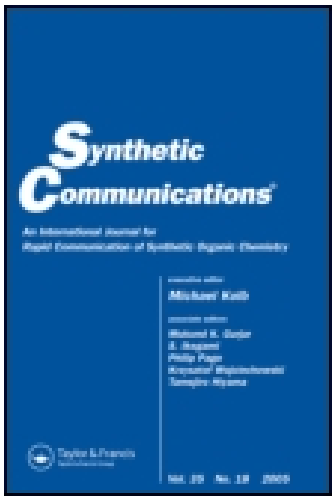

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Published online: 21 Aug 2006.

To cite this article: Xicun Wang , Zheng Li & Yuxia Da (2002) A NEW ROUTE TO 2-(5-ARYL-2-FUROYLAMIDO)-5-ARYLOXYMETHYL-1,3,4-THIADIAZOLES, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 32:7, 1105-1111, DOI: 10.1081/SCC-120003160

To link to this article: http://dx.doi.org/10.1081/SCC-120003160

SYNTHETIC COMMUNICATIONS, 32(7), 1105–1111 (2002)

A NEW ROUTE TO 2-(5-ARYL-2-FUROYLAMIDO)-5-ARYLOXYMETHYL-1,3,4-THIADIAZOLES

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ABSTRACT

The 2-(5-aryl-2-furoylamido)-5-aryloxymethyl-1,3,4-thiadiazoles $\mathbf{4_{1-18}}$ are synthesized by the reaction of 5-aryl-2-furoic acids **1** with phenylsulfonyl chloride and 2-amino-5-aryloxymethyl-1,3,4-thiadiazoles **3** under phase transfer catalysis.

5-Aryl-2-furoic acid derivatives have been used as antibacterial agent,[1] local anesthesia,[2] analgesic[3] and plant-growth regulator.[4–5] 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] anticonvulsant,[14] cardiotonic,[15] antihypertensive,[16] antiinflammatory[17] and antiulcer[18] activity. In view of the above facts, we report herein the preparation of a new series of compounds bearing both 5-aryl-2-furoyl and 1,3,4-thiadiazole moiety, with the objective of obtaining new biologically active compounds.

Generally, the 2-acylamido-1,3,4-thiadiazoles are synthesized via cyclization of 4-acyl-thiosemicarbazides in the presence of acid.[8] However, in

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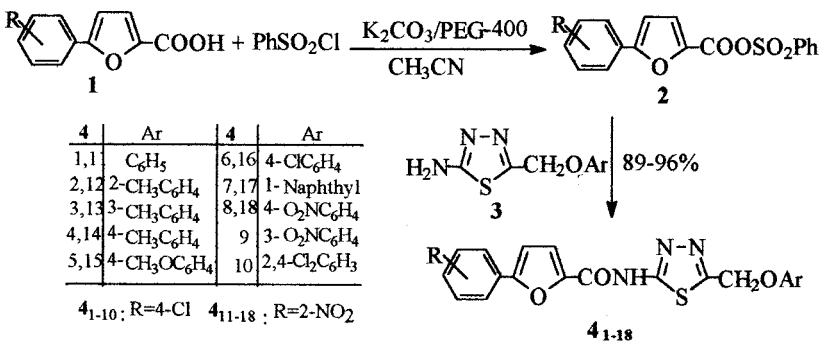
this paper we report a new route to 2-acylamido-5-substituted-1,3,4-thiadiazoles **4** by the reaction of 2-amino-5-substituted-1,3,4-thiadiazoles **3** with 5-aryl-2-furoic acid **1** in the presence of phenylsulfonyl chloride. Although the reactivity of the amino group in 1,3,4-thiadiazoles **3** is very low because of the steric hindrance, we are still able to synthesize the title compounds **4** successfully using phase transfer catalysis.[5,19–21]

Refluxing of 5-aryl-2-furoic acids **1** with phenylsulfonyl chloride and potassium carbonate catalyzed by polyethylene glycol-400 (PEG-400) in acetonitrile gives 5-aryl-2-furoyl phenylsulfonates **2** as intermediate, which on treatment with 2-amino-5-aryloxymethyl-1,3,4-thiadiazoles **3** in situ afford 2-(5-aryl-2-furoylamido)-5-aryloxymethyl-1,3,4-thiadiazoles $\mathbf{4_{1–18}}$ in excellent yield (Scheme).



4	Ar	4	Ar
1,11	C_6H_5	6,16	4-ClC_6H_4
2,12	2-$CH_3C_6H_4$	7,17	1-Naphthyl
3,13	3-$CH_3C_6H_4$	8,18	4-$O_2NC_6H_4$
4,14	4-$CH_3C_6H_4$	9	3-$O_2NC_6H_4$
5,15	4-$CH_3OC_6H_4$	10	2,4-$Cl_2C_6H_3$

$\mathbf{4_{1-10}}$: R=4-Cl $\mathbf{4_{11-18}}$: R=2-NO_2

Scheme.

The characterization of compounds $\mathbf{4_{1–18}}$ is based on their IR (KBr), ^{1}H NMR and elemental analyses. The IR spectra exhibit a characteristic strong absorption at 1665–1681 cm^{-1} for carbonyl. The ^{1}H NMR spectral data of $\mathbf{4_{1–18}}$ in d_6-dimethylsulfoxide show peaks at 13.17–13.50 (NH) and 5.39–5.50 ppm (CH_2). All found of C, H, N of $\mathbf{4_{1–18}}$ are in good agreement with the calculated.

EXPERIMENTAL

IR spectra were recorded using KBr pellets on an Alpha Centauri FTIR spectrophotometer and ^{1}H NMR spectra on an FT-80A instrument using $(CD_3)_2SO$ as solvent and Me_4Si as an internal standard. Elemental analyses were performed on a Carlo-Erba 1106 Elemental Analysis instru-

ment. Melting points were observed in an open capillary tube and uncorrected. 5-Aryl-2-furoic acids **1**[22] and 2-amino-5-aryloxymethyl-1,3,4-thiadiazoles **3**[23,24] were prepared according to literature procedures. Phenylsulfonyl chloride and PEG-400 were commercially available and used as received.

General Procedure for Preparation of 4_{1-18}

A mixture of 5-aryl-2-furoic acid **1** (1 mmol), K_2CO_3 (0.55 g, 4 mmol), phenylsulfonyl chloride (0.18 g, 1 mmol) and PEG-400 (0.01 g, 0.03 mmol) in 15 ml of acetonitrile was refluxed for 0.5 h, then 2-amino-5-aryloxymethyl-1,3,4-thiadiazole **3** (1 mmol) was added. The resulting mixture was refluxed for another 1 h. The solvent was removed under reduced pressure, and the residue was washed with water. The resulting solid was recrystallized from DMF–EtOH–H_2O (5 : 4 : 1) to yield $\mathbf{4}_{1-18}$ as crystals. The physical and spectral results of $\mathbf{4}_{1-18}$ are shown below.

2-(5-(4-Chlorophenyl)-2-furoylamido)-5-phenyloxymethyl-1,3,4-thiadiazole (4_1): White solid. Yield: 90%. m.p.: 235–236°C. ^{1}H NMR (80 MHz, DMSO-d_6) δ 13.17 (1H, s, NH), 7.0–8.4 (11H, m, Ar-H and Fu-H), 5.39 (2H, s, CH_2). IR (KBr, ν cm^{-1}): 3148 (N-H), 1669 (C=O), 1601, 1511, 1476, 1097 (C=N-N=C-S). Anal. calcd for $C_{20}H_{14}N_3O_3SCl$: C, 58.32; H, 3.43; N, 10.20. Found: C, 58.46; H, 3.36; N, 10.37.

2-(5-(4-Chlorophenyl)-2-furoylamido)-5-(2-tolyloxymethyl)-1,3,4-thiadiazole (4_2): White solid. Yield: 93%. m.p.: 221–222°C. ^{1}H NMR (80 MHz, DMSO-d_6) δ 13.20 (1H, s, NH), 7.0–8.5 (10H, m, Ar-H and Fu-H), 5.41 (2H, s, CH_2), 2.30 (3H, s, CH_3). IR (KBr, ν cm^{-1}): 3140 (N-H), 1677 (C=O), 1601, 1526, 1477, 1092 (C=N-N=C-S). Anal. calcd for $C_{21}H_{16}N_3O_3SCl$: C, 59.22; H, 3.79; N, 9.87. Found: C, 59.50; H, 3.96; N, 10.02.

2-(5-(4-Chlorophenyl)-2-furoylamido)-5-(3-tolyloxymethyl)-1,3,4-thiadiazole (4_3): White solid. Yield: 96%. m.p.: 203–204°C. ^{1}H NMR (80 MHz, DMSO-d_6) δ 13.26 (1H, s, NH), 7.0–8.5 (10H, m, Ar-H and Fu-H), 5.42 (2H, s, CH_2), 2.28 (3H, s, CH_3). IR (KBr, ν cm^{-1}): 3150 (N-H), 1665 (C=O), 1608, 1513, 1475, 1096 (C=N-N=C-S). Anal. calcd for $C_{21}H_{16}N_3O_3SCl$: C, 59.22; H, 3.79; N, 9.87. Found: C, 59.01; H, 3.82; N, 9.96.

2-(5-(4-Chlorophenyl)-2-furoylamido)-5-(4-tolyloxymethyl)-1,3,4-thiadiazole (4_4): White solid. Yield: 95%. m.p.: 201–202°C. ^{1}H NMR (80 MHz, DMSO-d_6) δ 13.21 (1H, s, NH), 7.0–8.4 (10H, m, Ar-H and Fu-H), 5.46 (2H, s, CH_2), 2.26 (3H, s, CH_3). IR (KBr, ν cm^{-1}): 3151 (N-H), 1670 (C=O), 1599, 1516, 1474, 1090 (C=N-N=C-S). Anal. calcd for $C_{21}H_{16}N_3O_3SCl$: C, 59.22; H, 3.79; N, 9.87. Found: C, 59.49; H, 3.99; N, 9.98.

2-(5-(4-Chlorophenyl)-2-furoylamido)-5-(4-methoxylphenyloxymethyl)-1,3,4-thiadiazole (4_5): White solid. Yield: 92%. m.p.: 196–197°C. ^{1}H NMR (80 MHz, DMSO-d_6) δ 13.23 (1H, s, NH), 7.0–8.4 (10H, m, Ar-H and Fu-H), 5.45 (2H, s, CH_2), 3.40 (3H, s, CH_3). IR (KBr, ν cm^{-1}): 3147 (N-H), 1668 (C=O), 1611, 1509, 1478, 1101 (C=N-N=C-S). Anal. calcd for $C_{21}H_{16}N_3O_4SCl$: C, 57.08; H, 3.65; N, 9.51. Found: C, 57.29; H, 3.71; N, 9.72.

2-(5-(4-Chlorophenyl)-2-furoylamido)-5-(4-chlorophenyloxymethyl)-1,3,4-thiadiazole (4_6): White solid. Yield: 94%. m.p.: 213–214°C. ^{1}H NMR (80 MHz, DMSO-d_6) δ 13.25 (1H, s, NH), 7.0–8.5 (10H, m, Ar-H and Fu-H), 5.40 (2H, s, CH_2). IR (KBr, ν cm^{-1}): 3152 (N-H), 1669 (C=O), 1607, 1510, 1473, 1105 (C=N-N=C-S). Anal. calcd for $C_{20}H_{13}N_3O_3SCl_2$: C, 53.82; H, 2.94; N, 9.41. Found: C, 54.03; H, 3.07; N, 9.60.

2-(5-(4-Chlorophenyl)-2-furoylamido)-5-(1-naphthyloxymethyl)-1,3,4-thiadiazole (4_7): White solid. Yield: 96%. m.p.: 238–239°C. ^{1}H NMR (80 MHz, DMSO-d_6) δ 13.26 (1H, s, NH), 7.0–8.4 (13H, m, Ar-H and Fu-H), 5.42 (2H, s, CH_2). IR (KBr, ν cm^{-1}): 3184 (N-H), 1669 (C=O), 1601, 1515, 1481, 1107 (C=N-N=C-S). Anal. calcd. for $C_{24}H_{16}N_3O_3SCl$: C, 62.40; H, 3.49; N, 9.10. Found: C, 62.29; H, 3.32; N, 8.90.

2-(5-(4-Chlorophenyl)-2-furoylamido)-5-(4-nitrophenyloxymethyl)-1,3,4-thiadiazole (4_8): White solid. Yield: 91%. m.p.: 234–235°C. ^{1}H NMR (80 MHz, DMSO-d_6) δ 13.27 (1H, s, NH), 7.1–8.5 (10H, m, Ar-H and Fu-H), 5.50 (2H, s, CH_2). IR (KBr, ν cm^{-1}): 3118 (N-H), 1678 (C=O), 1617, 1526, 1476, 1094 (C=N-N=C-S). Anal. calcd for $C_{20}H_{13}N_4O_5SCl$: C, 52.58; H, 2.87; N, 12.26. Found: C, 52.72; H, 2.94; N, 12.37.

2-(5-(4-Chlorophenyl)-2-furoylamido)-5-(3-nitrophenyloxymethyl)-1,3,4-thiadiazole (4_9): White solid. Yield: 93%. m.p.: 240–241°C. ^{1}H NMR (80 MHz, DMSO-d_6) δ 13.28 (1H, s, NH), 7.1–8.5 (10H, m, Ar-H and Fu-H), 5.48 (2H, s, CH_2). IR (KBr, ν cm^{-1}): 3150 (N-H), 1677 (C=O), 1620, 1518, 1477, 1099 (C=N-N=C-S). Anal. calcd for $C_{20}H_{13}N_4O_5SCl$: C, 52.58; H, 2.87; N, 12.26. Found: C, 52.69; H, 2.88; N, 12.38.

2-(5-(4-Chlorophenyl)-2-furoylamido)-5-(2,4-dichlorophenyloxymethyl)-1,3,4-thiadiazole (4_{10}): White solid. Yield: 89%. m.p.: 212–213°C. ^{1}H NMR (80 MHz, DMSO-d_6) δ 13.25 (1H, s, NH), 7.0–8.5 (9H, m, Ar-H and Fu-H), 5.46 (2H, s, CH_2). IR (KBr, ν cm^{-1}): 3146 (N-H), 1676 (C=O), 1613, 1514, 1470, 1101 (C=N-N=C-S). Anal. calcd for $C_{20}H_{12}N_3O_3SCl_3$: C, 49.86; H, 2.72; N, 8.72. Found: C, 50.01; H, 2.80; N, 8.90.

2-(5-(2-Nitrophenyl)-2-furoylamido)-5-phenyloxymethyl-1,3,4-thiadiazole (4_{11}): White solid. Yield: 93%. m.p.: 232–233°C. ^{1}H NMR (80 MHz, DMSO-d_6) δ 13.40 (1H, s, NH), 6.8–8.1 (11H, m, Ar-H and Fu-H), 5.40 (2H, s, CH_2). IR (KBr, ν cm^{-1}): 3119 (N-H), 1670 (C=O), 1603, 1508, 1456, 1103 (C=N-N=C-S). Anal. calcd for $C_{20}H_{14}N_4O_5S$: C, 56.87; H, 3.34; N, 13.26. Found: C, 57.06; H, 3.40; N, 13.36.

2-(5-(2-Nitrophenyl)-2-furoylamido)-5-(2-tolyloxymethyl)-1,3,4-thiadiazole (4_{12}): White solid. Yield: 92%. m.p.: 246–247°C. ^{1}H NMR (80 MHz, DMSO-d_6) δ 13.42 (1H, s, NH), 6.8–8.2 (10H, m, Ar-H and Fu-H), 5.43 (2H, s, CH_2), 2.25 (3H, s, CH_3). IR (KBr, ν cm^{-1}): 3167 (N-H), 1681 (C=O), 1601, 1520, 1470, 1100 (C=N-N=C-S). Anal. calcd for $C_{21}H_{16}N_4O_5S$: C, 57.79; H, 3.70; N, 12.84. Found: C, 57.91; H, 3.77; N, 12.98.

2-(5-(2-Nitrophenyl)-2-furoylamido)-5-(3-tolyloxymethyl)-1,3,4-thiadiazole (4_{13}): White solid. Yield: 90%. m.p.: 236–237°C. ^{1}H NMR (80 MHz, DMSO-d_6) δ 13.50 (1H, s, NH), 6.8–8.3 (10H, m, Ar-H and Fu-H), 5.44 (2H, s, CH_2), 2.28 (3H, s, CH_3). IR (KBr, ν cm^{-1}): 3170 (N-H), 1679 (C=O), 1605, 1513, 1465, 1098 (C=N-N=C-S). Anal. calcd for $C_{21}H_{16}N_4O_5S$: C, 57.79; H, 3.70; N, 12.84. Found: C, 57.60; H, 3.68; N, 12.76.

2-(5-(2-Nitrophenyl)-2-furoylamido)-5-(4-tolyloxymethyl)-1,3,4-thiadiazole (4_{14}): White solid. Yield: 96%. m.p.: 250–251°C. ^{1}H NMR (80 MHz, DMSO-d_6) δ 13.46 (1H, s, NH), 6.9–8.3 (10H, m, Ar-H and Fu-H), 5.41 (2H, s, CH_2), 2.26 (3H, s, CH_3). IR (KBr, ν cm^{-1}): 3162 (N-H), 1677 (C=O), 1616, 1520, 1457, 1100 (C=N-N=C-S). Anal. calcd for $C_{21}H_{16}N_4O_5S$: C, 57.79; H, 3.70; N, 12.84. Found: C, 57.96; H, 3.73; N, 12.92.

2-(5-(2-Nitrophenyl)-2-furoylamido)-5-(4-methoxylphenyloxymethyl)-1,3,4-thiadiazole (4_{15}): White solid. Yield: 94%. m.p.: 231–232°C. ^{1}H NMR (80 MHz, DMSO-d_6) δ 13.38 (1H, s, NH), 6.8–8.3 (10H, m, Ar-H and Fu-H), 5.42 (2H, s, CH_2), 3.36 (3H, s, CH_3). IR (KBr, ν cm^{-1}): 3171 (N-H), 1680 (C=O), 1620, 1523, 1470, 1099 (C=N-N=C-S). Anal. calcd for $C_{21}H_{16}N_4O_6S$: C, 55.75; H, 3.56; N, 12.38. Found: C, 55.96; H, 3.64; N, 12.54.

2-(5-(2-Nitrophenyl)-2-furoylamido)-5-(4-chlorophenyloxymethyl)-1,3,4-thiadiazole (4_{16}): White solid. Yield: 95%. m.p.: 228–229°C. ^{1}H NMR (80 MHz, DMSO-d_6) δ 13.42 (1H, s, NH), 6.8–8.2 (10H, m, Ar-H and Fu-H), 5.44 (2H, s, CH_2). IR (KBr, ν cm^{-1}): 3183 (N-H), 1676 (C=O), 1621, 1518, 1476, 1110 (C=N-N=C-S). Anal. calcd for $C_{20}H_{13}N_4O_5SCl$: C, 52.58; H, 2.87; N, 12.26. Found: C, 52.31; H, 2.73; N, 12.08.

2-(5-(2-Nitrophenyl)-2-furoylamido)-5-(1-naphthyloxymethyl)-1,3,4-thiadiazole (4_{17}): White solid. Yield: 90%. m.p.: 260–261°C. ^{1}H NMR (80 MHz, DMSO-d_6) δ 13.47 (1H, s, NH), 6.8–8.2 (13H, m, Ar-H and Fu-H), 5.50 (2H, s, CH_2). IR (KBr, ν cm^{-1}): 3159 (N-H), 1680 (C=O), 1611, 1523, 1480, 1099 (C=N-N=C-S). Anal. calcd for $C_{24}H_{16}N_4O_5S$: C, 61.01; H, 3.41; N, 11.86. Found: C, 61.27; H, 3.50; N, 11.98.

2-(5-(2-Nitrophenyl)-2-furoylamido)-5-(4-nitrophenyloxymethyl)-1,3,4-thiadiazole (4_{18}): White solid. Yield: 95%. m.p.: 231–232°C. ^{1}H NMR (80 MHz, DMSO-d_6) δ 13.41 (1H, s, NH), 6.9–8.4 (10H, m, Ar-H and Fu-H), 5.47 (2H, s, CH_2). IR (KBr, ν cm^{-1}): 3169 (N-H), 1677 (C=O),

1609, 1510, 1480, 1101 (C=N-N=C-S). Anal. calcd for $C_{20}H_{13}N_5O_7S$: C, 51.39; H, 2.80; N, 14.98. Found: C, 51.56; H, 2.76; N, 15.09.

ACKNOWLEDGMENT

The authors thank the Natural Science Foundation of Gansu Province for the financial support of this work.

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Received in the USA March 29, 2001