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OPTIMIZATION OF THE SYNTHESIS OF 3-FORMYL-4-HYDROXYBENZOIC ACID: A HIGH-YIELD PROTOCOL FOR A KEY BIOACTIVE BUILDING BLOCK

Vusala YUSIFLI^{1,2*}, Ali MURADOV², Mustafa SHARIFOV³, Elnar MAMMADOV^{1,3}¹Istanbul University, Faculty of Science, Department of Chemistry, Vezneciler, Fatih, İstanbul, Türkiye²Azerbaijan University of Technology, Department of Chemical and Metallurgical Engineering, Ganja, Azerbaijan³Baku Engineering University, Department of Chemical Engineering, Khirdalan city, Absheron, Azerbaijan

ARTICLE INFO	ABSTRACT
Article history: Received:2025-09-23 Received in revised form:2025-10-11 Accepted:2025-11-15 Available online: 2026-06-26	3-Formyl-4-hydroxybenzoic acid is an important aldehyde precursor widely used in the synthesis of biologically active thiosemicarbazone ligands and transition metal complexes. In this study, an optimized and cost-effective synthetic route for 3-formyl-4-hydroxybenzoic acid was developed using a modified Duff reaction. The reaction conditions, reagent ratios, and hydrolysis parameters were systematically optimized to improve reproducibility while minimizing raw material consumption. The target compound was obtained in 38% yield using significantly lower quantities of starting materials compared to previously reported methods. The synthesized compound was comprehensively characterized by FTIR, ¹ H NMR, and ¹³ C NMR spectroscopy. The developed protocol provides an economical and practical approach for obtaining high-purity aldehyde precursors suitable for further applications in coordination chemistry and anticancer metallodrug development.
Keywords: Duff reaction; thiosemicarbazone; aldehyde synthesis; bioactive ligands; anticancer agents	

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1. INTRODUCTION

Cancer remains one of the most serious global health problems in modern medicine. According to the GLOBOCAN 2022 report, approximately 20 million new cancer cases and 9.7 million cancer-related deaths were recorded worldwide within a single year [1]. The severe side effects and limited selectivity associated with conventional chemotherapeutic agents have accelerated research toward transition metal complexes as alternative anticancer agents with improved biological activity and selectivity [2].

Among the various ligand systems investigated in medicinal inorganic chemistry, thiosemicarbazones (TSCs) have attracted considerable attention due to their broad spectrum of biological activities, including antiviral, antibacterial, antifungal, and particularly antitumor properties [3-5].

The biological performance of TSC-based metal complexes is strongly dependent on the structural and electronic characteristics of the ligand framework. Therefore, the efficient synthesis of functionalized aldehyde precursors plays a crucial role in the development of next-generation metallodrugs [6-8].

In this context, 3-formyl-4-hydroxybenzoic acid represents a strategically important precursor for the preparation of water-soluble thiosemicarbazone ligands. The presence of the carboxylic acid functionality enhances water solubility and bioavailability, which are critical parameters in drug design. However, literature reports reveal substantial inconsistencies regarding the synthesis of this compound. Some methods provide relatively low yields of approximately 19% [9], whereas other protocols reporting yields near 40% require large-scale reagent consumption and complicated purification procedures [10]. Such limitations reduce the practical applicability and scalability of the synthesis.

Additionally, the high commercial price of 3-formyl-4-hydroxybenzoic acid significantly limits its accessibility for many research laboratories. Consequently, the development of an economical, reproducible, and efficient synthetic route remains highly desirable.

The primary objective of the present study was to optimize the synthesis of 3-formyl-4-hydroxybenzoic acid through a modified Duff reaction by carefully adjusting reaction parameters and reagent ratios. The developed method successfully afforded the target aldehyde in a reproducible 38% yield using substantially lower amounts of starting materials. The synthesized compound was thoroughly characterized using FTIR, ^1H NMR, and ^{13}C NMR spectroscopy. This optimized protocol establishes a practical foundation for the future synthesis of biologically active thiosemicarbazone-metal complexes.

2. MATERIALS AND EXPERIMENTAL METHODS

2.1. Materials

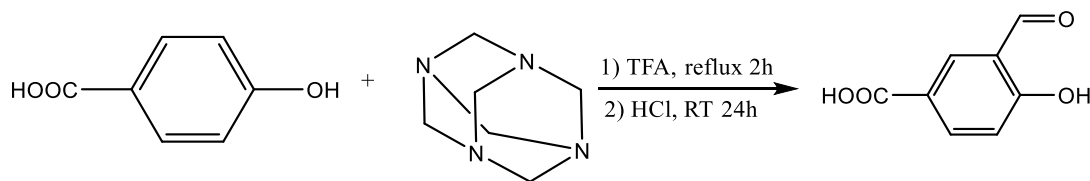
All chemicals and solvents were obtained from commercial suppliers and used without further purification unless otherwise specified. 4-Hydroxybenzoic acid, hexamethylenetetramine, trifluoroacetic acid (TFA), hydrochloric acid, sodium sulfate, and organic solvents were purchased from Sigma-Aldrich and Merck.

2.2. Synthesis of 3-formyl-4-hydroxybenzoic acid

The synthesis of 3-formyl-4-hydroxybenzoic acid was carried out using a modified Duff reaction (Scheme 1). In a typical experiment, 4-hydroxybenzoic acid (0.75 g, 5.43 mmol) was suspended in 2.5 mL of trifluoroacetic acid (TFA). This suspension was added dropwise to a solution of hexamethylenetetramine (0.78 g, 5.5 mmol) dissolved in TFA under continuous stirring.

The reaction mixture was refluxed for 2 h under a nitrogen atmosphere to minimize oxidative side reactions. After completion of the reaction, the mixture was cooled to room temperature and hydrolyzed using 75 mL of 4 M hydrochloric acid under vigorous stirring for 3 h.

The resulting yellow precipitate was filtered, washed thoroughly with cold distilled water, and dried. The crude product was dissolved in diethyl ether and extracted. The organic phase was dried over anhydrous sodium sulfate (Na_2SO_4), and the solvent was removed under reduced pressure. The target compound was obtained as a yellow crystalline powder (0.35 g, 38% yield, m.p. 247.3–249.1 °C).



Scheme 1. Synthesis of 3-Formyl-4-hydroxybenzoic acid.

3. RESULTS AND DISCUSSION

3.1. Synthesis and Process Optimization

In this study, 3-formyl-4-hydroxybenzoic acid was successfully synthesized using an optimized Duff reaction protocol. Previous literature reports demonstrated significant variability in reaction yields. Sardroud et al. reported yields of approximately 19% for structurally related aldehydes, whereas Irfan et al. achieved higher yields using substantially larger quantities of starting materials and more labor-intensive purification procedures.

The major achievement of the present work lies in the optimization of reagent ratios, reaction atmosphere, and hydrolysis conditions, enabling a reproducible yield of 38% while minimizing reagent consumption. The use of a nitrogen atmosphere effectively reduced possible oxidative side reactions, whereas controlled hydrolysis conditions improved product formation and isolation.

The developed method offers several advantages, including lower material consumption, simplified work-up procedures, improved reproducibility, and reduced overall synthesis cost. These improvements make the proposed protocol particularly suitable for future applications involving ligand synthesis and coordination chemistry.

Table 1. Comparison of synthetic parameters and yields for 3-formyl-4-hydroxybenzoic acid.

Method / Reference	Starting Material (Amount)	Reaction Conditions	Yield (%)	Observations / Limitations
Sardroud et al. (2020)	4-Hydroxybenzoic acid (22 mmol, 3.0 g)	Modified Duff Reaction / Argon	~19%	Reported significant yield inconsistencies and lower efficiency for the target aldehyde.
Irfan et al. (2016)	4-Hydroxybenzoic acid (108 mmol, 15 g)	Duff Reaction / High reagent volume	~40%	Achieved slightly higher yields but required substantially larger quantities of reagents.
This Work (Optimized)	4-Hydroxybenzoic acid (5.43 mmol, 0.75 g)	Modified Duff / N ₂ atm / Controlled hydrolysis	38%	Highly reproducible; minimized raw material consumption; cost-effective alternative to commercial sources.

3.2. Spectroscopic Characterization

The synthesized compound was structurally characterized using FTIR, ¹H NMR, and ¹³C NMR spectroscopy.

FTIR Analysis

In the FTIR spectrum, the strong absorption band observed at approximately 1672 cm⁻¹ was assigned to the aldehyde carbonyl (C=O) stretching vibration, while a distinct peak near 1700 cm⁻¹ confirmed the presence of the carboxylic acid C=O group. A broad and intense absorption

band centered in the 3300–2500 cm^{-1} region corresponded to the characteristic O-H stretching of the carboxylic acid, overlapping with the phenol O-H stretch observed around 3200 cm^{-1} . This broadness indicates extensive intermolecular hydrogen bonding within the structure.

Additionally, the aldehyde group was further confirmed by the characteristic C-H stretching vibrations appearing at 2850 cm^{-1} and 2750 cm^{-1} . The skeletal vibrations of the aromatic ring were clearly identified by the multiple C=C stretching bands located at approximately 1600, 1500, and 1450 cm^{-1} , supporting the presence of the aromatic framework in the synthesized compound.

FTIR (ATR) ν (cm^{-1}): 3300-2500 (O-H), 3200 (O-H), 2850-2750 (C-H_{ald}), 1700 (C=O_{acid}), 1680 (C=O_{ald}), 1600, 1500, 1450 (C=C_{ar}).

¹H NMR Analysis

The ¹H NMR spectrum (400 MHz, DMSO-d₆) provided clear confirmation of the target structure. The characteristic aldehyde proton appeared as a sharp singlet at δ 10.29 ppm. The hydroxyl and carboxylic acid proton signals were observed as a broad singlet at δ 11.52 ppm.

The aromatic region displayed three characteristic proton signals consistent with the substitution pattern of the aromatic ring. A doublet at δ 8.23 ppm (J = 2.3 Hz, 1H) was assigned to the proton at the C-2 position. A doublet of doublets at δ 8.03 ppm (J_1 = 8.7 Hz, J_2 = 2.3 Hz, 1H) corresponded to the C-6 proton, while the doublet at δ 7.07 ppm (J = 8.7 Hz, 1H) was attributed to the C-5 proton.

¹H NMR (400 MHz, DMSO-d₆): δ 11.52 (s, 1H), 10.29 (s, 1H), 8.23 (d, J = 2.3 Hz, 1H), 8.03 (dd, J = 8.7, 2.3 Hz, 1H), 7.07 (d, J = 8.7 Hz, 1H) ppm.

¹³C NMR Analysis

The ¹³C NMR spectrum (100 MHz, DMSO-d₆) further confirmed the molecular structure. Signals observed at δ 195.53 ppm and δ 169.21 ppm were assigned to the aldehyde and carboxylic acid carbonyl carbons, respectively. The resonance at δ 164.81 ppm corresponded to the aromatic carbon attached to the hydroxyl substituent.

Additional aromatic carbon signals were observed in the range of δ 123.75–135.56 ppm, consistent with the expected aromatic framework of the synthesized compound.

¹³C NMR (100 MHz, DMSO-d₆): δ 195.53, 169.21, 164.81, 135.56, 133.20, 123.80, 123.75 ppm.

3.3. Potential Applications in Anticancer Metal Complexes

The synthesized aldehyde precursor is highly suitable for the preparation of biologically active thiosemicarbazone ligands and transition metal complexes. The presence of the carboxylic acid group is expected to improve the water solubility and bioavailability of the resulting metal complexes.

Previous studies have demonstrated that water-soluble thiosemicarbazone-metal complexes exhibit enhanced biological activity and improved pharmacological properties. Therefore, the optimized synthetic protocol developed in this work provides a valuable foundation for future studies involving Cu(II), Ni(II), and Zn(II)-based anticancer complexes.

4. CONCLUSION

In the present study, an optimized and cost-effective synthetic route for 3-formyl-4-hydroxybenzoic acid was successfully developed using a modified Duff reaction. The optimization of reaction conditions, reagent ratios, and hydrolysis parameters enabled the reproducible synthesis of the target compound in 38% yield while significantly reducing raw material consumption compared to previously reported methods.

The synthesized aldehyde was thoroughly characterized by FTIR, ^1H NMR, and ^{13}C NMR spectroscopy, confirming the successful formation of the desired structure. The obtained spectroscopic data were consistent with the proposed molecular structure and demonstrated the presence of the aldehyde, hydroxyl, and carboxylic acid functional groups.

The developed protocol provides several practical advantages, including lower synthesis cost, simplified purification, improved reproducibility, and reduced chemical waste generation. These improvements make the method suitable for future laboratory-scale and preparative applications.

Moreover, the synthesized compound represents an important precursor for the preparation of biologically active thiosemicarbazone ligands and transition metal complexes with potential anticancer activity. Therefore, the present work establishes a useful and accessible synthetic foundation for future studies in medicinal inorganic chemistry and metallodrug development.

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