology of a powder sample from methanol product before recrystallization shows a crystalline product whereas the sample from water product shows small crystals coagulated together (see **Fig. 2a-d**). However, after recrystallization of both samples in water, the morphology was similar (see **Fig. 2e,f**).

After it was certified that the product from methanol extract was thiocarbohydrazide, 1,5-bis(2-hydroxybenzaldehyde)dithiocarbohydrazone was synthesized and fully characterized (see **Fig. 3).** In the FTIR spectra, the vibrations at 3022 can be assigned to NH_2, 2960 to C-H, 3211 to N-H, 1143 to C-N, 680 to C=S, while 977.97 to N-C-S. However, attempts to silylate 1,5-bis(2-hydroxybenzaldehyde)dithiocarbohydrazone using 3-(triethoxysilyl)-propyl isocyanate [3] bore no fruits as the resultant product was a mixture of compounds. On trying to separate the compounds using column chromatography, a yellow compound separated easily from the rest in large amounts (67% using the concentration of 1,5-bis(2-hydroxybenzaldehyde)dithiocarbohydrazone as limiting reagent). The other compounds were inseparable; hence another silylation method was applied. Nevertheless, apart from reporting the difficulty in silylation, the product that was separated from this method was fully characterized and found to be salicylaldehyde azine (see **Fig. 4**). The reaction mechanism of this compound is suggested in **Fig. 5**. This mechanism was proved by refluxing the 1,5-bis(2-

hydroxybenzaldehyde)dithiocarbohydrazone in pyridine at 80 °C for 24 hours and the same yellow compound was isolated (97% using the concentration of 1,5-bis(2-hydroxybenzaldehyde)dithiocarbohydrazone). Pyridine is a strong organic base destructs the hydrogen bonding in 1,5-bis(2-hydroxybenzaldehyde)dithiocarbohydrazone making it decompose via the indicated mechanisms. Replacing pyridine with acetone gave no observable changes to the reaction mixture. The whole reaction mechanisms of salicylaldehyde azine production are then schematically represented in **Fig. 6.**

The chemistry of salicylaldehyde azine has been studied/applied in many fields such as turn-on fluorescence probe for egg albumin detection [7], a fluorescent probe for thiols [8], two-photon laser absorption materials [6], Cu^{2+} electrochemical sensors [9], and inducing fluorescence in aggregation mixtures [10]. Therefore any new information on how this compound can be prepared is of great importance to the scientific community. Previously [6], salicylaldehyde azine has been prepared by taking 2-hydroxy-benzaldehyde (0.1 mol) and dissolving in 95% ethanol (60 mL). Then hydrazine hydrate (0.05 mol) was dissolved in 95% ethanol (25 mL) and added slowly with constant stirring to the aldehyde solution. The exothermic reaction is then driven to completion by reflux for two hours followed by cooling to room temperature (24 °C) that result in deposition of yellow crystals. Followed by filtration and recrystallized from ethanol/water (1:1) mixture and dried under vacuum.

Conclusions

In this article, a high yield of thiocarbohydrazide (96% based on [hydrazine]) is achieved when the reaction mixture is changed from water to methanol. This method saves on the loss of carbon disulfide that is relatively expensive. Furthermore, the ability of 1,5-bis(2-hydroxybenzaldehyde)dithiocarbohydrazone to decompose in pyridine and rearrangement to give salicylaldehyde azine is reported.

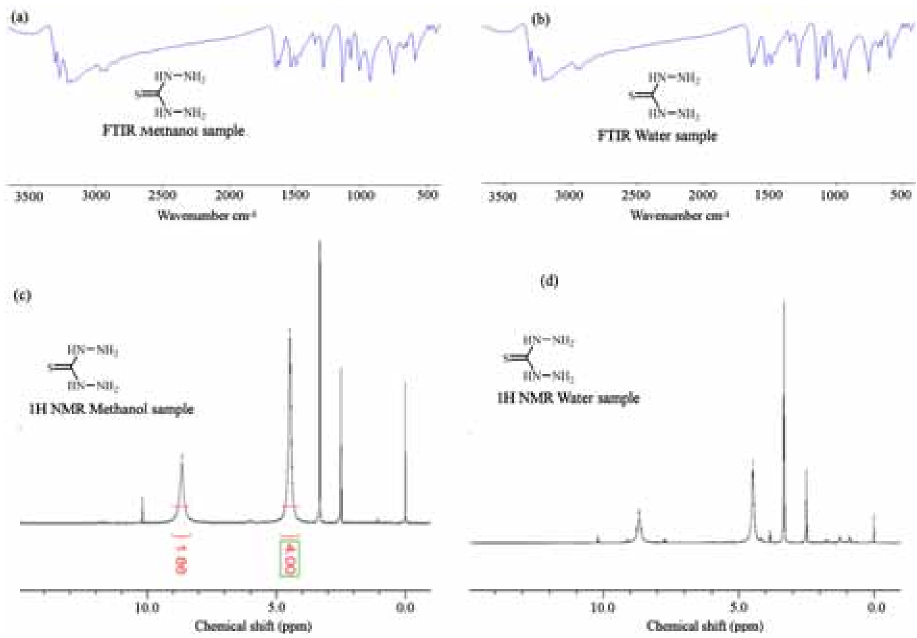

Fig. 1 FTIR and 1H NMR for thiocarbohydrazide prepared through methanol and water synthetic pathways

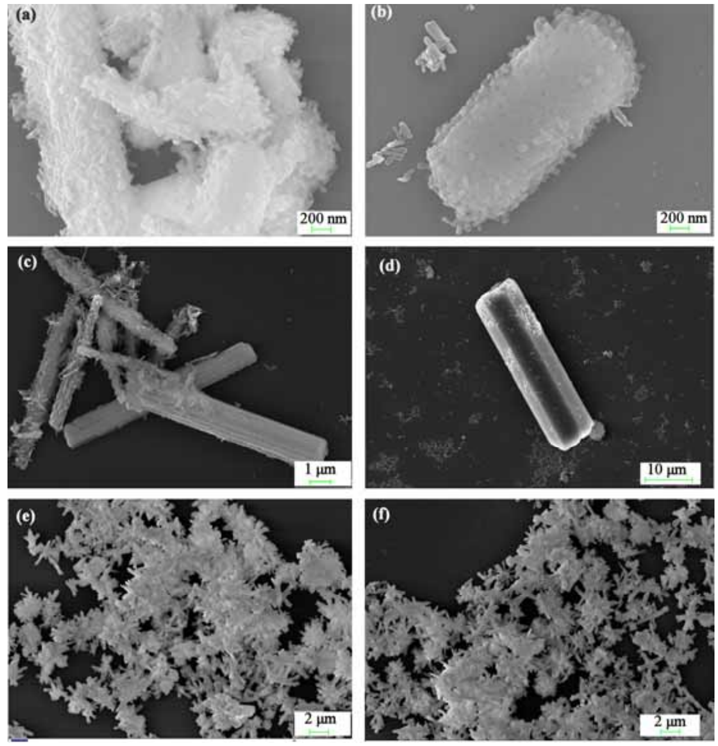

Fig. 2 Morphological differences between thiocarbohydrazide prepared in water (a, b), and in methanol (c, d) as reaction solvents. The monograms were taken after the two samples were powdered. Morphologies in (e and f) are for both samples after recrystallization in water.

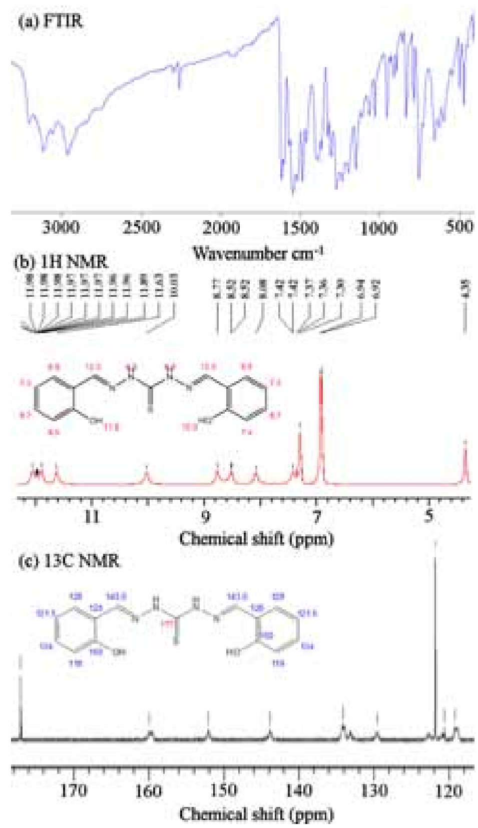

Fig. 3 FTIR (a), 1H NMR (b) and 13C NMR (c) for 1,5-bis(2-hydroxybenzaldehyde)dithiocarbohydrazone

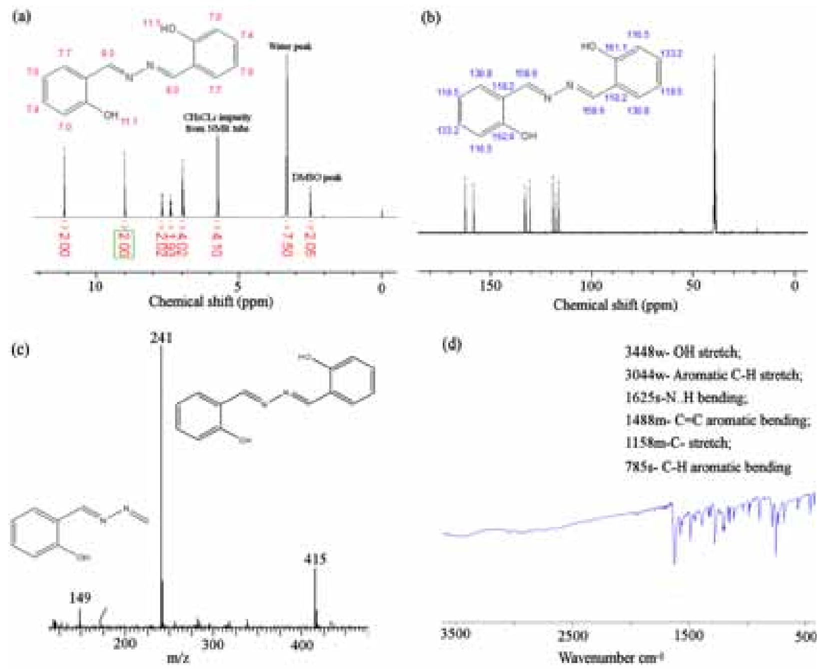

Fig. 4 1H NMR (a), 13C NMR (b), Mass spectrum (c) and FTIR (d) of Benzaldehyde,2-hydroxy-,2-[(2-hydroxyphenyl)methylene]hydrazine

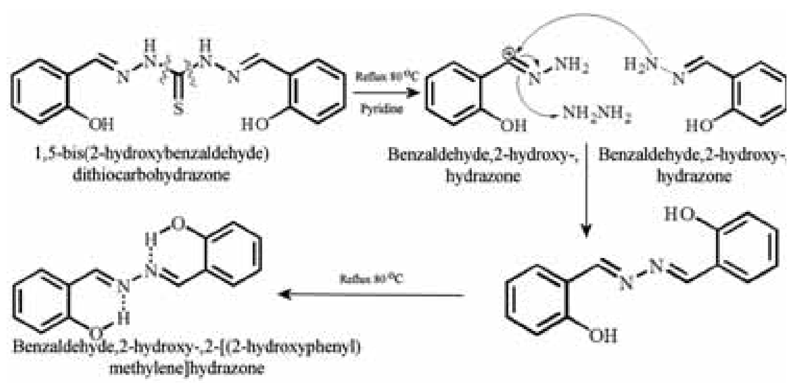

Fig. 5 Proposed reaction mechanism for the formation of Benzaldehyde,2-hydroxy-,2-[(2-hydroxyphenyl)methylene]hydrazine

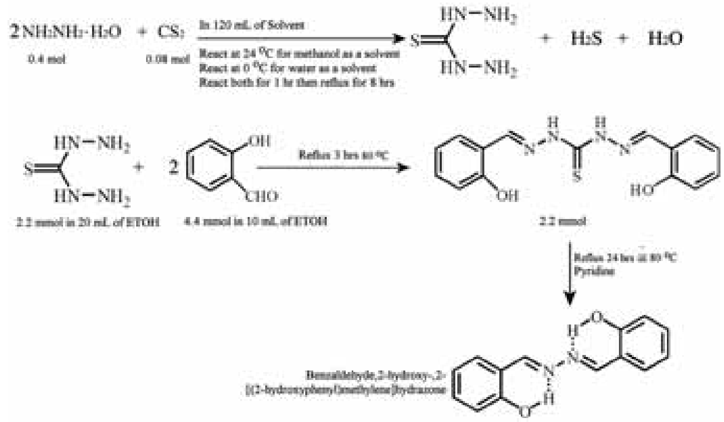

Fig. 6 Synthetic pathways of thiocarbohydrazide and benzaldehyde,2-hydroxy-,2-[(2-hydroxyphenyl)methylene]hydrazine compounds

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