

Regioselective Synthesis of 5-halo-2-Hydroxybenzaldehyde Derivatives by Green Chemistry Approach

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Abstract: Ecofriendly regioselective and high yielding 5-halo salicylaldehyde derivatives has been synthesized using NaCl, KBr, KI and green reagent H₂O₂ at room temperature in an aq. ethanol solvent. This method avoids the use of hazardous chemicals like Cl₂, Br₂, I₂, CHCl₃, CCl₄. Excellent yields (85%) were obtained for synthesized compounds, and they were isolated by simple vacuum filtration without utilizing the energy, chemical and solvent effective chromatographic separations methods. Confirmation of structure and isomeric purity were validated with the help of M.P., FT-IR, and H¹-NMR spectroscopy.

Keywords: Green, regioselective halo substituted, salicylaldehyde, oxidative

I. INTRODUCTION

Salicylaldehyde and their derivatives particularly their halo substituted derivatives, are important scaffolds in coordination chemistry, materials and inorganic chemistry, and pharmaceuticals. In 5-halo substituted salicylaldehyde halogen atom present para to the phenolic hydroxyl group which give electronic and steric significance to the ring system and attributes chelation of subsequent Schiff base ligands and their transition metal complexes having significant pharmaceutical properties.

Generally, in the synthesis of 5-halo-2-hydroxybenzaldehyde by electrophilic aromatic substitution there is utilization of highly toxic, hazardous, volatile chemicals and solvents such as liquid bromine, chlorine gas, carbon tetrachloride, dichloromethane was takes place. While in Direct formylation methods by various reactions gives low yields and regioselectivity with hazardous chemical wastes.

The present study applies the principles of green chemistry which replaces this protocol with eco-friendly synthetic method which is give active electrophilic halogen species by simple, cost-effective and safe method in situ.

II. EXPERIMENTAL

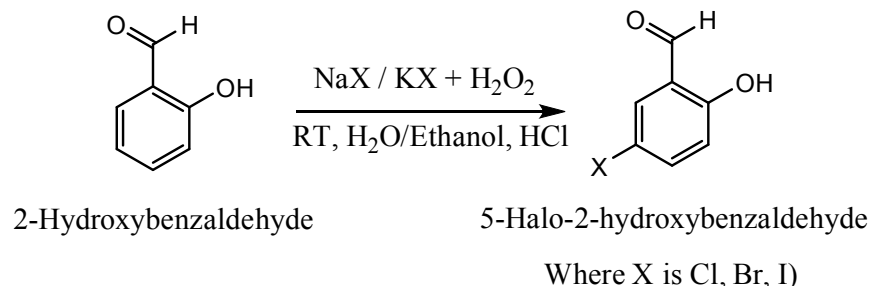
Materials and Instrumentation: All Chemicals, solvents and reagents of high purity were used from commercial chemical suppliers from Thomas Baker, Loba Chemicals, Sigma and Aldrich chemicals and used without further purification, such as 2-hydroxybenzaldehyde, potassium bromide, sodium chloride, potassium iodide, hydrogen peroxide.

Melting points were recorded on a simple capillary tube method and are uncorrected. Fourier-Transform Infrared (FT-IR) spectra were recorded on a spectrometer using KBr pellets on a Perkin Elmer System 2000., H¹-NMR and ¹³C-NMR spectra were acquired on a on a Bruker Avance NEO500 spectrometer at 500 MHz.

Green Synthesis Procedure for the Synthesis of 5-Halo-2-hydroxybenzaldehyde Derivatives: In a 100 mL RBF a mixture of a 10 mL absolute ethanol and 10 mL distilled water with 2-hydroxybenzaldehyde (1.22 g, 10.0 mmol, 1.0 equiv.) was added with corresponding alkali halide salt (1.1 equiv, 11 mmol). Further addition of aq. HCl (2.5 mL, 2.0 M) to the mixture for acidification and Hydrogen peroxide (30%, 1.25 mL, 12 mmol, 1.2 equiv.) was added dropwise



over 10 min at room temperature. The reaction mixture was allowed to be stirred vigorously at room temperature and monitored by TLC (hexane: ethyl acetate, 8:2 v/v). After 2–3 h completion, the reaction mixture was cooled in an ice-water bath for 15 min. The resulting solid precipitate was isolated by vacuum filtration via a Büchner funnel, washed with ice-cold distilled and dried. The crude product was purified by recrystallisation from hot ethanol.



III. RESULTS AND DISCUSSION

Spectroscopic and Physical Characterization:

A. 5-Chloro-2-hydroxybenzaldehyde: Synthesized by green approach using sodium chloride (0.64 g, 11.0 mmol). Reaction time: 3.0 h. Yield: 1.15 g (80%); white needles; mp 101 °C (lit. 99–101 °C); FTIR (KBr, cm⁻¹): 3140 (O–H), 2850, 2760 (C–H, aldehyde), 1665 (C=O), 1590, 1470 (C=C, aromatic), 710 (C–Cl); ¹H-NMR (500 MHz, DMSO, δ/ppm): 10.90 (s, 1H, OH), 9.80 (s, 1H, CHO), 7.50 (d, J = 2.4 Hz), 1H, Ar–H), 7.45 (dd, J = 8.8, 2.4 Hz), 1H, Ar–H), 6.95 (d, J = 8.8 Hz), 1H, Ar–H); ¹³C-NMR (500 MHz, DMSO, δ/ppm): 193.4, 159.2, 135.9, 133.1, 124.1, 120.2, 118.8.

B. 5-Bromo-2-hydroxybenzaldehyde: Synthesized by green approach procedure using potassium bromide (1.31 g, 11.0 mmol). Reaction time: 2.5 h. Yield: 1.65 g (85%); off-white crystalline powder; mp 103 °C (lit. 104–106 °C); FTIR (KBr, cm⁻¹): 3145 (O–H), 2846, 2756 (C–H, aldehyde), 1660 (C=O), 1585, 1466 (C=C, aromatic), 627 (C–Br); ¹H-NMR (500 MHz, DMSO, δ/ppm): 11.00 (s, 1H, OH), 9.82 (s, 1H, CHO), 7.60 (d, J = 2.5Hz), 1H, Ar–H), 7.55 (dd, J = 8.8, 2.5Hz), 1H, Ar–H), 6.96 (d, J = 8.8 Hz), 1H, Ar–H); ¹³C-NMR (500 MHz, DMSO, δ/ppm): 194.3, 161.6, 140.8, 138.1, 120.6, 122.2, 114.4.

C. 5-Iodo-2-hydroxybenzaldehyde: Synthesized by green approach procedure using potassium iodide (1.83 g, 11.0 mmol). Reaction time: 1.9h. Yield: 2.10 g (88%); light yellow powder; mp 100°C (lit. 109–111 °C); FTIR (KBr, cm⁻¹): 3160 (O–H), 2846, 2752 (C–H, aldehyde), 1669 (C=O), 1588, 1468 (C=C, aromatic), 590 (C–I); ¹H-NMR (500 MHz, DMSO, δ/ppm): 11.10 (s, 1H, OH), 9.83 (s, 1H, CHO), 7.80 (d, J = 2.1 Hz), 1H, Ar–H), 7.75 (dd, J = 8.6, 2.1 Hz), 1H, Ar–H), 6.85 (d, J = 8.6 Hz), 1H, Ar–H); ¹³C-NMR (500 MHz, DMSO, δ/ppm): 195.7, 164.2, 144.4, 142.2, 124.1, 125.7, 810.

The oxidative protocol shows high chemical conversions and regioselectivity. The generated halogen electrophiles acquired 5-position due to the directing forces of the highly activating -OH group which is para-directing and meta-directing -CHO group.

The FT-IR spectroscopy confirmed aldehydic compound with broad spectrum of intramolecular hydrogen-bonded phenolic hydroxyl (O-H) having stretching frequency 3140–3160 cm⁻¹. The characteristic carbonyl (C=O) stretching at 1660–1669 cm⁻¹, indicating inductive electron-withdrawing nature of substituted halogen atom. In fingerprint region, distinct carbon-halogen stretching frequencies observed such as C-Cl (710 cm⁻¹) C-Br (627 cm⁻¹), C-I (590 cm⁻¹). ¹H-NMR spectra give information about regioselective substitution at the C-5 position. During reaction multi-halogenated structural isomers are not formed. Which is confirmed by absence of additional aromatic splitting configurations.



IV. CONCLUSION

Synthesis of 5-halo-2-hydroxybenzaldehyde derivatives give highly efficient, and regioselective oxidative synthesis by green approach on a 10 mmol laboratory scale. In this method, water and ethanol as a solvent and utilize non-hazardous alkali halide salts while hydrogen peroxide act as wasteless oxidant. This green approach gives pure, sharp-melting crystalline compounds with high yields instead using any chemical, column chromatography techniques for extraction of compounds followed by clean spectroscopic techniques serves as an excellent, sustainable methods for synthesis of halogenated scaffolds in coordination chemistry as well as in synthetic chemistry.

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