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Microwave-prompted Rapid and Efficient Synthesis of Diacyl Thiosemicarbazides and Semicarbazides in Solvent and Catalyst Free Condition

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Abstract: Eighteen 1-aroyl-4-(2-iodobenzoyl)thiosemicarbazides and corresponding semicarbazides were synthesized in excellent yield under microwave irradiation in solvent and catalyst free condition.

Keywords: Microwave irradiation, 1,4-diaroyl thiosemicarbazides, 1,4-diaroyl semicarbazides, solvent-free synthesis.

Microwave-promoted solvent-free heterogeneous reactions are well known as environmentally benign methods, which usually provide improved selectivity, enhanced reaction rates, cleaner products and manipulative simplicity[1,2].

The chemistry of thiosemicarbazides and semicarbazides have attracted much attention in recent years due to their broad spectrum biological activities and as important intermediate in the preparations of corresponding semicarbazides, metal complexes and heterocyclic compounds[3-5].

Generally, thiosemicarbazide was prepared by the reaction of isothiocyanate with hydrazide. Acyl isothiocyanate has been prepared by acyl chloride with ammonium thioacyanate by refluxing[6-7] in aprotic solvent (such as acetonitrile and acetone) or by using tetrabutylammonium bromide as liquid-liquid phase-transfer catalyst[8]. Harrison[9] has reported that polymer-supported thiocyanate was treated with benzoyl chloride in benzene to yield benzoyl isothiocyanate. Recently, benzoyl isothiocyanate on soluble polymer support has been synthesized from polymer-supported benzoyl chloride[10-11]. In our precious work, isothiocyanates have been prepared quantitatively using solid-liquid phase-transfer catalysis PEG-400 at room temperature or irradiated by microwave[12-14].

In continuation of our ongoing program to synthesize biologically active compounds[11-16] and develop benign and rapid strategy for organic transformation, we have explored an expeditious solvent-free method to the synthesis of 1-aroyl-4-(2-iodobenzoyl)-thiosemicarbazides under microwave irradiation (MWI) without catalyst (**Scheme 1**).

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Scheme 1

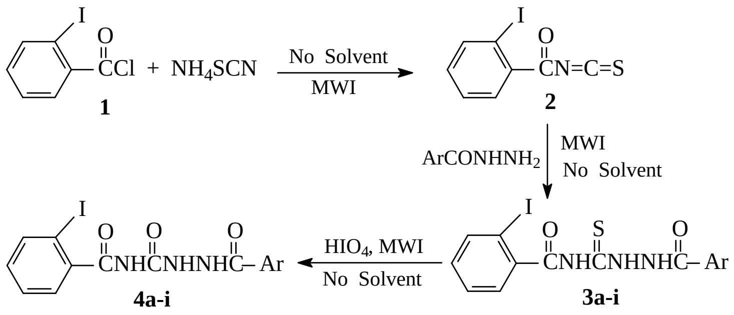

Table 1 Synthesis of **3a-i** and **4a-i** under MWI, solvent and catalyst free condition

Compd	Ar	m.p. (°C)	Yield (%)[a]		Elemental analysis (calcd.) (%)		
					C	H	N
3a	C_6H_5	159~160	88[b]	94[c]	42.45(42.37)	2.93(2.84)	9.76(9.88)
3b	4-$CH_3OC_6H_4$	202~203	83[b]	88[c]	42.12(42.21)	2.98(3.10)	9.41(9.23)
3c	2-ClC_6H_4	191~192	86[b]	86[c]	39.06(39.19)	2.30(2.41)	9.25(9.14)
3d	4-ClC_6H_4	183~184	85[b]	91[c]	39.11(39.19)	2.33(2.41)	9.24(9.14)
3e	2-IC_6H_4	264~265	84[b]	86[c]	32.73(32.69)	2.23(2.01)	7.58(7.62)
3f	4-BrC_6H_4	241~242	85[b]	88[c]	35.66(35.74)	2.34(2.20)	8.46(8.34)
3g	2-$NO_2C_6H_4$	199~200	80[b]	87[c]	38.24(38.31)	2.50(2.36)	11.87(11.91)
3h	4-$NO_2C_6H_4$	227~228	85[b]	88[c]	38.39(38.31)	2.41(2.36)	11.84(11.91)
3i	2-HOC_6H_4	169~170	84[b]	90[c]	40.74(40.83)	2.62(2.74)	9.68(9.52)
4a	C_6H_5	163~164	92[d]		43.94(44.03)	2.94(2.96)	10.33(10.27)
4b	4-$CH_3OC_6H_4$	220~221	94[d]		43.87(43.75)	3.33(3.21)	9.61(9.57)
4c	2-ClC_6H_4	209~210	93[d]		40.69(40.61)	2.68(2.50)	9.37(9.47)
4d	4-ClC_6H_4	201~202	96[d]		40.58(40.61)	2.63(2.50)	9.59(9.47)
4e	2-IC_6H_4	267~268	91[d]		33.74(33.67)	2.12(2.07)	7.93(7.85)
4f	4-BrC_6H_4	259~260	95[d]		36.84(36.91)	2.19(2.27)	8.69(8.61)
4g	2-$NO_2C_6H_4$	241~242	90[d]		39.73(39.67)	2.35(2.44)	12.41(12.36)
4h	4-$NO_2C_6H_4$	239~240	89[d]		39.76(39.67)	2.48(2.44)	12.52(12.36)
4i	2-HOC_6H_4	211~212	88[d]		42.45(42.37)	2.76(2.84)	9.93(9.88)

[a]Based on aroylhydrazine; [b]In the absence of catalyst; [c]In the presence of PEG-400. [d]Based on thiosemicarbazides.

Treated 2-iodobenzoyl chloride **1** with ammonium thiocyanate under MWI, in solvent and catalyst free condition, gave 2-iodobenzoyl isothiocyanate **2**. The crude compound could be reacted with aroyl hydrazines directly without purification affording 1-aroyl-4-(2-iodobenzoyl)thiosemicarbazides in excellent yields. These experiments confirmed that the phase transfer catalyst PEG-400 was not necessary in this reaction as in the traditional methods[13-15] (**Table 1**).

According to our previous studies[15-16] treatment of thiosemicarbazides with KIO_3 in water suspension was an efficient method for the synthesis of corresponding semicarbazides. Accordance with our previous work[15, 16], the thiosemicabazides **3a-i** can be efficiently converted into semicarbazides **4a-i** in water suspension with KIO_3 under microwave irradiation. The transformation of **3a-i** to **4a-i**, however, this reaction did not occur under MWI and solvent-free conditions with KIO_3. It was interesting to note

Table 2 IR and ^{1}H NMR Data of compounds **3a-i** and **4a-i**.

Compd	IR (cm^{-1})			^{1}H NMR (DMSO-d$_6$, δ in ppm)
	N-H	C=O	C=S	
3a	3171 3291	1691	1180	12.36 (s, 1H, NH), 12.01 (s, 1H, NH), 10.90 (s, 1H, NH), 6.90-7.80 (m, 9H, Ar-H)
3b	3169 3269	1696	1196	12.33 (s, 1H, NH), 11.97 (s, 1H, NH), 10.93 (s, 1H, NH), 7.12-7.86 (m, 8H, Ar-H), 3.41 (s, 3H, CH_3)
3c	3190 3260	1697	1182	12.42 (s, 1H, NH), 12.00 (s, 1H, NH), 10.99 (s, 1H, NH), 7.20-8.07 (m, 8H, Ar-H)
3d	3189 3271	1687	1179	12.40 (s, 1H, NH), 12.03 (s, 1H, NH), 11.01 (s, 1H, NH), 7.13-8.01 (m, 8H, Ar-H)
3e	3167 3284	1696	1180	12.44 (s, 1H, NH), 12.04 (s, 1H, NH), 11.03 (s, 1H, NH), 7.30-8.21 (m, 8H, Ar-H)
3f	3197 3290	1698	1176	12.38 (s, 1H, NH), 12.05 (s, 1H, NH), 10.97 (s, 1H, NH), 7.21-8.13 (m, 8H, Ar-H)
3g	3201 3269	1685	1184	12.43 (s, 1H, NH), 12.14 (s, 1H, NH), 11.02 (s, 1H, NH), 7.32-8.21 (m, 8H, Ar-H)
3h	3191 3260	1683	1182	12.45 (s, 1H, NH), 12.20 (s, 1H, NH), 11.05 (s, 1H, NH), 7.26-8.30 (m, 8H, Ar-H)
3i	3169 3284	1689	1185	13.01 (s, 1H, NH), 12.40 (s, 1H, NH), 11.31 (s, 1H, NH), 10.28 (s, 1H, OH), 7.30-8.21 (m, 8H, Ar-H)
4a	3170 3251	1692		12.19 (s, 1H, NH), 11.01 (s, 2H, NH), 6.93-7.81 (m, 9H, Ar-H)
4b	3174 3270	1696		12.18 (s, 1H, NH), 11.01 (s, 2H, NH), 7.08-7.91 (m, 8H, Ar-H), 3.39 (s, 3H, CH_3)
4c	3189 3269	1691		12.19 (s, 1H, NH), 11.08 (s, 2H, NH), 7.21-8.20 (m, 8H, Ar-H)
4d	3190 3272	1695		12.21 (s, 1H, NH), 11.13 (s, 2H, NH), 7.20-8.10 (m, 8H, Ar-H)
4e	3191 3269	1696		12.20 (s, 1H, NH), 11.21 (s, 2H, NH), 7.25-8.19 (m, 8H, Ar-H)
4f	3190 3270	1677		12.16 (s, 1H, NH), 11.10 (s, 2H, NH), 7.18-8.15 (m, 8H, Ar-H)
4g	3198 3272	1686		12.25 (s, 1H, NH), 11.13 (s, 2H, NH), 7.29-8.23 (m, 8H, Ar-H)
4h	3199 3270	1645		12.29 (s, 1H, NH), 11.10 (s, 2H, NH), 7.30-8.28 (m, 8H, Ar-H)
4i	3200 3290	1173		12.50 (s, 1H, NH), 11.48 (s, 2H, NH), 10.30 (s, 1H, OH), 7.09-8.15 (m, 8H, Ar-H)

that $HIO_4 \cdot 2H_2O$ was a quite efficient reagent for the transformation of C=S to C=O under the same conditions to afford 1-aroyl-4-(2-iodobenzoyl)semicarbazides **4a-i**.

2-Iodobenzoyl chloride **1** (1 mmol) and ammonium thiocyanate (1.5 mmol) were mixed thoroughly in an agate mortar. The mixture was subsequently irradiated in a domestic microwave oven at 350W for 0.5 min periodically up to a total irradiation time of 5 min. After disappearance of **1** (monitored by TLC using ethyl acetate-benzene-ethyl ether 2:1:1 as eluent), the mixture was cooled to room temperature and aroyl hydrazine (0.95 mmol) was added and mixed thoroughly. Then the mixture was subjected to microwave irradiation (490 W) for 0.5 min periodically up to a total irradiation time of 3 min. After the completion of the reaction (monitored by TLC using acetone as eluent), the resulting mixture was washed with water (3×10 mL) and the obtained solid product was recrystallized from DMF-EtOH-H_2O (6:3:1) giving the pure product **3a-i**. **3a-i** (1 mmol) and $HIO_4\cdot 2H_2O$ (1.5 mmol) were mixed thoroughly in an agate mortar and irradiated (490 W) in microwave oven for 3 min. After the reaction was completed (monitored by TLC using ethyl acetate-acetone-petroleum ether 2:1:1 as eluent), the reaction mixture was washed with water (3×10 mL) and the obtained solid product was recrystallized from DMF-EtOH-H_2O (6:4:1), giving the pure **4a-i** (**Table 1**, **Table 2)**.

In summary, to our best knowledge, this is the first report on the synthesis of 1-aroyl-4-(2-iodobenzoyl)thiosemicarbazides and corresponding semicarbazides under solvent and catalyst free condition by MWI.

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