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SHORT COMMUNICATIONS

Microwave-Assisted Synthesis of 2-Aryl(hetaryl)-5-phenylamino-1,3,4-thiadiazoles from 5-Substituted Tetrazoles

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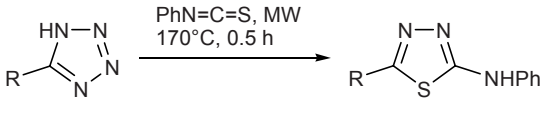
In the recent years 2-aryl-5-arylamino-1,3,4-thiadiazoles have attracted considerable attention due to their intrinsic high biological activity [1]. Compounds of the 2-aryl-5-arylamino-1,3,4-thiadiazole series were found to exhibit antimicrobial [2], antituberculous [3], and antiphlogistic properties [4], as well as to inhibit development of some cancer diseases [5]. However, the lack of convenient methods for the preparation of 2,5-disubstituted 1,3,4-thiadiazoles strongly restricts their potential application in medical practice. Known and widely used methods of synthesis of 2,5-disubstituted 1,3,4-thiadiazoles often include a number of steps and are insufficiently effective [1, 6]. On the other hand, as early as 1961 Huisgen et al. [7] reported a simple one-step procedure for the synthesis of 2-phenyl-5-phenylamino-1,3,4-thiadiazole from 5-phenyl-1*H*-tetrazole and phenyl isothiocyanate.

While continuing our studies on the synthesis and chemical transformations of tetrazoles under conditions of microwave irradiation (MW) [8, 9], we examined microwave-assisted reactions of 5-aryl(hetaryl)-tetrazoles with phenyl isothiocyanate and obtained the corresponding 2-aryl(hetaryl)-5-phenylamino-1,3,4-thiadiazoles **Ia**–**Ig** in good yields. Comparison of our results with those obtained in conventional thermal reactions showed that microwave irradiation strongly affects the reaction rate and makes it possible to shorten the reaction time by a factor of 4. No reaction occurred when a mixture of 5-(pyridin-2-yl)-1*H*-tetrazole and phenyl isothiocyanate was heated for 2 h at 170°C. Under conditions of microwave irradiation, the corresponding 1,3,4-thiadiazole (**Ig**) was formed in 50% yield in 0.5 h (170°C, 70 W). Our results are very important, for they open new prospects in using microwave irradiation in the chemistry of tetrazoles.



Ia–Ig

R = 4-$Me_2NC_6H_4$ (**a**), 4-$MeOC_6H_4$ (**b**), 4-MeC_6H_4 (**c**), Ph (**d**), 4-ClC_6H_4 (**e**), 4-$O_2NC_6H_4$ (**f**), pyridin-2-yl (**g**).

The yields of 1,3,4-thiadiazoles **Ia**–**Ig** obtained by MW-assisted reactions and by conventional heating are listed below, %: **Ia**, 77, 88; **Ib**, 82, 85; **Ic**, 64, 64; **Id**, 74, 43; **Ie**, 69, 74; **If**, 80, 80; **Ig**, 50, 0.

5-(4-Dimethylaminophenyl)-*N*-phenyl-1,3,4-thiadiazol-2-amine (Ia). A mixture of 0.5 g (2.6 mmol) of 5-(4-dimethylaminophenyl)-1*H*-tetrazole and 5 ml (42.2 mmol) of phenyl isothiocyanate was stirred for 0.5 h at 170°C under microwave irradiation (70 W). The mixture was cooled to 20°C, 40 ml of hexane was added, and the precipitate was filtered off, washed with hexane (2×20 ml), and dried in air. Yield 77%, mp 221–222°C (from acetonitrile) [10]. IR spectrum, ν, cm^{-1}: 3244, 3190, 3137, 3052, 2999, 2906, 2858, 2811, 1608, 1568, 1532, 1501, 1452, 1421, 1363, 1312, 1271, 1234, 1192, 1095, 1066, 1014, 975, 947, 869, 812, 745, 693, 652, 611. ^{1}H NMR spectrum, δ, ppm: 3.05 s (6H, NCH_3), 6.82 d (2H, H_{arom}), 7.04 m (1H, H_{arom}), 7.38 m (2H, H_{arom}), 7.70–7.74 m (4H, H_{arom}), 9.37 s (1H, NH).

2-Aryl(hetaryl)-5-phenylamino-1,3,4-thiadiazoles **Ib**–**Ig** were synthesized in a similar way.

5-(4-Methoxyphenyl)-*N*-phenyl-1,3,4-thiadiazol-2-amine (Ib). Yield 82%, mp 201°C (from ethanol) [11]. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.81 s (3H, OCH_3), 6.99–7.06 m (3H, H_{arom}), 7.32–

7.36 t (2H, H_{arom}), 7.63 d (2H, H_{arom}), 7.77 d (2H, H_{arom}), 10.44 s (1H, NH).

5-(4-Methylphenyl)-*N*-phenyl-1,3,4-thiadiazol-2-amine (Ic). Yield 64%, mp 224°C (from acetonitrile) [11]. ^{1}H NMR spectrum, δ, ppm: 2.41 s (3H, CH_3), 7.07 t (1H, H_{arom}), 7.32–7.40 m (4H, H_{arom}), 7.73–7.80 m (4H, H_{arom}), 9.53 s (1H, NH).

***N*,5-Diphenyl-1,3,4-thiadiazol-2-amine (Id).** Yield 74%, mp 203°C (from ethyl acetate) [7]. ^{1}H NMR spectrum, δ, ppm: 7.02–7.06 t (1H, H_{arom}), 7.33–7.38 m (2H, H_{arom}), 7.48 m (3H, H_{arom}), 7.72 d (2H, H_{arom}), 7.87 d (2H, H_{arom}), 9.55 s (1H, NH).

5-(4-Chlorophenyl)-*N*-phenyl-1,3,4-thiadiazol-2-amine (Ie). Yield 69%, mp 223°C (from ethyl acetate) [1]. ^{1}H NMR spectrum, δ, ppm: 7.09 t (1H, H_{arom}), 7.36–7.42 m (2H, H_{arom}), 7.56 d (2H, H_{arom}), 7.73 d (2H, H_{arom}), 7.92 d (2H, H_{arom}), 9.62 s (1H, NH).

5-(4-Nitrophenyl)-*N*-phenyl-1,3,4-thiadiazol-2-amine (If). Yield 80%, mp 258–260°C (from ethanol) [1]. ^{1}H NMR spectrum, δ, ppm: 7.12 t (1H, H_{arom}), 7.37–7.43 t (2H, H_{arom}), 7.76 d (2H, H_{arom}), 8.19 d (2H, H_{arom}), 8.39 d (2H, H_{arom}), 9.84 s (1H, NH).

***N*-Phenyl-5-(pyridin-2-yl)-1,3,4-thiadiazol-2-amine (Ig).** A mixture of 0.5 g (3.4 mmol) of 5-(pyridin-2-yl)-1*H*-tetrazole and 5 ml (42.2 mmol) of phenyl isothiocyanate was stirred for 0.5 h at 170°C under microwave irradiation (70 W). The mixture was cooled to 20°C, 40 ml of hexane was added, and the precipitate was filtered off, washed with hexane (2× 20 ml), dried in air, and additionally purified by column chromatography on silica gel using acetone–hexane (2:1) as eluent. Yield 50%, mp 223–224°C (from ethanol). IR spectrum, ν, cm^{-1}: 3258, 3201, 3141, 3053, 3005, 2942, 2901, 2823, 2784, 1622, 1603, 1572, 1502, 1451, 1428, 1347, 1310, 1279, 1222, 1154, 1116, 1081, 1009, 887, 783, 746, 743, 715, 686, 658, 619. ^{1}H NMR spectrum, δ, ppm: 7.09 t (1H, H_{arom}), 7.37–7.49 m (3H, H_{arom}), 7.77 d (2H, H_{arom}), 7.98 t (1H, H_{arom}), 8.22 d (1H, H_{arom}), 8.63 d (1H, H_{arom}), 9.68 s (1H, NH). Found, %: C 61.08; H 4.08; N 21.62; S 12.39. $C_{13}H_{10}N_4S$. Calculated, %: C 61.41; H 3.94; N 22.05; S 12.60.

The IR spectra were recorded from samples prepared as KBr pellets on a Shimadzu FTIR-8400s spectrometer. The ^{1}H NMR spectra were measured on a Bruker WM-400 instrument at 400 MHz from solutions in acetone-d_6. Microwave-assisted reactions were carried our in a Milestone P/N 44072 microwave oven. The purity of the products was checked by TLC on Silufol plates using acetone–hexane (1:2) as eluent. The procedure for the thermal reactions was the same as under microwave irradiation.

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