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PREPARATION OF 2,4-DIHYDROXYBENZALDEHYDE BY THE VILSMEIER-HAACK REACTION

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Abstract: An efficient synthesis of 2,4-dihydroxybenzaldehyde (**1**) from resorcinol via the Vilsmeier-Haack reaction has been developed. Either phosphorous oxychloride/DMF or oxalyl chloride/DMF produces **1** in yields of 65-75%. The intermediate formamidinium salts have been characterized.

We recently required a cost-effective preparation of 2,4-dihydroxybenzaldehylde (resorcylaldehyde) from resorcinol which would provide multi-kilogram quantities without the use of hazardous reagents or solvents. Although the Gatterman reaction is regarded as the accepted method for the preparation of **1**, we did not wish to handle large amounts of liquid hydrogen cyanide or zinc cyanide and ether.[1] Gross[2] reported the preparation of **1** as well as other aryl aldehydes using triethyl orthoformate or dichloromethyl methyl ether in combination with Lewis acids to formylate numerous activated aromatic substrates. This appeared to be an attractive, cost-effective approach.[3] In our hands we were consistently able to obtain the author's yields for crude 2,4 dihydroxybenzaldehyde from resorcinol using triethyl orthoformate/aluminum

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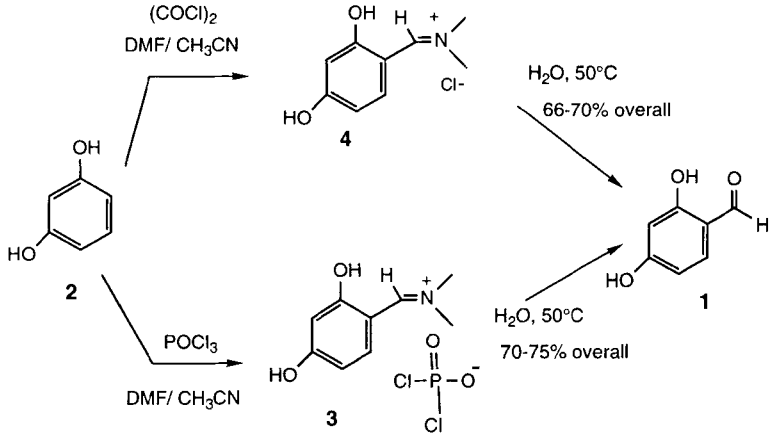
trichloride, but we were unable to remove a red contaminant without considerable loss of material.

We next turned our attention to the Vilsmeier-Haack aldehyde synthesis.[4] In an early report, Nenitzescu formylated resorcinol in ether solution with oxalyl chloride-formamide and produced **1** via a crystalline intermediate in unspecified yield.[5] Recently Downie and Heaney[6] used pyrophosphoryl chloride and DMF to efficiently formylate resorcinol as well as many heterocyclic systems. However, because of the expense and unavailability of pyrophosphoryl chloride for large scale work, we decided to reinvestigate the classical Vilsmeier-Haack formylation with the use of readily available activating agents phosphoryl chloride and oxalyl chloride. We now wish to report that by carrying out the Vilsmeier formylation of resorcinol with either phosphorous oxychloride/DMF or oxalyl chloride/DMF in acetonitrile and working below room temperature, resorcinol could be converted to **1** in high yield and with excellent product purity.



In our first example, the Vilsmeier reagent was prepared by the addition of $POCl_3$ (1.15 mole) in acetonitrile to DMF (1.35 mole) in acetonitrile at room

temperature. The reaction was then cooled to -15 °C, resorcinol (1 mole) in acetonitrile was added, and after 2 h at -15 °C the reaction was warmed to 28-30°C. The crystalline Vilsmeier-formamidinium phosphorodichloridate salt[6] was isolated by filtration, in a high state of purity in 75-80% yield. Isolation of this intermediate salt **3** by filtration provided a simple means of purification useful in application to large scale work. The salt was stable for several weeks in the dark at -10 °C, but it acquired a pink color on standing in the laboratory at ambient temperature for 2-3 days. Formamidinium salts were recently reported as useful intermediates for the preparation of 5-*tert*-butyl-pyrrole-2-aldehyde by the Vilsmeier reaction.[7]

The intermediate salt was readily converted to aldehyde **1** by hydrolysis with water at 50 °C. The desired aldehyde was isolated by precipitation directly from the aqueous solution as a single component in 70-75% overall yield. The progress of hydrolysis could also be followed in an NMR tube by adding D_2O to a sample of **3** in DMSO-$_{d6}$.

Similar results were obtained with the use of the Vilsmeier reagent prepared from the oxalyl chloride and DMF. In this case the Vilsmeier reagent, $[H(Cl)C=N(CH_3)_2]^+ Cl^-$, precipitates from acetonitrile as a thick solid, and higher dilution reactions were required to achieve efficient stirring. The Vismeier reagent subsequently dissolved upon addition of resorcinol at -15 °C, and the formamidinium chloride salt **4** precipitates from the reaction. This salt was converted to 2,4-dihydroxybenzaldehyde on crystallization from warm water in an overall yield of 69-70% from resorcinol. The employment of acetonitrile and low temperatures during the Vilsmeier coupling were important requirements in these efficient preparations of **1**.

EXPERIMENTAL

Oxalyl chloride (98%) and phosphorous oxychloride (99%) were obtained from Aldrich Chemical Co. and used without further purification. HPLC grade Baker Analyzed acetonitrile and Burdick & Jackson DMF were used as received. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d6 (unless otherwise indicated) on a Bruker AM-300 or a Bruker AR 360 spectrometer with TMS as the internal standard. Analytical HPLC (reverse phase) was carried out by dissolving about 0.05 ml of the reaction mixture in 50 ml of mobile phase and warming to 45 °C for 5 min and then sonicating for 3 min. This treatment totally converts salts **3** or **4** to the corresponding aldehyde (**1**). HPLC Conditions: Column: Bakerbond, 25 cm x 4.6 mm i.d.; Solvent: acetonitrile: water: TFA 20:80:0.1; Flow rate: 0.8 mL/min, uv detection at 275 nm.

General Procedure

Method A. Vilsmeier-Haack reaction with phosphorus oxychloride-DMF:

A 1-L 3 neck flask equipped with a temperature thermocouple and an overhead stirrer was charged with DMF (49.3 g, 0.675 mole) and acetonitrile (150 mL). The reaction was treated with $POCl_3$ (88.16 g, 0.575 mole) in acetonitrile dropwise over 20 min so that the temperature was maintained at 22-28 °C with a water bath. The reaction was stirred at ambient temperature for 1 h to insure complete conversion to the Vilsmeier reagent. The solution remains clear throughout. The reaction was cooled in a dry-ice bath to -14 to -17°C and a solution of resorcinol (55.06 g, 0.5 mole) in acetonitrile (150 mL) was slowly added to maintain -10 to -17 °C during the addition. Precipitation of the Vilsmeier-formamidinium phosphorodichloridate **3**, occurs during this addition. The reaction was stirred for an additional 2 h at -15 ± 2 ° C and then at 28-32 °C

for 1 h. The HPLC of the reaction solution indicated the presence of < 5% of the starting material. (A small amount of an unknown with similar retention time to **1** was present.) The reaction was cooled to 5 °C and after stirring for 1 h the product was isolated by filtration and rinsed with cold acetonitrile. The product was dried at 30 °C at 10 mm of Hg to constant weight. The light yellow solid, 123 g, mp 158-159 °C; HPLC wt/wt assay of 98.3% was best done by hydrolysis in the HPLC mobile phase to compound **1**. The corrected yield of the salt was 80%. The product could be stored in the dark at 5 °C for several weeks without significant coloration. FT-IR (KBr) (cm^{-1}) 3421, 3300-2350 (O-H, C-H, P-OH stretch), 1654 and 1642 (C=N stretch), 1617, 1582, 1473, 1346, 1323, 1311, 1262 and 1187 (P=O stretch, free/bonded, and C-O stretch), 1109 and 1077 (P-O-C stretch), 868, 834, 791, 541 and 494 (P-Cl vibrations); ^{1}H NMR (DMSO-$_{d6}$) δ 11.3-11.5 (br, 2 H, O-**H**) (may appear as 2 discrete signals depending upon sample concentration), 8.81 (s, 1 H, C**H**=N), 7.67 (d, 1 H, J = 9.07 Hz), 6.71 (d, 1 H, J = 2.22 Hz), 6.52 (dd, 1 H, J=9.03 and 2.22 Hz), 3.69 (s, 3 H, C=N-C**H$_3$**), 3.58 (s, 3 H, C=N-C**H$_3$**); ^{13}C NMR (DMSO-$_{d6}$) δ 167.0, 164.2, 163.7, 133.1, 109.5, 106.4, 102.4, 50.2, 43.3.

Hydrolysis of **3**. To water (680 mL) stirred at 40 °C was added the above salt **3** (122.6 g) in three portions. The reaction was heated to 52 °C for 0.5 h, and then cooled. When the temperature had reached 35 °C, sodium thiosulfate solution (0.09 M, 1-2 mL) was added to discharge the pink coloration. The reaction was cooled to 5 °C, and stirred for 2 h. The mixture was filtered, the solid was washed with cold water, and air dried for two hours. Vacuum drying at 30 °C at 0.05 mm of Hg yielded an off-white solid, 53.1g, mp 134-136 °C (Lit. 134-135 °C).[5]

^{1}H NMR ($CDCl_3$) δ 11.41 (s, 1H, O-**H**; hydrogen bonded), 9.70 (s, 1H, O=C-**H**),

7.42 (d, 1H, 6.47; **A**BX, J_{AB} = 8.5 Hz), 6.47 (dd, 1H, A**B**X; J_{BA} = 8.5 Hz, J_{BX} = 2.3 Hz), 6.373 (d, 1H, AB**X**; J_{BX} = 2.3 Hz), 5.7 (br.s, 1H, O-**H**); ^{13}C NMR ($CDCl_3$) δ 194.5, 164.4, 163.3 136.1, 115.6 108.6, 103.2. Analysis: Calc'd for $C_7H_6O_3$: C, 60.87; H, 4.38. Found: C, 60.34; H, 4.18.

Method B. Vilsmeier-Haack Reaction with Oxalyl Chloride:

A 1-L 3 neck flask equipped with a temperature thermocouple and an efficient overhead stirrer was charged with DMF (46.37 g, 0.63 mole) and acetonitrile (350 mL). The reaction was treated dropwise with a solution of oxalyl chloride (66.12 g, 0.521 mole) in acetonitrile over 20 min such that the temperature was maintained at 20-26 °C with a water bath. Gas evolution was noted and a thick precipitate formed. The reaction was stirred at ambient temperature for 1 h to ensure complete conversion to the Vilsmeier reagent. The reaction was cooled in a Dry-Ice bath to -14 to -17°C and a solution of resorcinol (26.87 g, 0.244 mole) in acetonitrile (75 mL) was added over 20 min. The Vilsmeier reagent dissolved as the reaction with resorcinol occurred, and soon afterward the precipitation of the chloride salt **4** began. The reaction was stirred at -15 °C for 35 min, then at 28-32 °C for 2 h. The HPLC analysis of the reaction solution showed < 6% of the starting material. A small amount (3-4% by area) of the same unknown component seen in Method A (similar retention time to **1**) was observed. After cooling to 3-5 °C for 2 h, the mixture was filtered and the solid was washed with cold acetonitrile (70 mL). The solid was washed with hexane (30-40 mL) and the product dried. The Vilsmeier-formamidinium chloride was dried at 30-35 °C at 0.05 mm of Hg for 24 h. The recovery was 42.3 g; the yield corrected for purity was 79%; it was a single component by HPLC; mp 170-173 °C. FT-IR (KBr) (cm^{-1}) 3414 (O-H stretch), 3000-3100, 2576, 1644/1615/1584/1472 (C=N

stretch), 1356, 1317 1242, 1217, 1146, 980, 882, 749, 721, 646, 492. The carbon and proton NMR of the chloride were the same as the spectra of the phosphorodichloridate salt prepared above.

Analysis: Calc'd for $C_9H_{12}ClNO_2$: C, 53.61; H, 6.00; Cl, 17.58; N, 6.95. Found: C, 53.38; H, 6.02; Cl, 17.54; N, 6.80.

Hydrolysis of **4**. The above salt **4** (42.3 g, 0.209 mole) was hydrolyzed in water (250 mL) at 50 °C as described above for **3**. After filtration, the product was dried at <35 °C for 24 h giving **1** (24.4 g, wt/wt assay by HPLC 97%; corrected yield: 69% from **2**). The melting point, as well as the proton and carbon NMR of this product were identical to that of the product produced by the $POCl_3$-DMF sequence.

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