Synthesis of benzothiazoyl salicylate moieties

Diepreye Ere* and Allen T. Ekubo

Department of Chemical Sciences, Niger Delta University, Wilberforce Island, Bayelsa State, Nigeria.

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Aminosalicylates are derivatives of the highly functionalized compound aminosalicylic acid. Benzothiazoyl salicylates were obtained in this work from the highly functionalized aminosalicylic acid by reacting ammonium thioureas as a nucleophile to aminosalicylates that were derived from aminosalicylic acid and bromine was used as the cyclising agent. Results obtained indicated that it was the brominated cyclised product that was formed.

Key words: Aminosalicylates, aminosalicylic acid, benzothiazoles, thioureas.

INTRODUCTION

Benzothiazoles are heterocycles in which benzene ring is fused with thiazole ring. Benzothiazoles are usually known as precursors (Sum et al., 2003; Gupta and Rawat, 2010) to natural products, pharmaceutical agents and other compounds that exhibit a wide spectrum of biological activity. Literature search indicates that benzothiazoles are very important. Leong et al. (2003) reported that benzothiazoles represent a potent and highly selective class of antitumour agents. Paraaminosalicylic acid is an old agent used for the treatment of tuberculosis. It is envisaged that benzothiazoles derived from para-aminosalicylic acid moieties would be useful for multidrug resistant tuberculosis which is becoming prevalent by the day (Gandhi et al., 2006). Therefore “benzothiazoles salicylates” was synthesized which could also become biological active compounds targeted at multidrug drug resistant tuberculosis (MDRTB). Jacobson synthesis (Jacobson, 1903) of benzothiazoles, via oxidative cyclisation of an arylthioamide on an unsubstituted ortho position using potassium fericyanide in a basic medium is one of the established methods used for the synthesis of substituted benzothiazoles. Downer and Jackson (2004) attributed the success of preparing their benzothiazoles to the formation of the intermediate arylthioanilides (Scheme 1).

Jordan et al. (2003) amongst others, have also reported an efficient conversion of substituted aryl thioureas to 2-aminobenzothiazoles using either bromine or benzyl trimethyl ammonium tribromide. A variation on this theme has also been used for making 2-aminobenzothiazoles directly in one pot using ammonium thiocyanate and aniline or p-toluidine to form the thiourea which was cyclised in situ.

Following the aforementioned methods, we have used para-aminosalicylic alkyl esters and reacted them with ammonium thiocyanate and benzyltrimethyl ammonium tribromide in dichloromethane to give benzothiazole products in very good yields (92 to 97%).

The aim of this work is to make benzothiazoles centered on para-aminoaminosalicylic acid that will be active against multi-drug resistant tuberculosis strands (Schemes 2 and 3).

MATERIALS AND METHODS

Reagents and reaction solvents

Reagents used in this study were without further purification unless otherwise stated.

Evaluation of materials

Proton nuclear magnetic resonance (\(^1\)H-NMR) spectroscopy. The structures of the products were confirmed by \(^1\)H-NMR and \(^13\)C-NMR spectroscopy using JOEL Lambda 400 spectrometer. An internal standard of trimethylsilane (TMS) was used. The following abbreviations are examples used to describe the splitting patterns: s-singlet, d-doublet, t-triplet, q-quartet, quint-q quintet, dd-double-doublet, m-multiplet, b-broad.

1. Mass spectrometry (MS): Mass spectra were recorded using a Finnigan-MAT 1020 GC/MS and a QP505A Schimadzu GC/MS.
Scheme 1. General synthesis of benzothiazoles.

$$\text{R} \quad \text{H} \quad \text{N} \quad \text{Ph} \quad \text{S} \quad \text{S} \quad \text{N} \quad \text{R} \quad \text{Ph}$$

$$\text{K}_3\text{Fe(CN)}_6, \text{aq. NaOH}, 90^\circ \text{C} \quad \rightarrow \quad \text{R} \quad \text{N} \quad \text{Ph}$$

Scheme 2. Experimental synthesis of 2-amino-4-bromo-5-hydroxybenzothiazoles.

(i) or (ii) \rt, 1 day

(i) = BrMe$_3$NBr$_3$ / DCM
(ii) = Br$_2$/ACOH/DCM

R = CH$_3$, CH$_3$CH$_2$, CH$_3$CH$_2$CH$_2$

Scheme 3. Experimental synthesis of 2-benzylamino benzothiazoles.

R = Me
R = Et
R = Pr
R' = Br
R' = H
The purity of compounds in this work was confirmed by column chromatography using silica gel 60 (230-400 Mesh). Glass or aluminium backed TLC plates coated with silica gel (60 F254 Merck) were monitored by thin layer chromatography (TLC). Glass or aluminium backed TLC plates coated with silica gel (60 F254 Merck) were monitored by thin layer chromatography (TLC) and were uncorrected.

**Methodology**

**2-Amino-4-bromo-5-hydroxybenzothiazole-6-carboxylic acid alkyl esters (A-D)**

To a stirred mixture of alkyl-4-aminosalicylate (0.06 mol) and ammonium thiocyanate (0.13 mol) in glacial acetic acid (90 ml) at 0°C was added drop wise bromine (0.06 mol) in glacial acetic acid (20 ml) over 45 min such that the temperature of the reaction mixture did not exceed 5°C. The reaction mixture was then allowed to stir for a further 1 h in ice-bath. The precipitates that were formed were collected and dissolved in hot water (100 ml) and then saturated sodium hydrogen carbonate added to neutralize the mixture. The precipitate that was formed were collected by filtration, washed with water and then dried in vacuo over calcium chloride to yield the compound subsequently stated.

**Synthesis of 2-Benzylamino-4-bromo-5-hydroxybenzothiazole-6-carboxylic acid alkyl esters (E)**

To a stirred solution of alkyl-4-(3-benzylthioureido)-2-hydroxybenzoate (3.4 mmol) in dichloromethane (10 ml) was added 10 (ten) drops of bromine from a Pasteur pipette and the resulting mixture stirred at room temperature for 2 h. Dichloromethane (10 ml) was added and the suspension that was formed was neutralized by the drop wise addition of saturated solution of sodium hydrogen carbonate. Dichloromethane (3 x 10 ml) was used to extract the solute and washed with water (2 x 10 ml) and then dried over magnesium sulphate and then filtered. Solvent was then removed in vacuo to obtain the crude product. The product was then purified by recrystallisation from methanol to yield the recorded products.

**RESULTS**

**2-Amino-4-bromo-5-hydroxybenzothiazole-6-carboxylic acid methyl ester (A)**

Yield (97%), mp 240 to 24°C, Rf = 0.9 (EtOAc); (Found: C, 35.86; H, 2.04; N, 9.27; S, 10.57% C₈H₇N₂O₃SBr requires C, 35.66; H, 2.33; N, 9.24; S, 10.58%); ¹H-NMR [d₆-DMF, 400 MHz] δH 3.90(3H, s, OCH₃), 8.13 (1H, s, Ar-H), 8.36 (2H, bs, NH₂), 11.39(1H, s, Ar-OH); ¹³C-NMR [d₆-DMF, 100 MHz] δC 52.7, 106.1, 121.1, 121.7, 129.2, 156.2, 157.4, 169.6, 171.8, m/z 304/302 (M⁺, 27 %), 272/270 (100), 244/242 (9), 135 (22), 93 (51).

**2-Amino-4-bromo-5-hydroxybenzothiazole-6-carboxylic acid ethyl ester (B)**

![结构式](image)

Yield (80%) mp 224-226 °C, Rf = 0.7 (EtOAc); (Found: C, 37.85; H, 2.88; N, 8.83; S, 10.11 C, 37.66; H, 2.86; Br 25.19; N, 8.83; S, 10.11; O, 15.13); ¹H-NMR [d₆-DMF, 400 MHz] δH 1.52 (3H, t, J =6, 2.4, 6 Hz -CH₃), 4.29 (2H, q, J =6, 2.4, 6 Hz -CH₂O-), 8.38 (2H, bs, NH₂), 8.60 (1H,s, Ar-H), 11.45 (1H, s, Ar-OH); ¹³C-NMR [d₆-DMF, 100 MHz]δC 14.2, 59.1, 105.6, 117.2, 117.3, 125.2, 157.1, 158.4, 172.4, 166.9; m/z 317/315 (M⁺, 32%).

**2-Amino-4-bromo-5-hydroxybenzothiazole-6-carboxylic acid propyl ester (C)**

![结构式](image)

Yield (72%) mp 218-219.5 °C, Rf = 0.75 (EtOAc); (Found: C = 39.80, H 3.32, N, 8.46, S 9.67, C₈H₇BrN₂O₃S requires C 39.89, H 3.35, Br 24.13, N 8.46, O 14.49, S 9.68); ¹H-NMR [d₆-DMF, 400 MHz] δH 0.98 (3H, t, J =2.5, 0.6, 2.5 Hz, CH₃), 1.82 (2H, m, CH₂), 4.27 (2H, t, J =2.5, 0.6, 2.5 Hz, CH₂), 8.27 (2H, bs, NH₂) 8.62 (1H, s, Ar-H), 11.40 (1H, s, Ar-OH); ¹³C-NMR [d₆-DMF, 100 MHz] δC 10.2, 22.7, 68.3, 103.8, 117.2, 117.3, 124.5, 157.2, 158.4, 167.2, 174.8 m/z 331/329 (M⁺, 43%).

**2-Amino-4-bromo-5-hydroxybenzothiazole-6-carboxylic acid benzyl ester (D)**

![结构式](image)
Yield (84%), mp 204 to 205°C, Rf = 0.58 (EtOAc); (Found: C 47.56, H 2.88, Br 21.07, N 7.39, S 8.44; C18H13BrN2O2S requires: C 47.51, H 2.92, Br 21.07, N 7.39, O 12.66, S 8.46); 1H-NMR [d6-DMSO, 400 MHz] δH = 5.52(2H, bs, NH2), 10.22(1H, s, Ar-OH) 7.25 (4H, s, 4 x Ar-H), 8.60 (1H, S, Ar-H); 13C-NMR [d6-DMSO, 100 MHz] δC 71.8, 103.8, 117.2, 117.3, 124.3, 127.3 (2 X), 127.4, 128.7 (2 X), 140.9, 157.1, 158.4, 167.0, 174.5; m/z 379/377 (M+ , 47%).

2-Benzylamino-4-bromo-5-hydroxy-benzothiazole-6-carboxylic acid methyl ester (E)

Yield (74%) mp 226 to 227°C, Rf = 0.62 (EtOAc); (Found: C 48.87, H 3.33, S 8.15, Br 7.12, C18H13BrN2O2S requires: C 48.87, H 3.33, Br 20.32, N 7.12, O 12.21, S 8.15), 1H-NMR [d6-DMSO, 400 MHz] δH = 3.87 (3H, s, OCH3), 4.60 (2H, d, J = 5.5 Hz, CH2), 6.85 (1H, s, Ar-H), 7.32-7.35 (5H, m, 5 x Ph-H), 8.09 (1H, s, Ar-H), 8.97 (1H, bt, J = 5.5 Hz, N-CH3), 10.65 (1H, s, Ar-OH); 13C-NMR [d6-DMSO, 100 MHz] δC 49.1, 56.8, 103.6, 117.2, 117.3, 124.3, 126.5, 127.1, 128.3, 142.4, 157.1, 158.4, 167.0, 174.5, m/z 394 (M+ , 20%), 393 (17), 362 (17), 361 (14), 106 (17), 91 (100), 65 (21).

DISCUSSION

Para-amino salicylic alkyl esters undergo nucleophilic addition with ammonium thiocyanate and benzyltrimethyl ammonium tribromide as the cyclisation agent in dichloromethane to give benzothiazole products in very good yield (92 to 97%). However spectroscopic evidence showed that it was the bromine products rather than the earlier envisaged products that were formed.

Earlier one had envisaged that cyclisation will occur para to the hydroxyl group, due to steric factors, but the products isolated were 2-amino-4-bromo-5-hydroxybenzothiazole-6-carboxylic acid alkyl esters (A-D) as shown in the Scheme 2. The possible explanation for this occurrence is that the electron rich nature of para-amino salicylic acid (PAS) may have caused bromination to take place prior to cyclisation or more likely bromination pre-thiourea formation. Therefore, the position of the bromine atom could either be ortho or para to the hydroxyl group and the products are likely to be 2-amino-4-bromo-5-hydroxybenzothiazole-6-carboxylic acid alkyl esters. Bromination of para-amino salicylic acid and N-acetyl para-amino salicylic acid gave a mixture of isomers 4-amino-5-bromo-2-hydroxybenzoic acid and 4-amino-3-bromo-2-hydroxybenzoic acid as well as 4-acetylamino-5-bromo-2-hydroxybenzoic acid and 4-acetylamino-3-bromo-2-hydroxybenzoic acid. It was difficult to confirm which isomers of the bromobenzothiazoles that were formed. Whichever of the isomers formed would possess the same one aromatic hydrogen in 1H-NMR. Due to the fact that the compounds are highly functionalized molecules, possessing many heteroatoms, neither the 1H nor 13C NMR chemical shifts would indicate which isomer is formed. Efforts to get crystalline material for X-ray crystallographic studies were unsuccessful; therefore the final confirmations for which isomers are formed are open to debate.

In order to obtain non-brominated benzothiazole carboxylic acid alkyl esters, several other routes were investigated. The reaction between the para-amino salicylic acid alkyl esters and ammonium thiocyanate were investigated in order to obtain the intermediate thioureas prior to cyclisation. The production of thioureas using this method was not very reliable as repeatability problem were encountered for all the alkyl esters. One method amongst several others that was tried in order to obtain intermediate thioureas was when para-amino salicylic acid alkyl esters and 1,1’-thiociarbonyl di-2,2’-pyridone (TD P) were reacted smoothly to produce 2-hydroxy-4-isothiocyanato benzoic acid alkyl esters in good yield (73 to 93%). This method was reported by Clarke and Boyle, 1999 and had been developed for the synthesis of isothiocyanatoporphrins from aminoporphyrins.

Once isothiocyanates were produced successfully efforts to synthesize the thiourea by addition of an amine was undertaken. Benzyamine was deliberately chosen because the benzyl group could be removed by hydrogenation at a later stage. The 2-hydroxy-4-isothiocyanatobenzoic acid alkyl esters underwent nucleophilic addition with benzylamine in dichloromethane at room temperature to form the cyclisation precursor, 2-hydroxy-4-(2-phenylaminothiocarbonyl) benzic acid alkyl esters in good yield (76 to 82 %). These thioureas were made in a “reverse way” using Para-amino salicylic alkyl ester and commercially available benzyl isothiocyanate as the analogous products using methyl isothiocyanate.

Conclusion

Benzothiazole is an important class of heterocycles which are known to exhibit a wide range of biological properties. Several other methods have been reported for the synthesis and cyclisation of benzothiazoles; however this is the first method for the synthesis of highly functionalised benzothiazoles which may possibly become effective for the cure of tuberculosis.
REFERENCES


