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SYNTHESIS OF 1- ARYLOXYACETYL-4- (5-(4- CHLOROPHENYL)-2-FUROYL)- SEMICARBAZIDES

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SYNTHESIS OF 1-ARYLOXYACETYL-4-(5-(4-CHLOROPHENYL)-2-FUROYL)-SEMICARBAZIDES

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ABSTRACT

A simple and efficient route to 1,4-diacyl semicarbazides is described. 1-Aryloxyacetyl-4-(5-(4-chlorophenyl)-2-furoyl)-thiosemicarbazides (**Ia–i**) on treatment with potassium iodate in the aqueous solution afford 1-aryloxyacetyl-4-(5-(4-chlorophenyl)-2-furoyl)-semicarbazides (**IIa–i**) in excellent yields.

1,4-Diacyl thiosemicarbazides have attracted much attention in recent years because of their fungicidal^{1,2} and bactericidal³ activities. The synthetic methods of these compounds have been established. They can be readily prepared by the reactions of acyl chloride with ammonium thiocyanate and acid hydrazides under the condition of phase transfer catalysis in high yields.^{4–13}

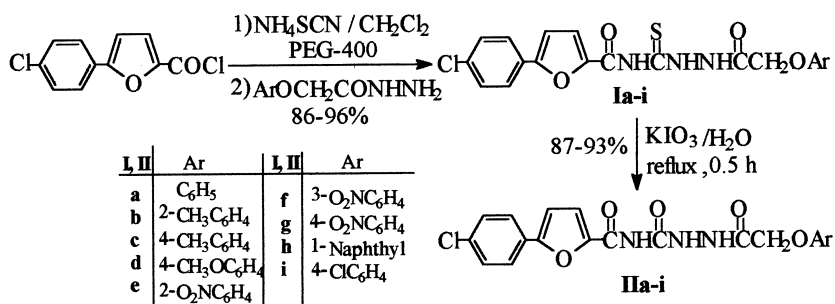
However, the analogous species, 1,4-diacyl semicarbazides, cannot be obtained using the similar methods because of the unstability of intermediates, acyl isocyanate. Therefore, there are no 1,4-diacyl semicarbazides reported yet in the literature in terms of our knowledge. This led us to investigate the efficient synthetic route and develop the application of them.

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In this paper, we report an efficient and convenient method for preparation of 1,4-diacyl semicarbazides in the aqueous solution, which uses easily made 1,4-diacyl thiosemicarbazides as starting materials and commercially available potassium iodate as reagent.

Reaction of 5-(4-chlorophenyl)-2-furoyl chloride with ammonium thiocyanate catalyzed by polyethylene glycol-400 (PEG-400) in the solution of methylene chloride gives 5-(4-chlorophenyl)-2-furoyl isothiocyanate first, which *in situ* treatment with aryloxyacetic acid hydrazides at room temperature affords 1-aryloxyacetyl-4-(5-(4-chlorophenyl)-2-furoyl)-thiosemicarbazides (**Ia-i**). Compounds **Ia-i** on further treatment with potassium iodate in the aqueous solution, result in the formation of 1-aryloxyacetyl-4-(5-(4-chlorophenyl)-2-furoyl)-semicarbazides (**IIa-i**) in excellent yields (Scheme).

It is observed that potassium iodate reacts spontaneously with 1,4-diacyl thiosemicarbazides (**Ia-i**) leading to the 1,4-diacyl semicarbazides (**IIa-i**) fairly rapidly in all cases studied. Moreover, these reactions can be easily carried out in the aqueous slurry under gentle reflux. The color change of aqueous solution from colorless to violet because of the release of iodine can conveniently indicate the progress of the reaction. All reactions studied can be finished within half an hour. The products can be obtained only by filtration. All yields are between 87% and 93%.



Scheme.

EXPERIMENTAL

IR spectra were recorded using KBr pellets on an Alpha Centauri FTIR spectrophotometer and ¹H NMR spectra on a FT-80A instrument using (CD₃)₂SO as solvent and Me₄Si as internal standard. Elemental analyses were performed on a Carlo-Erba 1106 Elemental Analysis instrument. Melting points were observed in an open capillary tube and uncorrected. 5-(4-Chlorophenyl)-2-furoyl chloride¹⁴ and aryloxyacetic acid

hydrazides¹⁵ were prepared according to literature procedures. Ammonium thiocyanate, potassium iodate and PEG-400 were commercially available and used as received.

General Procedure for the Preparation of Compounds Ia–i

To a solution of 5-(4-chlorophenyl)-2-furoyl chloride (0.72 g, 3 mmol) in methylene chloride (20 mL), ammonium thiocyanate (0.34 g, 4.5 mmol) and polyethylene glycol-400 (0.04 g, 0.1 mmol) were added. The mixture was stirred for 1 h at room temperature. Then an aryloxyacetic acid hydrazide (2.95 mmol) was added and the reaction mixture was stirred for another 0.5 h at room temperature. To the resulting mixture, water (10 mL) was added so that the inorganic salts were dissolved, then the slurry was filtered, the solid was washed with water (3×5 mL), and recrystallized from DMF-EtOH-H₂O, and the product was given. The physical and spectral data of compounds **Ia–i** are shown below.

1-Phenyloxyacetyl-4-(5-(4-chlorophenyl)-2-furoyl)-thiosemicarbazide (**Ia**)

Yield: 94%. m.p.: 212°–213°C. ¹H NMR (DMSO-d₆) δ 12.55 (s, 1H, NH), 11.74 (s, 1H, NH), 10.92 (s, 1H, NH), 7.04–8.31 (m, 11H, Ar-H, Fu-H), 4.66 (s, 2H, CH₂). IR(KBr, ν, cm⁻¹): 3272, 3150(N-H), 1689, 1669 (C=O), 1169(C=S). Anal. calc. for C₂₀H₁₆N₃O₄SCl: C, 55.88; H, 3.75; N, 9.77. Found: C, 55.64; H, 3.61; N, 9.60.

1-(2-Methylphenyloxyacetyl)-4-(5-(4-chlorophenyl)-2-furoyl)-thiosemicarbazide (**Ib**)

Yield: 90%. m.p.: 193°–194°C. ¹H NMR (DMSO-d₆) δ 12.53 (s, 1H, NH), 11.86 (s, 1H, NH), 10.98 (s, 1H, NH), 6.95–8.51 (m, 10H, Ar-H, Fu-H), 4.67 (s, 2H, CH₂), 2.31 (s, 3H, CH₃). IR(KBr, ν, cm⁻¹): 3225, 3119 (N-H), 1698, 1657(C=O), 1197(C=S). Anal. calc. for C₂₁H₁₈N₃O₄SCl: C, 56.82; H, 4.09; N, 9.47. Found: C, 57.12; H, 4.13; N, 9.20.

1-(4-Methylphenyloxyacetyl)-4-(5-(4-chlorophenyl)-2-furoyl)-thiosemicarbazide (**Ic**)

Yield: 96%. m.p.: 199°–200°C. ¹H NMR (DMSO-d₆) δ 12.62 (s, 1H, NH), 11.78 (s, 1H, NH), 11.03 (s, 1H, NH), 6.84–8.61 (m, 10H, Ar-H,

Fu-H), 4.62 (s, 2H, CH₂), 2.24 (s, 3H, CH₃). IR(KBr, ν , cm⁻¹): 3218, 3186 (N-H), 1687, 1668 (C=O), 1189 (C=S). Anal. calc. for C₂₁H₁₈N₃O₄SCl: C, 56.82; H, 4.09; N, 9.47. Found: C, 56.93; H, 4.06; N, 9.53.

1-(4-methoxyphenyloxyacetyl)-4-(5-(4-chlorophenyl)-2-furoyl)-thiosemicarbazide (Id)

Yield: 88%. m.p.: 171°–172°C. ¹H NMR (DMSO-d₆) δ 12.60 (s, 1H, NH), 11.84 (s, 1H, NH), 11.04 (s, 1H, NH), 7.08–8.02 (m, 10H, Ar-H, Fu-H), 4.68 (s, 2H, CH₂), 3.45 (s, 3H, CH₃). IR(KBr, ν , cm⁻¹): 3276, 3169 (N-H), 1691, 1672 (C=O), 1168 (C=S). Anal. calc. for C₂₁H₁₈N₃O₅SCl: C, 54.84; H, 3.94; N, 9.14. Found: C, 55.01; H, 4.03; N, 9.01.

1-(2-Nitrophenyloxyacetyl)-4-(5-(4-chlorophenyl)-2-furoyl)-thiosemicarbazide (Ie)

Yield: 86%. m.p.: 220°–221°C. ¹H NMR (DMSO-d₆) δ 12.80 (s, 1H, NH), 11.88 (s, 1H, NH), 11.09 (s, 1H, NH), 7.14–8.16 (m, 10H, Ar-H, Fu-H), 4.86 (s, 2H, CH₂). IR(KBr, ν , cm⁻¹): 3270, 3239 (N-H), 1705, 1667 (C=O), 1167 (C=S). Anal. calc. for C₂₀H₁₅N₄O₆SCl: C, 50.59; H, 3.18; N, 11.80. Found: C, 50.34; H, 2.93; N, 11.63.

1-(3-Nitrophenyloxyacetyl)-4-(5-(4-chlorophenyl)-2-furoyl)-thiosemicarbazide (If)

Yield: 89% m.p.: 226°–227°C. ¹H NMR (DMSO-d₆) δ 12.74 (s, 1H, NH), 11.84 (s, 1H, NH), 11.13 (s, 1H, NH), 7.11–8.12 (m, 10H, Ar-H, Fu-H), 4.89 (s, 2H, CH₂). IR(KBr, ν , cm⁻¹): 3278, 3176 (N-H), 1703, 1671 (C=O), 1172 (C=S). Anal. calc. for C₂₀H₁₅N₄O₆SCl: C, 50.59; H, 3.18; N, 11.80. Found: C, 50.73; H, 3.30; N, 11.80.

1-(4-Nitrophenyloxyacetyl)-4-(5-(4-chlorophenyl)-2-furoyl)-thiosemicarbazide (Ig)

Yield: 87%. m.p.: 208°–209°C. ¹H NMR (DMSO-d₆) δ 12.71 (s, 1H, NH), 11.86 (s, 1H, NH), 11.14 (s, 1H, NH), 7.19–8.04 (m, 10H, Ar-H, Fu-H), 4.87 (s, 2H, CH₂). IR(KBr, ν , cm⁻¹): 3321, 3210 (N-H), 1699, 1668 (C=O), 1169 (C=S). Anal. calc. for C₂₀H₁₅N₄O₆SCl: C, 50.59; H, 3.18; N, 11.80. Found: C, 50.43; H, 3.12; N, 11.73.

1-(1-Naphthyloxyacetyl)-4-(5-(4-chlorophenyl)-2-furoyl)-thiosemicarbazide (Ih)

Yield: 93%. m.p.: 196°–197°C. ^1H NMR (DMSO- d_6) δ 12.46 (s, 1H, NH), 11.70 (s, 1H, NH), 11.13 (s, 1H, NH), 7.28–8.31 (m, 13H, Ar-H, Fu-H), 4.81 (s, 2H, CH₂). IR(KBr, ν , cm^{-1}): 3277, 3210 (N-H), 1698, 1658 (C=O), 1178 (C=S). Anal. calc. for C₂₄H₁₈N₃O₄SCl: C, 60.06; H, 3.78; N, 8.76. Found: C, 60.37; H, 3.97; N, 8.91.

1-(4-Chlorophenyloxyacetyl)-4-(5-(4-chlorophenyl)-2-furoyl)-thiosemicarbazide (Ii)

Yield: 92%. m.p.: 203°–204°C. ^1H NMR (DMSO- d_6) δ 12.51 (s, 1H, NH), 11.73 (s, 1H, NH), 10.99 (s, 1H, NH), 6.94–8.15 (m, 10H, Ar-H, Fu-H), 4.86 (s, 2H, CH₂). IR(KBr, ν , cm^{-1}): 3267, 3129 (N-H), 1701, 1668 (C=O), 1170 (C=S). Anal. calc. for C₂₀H₁₅N₃O₄SCl₂: C, 51.73; H, 3.26; N, 9.05. Found: C, 51.92; H, 3.11; N, 10.10.

General Procedure for the Preparation of Compounds IIa–i

A suspension of compound **I** (0.5 mmol) and KIO₃ (0.75 mmol) in H₂O (30 mL) was refluxed for 0.5 h. The resulting mixture was filtered, the solid was washed with H₂O (3 \times 5 mL), and recrystallized from DMF-EtOH-H₂O, then the product was given. The physical and spectral data of compounds **IIa–i** are reported below.

1-Phenyloxyacetyl-4-(5-(4-chlorophenyl)-2-furoyl)-semicarbazide (IIa)

Yield: 91%. m.p.: 183°–184°C. ^1H NMR (DMSO- d_6) δ 11.87 (s, 1H, NH), 11.01 (s, 2H, NH), 7.01–8.23 (m, 11H, Ar-H, Fu-H), 4.65 (s, 2H, CH₂). IR(KBr, ν , cm^{-1}): 3351 (N-H), 1701, 1663 (C=O). Anal. calc. for C₂₀H₁₆N₃O₅Cl: C, 58.05; H, 3.90; N, 10.15. Found: C, 58.32; H, 4.11; N, 10.37.

1-(2-Methylphenyloxyacetyl)-4-(5-(4-chlorophenyl)-2-furoyl)-semicarbazide (IIb)

Yield: 92%. m.p.: 203°–204°C. ^1H NMR (DMSO- d_6) δ 11.85 (s, 1H, NH), 10.98 (s, 2H, NH), 6.93–8.63 (m, 10H, Ar-H, Fu-H), 4.68 (s, 2H, CH₂), 2.29 (s, 3H, CH₃). IR(KBr, ν , cm^{-1}): 3347 (N-H), 1708, 1665

(C=O). Anal. calc. for $C_{21}H_{18}N_3O_5Cl$: C, 58.95; H, 4.24; N, 9.82. Found: C, 58.71; H, 4.12; N, 9.60.

1-(4-Methylphenyloxyacetyl)-4-(5-(4-chlorophenyl)-2-furoyl)-semi-carbazide (IIc)

Yield: 89%. m.p.: 190°–191°C. 1H NMR (DMSO- d_6) δ 11.91 (s, 1H, NH), 10.83 (s, 2H, NH), 6.98–8.69 (m, 10H, Ar-H, Fu-H), 4.63 (s, 2H, CH₂), 2.25 (s, 3H, CH₃). IR(KBr, ν , cm^{-1}): 3353 (N-H), 1697, 1661 (C=O). Anal. calc. for $C_{21}H_{18}N_3O_5Cl$: C, 58.95; H, 4.24; N, 9.82. Found: C, 59.17; H, 4.31; N, 10.02.

1-(4-Methylphenyloxyacetyl)-4-(5-(4-chlorophenyl)-2-furoyl)-semi-carbazide (IIId)

Yield: 93%. m.p.: 178°–179°C. 1H NMR (DMSO- d_6) δ 11.93 (s, 1H, NH), 10.91 (s, 2H, NH), 7.07–8.21 (m, 10H, Ar-H, Fu-H), 4.67 (s, 2H, CH₂), 3.43 (s, 3H, CH₃). IR(KBr, ν , cm^{-1}): 3349 (N-H), 1701, 1659 (C=O). Anal. calc. for $C_{21}H_{18}N_3O_6Cl$: C, 56.83; H, 4.09; N, 9.47. Found: C, 56.62; H, 4.01; N, 9.29.

1-(2-Nitrophenyloxyacetyl)-4-(5-(4-chlorophenyl)-2-furoyl)-semi-carbazide (IIe)

Yield: 91%. m.p.: 193°–194°C. 1H NMR (DMSO- d_6) δ 11.97 (s, 1H, NH), 11.01 (s, 2H, NH), 7.11–8.17 (m, 10H, Ar-H, Fu-H), 4.84 (s, 2H, CH₂). IR(KBr, ν , cm^{-1}): 3362 (N-H), 1712, 1664 (C=O). Anal. calc. for $C_{20}H_{15}N_4O_7Cl$: C, 52.36; H, 3.30; N, 12.21. Found: C, 52.57; H, 3.41; N, 12.50.

1-(3-Nitrophenyloxyacetyl)-4-(5-(4-chlorophenyl)-2-furoyl)-semi-carbazide (IIIf)

Yield: 88%. m.p.: 200°–201°C. 1H NMR (DMSO- d_6) δ 11.89 (s, 1H, NH), 10.93 (s, 2H, NH), 7.09–8.15 (m, 10H, Ar-H, Fu-H), 4.87 (s, 2H, CH₂). IR(KBr, ν , cm^{-1}): 3358 (N-H), 1691, 1659 (C=O). Anal. calc. for $C_{20}H_{15}N_4O_7Cl$: C, 52.36; H, 3.30; N, 12.21. Found: C, 52.49; H, 3.28; N, 12.11.

1-(4-Nitrophenoxyacetyl)-4-(5-(4-chlorophenyl)-2-furoyl)-semi-carbazide (IIg)

Yield: 87%. m.p.: 181°–182°C. ^1H NMR (DMSO- d_6) δ 11.93 (s, 1H, NH), 10.88 (s, 2H, NH), 7.21–8.11 (m, 10H, Ar-H, Fu-H), 4.88 (s, 2H, CH₂). IR(KBr, ν , cm^{-1}): 3347 (N-H), 1690, 1657 (C=O). Anal. calc. for C₂₀H₁₅N₄O₇Cl: C, 52.36; H, 3.30; N, 12.21. Found: C, 52.14; H, 3.24; N, 12.08.

1-(1-Naphthyloxyacetyl)-4-(5-(4-chlorophenyl)-2-furoyl)-semi-carbazide (IIh)

Yield: 90%. m.p.: 192°–193°C. ^1H NMR (DMSO- d_6) δ 11.84 (s, 1H, NH), 10.86 (s, 2H, NH), 7.19–8.40 (m, 13H, Ar-H, Fu-H), 4.79 (s, 2H, CH₂). IR(KBr, ν , cm^{-1}): 3364 (N-H), 1683, 1664 (C=O). Anal. calc. for C₂₄H₁₈N₃O₅Cl: C, 62.14; H, 3.91; N, 9.06. Found: C, 62.26; H, 4.07; N, 9.18.

1-(2-Nitrophenoxyacetyl)-4-(5-(4-chlorophenyl)-2-furoyl)-semi-carbazide (IIi)

Yield: 92%. m.p.: 196°–197°C. ^1H NMR (DMSO- d_6) δ 11.86 (s, 1H, NH), 10.83 (s, 2H, NH), 6.97–8.21 (m, 10H, Ar-H, Fu-H), 4.84 (s, 2H, CH₂). IR(KBr, ν , cm^{-1}): 3349 (N-H), 1708, 1659 (C=O). Anal. calc. for C₂₀H₁₅N₃O₅Cl: C, 53.59; H, 3.37; N, 9.37. Found: C, 53.72; H, 3.42; N, 9.50.

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