International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.11 No.08, pp 309-313, 2018

Synthesis and Characterization Of two Novel Thiofibrates Bearing 1,3-Benzoxazole Moiety

Niranjan M S* and Chaluvaraju K C

Department Of Pharmaceutical Chemistry, Government College of Pharmacy, Bengaluru -560 027, India

Abstract : In the present study two novel thiofibrates ethyl-2-(1,3-benzoxazol-2-ylsulfanyl)-2-methyl propionate and ethyl2-[(7-amino-5-chloro-1,3-benzoxazol-2-yl)sulfanyl]-2- methyl propionate are synthesized by treating 2-mercapto benzoxazoles and 7-amino-5-chloro-1,3-benzoxazole-2-thiol respectively with ethyl 2-bromo isobutyrates in presence of anhydrous potassium carbonate. The required2-mercapto benzoxazoles is synthesized by reacting 2-amino phenol with carbon disulphide in presence potassium hydroxide and acetic acid. Whereas, 7-amino-5-chloro-1,3-benzoxazole-2-thiol is obtained from the reaction of 2,6-diamino-4-chloro phenol. The synthesized compounds were characterized by physical data (melting point, R_f) and spectral studies (IR,^{1}H NMR). The spectral characterization study proves the fact that the assigned structures are in good agreement.
Keywords : 1,3-benzoxazole, Bioisosteres, Thiofibrates, ethyl 2-bromo isobutyrates, Hyperlipidaemia

Introduction

The treatment of hyperlipidaemia remains a challenging task to physicians as it is a well-known risk factor in cardiovascular diseases. The most important such cardiovascular ailment include atherosclerotic coronary artery disease[1]. Currently, statins are used as one of the cornerstone for the effective lowering of low density lipoprotein-C and intern to reduce the risk of cardiovascular diseases. However, their use is not optimized because of their notable adverse effect such as myopathies, which leads to non-compliance with the regimen prescribed[2].This strikes us an idea in identifying alternative medicines for the treatment of hyperlipidaemia. Further literature survey revealed the facts that fibric acid derivatives(fibrates) were proven to be an important class of lipid modifying agents due to their interaction with the biological target-peroxisome proliferator activated receptors(PPARs)[3]. The search of literature also proves the fact that these fibrates are also associated with the adverse events. As oxygen and sulphur are bioisosters they can be replaced with each other[4]. Doing so fibrates can be converted into thiofibrates.

1,3-Benzoxazoles and their derivatives are one of the important hetero aromatic compounds having a wide range of biological activities such as anti-microbial, anti-depressant, local anaesthetic, anti-epileptic, analgesic *etc.*,[5]. There is a paucity of literature on their anti-hyperlipidaemic activity. All the above facts

DOI= http://dx.doi.org/10.20902/IJCTR.2018.110839

boosted our interest to progress the work on the synthesis of novel antihyperlipidaemic agents. Hence in the present study an effort has been made to synthesize the bioisoters of fibrates so that these are devoid of side effects and can be used effectively to lower lipid content.2-mercaptobenzoxazole/ substituted 2-mercaptobenzoxazole is treated with ethyl-2 bromo iso butyrate in order to obtain the title compounds.

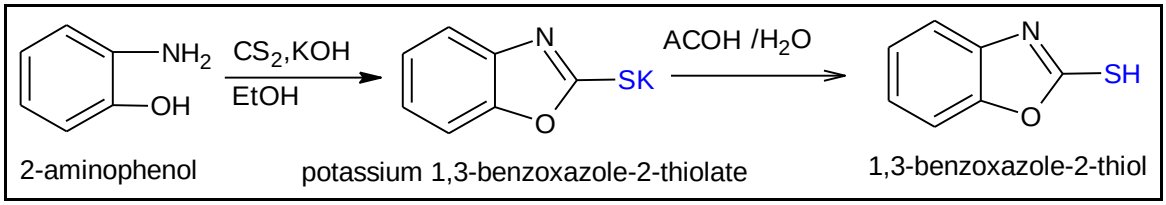
Experimental

Melting points of the synthesized compounds were determined in an open capillary tubes and are uncorrected. The purity of the compounds were checked by TLC on precoated silicagel plates using n-hexane: ethyl acetate (1:3)/ methanol: chloroform (1:9) as mobile phases. The developed chromatographic plates were observed under UV at 254 nm and also in iodine chamber[6]. IR spectral studies were carried out using ATR and ^{1}H NMR spectra was recorded on BRUKER 400 MHz using $CDCl_3$ as solvent and TMS as internal standard[7].

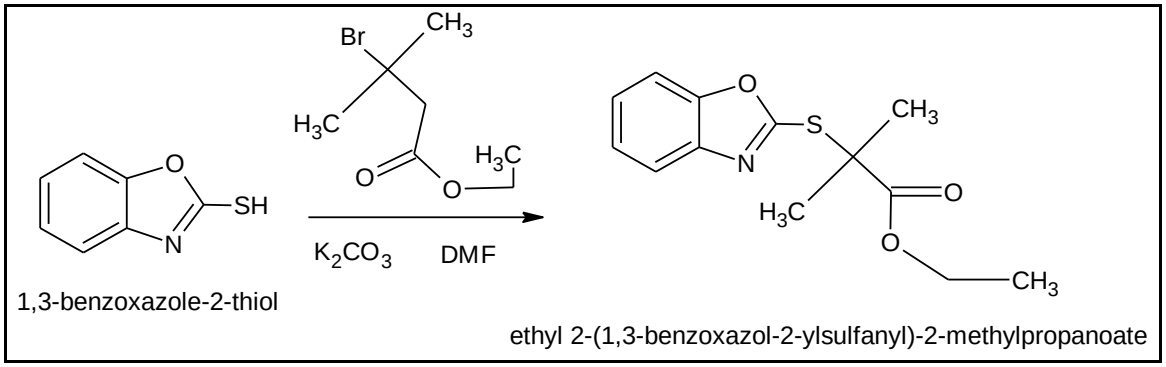
Synthesis of thiophenol: Synthesis of 2-mercaptobenzoxazoles: (Step1)

0.1mol (13g) of *o*-aminophenol, 0.1mol (5.6g) of powdered potassium hydroxide and 0.1mol (5.653g, 7ml) of carbondisulphide in 100ml of ethanol and 20ml of water were refluxed for 3 hours in a 250 ml round bottom flask.3-4g of activated animal charcoal was added to the above refluxed mixture and further heated to 10 min, cooled and filtered. The filtrate obtained was then heated to 60-70^{0}C on a water-bath with 10ml of acetic-acid and 20ml of water where, these were added under constant stirring of the filtrate. During this process glistering white crystals were formed and were allowed to crystallise in refrigerator overnight. The product thus obtained was collected by filtration, recrystallized from ethanol and dried(20mL)(**Scheme 1**).

Step 1:

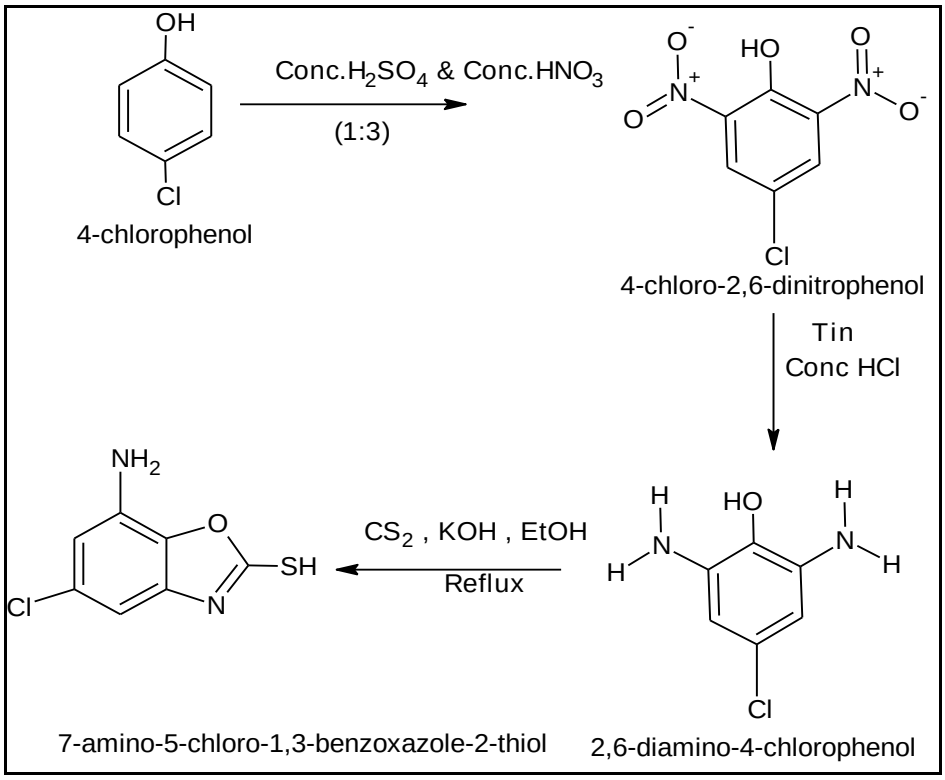


Step 2:



Scheme 1: Synthesis of ethyl-2-(1,3-benzoxazol-2-ylsulfanyl)-2-methyl propionate.

Molecular formula;C_7H_6NSO; Yield 57.88%; mp 60 ^{0}C; Rf=0.74; IR (KBr, cm^{-1}) 3308(NH str), 3066(CH str,Ar), 1506(C-Cstr, Ar),1276(CN str, Ar), 2359(Ar-SH str).



Scheme 2: Synthesis of 7-amino-5-chloro-1,3-benzoxazole-2-thiol

Synthesis of thiophenol: 4-amino- 6-chloro-1,3-benzoxazole-2-thiol (Scheme 2).

Synthesis of 4-chloro-2,6-dinitro phenol

In a dry 250 ml round bottom flask 10 g (0.078mol) of 4-chlorophenol, 12.5 ml of concentrated sulfuric acid were placed, warmed gently on a water bath and cooled. To this cooled mixture 38 ml of concentrated nitric acid was added drop wise with vigorous stirring and after the complete addition the reaction mixture was further heated on a water bath for two hours, cooled and poured into crushed ice. The separated orange yellow solid was filtered, washed with water, dried and recrystallized from ethanol water mixture (2:1).

Molecular formula; $C_6H_3N_2ClO_5$; Yield 52.00%; mp 87 ^{0}C; Rf=0.47; IR (KBr, cm^{-1}) 1533(N=O) str, 3093(Ar OH), 2906 (Ar H). ^{1}H NMR (δ ppm, CDCl3) 11.25(s,1H,ArOH) 8.31(m,2H,Ar-H).

Synthesis of 4-chloro-2, 6-diamino phenol

In a dry 100 ml round bottom flask 2 g (0.0115 mol) of 4-chloro-2,6-dinitro phenol, 2.7 g of tin were placed and 10 ml of concentrated hydrochloric acid was added drop wise. The mixture was then refluxed for two hours, cooled and filtered. The filtrate was poured into ice cold water and pH was adjusted to 6.5 to 7.0 with sodium hydroxide solution. Then extracted with ethyl acetate (20ml) in triplicate. The combined ethyl acetate extract was dried over anhydrous sodium sulfate. Ethyl acetate was distilled off using rotavapour and the product obtained was collected.

Synthesis of 4-amino- 6-chloro-1,3-benzoxazole-2-thiol

0.1mol (15.85g) of 4-chloro-2, 6-diamino phenol, 0.1mol (5.6g) of powdered potassium hydroxide and 0.1 mol (5.653g, 7ml) of carbon disulphide in 100ml of ethanol and 20ml of water were refluxed for 3 hours in a 250ml round bottom flask. 3-4g of activated animal charcoal was added to the above refluxed mixture and further heated to 10 min, cooled and filtered. The filtrate obtained was then heated to 60-70^{0}C on a water-bath with 10ml of acetic-acid and 20ml of water where these were added under constant stirring of the filtrate. During this process glistering white crystals were formed and were allowed to crystallise in a refrigerator, overnight. The product thus obtained was collected by filtration, recrystallized from ethanol and dried.

Molecular formula; C_7H_6NSO; Yield 50.00%; mp 138 ^{0}C; Rf=0.58; IR (KBr, cm^{-1}) 3311, 3284 (NH_2), 3230 (Ar H). ^{1}H NMR (δ ppm, $CDCl_3$); 11.38(s,^{1}H,Ar-SH) 6.6 7.28(m,2H,Ar-H).

Synthesis of thiofibrates

Synthesis of ethyl-2-(1,3-benzoxazol-2-ylsulfanyl)-2-methyl propionate from1,3-benzoxazole-2-thiol

0.01 mol (1.5g) of 1,3-benzoxazole-2-thiol dissolved in 10 ml of dimethyl formamide and 0.04 mol (4g) of anhydrous potassium carbonate were taken in a 100 ml round bottom flask attached with dropping funnel and calcium chloride guard tube. 0.01 mol (2.56 ml) of Ethyl 2 bromo isobutyrate in 10 ml of dimethyl formamide was added dropwise to the above solution with constant stirring at room temperature. The reaction mixture was then continuously stirred for about 24 hours and progress of the reaction was monitored by TLC.

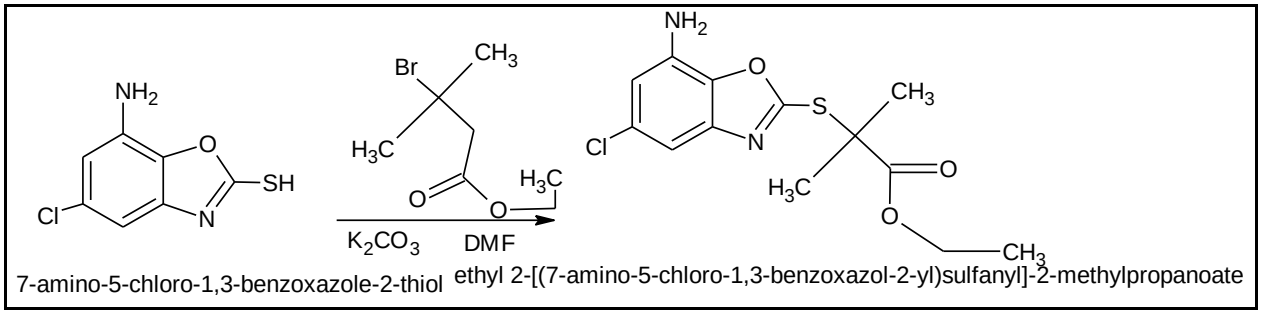
After completion of the reaction, the mixture was added to 300 ml of water and stirred well, the product was extracted with ethyl acetate (3 portions). From the combined extract ethyl acetate was distilled off using rotavapour and oily yellow coloured product separated was then collected (**Scheme 1**).

Molecular formula; $C_{13}H_{16}NSO_3$; Yield 35.00%; mp 84-86 ^{0}C; Rf=0.81; IR (KBr, cm^{-1}) 1734 (C=O), 2981 (CH alkanes), 806 (CH aromatic); ^{1}H NMR (δ ppm, $CDCl_3$); 7.245-7.641i+(m,4H,Ar-H), 4.177-4.230(q,2H,-CH_2), 1.79(s,6H, $(CH_3)_2$),1.169-1.204(t,3H,CH_3).

Synthesis of ethyl2-[(7-amino-5-chloro-1,3-benzoxazol-2-yl)sulfanyl methyl propionate from 4-amino- 6-chloro-1,3-benzoxazole-2-thiol

0.01 mol (2.10g) of 4-amino- 6-chloro-1,3-benzoxazole-2-thiol dissolved in 10 ml of dimethyl formamide and 0.04 mol (4g) of anhydrous potassium carbonate were taken in a 100 ml round bottom flask attached with dropping funnel and calcium chloride guard tube. 0.01 mol (2.56 ml) of Ethyl 2-bromo isobutyrate in 10 ml of dimethyl formamide was added drop wise to the above solution with constant stirring at room temperature. The reaction mixture was then continuously stirred for about 24 hours and progress of the reaction was monitored by TLC.

After completion of the reaction, the mixture was added to 300 ml of water and stirred well, the product was extracted with ethyl acetate (3 portions). From the combined extract ethyl acetate was distilled off using rota vapour and oily yellow coloured product separated was then collected (**Scheme 3**).



Scheme 3: Synthesis of ethyl2-[(7-amino-5-chloro-1,3-benzoxazol-2-yl)sulfanyl]-2- methyl propionate

Molecular formula; $C_{13}H_{16}N_2SO_3Cl$; Yield 37.00%; mp 80-81 ^{0}C; Rf=0.76; IR (KBr, cm^{-1}) 1734 (C=O), 2981 (CH alkanes), 806 (CH aromatic); ^{1}H NMR (δ ppm, $CDCl_3$); 6.60-7.018 (m,2H,Ar-H), 4.170-4.228(q,2H,-CH_2), 3.969(s,2H,-NH_2), 1.793(s,6H, $(CH_3)_2$),1.179-1.215(t,3H,CH_3).

Results and Discussion

4-chloro phenol was nitrated using the regular protocol of nitration in presence concentrated sulfuric acid and concentrated nitric acid. Though our target was to obtain a mononitro derivative ortho to phenolic – OH, the dinitro compound was the major product. Reduction of this dinitro derivative was achieved by metal/acid protocol. Some of the combinations that tried were iron/ HCl, zinc/HCl and tin/HCl *etc.*, From our study it was found that reduction was best achieved with tin/HCl combination. Isolation of the diamine in

quantitative yields was difficult because of the zwitter ionic nature of the molecule which resulted in high water solubility. Hence the mixture was directly taken up for conversion to thiophenol derivative in a one pot synthesis after making the mixture alkaline with potassium hydroxide, addition of CS_2 and refluxing for adequate amount of time. The final intermediate was finally achieved on acidification in fairly good yields. Each of the intermediates synthesized were confirmed by IR and ^{1}H NMR. Purification in certain cases was done by column chromatography. Further alternate protocols are being explored to control the rate of nitration and to improve the yields of mononitro chlorophenol as these are most important intermediates for our synthesis.

Conclusions

The reported compounds were synthesized by conventional methods. The structures of the compounds were characterized by melting point, Rf value, IR and ^{1}H NMR. The presence of SH as singlet at δ 11.38 ppm in the ^{1}H NMR spectra of the compound 1,3-benzoxazole-2-thiol confirms its formation. Also the existence of protons in methylene group quartet at δ 4.177-4.230 ppm, methyl group triplet at δ 1.169-1.204 ppm , dimethyl group singlet at δ 1.79 ppm and aromatic protons multiplet at δ 7.245-7.614 ppm in the ^{1}H NMR spectra of the compound indicates its assigned structures. Similarly the structures of the thiophenol and thiofibrate are in good agreement with their assigned structures.

Acknowledgment

The Authors would like to thanks drugs controller for the state of Karnataka Drug control department for providing the facilities to carry out the present work. The author also extended gratitude to Director NMR research centre IISc, Bangalore for providing spectral details.

References:

1. AijazAS, Tanwir ZK and SajidRS, Sch. Res. Lib.,8(14),109 (2016).
2. Stephan K, IvanaPM and Arnold V.E,Cross Mark.,76**,** 1175(2016)
3. Gamal AI, Omar MA, Gamal AAA El-Din.Radwan MF.Design, synthesis and hypolipidemic activity of novel 2-(m-tolyloxy) isobutyric acid derivatives. Eur. J. Med. Chem.,2009,44(10**):**3973 -3980
4. PriyankaGL., PriyankaSG, DeepaliMJ, VilasraoJ. Growing Advances and Applications of Click Reactions.Am. J. PharmTech Res.,2012,2(4):83-103
5. Mariola K, Boøena K, jerzy K , marta K , graøyna M , marcin C , Julia K, karolina kr”lewska and micha . Dobrowolski. Synthesis and biological activity of novel series of 1,3-benzoxazol-2(3h)-one derivatives. Acta Pol Pharm Drug Res., 2013, 70 (2) :245-253.
6. PeterAS and BrianC, Chromatographic separations, Wiley India Pvt. Ltd., p.53 (2008).
7. SilverstainRM, FrancisXW and DavidJK, spectrometric identification of organic compounds john wiley and sons Inc. New york.p.254 (1997).

*****