A Simple and Efficient Synthesis of New Mono- and Bis([1,2,4]-oxadiazol)-benzaldehyde Building Blocks

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Abstract: An efficient approach to bis([1,2,4]-oxadiazol)benzaldehydes as well as the corresponding mono-benzaldehyde derivatives has been developed starting from benzamidoxime, which is readily obtained from 4-cyanobenzaldehyde. All these new compounds were synthesized in a high-yielding, five-step procedure with few and simple purifications.

Key words: mono- and bis-benzaldehyde, 1,2,4-oxadiazole, benzamidoxime, O-acylation, acetal deprotection

The development of general and simple synthetic pathways for the generation of new and original libraries of organic compounds is currently one of the most important challenges in organic chemistry. In the course of our studies related to a new and selective route to the (Z,Z)-2,7-bis(4-cyanobenzylidene)cycloheptan-1-one (BABCH),1 we discovered a simple and efficient method for the synthesis of various new aromatic and aliphatic bis([1,2,4]-oxadiazol)benzaldehydes of type I. To obtain these compounds, we decided to synthesize benzamidoxime II, which was reacted with a range of dicarboxylic acids and/or acid chlorides III (Scheme 1).

Scheme 1 Considered strategy for the synthesis of bis([1,2,4]-oxadiazol)benzaldehydes

With this in mind, we first wanted to apply our methodology to the synthesis of a benzaldehyde with a 1,2,4-oxadiazole ring from 4-cyanobenzaldehyde (I), in order to test this strategy (Scheme 2). Initially, the aldehyde function of the starting material was protected as its 1,3-dioxolane, which is probably the most used carbonyl protective group.2 Thus, 4-cyanobenzaldehyde (I) was reacted with four equivalents of ethyleneglycol, in the presence of a catalytic amount of p-toluenesulfonic acid, in toluene, under reflux conditions for three hours, to give the product 2 in 89% yield.3,4 The nitrile was easily transformed into the corresponding amidoxime 3 in 90% yield, by treatment with hydroxylamine hydrochloride (3.5 equiv) and sodium carbonate (2 equiv) in aqueous ethanol at 100 °C.5 The 1,2,4-oxadiazole 6 was obtained quantitatively in two steps as follows: O-acylation5,6 was realized by the addition of pyridine (2 equiv) and phenylacetyl chloride (1.2 equiv) to a solution of benzamidoxime 3 in dichloromethane at room temperature, to afford O-acylated benzamidoxime 4, which was cyclized and dehydrated7 by heating in toluene for 1 hour. Deprotection of the acetal was carried out by the use of pyridinium p-toluenesulfonate8 (PPTS, 0.3 equiv) in aqueous acetone at 75 °C, to give the aldehydes 5 and 7, respectively, in 86% and 88% yield (Scheme 2). Thus, the desired mono-benzaldehyde was obtained in five steps with an overall yield of 70%.

After these encouraging results, we decided to study these reactions with various aromatic and aliphatic linkers in order to obtain the desired dibenzaldehydes. To introduce

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the linkers, two methodologies were studied: the use of a dicarboxylic acid (method A) and the use of an acid dichloride (method B).

In order to compare the yields, benzamidoxime was reacted with 1,3- and 1,4-phenylenediacetic acid with 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) as a coupling agent. The basic advantage of EDC was the water-solubility of the resulting urea, which avoided the necessity for further purifications. Thus, the coupling reaction in dichloromethane under reflux conditions for 12 hours, afforded the desired aromatic bis-amidoximes and , both in 53% yield (method A). These two diacetic acids were then converted into the corresponding acid dichlorides by reaction with oxalyl chloride and a catalytic amount of dimethylformamide in dichloromethane and poured, without further purification, into a solution of compound in dichloromethane and pyridine, to give the products and in a quantitative yield (method B). With commercially available suberoyl and sebacoyl chloride, the aliphatic bis-amidoximes and were obtained in a quantitative yield (Scheme 3, Table 1).

Depending on the solubility of the starting material in toluene, the bis-oxadiazoles - were obtained by heating either under reflux conditions (method C) or under solvent-free conditions at 110 °C (method D), for 12–18 hours, from the corresponding bis-amidoximes - in good to excellent yields (Scheme 3, Table 1).

Finally, deprotection of the acetal of the bis-oxadiazoles was performed either with PPTS (0.6 equiv) in aqueous acetone at 75 °C for 24 hours (method E) or with a catalytic amount of concentrated hydrochloric acid in aqueous tetrahydrofuran at 65 °C for 18 hours (method F), to give the desired dibenzaldehydes - in excellent yields (Scheme 3, Table 1).

In conclusion, we describe here a general and efficient method for the synthesis of new mono- and bis(1,2,4-oxadiazol)benzaldehydes with aromatic and aliphatic linkers, obtained from 4-cyanobenzaldehyde in five steps with overall yields between 66% and 80%, employing simple and convenient conditions and purification processes. Moreover, this method has already been scaled up for the synthesis of multigram amounts of the dibenzaldehydes. Many of these original compounds should prove to be valuable building blocks in organic chemistry for a wide range of applications. Further studies on this project will be reported in due course.

All commercial reagents were used as received without further purification. Reaction mixtures were stirred magnetically and monitored by TLC using 0.2 mm Macherey–Nagel Polygram SIL G/UV254 precoated plates. Column chromatography was performed using CarloErba-SDS 60A 70–200 mm silica gel. Melting points (reported uncorrected) were determined on a Köfler melting point apparatus. IR spectra were record with a Perkin–Elmer Spectrum 16PC FT-IR spectrometer. 1H NMR (250 MHz) and 13C NMR (62 MHz) spectra were recorded on a Brucker Avance DRX 250 instrument. Chemical shifts (δ) are expressed in ppm downfield from TMS as an internal standard and the coupling constants are in hertz.

### Table 1 Synthesis and Yields of Bis(1,2,4-oxadiazol)benzaldehydes -

<table>
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<tr>
<th>R</th>
<th>Method (%)</th>
<th>8</th>
<th>A (53)</th>
<th>9</th>
<th>A (53)</th>
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<td>C (85)</td>
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<td></td>
<td>Method (%)</td>
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<td>E (100)</td>
<td>17</td>
<td>F (94)</td>
<td>18</td>
<td>F (100)</td>
<td>19</td>
<td>F (100)</td>
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MS and HRMS (EI) were obtained on a Waters Micromass Q-ToF micro instrument and a JEOL JMS-AX500 spectrometer. Elemental analyses were performed with a Thermoquest NA 2500 instrument.

**4-[1,3]-Dioxolan-2-yl)benzonitrile (2)**
To a round-bottomed flask equipped with a Dean–Stark trap were successively added 4-cyanobenzaldehyde (1: 7.68 g, 58.6 mmol), a catalytic amount of p-TsOH and toluene (150 mL). After 5 min at r.t., ethylene glycol (13 mL, 234.3 mmol, 4 equiv) was added dropwise and the mixture was heated for 3 h under reflux conditions. The organic solution was washed successively with sat. aq Na2CO3 and the mixture was heated for 3 h under reflux conditions. The organic solution was washed successively with sat. aq Na2CO3 and the mixture was heated for 3 h under reflux conditions.

The orange oil obtained was triturated in pentane (20 mL) at –5 °C to give the product 2.

Yield: 14.27 g (90%); colorless solid; mp 150 °C; IR (KBr): 1638, 1068 cm–1.

Yield: 1.23 g (100%); colorless solid; mp 190 °C.

IR (KBr): 2352, 1738, 1734, 1622, 1616, 1558 cm–1.

**Synthesis of Acylated Amidoximes 4 and 8–11; General Procedure**
Pyridine (2 equiv) and acid chloride (1.2 equiv) or acid dichloride (0.7 equiv) were successively added dropwise, under nitrogen, to a solution of benzamidoxime 3 in CH2Cl2 (40 mL) at r.t. under stirring. The reaction mixture was stirred at r.t. for 1 h and then concentrated in vacuo. The crude material was poured into H2O (80 mL), stirred for 30 min then filtered to give the product 3.

Yield: 14.27 g (90%); colorless solid; mp 150 °C; Rf = 0.3 (CH2Cl2–MeOH, 9:1).

**Analysis of 4-[1,3]-Dioxolan-2-yl)benzamidoxime (4)**
Prepared from (4-[1,3]-dioxolan-2-yl)benzamidoxime (3). 2.20 g, 10.6 mmol), 1,3-benzenediacetyl dichloride (1.7 mL, 7.4 mmol) and pyridine (1.6 mL, 21.2 mmol).

Yield: 1.23 g (100%); colorless solid; mp 190 °C.

IR (KBr): 3354, 3346, 1734, 1618, 1084 cm–1.

**O,O’-Bis(4-[1,3]-dioxolan-2-yl)-O-carboxybenzamidoximido)-1,3-xylene (8)**
Prepared from (4-[1,3]-dioxolan-2-yl)benzamidoxime (3). 2.20 g, 10.6 mmol), 1,3-benzenediacetyl dichloride (1.7 mL, 7.4 mmol) and pyridine (1.6 mL, 21.2 mmol).

Yield: 1.23 g (100%); colorless solid; mp 202 °C.

**Bis(4-[1,3]-dioxolan-2-yl)-O-carboxybenzamidoximido)-1,6-hexane (10)**
Prepared from (4-[1,3]-dioxolan-2-yl)benzamidoxime (3). 0.65 g, 3.1 mmol), suberoyl chloride (0.4 mL, 2.2 mmol) and pyridine (0.5 mL, 6.2 mmol).

Yield: 0.95 g (100%); colorless solid; mp 169 °C.


**a,a’-Bis(4-[1,3]-dioxolan-2-yl)-O-carboxybenzamidoximido)-1,3-xylene (9)**
Prepared from (4-[1,3]-dioxolan-2-yl)benzamidoxime (3). 2.20 g, 10.6 mmol), 1,3-benzenediacetyl dichloride (1.7 mL, 7.4 mmol) and pyridine (1.6 mL, 21.2 mmol).

Yield: 1.23 g (100%); colorless solid; mp 202 °C.

**Bis(4-[1,3]-dioxolan-2-yl)-O-carboxybenzamidoximido)-1,4-xylene (9)**
Prepared from (4-[1,3]-dioxolan-2-yl)benzamidoxime (3). 2.20 g, 10.6 mmol), 1,4-benzenediacetyl dichloride (1.7 mL, 7.4 mmol) and pyridine (1.6 mL, 21.2 mmol).

Yield: 1.23 g (100%); colorless solid; mp 202 °C.

**Bis(4-[1,3]-dioxolan-2-yl)-O-carboxybenzamidoximido)-1,6-hexane (10)**
Prepared from (4-[1,3]-dioxolan-2-yl)benzamidoxime (3). 0.65 g, 3.1 mmol), suberoyl chloride (0.4 mL, 2.2 mmol) and pyridine (0.5 mL, 6.2 mmol).

Yield: 0.95 g (100%); colorless solid; mp 169 °C.

IR (KBr): 3295, 3334, 3352, 1736, 1618, 1560, 1558 cm–1.

**Analysis of 4-[1,3]-Dioxolan-2-yl)benzamidoxime (4)**
Prepared from (4-[1,3]-dioxolan-2-yl)benzamidoxime (3). 4.43 g, 21.3 mmol), phenylacetyl chloride (3.4 mL, 25.6 mmol) and pyridine (3.2 mL, 42.6 mmol).

Yield: 6.94 g (100%); pale-brown solid; mp 130 °C; Rf = 0.6 (CH2Cl2–MeOH, 9:1).
Bis[4-[1,3]-dioxolan-2-yl]-O-carboxybenzamidoximo]-1,8-octane (11)
Prepared from 4-[1,3]-dioxolan-2-yl]benzamidoxime (3; 0.65 g, 3.1 mmol), sebacoyl chloride (0.4 mL, 2.2 mmol) and pyridine (0.5 mL, 6.2 mmol).
Yield: 0.95 g (100%); colorless solid; mp 184 °C.

1H NMR (CDCl$_3$): δ = 4.05–4.15 (m, 8 H), 4.28 (s, 4 H), 5.86 (s, 2 H), 7.39–7.25 (s, 4 H), 7.58 (d, J = 8.3 Hz, 4 H), 8.08 (d, J = 8.3 Hz, 4 H).

13C NMR (CDCl$_3$): δ = 32.7, 65.4, 103.2, 126.9, 127.5, 129.6, 133.0, 141.0, 168.3, 177.8.

MS (EI): m/z (%) = 539 (75) [M + H$^+$], 366 (20), 193 (63), 176 (100).

HRMS (ESI): m/z [M + H$^+$] calcd for C$_{30}$H$_{35}$N$_4$O$_6$: 547.2557; found: 547.2565.

Synthesis of New Mono- and Bis[1,2,4]-oxadiazol]benzaldehydes

Prepared from (4-[1,3]-dioxolan-2-yl)benzamidoxime (4; 5 g, 15.3 mmol).

Yield: 0.95 g (100%); colorless solid; mp 184 °C.

3.1 mmol), sebacoyl chloride (0.4 mL, 2.2 mmol) and pyridine (0.5 mL, 6.2 mmol).

Yield: 0.74 g (86%); pale-orange solid; mp 108–110 °C.

1H NMR (CDCl$_3$): δ = 4.04–4.14 (m, 4 H), 4.29 (s, 2 H), 5.86 (s, 1 H), 7.15–7.38 (m, 5 H), 7.58 (d, J = 8.2 Hz, 2 H), 8.08 (d, J = 8.2 Hz, 2 H).

13C NMR (CDCl$_3$): δ = 33.4, 65.8, 103.6, 127.3, 127.9, 128.0, 129.0, 129.3, 130.5, 133.8, 141.4, 168.6, 178.4.

MS (EI): m/z (%) = 539 (100) [M$^+$], 308 (31), 263 (15), 217 (37), 191 (38), 174 (11), 146 (9), 119 (18), 118 (15), 104 (18), 91 (43), 73 (24), 65 (16).

Anal. Calcd for C$_{30}$H$_{35}$N$_4$O$_6$: C, 70.12; H, 5.23; N, 9.09. Found: C, 70.16; H, 5.63; N, 8.59.

α,α′-Bis[4-[1,3]-dioxolan-2-yl]-[1,2,4]oxadiazol-3-yl]-1,3-xylene (12)
Obtained by method D, starting from α,α′-bis[4-[1,3]-dioxolan-2-yl]-O-carboxybenzamidoximo]-1,3-xylene (8; 1.23 g, 2.1 mmol).
Yield: 1.15 g (100%); orange solid.

1H NMR (CDCl$_3$): δ = 3.91–4.03 (m, 8 H), 4.19 (s, 4 H), 5.76 (s, 2 H), 7.09–7.25 (m, 3 H), 7.31 (s, 1 H), 7.49 (d, J = 8.3 Hz, 4 H), 8.00 (d, J = 8.3 Hz, 4 H).

MS (EI): m/z (%) = 539 (100) [M$^+$], 493 (45), 366 (25), 193 (39), 176 (85).


α,α′-Bis[4-[1,3]-dioxolan-2-yl]-[1,2,4]oxadiazol-3-yl]-1,4-xylene (13)
Obtained by method D, starting from α,α′-bis[4-[1,3]-dioxolan-2-yl]-O-carboxybenzamidoximo]-1,4-xylene (9; 0.73 g, 1.3 mmol).
Yield: 0.60 g (87%); orange solid.

1H NMR (CDCl$_3$): δ = 4.05–4.15 (m, 8 H), 4.28 (s, 4 H), 5.86 (s, 2 H), 7.39–7.25 (s, 4 H), 7.58 (d, J = 8.3 Hz, 4 H), 8.08 (d, J = 8.3 Hz, 4 H).

13C NMR (CDCl$_3$): δ = 40.9, 127.7, 127.8, 129.2, 129.7, 130.3, 134.1, 136.9, 138.4, 155.8, 168.4, 191.9.

MS (EI): m/z (%) = 282 (3) [M$^+$], 264 (20), 136 (21), 118 (25), 104 (13), 92 (20), 91 (100), 77 (12), 65 (18).
Yield: 0.96 g (100%); orange solid.

Obtained by method E, starting from 5-benzyl-3-[4-(1,3-dioxolan-2-ylphenyl)-[1,2,4]oxadiazol-3-yl]-1,2,4-oxadiazole (6; 0.69 g, 2.2 mmol) and PPTS (0.17 g, 0.7 mmol).

HRMS (ESI): m/z (%) = 451 (100) [M + 1], 323 (13), 175 (14), 149 (16).

References


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4-(5-Benzyl-[1,2,4]oxadiazol-3-yl)benzaldehyde (7)

Yield: 0.42 g (100%); pale-yellow solid; mp 89 °C.


