

One-pot Synthesis of 1- Aryloxyacetyl - 4- (4'-nitrophenyloxyacetyl) - thiosemicarbazides under Phase Transfer Catalysis and Microwave Irradiation

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Abstract: The 1-aryloxyacetyl-4-(4'-nitrophenyloxyacetyl)-thiosemicarbazides (**3a-h**) are synthesized *via* reaction of 4-nitrophenyloxyacetyl chloride with ammonium thiocyanate and aryloxyacetic hydrazides (**2a-h**) under phase transfer catalysis and microwave irradiation in excellent yield.

Keywords: 1,4-Diaryloxyacetyl thiosemicarbazide, phase transfer catalysis, microwave irradiation.

1,4-Disubstituted thiosemicarbazides have attracted much attention in recent years because of their fungicidal¹⁻², bactericidal³⁻⁴ and tuberculostatic⁵⁻⁶ activities. Meanwhile, aryloxy acetic acid derivatives have also been used as herbicides and plant-growth regulators⁷⁻¹⁰. These applications prompt us to develop a simple and rapid synthetic method to prepare a series of new compounds bearing both thiosemicarbazide and aryloxyacetyl moieties, with the object of obtaining new biologically active compounds.

Recently we have reported a synthetic method for some 1,4-diaryloxyacetyl thiosemicarbazides under phase transfer catalysis¹¹⁻¹³. In this paper, we report a more convenient and efficient method for the preparation of a series of new 1,4-diaryloxyacetyl thiosemicarbazides in one-pot under solid-liquid phase transfer catalysis and microwave irradiation.

Reaction of 4-nitrophenyloxyacetyl chloride with ammonium thiocyanate using polyethylene glycol-400 (PEG-400) as phase transfer catalyst under 600 W microwave irradiation for 9 minutes, the 4-nitrobenzoyl thioisocyanate **1** was given as an intermediate, which *in situ* further reacted with aryloxyacetic hydrazides (**2a-h**) under 675 W microwave irradiation (Midea-W7022J, made by Shunde Meidi Microwave Oven Company) for 4 minutes to afford 1-aryloxyacetyl-4-(4'-nitrophenyloxyacetyl)-thiosemicarbazides (**3a-h**) in excellent yield (**Scheme**).

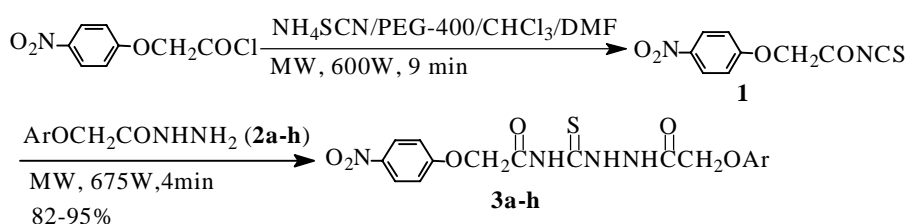
PEG-400 as a phase transfer catalyst is indispensable for these reactions. It can easily react with NH₄SCN to form complex [PEG-400-NH₄⁺]SCN⁻, which makes it possible for SCN⁻ to readily react with 4-nitrophenyloxyacetyl chloride and leads to the formation of intermediate **1**. However, if no PEG-400 is used, there is no intermediate

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1 formed, therefore no target compound **3a-h** are produced at all.

DMF used in these reactions can obviously improve the yield of **3a-h** in terms of two reasons: one is DMF as a polar aprotic solvent can promote the formation of reactive SCN^- and its nucleophilic substitution reaction; the other is DMF as a high dielectric constant solvent which is favorable to the efficient absorption of microwave irradiation.

Scheme



The microwave method used in this paper has the advantage of short reaction time and high reaction yield compared to the reported method¹¹⁻¹³. In addition, this method can also be extended to the preparation of other 1,4-disubstituted thiosemicarbazides.

The characterization of compounds **3a-h** is based on their IR (KBr), ^1H NMR, and elemental analysis (Table 1-2). The IR spectra exhibit characteristic strong absorptions at 1175-1193 cm^{-1} attributable to the C=S. The carbonyl absorptions are observed at 1709-1718 cm^{-1} . The ^1H NMR spectral data in d_6 -dimethylsulfoxide show peaks at 12.39-12.44 (NH), 10.98-11.04 (NH), 9.37-9.44 (NH) and 4.68-4.72 ppm (CH_2). All elemental analysis are good agreement with the desired values.

Experimental

IR spectra were recorded on an Alpha Centauri FTIR spectrophotometer and ^1H NMR spectra on a FT-80A instrument. Elemental analysis were performed on a Vario El Elemental Analysis instrument. Melting points were observed in an open capillary tube and uncorrected.

To a solution of 4-nitrophenoxycarbonyl chloride (0.65 g, 3.0 mmol) in 15 mL of CHCl_3 and 2 drops of DMF, NH_4SCN (0.34 g, 4.5 mmol) and PEG-400 (0.04 g, 0.1 mmol) were added. The mixture was exposed to 600 W microwave irradiation for 9 minutes. Then aryloxyacetic hydrazide (3.0 mmol) was added and the reaction mixture was exposed to 675 W microwave irradiation for another 4 minutes. The resulting mixture was evaporated to remove the part of the solvent, and the residue was poured into H_2O (10 mL). After filtration, the solid was recrystallized from DMF: $\text{C}_2\text{H}_5\text{OH}$: H_2O (6:3:1) to give the product **3a-h**.

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Table 1 The physical and elemental data of **3a-h**

Compd	Ar	Yield (%)	mp (°C)	Elemental analysis (calcd) (%)		
				C	H	N
3a	2-CH ₃ C ₆ H ₄	90	168-169	51.80 (51.67)	4.40 (4.34)	13.51 (13.39)
3b	3-CH ₃ C ₆ H ₄	93	120-121	51.71 (51.67)	4.32 (4.34)	13.44 (13.39)
3c	4-CH ₃ C ₆ H ₄	89	161-162	51.60 (51.67)	4.31 (4.34)	13.33 (13.39)
3d	2-O ₂ NC ₆ H ₄	91	198-199	45.56 (45.43)	3.39 (3.36)	15.66 (15.58)
3e	4-O ₂ NC ₆ H ₄	88	218-219	45.32 (45.43)	3.30 (3.36)	15.49 (15.58)
3f	4-ClC ₆ H ₄	90	176-177	46.69 (46.53)	3.53 (3.45)	12.90 (12.77)
3g	2,4-Cl ₂ C ₆ H ₃	92	177-178	43.06 (43.14)	3.02 (2.98)	11.96 (11.84)
3h	C ₆ H ₅	89	137-138	50.61 (50.49)	4.04 (3.99)	13.96 (13.85)

Table 2 IR and ¹H NMR data of compounds **3a-h**

Compd	IR (KBr cm ⁻¹)			¹ H NMR (DMSO-d ₆ , δ in ppm)
	N-H	C=O	C=S	
3a	3274, 3203	1712	1192	2.30 (s,3H,CH ₃), 4.70 (s,4H,CH ₂), 6.99-8.24 (m,8H,Ar-H), 9.38 (s,1H,NH), 10.99 (s,1H,NH), 12.40 (s,1H,NH)
3b	3281, 3214	1715	1193	2.29 (s,3H,CH ₃), 4.68 (s,4H,CH ₂), 6.73-8.30 (m,8H,Ar-H), 9.40 (s,1H,NH), 10.99 (s,1H,NH), 12.40 (s,1H,NH)
3c	3269, 3190	1713	1189	2.32 (s,3H,CH ₃), 4.71 (s,4H,CH ₂), 6.74-8.29 (m,8H,Ar-H), 9.37 (s,1H,NH), 10.98 (s,1H,NH), 12.38 (s,1H,NH)
3d	3266, 3179	1718	1179	4.69 (s,4H,CH ₂), 7.01-8.27 (m,8H,Ar-H), 9.41 (s,1H,NH), 11.03 (s,1H,NH), 12.43 (s,1H,NH)
3e	3276, 3180	1716	1183	4.71 (s,4H,CH ₂), 7.04-8.31 (m,8H,Ar-H), 9.38 (s,1H,NH), 11.02 (s,1H,NH), 12.44 (s,1H,NH)
3f	3281, 3194	1714	1175	4.70 (s,4H,CH ₂), 6.97-8.26 (m,8H,Ar-H), 9.43 (s,1H,NH), 10.99 (s,1H,NH), 12.41 (s,1H,NH)
3g	3286, 3190	1711	1180	4.72 (s,4H,CH ₂), 7.01-8.20 (m,7H,Ar-H), 9.44 (s,1H,NH), 11.04 (s,1H,NH), 12.43 (s,1H,NH)
3h	3257, 3176	1709	1188	4.68 (s,4H,CH ₂), 6.86-8.01 (m,9H,Ar-H), 9.41 (s,1H,NH), 11.01 (s,1H,NH), 12.43 (s,1H,NH)

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