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Synthesis of Chalcone Thiosemicarbazones Under Ultrasound Irradiation

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A novel and efficient method to synthesize chalcone thiosemicarbazones was developed. Thiosemicarbazones were obtained in 76-93 % yields from the reactions of chalcones with thiosemicarbazide hydrochloride in presence of sodium acetate using dehydrated ethanol as solvent under ultrasound irradiation for 1.5-2.0 h at room temperature. Compared with the method of synthesis of chalcone thiosemicarbazones from chalcones and thiosemicarbazide catalyzed by acid under refluxing condition. The main advantages of this present procedure are milder conditions, higher yields and shorter reaction time.

Key Words: Chalcone thiosemicarbazones, Chalcone, Thiosemicarbazide hydrochloride, Ultrasound irradiation.

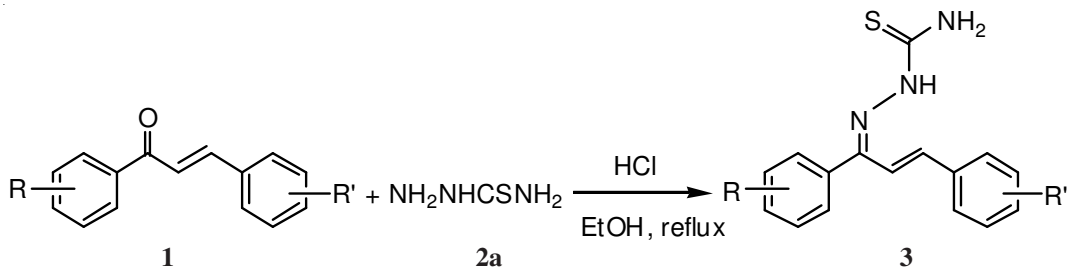
INTRODUCTION

Thiosemicarbazones are a class of small molecules that have activity of anticoncretion, antilepra, antirheumatism, antimalaria, antivirus, antivariola, antitumor and as antibacterium. They have been evaluated over the last 50 years as antivirals[1] and as antitumor therapeutics[2], as well as for their parasiticidal action against *Plasmodium falciparum*, *Trypanosoma brucei* and *Trypanosoma cruzi*[3,4]. Thiosemicarbazones and its complexes have remarkable activity of antitubercular, antibacterium, antiturmor, antifungal, anti HIV, anticonvulsant and antioxidant and so on[5-16]. However, there are few reports about the method to synthesize of chalcone thiosemicarbazones. Hans *et al.*[17] prepared some chalcone thiosemicarbazones (**3**) by refluxing chalcones (**1**) and thiosemicarbazide (**2a**) in dehydrated ethanol for more than 12 h (**Scheme-I**). However, the yields of those products weren't reported. We chose 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one to react with **2a** in dehydrated ethanol refluxing for 12 h by Hans's method[17], the corresponding product 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one thiosemicarbazone was obtained in only 40 % yield. The reaction time of this procedure was too long and the yield was not satisfactory.

Recently, ultrasonic chemistry has been received more and more attention. A large number of reactions can be carried out in higher yields, shorter reaction time and milder conditions under ultrasound irradiation[18-20]. In order to study metal complexes of **3**, we describe here a novel and efficient procedure for synthesizing **3** from **1** and thiosemicarbazide hydrochloride salt (**2b**) in presence of sodium acetate under ultrasound irradiation (**Scheme-II**).

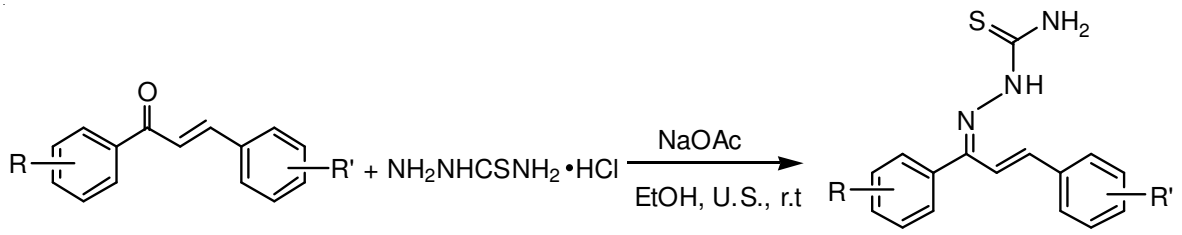
EXPERIMENTAL

Melting points were uncorrected. IR spectra were recorded on NICOLET 380 spectrometer instrument (KBr). ^{1}H and ^{13}C NMR spectra were measured on a Bruker AVANCE III 600 Plus spectrometer (600 MHz) using TMS as internal standard



1 **2a** **3**

Scheme-I: Synthesize chalcone thiosemicarbazone Schiff base by the method of Hans *et al.*[17]



1a-1m **2b** **3a-3m**

R = H; H; H; H; H; H; H; H; H; H; 4-Cl; 2-Cl; 4-OCH_3, R'= 4-NO_2; H; 4-Cl; 3-Cl; 2-Cl; 4-CH_3; 4-OCH_3; 2-OCH_3; 3,4-O_2CH_2; 4-$N(CH_3)_2$; 4-OCH_3; 4-OCH_3; 4-OCH_3; **a**; **b**; **c**; **d**; **e**; **f**; **g**; **h**; **i**; **j**; **k**; **l**; **m**

Scheme-II: Synthetic route to chalcone thiosemicarbazones, U.S. = Ultrasound, r.t. = Room temperature

and $CDCl_3$ as solvent. Sonication was performed in Shanghai Branson BUG25-06 (or 40-06) ultrasonic cleaner (with a frequency of 25 or 40 kHz and a nominal power 250 W).

General procedure: Chalcone (**1**, 0.3 mmol), thiosemicarbazide hydrochloride (**2b**, 0.3 mmol) and NaOAc (0.3 mmol) was added to 1 mL dehydrated ethanol. The reaction mixture was irradiated in the water bath of the ultrasonic cleaner with frequency of 25 kHz at 28-35 ºC. The reaction flasks were located in the maximum energy area in the cleaner (observation of the surface of the reaction solution during vertical adjustment of vessel depth will show the optimum position by the point at which maximum surface disturbance occurs). The reactions were followed by thin layer chromatography (TLC). After completion of the reaction, the products (**3**) were separated by column chromatography on silica gel (200-300 mesh, eluted with a mixture of petroleum ether and ethyl acetate).

3-(3-Chlorophenyl)-1-phenylallylidene thiosemicarbazide (3d): A slight yellow solid; ^{1}H NMR, δ: 6.40-6.42 (m, *J* = 16.4 Hz, 2H, 1H of CH=CH and 1H of NH_2), 7.10 (d, *J* = 16.4 Hz, 1H, CH=CH), 7.34-7.62 (m, 9H, Ph-H), 8.55 (s, 1H, NH_2); ^{13}C NMR, δ: 118.75, 125.19, 126.95, 128.26, 128.86, 129.26, 129.73, 130.03, 130.49, 134.85, 137.19, 137.69, 152.45, 181.48; IR (KBr, ν_{max}, cm^{-1}): 3410, 3308, 1582, 1498, 1444, 1278, 969; MS, m/z: 338.1.

3-(2-Chlorophenyl)-1-phenylallylidene thiosemicarbazide (3e): A yellow solid; ^{1}H NMR, δ: 6.40 (s, 1H, NH_2), 6.89 (d, *J* = 16.3 Hz, 1H, CH=CH), 7.04 (d, *J* = 16.3 Hz, 1H, CH=CH), 7.26-7.64 (m, 9H, Ph-H), 8.59 (s, 1H, NH_2); ^{13}C NMR, δ: 118.96, 126.79, 127.28, 128.27, 129.70, 129.83, 129.97, 130.20, 130.50, 133.90, 134.07, 134.83, 152.13, 179.27; IR (KBr, ν_{max}, cm^{-1}): 3405, 3236, 1595, 1474, 1437, 1285, 969; MS, m/z: 338.1.

3-(3,4-Methylenedioxy)phenyl-1-phenylallylidene thiosemicarbazide (3i): A orange yellow solid; ^{1}H NMR, δ: 5.99 (s, 2H, CH_2), 6.37 (d, *J* = 16.1 Hz, 1H, CH=CH,), 6.45 (s, 1H, NH_2), 6.89 (d, *J* = 16.1 Hz, 1H, CH=CH), 7.25-7.59 (m, 8H, Ph-H), 8.48 (s, 1H, NH_2); ^{13}C NMR, δ: 101.40, 105.77, 108.48, 122.88, 126.08, 128.30, 129.91, 130.11, 130.30, 130.38, 138.65, 148.33, 148.56, 152,58, 179.11; IR (KBr, ν_{max}, cm^{-1}): 3432, 3253, 1599, 1476, 1440, 1248, 960; MS, m/z: 348.1.

2-Chlorophenyl-3-(4-methoxyphenyl)allylidene thiosemicarbazide (3l): A slight yellow solid; ^{1}H NMR, δ: 3.73 (s, 3H, CH_3), 6.32 (d, *J* = 16.3 Hz, 1H, CH=CH), 6.53 (s, 1H, NH_2), 6.90 (d, *J* = 16.3 Hz, 1H, CH=CH), 7.30-7.64 (m, 8H, Ph-H), 8.46 (s, 1H, NH_2); ^{13}C NMR, δ: 57.78, 114.20, 118.72, 127.03, 127.41, 127.55, 129.74, 130.08, 131.11, 132.74, 133.67, 137.75, 155.63, 157.88, 178.84; IR (KBr, ν_{max}, cm^{-1}): 3412, 3255, 1603, 1482, 1442, 1248, 965; MS, m/z: 368.1.

RESULTS AND DISCUSSION

As shown in Table-1, the method for synthesizing **3** from **1** and **2b** in presence of sodium acetate is more efficient than that from **1** and **2a**. For example, when the reaction of 3-(4-nitrophenyl)-1-phenylprop-2-ene-1-one (**1a**) and **2b** was carried out in presence of sodium acetate at refluxing temperature for 5.5 h, the yield of **3a** was 71 % (Table-1, entry 4). Whereas, **3a** was obtained in 40 % yield by refluxing **1a** and **2a** in ethanol for 12 h (Table-1, entry 1) and in 55 % yield from **1a** and **2a** catalyzed by conc. HCl at refluxing temperature for 8 h (Table-1, entry 2). And using acetic acid as catalyst under refluxing for 6 h, **3a** was obtained in 60 % yield from **1a** and **2a** (Table-1, entry 3).

TABLE-1
THE REACTIONS OF **1a** AND **2a** OR **2b** UNDER DIFFERENT CONDITIONS

Entry	Reactant	Catalyst	Solvent	Condition	Time (h)	Yield* (%)
1	**1a, 2a**	–	Ethanol	Reflux	12	40
2	**1a, 2a**	HCl	Ethanol	Reflux	8	55
3	**1a, 2a**	HOAc	Ethanol	Reflux	6	60
4	**1a, 2b**, NaOAc	–	Ethanol	Reflux	5.5	71
5	**1a, 2a**	HOAc	Ethanol	u.s.; r.t.	2	0
6	**1a, 2a**	HCl	Ethanol	u.s.; r.t.	2	63
7	**1a, 2b**, NaOAc	–	Ethanol	u.s.; r.t.	1.5	85
8	**1a, 2b**, NaOAc	–	CH_2Cl_2	u.s.; r.t.	1.5	0
9	**1a, 2b**, NaOAc	–	Water	u.s.; r.t.	1.5	0
10	**1a, 2b**, NaOAc	–	70 % Aqueou ethanol	u.s.; r.t.	1.5	43

*Yield was based on chalcone; u.s.-Ultrasound; r.t.-Room temperature

Ultrasound irradiation improved the reaction of **1a** and **2b** in presence of sodium acetate. Under ultrasound irradiation with frequency of 25 kHz for 1.5 h at room temperature, **3a** was obtained in 85 % yield (Table-1, entry 7), whereas, **3a** was obtained in 71 % yield by refluxing **1a** and **2b** in presence of sodium acetate for 5.5 h. Ultrasound irradiation improved the reaction of **1a** and **2a** as well. Under ultrasound

irradiation for 2 h at room temperature, the reaction of **1a** and **2a** catalyzed by conc. HCl gave **3a** in 63 % yield (Table-1, entry 6), whereas, **3a** was obtained in 55 % yield from **1a** and **2a** catalyzed by conc. HCl at refluxing temperature for 8 h (Table-1, entry 2). But the reaction of **1a** and **2a** didn't take place by using acetic acid as catalyst at room temperature (Table-1, entry 5). The results above showed that the method for preparing **3a** from **1a** and **2b** in presence of sodium acetate under ultrasound irradiation at room temperature is efficiently.

The properties of the solvent affect the yield of this reaction. Using dehydrated ethanol as solvent, the reaction of **1a** and **2b** in presence of sodium acetate under ultrasound irradiation at room temperature gave **3a** in 85 % yield. However, the reaction gave **3a** in 43 % yield when using 70 % aqueous ethanol as solvent under the same condition (Table-1, entry 10). But this reaction didn't take place using CH_2Cl_2 or H_2O as solvent (Table-1, entrys 8, 9). The results showed that the dehydrated ethanol was the suitable solvent.

This method for synthesizing compound **3** could be applied in the reaction of various chalcones and **2b** and the good results were obtained under ultrasound irradiation (Table-2). The **1a-1m** reacted with **2b** in presence of sodium acetate under ultrasound irradiation with frequency of 25 kHz for 1.5-2.0 h at room temperature, giving **3a-3m** in 76-93 % yields.

TABLE-2
THE REACTIONS OF **1** AND **2b** AND NaOAc UNDER ULTRASOUND IRRADIATION IN ETHANOL

Entry	R	R'	Time (h)	Yield* (%)	m.p. (ºC) (Lit)
3a	H	4-NO_2	1.5	85	184-186 (185 [16])
3b	H	H	1.5	89	138-140 (143 [16])
3c	H	4-Cl	1.5	89	164-166 (164 [16])
3d	H	3-Cl	1.5	91	160-162
3e	H	2-Cl	1.5	88	186-188
3f	H	4-CH_3	1.5	89	152-154 (154 [16])
3g	H	4-OCH_3	1.5	90	140-142 (142 [16])
3h	H	2-OCH_3	1.5	87	176-178(174 [16])
3i	H	3,4-O_2CH_2	1.5	89	164-168
3j	H	4-$N(CH_3)_2$	1.5	88	160-162 (163 [16])
3k	4-Cl	4-OCH_3	1.5	93	210-212 (212 [16])
3l	2-Cl	4-OCH_3	2	76	164-166
3m	4-OCH_3	4-OCH_3	2	86	180-182 (180 [16])

*Yield was based on chalcone.

The steric effect of substituted groups affect the yields of compound **3**. When R was *ortho*-position substituent, the corresponding chalcone proved to be less reactive than that of R being *para*-position substituent and low yield of corresponding product was obtained. For example, the product **3l** was in 76 % yield under ultrasound irradiation for 2 h at room temperature, it was lower than that of compound **3k** (in 93 % yield under ultrasound irradiation for 1.5 h at room temperature). The electrical effects of substituted groups have little effect on the yields of compound **3** under ultrasound irradiation. The chalcone with electron-withdrawing or electron-donating groups showed high reactivity gave **3** in high yields (85-93 %) under ultrasound irradiation with frequency of 25 kHz for 1.5 h.

The reactions were carried out under ultrasound irradiation with frequency of 40 kHz as well. The results showed that the frequency of ultrasound irradiation had little effect on these reactions. The yields of these products were similarly under ultrasound irradiation for 25 kHz or 40 kHz.

Conclusion

In summary, a novel and efficient method for preparing chalcone thiosemicarbazones from chalcones and thiosemicarbazide hydrochloric salt in presence of sodium acetate under ultrasound irradiation is demonstrated. The reactions could be completed within 1.5-2.0 h at room temperature and the yields were improved to 76-93 %.

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