# Preparation of 2,6-dialkoxybenzaldehydes

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**Abstract**
Lithiation of 1,3-dialkoxybenzenes with *n*-BuLi, followed by formylation with DMF, furnished solely 2,6-dialkoxybenzaldehydes with high regioselectivity. Using this key step, different approaches have been developed for novel symmetrical and unsymmetrical 2,6-dialkoxybenzaldehydes.

**Keywords:** 1,3-Dialkoxybenzenes, 2,6-dialkoyxbenzaldehydes, lithiation, formylation

## Introduction

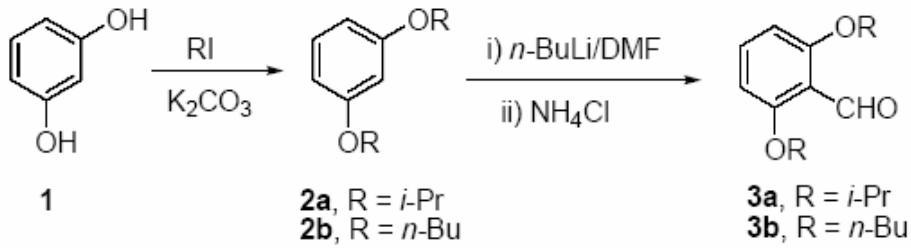
Dialkoxybenzaldehydes are useful and important precursors for pharmaceutical industry and for organic synthesis in general. *O*-Alkylations of 2,3- or 2,4-dihydroxy-benzaldehydes with benzyl bromide or ethyl iodide were reported to produce 2,3-dibenzyloxybenzaldehydes[1] or 2,4-dibenzyloxy- and 2,4-diethoxy-benzaldehydes.[2–4] However, this route is not appropriate for the preparation of 2,6-dialkoxybenzaldehydes due to lack of the commercially available 2,6-dihydroxybenzaldehyde. Even if 2,6-dihydroxybenzaldehyde is available, its alkylation with alkyl halides is not expected to generate unsymmetrical 2,6-dialkoxybenzaldehydes because of poor regioselectivity. Although the direct formylation of an aromatic ring with hexamethylenetetramine (HMTA) in acetic acid and/or trifluoroacetic acid is a known method to introduce a formyl group into an aromatic ring,[5–10] the formylation of 1,3-dialkoxybenzenes with HMTA is not appropriate for preparation of 2,6-dialkoxybenzaldehydes due to poor regioselectivity (one example will be discussed in this paper). A very recent paper reported the formylation of phenol derivatives with formaldehyde in the presence of KSF−Et3N, but the substituents attached to the benzene ring are limited to alkyl groups.[11] To our knowledge, no general method has previously been reported to prepare 2,6-dialkoxybenzaldehydes. In this paper, we develop several approaches for the title compounds.

## Results and Discussion

Our first approach was to use the ability of certain 1,3-substituents on aromatic systems to direct metallation at a position *ortho* to both of these groups using organolithium reagents. This phenomenon is of synthetic importance since electrophilic attack on aryllithium intermediates is a useful method for the functionalization of aromatic compounds. Therefore, many papers have reported the factors which control the regioselectivity and efficiency of lithiation of aromatic substrates.[12] Numerous functional groups are known to promote *ortho*-lithiation.[13, 14] However, with many of these groups, difficulties may arise due to lack of discrimination between non-equivalent *ortho* positions or between the ring positions and other acidic sites within the substrates.[15]

An early investigation revealed that lithiation can occur selectively at the common *ortho* site of 1,3-dialkoxybenzenes.[15] Encouraged by these results, we first synthesized symmetrical 2,6-dialkoxybenzaldehydes **3a** and **3b** in two steps by *O*-alkylation of benzene-1,3-diol (**1**) in the presence of potassium carbonate with an excess alkyl iodide, followed by the lithiation and subsequent formylation of the corresponding intermediate symmetrical 1,3-dialkoxybenzenes **2a** and **2b** (Scheme 1). The $^{1}$H NMR spectra (no singlet proton peak in the aromatic region) and $^{13}$C NMR spectra (four aromatic carbon peaks determining the molecular symmetry) clearly prove that the formyl group is introduced into the desired position with high regioselectivity between the two *ortho* directing alkoxy groups. No regio-isomers with the formyl group at other positions of the benzene ring were detected.



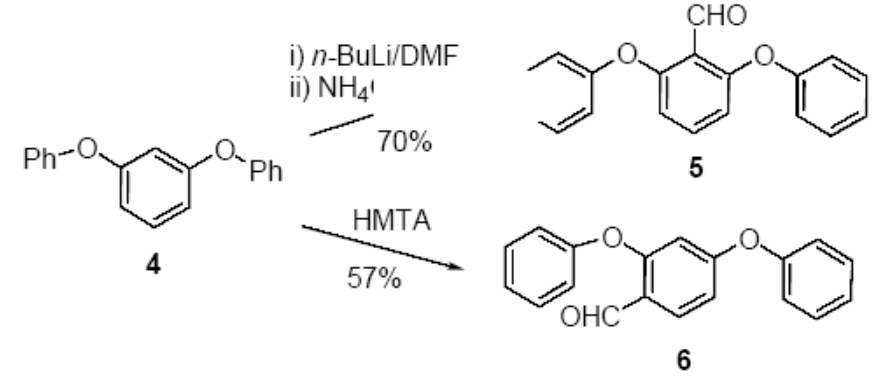

**Scheme 1**

We found that the formylation of 1,3-diphenoxybenzene (**4**) with *n*-BuLi/DMF gave a single regio-isomer, 2,6-diphenoxybenzaldehyde (**5**), in 70% yield. By contrast, the formylation of **4** with HMTA in the mixed-solvent (CF3COOH/CH3COOH = 1:1) produced solely 2,4-diphenoxybenzaldehyde (**6**) in 57% yield. The structures of **5** and **6** were clearly confirmed by their $^{13}$C NMR spectra. For **5**, only eight carbon peaks are found in the aromatic region due to its symmetrical structure; while for **6**, lack of symmetry in the structure results in fourteen carbon peaks. The two phenoxy groups in **4** activate the 2-position proton for *ortho*-lithiation by n-BuLi; however, when **4** reacts with the larger reagent HMTA, significant stereo hindrance at the 2-position by the two phenoxy groups directs the formylation to the less hindered 4-position. Therefore, the formylation of **4** with *n*-BuLi/DMF or HMTA afforded 2,6-

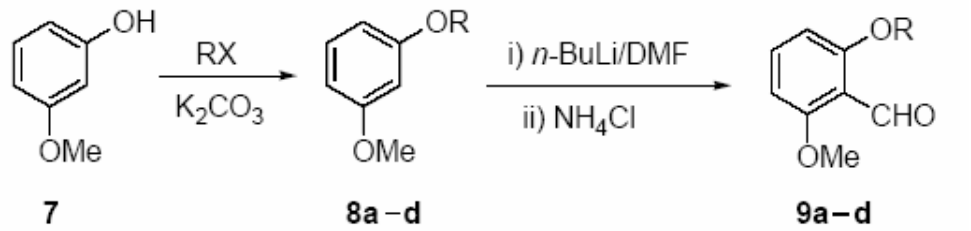
 

diphenoxybenzaldehyde (**5**) or 2,4-diphenoxybenzaldehyde (**6**), respectively, with high regioselectivity (Scheme 2).

For unsymmetrical 2-methoxy-6-alkoxybenzaldehydes, we used commercially available 3-methoxyphenol (**7**) as the starting material. *O*-Alkylation of **7** with the alkyl iodides readily produced 1-methoxy-3-alkoxybenzenes **8a−c**, which were subsequently lithiated and formylated as described above to generate 2-methoxy-6-alkoxybenzaldehydes **9a−c** in moderate yields (Scheme 3 and Table 1). The structures of **9a−c** were confirmed by their $^{1}$H NMR (no singlet peak in the aromatic region) and $^{13}$C NMR spectra. Notably, entry d in Table 1 shows that although the alkylation of 7 with benzyl bromide gave 75% yield of 1-methoxy-3-benzyloxybenzene (**8d**), treatment of **8d** with *n*-BuLi/DMF did not furnish the desired product 2-benzyloxy-6-methoxybenzaldehyde (**9d**). This could be rationalized by the high acidity of the benzyl hydrogens, which can be competitively deprotoned by *n*-BuLi, thus causing the formation of unexpected by-products. Therefore, another strategy was developed for preparation of **9d**.




**Scheme 2**



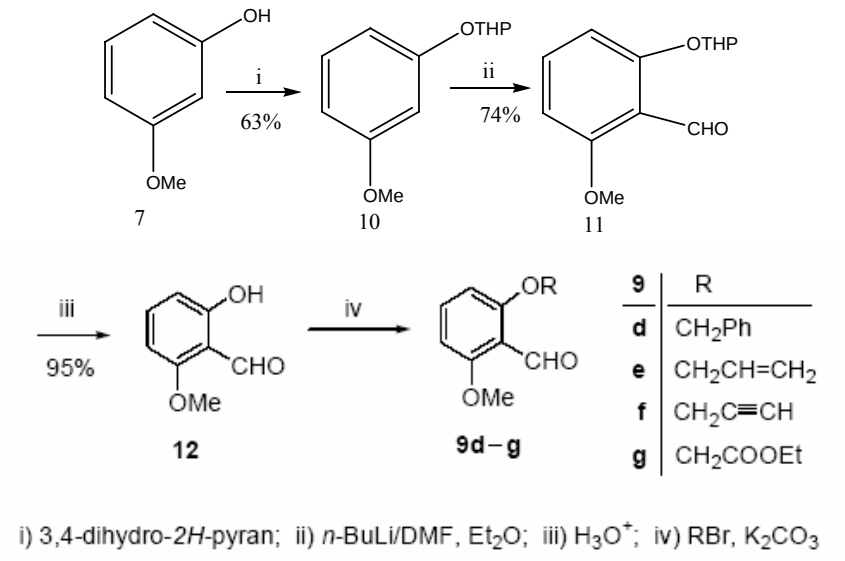

**Scheme 3**

**Table 1.** Preparation of 2-alkoxy-6-methoxybenzaldehydes **9a−c**

| Entry | RX | Y (%) of **8** | Y (%) of **9** |
|---|---|---|---|
| **a** | *n*-PrI | 70 | 60 |
| **b** | *i*-PrI | 68 | 57 |
| **c** | *n*-$C_8H_{17}I$ | 90 | 53 |
| **d** | $PhCH_2Br$ | 75 | 0 |

The prerequisite starting material for preparation of 9d is obtained by methodology from Zacharie's work.[16] 2-Hydroxy-6-methoxybenzaldehyde (**12**) was obtained from 3methoxyphenol (**7**) in three steps in overall 44% yield (reported yield[16]: 45%) (Scheme 4). Treatment of **12** with benzyl, allyl and propargyl bromide and ethyl 2-bromoacetate in the presence of potassium carbonate produced unsymmetrical 2-alkoxy-6-methoxybenzaldehydes **9d−g** in 63%−75% yields. The structures of **9d−g** were confirmed by their $^{1}H$, $^{13}C$ NMR spectra and elemental analyses or HRMS results. The method is therefore useful for preparation of 2-alkoxy-6-methoxybenzaldehydes with substituents containing acidic hydrogens. However, there is an obvious limitation that the 6-position has to be occupied by a methoxy group due to the starting material 3-methoxyphenol (**7**).

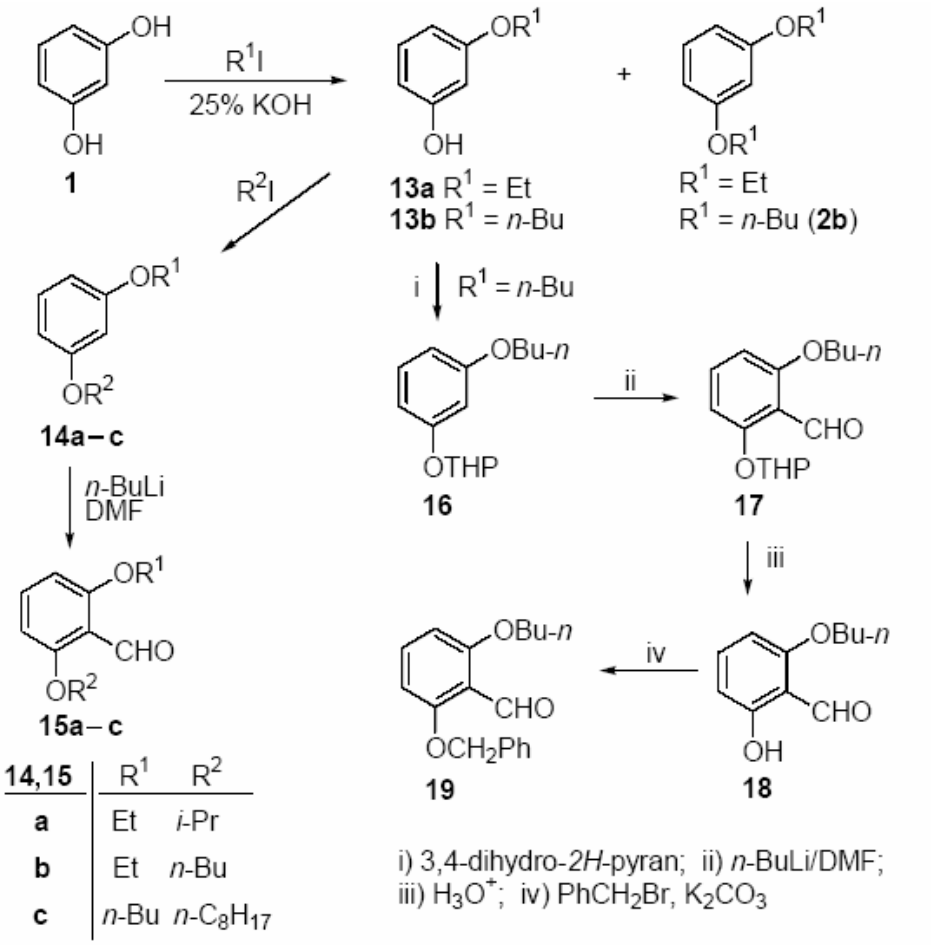



**Scheme 4**

Our preparation of other novel unsymmetrical 2,6-dialkoxybenzaldehydes from benzene-1,3-diol (**1**) was based on Klarmann's work.[17] The selective *O*-alkylation of **1** with one equivalent of ethyl iodide in the presence of 25% KOH aqueous solution for 5 h gave a mixture of 3-ethoxyphenol (**13a**), 1,3-diethoxybenzene and starting material **1** in a 2:1:1 ratio (determined by GC). Intermediate **13a** was isolated in 50% yield by column chromatography. Treatment of **13a** with *iso*-propyl iodide or *n*-butyl iodide generated the 1,3-dialkoxybenzenes **14a** or **14b**, which were subsequently lithiated and formylated to furnish 2-*iso*-propoxy-6-ethoxybenzaldehyde (**15a**) or 2-butoxy-6-ethoxybenzaldehyde (**15b**), respectively. Similar treatment of **1** with *n*-butyl iodide gave 47% of 3butoxyphenol (**13b**), which was reacted with *n*-octyl iodide to generate 1-octyloxy-3-butoxybenzene (**14c**). Formylation of **14c** with *n*-BuLi/DMF afforded 2-octyloxy-6-butoxybenzaldehyde (**15c**) (Scheme 5). For the introduction of a benzyloxy group at the 2-position, we protected the hydroxy group in **13b** with 3,4-dihydro-2*H*-pyran to obtain butyl 3-(tetrahydro-2*H*-pyran-2-yloxy)phenyl ether (**16**). Treatment of **16** with *n*-BuLi/DMF introduced the formyl group into the desired position between the two alkoxy groups. Deprotection of

intermediate **17** by acid hydrolysis gave 2-hydroxy-6-butoxybenzaldehyde (**18**), which easily underwent *O*-alkylation with benzyl bromide to afford 2-benzyloxy-6-butoxybenzaldehyde (**19**) (Scheme 5).




**Scheme 5**

In summary, several approaches have been developed for the preparation of symmetrical and unsymmetrical 2,6-dialkoxybenzaldehydes. The key step is the highly regioselective introduction of the formyl group into the desired position between two *ortho* directing alkoxy groups by the lithiation of 1,3-dialkoxybenzenes with *n*-BuLi, followed by formylation with DMF.

## Experimental Section

**General Procedures.** THF was distilled from sodium-benzophenone prior to use. Melting points were determined using a Bristoline hot-stage microscope and are uncorrected. $^{1}$H and $^{13}$C NMR spectra (300 MHz and 75 MHz respectively) were recorded on a Gemini 300 NMR spectrometer in $CDCl_3$ (with TMS for $^{1}$H and $CDCl_3$ for $^{13}$C as the internal reference). Elemental analyses were performed on a Carlo Erba-1106 instrument. Column chromatography was performed on

silica gel. All of the reactions were carried out under $N_2$.

**General procedure for the preparation of 1,3-dialkoxybenzene 2a and 2b from *O*-alkylation of benzene-1,3-diol (1) with alkyl iodide**

A mixture of benzene-1,3-diol (**1**; 1.10 g, 10 mmol), *iso*-propyl iodide or *n*-butyl iodide (20 mmol) and $K_2CO_3$ (6.9 g, anhydrous) was refluxed in dry acetone (50 mL). After refluxing for 5 h, more *iso*-propyl iodide or *n*-butyl iodide (20 mmol) was added to the mixture. Time for complete reaction (monitored by GC analysis) for 2a and 2b was 12 h and 14 h, respectively (GC purity for 2a: 58%; for 2b: 64%). The cooled mixture was poured into water (60 mL) and extracted with EtOAc (3 × 20 mL). The combined extracts were washed with water and dried over anhyd $Na_2SO_4$. After removal of solvent *in vacuo*, the product was purified by column chromatography with hexanes/EtOAc (4:1 to 2:1) as an eluent to give 1,3-di-*iso*-propoxybenzene (2a; 1.07 g, 55%), 1,3-dibutoxybenzene (2b; 1.33 g, 60%), respectively. The GC purity of 2a, 2b was more than 97%.

**General procedure for the formylation of symmetrical 1,3-dialkoxybenzene 2a, 2b and 1,3-diphenoxybenzene (4) with *n*-BuLi/DMF**

To a stirred solution of 1,3-dialkoxybenzene 2a, 2b (10 mmol) or 1,3-diphenoxybenzene (4; 2.62 g, 10 mmol) in dry THF (60 mL) at 0 °C, was added dropwise *n*-BuLi (8 mL, 1.5 M in hexanes). The mixture was stirred at rt for 2 h and then DMF (1.83 g, 25 mmol) was added. After 2 h, the mixture was poured into water. The THF phase was separated and the water phase was extracted with ether (3 × 30 mL). The combined organic phase was dried over anhyd $Na_2SO_4$. After removal of solvent *in vacuo*, the product was purified by column chromatography with hexanes/EtOAc (9:1 to 6:1) as an eluent to afford symmetrical 2,6-dialkoxybenzaldehydes 3a, 3b or 2,6-diphenoxybenzaldehyde (5). 2,6-Di-*iso*-propoxybenzaldehyde (3a): colorless oil; yield, 1.80 g (81%); $^1$H NMR δ1.36 (d, *J* = 6.0 Hz, 12H, 4 × -$CH_3$), 4.58 (qq, *J* = 6.0, 6.0 Hz, 2H, 2 × -OCH-), 6.52 (d, *J* = 8.5 Hz, 2H, H-3 and H-5), 7.33 (dd, *J* = 8.5, 8.5 Hz, 1H, H-4), 10.49 (s, 1H, CHO); $^{13}$C NMR δ 21.9, 71.3, 106.0 (C-3 and C-5), 116.4 (C-1), 135.0 (C-4), 160.5 (C-2 and C-6), 189.6 (C=O). HRMS Calcd for $C_{13}H_{19}O_3$: 223.1334 (M+1), found: 223.1358.

**2,6-Dibutoxybenzaldehyde (3b).** Colorless oil; yield, 1.90 g (76%); $^1$H NMR δ 0.94 (t, *J* = 7.5 Hz, 6H, 2 × -$CH_3$), 1.47−1.54 (m, 4H), 1.75−1.84 (m, 4H), 3.99 (t, *J* = 6.5 Hz, 4H, 2 × -$OCH_2$-), 6.50 (d, *J* = 8.5 Hz, 2H, H-3 and H-5), 7.34 (dd, *J* = 8.5, 8.5 Hz, 1H, H-4), 10.54 (s, 1H, CHO); $^{13}$C NMR δ 13.6, 19.0, 30.9, 68.3, 104.2 (C-3 and C-5), 114.4 (C-1), 135.4 (C-4), 161.3 (C-2 and C-6), 188.9 (C=O). HRMS Calcd for $C_{15}H_{23}O_3$: 251.1647 (M+1), found: 251.1657.

**2,6-Diphenoxybenzaldehyde (5).** Colorless needles; yield, 2.29 g (79%); mp 88−89 °C; $^1$H NMR δ 6.55 (d, *J* = 8.3 Hz, 2H), 7.06−7.10 (m, 4H), 7.14−7.19 (m, 2H), 7.28−7.40 (m, 5H), 10.60 (s, 1H, CHO); $^{13}$C NMR δ = 112.6 (C-3 and C-5), 118.3 (C-1), 119.6, 124.3, 129.9, 135.1 (C-4), 156.0, 159.8 (C-2 and C-6), 188.1 (C=O). Anal. Calcd for $C_{19}H_{14}O_3$: C, 78.61; H, 4.86. Found: C 78.42; H, 4.78

**Procedure for the formylation of 1,3-diphenoxybenzene (4) with HMTA.** A mixture of 1,3-

diphenoxybenzene (**4**; 2.62 g, 10 mmol) and HMTA (3.22 g, 23 mmol) in the mixed-solvent ($CF_3COOH/CH_3COOH$ = 1:1, 60 mL) was heated to reflux for 3 h. After cooling, the mixture was poured into water and extracted with EtOAc. The combined extracts were washed with water and dried over anhyd $Na_2SO_4$. After removal of the solvent *in vacuo*, the product was purified by column chromatography with hexanes/EtOAc (6:1) as an eluent to give 2,4-diphenoxybenzaldehyde (**6**).

**2,4-Diphenoxybenzaldehyde (6).** Colorless needles; yield, 1.65 g (57%); mp 52−53 °C; $^1$H NMR δ 6.46 (s, 1H, H-3), 6.65 (d, *J* = 6.7 Hz, 1H), 7.00−7.18 (m, 6H), 7.31−7.39 (m, 4H), 7.88 (d, *J* = 8.7 Hz, 1H), 10.39 (s, 1H, CHO); $^{13}$C NMR δ 106.8, 111.9, 119.4, 120.2, 121.8, 124.5, 124.9, 130.0, 130.04, 130.2, 154.7, 155.8, 161.7, 164.1, 187.8 (C=O). Anal. Calcd for $C_{19}H_{14}O_3$: C, 78.61; H, 4.86. Found: C, 78.97; H 4.87.

**General procedure for the preparation of 1-alkoxy-3-methoxybenzenes 8a-d from 7**

A mixture of 3-methoxyphenol (**7**; 1.24 g, 10 mmol), an appropriate alkyl iodide or benzyl bromide (25 mmol) and $K_2CO_3$ (4.5 g, anhydrous) was refluxed in dry acetone (50 mL). The reaction time monitored by TLC for **8a−d** was about 10 h. The cooled mixture was poured into water (60 mL) and extracted with EtOAc (3 × 20 mL). The combined extracts were washed with water and dried over anhyd $Na_2SO_4$. After removal of solvent *in vacuo*, the product was purified by column chromatography with hexanes/EtOAc (10:1 to 4:1) as an eluent to give 1-propoxy-3-methoxybenzene (**8a**; 1.16 g, 70%), 1-*iso*-propoxy-3-methoxybenzene (**8b**; 1.13 g, 68%), 1-octyloxy-3-methoxybenzene (**8c**; 2.13 g, 90%) and 1-benzyloxy-3-methoxybenzene (**8d**; 1.61 g, 75%), respectively. The GC purity of **8a−d** was more than 96%.

**General procedure for the formylation of 1-alkoxy-3-methoxybenzenes 8a−d with *n*-BuLi/DMF**

To a stirred solution of 1-alkoxy-3-methoxybenzene **8a−c** (10 mmol) in dry THF (60 mL) at 0 °C, *n*-BuLi (8 mL, 1.5 M in hexanes) was added dropwise. The mixture was stirred at rt for 2 h and then DMF (1.83 g, 25 mmol) was added. After 2 h, the mixture was poured into water. The THF phase was separated and the water phase was extracted with $CH_2Cl_2$ (3 × 30 mL). The combined organic phase was dried over anhyd $Na_2SO_4$. After removal of solvent *in vacuo*, the product was purified by column chromatography with hexanes/EtOAc (5:1) as an eluent to afford 2-alkoxy-6-methoxybenzaldehydes **9a−c**. Formylation of **8d** with *n*-BuLi/DMF failed to give the desired product **9d**.

**2-Propoxy-6-methoxybenzaldehyde (9a).** colorless oil; yield, 1.17 g (60%); $^1$H NMR δ1.02 (t, *J* = 7.4 Hz, 3H, -$CH_3$), 1.81−1.87 (m, 2H), 3.88 (s, 3H, -$OCH_3$), 3.97 (t, *J* = 6.4 Hz, 2H, -$OCH_2$-), 6.53 (d, *J* = 8.5 Hz, 1H), 6.54 (d, *J* = 8.5 Hz, 1H), 7.39 (dd, *J* = 8.5, 8.5 Hz, 1H, H-4), 10.53 (s, 1H, CHO); $^{13}$C NMR δ 10.3, 22.2, 55.8, 70.1, 103.4, 104.4, 114.0(C-1), 135.7 (C-4), 161.2, 162.1, 189.2 (C=O). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H,7.27. Found: C, 67.98; H, 7.66.

**2-*iso*-Propoxy-6-methoxybenzaldehyde (9b).** colorless oil; yield, 1.11 g (57%); $^1$H NMR δ 1.36 (d, *J* = 6.2 Hz, 6H, 2 × $CH_3$), 3.88 (s, 3H, $OCH_3$), 4.63 (qq, *J* = 6.0, 6.0 Hz, 1H, -OCH-), 6.53 (d, *J* = 8.5 Hz, 1H), 6.58 (d, *J* = 8.5 Hz, 1H), 7.38 (dd, *J* = 8.5, 8.5 Hz, 1H, H-4), 10.51 (s, 1H, CHO); $^{13}$C NMR δ 22.4, 56.4, 71.9, 104.0, 106.7, 115.7 (C-1), 136.1 (C-4), 161.7, 162.0, 190.2 (C=O). Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 67.80; H, 7.47.

**2-Octyloxy-6-methoxybenzaldehyde (9c).** colorless oil; yield, 1.40 g (53%); $^1$H NMR δ0.86 (t, *J* = 7.1 Hz, 3H, -$CH_3$), 1.28−1.30 (m, 8H), 1.44−1.48 (m, 2H), 1.79−1.84 (m, 2H), 3.87 (s, 3H, -$OCH_3$), 4.02 (t, *J* = 6.5 Hz, 2H, -$OCH_2$-), 6.54 (d, *J* = 8.5 Hz, 1H), 6.55(d, *J* = 8.5 Hz, 1H), 7.39 (dd, *J* = 8.5, 8.5 Hz, 1H, H-4), 10.53 (s, 1H, CHO); $^{13}$C NMR δ14.0, 22.5, 25.9, 28.9, 29.1, 29.2, 31.7, 55.8, 68.8, 103.5, 104.4, 114.1 (C-1), 135.9 (C-4), 161.3, 162.3, 189.5 (C=O). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C,72.82; H, 9.37.

**General procedure for the preparation of 2-alkoxy-6-methoxybenzaldehydes 9d-g from 7**

2-Hydroxy-6-methoxybenzaldehyde (**12**) was obtained from 3-methoxyphenol (**7**) in three steps in total 44% yield, according to the reported procedure (reported yield[16]: 45%). A mixture of 2-hydroxy-6-methoxybenzaldehyde (**12**; 1.52 g, 10 mmol), an appropriate alkyl bromide (25 mmol) and $K_2CO_3$ (4.5 g, anhydrous) in acetone (50 mL) was refluxed for 4 h. The cooled mixture was poured into water (60 mL) and extracted with EtOAc (3 × 20 mL). The combined extracts were washed with water and dried over anhyd $Na_2SO_4$. After removal of solvent *in vacuo*, the product was purified by column chromatography with hexanes/EtOAc (4:1 to 2:1) as an eluent to give **9d−g**.

**2-Benzyloxy-6-methoxybenzaldehyde (9d).** colorless needles (from $CHCl_3$/hexane); yield, 1.53 g (63%); mp 68−69 °C; $^1$H NMR δ 3.86 (s, 3H, -$OCH_3$), 5.14 (s, 2H, $PhCH_2$-), 6.55−6.62 (m, 2H), 7.30−7.45 (m, 6H), 10.59 (s, 1H, CHO); $^{13}$C NMR δ 55.9, 70.4, 104.0, 105.1, 114.5 (C-1), 126.8, 127.8, 128.4, 135.7 (C-4), 136.1, 161.4, 161.6, 189.2 (C=O). Anal. Calcd for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 74.28; H, 5.97.

**2-Allyloxy-6-methoxybenzaldehyde (9e).** colorless oil; yield, 1.38 g (72%); $^1$H NMR δ4.02 (s, 3H, -$OCH_3$), 4.74−4.77 (m, 2H, -$OCH_2$-), 5.44 (dd, *J* = 10.7, 1.5 Hz, 1H), 5.62 (dd, *J* = 17.3, 1.5 Hz, 1H), 6.13−6.23 (m, 1H, -CH=C), 6.70 (d, *J* = 8.5 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 7.56 (dd, *J* = 8.5, 8.5 Hz, 1H, H-4), 10.69 (s, 1H, CHO); $^{13}$C NMR δ55.8, 69.2, 103.8, 104.8, 114.3 (C-1), 117.5, 132.1, 135.6 (C-4), 161.1, 161.5, 189.0 (C=O). HRMS Calcd for $C_{11}H_{13}O_3$: 193.0865 (M+1), found: 193.0856.

**2-(Prop-2-ynoxy)-6-methoxybenzaldehyde (9f).** colorless needles; yield, 1.43 g (75%); mp 97−98 °C; $^1$H NMR δ 2.58 (s, 1H, -CH-), 3.89 (s, 3H, -$OCH_3$), 4.79 (s, 2H, -$OCH_2$-), 6.62 (d, *J* = 8.5 Hz, 1H), 6.70 (d, *J* = 8.5 Hz, 1H), 7.44 (dd, *J* = 8.5, 8.5 Hz, 1H, H-4), 10.49 (s, 1H, CHO); $^{13}$C NMR δ 55.9, 56.4, 76.2, 77.7, 104.7, 105.3, 114.7 (C-1), 135.6 (C-4), 159.9, 161.8, 189.0 (C=O). Anal. Calcd for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C,69.70; H, 5.50.

**Ethyl 2-(2-formyl-3-methoxyphenoxy)acetate (9g).** colorless flakes (from $CHCl_3$/hexanes); yield, 1.50 g (63%); mp 79−80 °C; $^1$H NMR δ 1.26 (t, *J* = 7.1 Hz, 3H, $CH_3$), 3.90 (s, 3H, $OCH_3$), 4.22 (q, *J* = 7.1 Hz, 2H, $CH_2$), 4.72 (s, 2H, $OCH_2CO$), 6.44 (d, *J* = 8.2 Hz, 1H), 6.62 (d, *J* = 8.4

Hz, 1H), 7.40 (dd, *J* = 8.2, 8.2 Hz, 1H, H-4), 10.56 (s, 1H, CHO); $^{13}$C NMR δ 13.9, 55.9, 61.3, 65.7, 104.6, 104.9, 114.6 (C-1), 135.5 (C-4), 160.4, 161.6, 168.0 (COO), 188.9 (CHO). Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.50; H, 5.92. Found: C, 60.12; H, 6.09.

**General procedure preparation of unsymmetrical 2,6-dialkoxybenzaldehydes 15a‑c from 1** According to the reported procedure,[17] 3-ethoxyphenol (**13a**) and 3butoxyphenol (**13b**) were obtained from **1** in 50% and 47% yields, respectively. The similar procedure as the preparation of 1-alkoxy-3-methoxybenzenes **8a-d** from **7** afforded 1-*iso*-propoxy-3-ethoxybenzene (**14a**, 1.15 g, 64% based on **13a**), 1-butoxy-3-ethoxybenzene (**14b**, 1.34 g, 69% based on **13a**) and 1-octyloxy-3-butoxybenzene (**14c**, 2.17 g, 78% based on **13b**). According to the above-mentioned procedure for the formylation of **8a‑c**, formylation of **14a‑c** (10 mmol) with *n*-BuLi/DMF produced **15a‑c**.

**2-*iso*-Propoxy-6-ethoxybenzaldehyde (15a).** colorless oil; yield, 1.31 g (63% based on **14a**); $^1$H NMR δ 1.36 (d, *J* = 6.1 Hz, 6H, 2 × -$CH_3$), 1.43 (t, *J* = 7.1 Hz, 3H, -$CH_3$), 4.07 (q, *J* = 7.1 Hz, 2H, -$OCH_2$-), 4.59 (h, *J* = 6.1 Hz, 1H, -OCH-), 6.50 (d, *J* = 8.1 Hz, 1H), 6.54 (d, *J* = 8.4 Hz, 1H), 7.38 (dd, *J* = 8.2 Hz, 1H, H-4), 10.51 (s, 1H, CHO); $^{13}$C NMR δ14.5, 21.9, 64.3, 71.4, 104.3, 106.1, 115.5 (C-1), 135.4 (C-4), 160.9, 161.1, 189.7 (C=O). HRMS Calcd for $C_{12}H_{17}O_3$: 209.1178 (M+1), found: 209.1176.

**2-Butoxy-6-ethoxybenzaldehyde (15b).** colorless oil; yield, 1.71 g (77% based on **14b**);$^1$H NMR δ 0.94 (t, *J* = 7.4 Hz, 3H, -$CH_3$), 1.42 (t, *J* = 7.0 Hz, 3H, -$CH_3$), 1.48−1.54 (m, 2H), 1.78−1.83 (m, 2H), 4.00 (t, *J* = 6.3 Hz, 2H, -$OCH_2$-), 4.06 (t, *J* = 7.0 Hz, 2H, $OCH_2$-), 6.52 (d, *J* = 8.4 Hz, 1H), 6.53 (d, *J* = 8.4 Hz, 1H), 7.35 (dd, *J* = 8.4, 8.4 Hz, 1H, H-4), 10.54 (s, 1H, CHO); $^{13}$C NMR δ 13.7, 14.5, 19.1, 30.9, 64.3, 68.4, 104.4 (C-3 and C-5), 114.5 (C-1), 135.5 (C-4), 161.1, 161.6, 189.2 (C=O). HRMS Calcd for $C_{13}H_{19}O_3$: 223.1334 (M+1), found: 223.1333.

**2-Butoxy-6-octyloxybenzaldehyde (15c).** colorless oil; yield: 2.48 g (81% based on **14c**); $^1$H NMR δ 0.88 (t, *J* = 6.9 Hz, 3H, -$CH_3$), 0.97 (t, *J* = 7.3 Hz, 3H, -$CH_3$), 1.28−1.31 (m, 8H), 1.44−1.55 (m, 4H), 1.75−1.84 (m, 4H), 3.99−4.05 (m, 4H), 6.53 (d, *J* = 8.5 Hz, 2H, H-3 and H-5), 7.37 (dd, *J* = 8.5, 8.5 Hz, 1H, H-4), 10.54 (s, 1H, CHO); $^{13}$C NMR δ13.7, 14.0, 19.1, 22.5, 25.9, 28.9, 29.1, 29.2, 31.0, 31.7, 68.4, 68.8, 104.4 (C-3 and C-5), 114.6 (C-1), 135.5 (C-4), 161.5, 161.6, 189.2 (C=O). HRMS Calcd for $C_{19}H_{31}O_3$: 307.2273 (M+1), found: 307.2272.

**Procedure for the preparation of 2-butoxy-6-benzyloxybenzaldehyde (19) from 3-butoxyphenol (13b):** Based on the procedure for the preparation of 2-hydroxy-6-methoxybenzaldehyde (**12**),[16] 2-hydroxy-6-butoxybenzaldehyde (**18**) was obtained in three steps from 3-butoxyphenol (**13b**, 4.98 g, 30 mmol) in total 20% yield. *O*-Alkylation of **18** (0.97 g, 5 mmol) with benzyl bromide (2.14 g, 13 mmol) in the presence of $K_2CO_3$ (2.3 g, anhydrous), after usual work-up, gave 2-butoxy-6-benzyloxybenzaldehyde (**19**).

**2-Hydroxy-6-butoxybenzaldehyde (18).** Colorless oil; yield: 1.16 g, 20% based on 3-butoxyphenol (**13b**); $^1$H NMR δ 0.96 (t, *J* = 7.5 Hz, 3H, -$CH_3$), 1.46−1.53 (m, 2H), 1.75−1.82 (m, 2H), 4.02 (t, *J* = 6.5 Hz, 2H, -$OCH_2$-), 6.34 (d, *J* = 8.3 Hz, 1H), 6.48 (d, *J* = 8.4 Hz, 1H), 7.36

(dd, *J* = 8.3, 8.3 Hz, 1H, H-4), 10.34 (s, 1H, CHO), 11.95 (s, 1H, OH); $^{13}$C NMR δ 13.7, 19.2, 30.9, 68.2, 101.6, 109.4, 110.8 (C-1), 138.3 (C-4), 162.0, 163.5, 194.3 (C=O). MS (EI): 194 ($M^+$, 24), 137 ($M^+-C_4H_9$, 100).

**2-Butoxy-6-benzyloxybenzaldehyde (19).** Colorless oil; yield: 0.85 g (60% based on **18**); $^1$H NMR δ 0.94 (t, *J* = 7.4 Hz, 3H, -$CH_3$), 1.47−1.54 (m, 2H), 1.77−1.82 (m, 2H), 3.99 (t, *J* = 6.4 Hz, 2H, -$OCH_2$-), 5.15 (s, 2H, $PhCH_2$-), 6.54 (d, *J* = 8.4 Hz, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 7.29−7.39 (m, 4H), 7.44 (d, *J* = 7.2 Hz, 2H), 10.59 (s, 1H, CHO); $^{13}$C NMR δ 13.7, 19.1, 31.0, 68.5, 70.3, 104.9, 105.0, 114.8 (C-1), 126.7, 127.7, 128.4, 135.5 (C-4), 136.3, 160.6, 161.8, 189.1 (C=O). Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.65; H, 7.47.

## References


1. Loev, B.; Dawson, C. R. *J. Am. Chem. Soc*. **1956**, *78*, 6095.
2. Reimann, E. *Chem. Ber*. **1969**, *102*, 2881.
3. Kimachi, T.; Tanaka, K.; Yoneda, F. *J. Het. Chem*. **1991**, *28*, 439.
4. Robinson, R.; Shah, R. C. *J. Chem. Soc*. **1934**, 1491.
5. Larrow, J. F.; Jacobsen, E. N.; Gao, Y.; Hong, Y.; Nie, X.; Zepp, C. M. *J. Org. Chem*. **1994**, *59*, 1939.
6. Petrov, O. I.; Kalcheva, V. B.; Antonova, A. T. *Collect. Czech. Chem. Commun*. **1997**, *62*, 494.
7. Crozet, M. P.; Sabuco, J.-F.; Tamburlin, I.; Barreau, M.; Giraud, L.; Vanelle, P. *Heterocycles* **1993**, *36*, 45.
8. Ubeda, J. I.; Avendano, C.; Menendez, J. C.; Villacampa, M. *Heterocycles* **1994**, *38*, 2677.
9. Weidner-Wells, M. A.; Fraga-Spano, S. A. *Synth. Commun*. **1996**, *26*, 2775.
10. Sukuzi, Y.; Takahashi, H. *Chem. Pharm. Bull*. **1983**, *31*, 1751.
11. Bigi, F.; Conforti, M. L.; Maggi, R.; Sartori, G. *Tetrahedron* **2000**, *56*, 2709.
12. For a review, see Snieckus, V. *Chem Rev*. **1990**, *90*, 879.
13. Klumpp, G. W.; Sinnige, M. J. *Tetrahedron Lett*. **1986**, *27*, 2247.
14. Meyers, A. I.; Avila, W. B. *Tetrahedron Lett*. **1980**, *21*, 3335.
15. Winkle, M. R.; Ronald, R. C. *J. Org. Chem*. **1982**, *47*, 2101.
16. Zacharie, B.; Attardo, G.; Barriault, N.; Penney, C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2925.
17. Klarmann, E.; Gatyas, L. W.; Shternov, V. A. *J. Am. Chem. Soc*. **1931**, *53*, 3397.