SYNTHESIS OF 3,6-DIMETHOXY-2-NAPHTHALDEHYDE

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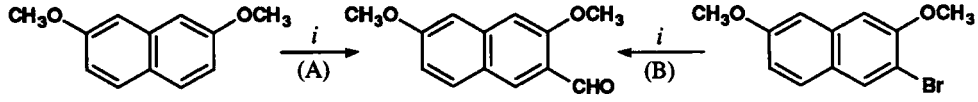
In continuation of our work directed toward the synthesis of new fluorescent thiol reagents[1] and cytosolic calcium indicators based on naphthopyranone fluorophores, we needed large quantities of previously unreported 3,6-dimethoxy-2-naphthaldehyde (**2**). We now describe two methods for the synthesis of **2**.

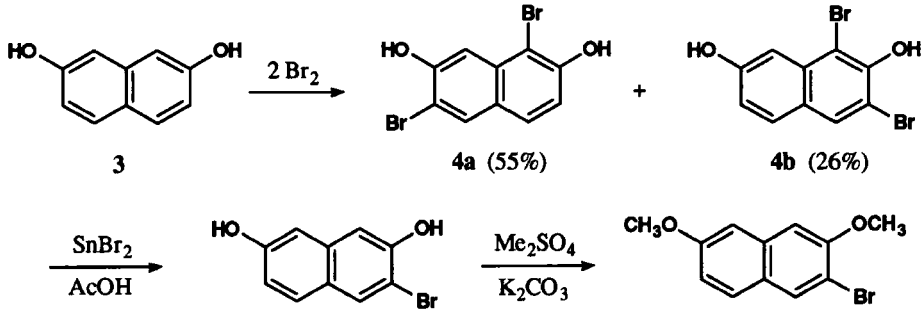
Formylation of 2-alkoxynaphthalenes *via* conventional electrophilic aromatic substitution yields only 1-naphthaldehyde derivatives.[2-4] On the other hand, Narasimhan and Mali[5] reported that the formylation of 2-methoxynaphthalene using *n*-butyllithium and N-methylformanilide affords the 2-naphthaldehyde derivative as the major product. Treatment of 2,7-dimethoxynaphthalene (**1**) with *n*-butyllithium gave a complex which was then reacted with N-methylformanilide to give **2** (10%) and several unidentified by-products (method A). In an alternative approach, the lithium salt was introduced *via* a lithium-bromine exchange with 2-bromo-3,6-dimethoxynaphthalene (**6**); this procedure (method B) gave only the 2-naphthaldehyde product in 62% yield.



1 **2** **6**

i) *n*-BuLi; PhNMeCHO

As compound **6** is not commercially available, we used the method of Ioffe and Fedevora[6] for its preparation. However, in contrast to the claim that treatment of 2,7-dihydroxynaphthalene (**3**) with one mole of bromine gave 2-bromo-3,6-dihydroxynaphthalene (**5**), only the 1-bromo-3,6-dihydroxynaphthalene was obtained (^{1}H NMR). Owen and co-workers[7] reported the synthesis of **5** by reduction



3 **4a** (55%) **4b** (26%)

5 (69%) **6** (78%)

of either the dibromo derivatives **4a** or **4b**. Bromination of **3** in acetic acid gave a ~ 2:1 mixture of **4a** and **4b** in 81% yield. Although the two isomers could be separated by chromatography on silica gel, separation of the two isomers (**4a** and **4b**) was not required since reduction of both isomers gave the same product. Treatment of a mixture of **4a** and **4b** with stannous bromide afforded the same monobromo derivative **5** in 69% yield. Methylation of **5** with dimethyl sulfate gave **6** in 78% yield.

The overall yield of method B was 27%. In addition, the purification of **2** in method B was relatively easy, making it practical for large scale synthesis.

EXPERIMENTAL SECTION

Melting points are uncorrected and were measured on a MEL-TEMP capillary melting point apparatus. IR spectra were recorded on an IBM FT/32 spectrophotometer. ^{1}H NMR spectra were obtained on a Varian XL-300 spectrometer using TMS as an internal standard. Elemental analyses were performed by Atlantic Microlab, Inc. (Norcross, GA).

3,6-Dimethoxy-2-naphthaldehyde (2) from 2,7-Dimethoxynaphthalene (1). Method A.- A solution of 2,7-dimethoxynaphthalene (7.4 g, 0.040 mol) in 80 mL of anhydrous ether was treated with *n*-butyllithium (2.5 M in hexane, 32 mL, 0.080 mol) and the mixture was refluxed for 24 hrs. Freshly distilled N-methylformanilide (10 mL, 0.088 mol) in 17 mL of ether was then added dropwise to the cooled mixture (5°) and reflux was resumed and continued for another 24 hrs. The reaction was worked up by addition of 5% aqueous hydrochloric acid (200 mL). The ethereal layer was separated and the aqueous phase extracted with chloroform. Removal of solvents from the combined organic layers yielded an orange oil. Ether was added to the residual oil and the resulting precipitate was collected. Purification of the crude solid by column chromatography over silica gel (eluted with 40% ether-hexane) afforded 0.83 g (10%) of **2**, mp. 135-136°. IR (KBr): 1676, 1618, 1392, 1226, 1020 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 10.50 (s, 1H, -CHO), 8.22 (s, 1H, H_1), 7.71 (d, 1H, J = 8.0 Hz, H_8), 7.08 (d, 1H, J = 8.0 Hz, H_7), 7.01 (s, 1H, H_4), 6.95 (s, 1H, H_5), 3.98 (s, 3H, -OCH_3), 3.90 (s, 3H, -OCH_3).
Anal. Calcd. for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59. Found: C, 72.11; H, 5.61

Bromination of 2,7-Dihydroxynaphthalene.- A solution of bromine (9.0 g, 0.056 mol) in glacial acetic acid (30 mL) was added to a stirred solution of **3** (5.4 g, 0.028 mol) in glacial acetic acid (90 mL) over a period of 0.5 hr. The reaction mixture was stirred at room temperature for 3 hrs, and at 90° for 0.5 hr, then poured into 250 mL of ice cold water. The precipitated product was collected, washed with water and dried to give a mixture of **4a** and **4b**. Chromatography on silica gel (elution with benzene) gave 4.9 g (55%) of **4a**, mp. 163-164°, lit.[7] 162-163°. IR (KBr): 3437, 1170 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 9.28 (s, 2H, two -OH), 8.09 (s, 1H, H_5), 7.71 (d, 1H, J = 8.1 Hz, H_4), 7.65 (s, 1H, H_8), 7.13 (d, 1H, J = 8.1 Hz, H_3). Continued elution with the same solvent then afforded 2.3 g (26%) of pure (**4b**), mp. 186-187°, lit.[7] 186-187°. IR (KBr): 3470, 1184 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 9.44 (br s, 2H, two -OH), 8.12 (s, 1 H, H_4), 7.76 (d, 1H, J = 8.1 Hz, H_5), 7.44 (d, 1H, J = 2.0 Hz, H_8), 7.08 (dd, 1H, J = 8.1 Hz, J = 2.0 Hz, H_6).

2-Bromo-3,6-dihydroxynaphthalene (5).- A mixture of **4a** and **4b** (4.0 g, 0.012 mol) in glacial acetic

acid (120 mL) was treated with stannous bromide (from 4.0 g, 0.034 mol tin and hydrobromic acid). The reaction mixture was stirred at 110° for 0.5 hr, then poured into ice cold water. The product was extracted with ethyl acetate and washed with aqueous sodium bicarbonate and brine. The ethyl acetate solution was dried over anhydrous magnesium sulfate and then filtered and the solvent was removed. The crude solid was purified by chromatography on silica gel. Elution with benzene containing 2% ethanol gave 2.0 g (69%) of pure **5**, mp. 191-192°, lit.[7] 191-192°. IR (KBr): 3399, 1234 cm^{-1}. ^1H NMR ($CDCl_3$): δ 9.02 (s, 1H, -OH), 8.68 (s, 1H, -OH), 8.01 (s, 1H, H_1), 7.66 (d, 1H, J = 8.1 Hz, H_8), 7.19 (s, 1H, H_4), 7.05 (d, 1H, J = 2.0 Hz, H_5), 6.95 (dd, 1H, J = 8.1 Hz, J = 2.0 Hz, H_7).

2-Bromo-3,6-dimethoxynaphthalene (6).- Solid potassium carbonate (2.2 g, 0.016 mol) and dimethyl sulfate (2.0 g, 0.016 mol) were added to a solution of 2-bromo-3,6-dihydroxy-naphthalene (**5**) (1.9 g, 0.008 mol) in acetone (20 mL). The reaction mixture was refluxed with stirring overnight under a nitrogen atmosphere. Potassium carbonate was removed by filtration and the solvent was evaporated. The oily residue was dissolved in 20 mL of dichloromethane and washed first with 0.05 N sodium hydroxide (8 mL x 2), then with brine (5 mL x 3). The solution was dried over anhydrous magnesium sulfate, filtered and the solvent was removed. The crude product was purified by flash chromatography over silica gel. Elution with a solution of hexane containing 10% ethyl acetate gave 1.6 g (78%) of the desired product **6**, mp. 108-109°, lit.[7] 108-109°. IR (KBr): 1209, 1039 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.98 (s, 1H, H_1), 7.67 (d, 1H, J = 8.0 Hz, H_8), 7.08 (dd, 1H, J = 8.0 Hz, J = 2.0 Hz, H_7), 7.05 (s, 1H, H_4), 7.03 (d, 1H, J = 2.0 Hz, H_5), 3.98 (s, 3H, $-OCH_3$), 3.91 (s, 3H, $-OCH_3$).

3,6-Dimethoxy-2-naphthaldehyde (2) from 2-Bromo-3,6-dimethoxynaphthalene(6), Method B.- To a solution of 2-bromo-3,6-dimethoxynaphthalene (1.5 g, 0.0056 mol) in dried tetrahydrofuran (20 mL), cooled to 0° and stirred under nitrogen atmosphere, was added a solution of *n*-butyllithium (4.8 mL, 0.012 mol, 2.5 M in hexane). After stirring at room temperature for 2 hrs, the solution was cooled to -78° and a solution of N-methyl-formanilide (1.6 g, 0.012 mol) in tetrahydrofuran (5 mL) was added dropwise over a period of 10 min. The reaction mixture was allowed to warm to 0° and then quenched by the dropwise addition of saturated aqueous ammonium chloride solution. The two layers were separated and the aqueous layer was extracted three times with ethyl acetate. The combined organic solution was washed with sodium bicarbonate solution (10 mL x 2) and brine (10 mL x 2), dried, filtered and evaporated. The oily residue was treated with petroleum ether and chloroform to yield a pale yellow solid. Recrystallization from chloroform-petroleum ether gave 0.75 g (62%) of 3,6-dimethoxy-2-naphthaldehyde **2**, mp. 135-136°. The IR and NMR spectra were identical with those recorded for product (**2**) obtained using method A.

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A PRACTICAL PROCEDURE FOR THE SYNTHESIS OF 5-SUBSTITUTED γ-LACTAMS

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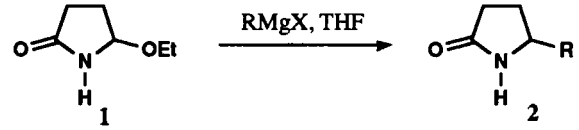
Many 5-substituted γ-lactam derivatives are useful synthons for the preparation of more complex molecules of biological importance.[1] γ-Lactams are generally synthesized using the intramolecular cyclization of the corresponding γ-amino acids,[2] and by the lactamization of γ,δ-unsaturated imidates.[3] These methods are often not practical since the γ-amino acid and γ,δ-unsaturated imidate precursors, in most cases, are not readily available. Other alternative procedures have also been reported,[4] but most of these methodologies frequently provide low yields or require multiple-step reaction sequences. α-Amidoalkylation at carbon has been shown to have great synthetic potential.[5] In this regard, the α-amidoalkylation of organometallic compounds has attracted significant attention since this C-C bond formation reaction has been used for the synthesis of 4-substituted β-lactams.[6] This communication describes an efficient utilization of this methodology for the general preparation of 5-substituted γ-lactams.

Thus, treatment of 5-ethoxy-2-pyrrolidinone (**1**)[7] with three equivalents of phenylmagnesium bromide afforded the 5-substituted γ-lactam (**2a**) in 78% yield. Since other Grignard reagents can be employed, as illustrated in the reaction scheme shown below, this versatile methodology is suitable for the synthesis of a variety of 5-substituted γ-lactams.



1 **2**

a) R = Ph (78%) b) R = CH_2=CH– (65%) c) R = *i*-Bu (74%)