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Research Article

Synthesis and Antioxidant Study Of 4-(1- Benzofuran-2-Yl)-1,3-Thiazole-2-Amine and its Derivatives

Vidyashri Kamble*, Bhalchandra Habade, Rupali Bendgude

Shri Ganapati Institute of Pharmaceutical sciences and Research, Tembhurni, Dist.-Solapur.

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ABSTRACT

Salicylaldehyde upon treatment with bromoacetone in presence of anhydrous potassium carbonate give 2-acetylbenzofuran. (III) This 2-acetylbenzzofuran after bromination give bromoacetylbenzofuran. (IV). This bromoacetylbenzofuran on treatment with thiourea in ethanol gives 4 (1-benzofuran-2-yl)1,3-thiazole -2-amine. (V) The corresponding compound (V) on treatment with various aldehydes to give different derivative (VI). The characterization of synthesized compounds was identified o the basis of IR, NMR, MASS and elementary analysis. The compound has been evaluated for anti-bacterial, anti-inflammatory, and analgesic activity. The present study is focused on the development of new potent bioactive molecule with less toxic, safer and easy available. Modern therapeutic is based on scientific observation supported by systematic assessment of activity of drug is simulated and clinical condition. The integrity of the drug molecule, optimization Antioxidant properties of drug from the dosage.

INTRODUCTION

The benzofuran nucleus and derivatives occupy a position of considerable significance for widespread occurrence in plants and their potential as important pharmaceuticals. It has also been reported that benzofuran derivative possess bacteriostatic, bactericidal, fungistatic, fungicidal activities. The natural products possessing benzofuran nucleus are frequently associated with useful pharmacological properties. This fact created interest in synthetic products containing benzofuran nucleus. Kreamer and Spilker discovered benzofuran in coal tar. It was synthesized by Perkin in 1870. Thus the chemistry of benzofuran has developed in a spectacular fashion during the last several years. The voluminous work accumulated in this area is based on one or the following lines.

***Corresponding Author:** Vidyashri Kamble
Address: Shri Ganapati Institute of Pharmaceutical sciences and Research, Tembhurni, Dist.-Solapur.
Email ✉: vidyashri.kamble@gmail.com

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1. Isolation, structural elucidation and synthesis of various natural products of plant origin enclosing benzofuran nucleus.
2. Synthesis of benzofuran derivatives with biological, pharmacological, therapeutic or toxic properties.
3. Study of physicochemical properties of both synthetic and natural benzofuran compounds. [1-6]

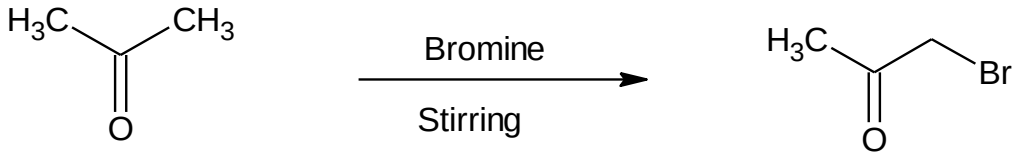
MATERIAL AND METHOD

All the chemical used were procured from Qualingens, Himedia and Loba-chemicals. Purity of starting materials used for reaction was confirmed by checking their melting point or boiling point and by thin layer chromatography.

All the reactions were monitored using thin layer chromatography. The appropriate mobile phase (solvent systems) as applicable were developed using 'silica gel G' as stationary phase. Melting point were determined in open capillary tube using PRECISION MELTING POINT APPARATUS and uncorrected. FT-IR (KBr) spectra were recorded on "SHIMADZU FT-IR 8400S" spectrophotometer. ^{1}H NMR spectra of synthesized compound were recorded on "FTNMR BRUCKER" spectrometer at 300 MHz frequency in DMSO using TMS as internal standard (chemical shift δ ppm) at Shimadzu Analytical Centre and NMR facility, Dept. of Chemistry, IIsc Bangalore. Mass spectra were recorded on "SHIMADZU GC-MS QP-5050" instrument by direct injection method at Shimadzu Analytical Centre, Dept. of Chemistry, University of Pune. Purity of compounds was checked on "Silica Gel G" coated on laboratory micro slides prepared by dipping method or precoated plates, eluent was the mixture of different polar and non-polar solvents in varying proportions and detection was done either by observing in UV (ultra-violet) light or exposure to iodine vapours as required. The absence of TLC spots for starting materials and appearance of new TLC spot at different R_f value ensured the completion of reaction.

The products of all the reactions were purified initially by different workup process to remove unreacted starting materials if any and then by recrystallization using suitable solvent. The absence of any impurity of starting materials or possible by product was ensured by performing qualitative organic analytical tests for various functional groups. All the compounds were prepared by standard methods as outlined in the Scheme.

1) Synthesis of 1- bromoacetone.



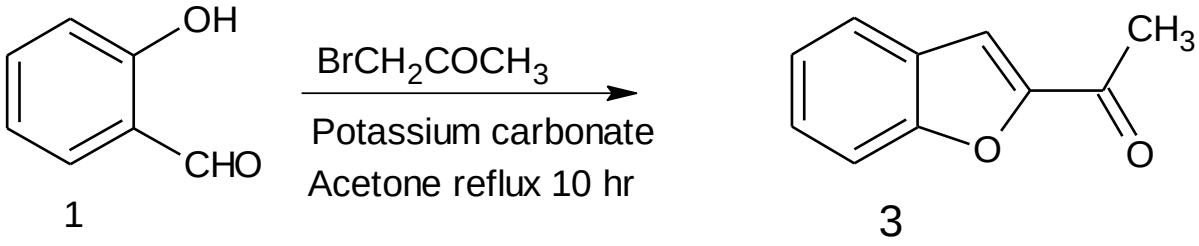
acetone 1-bromoacetone

Procedure

In 500 ml 3-necked round bottom flask charged with 160 ml water 50 ml pure acetone, 37.2 ml glacial acetic acid. The reaction mixture was warmed to a temperature of 60-70^0 C inside temperature. It was kept under stirring magnetically. one of the neck was connected to quick fit dropping funnel and few ml (2.3 ml) added drop wise initially the reaction mixture was exposed to lamp until the reaction mixture was initiated (disappearance of bromine colour) then the addition of bromine continued while observing disappearance of bromine colour after complete reaction the reaction mixture was stirred for a

further period of 30-60 min. The reaction mixture was poured in ice cool water. It was neutralized by addition of solid Sodium carbonate little by little. The oil separated after neutralization it was extracted with ether. Ether extract was dried over anhydrous calcium chloride. The clear ether solution was decanted into another dry conical flask and evaporated on hot water bath residual oil of removal ether and unreacted acetone the product is bromoacetone. It was stored in Amber colored bottle. [7-9]

2) Synthesis of 2-acetyl benzofuran



1 Salicylaldehyde

3 1-(1-benzofuran-2-yl)ethanone

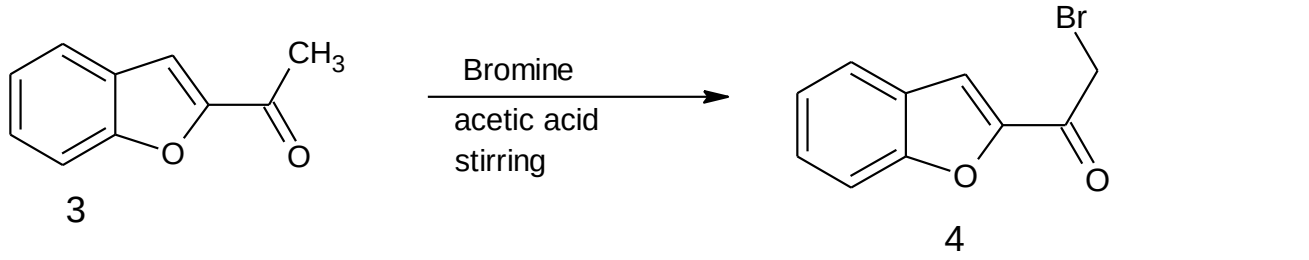
Procedure

In completely dried round bottom flask 12.2 ml of salicylaldehyde was taken then it is charged with Bromoacetone (8.3 ml) with addition of 150 ml anhydrous acetone to this reaction mixture 35 gm of anhydrous acetone was added. Round bottom flask was attach to condenser and reflux for 10 hr. in water bath by maintaing temperature for reflux and stirred iit continuously. After 10 hr reaction mixture cooled to room temperature and filtered by funnel to get clear solution then 10-15 ml acetone was used to to wash potassium carbonate filtrate was taken in dry flask and acetone was removed by vaccum pump crystallization was achieved by petroleum ether on hot plate.

Melting point of 2-acetylbenzofuran = 75^0 C

NMR of 2- acetyl benzofuran

3) Synthesis of 1-(1-benzofuran-2-yl)-2-bromoehanone

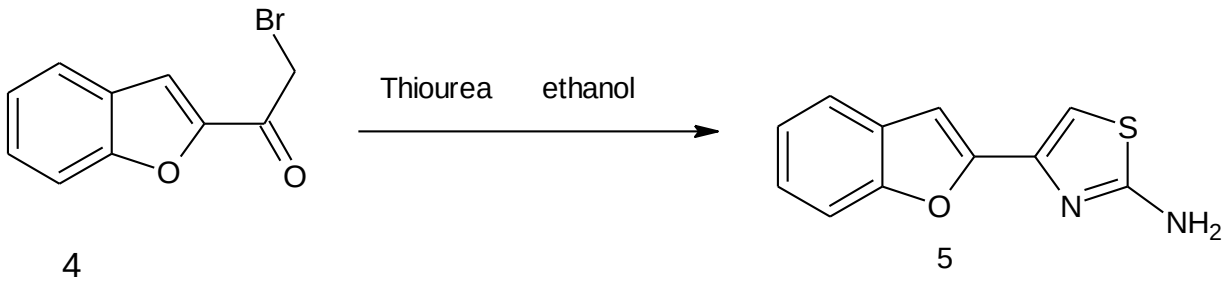


3 1-(1-benzofuran-2-yl)ethanone

4 1-(1-benzofuran-2-yl)-2-bromoethanone

A solution of bromine (12 gm 0.075 mole) in acetic acid (100ml) was added drop wise with stirring to a solution of 2-acetylbenzofuran (12gm, 0.075 mole) in acetic acid (100ml). after complete addition of bromine, the mixture was stirred for 45 min and allowed to stand for 30 min. then the mixture was decanted in crushed ice, the solid separated was collected and crystallized from ethanol as light green crystals mp =88^0 C.

4) Synthesis of 4(1-benzofuran -2-yl)-1,3-thiazole-2-amine



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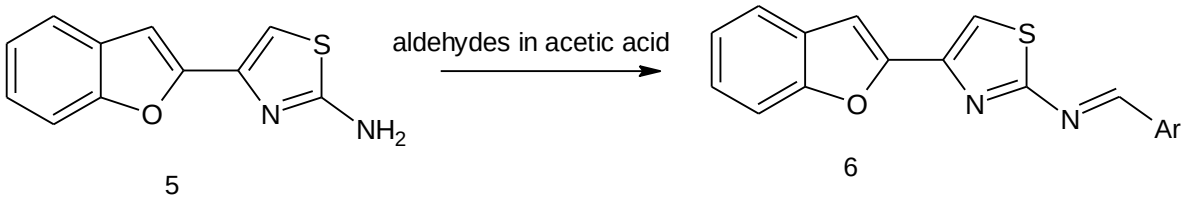
1-(1-benzofuran-2-yl)-2-bromoethanone

5

4-(1-benzofuran-2-yl)-1,3-thiazol-2-amine

A Solution of bromoacetylbenzofuran (11.95 gm, 0.05 mole) and thiourea (3.5gm, 0.05 mole) was refluxed in ethanol (250 ml) for 2 hrs. the reaction mixture was then cooled, poured in to cold water and neutralized with 5% aqueous sodium acetate. The solid thus obtained was collected and recrystallized from ethanol as colorless tiny crystals.

5) Synthesis of 4-(1-benzofuran-2-yl)1, 3-thiazole-2-amine derivative



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4-(1-benzofuran-2-yl)-1,3-thiazol-2-amine

6

4-(1-benzofuran-2-yl)-1,3-thiazole-2-amine derivative

In two necked round bottom flask take 20ml absolute ethanol. to this add 1gm of . 4-(1-benzofuran-2-yl)-1,3-thiazole-2-amine to this solution add equimolar amount of different aromatic aldehyde reflux for 7-8 hr. The resultant reaction mixture was cooled, poured into the ice-cold water. The solid separated was filtered and dried. The solid was recrystalized into ethanol. [11-14]

Compound	Molecular Formula	Molecular Weight	% yield	Melting point (uncorrected)
VI-a	$C_{18}H_{12}N_20S$	304	62.4%	235^0C
VI -b	$C_{18}H_{11}N_30_3S$	349	71.1%	245^0C
VI -c	$C_{18}H_{11}BrN_20S$	383	74.3%	285^0C
VI -d	$C_{18}H_{11}FN_20S$	322	68.4%	254^0C
VI -e	$C_{20}H_{17}N_30S$	347	69.4%	225^0C

IR data in KBr (cm^{-1}) of 4-(1-benzofuran-2-yl)-*N*-[(1*Z*)-phenylmethylene]-1,3-thiazol-2-amine.(VI-a):

Group	Wavenumber In CM $^{-1}$
Aromatic C=C stretch	1607.70
Aromatic C – H stretch	2979.83,
Aliphatic C – H stretch	2966.48,
C=O stretch	1660
C-O Stretch of C – O – C	1235.50, 1022.06
C – S stretch	681.12

Antioxidant Study of Derivatives

There are number of *in vitro* methods to measure the efficiency of antioxidants either as pure compounds or as plant extracts. *In vitro* methods

can be divided into two major groups: 1) Hydrogen atom transfer reactions like Oxygen Radical Absorbance Capacity (ORAC), Total radical trapping antioxidant potential (TRAP) and carotene bleaching; 2) Electron transfer reactions like trolox equivalent antioxidant capacity (TEAC), Ferric reducing antioxidant power (FRAP), diphenyl- -picryl-hydrazyl radical scavenging assay (DPPH), Superoxide anion radical scavenging assay, Hydroxyl radical scavenging assay, Nitric oxide radical scavenging assay and Total phenol assay. These methods are popular due to their high speed and sensitivity.

DPPH Assay

Procedure

The DPPH assaying of compounds VI-d and VI-e was performed using Trolox as reference compound. 0.01mg/mL solution of DPPH in methyl alcohol was prepared and 1ml was transferred to 4 ml of sample in methyl alcohol to obtain divers dilution (0.5, 1.0, 3.0, 5.0, 7.0 mg/mL) Absorbance was noted and compared to blank at wavelength max 517 nm by UV- Visible spectrophotometer. The radical scavenging capacity was articulating in IC_{50} . In the presence of antioxidants, DPPH generates a violet/purple color in methanol solution and diminishes to shades of yellow. [15]

% Inhibition = [(Abs of compound – Abs of sample)/ Abs of compound x 100.

Compound VI d

Sr	Conc. mg/mL	% Inhibition
1	0.5	24
2	1.00	32
3	3.00	42
4	5.00	54
5	7.00	65

Compound VI e

Sr	Conc. mg/mL	% Inhibition
1	0.5	20
2	1.00	28
3	3.00	36
4	5.00	44
5	7.00	53

RESULT AND DISCUSSION-

All the reactions were monitored by TLC, structures and purity of the anticipated compounds were characterize by physical constant and FTIR spectral studied. Absence of TLC spots for starting materials and appearance of new TLC spot at different R_f value were ensured to declare completion of reaction. The TLC plates were visualized either by Iodine vapours or by viewing in UV-Visible chamber. The reaction products of all the reactions were purified by different workup processes to remove unreacted starting materials if any and then by recrystallisation using suitable solvents. Most of the steps were optimized in order to achieve quantitative yields i.e. more than 70% yields. The FT-IR in KBr (cm^{-1}) spectra of compound 3, indicated decrease in band strength of C=O (1664) due to intermolecular hydrogen bonding and specific band of C=C at 1588, C-O-C at 1080 thus confirming the formation of 2-Acetyl benzofuran. The FT-IR in KBr (cm^{-1}) spectra of compound 4 showing bands at 1583.23 (Ar-CH), 1088 (C-O-C), 828.42 (C-Br), 1345. The FT-IR in KBr (cm^{-1}) spectra of compound 5 showing a characteristic band at 3315.90 ($–NH_2$) which confirms the attachment of thiourea and formation of 2-amino-4-(benzofuran-2-yl) thiazole Final derivatives showed the expected bands for the characteristic groups which are present in the compounds such as-C-N and C-O-C bands. Formation of new peaks at around 3000, 600-800 confirms the formation of derivatives.

Antioxidant activity was also performed by using DPPH method the intensity of colour compound was measured by using UV-Visible spectrophotometer.

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