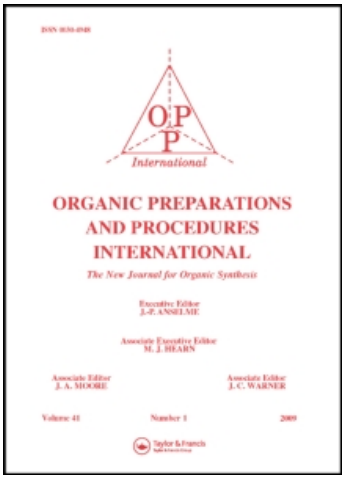

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A RELIABLE, HIGH-YIELDING PREPARATION OF 2, 6-DIMETHYL-4-HYDROXYBENZALDEHYDE

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A RELIABLE, HIGH-YIELDING PREPARATION OF 2,6-DIMETHYL-4-HYDROXYBENZALDEHYDE

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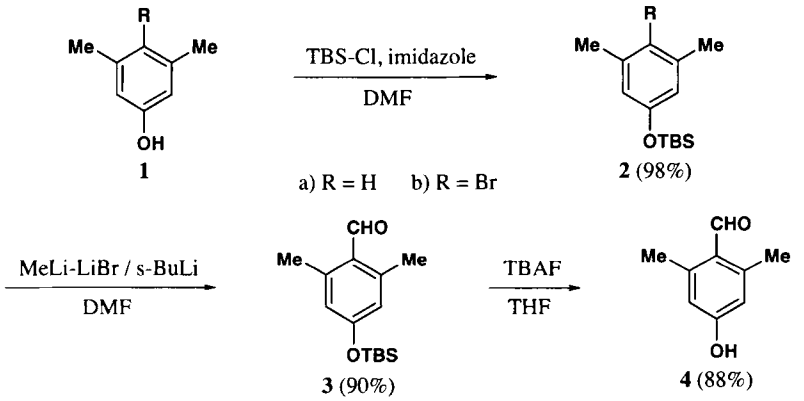
2,6-Dimethyl-4-hydroxybenzaldehyde (**4**) is a versatile intermediate in the preparation of compounds which are useful as neuro-protective agents,[1] analgesics,[2] PPARα agonists,[3] protein kinase C inhibitors,[4] herbicides[5] and BODIPY probes for multicolor fluorescence imaging of membrane dynamics.[6] Several preparations of **4** have been reported and all suffer from either low yield or the use of toxic reagents. Treatment of 3,5-dimethylphenol (**1a**) with dichloromethyl methyl ether in the presence of $TiCl_4$ produced **4** as a minor product in 15% yield.[5] A Reimer-Tiemann reaction of **1a** with $KOH/CHCl_3$ gave **4** in 10% yield[6] and a modified

Gatterman reaction with $Zn(CN)_2/AlCl_3/HCl$ afforded the product in 40% yield.[7] A three-step sequence for the preparation of **4** required the protection of the phenol moiety of **1a** with an allyl group followed by the introduction of the formyl group by a Vilsmeier-Haack reaction using N-methylformanilide/$POCl_3$. Removal of the allyl group with $Pd(OAc)_2/Ph_3P/HCOOH$ furnished the product in 26% overall yield.[1]

Our procedure is also a three-step process; however, it starts with commercially available 4-bromo-3,5-dimethylphenol (**1b**). Protection of the phenol with a *tert*-butyldimethylsilyl (TBS) group gave **2b** in nearly quantitative yield. Lithium-halogen exchange followed by reaction with DMF furnished virtually pure aldehyde **3** in quantitative yield (90% yield if further purification by column chromatography is performed). Removal of the silyl protecting group with fluoride ion gives the desired product in 88% yield (78% overall yield for the three-step sequence).



The presence of all three components in the lithium-halogen exchange reaction appears to be required for rapid complete reaction. Under identical conditions, no reaction occurred using only *s*-BuLi or only MeLi-LiBr complex. With *s*-BuLi and LiBr, a 5:1 mixture of **2a** and **3** was obtained and with *s*-BuLi and MeLi a 1:1:1 mixture of **1b**, **2a** and **3** was produced. The use of *n*-BuLi in place of *s*-BuLi gave comparable results in the three component system, however, if the MeLi-LiBr complex is omitted, a 2:1 mixture of **3** and **2a** was obtained.

EXPERIMENTAL SECTION

Commercially available reagents and compounds were purchased from Aldrich Chemical Company. Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The IR spectrum was recorded on a Nicolet 380 FT-IR spectrometer with ATR capability. The ^{1}H-NMR spectrum was measured on a Brucker 400 Ultrashield spectrometer. Chemical shifts are reported in ppm from internal TMS. The purity of starting material **1b** was checked by HPLC prior to use and was determined to be >99%. All other reagents were used as received from the supplier.

(4-Bromo-3,5-dimethylphenoxy)-*tert*-butyldimethylsilane (2b).- To a solution of 4-bromo-3,5-dimethylphenol (**1b**) (2.01 g, 10 mmol) and imidazole (1.49 g, 22 mmol) in 15 mL of DMF at 0°C under a nitrogen atmosphere was added *tert*-butyldimethylsilyl chloride (1.66 g, 11 mmol) in portions, and the mixture was stirred at room temperature for 30 min. The mixture was re-cooled to 0°C; then water was added. The mixture was extracted with methylene chloride, and the organic phase was washed with water and brine then was dried over sodium sulfate. The solvent was removed under reduced pressure, and the residue was purified by chromatography using heptane/ethyl acetate (10:1) as the mobile phase. Removal of the solvent under reduced pressure furnished 3.1 g (98% yield) of **2b** as a colorless oil. ^{1}H-NMR ($CDCl_3$): δ 6.57 (s, 2H), 2.34 (s, 6H), 0.97 (s, 9H), 0.18 (s, 6H).

Anal. Calcd. for $C_{14}H_{23}BrOSi$: C, 53.33; H, 7.35. Found: C, 53.52; H, 7.31.

4-(*tert*-Butyldimethylsilanyloxy)-2,6-dimethylbenzaldehyde (3).- To a solution of **2b** (2.4 g, 7.62 mmol) in 25 mL of THF at –78°C under a nitrogen atmosphere was added MeLi/LiBr complex (7.11 mL of a 1.5 M sol. in ether, 10.67 mmol) dropwise. The mixture was stirred at –78°C for 5 min; then *s*-BuLi (7.62 mL of a 1.4 M sol. in cyclohexane, 10.67 mmol) was added dropwise. The mixture was stirred at –78°C for 5 min; then DMF (1.17 mL, 15.24 mmol) was added dropwise. The mixture was allowed to warm to room temperature and stirred for 30 min. Water was added, and the mixture was extracted with EtOAc. The organic phase was washed with water and brine and then was dried over sodium sulfate. The solvent was removed under reduced pressure and the residue purified by chromatography on silica gel using heptane/ethyl acetate (10:1) as the mobile phase. Removal of the solvent furnished 1.8 g (90% yield) of **3** as a pale-yellow oil. IR (neat): 1683, 1592, 1310, 1156, 836, 780 cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 10.48 (s, 1H), 6.53 (s, 2H), 2.57 (s, 6H), 0.99 (s, 9H), 0.24 (s, 6H). ^{13}C-NMR ($CDCl_3$): δ 191.76, 159.60, 144.31, 126.53, 120.99, 25.59, 20.88, 18.23.

Anal. Calcd. for $C_{15}H_{24}O_2Si$: C, 68.13; H, 9.15. Found: C, 68.23; H, 9.05.

2,6-Dimethyl-4-hydroxybenzaldehyde (4).- To a solution of **3** (1.8 g, 6.82 mmol) in 10 mL of THF was added tetra-*n*-butylammoniun fluoride (10.23 mL of a 1 M sol. in THF, 10.23 mmol), and the mixture was stirred at room temperature for 1 h. Water was added, and the mixture was extracted with EtOAc. The organic phase was washed with water and brine and then was dried over sodium sulfate. The solvent was removed under reduced pressure, and the residual solid was recrystallized from CH_2Cl_2 to give 0.9 g (88% yield) of **4** as a pale-yellow solid, mp 190-191°C, *lit.*[7] mp 190-193°C. ^{1}H-NMR (acetone-d6): δ 10.41 (s, 1H), 9.01 (s, 1H), 6.58 (s, 2H), 2.52 (s, 6H).

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