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Rapid and efficient microwave-assisted synthesis of 5-amino-3-aralkoxy(methoxy)amino-1,2,4-oxadiazoles

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Abstract—The microwave-assisted synthesis of 5-amino-3-aralkoxy(methoxy)amino-1,2,4-oxadiazoles starting from N^1-aralkoxy-(methoxy)-N^3-cyano-*O*-phenylisoureas and hydroxylamine is described. N^1-Aralkoxy(methoxy)-N^3-cyano-*O*-phenylisoureas are readily accessible by treatment of diphenyl *N*-cyanimidocarbonate with O-substituted hydroxylamines.

Microwave-assisted synthesis represents an important tool in organic and medicinal chemistry.[1] Besides high yields and clean reactions microwave chemistry offers the advantage of extremely short reaction times. Due to the increasing number of novel drug targets the rapid construction and modification of biologically active heterocyclic compounds is becoming more and more important in drug development.[1] Among nitrogen–oxygen containing heterocycles the 1,2,4-oxadiazole nucleus is of particular interest for organic and medicinal chemists, because it is present in various biologically active compounds and natural products (Fig. 1).[3–8]

1,2,4-Oxadiazoles have for instance been identified as anti-inflammatory agents,[2] antitumor agents,[3] as 5-HT_3,[4] histamine H_2 and H_3 receptor antagonists[5] as well as monoamine oxidase[6] and βII-tryptase inhibitors.[7] In addition, 1,2,4-oxadiazoles are widely used as hydrolysis-resisting amide bioisosteres in the development of peptidomimetics.[8]

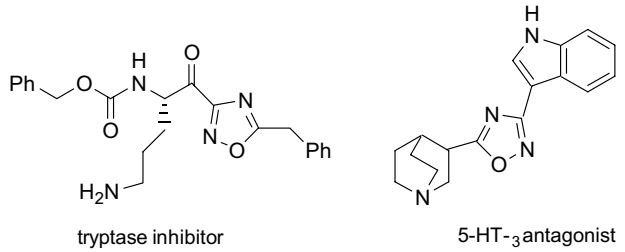

Figure 1. Selected biologically active 1,2,4-oxadiazoles.

1,2,4-Oxadiazoles are commonly prepared by reactions of amidoximes with reactive carboxylic acid derivatives.[9,10] Other methods to generate 1,2,4-oxadiazoles include 1,3-dipolar cycloadditions of nitrile oxides to nitriles[10] and the oxidation of 4,5-dihydro-1,2,4-oxadiazoles.[10] 3,5-Diamino-1,2,4-oxadiazoles are accessible starting from N^1-arylalkylamino-N^3-cyano-*O*-phenylisoureas and hydroxylamine.[5b] To the best of our knowledge the structurally related 5-amino-3-aralkoxy(alkoxy)amino-1,2,4-oxadiazoles (**3**) have not been described in the literature so far. We herein report a rapid and efficient microwave-assisted method for the preparation of 5-amino-3-aralkoxy(alkoxy)amino-1,2,4-oxadiazoles (**3**).

N^1-Aralkoxy(methoxy)-N^3-cyano-*O*-phenylisoureas **2** have been prepared by reacting diphenyl *N*-cyanimidocarbonate (**1**) with O-substituted hydroxylamines in 2-propanol in 66–82% yield (Scheme 1, Table 1).[11] During the formation of compounds **2** the (CN)-absorption band of **1** at 2222 cm^{-1} disappeared gradually, while a new absorption band at 2190–2200 cm^{-1} appeared in the IR spectra. It should be noted that the formation of 1,3-diaralkoxy(methoxy)-2-cyanoguanidines as by products was not observed.

Treatment of *O*-phenylisoureas **2** with hydroxylamine hydrochloride in the presence of triethylamine in

Keywords: Microwave-assisted synthesis; 1,2,4-Oxadiazoles; N^1-Aralkoxy(methoxy)-N^3-cyano-*O*-phenylisoureas; Diphenyl *N*-cyanimidocarbonate; O-Substituted hydroxylamines.
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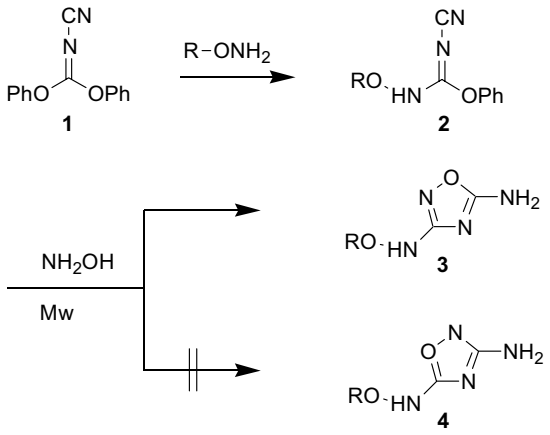

Scheme 1. 5-Amino-3-aralkoxy(methoxy)amino-1,2,4-oxadiazoles (**3a**–**h**).

Table 1. N^1-Aralkoxy(methoxy)-N^3-cyano-*O*-phenylisoureas (**2a**–**h**)

2	R	Yield (%)
a	Bn	82
b	4-Br–$C_6H_4CH_2$	80
c	2,4-Cl–$C_6H_3CH_2$	72
d	Naphthylmethyl	70
e	$C_6H_5(CH_2)_2$	71
f	$C_6H_5(CH_2)_3$	68
g	4-CH_3–Ph	80
h	CH_3	66

methanol at 50 °C afforded 5-amino-3-aralkoxy(methoxy)amino-1,2,4-oxadiazoles **3a**–**h** in 62–80% yield within 3–5 h (Scheme 1, Table 2).[12] The 1,2,4-oxadiazole formation was monitored by IR spectroscopy and was accompanied by the disappearance of the (CN)-absorption band at 2190–2200 cm^{-1} and the appearance of a novel (C=N)-absorption band at 1650–1670 cm^{-1}. However, all attempts to increase the yields and to shorten the reaction time under conventional reaction conditions failed. Therefore we turned our attention to the microwave-assisted synthesis of compounds **3**. The reaction of *O*-phenylisourea **2a** with hydroxylamine hydrochloride in the presence of triethylamine in methanol at 200 W furnished the expected 1,2,4-oxadiazole **3a** within only 1 min in 80% yield.[13] To simplify the method hydroxylamine hydrochloride was now replaced

Table 2. 5-Amino-3-aralkoxy(methoxy)amino-1,2,4-oxadiazoles (**3**)

3	R	Yield (%) conv.	Yield (%) M_w	Hold time[a] (min)
a	Bn	80	82	1
b	4-Br–$C_6H_5CH_2$	78	81	1
c	2,4-Cl–$C_6H_3CH_2$	68	76	1
d	Naphthylmethyl	69	77	1
e	$C_6H_5(CH_2)_2$	77	81	1
f	$C_6H_5(CH_2)_3$	72	79	1
g	4-CH_3–Ph	77	84	1
h	CH_3	62	69	1

[a] Ramp time 0.5 min, see Ref. 14 for more detailed conditions.

by an aqueous solution of hydroxylamine. *O*-Phenylisoureas **2a**–**h** were reacted with 5 equiv of hydroxylamine in methanol using microwave pressure tubes at 200 W to afford the target compounds **3a**–**h** within only 1 min (Scheme 1, Table 2). Again the formation of the 1,2,4-oxadiazole ring was confirmed by IR spectroscopy. In addition, no byproducts were detected by thin layer chromatography. After removal of the solvent, filtration through a short column provided analytical pure samples of **3a**–**h** in 69–84% yield.[14] To differentiate between 1,2,4-oxadiazoles **3** and **4**, X-ray crystallography was used. The crystal structure of compound **3b** revealed that the 4-bromobenzyloxyamino group is located at carbon atom 3 of the 1,2,4-oxadiazole nucleus and that the amino group is attached to carbon atom 5 (Fig. 2).

The structures of all novel compounds (**2**, **3**) were elucidated by ^1H, ^{13}C NMR spectroscopy, and elemental analysis.[11,14]

In summary, we have developed a practical and rapid method for the efficient, microwave assisted synthesis of previously unreported 5-amino-3-aralkoxy(methoxy)amino-1,2,4-oxadiazoles (**3**), which offers advantages over conventional heating.

Acknowledgment

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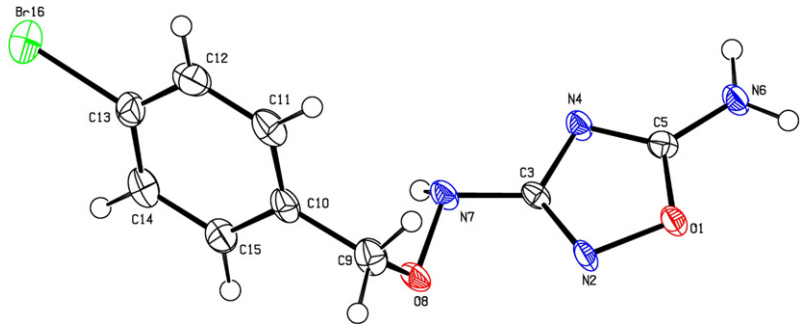

Figure 2. X-ray crystal structure of **3b**.

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11. *General procedure for the preparation of N^1-aralkoxy(methoxy)-N^3-cyano-O-phenylisoureas* **2a–h**. To a suspension of diphenyl *N*-cyanimidocarbonate (2 mmol) in 2-propanol (5 mL) was added the appropriate O-substituted hydroxylamine (2.2 mmol) dropwise at 0–5 °C. After stirring for 2–6 h the product was isolated by filtration and washed with 2-propanol/petrolether (5 mL). The filtrate was removed under reduced pressure, the remaining oil was dried and the resulting crude solid was suspended in diethyl ether/petrolether. After filtration, analytically pure products have been obtained by recrystallization from THF/petrolether. Experimental data for selected examples: *N^1-(4-Brombenzoxy)-N^3-cyano-O-phenylisourea* (**2b**). Colorless crystals (80%). Mp 134 °C (THF/petrolether); IR (KBr): $\nu = 3095$ (NH), 2191 (CN), 1636 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 5.03 (s, 2H), 7.19–7.7 (m, 9H), 12.52 (s, 1H), ^{13}C NMR (DMSO-d_6) δ (ppm): 78.2, 113.1, 121.5, 122.5, 126.7, 130.1, 131.7, 132.1, 138.8, 151.9, 158.4. Anal. Calcd for $C_{15}H_{12}BrN_3O_2$: C, 52.04; H, 3.49; N, 12.14. Found: C, 51.76; H, 3.58; N, 12.06. *N^1-Phenylethoxy-N^3-cyano-O-phenylisourea* (**2e**). Colorless crystals (71%). Mp 95 °C (THF/petrolether); IR (KBr): $\nu = 3107$ (NH), 2200 (CN), 1635 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 2.82 (t, $J = 6.35$, 2H), 3.99 (t, $J = 6.35$, 2H), 7.02–7.27 (m, 10H), 12.30 (s, 1H), ^{13}C NMR (DMSO-d_6) δ (ppm): 33.7, 77.9, 112.9, 121.7, 126.7, 128.7, 129.3, 130.1, 138.1, 151, 158.9. Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.37; N, 14.94. Found: C, 68.10; H, 5.33; N, 14.74.
12. *General procedure for the conventional synthesis of 5-amino-3-aralkoxy(methoxy)amino-1,2,4-oxadiazoles* **3a–h**. To a solution of *O*-phenylisoureas **2a–h** (1 mmol) in methanol (5 mL) was added a solution of hydroxylamine in THF (15 mL)-prepared from hydroxylamine hydrochloride (10 mmol) and triethylamine (10 mmol) in 15 mL of THF. The reaction mixture was stirred for 3–5 h at 50 °C and IR spectra were recorded every 30 min. Afterwards the reaction mixture was allowed to cool to room temperature, the suspension was filtered, the solvent removed under reduced pressure and the resulting oily residue purified by column chromatography using diethyl ether/ethyl acetate (9:1) as an eluent. Analytically pure products have been obtained after recrystallization from THF/petrolether (Table 2).
13. To 1 mmol of compound **3a** in a 10 mL glass pressure microwave tube equipped with a magnetic stirrer bar was added a solution of hydroxylamine in THF (5 mL) prepared from hydroxylamine hydrochloride (5 mmol) and triethylamine (5 mmol) in 5 mL of THF. Afterwards the reaction mixture was subjected to microwave irradiation for 1 min. For detailed reaction conditions see Ref. 14.
14. *General procedure for the microwave-assisted synthesis of 5-amino-3-aralkoxy(methoxy)amino-1,2,4-oxadiazoles* **3a–h**. Compound **3a–h** (1 mmol), 5 mL of methanol and an aqueous solution of hydroxylamine (5 mmol, 50%) were added into a 10 mL glass pressure microwave tube equipped with a magnetic stirrer bar. The tube was closed with a silicon septum and the reaction mixture was subjected to microwave irradiation for 1 min (Table 2, ramp time: 30 s). The reaction mixture was allowed to cool to room temperature and was transferred to a round bottom flask. The solvent was evaporated and the crude products were purified by column chromatography using diethyl ether/ethyl acetate (9:1) as an eluent. Microwave assisted reactions were carried out using a CEM microwave reactor model Discover. *Parameters*: Discover mode; power: 200 W; ramp time: 30 s; hold time 1 min; temperature: 65 °C; pressure: 2 bar; PowerMax-cooling mode (Table 2). Increased temperatures and power are not leading to improved yields. Experimental data for selected compounds: *5-Amino-3-(4-brombenzoxyamino)-1,2,4-oxadiazole* (**3b**). Colorless crystals (81%). Mp 131 °C (THF/petrolether); IR (KBr): $\nu = 3460$ (NH_2), 3128 (NH), 1649 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 4.78 (s, 2H), 7.35–7.37 (d, $J = 8.39$ Hz, 2H), 7.55–7.57 (d, $J = 8.39$ Hz, 2H), 7.59 (s, 2H), 9.59 (s, 1H), ^{13}C NMR (DMSO-d_6) δ (ppm): 75.9, 121.4, 130.9, 131.5, 136.8, 170.8, 171.1. Anal. Calcd for $C_9H_9BrN_4O_2$: C, 37.92; H, 3.18; N, 19.65. Found: C, 37.66; H, 3.26; N, 19.51. Crystallographic data for compound **3b** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Nos. CCDC 632622. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 (0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk]. *5-Amino-3-(phenylethoxyamino)-1,2,4-oxadiazole* (**3e**). Colorless crystals (81%). Mp 124. °C (THF/petrolether); IR (KBr): $\nu = 3401$ (NH_2), 3188 (NH), 1664 (C=N) cm^{-1}; ^1H NMR (DMSO-d_6) δ (ppm): 2.88 (t, $J = 6.87$ Hz, 2H), 3.97 (t, $J = 6.87$ Hz, 2H), 7.17–7.31 (m, 5H), 7.56 (s, 2H), 9.49 (s, 1H), ^{13}C NMR (DMSO-d_6) δ (ppm): 34.1, 75.2, 125.9, 128.2, 128.7, 138.4, 170.4, 171.6. Anal. Calcd for $C_{10}H_{12}N_4O_2$: C, 54.54; H, 5.49; N, 25.44. Found: C, 54.35; H, 5.46; N, 25.21.