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A facile synthesis of thiosemicarbazides containing the 4-antipyrinyl group under microwave irradiation in solvent-free conditions

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A simple, efficient and eco-friendly method for the synthesis of a series of thiosemicarbazides containing 4-antipyrinyl group under microwave irradiation has been reported, no solvent and catalyst was used. Five of them are new compounds.

Keywords: Thiosemicarbazides; 4-Antipyrinyl isothiocyanate; Microwave; Solvent-free

1. Introduction

Thiosemicarbazides are a class of very important substances are associated with various biological activities such as antifungal [1, 2], anti-HIV [3, 4], and herbicidal activities [5]. Recent studies have shown that some of these compounds can be used as corrosion inhibitors of steel [6, 7], and some can be used as semiconductors [8]. Moreover, the complexes [9–13] and cyclized [14–18] products of them are also intensively studied because of their biological and other properties.

4-Aminoantipyrine is a versatile reagent which has been extensively utilized in heterocyclic synthesis. It has been found that 4-aminoantipyrine and its derivatives possess antibacterial [19] and anti-innanunatory [20] properties, meanwhile, the Schiff bases of 4-aminoantipyrine and its complexes have a variety of applications including the biological, clinical, analytical and pharmacological areas [21–25], too. Here, we reported a synthesis of 4-antipyrinyl isothiocyanate, and synthesized a series of new heterocyclic compounds that derived from it.

Microwave-assisted heating has been shown to be an invaluable technology in synthesis [26], since it often dramatically reduces reaction times, typically from days or hours to minutes or even seconds. And it can also provide pure products in quantitative yields. Solvent-free reaction techniques were successfully coupled with microwave because they avoid the using of low boiling points and high vapor pressure solvents, which may sometimes lead to explosions.

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Additionally, it can also avoid the use of poisonous and expensive solvent, and as such can be environmentally benign, and make manipulations much easier.

So, we introduce the microwave-assisted solvent-free method to the synthesis of thiosemicarbazides containing 4-antipyrinyl group, to find more rapid and efficient procedure. Microwave synthesis can accelerate the availability of compounds for screening protocols which in turn can identify compounds with functional qualities.

As a part of our former work on the reaction of 4-antipyrinyl isothiocyanate with various amino acids [27], aryl hydrazine, aromatic amines [28], heterocyclic amines, we studied the reaction of 4-antipyrinyl isothiocyanate with five acylhydrazines, and five substituted phenylhydrazines that were not synthesized in our early work.

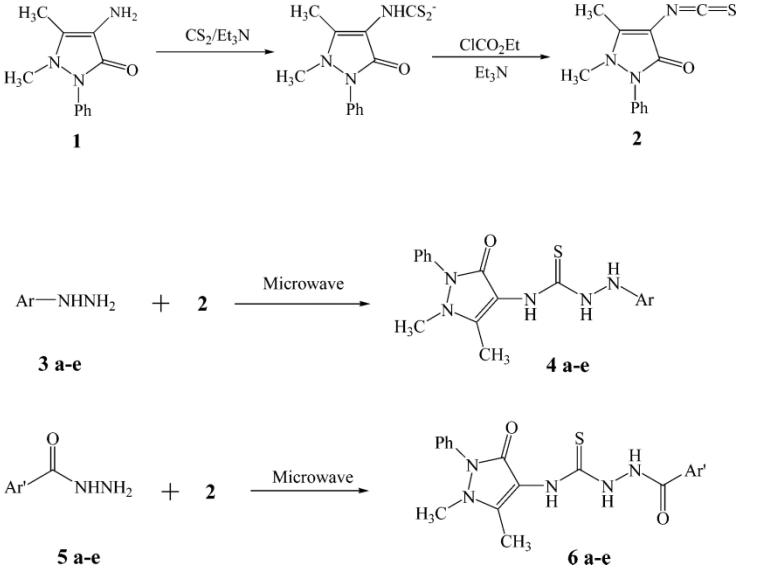
As shown in scheme 1, the 4-antipyrinyl isothiocyanate **2** was obtained on the reaction of 4-aminoantipyrine **1** with carbon disulfide and ethyl chlorocarbonate in the presence of triethylamine as catalyst, and then it reacted with various substituted phenylhydrazines **3a–e** to afford corresponding products **4a–e**. Also, thiocyante **2** was reacted with five acylhydrazines **5a–e** to obtain thiosemicarbazides **6a–e**. The structures of **4a–e** and **6a–e** were characterized by IR, ^{1}H NMR, ^{13}C NMR, and elemental analysis.

Compared with conventional heating condition, the use of microwave for the synthesis of thiosemicarbazides under solvent-free condition proved to be an efficient, safe and environmentally benign technique that with short reaction time (from about 2 hours to several minutes), high yields, and easier manipulation.

And more detailed work about the application of these compounds in analytical chemistry and physiological activity is in progress in other laboratory. The preliminary results show that some compounds could be used to measure microcopper in the aluminium alloycan and some can promote chrysanthemums to transplant and take root.

2. Experimental

Melting points were determined with an XRC-1 micro melting point apparatus and were uncorrected. Infrared spectra were recorded on a FTS-40 spectrophotometer using KBr Pellets.



SCHEME 1

^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker DPX-400 spectrometer at 400 and 100 MHz, respectively, using TMS as internal standard and DMSO-d_6 as solvent. Chemical shifts (δ) were expressed in ppm downfield from internal standard TMS. Elemental analysis were performed on PE-2400 elemental analyzer. The experiment was carried out in Galanz domestic microwave oven (750 W).

2.1 *General procedure for 2*

According to ref. [27] 4-aminoantipyrine reacted with carbon disulfide and ethyl chlorocarbonate in presence of triethylamine as catalyst to get the intermediate 4-antipyrinyl isothiocyanate **2.**

2.2 *General procedure for 3a–e*

According to ref. [29] the aromatic amines was treated with $NaNO_2$/HCl, then was reduced by $SnCl_2$ in HCl liquid at -11°C to afford corresponding substituted phenylhydrazines.

2.3 *General procedure for 5a–d*

In a typical procedure, the substituted phenoxyacetic acids **5a–c/**1-naphthylacetic acid **5d** 0.1 mol was dissolved in 0.4 mol 85% hydrazine hydrate, the mixture was heated at 90°C for 4 h, on cooling, a white crystal was separated out, then was recrystallized with ethanol to get the pure acylhydrazides.

2.4 *General procedure for 4a–e and 6a–e*

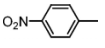
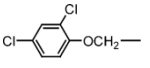
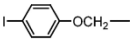
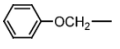
Equimolar quantities of substituted phenylhydrazines **3a–e/**acylhydrazides **5a–e** (0.1 mmol) and 4-antipyrinyl isothiocyanate **2** (0.1 mmol) was thoroughly mixed in an agate mortar, then the mixture was put into microwave oven at 495W for specified time (see table 1) under solvent-free condition (the end of the reaction was monitored by TLC). After the reaction was completed, the crude products were recrystallised from ethanol, and dried in vacuum to yield the pure products. Among them **4b**, **4c**, **6b**, **6c**, **6d** are new compounds.

2.5 *Spectroscopic data of compounds 4a–e and 6a–e*

2.5.1 1-Phenyl-4-antipyrinyl thiosemicarbazide (4a). Yellow-needle; IR(KBr) ν: 3284 (N−H), 3194 (N−H), 3149 (N−H), 1670 (C=O), 1644 (C=C), 1598, 1542, 1488, 1293 (C=S) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.13 (s, 3H, CH_3), 3.06 (s, 3H, CH_3), 6.78–7.52 (m, 10H, ArH), 8.01 (s, 1H, N−H), 8.86 (s, 1H, N−H), 9.68 (s, 1H, N−H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 184.69 (C=S), 163.33 (C=O), 155.35, 149.08, 136.49, 130.00, 129.77, 127.01, 124.34, 120.66, 114.07, 110.81, 36.99, 12.12; Anal. Calcd for $C_{18}H_{19}N_5OS$: C, 61.17; H, 5.42; N, 19.81. Found: C, 61.09; H, 5.55; N, 19.87.

2.5.2 1-(2,3-Dimethylphenyl)-4-antipyrinyl thiosemicarbazide (4b). Yellow-needle; IR(KBr) ν: 3293 (N−H), 3261 (N−H), 3175 (N−H), 1668 (C=O), 1643 (C=C), 1590, 1541, 1488, 1300 (C=S) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.10 (s, 6H, 2CH_3), 2.22 (s, 3H, CH_3), 3.02 (s, 3H, CH_3), 6.62–7.50 (m, 8H, ArH), 7.52 (s, 1H, N−H), 8.82 (s, 1H, N−H), 9.61 (s, 1H, N−H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 184.31 (C=S), 163.39 (C=O), 155.44,

Table 1. The reaction time, Yield and M.p. of the thiosemicarbazides.

Product	Ar/Ar′	Reaction time (min)	Yield (%)	M.p. (°C)
4a		2	81	235–237
4b		3	98	236–238
4c		5	92	230–232
4d		3	94	226–228
4e		10	95	221–222
6a		5	92	192–194
6b		6	89	198–200
6c		5	94	196–198
6d		5	91	206–208
6e		3	97	209–210

146.43, 137.13, 136.50, 130.18, 130.00, 127.00, 126.56, 124.31, 122.59, 122.06, 110.77, 37.00, 20.93, 13.48, 12.16; Anal. Calcd for $C_{20}H_{23}N_5OS$: C, 62.97; H, 6.08; N, 18.36. Found: C, 63.09; H, 6.02; N, 18.21.

2.5.3 1-(2-Chlorophenyl)-4-antipyrinyl thiosemicarbazide (4c). Yellow-needle; IR (KBr) ν: 3335 (N−H), 3173 (N−H), 1660 (C=O), 1615 (C=C), 1595, 1536, 1490, 1294 (C=S) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.14 (s, 3H, CH_3), 3.07 (s, 3H, CH_3), 6.81–7.52 (m, 9H, ArH), 7.94 (s, 1H, N−H), 8.94 (s, 1H, N−H), 9.74 (s, 1H, N−H); Anal. Calcd for $C_{18}H_{18}N_5ClOS$: C, 55.74; H, 4.68; N, 18.06. Found: C, 55.60; H, 4.61; N, 18.15.

2.5.4 1-(4-Chlorophenyl)-4-antipyrinyl thiosemicarbazide (4d). Yellow-tabular; IR (KBr) ν: 3330 (N−H), 3186 (N−H), 3117 (N−H), 1669 (C=O), 1640 (C=C), 1592, 1536, 1494, 1300 (C=S) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.12 (s, 3H, CH_3), 3.06 (s, 3H, CH_3), 6.77–7.52 (m, 9H, ArH), 8.19 (s, 1H, N−H), 8.93 (s, 1H, N−H), 9.73 (s, 1H, N−H); Anal. Calcd for $C_{18}H_{18}N_5ClOS$: C, 55.74; H, 4.68; N, 18.06. Found: C, 55.85; H, 4.60; N, 18.03.

2.5.5 1-(4-Nitrophenyl)-4-antipyrinyl thiosemicarbazide (4e). Yellow-needle; IR(KBr) ν: 3317 (N−H), 3163 (N−H), 3130 (N−H), 1670 (C=O), 1631 (C=C), 1594, 1508, 1496, 1330 (C−NO_2), 1302 (C=S) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.13 (s, 3H, CH_3), 3.06 (s, 3H, CH_3), 6.79–8.12 (m, 9H, ArH), 9.11 (s, 1H, N−H), 9.17 (s, 1H, N−H), 9.90 (s, 1H, N−H); Anal. Calcd for $C_{18}H_{18}N_6O_3S$: C, 54.26; H, 4.55; N, 21.09. Found: C, 54.15; H, 4.59; N, 21.15.

2.5.6 1-(2,4-Dichlorophenoxyacetyl-4-antipyrinyl thiosemicarbazide (6a). White-tabular; IR(KBr) ν: 3225 (N−H), 3168 (N−H), 3137 (N−H), 1724, 1680 (C=O), 1635 (C=C), 1581, 1269 (C=S) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.06 (s, 3H, CH_3), 3.05 (s, 3H, CH_3), 4.73 (s, 2H, CH_2), 7.10–7.57 (m, 8H, ArH), 8.90 (s, 1H, N−H), 9.65 (s, 1H, N−H), 10.22 (s, 1H, N−H); Anal. Calcd for $C_{20}H_{19}Cl_2N_5O_3S$: C, 50.01; H, 3.99; N, 14.58. Found: C, 49.94; H, 4.07; N, 14.45.

2.5.7 1-(4-Iodophenoxyacetyl)-4-antipyrinyl thiosemicarbazide (6b). Yellow-needle; IR(KBr) ν: 3365 (N−H), 3193 (N−H), 3155 (N−H), 1726, 1662 (C=O), 1624 (C=C), 1593, 1549, 1310, 1229 (C=S) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ2.06 (s, 3H, CH_3), 3.04 (s, 3H, CH_3), 4.56 (s, 2H, CH_2), 6.82–7.58 (m, 9H, ArH), 8.95 (s, 1H, N−H), 9.64 (s, 1H, N−H), 10.24 (s, 1H, N−H); Anal. Calcd for $C_{20}H_{20}IN_5O_3S$: C, 44.70; H, 3.75; N, 13.03. Found: C, 44.62; H, 3.89; N, 13.15.

2.5.8 1-phenoxyacetyl-4-antipyrinyl thiosemicarbazide (6c). White-needle; IR(KBr) ν: 3376 (N−H), 3279 (N−H), 3166 (N−H), 1703, 1667 (C=O), 1631 (C=C), 1592, 1523, 1496, 1242 (C=S) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.07 (s, 3H, CH_3), 3.04 (s, 3H, CH_3), 4.56 (s, 2H, CH_2), 6.92–7.49 (m, 10H, ArH), 8.96 (s, 1H, N−H), 9.65 (s, 1H, N−H), 10.25 (s, 1H, N−H). Anal. Calcd for $C_{20}H_{21}N_5O_3S$: C, 58.38; H, 5.14; N, 17.02; Found: C, 58.25; H, 5.09; N, 17.15.

2.5.9 1-(1-Naphthylacetyl)-4-antipyrinyl thiosemicarbazide (6d). White-needle; IR-(KBr) ν: 3235 (N−H), 3177 (N−H), 3140 (N−H), 1708, 1658 (C=O), 1627 (C=C), 1593, 1531, 1497, 1315 (C=S) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.07 (s, 3H, CH_3), 3.04 (s, 3H, CH_3), 3.97 (s, 2H, CH_2), 7.27–7.91 (m, 12H, ArH), 8.99 (s, 1H, N−H), 9.62 (s, 1H, N−H), 10.26 (s, 1H, N−H); Anal. Calcd for $C_{24}H_{23}N_5O_2S$: C, 64.70; H, 5.20; N, 15.72. Found: C, 64.62; H, 5.39; N, 15.65.

2.5.10 1-Benzoyl-4-antipyrinyl thiosemicarbazide (6e). White-needle; IR(KBr) ν: 3237 (N−H), 3174 (N−H), 3139 (N−H), 3130 (N−H), 1686, 1654 (C=O), 1648 (C=C), 1593, 1545, 1486, 1312 (C=S) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.10 (s, 3H, CH_3), 3.02 (s, 3H, CH_3), 7.28–7.91 (m, 10H, ArH), 9.06 (s, 1H, N−H), 9.69 (s, 1H, N−H), 10.52 (s, 1H, N−H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 183.54 (C=S), 166.38 (C=O), 162.83, 155.12, 135.87, 132.96, 132.17, 129.49, 128.60, 128.41, 126.48, 123.76, 110.35, 36.41, 11.51; Anal. Calcd for $C_{19}H_{19}N_5O_2S$: C, 59.82; H, 5.02; N, 18.36. Found: C, 59.79; H, 5.15; N, 18.31.

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