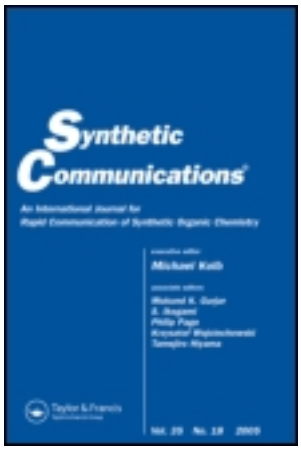

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SYNTHESIS OF 1-ARYLOXYACETYL- 4-(4-NITROBENZOYL)-THIOSEMICARBAZIDES UNDER PHASE TRANSFER CATALYSIS AND MICROWAVE IRRADIATION

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SYNTHESIS OF 1-ARYLOXYACETYL-4-(4-NITROBENZOYL)-THIOSEMICARBAZIDES UNDER PHASE TRANSFER CATALYSIS AND MICROWAVE IRRADIATION

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ABSTRACT

The 1-aryloxyacetyl-4-(4-nitrobenzoyl)-thiosemicarbazides (**3a–m**) are synthesized via reaction of 4-nitrobenzoyl chloride with ammonium thiocyanate and aryloxyacetic acid hydrazides (**2a–m**) under phase transfer catalysis and microwave irradiation in excellent yield.

1,4-Diacyl thiosemicarbazides have attracted much attention in recent years because of their fungicidal,[1,2] bactericidal[3,4] and tuberculostatic[5,6] activities. Meanwhile, aryloxyacetic acid derivatives have also been used as herbicides and plant-growth regulators.[7–10] These applications prompt us to synthesize a new series of compounds bearing both thiosemicarbazide

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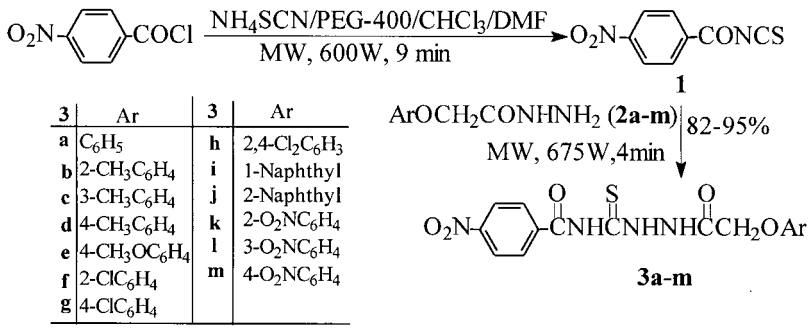

3	Ar	3	Ar
a	C_6H_5	h	2,4-$Cl_2C_6H_3$
b	2-$CH_3C_6H_4$	i	1-Naphthyl
c	3-$CH_3C_6H_4$	j	2-Naphthyl
d	4-$CH_3C_6H_4$	k	2-$O_2NC_6H_4$
e	4-$CH_3OC_6H_4$	l	3-$O_2NC_6H_4$
f	2-ClC_6H_4	m	4-$O_2NC_6H_4$
g	4-ClC_6H_4		

Scheme 1.

and aryloxyacetyl moiety, with the objective of obtaining new biologically active compounds.

Recently we have synthesized some 1,4-diacyl thiosemicarbazides under phase transfer catalysis.[11–18] However, in this paper, we report a convenient and efficient method for the preparation of a series of new 1,4-diacyl thiosemicarbazides under solid–liquid phase transfer catalysis and microwave irradiation.

Reaction of 4-nitrobenzoyl chloride with ammonium thiocyanate using polyethylene glycol-400 (PEG-400) as phase transfer catalyst under 600 W microwave irradiation for 9 min, the 4-nitrobenzoyl thioisocyanate (**1**) is given as intermediate, which in situ reacts with aryloxyacetic acid hydrazides (**2a–m**) under 675 W microwave irradiation for 4 min to afford 1-aryloxyacetyl-4-(4-nitrobenzoyl)-thiosemicarbazides (**3a–m**) in excellent yield (Sch. 1).

PEG-400 as phase transfer catalyst is indispensable for these reactions. It can easily react with NH_4SCN to form complex [PEG-400-NH_4^+]SCN^-, which makes the SCN^- possible to readily react with 4-nitrobenzoyl chloride and lead to the formation of intermediate **1**. However, if no PEG-400 is used, there is no intermediate **1** formed, therefore no any target compound **3a–m** are produced at all.

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

The microwave method used in this paper has the advantage of short reaction time and high reaction yield compared to the conventional method.[11–18] In addition, this method can also be extended to the preparation of other 1,4-diacyl thiosemicarbazides.

The characterization of compounds **3a–m** in based on their IR (KBr), ^{1}H NMR, MS and elemental analyses. The IR spectra exhibit a characteristic strong absorption at 1162–1194 cm^{-1} attributable to the C=S. The cabonyl absorption is observed at 1655–1710 cm^{-1}. The ^{1}H NMR spectral data in d_6-dimethylsulfoxide show peaks at 12.29–12.84 (NH), 11.89–12.09 (NH), 10.01–11.15 (NH) and 4.69–5.06 ppm (CH_2). All elemental analyses and MS are good agreement with the structure prepared.

EXPERIMENTAL

IR spectra were recorded using KBr pellets on an Alpha Centauri FTIR spectrophotometer and ^{1}H NMR spectra on a FT-80A instrument using $(CD_3)_2SO$ as solvent and Me_4Si as internal standard. Elemental analyses were performed on a Vario E1 Elemental Analysis instrument. Mass spectra were recorded on a QP-1000A GC-MS using the impact mode (70 eV). Melting points were observed in an open capillary tube and uncorrected. 4-Nitrobenzoyl chloride[19] and aryloxyacetic acid hydrazides[20] were prepared according to literature procedure. Ammonium thiocyanate and PEG-400 were commercially available and used as received.

General Procedure for the Preparation of Compounds 3a–m

To a solution of 4-nitrobenzoyl chloride (0.56 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 on 600 W of microwave irradiation for 9 min. Then aryloxyacetic acid hydrazide (3.0 mmol) was added and the reaction mixture was exposed on 675 W of microwave irradiation for 4 min again. The resulting mixture was evaporated to remove part of solvent, and the residue was poured into H_2O (10 mL). After the filtration, the solid was recrystallized from DMF-C_2H_5OH-H_2O (6 : 3 : 1) to give product. The physical and spectral results of **3a–m** were shown below.

1-Phenyloxyacetyl-4-(4-nitrobenzoyl)-thiosemicarbazide (3a): White solid. Yield: 88%. M.p.: 243–244°C. ^{1}H NMR (DMSO-d_6) δ 12.36 (1H, s, NH), 11.98 (1H, s, NH), 11.03 (1H, s, NH), 6.83–8.29 (9H, m, ArH), 4.69 (2H, s, CH_2). IR (KBr, ν, cm^{-1}): 3292 (N-H), 1698, 1679 (C=O), 1168 (C=S). MS: m/z, 374 (M^+). Anal. Calcd. for $C_{16}H_{14}N_4O_5S$: C, 51.33; H, 3.77; N, 14.97. Found: C, 51.18; H, 3.59; N, 15.13.

1-(2-Methylphenyloxyacetyl)-4-(4-nitrobenzoyl)-thiosemicarbazide (3b): White solid. Yield: 86%. M.p.: 271–272°C. ^{1}H NMR (DMSO-d_6) δ 12.31 (1H, s, NH), 11.96 (1H, s, NH), 10.95 (1H, s, NH), 6.61–8.42 (8H, m, ArH), 4.70 (2H, s, CH_2), 2.29 (3H, s, CH_3). IR (KBr, ν, cm^{-1}): 3228 (N-H), 1700, 1678 (C=O), 1189 (C=S). MS: m/z, 388 (M^+). Anal. Calcd. for $C_{17}H_{16}N_4O_5S$: C, 52.57; H, 4.15; N, 14.42. Found: C, 52.44; H, 4.11; N, 14.87.

1-(3-Methylphenyloxyacetyl)-4-(4-nitrobenzoyl)-thiosemicarbazide (3c): White solid. Yield: 94%. M.p.: 210–211°C. ^{1}H NMR (DMSO-d_6) δ 12.30 (1H, s, NH), 11.97 (1H, s, NH), 10.98 (1H, s, NH), 6.72–8.37 (8H, m, ArH), 4.72 (2H, s, CH_2), 2.30 (3H, s, CH_3). IR (KBr, ν, cm^{-1}): 3231 (N-H), 1699, 1678 (C=O), 1194 (C=S). MS: m/z, 388 (M^+). Anal. Calcd. for $C_{17}H_{16}N_4O_5S$: C, 52.57; H, 4.15; N, 14.42. Found: C, 52.58; H, 4.12; N, 14.68.

1-(4-Methylphenyloxyacetyl)-4-(4-nitrobenzoyl)-thiosemicarbazide (3d): White solid. Yield: 91%. M.p.: 203–204°C. ^{1}H NMR (DMSO-d_6) δ 12.29 (1H, s, NH), 12.00 (1H, s, NH), 10.96 (1H, s, NH), 6.74–8.40 (8H, m, ArH), 4.71 (2H, s, CH_2), 2.32 (3H, s, CH_3). IR (KBr, ν, cm^{-1}): 3293, 3150 (N-H), 1692, 1667 (C=O), 1158 (C=S). MS: m/z, 388 (M^+). Anal. Calcd. for $C_{17}H_{16}N_4O_5S$: C, 52.57; H, 4.15; N, 14.42. Found: C, 52.60; H, 4.13; N, 14.58.

1-(4-Methoxylphenyloxyacetyl)-4-(4-nitrobenzoyl)-thiosemicarbazide (3e): White solid. Yield: 87%. M.p.: 201–202°C. ^{1}H NMR (DMSO-d_6) δ 12.29 (1H, s, NH), 11.89 (1H, s, NH), 10.98 (1H, s, NH), 6.70–8.29 (8H, m, ArH), 4.70 (2H, s, CH_2), 3.47 (3H, s, CH_3). IR (KBr, ν, cm^{-1}): 3298, 3282 (N-H), 1701, 1695 (C=O), 1162 (C=S). MS: m/z, 404 (M^+). Anal. Calcd. for $C_{17}H_{16}N_4O_6S$: C, 50.49; H, 3.99; N, 13.85. Found: C, 50.46; H, 3.89; N, 13.73.

1-(2-Chlorophenyloxyacetyl)-4-(4-nitrobenzoyl)-thiosemicarbazide (3f): White solid. Yield: 82%. M.p.: 238–239°C. ^{1}H NMR (DMSO-d_6) δ 12.70 (1H, s, NH), 12.02 (1H, s, NH), 11.04 (1H, s, NH), 6.79–8.26 (8H, m, ArH), 4.88 (2H, s, CH_2). IR (KBr, ν, cm^{-1}): 3268 (N-H), 1699, 1676 (C=O), 1164 (C=S). MS: m/z, 408 (M^+). Anal. Calcd. for $C_{16}H_{13}N_4O_5SCl$: C, 47.01; H, 3.21; N, 13.70. Found: C, 47.06; H, 3.18; N, 13.46.

1-(4-Chlorophenyloxyacetyl)-4-(4-nitrobenzoyl)-thiosemicarbazide (3g): White solid. Yield: 88%. M.p.: 263–264°C. ^{1}H NMR (DMSO-d_6) δ 12.71 (1H, s, NH), 12.01 (1H, s, NH), 11.01 (1H, s, NH), 6.83–8.26 (8H, m, ArH), 4.89 (2H, s, CH_2). IR (KBr, ν, cm^{-1}): 3307, 3150 (N-H), 1692, 1655 (C=O), 1174 (C=S). MS: m/z, 408 (M^+). Anal. Calcd. for $C_{16}H_{13}N_4O_5SCl$: C, 47.01; H, 3.21; N, 13.70. Found: C, 47.18; H, 3.13; N, 13.37.

1-(2,4-Dichlorophenyloxyacetyl)-4-(4-nitrobenzoyl)-thiosemicarbazide (3h): White solid. Yield: 90%. M.p.: 218–219°C. ^{1}H NMR (DMSO-d_6) δ 12.74 (1H, s, NH), 12.04 (1H, s, NH), 11.05 (1H, s, NH), 6.90–8.23 (7H, m, ArH),

4.92 (2H, s, CH_2). IR (KBr, ν, cm^{-1}): 3254 (N-H), 1698, 1675 (C=O), 1162 (C=S). MS: m/z, 443 (M^+). Anal. Calcd. for $C_{16}H_{12}N_4O_5SCl_2$: C, 43.35; H, 2.73; N, 12.64. Found: C, 43.15; H, 2.61; N, 12.75.

1-(1-Naphthyloxyacetyl)-4-(4-nitrobenzoyl)-thiosemicarbazide (3i): White solid. Yield: 86%. M.p.: 218–219°C. ^{1}H NMR (DMSO-d_6) δ 12.36 (1H, s, NH), 11.95 (1H, s, NH), 10.01 (1H, s, NH), 6.94–8.30 (11H, m, ArH), 4.80 (2H, s, CH_2). IR (KBr, ν, cm^{-1}): 3247 (N-H), 1701, 1672 (C=O), 1174 (C=S). MS: m/z, 424 (M^+). Anal. Calcd. for $C_{20}H_{16}N_4O_5S$: C, 56.60; H, 3.80; N, 13.20. Found: C, 56.42; H, 3.68; N, 13.26.

1-(2-Naphthyloxyacetyl)-4-(4-nitrobenzoyl)-thiosemicarbazide (3j): White solid. Yield: 89%. M.p.: 231–232°C. ^{1}H NMR (DMSO-d_6) δ 12.41 (1H, s, NH), 11.96 (1H, s, NH), 10.03 (1H, s, NH), 6.96–8.29 (11H, m, ArH), 4.79 (2H, s, CH_2). IR (KBr, ν, cm^{-1}): 3243 (N-H), 1700, 1673 (C=O), 1178 (C=S). MS: m/z, 424 (M^+). Anal. Calcd. for $C_{20}H_{16}N_4O_5S$: C, 56.60; H, 3.80; N, 13.20. Found: C, 56.62; H, 3.76; N, 13.44.

1-(2-Nitrophenyloxyacetyl)-4-(4-nitrobenzoyl)-thiosemicarbazide (3k): White solid. Yield: 90%. M.p.: 261–262°C. ^{1}H NMR (DMSO-d_6) δ 12.75 (1H, s, NH), 12.03 (1H, s, NH), 11.13 (1H, s, NH), 7.10–8.45 (8H, m, ArH), 5.05 (2H, s, CH_2). IR (KBr, ν, cm^{-1}): 3238 (N-H), 1710, 1677 (C=O), 1169 (C=S). MS: m/z, 419 (M^+). Anal. Calcd. for $C_{16}H_{13}N_5O_7S$: C, 45.82; H, 3.12; N, 16.70. Found: C, 45.68; H, 3.02; N, 16.81.

1-(3-Nitrophenyloxyacetyl)-4-(4-nitrobenzoyl)-thiosemicarbazide (3l): White solid. Yield: 87%. M.p.: 276–277°C. ^{1}H NMR (DMSO-d_6) δ 12.84 (1H, s, NH), 12.09 (1H, s, NH), 11.16 (1H, s, NH), 7.08–8.39 (8H, m, ArH), 5.03 (2H, s, CH_2). IR (KBr, ν, cm^{-1}): 3289, 3226 (N-H), 1703, 1678 (C=O), 1167 (C=S). MS: m/z, 419 (M^+). Anal. Calcd. for $C_{16}H_{13}N_5O_7S$: C, 45.82; H, 3.12; N, 16.70. Found: C, 45.85; H, 3.10; N, 16.96.

1-(4-Nitrophenyloxyacetyl)-4-(4-nitrobenzoyl)-thiosemicarbazide (3m): White solid. Yield: 95%. M.p.: 281–282°C. ^{1}H NMR (DMSO-d_6) δ 12.80 (1H, s, NH), 12.06 (1H, s, NH), 11.15 (1H, s, NH), 7.02–8.36 (8H, m, ArH), 5.06 (2H, s, CH_2). IR (KBr, ν, cm^{-1}): 3279, 3236 (N-H), 1708, 1676 (C=O), 1170 (C=S). MS: m/z, 419 (M^+). Anal. Calcd. for $C_{16}H_{13}N_5O_7S$: C, 45.82; H, 3.12; N, 16.70. Found: C, 45.74; H, 3.06; N, 16.48.

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