SYNTHESIS AND X-RAY STRUCTURAL ANALYSIS OF AMIDINO-SUBSTITUTED 2-AMINOPHENOLES

SINTEZA I RENDGENSKA STRUKTURNA ANALIZA AMIDINO-SUPSTITUIRANIH 2-AMINOFENOLA

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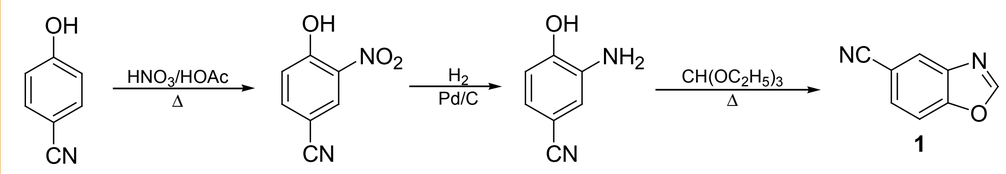
INTRODUCTION

Amidino-substituted benzazole derivatives exhibit various biological activities and have been continuously studied by several research groups. In contrast to a great number of biologically active amidino-substituted benzimidazole and benzothiazole derivatives reported in recent literature, amidino-substituted benzoxazoles are still rare. There are only a few reports that deal with the synthesis of amidino-substituted benzoxazole derivatives and their antitumor [1], antimicrobial [2] activities as well as their DNA binding properties [3]. The reason is lack of general method for their preparation, which would be based on the condensation reaction of amidino-substituted 2-aminophenoles, as the key intermediates, with carboxylic acids, carboxylic acid derivatives or aldehydes. Recently, our research has been directed towards the synthesis of 2-aryl and 2-heteroaryl benzoxazole molecules substituted with different amidinic group, as well as towards studying their biological activity. Here, we report the synthesis of amidino (**2a**), 2-imidazolinyl (**2b**), and *N*-isopropylamidino (**2c**) substituted 2-aminophenole as the key precursors in the synthesis of targeted benzoxazoles.

RESULTS AND DISCUSSION

Preparation of 5-cyanobenzoxazole (**1**) was carried out by multistep synthesis (Scheme 1) from 4-hydroxybenzonitrile in a good overall yield of 65 %. The synthetic approach for the preparation of amidino-substituted cyanophenoles (**2a-2c**) follows our previously developed method for the preparation of amidino-substituted 2-aminothiophenoles [4] by Pinner reaction according to Scheme 2. The imidate hydrochloride isolated in the first step of Pinner reaction was converted into 4-amidinium-2-aminobenzophenolate in the reaction with gaseous ammonia. Crystallization of the crude product at neutral pH afforded **2a** in the zwitterionic form with half equivalent of HCl, while crystallization at pH>10 afforded pure zwitterionic form **2a'**. Reaction of imidate hydrochloride with ethylenediamine afforded 4-(imidazolinium-2-yl)-2-aminobenzophenolate and after crystallization at neutral pH zwitterionic form with half equivalent of HCl **2b** was isolated. Crystallization at pH>10 afforded zwitterionic form **2b'** isolated as hydrate. Reaction of imidate hydrochloride with isopropylamine afforded 4-*N*-isopropylamidinium-2-aminobenzophenole chloride isolated in the form of ethanol solvate **2c**. Attempt to obtain pure zwitterionic form of **2c** by crystallization at pH>10 was unsuccessful. Structures of presented compounds were consistent with the data obtained by ^{1}H and ^{13}C NMR, LC–MS and elemental analysis. Additionally, water content by Karl Fisher method was determined for compound **2b'**.

Scheme 1. Synthesis of 5-cyanobenzoxazole



Scheme 2. Synthesis of amidino-supstituted 2-aminophenoles

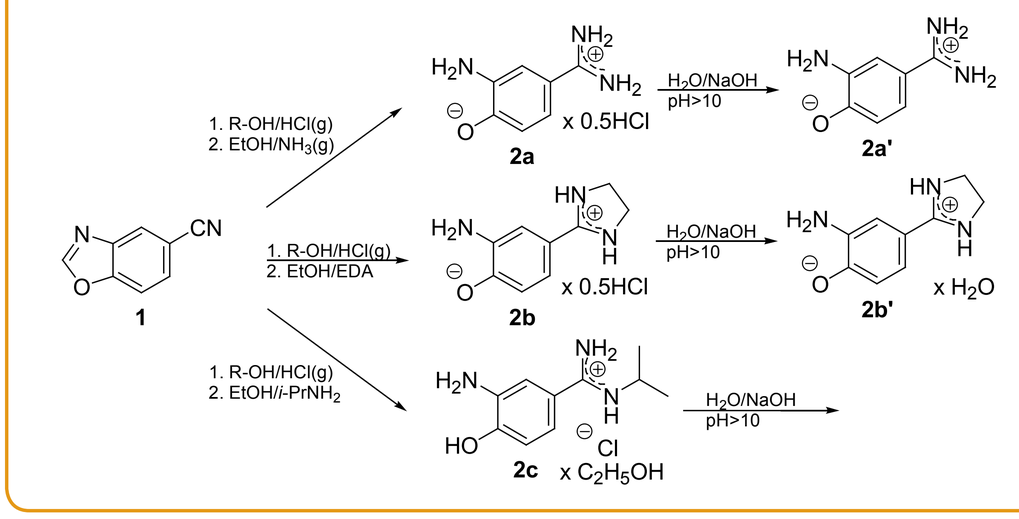
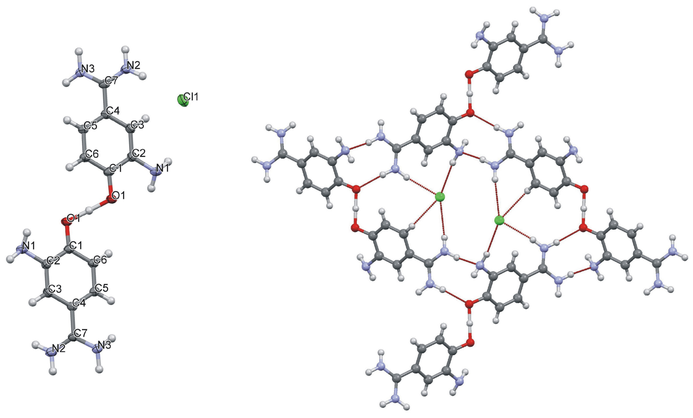


Table 1. Selected bond distances (Å) for compounds **2a**, **2a'**, **2b** and **2c**

Selected bonds	Compound			
	2a	**2a'**	**2b**	**2c**
C4–C7	1.464(3)	1.469(6)	1.457(3) 1.455(3)	1.475(2)
C7–N2	1.314(3)	1.324(6)	1.323(3) 1.324(3)	1.316(2)
C7–N3	1.306(3)	1.318(6)	1.317(3) 1.320(3)	1.320(2)
C1–O1	1.334(2)	1.327(5)	1.336(3) 1.337(2)	1.355(2)

Molecular and crystal structures for compounds **2a**, **2a'**, **2b** and **2c** were determined by X-ray diffraction method (Table 1; Figures 1 – 4). In the solid state, compound **2a** crystallized in a zwitterionic form with the C7–N2 and C7–N3 bonds in amidinium moiety approximately equal (*i.e.* within 3σ values), and with half of the HCl molecule in the asymmetric unit (Figure 1a; Table 1). Such form is also confirmed by the C1–O1^{-} bond distance being shorter than the usual C–O–H bond. The negatively charged oxygen atom O1 and a symmetry related atom of a neighbouring molecule share the same hydrogen ion located on the inversion centre, forming a cationic dimer. The dimers are linked mutually, as well as with chlorides, by numerous hydrogen bonds, thus forming a three-dimensional network (Figure 1b). We also succeeded in obtaining a single crystal of this compound only in the zwitterionic form, *i.e.* without hydrochloride (Figure 2a). Hydrogen bonding of **2a'** is largely dictated by the amino groups which, together with the amidinium groups, form one-dimensional *zig-zag* infinite chains (Figure 2b). Compound **2b** crystallized with two independent molecules of **2b** and one HCl molecule in the asymmetric unit (Figure 3a). As in **2a**, two zwitterionic molecules are bridged by a hydrogen ion and are mutually linked by hydrogen bonds, as well as with chlorides, thus forming an intricate array of hydrogen bonds and a three-dimensional network (Figure 3b). Finally, compound **2c** crystallized as a hydrochloride, but the molecule is not in zwitterionic form (Figure 4a), as confirmed by longer C1–O1 bond length. However, the nitrogen N3 atom is protonated and therefore amidinium moiety in this compound is maintained (C7–N2 and C7–N3 bonds are within 2σ values). Interestingly, the cations and chlorides are linked in such a way that they only form a two-dimensional network (Figure 4b).

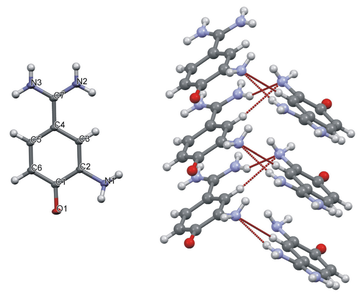
Figure 1.



a) Molecular structure of **2a**, with the atom numbering scheme.

b) Part of the crystal structure of **2a**, showing hydrogen bonds between cationic dimers, as well as between dimers and chlorides.

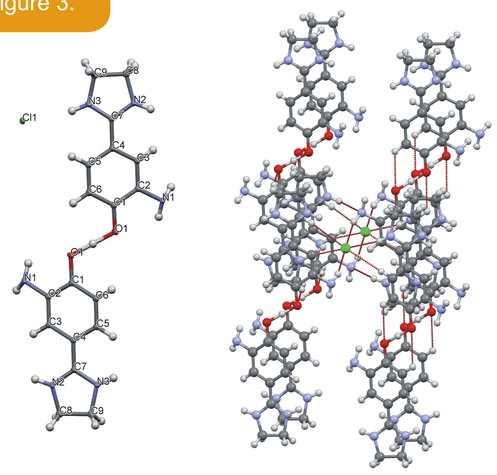
Figure 2.



a) Molecular structure of **2a'**, with the atom numbering scheme.

b) Part of the crystal structure of **2a'**, showing hydrogen bonds that link the molecules into *zig-zag* infinite chains.

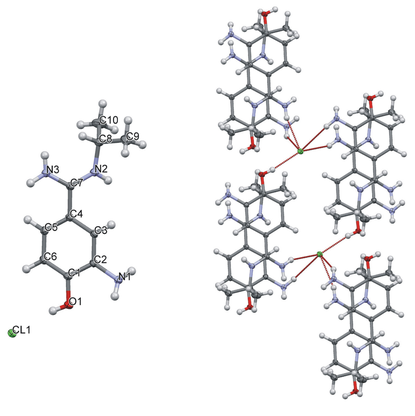
Figure 3.



a) Molecular structure of **2b**, with the atom numbering scheme.

b) Part of the crystal structure of **2b**, showing hydrogen bonds between cationic dimers and chlorides.

Figure 4.



a) Molecular structure of **2c**, with the atom numbering scheme.

b) Part of the crystal structure of **2c**, showing hydrogen bonds between the cations and chlorides.

References

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