ISSN 1070-4280, Russian Journal of Organic Chemistry, 2008, Vol. 44, No. 9, pp. 1345–1347. © Pleiades Publishing, Ltd., 2008.
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Tetrazoles: LIII.* Microwave-Activated Acylation of 5-Substituted Tetrazoles

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Received March 15, 2008

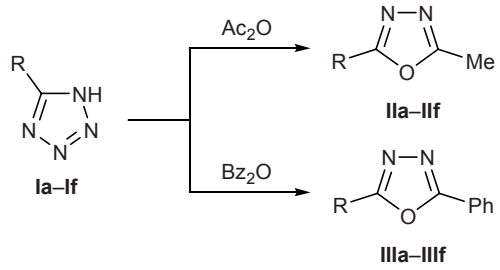
Abstract—The acylation of 5-aryl(hetaryl)tetrazoles with acetic and benzoic anhydrides under microwave irradiation gave the corresponding 2-substituted 5-methyl- and 5-phenyl-1,3,4-oxadiazoles in high yields. The use of microwave activation reduces the reaction temperature by 30–40°C and shortens the reaction time by a factor of 5 to 7.

DOI: 10.1134/S1070428008090169

In continuation of our studies on the synthesis and properties of functionally substituted tetrazoles, in the present work we examined acylation of 5-substituted tetrazoles under conditions of microwave activation. Analysis of vast experimental data published in the past decade showed that thermal transformation of *N*-acyltetrazoles obtained by acylation of 5-substituted tetrazoles was widely used for the synthesis of various 2,5-disubstituted 1,3,4-oxadiazoles [2–10]. On the other hand, it should be noted that this procedure is not free from some disadvantages related mostly to thermal instability of initial tetrazoles.

These disadvantages can be partially eliminated by using trifluoroacetic anhydride as acylating agent [11, 12]. However, in this case, only 2-substituted 5-trifluoromethyl-1,3,4-oxadiazoles can be obtained. We presumed that the above problems could be solved by carrying out acylation of 5-substituted tetrazoles under conditions of microwave activation. For this purpose we tried to perform acylation of a series of 5-aryl(hetaryl)tetrazoles with acetic and benzoic anhydrides under microwave irradiation. In fact, the acylation of tetrazoles **Ia**–**If** with acetic and benzoic anhydrides gave the corresponding 2,5-disubstituted 1,3,4-oxadiazoles **IIa**–**IIf** and **IIIa**–**IIIf** in good yields (Scheme 1). The reactions were carried using the acylating agent as solvent.

Scheme 1.



R = 4-$MeOC_6H_4$ (**a**), Ph (**b**), 4-BrC_6H_4 (**c**), 4-$O_2NC_6H_4$ (**d**), pyridin-2-yl (**e**), pyridin-3-yl (**f**).

In the acylation of 5-phenyltetrazole (**Ib**) with acetic anhydride under microwave irradiation at 80°C, the yield of 2-methyl-5-phenyl-1,3,4-oxadiazole (**IIb**) in 1 and 2 h was 32 and 66%, respectively. The yield of **IIb** increased to 75% when the reaction was performed at 90°C (1 h). These conditions were assumed to be optimal for the acylation of tetrazoles **Ia**–**Ic**. The reactions with tetrazoles **Id**–**If** were carried out at 100°C, for no oxadiazoles were formed at 90°C. These findings are very consistent with our previous data on the thermal stability of 1- and 2-acyltetrazoles having electron-withdrawing substituents [13].

The optimal conditions of the acylation of tetrazoles **Ia**–**Ic** with benzoic anhydride under microwave activation were temperature 110°C and reaction time 15 min. In the reactions with compounds **Id**–**If** good results were obtained at higher temperature, which provides further evidence in favor of higher thermal stability of 1- and 2-acyltetrazoles with electron-withdrawing substituents.

Comparison of the results obtained in the present work with published data [14, 15] shows that micro-

* For communication LII, see [1].

wave activation is most effective when the reaction is carried in a nonpolar solvent or under solvent-free conditions. This conclusion agrees well with the assumption that the effect of microwave irradiation on the rate and selectivity of organic reactions depends on the solvent [16].

EXPERIMENTAL

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 spectrometer from solutions in acetone-d_6. Microwave-assisted reactions were carried out in a Milestone P/N 44072 reactor. The purity of the products was checked by TLC on Silufol plates using ethyl acetate–carbon tetrachloride (2:3) as eluent.

2-(4-Methoxyphenyl)-5-methyl-1,3,4-oxadiazole (IIa). A mixture of 5.7 mmol of 5-(4-methoxyphenyl)-tetrazole in 15 ml of acetic anhydride was stirred for 1 h at 90°C under microwave irradiation. The mixture was cooled to 20°C, excess acetic anhydride was removed under reduced pressure, and the solid residue was washed in succession with 15 ml of 10% aqueous sodium hydroxide and 20 ml of water and dried in air. Yield 76%, mp 88°C (from water) [17]. ^{1}H NMR spectrum, δ, ppm: 2.54 s (3H, CCH_3), 3.88 s (3H, OCH_3), 7.08–7.11 d (2H, H_{arom}), 7.91–7.94 d (2H, H_{arom}).

Oxadiazoles **IIb** and **IIc** were synthesized in a similar way, while in the synthesis of oxadiazole **IId** the reaction mixture was stirred for 1 h at 100°C.

2-Methyl-5-phenyl-1,3,4-oxadiazole (IIb). Yield 87%, mp 66°C (from ethanol) [17]. ^{1}H NMR spectrum, δ, ppm: 2.57 s (3H, CH_3), 7.56–8.00 m (5H, H_{arom}).

2-(4-Bromophenyl)-5-methyl-1,3,4-oxadiazole (IIc). Yield 73%, mp 118°C (from ethanol) [17]. ^{1}H NMR spectrum, δ, ppm: 2.57 s (3H, CH_3), 7.76–7.78 d (2H, H_{arom}), 7.93–7.95 d (2H, H_{arom}).

2-Methyl-5-(4-nitrophenyl)-1,3,4-oxadiazole (IId). Yield 80%, mp 170°C (from ethanol) [17]. ^{1}H NMR spectrum, δ, ppm: 2.63 s (3H, CH_3), 8.27–8.29 d (2H, H_{arom}), 8.42–8.44 d (2H, H_{arom}).

2-Methyl-5-(pyridin-2-yl)-1,3,4-oxadiazole (IIe). A mixture of 3.4 mmol of 5-(pyridin-2-yl)tetrazole in 15 ml of acetic anhydride was stirred for 1 h at 100°C under microwave irradiation. The resulting solution was cooled to 20°C, excess acetic anhydride was removed under reduced pressure, the solid residue was dissolved in 20 ml of chloroform, the solution was washed with 20 ml of 2% aqueous sodium hydroxide, the organic phase was separated and evaporated under reduced pressure, and the solid residue was dried in air. Yield 84%, mp 99°C (from hexane) [18]. ^{1}H NMR spectrum, δ, ppm: 2.60 s (3H, CH_3), 7.55–7.57 t (1H, H_{arom}), 7.99–8.02 t (1H, H_{arom}), 8.15–8.17 d (1H, H_{arom}), 8.73 d (1H, H_{arom}).

2-Methyl-5-(pyridin-3-yl)-1,3,4-oxadiazole (IIf) was synthesized in a similar way. Yield 77%, mp 113–114°C (from heptane). IR spectrum, ν, cm^{-1}: 617, 679, 823, 960, 1016, 1046, 1086, 1132, 1252, 1350, 1429, 1468, 1550, 1740, 2856, 2927, 2999, 3043, 3075, 3438. ^{1}H NMR spectrum, δ, ppm: 2.60 s (3H, CH_3), 7.57–7.60 t (1H, H_{arom}), 8.31–8.34 d (1H, H_{arom}), 8.75 d (1H, H_{arom}), 9.15 s (1H, H_{arom}). Found, %: C 59.78; H 4.40; N 25.95. $C_8H_7N_3O$. Calculated, %: C 59.63; H 4.35; N 26.09.

2-(4-Methoxyphenyl)-5-phenyl-1,3,4-oxadiazole (IIIa). A mixture of 6.8 mmol of 5-(4-methoxyphenyl)-tetrazole and 2 g of benzoic anhydride was stirred for 15 min at 110°C under microwave irradiation. The mixture was cooled to 20°C, 20 ml of 10% aqueous sodium hydroxide was added, the mixture was stirred for 1 h at 40°C, and the precipitate was filtered off, washed with 20 ml of water, and dried in air. Yield 96%, mp 150°C (from ethanol) [19]. ^{1}H NMR spectrum, δ, ppm: 3.16 s (3H, OCH_3), 6.37–6.42 d (2H, H_{arom}), 6.84-6.87 m (3H, H_{arom}), 7.33–7.41 m (4H, H_{arom}).

Oxadiazoles **IIIb** and **IIIc** were synthesized in a similar way, while in the synthesis of oxadiazole **IIId** the reaction mixture was stirred for 30 min at 110°C.

2,5-Diphenyl-1,3,4-oxadiazole (IIIb). Yield 83%, mp 139°C (from ethanol) [20]. ^{1}H NMR spectrum, δ, ppm: 6.88 s (6H, H_{arom}), 7.40–7.43 m (4H, H_{arom}).

2-(4-Bromophenyl)-5-phenyl-1,3,4-oxadiazole (IIIc). Yield 74%, mp 170°C (from ethanol) [19]. ^{1}H NMR spectrum, δ, ppm: 6.67 m (3H, H_{arom}), 7.05–7.09 d (2H, H_{arom}), 7.32–7.43 m (4H, H_{arom}).

2-(4-Nitrophenyl)-5-phenyl-1,3,4-oxadiazole (IIId). Yield 89%, mp 210–211°C (from ethanol) [13]. ^{1}H NMR spectrum, δ, ppm: 6.90 m (3H, H_{arom}), 7.46 d (2H, H_{arom}), 7.72 s (4H, H_{arom}).

2-Phenyl-5-(pyridin-2-yl)-1,3,4-oxadiazole (IIIe). A mixture of 3.4 mmol of 5-(pyridin-2-yl)tetrazole and 5 g of benzoic anhydride was stirred for 15 min at 120°C under microwave irradiation. The mixture was cooled to 20°C, 50 ml of 15% aqueous ammonia was added, the mixture was stirred for 2 h at 40°C, and the precipitate was filtered off, washed with 20 ml of water, and dried in air. Yield 78%, mp 124–125°C

(from hexane) [21]. ^{1}H NMR spectrum, δ, ppm: 6.89 m (4H, H_{arom}), 7.31–7.57 m (4H, H_{arom}), 8.04 d (1H, H_{arom}).

2-Phenyl-5-(pyridin-3-yl)-1,3,4-oxadiazole (IIIf) was synthesized in a similar way. Yield 73%, mp 124°C (from ethanol) [22]. ^{1}H NMR spectrum, δ, ppm: 6.89 s (4H, H_{arom}), 7.44 m (2H, H_{arom}), 7.73–7.77 d (1H, H_{arom}), 8.04 d (1H, H_{arom}), 8.56 s (1H, H_{arom}).

This study was performed under financial support by the Russian Foundation for Basic Research (project no. 08-03-00342a).

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