WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 10, Issue 2, 1046-1052. Research Article ISSN 2277– 7105

ON THE SYNTHESIS AND CHARACTERIZATION OF METHYL ESTER OF 3-AMINO-4- HYDROXY BENZOIC ACID

***Pralay A. Barhewar,Nagmani W. Pendor, Manoj S. Charde and Rita D. Chakole**

Department of Pharmaceutical Chemistry, Government College of Pharmacy Karad, Saidapur,-415124. Maharashtra, India.

Article Received on
07 Dec. 2020,

Revised on 27 Dec. 2020,
Accepted on 17 Jan. 2021

DOI: https://doi.org/10.17605/OSF.IO/WA4PT

***Corresponding Author**
Pralay A. Barhewar
Department of Pharmaceutical Chemistry, Government College of Pharmacy Karad, Saidapur,-415124. Maharashtra, India.

ABSTRACT

The main objective of medicinal chemistry is to synthesize the methyl ester of 3-amino-4- hydroxy benzoic acid which has a topical as well as local anaesthetic. This anaesthetic have been reported to synthesized by 3-nitro toluene and 4-hydroxy benzoic acid followed by esterification. Here, we reported the synthesis by para hydroxy methyl benzoate. Anaesthetics are a diverse group of drugs that are used for relieving from pain. The administration of anaesthetics is necessary to inhibit the individuals pain pathway and for easiest and safety local surgical procedures. This article describes the easiest, safest, economical way of synthesis of orthocaine. Orthocaine is the methyl ester of 3-amino-4- hydroxy benzoic acid. The synthesis of orthocaine was carried out by nitration followed by reduction of 4-hydroxy methyl benzoate. The reduction procedure are optimized by using various reductive agents. The synthesized compound was further investigated by Thin Layer Chromatography, spectroscopic techniques such as MASS, NMR, ATR-IR and physical constant.

KEYWORDS: Orthocaine, Thin layer chromatography, spectroscopic technique, physical constant, 4-hydroxy methyl benzoate.

INTRODUCTION

The main objective of medicinal chemistry is to synthesize the methyl ester of 3-amino-4-hydroxy benzoic acid.[1] The 4-hydroxy-methyl benzoate is also known as methyl paraben which is used as preservative in many pharmaceutical formulations. Orthocaine is the methyl ester of 3-amino-4-hydroxy benzoic acid which is local anaesthetic. It was found to be limited use due to its low solubility in water but soluble in organic solvents.[2] It is used as dusting

powder for painful wounds, it is ineffective on unbroken skin. It is use as an anaesthetic, but restricted principally to powders and ointments because of its low order of solubility. It occurs as a fine white crystalline powder that is tasteless and odourless.[2] saritha garrepalli reported this methyl ester of 3-amino-4-hydroxy benzoic acid as intermediate from methyl paraben followed by nitration at m-position and then reduction of nitro group into amine by using sodium dithionite.[1] The ortho isomer of nitration was faint in colour and light in weight, here we carried out TLC of intermediate II by using ethylacetate : methanol (2:8) and compound III in dichloromethane : methanol (8:2) rather than saturated methanol. The reduction step was optimized for better yield using various reducing agent such as stannous chloride (SnCl2), $CuSO_4.7H2O$ and sodium borohydride, zinc/HCl but not obtained the desired resulting product, only sodium dithionite gives desired product. The ethanol used dilute (30%) give faster reaction rather than 50% at low yield.[1] The orthocaine solubility found in methanol, ethanol. The intermediates II formed are evaluated by TLC, physical constant and by IR spectrophotometer. This orthocaine usually synthesized by m-toluene and 4-hydroxy benzoic acid, while here it synthesized from p-hydroxy methyl benzoate and this also found as intermediates in synthesis but till this not reported yet. The benzoxazole is formed from methyl ester of 3-amino-4-hydroxy benzoic acid by aldehyde, carboxylic and acyl chloride conventionally as well as microwave assisted reaction.[4] saritha garrepalli report their melting point 110-112℃ but found that 98-100℃.[1]

MATERIALS AND METHODS

All the reagents and solvents used were synthesis grade. The melting point of synthesise compounds were determined by open capillary method and were uncorrected. The purity of compound were checked using TLC. IR spectra of compound were recorded using bruker ATR-IR.[3]

Experiment

Procedure for synthesis of aminated methyl ester of benzoic acid

1) 4-Hydroxy-3-nitro benzoic acid methyl ester (II)

In a 1 litre three necked round bottom equipped with water condenser, mechanical stirrer and thermometer, p-hydroxy methyl benzoate (10 gm, 0.065 mol) was placed. A mixture of concentrated nitric acid (6.2 ml) and concentrated sulphuric acid (6.2 ml)in a dropping funnel, cool the flask in an ice bath to 0-10℃ and then run in the nitrating mixture in para hydroxy methyl benzoate with stirring, while maintaining the temperature of reaction

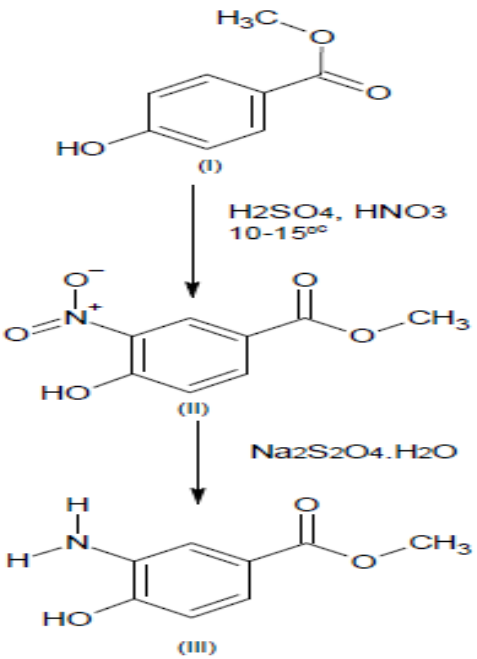
between 5-15℃, the addition continued up to 1 hour. Poured the reaction mixture in to crushed ice. Filter off the crude m-nitro-p-hydroxy methyl benzoate and wash with cold water. Transfer the solids into 500 ml flask and stirred it with ice cold methanol in order to remove a small amount of ortho isomer and other impurities. The mixture was filtered and washed with little methanol and dried in the air. The product was recrystallised by methanol as solvent.[1]

Percentage yield – 95%, **M.P.**-66-69℃.

2) 3-Amino-4-hydroxy-benzoic acid methyl ester (III)

In a 500 ml three necked flat bottom flask equipped with reflux condenser with guard tube, compound II (0.065 mol) was dissolved in boiling alcohol (30%,100 ml) and sodium dithionate was added to this boiling alcohol solution until it becomes almost colourless. Then the alcohol was reduced to one third of its volume by distillation and the residual liquid was triturated with ice cold water. The resulting colourless, shiny product was filtered, washed with cold water, dried and recrystallise with hot water. The reduction process is optimized for better yield (compound III) by stannous chloride (Sncl2), zinc/HCL, sodium borohydride but there is no desired product obtained.[1]

Percentage yield- 46.36%, **M.P.**-98-100℃.



Scheme of synthesis.

RESULTS AND DISCUSSION

1. Thin layer chromatography (TLC)

Thin layer chromatography of synthesised compound (III) was carried out by using precoated silica plate. The selected mobile phase for run the compound is dichloromethane: methanol (8:2). Then the sample is run on the plate and developed the chromatogram. The spot is visualised under UV 254 nm, 365 nm and under visible light.

Compound II: ethyl acetate: methanol (2:8), retention factor- 0.70 Compound III: dichloromethane: methanol (8:2), retention factor- 0.63.

2. Melting point

The melting point of synthesised compound II and III was determined by the open capillary method using digital melting point apparatus, the resulting melting point was found to be Compound II - 66-69℃.

Compound III - 98-100℃ .

3. IR Spectroscopy

The ATR-IR spectra of synthesized compound II and III was recorded from government college of pharmacy karad by using bruker ECO ATR-IR crystal spectrophotometer. The resulting wavenumbers of compound are as follows.

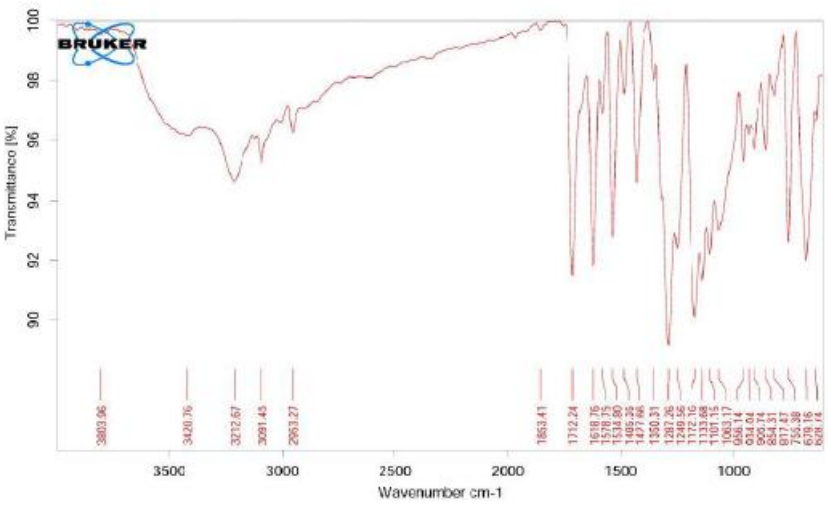


Fig. no. 1: ATR-IR spectra of compound II.

Table no. 1: ATR-IR ranges of compound II.

Functional group	Wavenumbers (cm^{-1})	Functional group	Wavenumbers(cm^{-1})
O-H stretch	3420	N-O sym.	1534
C=O	1712	N-O asym.	1350
C=C	1618	C-O	1172

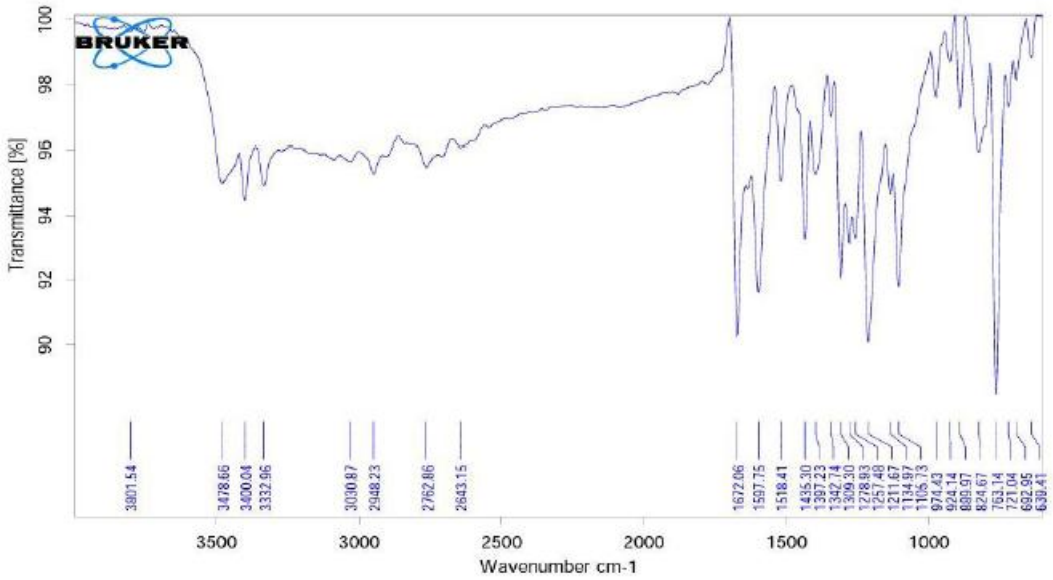


Fig. No. 2: ATR-IR of methyl ester of 3-amino-4-hydroxy benzoic acid(comp.III).

Table No. 2: ATR-IR ranges of methyl ester of 3-amino-4-hydroxy benzoic acid.

Functional group	Wavenumber (cm^{-1})	Functional group	Wavenumber (cm^{-1})
N-H sym. Stretch	3332	C=N	1597
N-H asym. stretch	3478	C=C	1518
O-H stretch	3400	C-O alkoxy	1211
C=O	1672	C-H bend	763

4. MASS spectroscopy

The mass of the synthesised compound was determined by GC-MS spectrophotometer from Punyashlok Ahilyadevi Holkar Solapur university, Solapur. MS (m/z):100% 167 [M+] 100%) calculated 167, found 167. Molecular ion peak found at m/z 167 and base peak at m/z 136, Fragments of compound are follows.

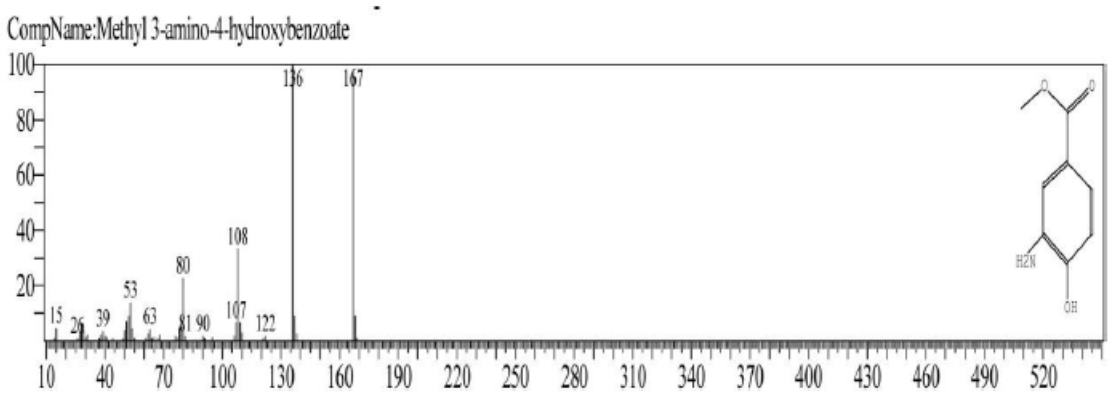


Fig. no. 3: mass spectra of methyl ester of 3-amino-4-hydroxy benzoic acid.

Table no. 3: Fragments of methyl ester of 3-amino-4-hydroxy benzoic acid.

Fragments	m/z ratio	Fragments	m/z ratio
C8H9NO3	167	C4H2NO	80
C7H6NO2	136	C4HN	63
C6H6NO	108	C2HN	39

5. NMR spectroscopy

NMR spectroscopy of methyl ester of 3-amino-4-hydroxy benzoic acid was determined by bruker NMR (400 MHz) using DMSO as solvent at Punyashlok Ahilyadevi Holkar Solapur University, Solapur. The 1H NMR chemical shift of methyl ester of 3-amino-4-hydroxy benzoic acid was found to be-

1H NMR **(**DMSO) 7.46 (s, 1H), 7.43 (m, 2H), 7.26 (s, 3H), 6.76 (m, 4H), 3.83 (s, 5H), 7.44(s, 1H), 6.74 (m 4H).

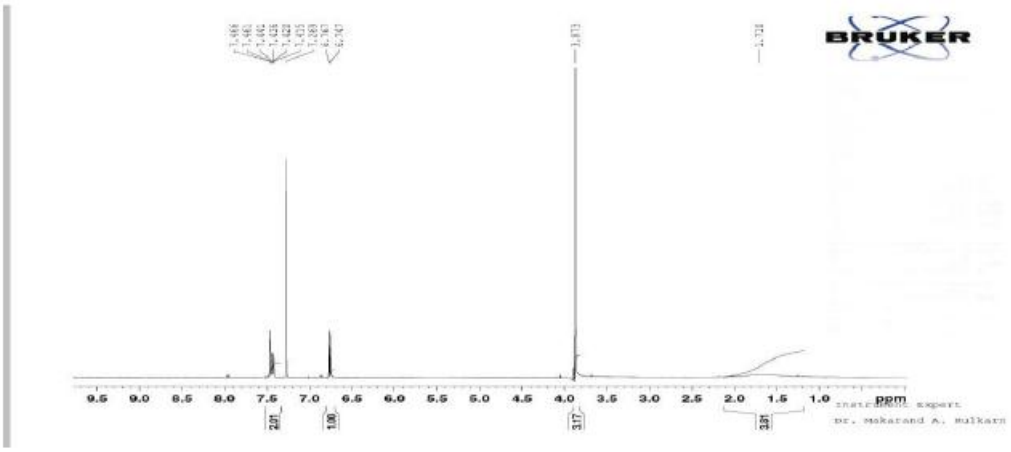


Fig. no. 4: 1H NMR spectra of methyl ester of 3-amino-4-hydroxy benzoic acid.

6. UV spectroscopy

The UV spectra of the compound III was recorded by using SHIMADZU UV win 1800 containing deuterium lamp, the compound (10 mg) was dissolved in methanol (100 ml) (AR), make dilutions to 10 µg concentration. The maximum wavelength was found to be 264 nm, calculated-268 nm.

Table No. 4: Physical properties of comp. II and III.

Sr. No.	% Yield	TLC	Melting point	Solubility
Comp. II	95.00 %	0.70	66-69 ℃	Soluble in ethyl acetate, dichloromethane Insoluble in ethanol, methanol, water, diethyl ether
Comp. III	46.36 %	0.63	98-100 ℃	Insoluble in cold water Soluble in methanol, ethanol

CONCLUSION

Synthesis of methyl ester of 3-amino-4-hydroxy benzoic acid from p-Hydroxy methyl benzoate in two step is easier, convenient and economical. The reduction of 3-nitro-4-hydroxy methyl benzoate using sodium dithionite gives the desired reductive product while the other reductive reagents not gives the resulting product. The diluted ethanol (30%) was best suitable and proceed fast reaction of reduction step. The synthesis was carried out without any hazards and in safety, easiest and economical ways.

ACKNOWLEDGEMENTS

The author are grateful thank to Head, pharmaceutical chemistry department, government college of pharmacy karad and my colleagues for providing necessary facilities and helping me to carry out the research work.

REFERENCES

1. Saritha Garrepalli et. al. Journal of Pharmacy Research, 2012; 5(2): 1191-1194. ISSN: 0974-6943.
2. Rajbir singh Synthetic drugs, mittal publications, 2002; pp.167-8. ISBN 978-81-7099-831-0.
3. Shiyang Zhou, Guangying Chen, Huiying Zou, Royal Society of Chemistry, 2019; 9, 6627-6635.
4. K.Srinivas et, al. International Journal of Chemical Science, 10(2): 2012; 619-626 ISSN 0972-768X.