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SYNTHESIS OF 1-ARYLOXYACETYL-4-(4-CHLOROPHENYLOXYACETYL)-SEMICARBAZIDES

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ABSTRACT: 1-Aryloxyacetyl-4-(4-chlorophenyloxyacetyl)-semicarbazides (**IIa-j**) are synthesized using 1-aryloxyacetyl-4-(4-chlorophenyloxyacetyl)-thiosemicarbazides (**Ia-j**) as starting materials and KIO_3 as reagent in the aqueous solution.

Although many substituted thiosemicarbazides have been applied in the agriculture and medicine[1-3], the analogous species, substituted semicarbazides, are still quite scarce[4-6].

Especially, the synthetic method of 1,4-diacyl thiosemicarbazides have been established by our research group[7-15], which can be readily prepared by the reaction of acyl chloride with ammonium thiocyanate and acid hydrazides under

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the condition of the phase transfer catalysis using polyethylene glycol-400 (PEG-400) as the catalyst. However, the 1,4-diacyl semicarbazides have not been reported in the literature in the light of our knowledge. These compounds can not be obtained by similar route to thiosemicarbazides using ammonium cyanate instead of ammonium thiocyanate because of the unstability of intermediates, acyl isocyanates.

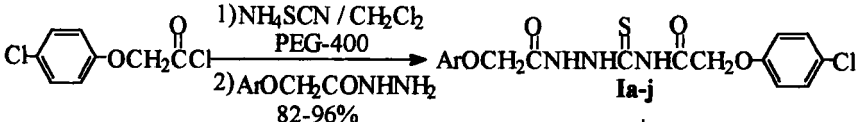
Keeping in view of the above facts, we report herein a convenient and efficient route to 1,4-diacyl semicarbazides bearing two aryloxyacetyls, which uses easily-made 1,4-diacyl thiosemicarbazides as starting materials and commercially-available potassium iodate as reagent.

The reaction of 4-chlorophenyloxyaetyl chloride with ammonium thiocyanate catalyzed by PEG-400 in the solution of methylene chloride gives 4-chlorophenyloxyaetyl isothiocyanate, which *in situ* reacts with aryloxyacetic acid hydrazides at room temperature to afford 1-aryloxyacetyl-4-(4-chlorophenyloxyacetyl)-thiosemicarbazides (**Ia-j**). Compounds **Ia-j** on further treatment with potassium iodate in the aqueous solution result in the formation of 1-aryloxyacetyl-4-(4-chlorophenyloxyacetyl)-semicarbazides (**IIa-j**) in excellent yields (Scheme).

It is observed that potassium iodate reacts spontaneously with 1,4-diacyl thiosemicarbazides (**Ia-j**) leading to the 1,4-diacyl semicarbazides (**IIa-j**) fairly

rapidly in the all of cases studied. Moreover, these reactions can easily carry out in the aqueous slurry under gentle reflux. The color changes of aqueous solution from colorless to violet because of the release of iodine can conveniently indicate the progress of the reactions. All reactions studied can be completed within half an hour. The products can be obtained only by filtration. All yields are between 91% and 96%.

Scheme



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

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 Carlo-Erba 1106 Elemental Analysis instrument. Melting points were observed in an open capillary tube and uncorrected. 4-chlorophenyloxyacetyl chloride[16,17] and aryloxyacetic acid hydrazides[18] were prepared according to literature

procedures. Ammonium thiocyanate, potassium iodate and PEG-400 were commercially available and used as received.

General procedure for preparation of Ia-j.

A suspension of 4-chlorophenyloxyacetyl chloride (0.31 g, 1.5 mmol), ammonium thiocyanate (0.20 g, 2.6 mmol) and PEG-400 (0.02 g, 0.05 mmol) in 40 mL of methylene chloride was stirred for 1 h at room temperature, then a kind of aryloxyacetic acide hydrazides (1.45 mmol) was added. The mixture was stirred for another 0.5 h, and a precipitate was observed immediately. The resulting mixture was filtered and washed with water to remove inorganic salts. The residue was recrystallized from DMF-EtOH-H_2O, and crystals of compound **I** were given. The physical and spectral data are shown in below.

1-phenyloxyacetyl-4-(4-chlorophenyloxyacetyl)-thiosemicarbazide (Ia): Yield: 91%. m.p.: 133-134℃. ^{1}H NMR (DMSO-d_6) δ 12.69 (1H,s,NH), 10.12 (1H,s,NH), 9.50 (1H,s,NH), 6.83-7.52 (9H,m,ArH), 4.72 (4H,s,CH_2). IR(KBr, ν ,cm^{-1}): 3283, 3194(N-H), 1698(C=O), 1179(C=S). Anal. Calcd. for $C_{17}H_{16}N_3O_4SCl$: C,51.84; H,4.09; N,10.67. Found: C,51.62; H,3.93; N,10.51.

1-(2-methylphenyloxyacetyl)-4-(4-chlorophenyloxyacetyl)-thiosemicarbazide (Ib): Yield: 86%. m.p.: 162-163℃. ^{1}H NMR (DMSO-d_6) δ 12.56 (1H,s,NH), 10.03 (1H,s,NH), 9.47 (1H,s,NH), 6.80-7.63 (8H,m,ArH), 4.69 (4H,s,CH_2), 2.30(3H,s,CH_3). IR(KBr, ν ,cm^{-1}): 3291, 3153(N-H), 1713(C=O), 1190(C=S). Anal. Calcd. for $C_{18}H_{18}N_3O_4SCl$: C,53.01; H,4.45; N,10.30. Found: C,53.27; H,4.50; N,10.50.

1-(4-methylphenyloxyacetyl)-4-(4-chlorophenyloxyacetyl)-thiosemicarbazide (Ic): Yield: 85%. m.p.: 166-167℃. ^{1}H NMR (DMSO-d_6) δ 12.50 (1H,s,NH), 10.10 (1H,s,NH), 9.43 (1H,s,NH), 6.72-7.54 (8H,m,ArH), 4.64 (4H,s,CH_2), 2.29(3H,s,CH_3). IR(KBr, ν ,cm^{-1}): 3316, 3184(N-H), 1712(C=O), 1192(C=S). Anal. Calcd. for $C_{18}H_{18}N_3O_4SCl$: C,53.01; H,4.45; N,10.30. Found: C,52.87; H,4.36; N,10.11.

1-(4-methoxylphenyloxyacetyl)-4-(4-chlorophenyloxyacetyl)-thiosemicarbazide (Id): Yield: 84%. m.p.: 154-155℃. ^{1}H NMR (DMSO-d_6) δ 12.49 (1H,s,NH), 10.08 (1H,s,NH), 9.39 (1H,s,NH), 6.79-7.61 (8H,m,ArH), 4.73 (4H,s,CH_2), 3.41(3H,s,CH_3). IR(KBr, ν ,cm^{-1}): 3327, 3169(N-H), 1709(C=O), 1201(C=S). Anal. Calcd. for $C_{18}H_{18}N_3O_5SCl$: C,51.00; H,4.28; N,9.91. Found: C,51.26; H,4.36; N,10.21.

1-(4-chlorophenyloxyacetyl)-4-(4-chlorophenyloxyacetyl)-thiosemicarbazide (Ie): Yield: 83%. m.p.: 181-182℃. ^{1}H NMR (DMSO-d_6) δ 12.71 (1H,s,NH), 10.13 (1H,s,NH), 9.60 (1H,s,NH), 6.69-7.42 (8H,m,ArH), 4.67 (4H,s,CH_2). IR(KBr, ν ,cm^{-1}): 3369, 3194(N-H), 1705(C=O), 1203(C=S). Anal. Calcd. for $C_{17}H_{15}N_3O_4SCl_2$: C,47.67; H,3.53; N,9.81. Found: C,47.89; H,3.66; N,9.97.

1-(1-naphthyloxyacetyl)-4-(4-chlorophenyloxyacetyl)-thiosemicarbazide (If): Yield: 96%. m.p.: 179-180 ℃. ^{1}H NMR (DMSO-d_6) δ 12.72 (1H,s,NH), 10.12 (1H,s,NH), 9.41 (1H,s,NH), 6.80-7.59 (11H,m,ArH), 4.70 (4H,s,CH_2). IR(KBr, ν ,cm^{-1}): 3274, 3175(N-H), 1719(C=O), 1187(C=S). Anal. Calcd. for $C_{21}H_{18}N_3O_4SCl$: C,56.82; H,4.09; N,9.47. Found: C,57.01; H,4.20; N,9.64.

1-(2-naphthyloxyacetyl)-4-(4-chlorophenyloxyacetyl)-thiosemicarbazide (Ig): Yield: 93%. m.p.: 195-196 ℃. ^{1}H NMR (DMSO-d_6) δ 12.66 (1H,s,NH), 10.04 (1H,s,NH), 9.50 (1H,s,NH), 6.82-7.48 (11H,m,ArH), 4.66 (4H,s,CH_2). IR(KBr, ν ,cm^{-1}): 3354, 3193(N-H), 1721(C=O), 1193(C=S). Anal. Calcd. for $C_{21}H_{18}N_3O_4SCl$: C,56.82; H,4.09; N,9.47. Found: C,57.08; H,4.23; N,9.57.

1-(4-nitrophenyloxyacetyl)-4-(4-chlorophenyloxyacetyl)-thiosemicarbazide (Ih): Yield: 91%. m.p.: 197-198℃. ^{1}H NMR (DMSO-d_6) δ 12.81 (1H,s,NH), 10.21 (1H,s,NH), 9.52 (1H,s,NH), 6.84-7.60 (8H,m,ArH), 4.71 (4H,s,CH_2). IR(KBr, ν ,cm^{-1}): 3271, 3126(N-H), 1718(C=O), 1189(C=S). Anal. Calcd. for $C_{17}H_{15}N_4O_6SCl$: C,46.53; H,3.45; N,12.77. Found: C,46.77; H,3.58; N,12.91.

1-(3-nitrophenyloxyacetyl)-4-(4-chlorophenyloxyacetyl)-thiosemicarbazide (Ii): Yield: 95%. m.p.: 203-204 ℃. ^{1}H NMR (DMSO-d_6) δ 12.86 (1H,s,NH), 10.13 (1H,s,NH), 9.57 (1H,s,NH), 6.81-7.57 (8H,m,ArH), 4.68 (4H,s,CH_2). IR(KBr, ν ,cm^{-1}): 3321, 3201(N-H), 1716(C=O), 1190(C=S). Anal. Calcd. for $C_{17}H_{15}N_4O_6SCl$: C,46.53; H,3.45; N,12.77. Found: C,46.68; H,3.50; N,12.96.

1-(2-nitrophenyloxyacetyl)-4-(4-chlorophenyloxyacetyl)-thiosemicarbazide (Ij): Yield: 82%. m.p.: 199-200℃. ^{1}H NMR (DMSO-d_6) δ 12.90 (1H,s,NH), 10.09 (1H,s,NH), 9.60 (1H,s,NH), 6.80-7.63 (8H,m,ArH), 4.75 (4H,s,CH_2). IR(KBr, ν ,cm^{-1}): 3384, 3196(N-H), 1721(C=O), 1205(C=S). Anal. Calcd. for $C_{17}H_{15}N_4O_6SCl$: C,46.53; H,3.45; N,12.77. Found: C,46.80; H,3.52; N,12.99.

General procedure for the preparation of compounds IIa-j

A suspension of compound **I** (0.5 mmol) and KIO_3 (0.75 mmol) in H_2O (30 mL) was refluxed for 0.5 h. The resulting mixture was filtered, the solid was washed with H_2O (3×5 mL) and recrystallized from DMF-EtOH-H_2O, then the product was given. The physical and spectral data of compounds **IIa-j** are reported below.

1-phenyloxyacetyl-4-(4-chlorophenyloxyacetyl)-semicarbazide (IIa): Yield: 91%. m.p.: 140-141℃. ^{1}H NMR (DMSO-d_6) δ 12.66(s,1H,NH), 10.08(s,2H,NH), 6.80-7.49(m,9H,Ar-H), 4.70(s,4H,CH_2). IR(KBr, ν ,cm^{-1}): 3173(N-H), 1701(C=O). Anal. Calcd. for $C_{17}H_{16}N_3O_5Cl$: C,54.05; H,4.27; N,11.12. Found: C,54.32; H,4.36; N,11.23.

1-(2-methylphenyloxyacetyl)-4-(4-chlorophenyloxyacetyl)-semicarbazide (IIb): Yield: 93%. m.p.: 185-186 ℃. ^{1}H NMR (DMSO-d_6) δ 12.58(s,1H,NH), 10.06(s,2H,NH), 6.96-7.71(m,8H,Ar-H), 4.68(s,4H,CH_2), 2.29(3H,s,CH_3). IR(KBr, ν ,cm^{-1}): 3190(N-H), 1711(C=O). Anal. Calcd. for $C_{18}H_{18}N_3O_5Cl$: C,55.18; H,4.63; N,10.72. Found: C,55.45; H,4.76; N,10.95.

1-(4-methylphenyloxyacetyl)-4-(4-chlorophenyloxyacetyl)-semicarbazide (IIc): Yield: 94%. m.p.: 176-177 ℃. ^{1}H NMR (DMSO-d_6) δ 12.52(s,1H,NH), 10.09(s,2H,NH), 6.80-7.49(m,8H,Ar-H), 4.67(s,4H,CH_2), 2.31(3H,s,CH_3). IR(KBr, ν ,cm^{-1}): 3187(N-H), 1703(C=O). Anal. Calcd. for $C_{18}H_{18}N_3O_5Cl$: C,55.18; H,4.63; N,10.72. Found: C,55.37; H,4.70; N,10.91.

1-(4-methoxylphenyloxyacetyl)-4-(4-chlorophenyloxyacetyl)-semicarbazide (IId): Yield: 92%. m.p.: 143-144℃. ^{1}H NMR (DMSO-d_6) δ 12.47(s,1H,NH), 10.10(s,2H,NH), 6.82-7.59(m,8H,Ar-H), 4.71(s,4H,CH_2), 3.39(3H,s,CH_3). IR(KBr, ν ,cm^{-1}): 3210(N-H), 1706(C=O). Anal. Calcd. for $C_{18}H_{18}N_3O_6Cl$: C,53.01; H,4.45; N,10.30. Found: C,53.27; H,4.66; N,10.51.

1-(4-chlorophenyloxyacetyl)-4-(4-chlorophenyloxyacetyl)-semicarbazide (IIe): Yield: 94%. m.p.: 190-191 ℃. ^{1}H NMR (DMSO-d_6) δ 12.70(s,1H,NH), 10.15(s,2H,NH), 6.61-7.50(m,8H,Ar-H), 4.69(s,4H,CH_2). IR(KBr, ν ,cm^{-1}): 3210(N-H), 1719(C=O). Anal. Calcd. for $C_{17}H_{15}N_3O_5Cl_2$: C,49.53; H,3.67; N,10.19. Found: C,49.73; H,3.73; N,10.30.

1-(1-naphthyloxyacetyl)-4-(4-chlorophenyloxyacetyl)-semicarbazide (IIf): Yield: 96%. m.p.: 197-198 ℃. ^{1}H NMR (DMSO-d_6) δ 12.69(s,1H,NH), 10.11(s,2H,NH), 6.77-7.60(m,11H,Ar-H), 4.68(s,4H,CH_2). IR(KBr, ν ,cm^{-1}): 3192(N-H), 1730(C=O). Anal. Calcd. for $C_{21}H_{18}N_3O_5Cl$: C,58.95; H,4.24; N,9.82. Found: C,59.19; H,4.37; N,9.97.

1-(2-naphthyloxyacetyl)-4-(4-chlorophenyloxyacetyl)-semicarbazide (IIg): Yield: 95%. m.p.: 199-200 ℃. ^{1}H NMR (DMSO-d_6) δ 12.68(s,1H,NH), 10.06(s,2H,NH), 6.79-7.50(m,11H,Ar-H), 4.70(s,4H,CH_2). IR(KBr, ν ,cm^{-1}): 3201(N-H), 1724(C=O). Anal. Calcd. for $C_{21}H_{18}N_3O_5Cl$: C,58.95; H,4.24; N,9.82. Found: C,59.22; H,4.34; N,9.99.

1-(4-nitrophenyloxyacetyl)-4-(4-chlorophenyloxyacetyl)-semicarbazide (IIh):

Yield: 95%. m.p.: 201-202 ℃. ^{1}H NMR (DMSO-d_6) δ 12.82(s,1H,NH), 10.19(s,2H,NH), 6.86-7.60(m,8H,Ar-H), 4.72(s,4H,CH_2). IR(KBr, ν ,cm^{-1}): 3221(N-H), 1727(C=O). Anal. Calcd. for $C_{17}H_{15}N_4O_7Cl$: C,48.30; H,3.58; N,13.25. Found: C,48.11; H,3.50; N,13.20.

1-(3-nitrophenyloxyacetyl)-4-(4-chlorophenyloxyacetyl)-semicarbazide (IIi): Yield: 91%. m.p.: 196-197 ℃. ^{1}H NMR (DMSO-d_6) δ 12.91(s,1H,NH), 10.09(s,2H,NH), 6.80-7.58(m,8H,Ar-H), 4.70(s,4H,CH_2). IR(KBr, ν ,cm^{-1}): 3214(N-H), 1720(C=O). Anal. Calcd. for $C_{17}H_{15}N_4O_7Cl$: C,48.30; H,3.58; N,13.25. Found: C,48.51; H,3.76; N,13.40.

1-(2-nitrophenyloxyacetyl)-4-(4-chlorophenyloxyacetyl)-semicarbazide (IIj): Yield: 92%. m.p.: 160-161 ℃. ^{1}H NMR (DMSO-d_6) δ 12.88(s,1H,NH), 10.11(s,2H,NH), 6.77-7.61(m,8H,Ar-H), 4.71(s,4H,CH_2). IR(KBr, ν ,cm^{-1}): 3209(N-H), 1731(C=O). Anal. Calcd. for $C_{17}H_{15}N_4O_7Cl$: C,48.30; H,3.58; N,13.25. Found: C,48.10; H,3.53; N,13.16.

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