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Short Note

1,2-Dibenzoylthiosemicarbazide

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Abstract: When 1-benzoylthiosemicarbazide (**2**) or thiosemicarbazide (**1**) were treated with benzoyl chloride in a basic medium, a mixture of two compounds was obtained: 1,2-dibenzoylthiosemicarbazide (**3**) and 1,4-dibenzoylthiosemicarbazide (**4**). To determine the structure of the novel compounds, 2D NMR spectroscopy techniques such as ^{1}H-^{13}C and ^{1}H-^{15}N were employed.

Keywords: benzoylation; thiosemicarbazide; 1-benzoylthiosemicarbazide; 1,2-dibenzoylthiosemicarbazide; 1,4-dibenzoylthiosemicarbazide

1. Introduction

The great interest in the last years for 3-substituted 4*H*-5-mercapto-1,2,4-triazoles (**6**) and their derivatives is due to their various uses, especially as biologically active compounds [1–5].

Within our studies on obtaining *S*-glycosides [6], we have synthesized 1*H*-3-phenyl-5-mercapto-1,2,4-triazoles (**6**) by the benzoylation of thiosemicarbazide with benzoyl chlorides in the presence of pyridine in organic solvent, followed by the cyclization of 1-benzoylthiosemicarbazides with bases in aqueous-alcoholic medium [7].

During monobenzoylation of thiosemicarbazide, the formation of several secondary compounds was observed, but they were easily removed during the cyclization of crude 1-benzoylthiosemicarbazides (**2**) to 5-mercapto-1,2,4-triazoles (**6**).

1-Acylthiosemicarbazides are used in the preparation of heterocyclic compounds [8,9], but the literature reports few details on the acylation reaction as follows:

- During monobenzoylation of thiosemicarbazide with benzoyl chloride in pyridine, 1-benzoylthiosemicarbazide (**2**) is formed as the main product, along with small amounts of 1,4-dibenzoylthiosemicarbazide (**4**) [10];
- After treatment of 1-benzoylthiosemicarbazide (**2**) with benzoyl chloride at 0 °C, 1,4-dibenzoylthiosemicarbazide (**4**) and 1,2-dibenzoylhydrazine (**5**) are formed in ~15% and ~25% yield, respectively [11];
- Upon treatment of benzoyl chloride with excess thiosemicarbazide, 1-benzoylthiosemicarbazide (**2**) is formed with a high yield [12].

As a result, we were motivated to conduct experiments with the aim of separating and characterizing the compounds generated when thiosemicarbazide (**1**) reacted with two equivalents of benzoyl chloride, and when 1-benzoylthiosemicarbazide (**2**) reacted with one equivalent of benzoyl chloride in the presence of pyridine, using DMF as the solvent.

2. Results and Discussion

Following some preliminary experiments [13,14], we found that heating the crude products formed in the two reactions in an alkaline medium led to 1*H*-5-mercapto-3-phenyl-1,2,4-triazole (**6**) (η = 20%), originating from the cyclization and hydrolysis of 1,4-dibenzoylthiosemicarbazide (**4**) or from the cyclization of 1-benzoylthiosemicarbazide (**2**), and to 1,2-dibenzoylhydrazine (**5**) (η = 75%), which can originate only from the hydrolysis of 1,2-dibenzoylthiosemicarbazide (**3**). The reaction scheme is shown in Scheme 1:

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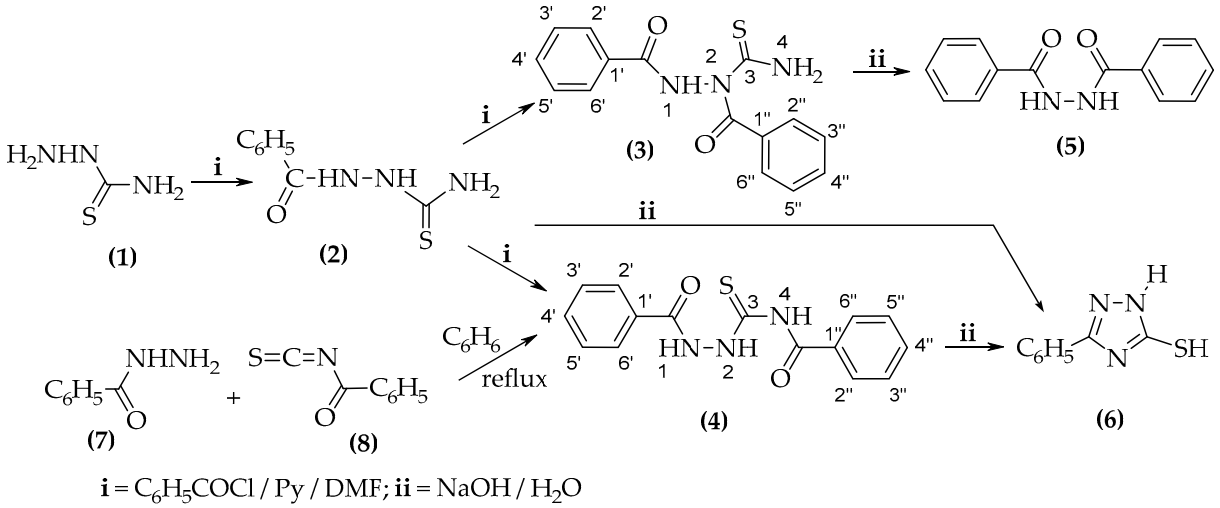

Scheme 1. Synthesis of 1,2-dibenzoylthiosemicarbazide (**3**) and 1,4-dibenzoylthiosemicarbazide (**4**).

In this study, we provide an analysis of the isolation and identification process of 1,2-dibenzoylthiosemicarbazide (**3**). Furthermore, we present the outcomes obtained from the benzoylation reactions of thiosemicarbazide (**1**) and 1-benzoylthiosemicarbazide (**2**) with different amounts of benzoyl chloride in the presence of pyridine and NaH, using DMF as the solvent.

Using HPLC, we monitored the progress of the benzoylation process involving thiosemicarbazide (**1**) and 1-benzoylthiosemicarbazide (**2**) in the presence of pyridine and benzoyl chloride. The results revealed the development of a diverse mixture containing benzoylthiosemicarbazides (**2**), (**3**), and (**4**). Tables 1 and 2 provide the molar percentages of these compounds at different stages of the reaction.

Table 1. Benzoylation of thiosemicarbazide (**1**) conditions and products' molar percentages.

No.	Benzoylation of (1) Molar Ratio and Temperature	Time	(2) (%)	(3) (%)	(4) (%)
1.	(**1**)/BzCl/Py = 1/1.05/2 ~20 °C	15 min	94.79	4.4	0.8
		30 min	56.9	37.1	6
2.	(**1**)/BzCl/Py = 1/2.1/ 2.2 ~20 °C	2 h	61.0	35.1	3.9
		24 h	48.2	46.7	5.1
3.	(**1**)/BzCl/NaH = 1/1.05/1.1 ~20 °C	15 min	99.9	0.01	0.08
		24 h	99.9	0.01	0.08

Table 2. Benzoylation of 1-benzoylthiosemicarbazide (2) conditions and products' molar percentages.

No.	Benzoylation of (2) Molar Ratio and Temperature	Time	(2) (%)	(3) (%)	(4) (%)
1.	(**2**)/BzCl/Py = 1/1.05/1.2 ~20 °C	2 h	43.0	55.4	1.6
		24 h	38	59.9	2.1
2.	(**2**)/BzCl/NaH = 1/1.05/1.1 ~20 °C	15 min	79.97	17.65	3.26
		24 h	84.38	15.53	0.09

During the process of the dibenzoylation of thiosemicarbazide (**1**) and the benzoylation of 1-benzoylthiosemicarbazide (**2**), we observed an increase over time of the percentage of 1,2-dibenzoylthiosemicarbazide (**3**) over the percentage of 1,4-dibenzoylthiosemicarbazide (**4**) and also the formation of the monobenzoylation product when starting from thiosemicarbazide (**1**).

For the benzoylation reaction of thiosemicarbazide (**1**), when using NaH as the base, only 1-benzoylthiosemicarbazide (**2**) is formed, while using the same base in the benzoylation reaction of 1-benzoylthiosemicarbazide (**2**) besides the unreacted starting material, a majority formation of 1,2-dibenzoylthiosemicarbazide (**3**) is observed.

Using the 2D ^{1}H-^{13}C and ^{1}H-^{15}N NMR spectra (HMBC and HSQC), we were able to accurately assign the corresponding proton and carbon signals. The chemical shifts of nitrogen atoms in the synthesized compounds were obtained from the inverse correlation spectra of ^{1}H-^{15}N type of direct coupling (HSQC or HMQC) or long-range coupling over two or three bonds (HMBC). In the case of 1,2-dibenzoylthiosemicarbazide, the chemical shifts for the nitrogen atoms 1-N and 4-N, respectively, were determined from the direct coupling ^{1}H-^{15}N HMQC spectrum and for the nitrogen atom 2-N from the long-range coupling ^{1}H-^{15}N HMBC spectrum, when long-range couplings over two bonds with the hydrogen atom 1-N-H and over three bonds with the hydrogen atoms 4-N-H, respectively. For 1,4-dibenzoylthiosemicarbazide, the chemical shifts for all the nitrogen atoms could be determined only from the direct coupling ^{1}H-^{15}N HMQC spectrum.

It can be observed that the protons bound to the nitrogen atom 4-N both in the case of 1,2-dibenzoylthiosemicarbazide and 1,4-benzoylthiosemicarbazide are diastereotopic, exhibiting different chemical shifts. Thus, in the ^{1}H-^{15}N HMQC spectra of these two compounds, two cross-peaks can be observed for the nitrogen atom 4-N, corresponding to the couplings with the two diastereotopic hydrogen atoms, H_a and H_b, respectively.

3. Materials and Methods

All of the compounds were purified and kept under argon; the reactions were also performed under an argon atmosphere. The solvents were purchased from commercial sources (Chimopar, Bucharest, Romania, Acros Organics, Geel, Belgium) and used after distillation and drying. Commercial thiosemicarbazide was recrystallized from water.

TLC analysis was performed on 60 F254 silica gel plates from Merck, using 1:1 hexane: ethyl acetate or 7:3 (*v*/*v*) as eluent.

Melting points were measured on a Böetius PHMK apparatus (Veb Analytik, Dresden, Germany) and were uncorrected.

IR spectra were recorded on a Jasco FT/IR-410 spectrophotometer (Jasco Corporation, Tokyo, Japan) in KBr pellets.

HPLC determinations were carried out on a Jasco HPLC system (quaternary pump and UV-VIS detector) with a C18 Phenomenex or Synergi 4u Hydro-RP 80 A column, with acetonitrile:water = 86:14 (*v*/*v*) flow 0.4 mL/min (25 °C) and a UV-2070 Plus detector.

GC-MS analysis was performed by using an ion trap mass spectrometer ITQ 1100 coupled with Gas Chromatograph Trace 1310 (Thermo Scientific, Waltham, MA, USA). MS parameters were set as follows: transfer line temperature at 300 °C, source temperature at 170 °C, a scan range between 50 and 700 amu, and a 70 eV electron was used for ionization. Separation was achieved on a capillary column of 30 m × 0.25 mm ID, 0.25 µm (TG–5MS, Thermo Scientific); the injection port temperature was set at 310 °C. An automated sample delivery system (TriPlus RSH, Thermo Scientific, Waltham, MA, USA) with a split ratio of 1/30 for 1.5 min followed by a splitless mode was used for sample injection. The oven program was set as follows: 100 °C (held 1 min) to 300 °C (held 3 min) with 10 °C/min.

NMR spectra were recorded on a Bruker DRX 400 MHz, Bruker AVANCE III 400 MHz and 500 MHz spectrometers (Bruker, Karlsruhe, Germany), in DMSO-*d6* using TMS as an internal standard for protons and carbons. Chemical shifts are reported in ppm units and the coupling constants are given in Hz.

4. Experimental

Synthesis of Benzoylthiosemicarbazides

(a) Benzoylation of thiosemicarbazide (I)

To a solution of 0.01 mol thiosemicarbazide (**1**) in 5 mL DMF, 0.012 mol or 0.022 mol pyridine was added, at room temperature, and 0.01 and 0.02 mol benzoyl chloride, respectively.

(b) Benzoylation of 1-benzoylthiosemicarbazide (II)

To a solution of 0.01 mol of 1-benzoylthiosemicarbazide (**2**) in 5 mL of DMF, 0.012 mol of pyridine was added, at room temperature, and 0.01 mol of benzoyl chloride.

The benzoylated thiosemicarbazide mixtures I and II were used to monitor the benzoylation of thiosemicarbazide (**1**) and 1-benzoylthiosemicarbazide (**2**) by HPLC.

1-benzoylthiosemicarbazide (**2**) was obtained by the reaction of thiosemicarbazide with benzoyl chloride in DMF in the presence of pyridine at 50 °C and precipitation in water. White crystalline powder (η = 62%), m.p.= 191–194 °C (MeOH) (lit. 196–198 °C) [14]. IR (ν/cm^{-1}): ν_{asNH2} = 3542; ν_{sNH2} = 3418; ν_{NH} = 3240; $\nu_{C=O}$ = 1684, ν_{skC6H5} = 1605; $\nu_{C=S}$ = 1086; γ_{skC6H5} = 704; ^{1}H-NMR $\boldsymbol{\delta_H}$ (DMSO-*d6*, 500 MHz): 10.40 (s, 1H, 1-N-H), 9.36 (s, 1H, 2-N-H), 7.90 (d, 2H, *J* = 7.4 Hz, 2′-H, 6′-H), 7.89 (br. s, 1H, 4-N-H_a), 7.65 (br. s, 1H, 4-N-H_a), 7.56 (t, 1H, *J* = 7.4 Hz, 4′-H), 7,47 (t, 2H, *J* = 7.6 Hz, 3′-H, 5′-H); ^{13}C-NMR $\boldsymbol{\delta_C}$ (DMSO-*d6*, 125 MHz): 181.9 (C=S), 165.7 (C=O), 132.3 (1′-C), 131.6 (4′-C), 128.0 (3′-C, 5′-C), 127.7 (2′-C, 6′-C); ^{15}N-NMR δ_N (DMSO-*d6*, 50.6 MHz): 132.1 (1-N), 121.8 (2-N), 108.6 (4-N). All related spectra can be found in Supplementary Materials section.

1,4-Dibenzoylthiosemicarbazide (**4**) was obtained from benzoylhydrazine (**7**) and benzoyl isothiocyanate (**8**), according to a method from the literature [15]. White crystalline powder (η = 67%), m.p. = 179–180 °C (EtOH) (lit. 178 °C) [16]; IR (ν/cm^{-1}): ν_{NH} = 3298, 3270; $\nu_{C=O}$ =1666, 1655; ν_{skC6H5} = 1598, 1579; $\nu_{C=S}$ = 1076; γ_{skC6H5} = 711, 698; ^{1}H-NMR $\boldsymbol{\delta_H}$ (DMSO-*d6*, 400 MHz): 12.44 (s, 1H, 1-N-H), 11.79 (s, 1H, 4-N-H), 11.16 (s, 1H, 2-N-H), 8.00 (d, 2H, *J* = 7.6 Hz, 2″-H, 6″-H), 7.96 (d, 2H, *J* = 7.6 Hz, 2′-H, 6′-H), 7.66 (t, 1H, *J* = 7.4 Hz, 4″-H), 7,61 (t, 1H, *J* = 7.4 Hz, 4′-H), 7.54 (t, 4H, *J* = 7.6 Hz, 3′-H, 5′-H, 3″-H, 5″-H); ^{13}C-NMR $\boldsymbol{\delta_C}$ (DMSO-*d6*, 100 MHz): 180.4 (C=S), 167.7 (4-N-C=O), 164.4 (1-N-C=O), 133.1 (4″-C); 132.0 (1′-C, 1″-C), 131.8 (4′-C), 128.6 (2″-C, 6″-C), 128.4 (3″-C, 5″-C), 128.3 (3′-C, 5′-C), 127.6 (2′-C, 6′-C); ^{15}N-NMR $\boldsymbol{\delta_N}$ (DMSO-*d6*, 40 MHz): 155.1 (4-N), 146.1 (1-N), 138.3 (2-N); MS (70 eV) *m*/*z*: 299 (M+, 1%), 281 (M+-H_2O, 7%), 222 (M+-·C_6H_5, 25%), 105 (M+-$C_8H_8N_3OS$, 100%) Calcd. for $C_{15}H_{13}N_3O_2S$: C, 60.19; H, 4.38; N, 14.04; S, 10.71. Found (%): C, 59.99; H, 4.18; N, 13.87; S, 10.49. All related spectra can be found in Supplementary Materials section.

1,2-Dibenzoylthiosemicarbazide (**3**) was obtained from the reaction mixture from the benzoylation of thiosemicarbazide (**1**) with two equivalents of benzoyl chloride in DMF in the presence of pyridine or from the benzoylation of 1-benzoylthiosemicarbazide (**2**) with one equivalent of benzoyl chloride in DMF in the presence of pyridine, precipitation in water, and two recrystallizations from acetonitrile, in 42% and 45% yield, respectively. White crystalline powder, m.p. = 159–161 °C. IR (ν/cm^{-1}): ν_{NH} = 3386, 3125; $\nu_{C=O}$ = 1711, 1672; ν_{skC6H5} = 1600, 1580; $\nu_{C=S}$ = 1073; γ_{skC6H5} = 706, 735.

^{1}H-NMR $\boldsymbol{\delta_H}$ (DMSO-*d6*, 400 MHz): 11.37 (s, 1H, 1-N-H), 9.84 (s, 1H, 4-N-H_a), 9.52 (s, 1H, 4-N-H_b), 7.70–7.69 (m, 2H, 2′-H, 6′-H), 7.69–7.68 (m, 2H, 2″-H, 6″-H), 7.53 (tt, 1H, *Jo* = 7.3 Hz, *Jm* = 1.3 Hz, 4″-H), 7.47–7.38 (m, 5-H, 3′-H, 4′-H, 5′-H, 3″-H, 5″-H); ^{13}C-NMR $\boldsymbol{\delta_C}$ (DMSO-*d6*, 100 MHz): 183.7 (C=S), 172.1 (2-N-C=O), 165.1 (1-N-C=O), 134.8 (1″-C); 132.0 (4″-C), 131.6 (1′-C), 131.1 (4′-C), 128.3 (3′-C, 5′-C), 127.6 (3″-C, 5″-C), 127.4 (2′-C, 6′-C); 127.3 (2″-C, 6″-C); ^{15}N-NMR δN (DMSO-*d6*, 40 MHz): 168.4 (2-N), 145.9 (1-N); 130.8 (4-N)); MS (70 eV) *m*/*z*: 299 (M+, 1%), 281(M+-H_2O,18%), 222 (M+-·C_6H_5, 14%), 105 (M+-$C_8H_8N_3OS$, 100%); Calcd. (%) for $C_{15}H_{13}N_3O_2S$: C, 60.19; H, 4.38; N, 14.04; S, 10.71. Found (%): C, 59.98; H, 4.18; N, 13.78; S, 10.51. All related spectra can be found in Supplementary Materials section.

5. Conclusions

The benzoylation and dibenzoylation of thiosemicarbazide (**1**), as well as the benzoylation of 1-benzoylthiosemicarbazide (**2**) with benzoyl chloride in DMF in the presence of pyridine or NaH, lead to mixtures of compounds, from which the two isomers, 1,2-dibenzoylthiosemicarbazide (**3**) and 1,4-dibenzoylthiosemicarbazide (**4**), have been identified, isolated, and characterized.

1,2-Dibenzoylthiosemicarbazide (**3**) is, surprisingly, a compound that has not been isolated to date, which is formed preferentially over its isomer, 1,4-dibenzoylthiosemicarbazide (**4**).

Supplementary Materials: The following supporting information can be downloaded. Figure S1. ^{1}H NMR spectrum of the compound (**2**), Figure S2. ^{13}C NMR spectrum of the compound (**2**), Figure S3. ^{13}C DEPT135 spectrum of the compound (**2**), Figure S4. COSY ^{1}H-^{1}H spectrum of the compound (**2**), Figure S5. HSQC ^{1}H-^{13}C spectrum of the compound (**2**), Figure S6. HMBC ^{1}H-^{13}C spectrum of the compound (**2**), Figure S7. HMBC ^{1}H-^{15}N spectrum of the compound (**2**), Figure S8. HSQC ^{1}H-^{15}N spectrum of the compound (**2**), Figure S9. FT-IR spectrum of the compound (**2**), Figure S10. ^{1}H NMR spectrum of the compound (**3**), Figure S11. ^{13}C NMR spectrum of the compound (**3**), Figure S12. ^{13}C DEPT135 spectrum of the compound (**3**), Figure S13. COSY ^{1}H-^{1}H spectrum of the compound (**3**), Figure S14. HMQC ^{1}H-^{13}C spectrum of the compound (**3**), Figure S15. HMBC ^{1}H-^{15}N spectrum of the compound (**3**), Figure S16. HMQC ^{1}H-^{15}N spectrum of the compound (**3**), Figure S17. FT-IR spectrum of the compound (**3**), Figure S18. MS spectrum of the compound (**3**), Figure S19. ^{1}H NMR spectrum of the compound (**4**), Figure S20. ^{13}C NMR spectrum of the compound (**4**), Figure S21. ^{13}C DEPT135 spectrum of the compound (**4**), Figure S22. COSY ^{1}H-^{1}H spectrum of the compound (**4**), Figure S23. HMQC ^{1}H-^{13}C spectrum of the compound (**4**), Figure S24. HMBC ^{1}H-^{13}C spectrum of the compound (**4**), Figure S25. HMQC ^{1}H-^{15}N spectrum of the compound (**4**), Figure S26. FT-IR spectrum of the compound (**4**), Figure S27. MS spectrum of the compound (**4**).

Author Contributions: B.V. designed the experiments; B.I., T.A. and B.V.-N. performed the experiments; B.V. analyzed the spectral data; B.I. wrote the manuscript; B.V.-N provided supervision. All authors have read and agreed to the published version of the manuscript.

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