Simple, Short and Efficient Procedure for the Preparation of Hydroxyl- and Hydroxymethyl-Substituted 2,6-Dichlorobenzaldehydes

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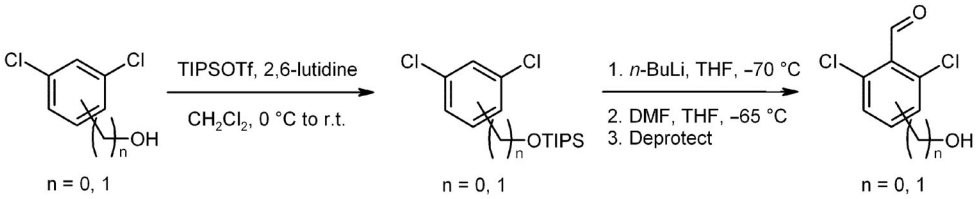
Abstract: Hydroxyl- and hydroxymethyl-substituted 2,6-dichlorobenzaldehydes **1**–**4** have been obtained by lithiation of the corresponding TIPS-protected dichlorophenols or dichlorobenzylic alcohols followed by reaction with DMF and subsequent deprotection of the hydroxy group. Yields are high and formation of regioisomers is not observed.

Key words: aldehydes, lithiation, protection groups, steric hindrance, regioselectivity



Scheme 1

2,6-Dichlorosubstitution is a common motif in pharmaceuticals[1] and therefore 2,6-dichlorobenzaldehydes are valuable building blocks. Additional hydroxyl groups decrease the lipophilicity and thus increase the solubility of a drug candidate and provide the possibility of further derivatization.

2,6-Dichloro-4-hydroxybenzaldehyde (**1**) and 2,6-dichloro-3-hydroxybenzaldehyde (**2**) are already known in the literature (Figure 1). Compound **1** can be prepared by either a Reimer–Tiemann reaction[2] or by a bromination/Grignard sequence.[3] The Reimer–Tiemann procedure does not allow an economical preparation due to very low yields (3–10%). In addition, the required use of chloroform causes substantial ecological problems. The reaction via a bromination/Grignard reaction sequence requires four steps, including stoichiometric bromination with bromine and the use of carcinogenic chloromethyl methyl ether to protect the phenol. In addition, the total yield is only 40%. A third method, which is very similar to that we present in this paper, has been described by Bringmann et al.[4] after the filing of our patent application.[5] In addition, we show that our method is not limited to the synthesis of **1** but allows for a broader application (Scheme 1).

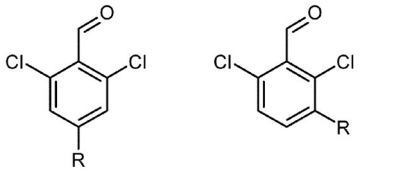


Figure 1 2,6-Dichloro-substituted benzaldehydes **1**–**4** prepared

Compound **2** has been synthesized from 3-hydroxybenzaldehyde,[6] but this requires the use of highly toxic chlorine gas and leads to side products due to overreaction. To the best of our knowledge, the corresponding hydroxymethyl-substituted 2,6-dichlorobenzaldehydes **3** and **4** have not been reported in the literature so far.

Aromatic 1,3-dichloro substitution is a known motif for directed lithiation.[7] Unfortunately the lithiation of 3,5-dichloroanisole, which would be a cheap precursor for **1**, leads to two regioisomers.[8,9] Moreover, it might be difficult to find suitable conditions for the cleavage of the methoxy group to obtain the free hydroxyl function. The use of a bulky silyl protection group (e.g. TIPS) should avoid both disadvantages: the bulk of the TIPS group is known to direct metalation away from the silyl group[10] and the silyl ether can easily be cleaved under acidic conditions.

The silyl ethers were prepared from the phenols (or benzylic alcohols) with triisopropylsilyl trifluoromethane-

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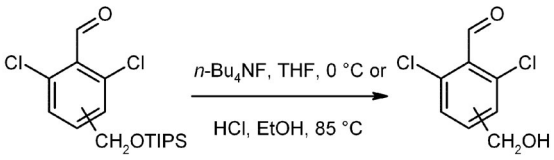
sulfonate (TIPSOTf) and 2,6-lutidine in CH_2Cl_2 at 0 °C almost quantitatively. Lithiation of the protected phenols with *n*-BuLi in anhydrous THF under nitrogen at –78 °C and subsequent reaction with DMF followed by hydrolysis with aqueous HCl gave the corresponding aldehydes in yields above 90%. In both cases formation of regioisomers was not observed. Cleavage of the silyl ether already occurred under the acidic workup conditions in the case of **1** (98% yield) or was achieved following a protocol by Sinhababu et al.[11] using NaF/HBr in DMF in the case of **2** (78% yield), respectively. The products could be purified by washing with *n*-hexane and/or by recrystallization.

The same reaction sequence as described above is suitable for the preparation of the corresponding benzylic alcohols **3** and **4** with the exception that the cleavage of the silyl ether in both cases had to be done in an additional step with Bu_4NF in THF at room temperature or HCl in EtOH at 85 °C, respectively (Scheme 2). The overall yield of **3** was 72% on a multigram scale. In the case of **4**, the yield of the formylation was very high (92% yield) whereas the deprotection of the hydroxyl group using Bu_4NF/THF was not satisfactory (32%).[12] Again in both cases **3** and **4**, the formation of regioisomers was not observed.



Scheme 2

In summary, a simple, short and efficient route to hydroxyl- and hydroxymethyl-2,6-dichlorobenzaldehydes is described, which gives the products without undesired regioisomers in high yields.

Petroleum ether used refers to the fraction boiling at 60–90 °C. All reagents and solvents were purchased from commercial suppliers and were used as received without further purification. NMR spectra were recorded on a Bruker Avance DPX 250 or a Bruker Avance DPX 400, respectively. NMR shifts were reported relative to a TMS internal standard or relative to the residual solvent, respectively. HRMS were obtained on a MAT 95 XL spectrometer at 70 eV using perfluorokerosine (PFK) as reference. Melting points are uncorrected.

3,5-Dichlorotriisopropylsilyloxybenzene

To a stirred solution of 3,5-dichlorophenol (4.08 g, 25 mmol) and 2,6-lutidine (6.70 g, 62.5 mmol) in anhyd CH_2Cl_2 (75 mL) was added TIPSOTf (9.96 g, 32.5 mmol) at 0 °C and the mixture was stirred for 2 h at this temperature. After hydrolysis with H_2O (15 mL), the organic layer was washed with brine, dried ($MgSO_4$) and evaporated to dryness. Chromatography of the crude product on silica gel using isohexane as eluent gave the title compound as a colorless oil in quantitative yield.

^{1}H NMR (250 MHz, $CDCl_3$):[13] δ = 1.03–1.15 (m, 18 H, CH_3), 1.16–1.35 (m, 3 H, CH), 6.73–6.80 (m, 2 H, CH), 6.92–6.98 (m, 1 H, CH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 12.7 (CH), 18.0 (CH_3), 119.0, 121.6 (CH), 135.2, 157.4 (C).

Scale-Up

To a solution of 3,5-dichlorophenol (200 g, 1.23 mol) and 2,6-lutidine (330 mL, 2.83 mol) in anhyd CH_2Cl_2 (3 L) was added triisopropylsilyl triflate (400 g, 1.305 mol) was added at 0 °C within 1 h and the mixture was stirred for additional 3 h at this temperature. After hydrolysis with H_2O (1 L), the organic layer was washed with brine, dried ($MgSO_4$) and evaporated to dryness (70 °C/80 mbar). The residue was taken up in petroleum ether and filtered through silica gel to yield 360 g (92%) of the title compound as a colorless oil.

2,6-Dichloro-4-hydroxybenzaldehyde (1)

A solution of *n*-BuLi (2.5 M in hexane, 9.4 mL, 23 mmol) was added to a stirred solution of 3,5-dichlorotriisopropylsilyloxybenzene (7.49 g, 23 mmol) in anhyd THF (30 mL) under N_2 keeping the temperature below –67 °C. After stirring for 45 min at –78 °C, anhyd DMF (2.14 g, 29 mmol) was added keeping the temperature below –65 °C. The mixture was allowed to warm up to –10 °C. After hydrolysis with NaCl-saturated 2 N HCl (25 mL), the layers were separated and the organic layer was dried ($MgSO_4$) and evaporated to dryness. To the residue was added hexane (20 mL) and the precipitate (4.37 g, quant) was filtered off and washed with hexane (5 mL); mp 229–230 °C (Lit.[2a] mp 223.5–224.5 °C).

^{1}H NMR (250 MHz, DMSO-d_6): δ = 6.94 (s, 2 H, CH), 10.25 (s, 1 H, CH=O), 11.46 (br s, 1 H, OH).

^{13}C NMR (62.9 MHz, DMSO-d_6): δ = 117.0 (CH), 120.7, 137.8, 162.1 (C), 187.2 (CH=O).

HRMS (EI): *m*/*z* calcd for $C_7H_4Cl_2O_2$: 189.9583; found: 189.9582.

Scale-Up

To a solution of 3,5-dichlorotriisopropylsilyloxybenzene (360 g, 1.11 mol) in anhyd THF (2.6 L) was added *n*-BuLi (440 mL of a 2.7 M solution in hexane) under N_2 keeping the temperature below –65 °C. After stirring for 2 h at –70 °C, anhyd DMF (120 mL, 1.55 mol) was added keeping the temperature below –65 °C. The mixture was allowed to warm up to r.t. overnight. After the addition of 4 M HCl (700 mL), the mixture was stirred vigorously for 1 h at r.t. Then the phases were separated (addition of solid NaCl may be necessary) and the organic layer was dried (Na_2SO_4) and was concentrated in vacuo. Recrystallization of the precipitate from toluene–THF yielded 154 g (70%) of the title compound. A small amount of 2,6-dichloro-4-triisopropylsilyloxybenzaldehyde was isolated from the mother liquor by column chromatography on silica gel (isohexane–EtOAc, 20:1).

^{1}H NMR (250 MHz, $CDCl_3$):[13] δ = 1.05–1.17 (m, 18 H, CH_3), 1.19–1.39 (m, 3 H, CH), 6.88 (s, 2 H, CH), 10.41 (s, 1 H, CH=O).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 12.7 (CH), 17.9 (CH_3), 121.5 (CH), 123.4, 138.9, 160.4 (C), 187.9 (CH=O).

2,4-Dichlorotriisopropylsilyloxybenzene

An analogous reaction to that described above, but starting with 2,4-dichlorophenol gave the title compound as a colorless oil in quantitative yield.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.07–1.18 (m, 18 H, CH_3), 1.20–1.40 (m, 3 H, CH), 6.82 (d, *J* = 8.8 Hz, 1 H, CH), 7.07 (dd, *J* = 8.8 Hz, *J* = 2.5 Hz, 1 H, CH), 7.34 (d, *J* = 2.5 Hz, 1 H, CH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 13.0 (CH), 18.0 (CH_3), 120.8 (CH), 125.9 (C), 126.2 (C), 127.6, 130.1 (CH), 151.0 (C).

2,6-Dichloro-3-triisopropylsilyloxybenzaldehyde

A solution of *n*-BuLi (2.5 M in hexane, 3.1 mL, 7.8 mmol) was added to a stirred solution of 2,4-dichlorotriisopropylsilyloxybenzene (2.5 g, 7.8 mmol) in anhyd THF (10 mL) under N_2 keeping the temperature below –70 °C. After stirring for 45 min at –78 °C, anhyd DMF (0.72 g, 9.8 mmol) was added keeping the temperature below –68 °C. The mixture was allowed to warm up to –10 °C. After hy-

drolysis with NaCl-saturated 2 N HCl (25 mL), the layers were separated and the organic layer was dried ($MgSO_4$) and evaporated to dryness. The obtained yellow oil (2.56 g) was a 9:1 mixture of the title compound and **2**, and was used without further purification.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.09 (d, *J* = 7.5 Hz, 18 H, CH_3), 1.35 (sept, *J* = 7.5 Hz, 3 H, CH), 7.23 (d, *J* = 9.0 Hz, 1 H, CH), 7.46 (d, *J* = 9.0 Hz, 1 H, CH), 10.33 (s, 1 H, CH=O).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 12.5 (CH), 18.0 (CH_3), 124.3 (CH), 125.9, 126.2 (C), 130.5 (CH), 132.2, 151.4 (C), 190.3 (CH=O).

2,6-Dichloro-3-hydroxybenzaldehyde (2)
To a solution of a 9:1 mixture of 2,6-dichloro-3-triisopropylsilyloxybenzaldehyde and **2** (2.56 g, see above) in DMF (25 mL) were added NaF (660 mg, 15.7 mmol) and aq 48% HBr (0.26 mL) and the mixture was stirred overnight at r.t.. All volatiles were removed in vacuo and the residue was treated with H_2O (20 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4) and evaporated to dryness; yield: 1.26 g (84%); light yellow solid.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.19 (d, *J* = 8.8 Hz, 1 H, CH), 7.38 (d, *J* = 8.8 Hz, 1 H, CH), 10.33 (s, 1 H, CH=O), 10.90 (s, 1 H, OH).

^{13}C NMR (100.6 MHz, DMSO-d_6): δ = 121.1 (CH), 121.9, 123.8 (C), 130.1 (CH), 131.6, 153.5 (C), 190.4 (CH=O).

HRMS (EI): *m*/*z* calcd for $C_7H_4Cl_2O_2$: 189.9583; found: 189.9586.

3,5-Dichloro(triisopropylsilyloxymethyl)benzene
An analogous reaction to that described for 3,5-dichlorotriisopropylsilyloxybenzene, but starting with 3,5-dichlorobenzyl alcohol gave the title compound as a colorless oil in quantitative yield.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.96–1.25 [m, 21 H, 3 $CH(CH_3)_2$], 4.78 (s, 2 H, OCH_2), 7.23 [s, 2 H, CH).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 12.1 (CH), 18.1 (CH_3), 64.0 (OCH_2), 124.2, 127.0 (CH), 134.9, 145.3 (C).

2,6-Dichloro-4-(triisopropylsilyloxymethyl)benzaldehyde
An analogous reaction to that described for 2,6-dichloro-4-hydroxybenzaldehyde, but starting with 3,5-dichloro(triisopropylsilyloxymethyl)benzene and hydrolyzing with ice water instead of aq HCl yielded the title compound as a colorless oil that solidified on cooling in an ice bath (eluent: isohexane–EtOAc, 20:1).

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.03–1.28 [m, 21 H, 3 $CH(CH_3)_2$], 4.82 (s, 2 H, OCH_2), 7.37 (s, 2 H, CH), 10.48 (s, 1 H, CH=O).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 12.0 (CH), 18.1 (CH_3), 63.6 (OCH_2), 126.8 (CH), 128.6, 137.2, 149.0 (C), 188.8 (CH=O).

Scale-Up
To a solution of 3,5-dichloro(triisopropylsilyloxymethyl)benzene (70 g) in anhyd THF (220 mL) was added *n*-BuLi (131 mL, 1.6 M in hexane) was added under N_2 keeping the temperature below –70 °C. After stirring for 45 min at –75 °C, anhyd DMF (28 mL, 0.36 mol) was added keeping the temperature below –65 °C. The mixture was stirred for an additional 30 min at –75 °C and then was allowed to warm up to 0 °C within 3 h. After 2 h at 0 °C, ice water (150 mL) and Et_2O (150 mL) were added. The phases were separated and the aqueous layer extracted with Et_2O (100 mL). The combined organic layers were washed with aq NaCl, dried (Na_2SO_4) and evaporated to dryness; yield: 73 g (95%); light brown oil, that solidified on cooling in an ice bath.

2,6-Dichloro-4-hydroxymethylbenzaldehyde (3)
2,6-Dichloro-4-(triisopropylsilyloxymethyl)benzaldehyde (426 mg, 1.2 mmol) was dissolved in anhyd THF (20 mL) and a solution of Bu_4NF (1.3 mL, 1 M in THF, 1.3 mmol) was added at r.t. and stirred overnight. After concentration in vacuo, 134.0 mg of 2,6-dichloro-4-hydroxymethylbenzaldehyde was isolated by column chromatography on silica gel (isohexane–EtOAc, 2:1) as a colorless solid; mp 109–110 °C.

^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.99 (t, *J* = 4.4 Hz, 1 H, OH), 4.74 (d, *J* = 4.4 Hz, 2 H, OCH_2), 7.40 (s, 2 H, CH), 10.48 (s, 1 H, CH=O).

^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 63.4 (OCH_2), 127.5 (CH), 129.2, 137.4, 147.9 (C), 188.7 (CH=O).

HRMS (EI): *m*/*z* calcd for $C_8H_6Cl_2O_2$: 203.9739; found: 203.9740.

Scale-Up
To a solution of 2,6-dichloro-4-(triisopropylsilyloxymethyl)benzaldehyde (65 g, 0.18 mol) in EtOH (1100 mL) at 50 °C was added 0.25 N HCl (180 mL) and the mixture was stirred for 6 h at 85 °C. The EtOH was removed in vacuo whereupon the product precipitated. EtOAc–petroleum ether (2:1, 700 mL) was added and the organic layer was washed with H_2O and aq NaCl and dried (Na_2SO_4). The solution was reduced to about 100 mL and warm petroleum ether (200 mL) was added and shortly warmed up to 50 °C. After standing at r.t. overnight, the precipitate was filtered off and washed with petroleum ether–EtOAc (15:1); yield: 24.3 g (66%). Purification of the mother liquor by column chromatography yielded another 4 g (11%) product.

2,4-Dichloro(triisopropylsilyloxymethyl)benzene
An analogous reaction to that described above, but starting with 2,4-dichlorobenzyl alcohol gave the title compound as a colorless oil in quantitative yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.1 (d, *J* = 7 Hz, 18 H, CH_3), 1.15–1.29 (m, 3 H, CH), 4.83 (s, 2 H, OCH_2), 7.28 (dd, *J* = 8.4, 2.0 Hz, 1 H, CH), 7.32 (d, *J* = 2.0 Hz, 1 H, CH), 7.59 (d, *J* = 8.4 Hz, 1 H, CH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 12.4 (CH), 18.4 (CH_3), 62.5 (OCH_2), 127.4, 128.5, 128.9 (CH), 132.0, 133.1, 138.1 (C).

2,6-Dichloro-3-(triisopropylsilyloxymethyl)benzaldehyde
An analogous reaction to that described above, but starting with 2,4-dichloro(triisopropylsilyloxymethyl)benzene yielded 92% of the title compound as a colorless oil that solidifies on standing overnight.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.03–1.15 (m, 18 H, CH_3), 1.15–1.29 (m, 3 H, CH), 4.88 (s, 2 H, OCH_2), 7.44 (d, *J* = 8.4 Hz, 1 H, CH), 7.80 (d, *J* = 8.4 Hz, 1 H, CH), 10.50 (s, 1 H, C=O).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 12.3 (CH), 18.4 (CH_3), 62.3 (OCH_2), 129.8 (CH), 130.4 (C_{arom}), 131.6 (CH), 133.4, 135.0, 140.3 (C_{arom}), 189.5 (C=O).

2,6-Dichloro-3-hydroxymethylbenzaldehyde (4)
An analogous reaction to that described above using Bu_4NF/THF at r.t., but starting with 2,6-dichloro-3-(triisopropylsilyloxymethyl)benzaldehyde yielded 32% of the title compound as a colorless solid; mp 93–95 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.82 (s, 2 H, OCH_2), 7.41 (d, *J* = 8.4 Hz, 1 H, CH), 7.67 (d, *J* = 8.4 Hz, 1 H, CH), 10.48 (s, 1 H, C=O).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 61.7 (OCH_2), 129.5 (CH), 130.5 (C), 132.1(CH), 134.2, 135.2, 139.1 (C), 189.2 (C=O).

HRMS (EI): *m*/*z* calcd for $C_8H_6Cl_2O_2$: 203.9739; found: 203.9743.

References

(1) Examples from the patent literature, especially in the field of kinase inhibitors, are legion by now. In addition, the Derwent World Drug Index is a (commercial) source of

information for marketed and development drugs. It contains well over 100 examples of compounds with 2,6-dichlorophenyl substitution.
(2) (a) Baldwin, J. J.; Engelhardt, E. L.; Hirschmann, R.; Lundell, G. F.; Ponticello, G. S.; Ludden, C. T.; Sweet, C. S.; Scriabine, A.; Share, N. N.; Hall, R. *J. Med. Chem.* **1979**, *22*, 687. (b) Knuutinen, J. S.; Kolehmainen, E. T. *J. Chem. Eng. Data* **1983**, *28*, 139.
(3) Katsurda, M.; Kawata, S.; Kyomura, N.; Shiga, Y.; Fukuchi, T.; Yamada, R. PCT Int. Appl. WO 2001044154, **2001**; *Chem. Abstr.* **2001**, *135*, 46183.
(4) Bringmann, G.; Menche, D.; Mühlbacher, J.; Reichert, M.; Saito, N.; Pfeiffer, S. S.; Lipshutz, B. H. *Org. Lett.* **2002**, *4*, 2833.
(5) Brandt, M.; Fertig, G.; Krell, H.-W.; von Hirschheydt, T.; Voss, E. PCT Int. Appl. WO 2003087026, **2003** (priority date 18.04.2002); *Chem. Abstr.* **2003**, *139*, 337979.
(6) Gust, R.; Schoenenberger, H. *Eur. J. Med. Chem.* **1993**, *28*, 103.
(7) (a) Kress, T. H.; Leanna, M. R. *Synthesis* **1988**, 803. (b) Saednya, A.; Hart, H. *Synthesis* **1996**, 1455.
(8) Pascal, R. A. Jr.; Chen, Y.-C. J. *J. Org. Chem.* **1985**, *50*, 408.
(9) We have found that the lithiation of 3,5-dichloroanisole in THF at –78 °C and subsequent reaction with DMF leads to a 2:1 mixture of 2,4-dichloro-6-methoxybenzaldehyde and 2,6-dichloro-4-methoxybenzaldehyde, which had to be separated by tedious column chromatography.
(10) Landi, J. J. Jr.; Ramig, K. *Synth. Commun.* **1991**, *21*, 167.
(11) Sinhababu, A. K.; Kawase, M.; Borchardt, R. T. *Synthesis* **1988**, 710.
(12) Other desilylating agents should easily overcome this disadvantage.
(13) The bulk of the TIPS group hinders the rotation of the phenolic C–O bond and causes a symmetry breakdown on ^{1}H NMR timescale. Therefore a spin system of higher order was observed.