A convenient and efficient synthesis of 2,6-dihydroxynaphthalene

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A convenient synthesis of 2,6-dihydroxynaphthalene from 6-bromo-2-naphthol has been achieved with high overall yield (52%) and good purity (95.7%) based on the conversion of 6-(methoxymethoxy)-2-naphthaldehyde to 6-(methoxymethoxy)-2-naphthol formate by a Baeyer–Villiger oxidation-rearrangement. Compared with the reported methods, the reaction conditions are milder and the work-up of each step is much simpler. Moreover, 6-bromo-2-naphthol as the starting material for the synthesis is readily available.

Keywords: 2,6-dihydroxynaphthalene, Baeyer–Villiger oxidation-rearrangement, 6-bromo-2-naphthol, 6-(methoxymethoxy)-2-naphthaldehyde

2,6-Dihydroxynaphthalene (**1**) is an important fine chemical in organic synthesis and has attracted considerable interest from scientists. It is one of the essential building blocks for 'intelligent' materials such as molecular tubes and liquid crystalline polymers.[1–3] It serves as the starting material for the preparation of several drugs such as the 2-aminotetralins,[4–8] which act as dopaminergic agonists in the treatment of Parkinson's disease.[9] It is also used as the key intermediate in the synthesis of many other naphthalene derivatives.[10,11]

2,6-Dihydroxynaphthalene (**1**) has been prepared by two general methods.[12–17] One was the alkali fusion of sodium 2-naphthol-6-sulfonate or sodium naphthalene-2,6-disulfonate followed by the acidification of the reaction mixture.[12,13] This is not an economically attractive process because of the excessive use of strong alkali and it is accompanied by a low yield and poor purity of the product.[16]

The other method involved the oxidation of the expensive chemical 2,6-diisopropylnaphthalene by oxygen under stringent conditions and the subsequent decomposition of the resultant 2,6-bis(2-hydroperoxy-2-propyl)naphthalene.[14–17] The mixture obtained not only contained the desired 2,6-dihydroxynaphthalene but also the large amount of by-products which were formed in the oxidation and acid decomposition.[16]

The demethylation of 6-methoxy-2-naphthol[18] with butylpyridinium bromide under microwave irradiation and the oxidation of β-naphthol[19] by hydrogen peroxide in the presence of SbF_5–HF have also been reported, but they have not been employed for large-scale preparations. Thus a convenient synthesis of **1** with efficient steps and inexpensive starting materials is desirable.

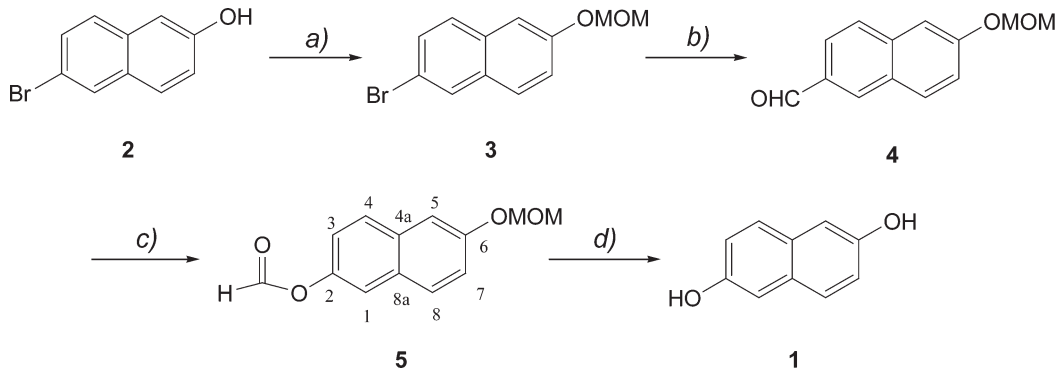
Results and discussion

A convenient synthesis of **1** has been achieved with high overall yield (52%) and good purity (95.7%), (Scheme 1) based on the conversion of 6-(methoxymethoxy)-2-naphthaldehyde (**4**) to 6-(methoxymethoxy)-2-naphthol formate (**5**) by a Baeyer–Villiger oxidation-rearrangement. The synthetic method used 6-bromo-2-naphthol (**2**) as the starting material which was easily prepared from β-naphthol according to Koelsch's method.[20] The phenolic hydroxyl group of **2** was first protected as the methoxymethyl (MOM) ether under mild conditions. Halogen-metal exchange in the presence of n-butyllithium was followed by the addition of DMF to afford the aldehyde **4**.

The Baeyer–Villiger oxidation-rearrangement of **4** was conducted using *m*-chloroperoxybenzoic acid (*m*-CPBA) to give **5** in high yield. The spectroscopic data of **5** were in agreement with the structural change. Upon the oxidation-rearrangement reaction, the strong absorption band of the carbonyl group shifted from 1682 cm^{-1} to 1739 cm^{-1} in IR spectra and the partially positive carbon in this group was shield to an extent of 32 ppm in ^{13}C NMR spectra. These characteristics were ascribed to an increase of the electron density in the C=O bond from the aldehyde **4** to the formate **5**. We devised a series of experiments to find the best ratio of **4** to *m*-CPBA which was 1: 1.3 whilst the optimum reaction temperature was 10 °C. When the reaction temperature was lower than 10 °C, the reaction preceded more slowly. However, an increase in the number of impurities was observed at a much higher temperature. Afterwards **1** was obtained by the acidic hydrolysis of the MOM ether and the formate group with hydrochloric acid as the catalyst in one-pot.

Conclusion

A convenient synthesis of **1** has been achieved with high overall yield (52%) and good purity (95.7%) based on the conversion of the aldehyde **4** to the formate **5** through Baeyer–Villiger oxidation-rearrangement. Compared with the reported methods,[12–17] the reaction conditions are milder and the



Scheme 1 (a) NaH, MOMCl, DMF; 93%. (b) n-BuLi, THF, –78 °C; DMF; 81%. (c) m-CPBA, CH_2Cl_2, 10 °C; 72%. (d) HCl, MeOH–H_2O; 95%.

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work-up of each step is much simpler. Moreover, 6-bromo-2-naphthol (**2**) as the starting material for the synthesis is cheap and easy to obtain.

Experimental

Reagents and solvents were obtained from commercial suppliers. Solvents were dried and purified using standard techniques.[21] Column chromatography was conducted on silica gel (100–200 mesh) from Qingdao Ocean Chemical Factory. 6-Bromo-2-naphthol (**2**) was prepared by Koelsch's method.[20] Melting points were determined on a SGW X-4 micromelting point apparatus. ^{1}H NMR spectra were recorded on a Varian Mercury-300 spectrometer (300 MHz) and ^{13}C NMR spectra were determined on a Bruker Avance 400 spectrometer (400 MHz). Chemical shifts in ^{1}H and ^{13}C spectra were recorded with tetramethylsilane as the internal standard. IR spectra were measured using a ThermoFisher Nicolet-6700 FT-IR spectrometer. HRMS were measured on a Waters Q-TOF Premier mass spectrometer.

The HPLC analysis was performed on an Agilent 1260 liquid chromatograph system (Agilent Technologies), equipped with a diode array detector that recorded the UV spectra in the range of 210–400 nm. Chromatography was carried out using a SUPELCO Discovery® C18 column (150×4.6 mm, 5 mm) at room temperature. The mobile phase consisted of water (**A**) and methanol (**B**) and a gradient elution (20% of **B** at 0–5 min, 20% to 40% of **B** at 5–7 min and 40% of **B** at 7–20 min) was employed. The flow rate was 1.0 mL min^{-1} and the injection volume was 20 μL. The detecting wavelength was set at 254 nm. The Agilent ChemStation for LC&LC/MS systems was used for the data capture and processing.

2-Bromo-6-(methoxymethoxy)naphthalene (**3**): NaH (0.48 g, 12 mmol, 60% dispersion in mineral oil) was added in portions to a solution of **2** (2.23 g, 10 mmol) in dry DMF (16 mL), and the mixture was stirred vigorously for 5 min. Freshly distilled methoxymethyl chloride (MOMCl, 1.05 g, 15 mmol) was added dropwise over 3 min under a nitrogen atmosphere to the mixture which was cooled in an ice-water bath. After the addition, the temperature of the solution was allowed to rise to room temperature and the mixture was stirred for 1 h. After completion of the reaction, the mixture was poured into a saturated $NaHCO_3$ solution (200 mL) at 0 °C. The white precipitate was collected by simple filtration and was carefully washed with cold water (60 mL). The crude product was dried *in vacuo* and purified by column chromatography (petroleum-ether:ethyl acetate, 10:1) to give **3** as white solid. Yield: 2.48 g (93%). m.p. 50–51 °C (lit.[22] 46.8–49.2 °C). ^{1}H NMR (300 MHz, d^6-DMSO): δ 8.12 (s, 1H, H-1), 7.86 (d, *J* = 9.0 Hz, 1H), 7.78 (d, *J* = 8.7 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 1H), 7.47 (s, 1H, H-5), 7.30 (d, *J* = 9.0 Hz, 1H), 5.32 (s, 2H, CH_2O), 3.42 (s, 3H, CH_3O). IR (KBr), ν/cm^{-1}: 1589, 1498, 1253, 1200, 1158, 1079, 1000.

6-(Methoxymethoxy)-2-naphthaldehyde (**4**): A solution of **3** (2.67 g, 10 mmol) in dry THF (30 mL) cooled in an acetone-dry ice bath to –78 °C was treated with n-BuLi (2.4 M in n-hexane, 5.0 mL, 12 mmol). The mixture was stirred at –78 °C for 30 min and dry DMF (3.8 mL) was slowly added at the same temperature. After the addition, the reaction temperature was allowed to rise to 0 °C over 2 h. Then the reaction was quenched with a saturated NH_4Cl solution (30 mL) and the organic layer was separated. The aqueous phase was extracted with ethyl acetate (15 mL×5). The combined organic layer was washed with a saturated NH_4Cl solution (15 mL) and brine, dried over Na_2SO_4 and concentrated. The residue was subject to column chromatography (petroleum-ether:ethyl acetate, 6:1) to afford **4** first as a light-yellow oil, which gradually solidified into a homogeneous white solid upon standing at room temperature. Yield: 1.75 g (81%). The white solid melted from 67 °C to 69 °C and the crystalline sample obtained by the recrystallisation of the solid from n-hexane exhibited a melting point at 70 °C. (lit.[23] 47–52 °C). The spectroscopic data of the white solid was in accordance with the reported values.[24] ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.10 (s, 1H, HCO), 8.25 (s, 1H, H-1), 7.92 (d, 2H, H-3, H-8), 7.81 (d, *J* = 8.4 Hz, 1H, H-4), 7.44 (d, *J* = 2.4 Hz, 1H, H-5), 7.31 (dd, *J* = 2.4, 9.0 Hz, 1H, H-7), 5.33 (s, 2H, CH_2O), 3.53 (s, 3H, CH_3O). ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9 (C=O), 157.5 (quat., C-2), 137.9, 132.5, 128.3 (quat., C-6, C-4a, C-8a), 134.1, 131.1, 128.0, 123.4, 120.0, 109.9 ($C_{Ar}H$, C-1, C-3, C-4, C-5, C-7, C-8), 94.2 (CH_2O), 56.2 (CH_3O). IR (KBr), ν/cm^{-1}: 2962, 2934, 1682 *vs* (C=O), 1625, 1480, 1265, 1172, 1151, 1000.

6-(Methoxymethoxy)-2-naphthol formate (**5**): A solution of **4** (2.16 g, 10 mmol) and m-CPBA (2.64 g, 13 mmol, 85%) in CH_2Cl_2 (30 mL) was stirred rapidly for 2.5 h at 10 °C. Then a solution of sodium dithionite ($Na_2S_2O_4$, 8.70 g, 50 mmol) in water (15 mL) was added. The reaction mixture was stirred for 30 min and poured into a saturated $NaHCO_3$ solution (20 mL) and shaken vigorously. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (10 mL×5). Then the combined organic layer was successively washed with a $Na_2S_2O_4$ solution (8.70 g of $Na_2S_2O_4$ in 30 mL of water) and brine, dried over Na_2SO_4 and concentrated. The crude formate was purified by column chromatography (petroleum-ether:ethyl acetate, 10:1) to give **5** as a white solid. Yield: 1.67 g (72%). m.p. 53–54 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.38 (s, 1H, HCOO), 7.75 (t, 2H, H-4, H-8), 7.54 (s, 1H), 7.42 (s, 1H), 7.24 (m, 2H, H-3, H-7), 5.29 (s, 2H, CH_2O), 3.52 (s, 3H, CH_3O). ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.5 (C=O), 155.1, 146.2, 132.6, 129.4 (quat., C-2, C-6, C-4a, C-8a), 129.0, 128.7, 120.8, 120.0, 118.0, 109.9 ($C_{Ar}H$, C-1, C-3, C-4, C-5, C-7, C-8), 94.5 (CH_2O), 56.1 (CH_3O). IR (KBr), ν/cm^{-1}: 2957, 2925, 1739 *vs* (C=O), 1602, 1509, 1217, 1154, 1126, 995. HRMS: Calcd for $C_{13}H_{11}O_4$ 231.0657; found 231.0661 [M-H]$^-$.

2,6-Dihydroxynaphthalene (**1**): Conc. hydrochloride acid (12 M, 2.1 mL) was added dropwise to a solution of **5** (2.32 g, 10 mmol) in methanol (35 mL), and the colourless solution was stirred at room temperature under a nitrogen atmosphere for 5 h. Then the solvent was evaporated to one-half volume under reduced pressure and water (30 mL) was added. The mixture was extracted with ethyl acetate (15 mL×5). The extract was washed with water, a phosphate buffer (0.23 g of KH_2PO_4 and 0.31 g of K_2HPO_4 in 30 mL of water, pH 7.0) and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was suspended in n-hexane (80 mL) and the mixture was refluxed for 3 min. Then the suspension was cooled to room temperature over about 1.5 h and the light-yellow crystals were collected by simple filtration and washed with n-hexane (10 mL). Yield: 1.52 g (95%). m.p. 212–216 °C. The crystals contained 95.7% of pure **1** based on the HPLC analysis (t_R 9.26 min, the purity was calculated by the area normalisation method) and its spectroscopic characters were consistent with the reported values.[25] ^{1}H NMR (300 MHz, d^6-DMSO): δ 9.29 (s, 2H, D_2O exchangeable, 2 OH), 7.51 (d, *J* = 8.4 Hz, 2H, H-4, H-8), 7.04–6.90 (m, 4H, H-1, H-3, H-5, H-7). IR (KBr), ν/cm^{-1}: 3267 (broad, OH), 1605, 1514, 1420, 1375, 1265, 1224, 1149, 1112, 941. Purified **1** was obtained as white crystals by flash chromatography of the light-yellow crystals on silica gel with petroleum-ether:ethyl acetate (3:1, V/V) as the eluent. m.p. 221–223 °C (lit.[26] 220.5–223 °C).

Its structure was also confirmed by the conversion of it to 2,6-dimethoxynaphthalene, which was prepared by the methylation of **1** with 5.0 equivalent of K_2CO_3 and 2.8 equivalent of CH_3I in dry DMF. m.p. 148–149 °C (lit.[27] 149.5 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (d, *J* = 8.7 Hz, 2H, H-4, H-8), 7.15–7.06 (m, 4H, H-1, H-3, H-5, H-7), 3.89 (s, 6H, 2 CH_3O).

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