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ENHANCED FISCHER'S SYNTHESIS OF BROMO DERIVATIVES OF BRIDGED CARBAZOLE AND ANTIBACTERIAL EVALUATION

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ABSTRACT

Heterocyclic compounds are organic compounds with ring structure containing hetero atoms like sulfur, oxygen or nitrogen in addition to carbon atoms. Many heterocyclic compounds due to their specific activity are employed in the treatment of many infectious diseases. Carbazole derivatives have been found to possess a wide range of biological activities. 6-bromo-1,2,3,4-tetrahydro-5H-carbazole **A**, 8-bromo-6,11dihydro-5H-benzo[b]carbazole **B** have been synthesized by enhanced Fischer's method using a medium of acetic acid. 3,7-dibromo 5,10-dihydro diindolo[3,2-b]carbazole **C, D** was synthesized with suitable solvent by Fischer's method. 1-benzyl 8-bromo-2,3,4,5-tetrahhydro-1H-pyrido[3,2-b]indole **E**, 7-bromo-1,2,3,4-tetrahydro cyclopenta[b]indole **F** has also been synthesized in good yield by Fischer's synthesis with the solvent acetic acid in addition to sulphuric acid. All the synthesized compounds were characterized and confirmed by various instrumental techniques *Viz,* UV, FTIR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy. To examine the antibacterial activity of all the synthesized compounds, the antibacterial activity have been carried out for the pathogens like *Staphylococcus Aureus, Streptococcus faecalis, Escherichia coli, Salmonella typhi* by zone of inhibition method using ciprofloxacin as reference. The result showed that the synthesized compounds exhibit excellent antibacterial activity with respect to the reference ciprofloxacin.

Key words: Acetic acid, 4-bromo phenylhydrazine hydrochloride, ciprofloxacin, cyclohexane -1,4-dione.

INTRODUCTION

Among, all heterocyclic compounds discovered so far, nitrogen containing heterocycles are most important class of compounds in pharmaceutical and agrochemical industries. Nitrogen heterocycles appear in the core structure of several drugs marketed worldwide. Due to importance of nitrogen heterocycles in medicinal chemistry, pharmaceutical industry, various drug development areas and their importance in the material science are given for their synthesis and characterization. An indole is characterized as a benzene ring fused to a nitrogen-containing five membered heterocylic ring. [i]. Carbazole derivatives are well

known for their pharmacological activities. These compounds have been reported to possess diverse biological activity like antibacterial and antifungal activities.

Carbazole derivatives like ellipticin, and alkaloids such as vincristine, vinblastine found to have a well established role in the treatment of cancer. [ii-iv]. Scmeiss., *et al,* has been reported the synthesis of 1-Substituted and 1,9-disubstituted-1,2,3,4-tetrahydro-9H-Carbazole using Carbazole derivative. Deoxygenation of o-nitrobiphenyl to carbazole was first reported by waterman and Viviens by using iron oxalate at 200ºC. The widely accepted mechanism involves exhaustive deoxygenation to singlet nitrene that undergoes a downstream C-H insertion. Cadogen *et al 1991* have been reported a similar deoxygenative cyclization of o-nitrobiphenyl to carbazole under using trithylphosphite as solvent.

The Spread of drug resistant bacteria has badly affected the efficiency of many known antibacterial agents [v]. The emergence of fungal infections in the immuno-compromised population have also significantly increased over past few decades [vi-vii]. Carbazoles are considered to be one of the important classes of antimicrobial agents [viii-ix]. Zhang *et al.*2014 [x] have reported the antibacterial and antifungal activities of series of *N*-substituted carbazoles. The main aim of this study is to develop novel, efficient, convenient, selective and eco friendly synthetic methods in organic chemistry, which helps the drug discovery and medicinal chemistry. Here in, the present investigation delineate a general and facile approach for the construction of heteroyclo[b]fused carbazoles.

RESULT AND DISCUSSION

3,7-dibromo 5,10-dihydro diindolo[3,2-b]carbazole.

The FTIR spectrum **compound A** shows the band present at 3410 cm^{-1} and 3169 cm^{-1} have assigned to N-H and =C-H stretching vibrations respectively. The sharp band appeared at 2858 cm^{-1} associated the aliphatic C-H stretching vibration. The intensity band at 1627 cm^{-1} due to C=C stretching vibration. The stretching frequency observed at 1373 cm^{-1} was related to the C-N stretching vibration. The intensity band occur at 1234 cm^{-1} observed due to C-C stretching vibration. The stretching frequency observed at 711 cm^{-1} due to C-Br stretching vibration.

The ^{1}H NMR spectrum of 3,7-dibromo 5,10-dihydro diindolo[3,2-b]carbazole, the chemical shift at 12.1 ppm attributed to the N-H proton. The two doublet of two protons appeared at 7.1-7.3 ppm represented by **'a'** protons. The two doublet signal of two protons appeared at 7.5-7.9 ppm denoted as **'b'** protons. The four protons singlet appeared at 3.17-3.34 ppm corresponds to **'c'** proton. . The two protons singlet appeared at 7.3-7.5 ppm corresponds to **'d'** proton. The solvent peak appeared at 2.5 ppm. [xi].

The **compound A** have also confirmed using ^{13}C NMR spectrum. The aliphatic peak observed at 23.13 represented as '**a'**. The chemical shift value 154.02 ppm corresponds to the carbon **'b'** present neighbouring to nitrogen atom. The carbon signal observed at 193.4 ppm corresponds to '**c'** carbon. The peak appeared at 111.7 ppm -135.1 ppm attributed aromatic carbons. The solvent peak appeared at 40 ppm [xii].

The mass spectrum of 3,7-dibromo 5,10-dihydro diindolo[3,2-b]carbazole has molecular ion peak at m/z 418.049(M+2). Calculated and observed molecular mass is good agreement with each other. The base peak value at m/z 173.

3,7-dibromo 5,10-dihydro diindolo[3,2-b]carbazole.

The FTIR spectrum of 3,7-dibromo 5,10-dihydro diindolo[3,2-b]carbazole has the intensity band at 3400cm^{-1} observed due to the N-H stretching vibration. The medium at 3064 cm^{-1} have assigned to the aromatic =C-H stretching vibration. The sharp band appeared at 2924 cm^{-1} associated the aliphatic C-H stretching vibration. The stretching frequency obtained at 1589 cm^{-1} due to C=C stretching vibration. The stretching absorption occur at

1315 cm^{-1} have assigned to the C-N stretching vibration. The stretching frequency obtained at 1257 cm^{-1} observed due to C-C stretching vibration. The intensity band occur at 667 cm^{-1} was related to C-Br stretching vibration.

In the ^{1}H NMR spectrum of 3,7-dibromo 5,10-dihydro diindolo[3,2-b]carbazole, a singlet peak appeared at 11.8 ppm due to N-H proton.. For two protons two doublet signal appeard at 6.7-6.9 ppm have denoted by **'a'** protons. The multiplet signals appeared at 7.0-7.4 ppm equivalent to two protons represented by **'b'** proton. For four protons two doublet signal appeard at 3.3 ppm denoted as **'c'** protons. The singlet peak appeared at 7.5 ppm denoted by '**d'** proton. The solvent peak appeared at 2.5 ppm [xiii].

The signal appeared at 29 ppm represented as '**a'** carbon. The chemical shift value 132.6 ppm corresponds to the '**b'** carbon present neighbouring to nitrogen atom. The signal at 137.8 ppm corresponds to the '**c'** carbon. The signal appeared in the range 113 ppm- 131 ppm attributed to the aromatic carbons. The solvent peak appeared at 40 ppm [xii].

The mass spectrum of 3,7-dibromo 5,10-dihydro diindolo(3,2-b)carbazole have assigned the molecular ion peak at m/z 418.04(M+2). The base peak appeared at 43.1.

1-benzyl 8-bromo-2,3,4,5-tetrahhydro-1H-pyrido[3,2-b]indole.

The FTIR spectrum of the **compound C** shows the sharp intensity band at 3414 cm^{-1} observed due to the N-H stretching vibration. The band at 3059 cm^{-1} assigned to the aromatic =C-H stretching vibration. The sharp band appeared at 2856 cm^{-1} and 2924 cm^{-1} associated the aliphatic C-H stretching vibration. The stretching absorption occur at 1595 cm^{-1} attributed C=C stretching vibration. The frequency appeared at 1311 cm^{-1} assigned to the C-N stretching vibration. The stretching frequency obtained at 1253 cm^{-1} observed due to C-C stretching vibration. The intensity band at 700 cm^{-1} due to C-Br stretching vibration.

In the ^{1}H NMR spectrum of 1-benzyl 8-bromo-2,3,4,5-tetrahhydro-1H-pyrido[3,2-b]indole, a singlet peak appeared at 10.2 ppm due to N-H proton. The two doublet signal appeared at 7.1 ppm for **'a'** protons.The multiplet signal appreared at 7.4-7.7 ppm due to **'b'** proton. The chemical shift of two doublet appeared at 7.3 ppm denoted as **'c'** proton. The singlet appeared at 3.3 ppm for **'d'** proton.The chemical shift of three triplet signal appeared at 2.2, 1.2, 2.5 ppm denoted as **'e', 'f'** and **'g'** proton. The singlet signal appeared at 7.2 ppm represented by **'h'** proton. The solvent peak appeared at 2.5 ppm. [xiv].

The aliphatic carbon signals appeared at 24 ppm, 29 ppm and 39 ppm represented by '**a', 'b', 'c'.** The carbon signal observed at 40 ppm and 135 ppm corresponds to '**d'** and '**l'** carbon. The carbon present at the condensed position denoted as **'e'** and **'i'** signal appeared at 110 ppm and 122 ppm. In ^{13}C spectra signals at around 113 ppm 116 ppm, 121 ppm, 127 ppm, 129 ppm and 135 ppm confirms the presence of nine aromatic carbon represented by **'f', 'g', 'h', 'j' and 'k'**. The carbon signal observed at 136 ppm and 137 ppm corresponds to **'m'** and '**n'** carbon adjacent to nitrogen atom. The solvent peak appeared at 40 ppm. **.**

The molecular ion peak of the **compound C** observed at m/z 342.8(M+1). The mass spectrum of 1-benzyl 8-bromo-2,3,4,5-tetrahhydro-1H-pyrido[3,2-b]indole has the base peak value observed at m/z 171.

Antibacterial activity

The results of antibacterial activity of synthesized compounds **A, B & C** have shown Table **1**. The zone of inhibition was indicated the nature of antibacterial activity. The synthesized compounds were subjected to *Staphylococcus aureus, Streptococcus faecalis, Escherichia coli, Salmonella typhi*. Compound **A** shows no zone of inhibition against *Staphylococcus aureus, Escherichia coli* indicates that these compounds shows no antibacterial activity. Compound A found to posses excellent activity against *Streptococcus faecalis.* The synthesized compounds **B & C** shows similar antibacterial activity against *Staphylococcus aureus.* Based on the survey of the antibacterial activity, among the synthesized compounds

A, B & C , Compound C found to have good antibacterial activity.

EXPERIMENTAL SECTION

Synthesis of 3,7-dibromo 5,10-dihydro diindole[3,2-b]carbazole

Scheme **1** indicates the synthesis of **compound A** by Fischer's synthesis of 4-bromo phenylhydrazine hydrochloride (0.0024mmol, 0.5371g) with 1,3 cyclohexane dione (0.0024mmol, 0.5388g) using glacial acetic acid as a suitable solvent medium (20ml). The reaction mixture was heated to reflux for about 3 hours due to the completion of reaction. The progress of the reaction was monitored by TLC. After the reaction was over, the reaction mixture was poured in to crushed ice with vigorous stirring up to 30 minutes. The crude solid was filtered, washed with water and dried. The dried product was recrystallized using methanol hence obtained the pure product 3,7-dibromo 5,10-dihydro diindolo[3,2-b]carbazole.

Yield: 70 %, Melting point 162℃, FTIR(KBr): N-H- 3410 cm^{-1} , =C-H- 2935 cm^{-1} , C-H- 2858 cm^{-1} , C=C- 1469 cm^{-1} , C-Br- 711 cm^{-1}. ^{1}H NMR (DMSO d-6) in ppm: 12.1 N-H, (7.3-7.5, 2H- t) , 7.5-7.9(m,2H) & 3.1-3.3(s,4H). ^{13}C NMR (DMSO d-6) aliphatic carbons 29 ppm , aromatic carbons 111-135ppm, C-Br carbon at 193ppm. Mass spectrum: m/e ratio 418.2 (M+2).

Synthesis of 3,7-dibromo 5,10-dihydro diindole[3,2-b]carbazole

To a mixture of 1,4-cyclohexane dione (2.4mmol, 0.2694g) and glacial acetic acid (20ml) were taken in a round bottom flask fitted with reflux condenser. 4-bromo phenylhydrazine hydrochloride (2.4mmol, 0.5371g) was added drop wise to the reaction mixture with uniform stirring using a magnetic stirrer. The reaction mixture was refluxed for about 4-5 hours. The completion of the reaction was monitored by TLC. The mixture was poured into crushed ice cold water, the formed precipitate was filtered off and washed with water. The crude product was purified by recrystallization from suitable solvent methanol in order to obtained pure 3,7-dibromo 5,10-dihydro diindolo[3,2-b]carbazole **B**.

Yield: 75 %, Melting point 170 ℃, FTIR(KBr): N-H- 3400 cm^{-1} , C-H- 2852 cm^{-1} , C=C- 1498 cm^{-1} , C-Br- 667 cm^{-1}. ^{1}H NMR (DMSO d-6) in ppm: 11.8 N-H, 7.07-7.4(m,2H), 6.71-6.9(2d,2H), 7.5(s,2H) & 3.3(s,4H) . ^{13}C NMR (DMSO d-6) aliphatic carbons 29 ppm , aromatic carbons 113-137ppm. Mass spectrum: m/e ratio 418.04 (M+2).

Synthesis of 1-benzyl-8-bromo-2,3,4,5-tetra hydro-1H-pyrido [3,2-b] indole

Compound C was synthesized using Fischer's method by taking the mixture of benzyl-4-piperidone (2.9mmol, 0.5545g) and 4-bromo-phenylhydrazine hydrochloride (2.9mmol, 0.6548g) in glacial acetic acid (10ml) in RB flask. The resulting reaction mixture was refluxed with constant stirring for 5 hours at 80ºC.The progress of the reaction was monitored by thin layer chromatography. After the completion of the reaction, the mixture was poured into ice cold water with vigorous stirring. The formed precipitate was filtered off and washed with water. The crude product were purified by recrystallization with methanol.

Yield: 65 %, Melting point 112-114 ℃, FTIR(KBr): N-H- 3414 cm^{-1} , =C-H- 3059 cm^{-1} , C-H- 2856 cm^{-1} , C=C- 1489 cm^{-1} , C-Br- 700 cm^{-1}. ^{1}H NMR (DMSO d-6) in ppm: 10.2 N-H, 7.4-7.7(m,3H), 7.3(2d,2H), 7.2(s,H), 2.5(t,2H), 2.0(t,2H), 1.2(t,2H) . ^{13}C NMR (DMSO d-6)

aliphatic carbons 24- 40 ppm , aromatic carbons 110-137 ppm. Mass spectrum: m/e ratio 342.8 (M+1).

BACTERIAL CULTURES AND EVALUATION OF ANTIMICROBIAL ACTIVITIES

Agar well diffusion method

Antimicrobial analysis was followed using standard agar well diffusion method to study the antibacterial activity of compounds (Perez *et al*., 1990; Erdemoglu *et al*., 2003; Bagamboula *et al*., 2004). Each bacterial isolate was suspended in Brain Heart Infusion (BHI) broth and diluted to approximately 10^5 colony forming unit (CFU) per ml. The test organisms were flood-inoculated on to the surface of BHI agar and then dried. Five-millimeter diameter wells were cut from the agar using a sterile cork-borer and 30µL (50µg compound in 1 ml of solvent-Ethanol) of the sample solution were poured into the wells. The plates were incubated for 18hours at 37ºC for bacteria. Antibacterial activity was evaluated by measuring the diameter of the zone inhibition in mm against the test microorganisms. DMSO was used as solvent control. Ciprofloxacin was used as reference antibacterial agent. The tests were carried out in triplicate.

CONCLUSION

Carbazole derivatives **A, B & C** have been synthesized by simple and easier Fischer indole synthesis with solvent such as Sulphuric acid and acetic acid in (18, 8.5). The solvent selected must be suitable for reaction condition and temperature.

The formation of the various compounds were indentified using thin layer chromatography and purified by column chromatography. All the synthesized compounds have been confirmed by various spectral techniques *Viz* FTIR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy.

Antibacterial activities have been carried out for pathogens *Staphylococcus Aureus, Streptococcus faecalis, Escherichia coli, Salmonella typhi* using zone of inhibition method with reference ciprofloxacin. The synthesized compounds found to have good antibacterial activity. Among all the synthesized compounds. Compound **C** posses good antibacterial activity than others.

METHODS AND MATERIALS

All the chemicals used were purchased from Merck and Aldrich and used without further purification.

The melting points of synthesized compounds were determined by open capillary tubes using an X-5A Melting point apparatus and were uncorrected. Thin layer chromatography among to most useful tools for following the progress of organic chemical reaction and for assaying the purity of organic compounds. FTIR spectra was recorded on a Alpha Bruker FTIR Spectrometer using KBr pellets. The ^{1}H NMR Spectra were measured on a Bruker proton NMR-Avance 400 MHz with chemical shift expressed in ppm downlfield from TMS as internal standard in DMSO(d-6). The ^{13}C NMR Spectra were determined at 400 MHz with a Bruker Avance Spectrometer. Mass Spectra were recorded on GC-MASS Spectrometer using methanol as a solvent.

CONFLICT OF INTEREST

The authors declare that this article contain no conflict of interest.

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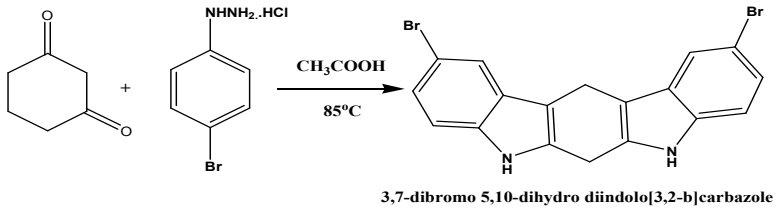
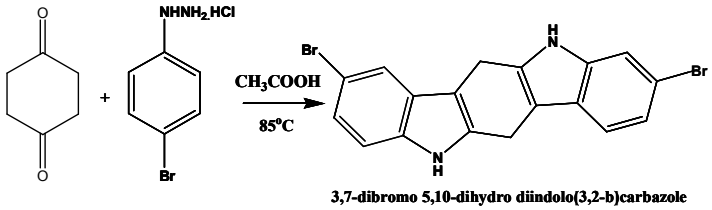
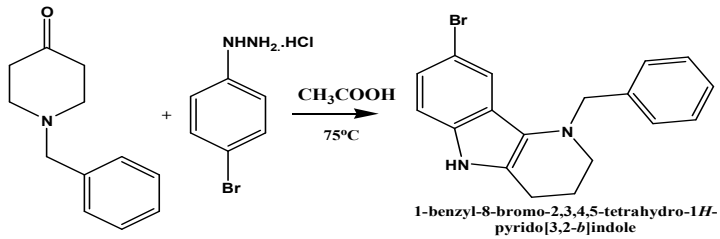


Scheme 1. Synthesis of 3,7-dibromo 5,10-dihydro diindolo[3,2-b]carbazole



Scheme 2. Synthesis of 3,7-dibromo 5,10-dihydro diindolo[3,2-b]carbazole



Scheme 3. Synthesis of 1-benzyl 8-bromo-2,3,4,5-tetrahhydro-1H-pyrido[3,2-b]indole

Zone of inhibition of synthesized compounds

TABLE 1 Antibacterial activity of various synthesized compounds

Compound	**ZONE OF INHIBITION**							
	Staphylococcus Aureus		*Streptococcus faecalis*		*Escherichia coli*		*Salmonella typhi*	
	mm	%	Mm	%	mm	%	Mm	%
Ciprofloxacin	19	100	16	100	12	100	14	100
A	-	-	5	31.2	-	-	6	42.8
B	5	26.3	6	37.5	8	66.7	6	42.8
C	7	36.8	7	43.7	7	58.3	9	64.3

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