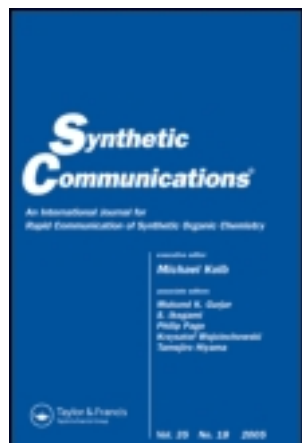




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SYNTHESIS OF 2-(4-TOLYLOXYACETYLAMIDO)-5-ARYLOXYMETHYL-1,3,4-THIADIAZOLES UNDER MICROWAVE IRRADIATION

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SYNTHESIS OF 2-(4-TOLYLOXYACETYLAMIDO)-5- ARYLOXYMETHYL-1,3,4-THIADIAZOLES UNDER MICROWAVE IRRADIATION

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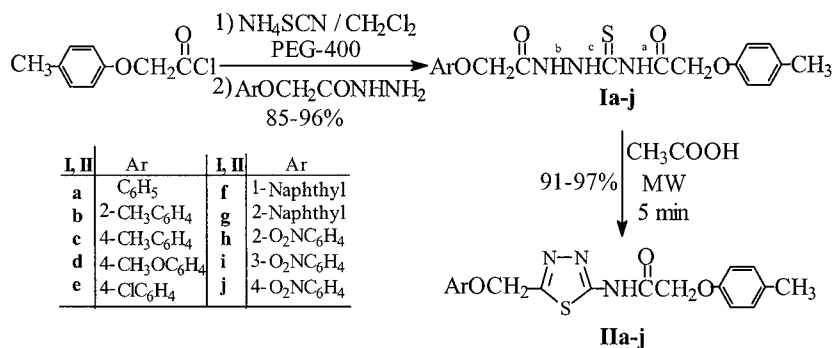
ABSTRACT

2-(4-Tolyloxyacetylamido)-5-aryloxymethyl-1,3,4-thiadiazoles (**IIa–j**) are synthesized under microwave irradiation by the cyclization of 1-aryloxyacetyl-4-(4-tolyloxyacetyl)-thiosemicarbazides (**Ia–j**) in the presence of glacial acetic acid.

Aryloxyacetic acid derivatives have been used as herbicides (1), diuretics (2), and plant-growth regulators (3–5). Meanwhile, substituted 1,3,4-thiadiazoles have also attracted much attention due to their diverse biological activities, such as antimicrobial (6–11), antibacterial (12), anesthetic (13), antithrombotic (14), anticonvulsant (15), cardiogenic (16), antihypertensive (17), antiinflammatory (18), and antiulcer (19) activity.

Keeping in view the above facts, we report herein the preparation of a new series of compounds bearing both 1,3,4-thiadiazole and aryloxyacetyl moiety, with the objective of obtaining new biologically active compounds.

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Scheme

Although the substituted 1,3,4-thiadiazoles can be prepared from the substituted thiosemicarbazides by conventional method (20,21), the reaction yield is often not high and the reaction time is always very long. This paper introduces a convenient and efficient microwave method.

Reaction of 4-toloxycarbonyl chloride with ammonium thiocyanate catalyzed by polyethylene glycol-400 (PEG-400) at room temperature gives 4-toloxycarbonyl isothiocyanate, which, on treatment with aryloxyacetic acid hydrazides *in situ* at room temperature, affords 1-aryloxyacetyl-4-(4-toloxycarbonyl)-thiosemicarbazides (**Ia-j**) in excellent yields. Compounds (**Ia-j**) on exposure to microwave irradiation in the presence of glacial acetic acid result in the formation of 2-(4-toloxycarbonylamido)-5-aryloxymethyl-1,3,4-thiadiazoles (**IIa-j**) (Scheme).

The characterization of compounds **Ia-j** and **IIa-j** is based on their IR (KBr), ¹H NMR and elemental analyses. The IR spectra exhibit a characteristic strong absorption at 1185–1195 cm⁻¹ for compounds **Ia-j** attributable to the C=S of the thio residue. The carbonyl absorption is observed at 1708–1718 cm⁻¹ for **Ia-j** and 1697–1717 cm⁻¹ for **IIa-j**. The ¹H NMR spectral data of **Ia-j** in d₆-dimethylsulfoxide show peaks at 12.68–12.85 (NH^a), 10.03–10.66 (NH^b), 9.38–9.60 (NH^c) and 4.62–4.76 ppm (CH₂). In contrast, the ¹H NMR spectral data of **IIa-j** in the same deuterated solvent show signals at 12.87–13.03 (NH), indicating a significant downfield shift (ca. 0.2 ppm), compared to the corresponding NH^a of **Ia-j**, and two singlet at 5.58–5.71, 4.70–4.91 ppm (CH₂), although only one singlet for two CH₂ in the **Ia-j**, indicating the obviously environmental changes of CH₂ in the **IIa-j**, in comparison with **Ia-j**. All found of C, H, N of **Ia-j** and **IIa-j** are in good agreement with the calculated.

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



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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. 4-tolyloxyacetyl chloride (22) and aryloxyacetic acid hydrazides (23) were prepared according to literature procedures. Ammonium thiocyanate, glacial acetic acid, and PEG-400 were commercially available and used as received.

General Procedure for Preparation of Ia–j

A suspension of 4-tolyloxyacetyl chloride (0.28 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 aryloxyacetic acid hydrazide (1.45 mmol) was added. The mixture was stirred for another 0.5 h, and a precipitate was formed. The resulting mixture was filtered and washed with water to remove inorganic salts. The residue was recrystallized from DMF-EtOH-H₂O to yield **I** as crystals. The physical and spectral results are shown below.

1-phenyloxyacetyl-4-(4-tolyloxyacetyl)-thiosemicarbazide (Ia)

White solid. Yield: 85%. m.p.: 154°–155°C. ¹H NMR (80 MHz, DMSO-d₆) δ 12.81 (1H, s, NH), 10.03 (1H, s, NH), 9.41 (1H, s, NH), 6.70–7.44 (9H, m, ArH), 4.69 (4H, s, CH₂), 2.33 (3H, s, CH₃). IR (KBr, γ cm⁻¹): 3387, 3270 (N-H), 1713 (C=O), 1189 (C=S). MS: *m/z*, 373. Anal. calcd. for C₁₈H₁₉N₃O₄S: C, 57.89; H, 5.13; N, 11.25. Found: C, 58.01; H, 5.04; N, 11.12.

1-(2-tolyloxyacetyl)-4-(4-tolyloxyacetyl)-thiosemicarbazide (Ib)

White solid. Yield: 93%. m.p.: 189°–190°C. ¹H NMR (80 MHz, DMSO-d₆) δ 12.78 (1H, s, NH), 10.09 (1H, s, NH), 9.43 (1H, s, NH), 6.76–7.19 (8H, m, ArH), 4.66 (4H, s, CH₂), 2.30 (6H, s, CH₃). IR (KBr, γ cm⁻¹): 3376, 3280 (N-H), 1710 (C=O), 1195 (C=S). MS: *m/z*, 387. Anal. calcd. for C₁₉H₂₁N₃O₄S: C, 58.90; H, 5.46; N, 10.85. Found: C, 58.72; H, 5.36; N, 10.63.

1-(4-tolyloxyacetyl)-4-(4-tolyloxyacetyl)-thiosemicarbazide (Ic)

White solid. Yield: 96%. m.p.: 167°–168°C. ¹H NMR (80 MHz, DMSO-d₆) δ 12.80 (1H, s, NH), 10.15 (1H, s, NH), 9.38 (1H, s, NH), 6.71–7.30 (8H, m, ArH), 4.62 (4H, s, CH₂), 2.26 (6H, s, CH₃). IR (KBr, γ cm⁻¹): 3390, 3287 (N-H), 1716 (C=O), 1193 (C=S). MS: *m/z*, 387. Anal. calcd. for C₁₉H₂₁N₃O₄S: C, 58.90; H, 5.46; N, 10.85. Found: C, 58.67; H, 5.30; N, 10.57.



1-(4-methoxyphenyloxyacetyl)-4-(4-tolyloxyacetyl)-thiosemicarbazide (Id)

White solid. Yield: 88%. m.p.: 143°–144°C. ^1H NMR (80 MHz, DMSO- d_6) δ 12.82 (1H, s, NH), 10.21 (1H, s, NH), 9.46 (1H, s, NH), 6.72–7.20 (8H, m, ArH), 4.70 (4H, s, CH₂), 3.49 (3H, s, CH₃), 2.27 (3H, s, CH₃). IR (KBr, γ , cm⁻¹): 3286, 3261 (N-H), 1718 (C=O), 1190 (C=S). MS: m/z , 403. Anal. calcd. for C₁₉H₂₁N₃O₅S: C, 56.56; H, 5.25; N, 10.41. Found: C, 56.84; H, 5.31; N, 10.64.

1-(4-chlorophenyloxyacetyl)-4-(4-tolyloxyacetyl)-thiosemicarbazide (Ie)

White solid. Yield: 90%. m.p.: 157°–158°C. ^1H NMR (80 MHz, DMSO- d_6) δ 12.77 (1H, s, NH), 10.18 (1H, s, NH), 9.54 (1H, s, NH), 6.80–7.32 (8H, m, ArH), 4.71 (4H, s, CH₂), 2.31 (3H, s, CH₃). IR (KBr, γ , cm⁻¹): 3381, 3276 (N-H), 1714 (C=O), 1187 (C=S). MS: m/z , 407. Anal. calcd. for C₁₈H₁₈N₃O₄SCl: C, 53.00; H, 4.45; N, 10.30. Found: C, 52.79; H, 4.31; N, 10.52.

1-(1-naphthyloxyacetyl)-4-(4-tolyloxyacetyl)-thiosemicarbazide (If)

White solid. Yield: 88%. m.p.: 177°–178°C. ^1H NMR (80 MHz, DMSO- d_6) δ 12.68 (1H, s, NH), 10.63 (1H, s, NH), 9.43 (1H, s, NH), 6.75–7.51 (11H, m, ArH), 4.73 (4H, s, CH₂), 2.36 (3H, s, CH₃). IR (KBr, γ , cm⁻¹): 3389, 3301 (N-H), 1713 (C=O), 1186 (C=S). MS: m/z , 423. Anal. calcd. for C₂₂H₂₁N₃O₄S: C, 62.40; H, 5.00; N, 9.92. Found: C, 62.27; H, 4.91; N, 10.14.

1-(2-naphthyloxyacetyl)-4-(4-tolyloxyacetyl)-thiosemicarbazide (Ig)

White solid. Yield: 92%. m.p.: 160°–161°C. ^1H NMR (80 MHz, DMSO- d_6) δ 12.70 (1H, s, NH), 10.66 (1H, s, NH), 9.40 (1H, s, NH), 6.76–7.53 (11H, m, ArH), 4.69 (4H, s, CH₂), 2.30 (3H, s, CH₃). IR (KBr, γ , cm⁻¹): 3381, 3314 (N-H), 1714 (C=O), 1190 (C=S). MS: m/z , 423. Anal. calcd. for C₂₂H₂₁N₃O₄S: C, 62.40; H, 5.00; N, 9.92. Found: C, 62.59; H, 5.07; N, 9.81.

1-(2-nitrophenyloxyacetyl)-4-(4-tolyloxyacetyl)-thiosemicarbazide (Ih)

White solid. Yield: 93%. m.p.: 206°–207°C. ^1H NMR (80 MHz, DMSO- d_6) δ 12.80 (1H, s, NH), 10.08 (1H, s, NH), 9.42 (1H, s, NH), 6.77–7.45 (8H, m, ArH),



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4.69 (4H, s, CH₂), 2.26 (3H, s, CH₃). IR (KBr, γ , cm⁻¹): 3376, 3281 (N-H), 1708 (C=O), 1186 (C=S). MS: *m/z*, 418. Anal. calcd. for C₁₈H₁₈N₄O₆S: C, 51.67; H, 4.34; N, 13.39. Found: C, 51.84; H, 4.30; N, 13.59.

1-(3-nitrophenyloxyacetyl)-4-(4-tolyloxyacetyl)-thiosemicarbazide (Ii)

White solid. Yield: 90%. m.p.: 171°–172°C. ¹H NMR (80 MHz, DMSO-d₆) δ 12.85 (1H, s, NH), 10.13 (1H, s, NH), 9.46 (1H, s, NH), 6.89–7.53 (8H, m, ArH), 4.73 (4H, s, CH₂), 2.37 (3H, s, CH₃). IR (KBr, γ , cm⁻¹): 3384, 3286 (N-H), 1712 (C=O), 1187 (C=S). MS: *m/z*, 418. Anal. calcd. for C₁₈H₁₈N₄O₆S: C, 51.67; H, 4.34; N, 13.39. Found: C, 51.51; H, 4.20; N, 13.19.

1-(4-nitrophenyloxyacetyl)-4-(4-tolyloxyacetyl)-thiosemicarbazide (Ij)

White solid. Yield: 95%. m.p.: 184°–185°C. ¹H NMR (80 MHz, DMSO-d₆) δ 12.77 (1H, s, NH), 10.16 (1H, s, NH), 9.60 (1H, s, NH), 6.73–7.51 (8H, m, ArH), 4.76 (4H, s, CH₂), 2.38 (3H, s, CH₃). IR (KBr, γ , cm⁻¹): 3391, 3293 (N-H), 1709 (C=O), 1185 (C=S). MS: *m/z*, 418. Anal. calcd. for C₁₈H₁₈N₄O₆S: C, 51.67; H, 4.34; N, 13.39. Found: C, 51.73; H, 4.31; N, 13.42.

General Procedure for the Preparation of Compounds IIa–j

A mixture of compound **I** (0.5 mol) and glacial acetic acid (5 mL) was irradiated in a microwave oven at 375W for 5 min, and the completion of the reaction was monitored by TLC. The excess of glacial acetic acid was removed by evaporation, the residue was poured into ice (100 g), and the precipitate was collected by filtration and washed with water (3 $\times$ 20 mL). The product was obtained as white crystals after recrystallization from DMF-EtOH-H₂O. The physical and spectral data of compounds **IIa–j** are shown below.

2-(4-tolyloxyacetylamido)-5-phenyloxymethyl-1,3,4-thiadiazole (IIa)

White solid. Yield: 92%. m.p.: 173°–174°C. ¹H NMR (80 MHz, DMSO-d₆) δ 12.87 (1H, s, NH), 7.18–8.01 (9H, m, Ar-H), 5.58 (2H, s, CH₂), 4.87 (2H, s, CH₂), 2.20 (3H, s, CH₃). IR (KBr, γ , cm⁻¹): 3166 (N-H), 1707 (C=O), 1591, 1486, 1301, 1063 (C=N-N-C=S). MS: *m/z*, 355. Anal. calcd. for C₁₈H₁₇N₃O₃S: C, 60.83; H, 4.82; N, 11.82. Found: C, 60.98; H, 4.79; N, 11.76.



2-(4-tolyloxyacetylamido)-5-(2-tolyloxymethyl)-1,3,4-thiadiazole (IIb)

White solid. Yield: 95%. m.p.: 182°–183°C. ¹H NMR (80 MHz, DMSO-d₆) δ 12.92 (1H, s, NH), 6.80–8.03 (8H, m, Ar-H), 5.60 (2H, s, CH₂), 4.90 (2H, s, CH₂), 2.19 (6H, s, CH₃). IR (KBr, γ, cm⁻¹): 3164 (N-H), 1708 (C=O), 1510, 1495, 1306, 1060 (C=N-N-C=S). MS: *m/z*, 369. Anal. calcd. for C₁₉H₁₉N₃O₃S: C, 61.77; H, 5.18; N, 11.37. Found: C, 61.56; H, 4.83; N, 11.21.

2-(4-tolyloxyacetylamido)-5-(4-tolyloxymethyl)-1,3,4-thiadiazole (IIc)

White solid. Yield: 91%. m.p.: 188°–189°C. ¹H NMR (80 MHz, DMSO-d₆) δ 12.89 (1H, s, NH), 6.79–8.01 (8H, m, Ar-H), 5.61 (2H, s, CH₂), 4.89 (2H, s, CH₂), 2.21 (6H, s, CH₃). IR (KBr, γ, cm⁻¹): 3168 (N-H), 1711 (C=O), 1509, 1488, 1306, 1061 (C=N-N-C=S). MS: *m/z*, 369. Anal. calcd. for C₁₉H₁₉N₃O₃S: C, 61.77; H, 5.18; N, 11.37. Found: C, 61.86; H, 5.03; N, 11.49.

2-(4-tolyloxyacetylamido)-5-(4-methoxyphenyloxymethyl)-1,3,4-thiadiazole (IId)

White solid. Yield: 96%. m.p.: 170°–171°C. ¹H NMR (80 MHz, DMSO-d₆) δ 12.90 (1H, s, NH), 6.71–7.86 (8H, m, Ar-H), 5.58 (2H, s, CH₂), 4.70 (2H, s, CH₂), 3.86 (3H, s, CH₃), 2.19 (3H, s, CH₃). IR (KBr, γ, cm⁻¹): 3178 (N-H), 1691 (C=O), 1509, 1463, 1309, 1081 (C=N-N-C=S). MS: *m/z*, 385. Anal. calcd. for C₁₉H₁₉N₃O₄S: C, 59.21; H, 4.97; N, 10.90. Found: C, 59.46; H, 5.09; N, 11.16.

2-(4-tolyloxyacetylamido)-5-(4-chlorophenyloxymethyl)-1,3,4-thiadiazole (IIe)

White solid. Yield: 93%. m.p.: 185°–186°C. ¹H NMR (80 MHz, DMSO-d₆) δ 12.88 (1H, s, NH), 6.79–8.28 (8H, m, Ar-H), 5.59 (2H, s, CH₂), 4.81 (2H, s, CH₂), 2.18 (3H, s, CH₃). IR (KBr, γ, cm⁻¹): 3196 (N-H), 1697 (C=O), 1512, 1492, 1326, 1040 (C=N-N-C=S). MS: *m/z*, 389. Anal. calcd. for C₁₈H₁₆N₃O₃SCl: C, 55.45; H, 4.14; N, 10.78. Found: C, 55.61; H, 4.30; N, 10.93.

2-(4-tolyloxyacetylamido)-5-(1-naphthyloxymethyl)-1,3,4-thiadiazole (IIIf)

White solid. Yield: 97%. m.p.: 190°–191°C. ¹H NMR (80 MHz, DMSO-d₆) δ 12.92 (1H, s, NH), 6.78–7.90 (11H, m, Ar-H), 5.63 (2H, s, CH₂), 4.90 (2H, s, CH₂), 2.20 (3H, s, CH₃). IR (KBr, γ, cm⁻¹): 3201 (N-H), 1711 (C=O), 1510, 1489, 1301, 1070 (C=N-N-C=S). MS: *m/z*, 405. Anal. calcd. for C₂₂H₁₉N₃O₃S: C, 65.17; H, 4.72; N, 10.36. Found: C, 65.22; H, 4.63; N, 10.53.



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2-(4-tolyloxyacetylamido)-5-(2-naphthyloxymethyl)-1,3,4-thiadiazole (IIg)

White solid. Yield: 96%. m.p.: 181°–182°C. ^1H NMR (80 MHz, DMSO- d_6) δ 12.90 (1H, s, NH), 6.76–7.89 (11H, m, Ar-H), 5.66 (2H, s, CH_2), 4.89 (2H, s, CH_2), 2.19 (3H, s, CH_3). IR (KBr, γ , cm^{-1}): 3179 (N-H), 1708 (C=O), 1513, 1490, 1306, 1061 (C=N-N-C=S). MS: m/z , 405. Anal. calcd. for $\text{C}_{22}\text{H}_{19}\text{N}_3\text{O}_5\text{S}$: C, 65.17; H, 4.72; N, 10.36 Found: C, 65.31; H, 4.66; N, 10.49.

2-(4-tolyloxyacetylamido)-5-(2-nitrophenyloxymethyl)-1,3,4-thiadiazole (IIh)

White solid. Yield: 94%. m.p.: 218°–219°C. ^1H NMR (80 MHz, DMSO- d_6) δ 12.98 (1H, s, NH), 6.99–8.31 (8H, m, Ar-H), 5.69 (2H, s, CH_2), 4.89 (2H, s, CH_2), 2.21 (3H, s, CH_3). IR (KBr, γ , cm^{-1}): 3188 (N-H), 1712 (C=O), 1510, 1495, 1304, 1071 (C=N-N-C=S). MS: m/z , 400. Anal. calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_5\text{S}$: C, 53.99; H, 4.03; N, 13.99. Found: C, 53.85; H, 4.10; N, 13.82.

2-(4-tolyloxyacetylamido)-5-(3-nitrophenyloxymethyl)-1,3,4-thiadiazole (IIi)

White solid. Yield: 96%. m.p.: 187°–188°C. ^1H NMR (80 MHz, DMSO- d_6) δ 13.03 (1H, s, NH), 6.93–8.29 (8H, m, Ar-H), 5.71 (2H, s, CH_2), 4.91 (2H, s, CH_2), 2.22 (3H, s, CH_3). IR (KBr, γ , cm^{-1}): 3191 (N-H), 1703 (C=O), 1511, 1493, 1307, 1079 (C=N-N-C=S). MS: m/z , 400. Anal. calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_5\text{S}$: C, 53.99; H, 4.03; N, 13.99. Found: C, 53.88; H, 4.09; N, 13.89.

2-(4-tolyloxyacetylamido)-5-(4-nitrophenyloxymethyl)-1,3,4-thiadiazole (IIj)

White solid. Yield: 95%. m.p.: 206°–207°C. ^1H NMR (80 MHz, DMSO- d_6) δ 13.01 (1H, s, NH), 7.01–8.33 (8H, m, Ar-H), 5.68 (2H, s, CH_2), 4.87 (2H, s, CH_2), 2.19 (3H, s, CH_3). IR (KBr, γ , cm^{-1}): 3186 (N-H), 1717 (C=O), 1510, 1496, 1305, 1072 (C=N-N-C=S). MS: m/z , 400. Anal. calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_5\text{S}$: C, 53.99; H, 4.03; N, 13.99. Found: C, 53.86; H, 4.08; N, 13.87.

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