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Note

Microwave promoted efficient synthesis of 2,5-disubstituted 1,3,4-thiadiazole

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A rapid and efficient method for the synthesis of substituted 1,3,4-thiadiazoles is described. The products have been characterized by analytical and spectral (IR and H'NMR) data.

Keywords: Microwave, 1,3,4-thiadiazoles, synthesis

IPC Code: Int Cl[8]. C07D

Substituted 1,3,4-thiadiazoles have become very useful compounds in medicine, agriculture and many fields of technology. Some of the technological applications involve dyes[1], lubricating composition[2], optically active liquid crystals[3], photographic materials[4] and many others. Moreover, a large number of 1,3,4-thiadiazoles have been patented in the agricultural field as herbicides[5], fungicides[6] and bacteriocides[7]. In the medical field one of the best known drugs based on a 1,3,4-thiadiazole is acetazolamide (acetazola)[8], (**Figure 1**) a carbonic anhydrase inhibitor launched in 1954. Its indications and usage are many, including the treatment of glaucoma, epilepsy and congestive cardiac failure. Recently, we have reported an efficient method for the synthesis of 1,4-disubstituted thiosemicarbazide derivatives under the condition of phase transfer catalysis using polyethylene glycol-400 as the catalyst[9]. As an extension of these studies we investigated the cyclization of 1,4-disubstituted thiosemicarbazide.

In view of these observations and in continuation of our earlier work on the synthesis of biological activity of 1,4-disubstitued thiosemicarbazide derivatives[10-12] and application of microwave irradiation in organic synthesis[13], we report herein, a convenient and efficient method for the rapid preparation of 2,5-disubstituted 1,3,4-thiadiazoles by using acetic acid as solvent under the condition of microwave irradiation (**Scheme I**).

There are many reports of 2,5-disubstituted 1,3,4-thiadiazoles. Generally they were obtained from 1-acyl-4-aroylthiosemicarbazides by cyclized in the presence of concentrated sulphuric acid[14], phosphoric acid[15] or hydrochloric acid[16] under refluxing condition, which produced much more waste water that contained acid and does not result environmental benefits. Furthermore, these methods usually have to reflux reactants for several hours at high temperature, and the isolated yields are always not very good.

In order to overcome these shortcomings and in view of the requirements of green chemistry for energy-saving, high efficiency and environmental benevolence, we carried out a series of reactions in acetic acid under the condition of microwave irradiation. It was found that 1-acyl-4-aroylthio-semirarbazides were cyclized smoothly and 2,5-disubstituted 1,3,4-thiadiazoles were obtained in good to excellent yields (**Table I**). By distillation under reduced pressure, the solvent, acetic acid, was also obtained and could be used again. When compared with other classical methods, our procedure has the advantages of simple operation, short reaction time, high yield, easy work-up and environmental

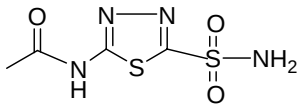
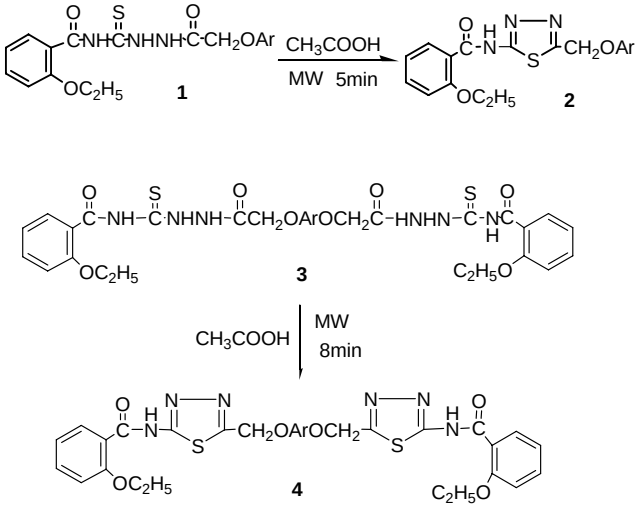


Figure 1



Scheme I

Table I — 2,5-Disubstituted 1,3,4-thiadiazoles.

Compd	Ar	Time of MWI (min)	Yields[a] (%)	m.p. °C
2a	4-$CH_3C_6H_4$	5	92	151-52
2b	3-$CH_3C_6H_4$	5	90	146-47
2c	2-$CH_3C_6H_4$	5	88	152-53
2d	4-Cl C_6H_4	5	85	216-17
2e	2-Cl C_6H_4	5	93	140-42
2f	4-O_2N C_6H_4	5	86	267-68
2g	α-naphthal	5	89	142-43
2h	β-naphthal	5	91	141-42
4a	1,4-C_6H_4	8	92	290-91
4b	1,3- C_6H_4	8	93	236-37

[a]Isolated yields

benefits over the reported methods. It is a facile and convenient method for the rapid preparation of 2,5-disubstituted 1,3,4-thiadiazole derivations.

Experimental Section

Melting points were determined in open capillaries and uncorrected, IR spectra were recorded in KBr on an Alpha Centauri FT-IR spectrophotometer and ^{1}HNMR spectra on a FT-80A instrument using DMSO-d_6 as solvent and TMS as internal reference. Elemental analysis was determined on PE-2400 CHN instrument. Microwave irradiation was carried out with a WP 750B commercial microwave oven at 2450 MHz.

General procedure for the preparation of title compounds 2. A mixture of compound **1** (3 mmoles) and glacial acetic acid (5 mL) was irradiated in microwave even (375 W) for 5 min, and the completion of the reaction was monitored by TLC. The excess of gl. acetic acid was removed by evaporation. The precipitation was washed with water and recrystallized from DMF-EtOH-H_2O to afford the pure product.

Compounds 4. A mixture of compound **3** (3 mmoles), gl. acetic acid (5 mL) and DMF (1 mL) was irradiated in microwave even (375W) for 8 min, and the completion of the reaction was monitored by TLC. The excess of gl. acetic acid was removed by evaporation, and processed as above to give **4a** and **4b**. The physical and spectral date of compounds **2a-h** and **4a-b** are shown in below.

2a. Yield. 92%; m.p. 151-152°C; IR (KBr) ν: 3290 (NH), 1659 (C=O), 2982, 2923 (CH_3, CH_2), 1237, 1031 (Ar-O-), 1604, 1535, 1513, 1480 (C=C, C=N), 661 cm^{-1} (C-S-C); ^{1}H NMR (DMSO-d_6): δ1.47 (t, 3H, CH_3), 2.25 (s, 3H, CH_3), 4.36 (q, 2H, CH_2), 4.69 ($ArOCH_2$), 6.73-7.92 (m, 8H, Ar-H), 13.25 (s, 1H, NH); Anal. Calc. For $C_{19}H_{19}N_3O_3S$: C, 61.77; H, 5.18; N, 11.37. Found: C, 61.92; H, 5.07; N, 11.35%.

2b. Yield. 90%; m.p. 146-147°C; IR (KBr) ν: 3322(NH), 1663(C=O), 2984, 2910(CH_3, CH_2), 1263, 1041(Ar-O-), 1602, 1529, 1486 (C=C, C=N), 669 cm^{-1} (C-S-C); ^{1}H NMR (DMSO-d_6):δ 1.48 (t, 3H, CH_3), 2.25 (s, 3H, CH_3), 4.37 (q, 2H, CH_2), 4.68 ($ArOCH_2$), 6.71-7.92 (m, 8H, Ar-H), 13.26(s, 1H, NH); Anal. Calc. For $C_{19}H_{19}N_3O_3S$: C, 61.77; H, 5.18; N, 11.37. Found: C, 61.89; H, 5.22; N, 11.45%.

2c. Yield. 88%; m.p. 152-153°C; IR (KBr) ν: 3207(NH), 1671(C=O), 2978, 2910(CH_3,CH_2), 1252, 1031(Ar-O-), 1603, 1527, 1495, 1485(C=C, C=N), 669 cm^{-1} (C-S-C); ^{1}H NMR (DMSO-d_6): δ 1.47 (t, 3H, CH_3), 2.26 (s, 3H, CH_3), 4.35 (q, 2H, CH_2), 4.69 ($ArOCH_2$), 6.81-7.98 (m, 8H, Ar-H), 13.30 (s, 1H, NH); Anal. Calc. For $C_{19}H_{19}N_3O_3S$: C, 61.77; H, 5.18; N, 11.37. Found: C, 61.91; H, 5.03; N, 11.54%.

2d. Yield. 85%; m.p. 216-217°C; IR (KBr) ν: 3308 (NH), 1660 (C=O), 2985, 2917 (CH_3,CH_2), 1237, 1029 Ar-O-), 1604, 1538, 1490 (C=C, C=N), 663 cm^{-1} (C-S-C); ^{1}H NMR (DMSO-d_6): δ 1.48 (t, 3H, CH_3), 4.33 (q, 2H, CH_2), 4.74 (s, 2H, $ArOCH_2$), 6.95-7.98 (m, 8H, Ar-H), 13.37 (s, 1H, NH); Anal. Calc. For $C_{18}H_{16}ClN_3O_3S$: C, 55.45; H, 4.14; N, 10.78. Found: C, 55.67; H, 4.08; N, 10.65%.

2e. Yield. 93%; m.p. 140-142°C; IR (KBr) ν: 3209(NH), 1660(C=O), 2984, 2921 (CH_3, CH_2), 1240, 1028 (Ar-O-), 1604, 1532, 1481 (C=C, C=N), 669 cm^{-1} (C-S-C); ^{1}H NMR (DMSO-d_6):δ 1.48 (t, 3H, CH_3), 4.21 (q, 2H, CH_2), 4.80 (s, 2H, $ArOCH_2$), 7.18-7.99 m, 8H, Ar-H), 13.47 (s, 1H, NH); Anal. Calc. For $C_{18}H_{16}ClN_3O_3S$: C, 55.45; H, 4.14; N, 10.78. Found: C, 55.46; H, 4.29; N, 10.92%.

2f. Yield. 86%; m.p. 267-268°C; IR (KBr) ν: 3205(NH), 1659 (C=O), 2988, 2944, 2898 (CH_3, CH_2), 1245, 1036 (Ar-O-), 1592, 1526, 1507,1486 (C=C, C=N), 663 cm^{-1} (C-S-C); ^{1}H NMR (DMSO-d_6):δ 1.47 (t, 3H, CH_3), 4.31 (q, 2H, CH_2), 4.92 (s, 2H, $ArOCH_2$), 7.05, 8.31(m, 8H, Ar-H), 13.57 (s, 1H, NH); Anal. Calc. For $C_{18}H_{16}N_4O_5S$: C, 53.99; H, 4.03; N, 13.99. Found: C, 54.07; H, 4.05; N, 14.25%.

2g. Yield. 89%; m.p. 142-143°C; IR (KBr) ν: 3298(NH), 1668 (C=O), 2989, 2921 (CH_3, CH_2), 1231, 1031 (Ar-O-), 1615, 1581, 1526,1486(C=C, C=N), 667 cm^{-1} (C-S-C); ^{1}H NMR (DMSO-d_6): δ 1.48(t, 3H, CH3), 4.25 (q, 2H, CH_2), 4.86 (s, 2H, $ArOCH_2$), 6.92-8.41 (m, 11H, Ar-H), 13.35 (s, 1H,

NH); Anal. Calc. For $C_{22}H_{19}N_3O_3S$: C, 65.17; H, 4.72; N, 10.36. Found: C, 65.32; H, 4.77; N, 10.39%.

2h. Yield. 91%; m.p. 141-142°C; IR (KBr) ν: 3330 (NH), 1651 (C=O), 2981, 2919 (CH_3, CH_2), 1261, 1029 (Ar-O-), 1620, 1600, 1523, 1489 (C=C, C=N), 670 cm^{-1} (C-S-C); ^{1}H NMR (DMSO-d_6): δ 1.48 (t, 3H, CH3), 4.29 (q, 2H, CH_2), 4.89 (s, 2H, $ArOCH_2$), 7.05-7.89 (m, 1H, Ar-H), 13.47 (s, 1H, NH); Anal. Calc. For $C_{22}H_{19}N_3O_3S$: C, 65.17; H, 4.72; N, 10.36. Found: C, 65.28; H, 4.69; N, 10.44%.

4a. Yield. 92%; m.p. 290-291°C; IR (KBr) ν: 3273 (NH), 1660 (C=O), 2987, 2911 (CH_3,nCH_2), 1225, 1020 (Ar-O-), 1600, 1524, 1505, 1486 (C=C, C=N), 673 (C-S-C); ^{1}H NMR (DMSO-d_6): δ 1.48 (t, 6H, CH_3), 4.39 (q, 4H, CH_2), 4.62 (s, 4H, $ArOCH_2$), 6.93-8.05 (m, 12H, Ar-H), 13.53 (s, 2H, NH); Anal. Calc. For $C_{30}H_{28}N_6O_6S_2$: C, 56.95; H, 2.87; N, 13.28. Found: C, 57.18; H, 2.84; N, 13.35%.

4b. Yield. 93%; m.p. 236-237°C. IR (KBr) ν: 3292 (NH), 1657(C=O), 2993, 2915 (CH_3, CH_2), 1242, 1034 (Ar-O-), 1602, 1524, 1486 (C=C, C=N), 673 cm^{-1} (C-S-C); ^{1}H NMR (DMSO-d_6):δ 1.48(t, 6H, CH_3), 4.22 (q, 4H, CH_2), 4.75 (s, 4H, $ArOCH_2$), 6.67-7.99 (m, 12H, Ar-H), 13.53 (s, 2H, NH); Anal. Calc. For $C_{30}H_{28}N_6O_6S_2$: C, 56.95; H, 2.87; N, 13.28. Found: C, 57.45; H, 2.91; N, 13.47%.

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