

Heterocyclic Aldehydes Based on Thieno[3,2-*b*]thiophene Core: Synthesis and Preliminary Studies as Ion Optical Chemosensors [†]

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Abstract: Heterocyclic aldehydes show a variety of optical properties and the versatility of their reactivity allows them to yield a wide range of more complex compounds, with application in areas such as medicinal, materials and supramolecular chemistry. The biological and environmental relevance of certain molecules and ions turns them into targets for the design of molecular recognition systems. Recently, heterocyclic aldehydes have been reported in the literature as ion chemosensors. Following the group's work on optical chemosensors, for the detection and quantification of ions and molecules with environmental and medicinal relevance, this work reports the synthesis and characterization of two heterocyclic aldehydes based on the thieno[3,2-*b*]thiophene core, by Suzuki coupling, as well as the synthesis of the corresponding precursors. Preliminary chemosensory studies for the synthesized heterocyclic aldehydes in the presence of selected cations were also performed, in solution, in order to determine their potential application as optical chemosensors.

Keywords: synthesis; Suzuki cross coupling; heterocyclic aldehydes; optical chemosensors

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1. Introduction

Aldehydes are one of the most recurrent functional groups in organic molecules. Aldehydes can be found in nature as flavouring agents, such as benzaldehyde and cinnamaldehyde, carbohydrates or steroid hormones. This group can be introduced into heterocyclic moieties through several synthetic methodologies, being the most used methods Vilsmeier–Haack formylation and metalation followed by addition of DMF (dimethylformamide) [1–5].

Vilsmeier–Haack formylation is a known synthetic method to introduce a formyl group into electron-rich aromatic compounds using the Vilsmeier reagent. This reagent is prepared by reacting a *N,N*-disubstituted formamide, normally DMF, and an acid chloride, generally POCl₃. An electrophilic aromatic substitution of the substrate takes place, followed by hydrolysis to yield the heterocyclic carbaldehyde [3]. π -Conjugated heterocyclic aldehydes can also be prepared through a Suzuki cross-coupling reaction using the appropriate coupling components [6–9].

Due to its versatility, the carbaldehyde group, linked to heterocyclic moieties, can be converted to stronger electron-withdrawing groups, yielding π -conjugated push-pull systems with a wide variety of optical applications. Such applications include, for instance, non-linear optics (NLO) [10,11], photodynamic therapy (PDT) [12], dye-sensitized solar cells (DSSCs) [6,13,14], organic light emitting diodes (OLEDs) [15] or optical

chemosensors for cations (Cu^{2+} , Hg^{2+}) or anions (F^-) [7,16–18].

Carrying on the research group's investigation on optical chemosensors [7,9,19–22], this work reports the synthesis and characterization of two heterocyclic aldehydes by Suzuki coupling of 5-bromothieno[3,2-*b*]thiophene-2-carbaldehyde with two different phenylboronic acids. The synthesis and the characterization of the thieno[3,2-*b*]thiophene precursors is also included.

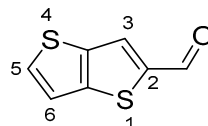
Preliminary chemosensory studies for the synthesized heterocyclic aldehydes in the presence of selected cations were also performed, in solution, in order to determine their potential application as optical sensors.

2. Experimental Section

2.1. Methods and Materials

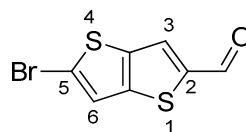
Nuclear magnetic resonance (NMR) spectra were obtained on a Bruker Avance III 400 at an operating frequency of 400 MHz for ^1H and 100.6 MHz for ^{13}C using the solvent peak as internal reference. The solvents (deuterated chloroform; CDCl_3 and dimethyl sulfoxide- d_6 ; $\text{DMSO-}d_6$) are indicated in parenthesis before the chemical shifts values (δ relative to tetramethylsilane (TMS)). Peak assignments were supported by spin decoupling-double resonance and bidimensional heteronuclear correlation techniques. All reagents were purchased from Sigma-Aldrich, Acros and Fluka and used as received. Compounds **1**, **2** and **3a–c** were synthesized as previously reported [6,23–24]. TLC (thin layer chromatography) analysis were carried out on 0.25 mm thick precoated silica plates (Merck Fertigplatten Kieselgel 60F254) and the spots were observed under ultraviolet (UV) light. Chromatography on silica gel was carried out on Merck Kieselgel (230–400 mesh).

2.2. Synthesis of Thieno[3,2-*b*]thiophene-2-Carbaldehyde (**1**)



Thieno[3,2-*b*]thiophene (1.00 g, 7.13 mmol) was dissolved in DMF (5 mL) and cooled to 0 °C. A mixture of phosphorus oxychloride (1.96 mL, 21.39 mmol) and DMF (5 mL), cooled to 0 °C, was added dropwise with stirring. The reaction mixture was allowed to reach room temperature and was then stirred at 60 °C for 11 h. The resulting intermediate was poured over cold water and the pH was adjusted to 8–9 by adding saturated aqueous Na_2CO_3 . The product was extracted with dichloromethane (DCM) (3×100 mL), the organic extract was washed with water (3×200 mL), dried with anhydrous MgSO_4 , filtered and the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography using DCM/hexane (1:1) as eluent. The obtained product was an orange solid (1.034 g, 88%). ^1H NMR (400 MHz, CDCl_3): δ = 7.35 (dd, 1H, J = 5.2 and 0.8 Hz, H-6), 7.71 (d, 1H, J = 5.2 Hz, H-5), 7.96 (d, 1H, J = 0.4 Hz, H-3), 9.99 (s, 1H, CHO) ppm.

2.3. Synthesis of 5-Bromothieno[3,2-*b*]thiophene-2-Carbaldehyde (**2**)

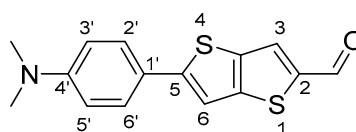


A solution of *N*-bromosuccinimide (NBS, 0.500 g, 3 mmol) in DMF (6 mL) was added dropwise to a solution of **1** (0.100 g, 3 mmol) in DMF (9 mL) in the dark at ambient temperature and the reaction was stirred for 4 h also in the dark. The reaction mixture was poured into water and the solid formed was filtered off and a white solid was obtained (0.57 g, 77%). ^1H NMR (400 MHz, CDCl_3): δ = 7.37 (d, 1H, J = 0.4 Hz, H-6), 7.85 (d, 1H, J = 0.8 Hz, H-3), 9.98 (s, 1H, CHO) ppm.

2.4. General Procedure for the Synthesis of Heterocyclic Aldehydes by Suzuki Cross-Coupling Reaction **3a–b**

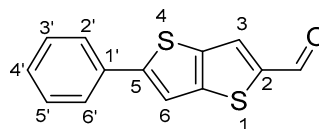
Precursor **2** (0.100 g, 0.4 mmol) was coupled with different phenylboronic acids (0.5 mmol) in a mixture of 1,2 dimethoxyethane (DME, 6 mL), aqueous Na₂CO₃ 2 M (0.4 mL) and Pd(PPh₃)₄ (6 mol %) at 80 °C under nitrogen. The reactions were monitored by TLC, which determined reaction times. After cooling, the mixtures were filtered, and the solid was washed with an organic solvent and a saturated solution of NaCl. After phase separation, the organic phase was washed with water (3 × 10 mL) and a solution of 10% NaOH (1 × 10 mL). The organic phase obtained was dried with anhydrous MgSO₄, filtered, and the solvent removed under vacuum.

2.4.1. Synthesis of 4-*N,N*-Dimethylaminophenylthieno[3,2-*b*]thiophene-2-Carbaldehyde (**3a**)



After extraction, the compound **3a** was obtained pure as an orange solid (0.113 g, 98%). ¹H NMR (400 MHz, DMSO-*d*₆): δ = 2.97 (s, 6H, N(CH₃)₂), 6.78 (d, 2H, *J* = 8.8 Hz, H-3' and H-5'), 7.57 (d, 2H, *J* = 8.8 Hz, H-2' and H-6'), 7.76 (s, 1H, H-6), 8.32 (s, 1H, H-3), 9.91 (s, 1H, CHO) ppm.

2.4.2. Synthesis of 5-Phenylthieno[3,2-*b*]thiophene-2-Carbaldehyde (**3b**)



The crude product, obtained from extraction, was submitted to column chromatography on silica gel with petroleum ether/ethyl acetate (5:1) as eluent. Compound **3b** was obtained as a yellow solid (0.063 g, 65%). ¹H NMR (400 MHz, CDCl₃): δ = 7.40–7.48 (m, 3H, H-3', H-4' and H-5'), 7.55 (s, 1H, H-6), 7.67 (br d, 2H, *J* = 6.8 Hz, H-2' and H-6'), 7.94 (s, 1H, H-3), 9.97 (s, 1H, CHO) ppm.

2.5. Preliminary Chemosensing Studies of Heterocyclic Aldehydes **3a–b**

Evaluation of heterocyclic aldehydes **3a–b** as chemosensors was carried out in the presence of several cations (Ag⁺, K⁺, Li⁺, Pb²⁺, Mn²⁺, Cd²⁺, Cu²⁺, Co²⁺, Pd²⁺, Ni²⁺, Ca²⁺, Hg²⁺, Zn²⁺, Fe²⁺, Fe³⁺ and Al³⁺) with environmental and biomedical relevance. Solutions of the compound (1.0 × 10⁻⁵ M) and solutions of the cations under study (1.0 × 10⁻² M) were prepared in acetonitrile. A preliminary study was carried out by addition of up to 50 equivalents of each cation to the solution of compounds **3a–b** in acetonitrile. The solutions were analyzed on a Vilber Lourmat CN6 viewing cabinet under an ultraviolet (UV) lamp at 365 nm.

3. Results and Discussion

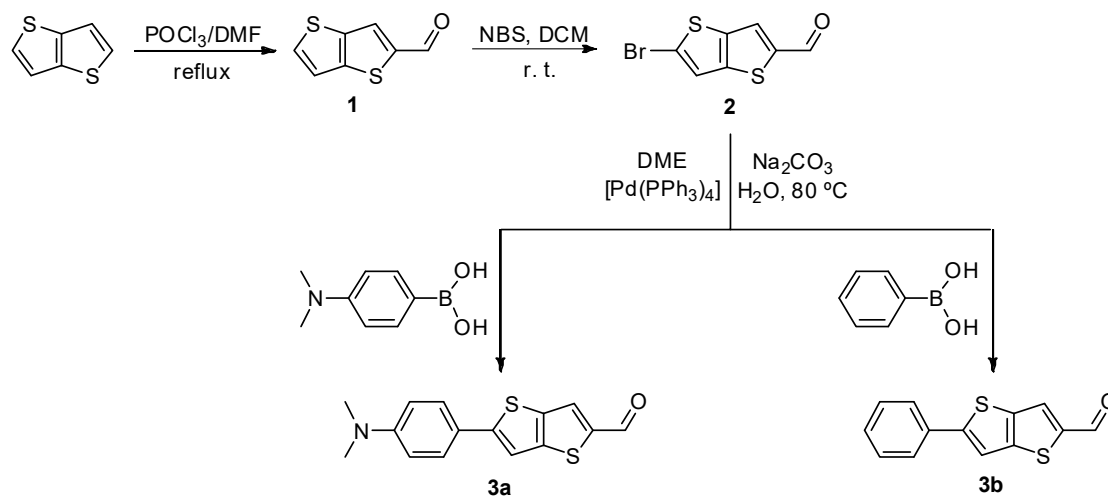
3.1. Synthesis of Intermediates **1** and **2** and Heterocyclic Aldehydes **3a–b**

The synthesis of thieno[3,2-*b*]thiophene-2-carbaldehyde (**1**) was performed through Vilsmeier–Haack formylation of thieno[3,2-*b*]thiophene precursor [23]. The intermediate **1** was obtained as an orange solid with a yield of 88%, after purification by flash chromatography using a mixture of DCM/hexane (1:1) as eluent. The structure was confirmed by ¹H NMR, with the typical carbaldehyde singlet at 9.99 ppm.

Precursor **1** was then used in the synthesis of 5-bromothieno[3,2-*b*]thiophene-2-carbaldehyde (**2**), by bromination with *N*-bromosuccinimide (NBS), in DMF, in the

dark [24]. The brominated precursor **2** obtained was a white solid with a yield of 77%. ^1H NMR confirmed the disappearance of the H-5 signal at 7.71 ppm.

Heterocyclic aldehydes **3a–b** were synthesized by Suzuki coupling [6] using as couplings components precursor **2** and the appropriate aryl boronic acids, in a mixture of 1,2 dimethoxyethane (DME), aqueous Na_2CO_3 and $\text{Pd}(\text{PPh}_3)_4$ at 80°C , under nitrogen atmosphere (see Scheme 1).



Scheme 1. Synthesis of thieno[3,2-*b*]thiophene precursors **1** and **2**, and heterocyclic aldehydes **3a–b**.

Thieno[3,2-*b*]thiophene **3a** was obtained pure, as an orange solid with a yield of 98%, without needing purification by chromatography. ^1H NMR confirmed the purity of the compound with the characteristic aliphatic singlet at 2.97 ppm due to the $(\text{N}(\text{CH}_3)_2)$ protons and two duplets at 6.78 and 7.57 ppm due to four aromatic protons of the di-substituted phenyl group besides the singlets concerning the thieno[3,2-*b*]thiophene protons at 7.76 and 8.32 due to H-6 and H-3, respectively. Compound **3b** was obtained as a yellow solid with a yield of 65%, after column chromatography on silica gel. In this case, ^1H NMR showed the typical thieno[3,2-*b*]thiophene-2-carbaldehyde signals and two other aromatic signals from the five protons of the introduced phenyl moiety, at 7.40–7.48 and 7.67 ppm.

For the synthesis of **3a**, different reaction conditions for Suzuki coupling, with toluene as solvent and K_2CO_3 instead of Na_2CO_3 , were also used, since previous reports for other coupling products showed enhanced yields and shorter reaction times [6]. However, in this case, a considerably lower yield was obtained (14%) (Table 1).

Table 1. Synthesis of heterocyclic aldehydes **3a–b** by Suzuki coupling.

Compound	Method	n(2)/Eq.	n(Boronic Acid)/Eq.	t/h	$\eta/\%$
3a	A	1	1.3	5	98
	B	1	1.3	3	14
3b	A	1	1.3	10	65

Method A: 1,2 dimethoxyethane (DME), $[\text{Pd}(\text{PPh}_3)_4]$ (6 mol %), Na_2CO_3 , H_2O , 80°C ; Method B: toluene, $[\text{Pd}(\text{PPh}_3)_4]$ (10 mol %), K_2CO_3 , H_2O , EtOH , 60°C .

3.2. Preliminary Chemosensing Studies of Heterocyclic Aldehydes **3a–b**

A preliminary colorimetric and fluorimetric chemosensing study was performed for heterocyclic aldehydes **3a–b**. Evaluation of the two compounds as chemosensors was performed in acetonitrile solutions, in the presence of 50 equivalents of different cations. It was observed that only 4-*N,N*-dimethylaminophenylthieno[3,2-*b*]thiophene-2-carbaldehyde **3a** exhibited fluorescence quenching in the presence of Hg^{2+} , Fe^{2+} , Cu^{2+} ,

Pd²⁺, Fe³⁺, and Al³⁺ cations (see Figure 1). Color changes were not observed for any interaction with the ions.

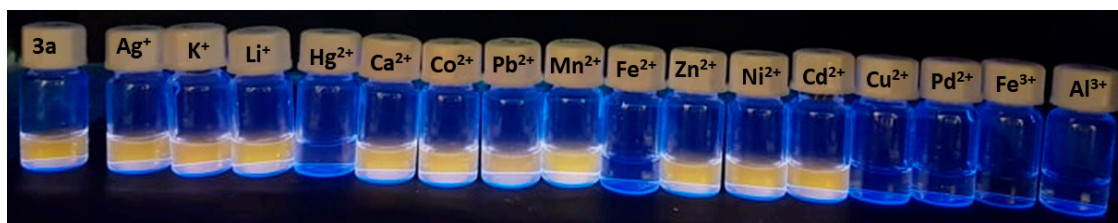


Figure 1. Preliminary chemosensing study of heterocyclic aldehyde **3a**, in acetonitrile solutions and in the presence of 50 equivalents of each cation, on a viewing cabinet under an ultraviolet (UV) lamp at 365 nm.

4. Conclusions

Two heterocyclic aldehydes **3a–b** were successfully synthesized by Suzuki coupling, with yields of 98% (**3a**) and 65% (**3b**). The synthesis of **3a** under different reaction conditions (Method B; solvent and base) resulted in a significantly lower yield (14%). The thieno[3,2-*b*]thiophene precursors **1–2** were also synthesized, with yields of 88% and 77%, respectively. Preliminary chemosensing studies of heterocyclic aldehyde **3a** showed fluorescence quenching in the presence of Hg²⁺, Fe²⁺, Cu²⁺, Pd²⁺, Fe³⁺, and Al³⁺. In the near future, further studies will be performed to assess the coordination ratio and limits of detection.

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Conflicts of Interest: The authors declare no conflicts of interest.

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