Expedient Microwave-Assisted Synthesis of Novel 6-Substituted 5-Alkoxy(benzylxyoxy)-3,6-dihydro-2H-1,3,4-oxadiazin-2-ones

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General methods

Melting points (uncorrected) were determined on a Electrothermal 9100 apparatus. Elemental analysis were carried out with a Heraeus CHN-O-Rapid instrument. IR spectra were recorded on a Varian 800 FT-IR. $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on a Bruker AMX 400 spectrometer using tetramethylsilane as an internal standard and DMSO-$d_6$ as solvent. X-ray crystal analysis was performed on a Bruker Smart APEX CCD diffractometer with Mo Kα-radiation at 100 K. All intermediates 4a-j were prepared according to our previously published method.$^1$ Microwave-assisted synthesis of compounds 5a-j was carried out using a CEM Corporation Focused Microwave System, Model Discover.

General procedure for the preparation of compound 5a-j

A mixture of sodium ethoxide (68 mg, 1 mmol) and the respective α-hydroxy hydrazonates 4a-j (1 mmol) in ethanol (2 mL) was 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 (Discover mode; power: 200 W; ramp time: 30 sec.; hold time as indicated in Table 2; temperature: 100 °C; pressure: 10 bar; PowerMax-cooling mode).

The reaction mixture was allowed to cool to room temperature and transferred to a round bottomed flask. The solvent was evaporated and the residue was dissolved in diethyl ether (20 mL). The organic solution was extracted with water (3 x 5 mL), dried over MgSO$_4$ and evaporated. Recrystallization from diethyl ether:hexane furnished analytically pure products.
6-Cyclopropyl-5-ethoxy-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one (5a). Colorless microcrystals, 80% yield, mp. 74.4 °C; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 0.30-0.58 (m, 4H), 1.21-1.27 (m, 1H), 1.24 (t, \(J = 7.1\) Hz, 3H), 1.40 (s, 3H), 4.03-4.08 (m, 2H), 10.09 (s, 1H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 0.9, 13.5, 16.5, 21.3, 62.3, 78.9, 145.7, 153.8. Anal. Calcd for C\(_9\)H\(_{14}\)N\(_2\)O\(_3\): C 54.53; H 7.12; N 14.13. Found: C 54.48; H 7.13; N 14.15.

5-Ethoxy-6-methyl-6-(naphthalen-2-yl)-3,6-dihydro-2H-1,3,4-oxadiazin-2-one (5b). Colorless microcrystals, 87% yield, mp. 142.1 °C; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 1.44 (t, \(J = 7.0\) Hz, 3H), 1.87 (s, 3H), 4.26-4.31 (m, 2H), 7.46-7.87 (m, 7H), 10.42 (s, 1H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 9.3, 20.9, 59.2, 76.3, 117.1, 118.6, 121.8, 121.9, 122.7, 123.6, 124.1, 128.0, 128.4, 131.6, 146.1, 151.4. Anal. Calcd for C\(_{16}\)H\(_{16}\)N\(_2\)O\(_3\): C 67.59; H 5.67; N 9.85. Found: C 67.40; H 5.69; N 9.97.

5-Ethoxy-6-ethyl-6-phenyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one (5c). Colorless microcrystals, 86% yield, mp. 118.2 °C; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 0.92 (t, \(J = 7.1\) Hz, 3H), 1.33 (t, \(J = 7.1\) Hz, 3H), 1.89-2.15 (m, 2H), 4.16-4.26 (m, 2H), 7.34-7.46 (m, 5H), 10.19 (s, 1H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 8.4, 14.4, 31.7, 63.7, 83.1, 124.6, 124.7, 129.0, 129.2, 139.4, 150.0, 154.8. Anal. Calcd for C\(_{13}\)H\(_{16}\)N\(_2\)O\(_3\): C 62.89; H 6.50; N 11.28. Found: C 62.93; H 6.55; N 11.14.

5-Ethoxy-6-phenyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one (5d). Colorless microcrystals, 84% yield, mp. 139.1 °C; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 1.22 (t, \(J = 7.1\) Hz, 3H), 4.07-4.20 (m, 2H), 6.01 (s, 1H), 7.35-7.49 (m, 5H), 10.29 (s, 1H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 14.3, 63.6, 75.3, 127.3, 129.4, 129.9, 134.8, 149.2, 153.7. Anal. Calcd for C\(_{11}\)H\(_{12}\)N\(_2\)O\(_3\): C 59.99; H 5.49; N 12.72. Found: C 59.61; H 5.58; N 12.73.
5-Ethoxy-6-methyl-6-(4-methylphenyl)-3,6-dihydro-2H-1,3,4-oxadiazin-2-one (5e). Colorless microcrystals, 86% yield, mp. 123.1 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.32 (t, $J = 7.1$ Hz, 3H), 1.68 (s, 3H), 2.30 (s, 3H), 4.16-4.22 (m, 2H), 7.18-7.26 (s, 4H), 10.18 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 14.4, 21.0, 25.5, 63.7, 80.0, 124.4, 124.7, 129.6, 129.9, 136.9, 138.6, 150.1, 155.8. Anal. Calcd for C$_{13}$H$_{16}$N$_2$O$_3$: C 62.89; H 6.50; N 11.28. Found: C 62.54; H 6.52; N 11.14.

6-(4-Chlorophenyl)-5-ethoxy-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one (5f). Colorless microcrystals, 81% yield, mp. 123.1 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.40 (t, $J = 7.1$ Hz, 3H), 1.77 (s, 3H), 4.21-4.26 (m, 2H), 7.33-7.37 (m, 4H), 7.66 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 14.1, 25.7, 64.1, 80.5, 125.7, 125.8, 129.0, 129.2, 134.8, 137.9, 150.7, 155.9. Anal. Calcd for C$_{12}$H$_{13}$ClN$_2$O$_3$: C 53.64; H 4.88; N 10.43. Found: C 53.25; H 4.95; N 10.25.

6-(3,4-Dimethylphenyl)-5-ethoxy-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one (5g). Colorless microcrystals, 80% yield, mp. 127.8 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.40 (t, $J = 7.1$ Hz, 3H), 1.76 (s, 3H), 2.24 (s, 3H), 2.26 (s, 3H), 4.21-4.24 (m, 2H), 7.09-7.26 (m, 3H), 7.70 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 14.2, 19.5, 20.0, 25.8, 63.8, 81.0, 121.7, 125.4, 130.0, 136.8, 137.2, 137.4, 151.2, 156.5. Anal. Calcd for C$_{14}$H$_{18}$N$_2$O$_3$: C 64.11; H 6.92; N 10.68. Found: C 63.81; H 6.94; N 10.58.

6-(3,4-Dichlorophenyl)-5-methoxy-6-methyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one (5h). Colorless microcrystals, 84% yield, mp. 163.7 °C; $^1$H NMR (300 MHz, DMSO-$d_6$) δ 1.74 (s, 3H), 3.82 (s, 3H), 7.32-7.74 (m, 3H), 10.42 (s, 1H); $^{13}$C NMR (75 MHz, DMSO-$d_6$) δ 24.9, 55.5, 79.4, 125.3, 127.0, 131.6, 132.1, 132.2, 140.6, 149.5, 155.5. Anal. Calcd for C$_{11}$H$_{10}$Cl$_2$N$_2$O$_3$: C 45.70; H 3.49; N 9.69. Found: C 45.80; H 3.74; N 9.72.
5-Methoxy-6-methyl-6-(naphthalen-2-yl)-3,6-dihydro-2H-1,3,4-oxadiazin-2-one (5i). Colorless microcrystals, 85% yield, mp. 163.7 °C; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 1.82 (s, 3H), 3.88 (s, 3H), 7.51-8.02 (m, 7H), 10.32 (s, 1H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 25.3, 55.4, 80.4, 122.6, 123.6, 127.2, 127.3, 127.9, 128.6, 129.3, 132.7, 133.1, 137.0, 150.0, 156.3. Anal. Calcd for C\(_{12}\)H\(_{14}\)N\(_2\)O\(_3\): C 61.53; H 6.02; N 11.96. Found: C 61.30; H 6.07; N 12.11.

5-(Benzyloxy)-6,6-dimethyl-3,6-dihydro-2H-1,3,4-oxadiazin-2-one (5j). Colorless microcrystals, 78% yield, mp. 122.6 °C; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 1.56 (s, 6H), 5.09 (s, 2H), 7.32-7.41 (m, 5H), 7.70 (s, 1H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 24.2, 69.6, 78.5, 127.9, 128.3, 128.8, 129.0, 135.9, 151.0, 157.0. Anal. Calcd for C\(_{12}\)H\(_{14}\)N\(_2\)O\(_3\): C 61.53; H 6.02; N 11.96. Found: C 61.30; H 6.07; N 12.11.

**General procedure for the isolation of amidrazone by-products 6a-d**

The appropriate carbazate (5.5 mmol) was added dropwise to a solution of the imidate hydrochloride salt (5 mmol) in anhydrous ethanol (10 mL) and the reaction mixture was stirred at room temperature for 24 hours. Afterward, the solvent was evaporated and the remaining residue was dissolved in diethyl ether (30 mL). The organic layer was extracted with water (3 x 15 mL). The combined aqueous phases were treated with saturated NaHCO\(_3\) solution until pH ~ 12 and extracted with diethyl ether (3x 30 mL). The combined organic layers were dried with MgSO\(_4\), filtered and concentrated in vacuo. The residue was crystallized from diethyl ether:hexane to yield analytically pure amidrazone derivatives 6a-d.

**Methyl 2-(1-amino-2-hydroxy-2-(naphthalen-2-yl)propylidene)hydrazinecarboxylate (6b).** Colorless microcrystals, 39% yield, mp. 157.3 °C; \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 1.69 (s, 3H), 3.60 (s, 3H), 5.77 (s, 2H), 5.93 (s, 1H), 7.45-8.01 (m, 7H), 8.95 (s, 1H); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 25.3, 55.4, 80.4, 122.6, 123.6, 127.2, 127.3, 127.9, 128.6, 129.3, 132.7, 133.1, 137.0, 150.0, 156.3. Anal. Calcd for C\(_{12}\)H\(_{14}\)N\(_2\)O\(_3\): C 61.53; H 6.02; N 11.96. Found: C 61.30; H 6.07; N 12.11.
DMSO-\textit{d}_6 \ \delta \ 28.2, \ 51.2, \ 74.0, \ 122.9, \ 124.0, \ 125.5, \ 125.8, \ 127.0, \ 127.2, \ 127.9, \ 131.9, \ 132.4, \ 144.2; \text{ Anal. Calcd} \text{ for } \text{C}_{15}\text{H}_{17}\text{N}_{3}\text{O}_{3}: \text{ C} \ 62.71; \text{ H} \ 5.96; \text{ N} \ 14.62. \text{ Found: C} \ 62.67; \text{ H} \ 6.14; \text{ N} \ 14.55.

References