Synthesis of Organophosphorous Carbazole Derivatives and their Antimicrobial 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 wide range of biological activities. Carbazole derivatives were treated with phosphorusoxychloride at 0°C in tetrahydrofuran to obtain organophosphonyl carbazole derivatives. 5,6,7,8-tetrahydrocarbazole-9-phosphonyl dichloride, 5,6-dihydrobenzo[α]carbazole-11-phosphonyl dichloride and 2,3-dihydrocyclopenta[b]indole-4(1H)-phosphonyl D dichloride have been synthesized by using phosphorusoxychloride at 0°C in tetrahydrofuran. The formation of the compounds was characterized and confirmed by various instrumental techniques viz UV, FTIR, ¹H NMR, ¹³C NMR, ³¹PNMR and Mass spectroscopy. The antibacterial activity of all the synthesized compounds have been carried out for the pathogens like Staphylococcus aureus and Escherichia coli 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. All the synthesized compounds were subjected to the antifungal activity against pathogen Aspergillus niger by using zone of inhibition method with standard Amphotericin-B. The result showed that there is no fungal activity for the synthesized compounds.

Keywords
5,6,7,8-tetrahydrocarbazole-9-phosphonyl dichloride, Phosphorusoxy chloride, Organophosphorous, Tetrahydrofuran, Staphylococcus aureus, Ciprofloxacin, Amphotericin-B.

INTRODUCTION

A heterocyclic compound is a cyclic compound that has atoms of at least two different elements in its ring.¹ Heterocyclic compounds were usually considered to replace carbon atoms, like Nitrogen, Oxygen and Sulphur. Heterocyclic compounds can be classified based on their electronic structure. The saturated heterocycles are acyclic derivatives of piperidine and tetrahydrofuran. Therefore, the study of heterocyclic chemistry focus especially on unsaturated derivatives.
involves unstrained 5- and 6-membered rings including pyridine, thiophene, pyrrole and furan. They are formed due to the condensation of two cyclic compounds, of which at least one would be heterocyclic compound. Examples are indole, quinoline and isoquinoline.[2] Fusion of two benzene rings give rise to a third large family of compounds, respectively acidine, dibenzo thiophene, carbazole and dibenzofuran. Nitrogen heterocycles appear in the core structure of several drugs. Due to importance in medicinal chemistry, pharmaceutical industry and various drug development importance have been drawn for their synthesis and characterization. Carbazole and its derivatives are one of the most important types of organic heterocyclic aromatic compounds.[3] Organophosphorus compounds are chemical compounds containing carbon-phosphorus bonds. Organophosphorus chemistry is the corresponding science exploring the properties and reactivity of organophosphorus compounds.[4] Organophosphorus compounds, have widespread use throughout the world, mainly in agriculture as insecticides, herbicides, and plant growth regulators.[5] They have also been used as nerve agents in chemical warfare and as therapeutic agents, such as ecopoxide used in the treatment of glaucoma.[6] In academic research organophosphorus compounds find important application in organic synthesis (Wittig, Mitsunobu, Staudinger, organocatalysis etc.).[7] The use of organophosphorus compounds as achiral or chiral ligands for transition metal catalyzed transformations is also rapidly growing in both laboratory synthesis and industrial production.[8] Furthermore, organophosphorus compound, can be used as flame retardants for fabrics and plastic plasticising and stabilising agents in the plastics industry, selective extractants for metal salts from ores, additives for petroleum products, and corrosion inhibitors. Organophosphonyl carbazole compounds have tremendous importance in the field of food technology, animal foodstuff, pesticides, medicinal compounds, synthetic polymers, fire retardance and natural products. [9-11] Organophosphonyl carbazole compounds have many folds uses as medicinal compounds.

To purify the starting materials and solvent and synthesized the functionalized organophosphonyl carbazole derivatives by using POCl₃ at 0°C. To establish the structure of the synthesized products by various physical methods and spectroscopy evidences such as UV, FTIR, ¹H NMR, ³¹P NMR and Mass spectroscopy study and analysis the antibacterial antifungal activity of synthesized product.

**EXPERIMENTAL SECTION**

**MATERIALS AND METHODS**

The chemicals alphatetralone, cyclohexanone, cyclopentanone, glacial acetic acid, phenylhydrazine were commercially available from Avra chemicals, Hyderabad and were used as such. Tetrahydrofuran, phosphoroyloxychloride, pyridine silica gel (TLC and Column grade) was purchased from Merck. The solvents were purified as per the standard procedure reported elsewhere. ¹H NMR (400 MHz) spectra were recorded on a Bruker Advance III 300 MHz multinoi nuclei solution NMR. FTIR spectra (KBr pellets) were measured on the Alpha Bruker FTIR instrument scanning the entire region of 4000 - 400 cm⁻¹ with typical resolution of 1.0 cm⁻¹.

**SYNTHESIS OF 5,6,7,8-TETRAHYDROCARBAZOLE-9-PHOSPHONYL DICHLORIDE**

The equimolar quantities of 1,2,3,4-tetrahydrocarbazole (0.171g, 1mmol) and of phosphorousoxy chloride (0.153g, 1mmol) were dissolved separately in 20 ml of dry THF. The 1,2,3,4-tetrahydrocarbazole in 20ml dry THF with few drops of pyridine were taken in round bottom flask fitted with dropping funnel. Phosphorousoxychloride in 20 ml of THF were added slowly by using dropping funnel with constant stirring for 30minutes at 0°C. The reaction has been carried out for 3 hours. The progress of the reaction was monitored by TLC. Then the reaction mixture was filtered, and the solvent was evaporated to get brown colour waxy organophosphorous compound A 5, 6, 7, 8-tetrahydrocarbazole-9-phosphonyl dichloride. The formed waxy compound A was recrystallized from hot ethanol.

Physical State of compound : Brown colour waxy, Yield: 77%, FTIR (KBr pellet, cm⁻¹): 536 (P=O), 1233 (P-N), 1377 (P=O), 1479 (C=C), 2873 (C-H), 3068 (C=C-H), ¹H-NMR (CDCl₃, ppm) δ : a=2.23-2.28 (2H), b=1.4-1.8 (m,4H), c =7.33-7.35 (2H), d=7.3-7.4 (m,2H), ³¹P (DMSO, ppm) δ : -1.11 (N-P), GC-MASS (methanol): Mol. For: C₁₅H₁₂Cl₁ NOP, calculated=288.1, observed=290.1(M+2).
SYNTHESIS OF 5,6-DIHYDRO BENZO[A]CARBAZOLE-11-PHOSPHONYL DICHLORIDE

6,11-dihydro-5H-benzo[a]carbazole (1mmol, 0.219 g) in 20ml dry THF with few drops of pyridine were taken in round bottom flask. Phosphorousoxychloride (1mmol, 0.153 g) in 20ml dry THF were added slowly by using dropping funnel with constant stirring for 30minutes at 0ºC. The reaction has been carried out for 3 hours. The progress of the reaction was monitored by TLC. Then the reaction mixture was filtered, and the solvent was evaporated to get brown colour waxy organophosphorous compound B. 5,6-dihydrobenzo[a]carbazole-11-phosphonyl dichloride and recrystallized from hot ethanol.

Brown colour waxy compound, Yield: 75%, FTIR (KBr pellet, cm⁻¹): 536 (P-Cl), 1244 (P=N), 1347 (P=O), 2863 (-C-H), 3069 (≡C-H), 1³H-NMR (CDCl₃, ppm) δ : a=7.24-7.26 (2d,2H), b=7.34-7.36 (m,2H), c=7.4-7.5 (2d,2H), d=7.35-7.37 (m,2H), e=2.51-2.63 (2d,4H), ³¹P (DMSO, ppm) δ : -1.07 (N-P), GC-MASS in methanol: Mol. For: C₁₁H₁₂Cl₂NOP, Calculated=337.1, observed=341.2(M+4).

SYNTHESIS OF 2,3-DIHYDROCYCLOPENTA[B]INDOLE-4(1H)-PHOSPHONYL DICHLORIDE

A mixture 1mmol (0.157 g) of 1,2,3,4-tetrahydrocyclopenta[b]indole and 1mmol (0.153 g) of phosphorousoxochloride were dissolved separately in 20 ml of dry THF. The 1,2,3,4-tetrahydrocyclopenta[b]indole in 20ml dry THF with catalytic amount of pyridine were taken in round bottom flask fitted with dropping funnel. Phosphorousoxochloride in 20 ml of THF were added slowly by using dropping funnel with constant stirring for 30minutes at 0ºC. The reaction has been carried out for 3 hours. After the completion of reaction using TLC, the reaction mixture was filtered, and the solvent was evaporated to get brown colour waxy 2,3-dihydrocyclopenta[b]indole-4(1H)-phosphonyl dichloride organophosphorous compound C. The product was recrystallized from hot ethanol.

Nature of compound: Brown colour waxy, Yield: 72%, FTIR (KBr pellet, cm⁻¹): 587 (P-Cl), 1244 (P=N), 1387 (P=O), 2853 (-C-H), 3069 (≡C-H), 1³H-NMR (CDCl₃, ppm) δ : a=2.4-2.5 (m,4H), b=1.2-1.8 (t,2H), c=7.26 (2d,2H), d=7.54 (m,2H), ³¹P (DMSO, ppm) δ : -1.15 (N-P), GC-MASS (methanol): Mol. For: C₁₁H₁₀Cl₂NOP, calculated=275.0, observed =279.2(M+4).

ANTIMICROBIAL ACTIVITY

Antimicrobial analysis was followed using standard agar well diffusion method to study the antimicrobial activity of compounds. Each bacterial isolate was suspended in Brain Heart Infusion (BHI) broth and diluted to approximately 10⁸ colony forming unit (CFU) per mL. They were flood-inoculated onto the surface of Media (Mueller Hinton Agar for Bacteria and Sabouraud’s Dextrose agar for fungi) and then dried. Five-millimeter diameter wells were cut from the agar using a sterile cork borer and 30 µL (5µg compound in 500 µL DMSO) of the sample solution were poured into the wells. The plates were incubated for 18 h at 37°C for bacteria. Similarly, fungal plates were incubated at room temperature for 48 h. Antimicrobial activity was evaluated by measuring the diameter of the zone of inhibition in mm against the test microorganisms and the solvent. DMSO was used as solvent control. Ciprofloxacin was used as reference antibacterial agent. Amphotericin B was used as reference antifungal agent, for mold and Ketoconazole was used for Candida sps. The tests were carried out in triplicates.

$$\text{POCl}_3 \text{ in THF}$$

$$\text{0ºC, Pyridine}$$

1,2,3,4-tetrahydrocarbazole 5,6,7,8-tetrahydrocarbazole-9-phosphonyl dichloride (A)

Scheme 1. Synthesis of 5,6,7,8-tetrahydro carbazole-9-phosphonyl dichloride
RESULT AND DISCUSSION

5,6,7,8-TETRAHYDROCARBAZOLE-9-PHOSPHONYL DICHLORIDE

The FTIR spectrum of 5,6,7,8-tetrahydrocarbazole-9-phosphonyl dichloride A have shown in Fig 1 was confirmed by the disappearance of N-H stretching and appearance of N-P and P=O stretching at 1233 cm\(^{-1}\) and 1377 cm\(^{-1}\) respectively. P-Cl stretching shown around 536 cm\(^{-1}\). \(^1\)H NMR (Fig 2) spectrum a two-triplet peak appeared at 2.23-2.28 \(\delta\) corresponds to four protons. The aromatic protons observed at 7.3-7.4 \(\delta\). The multiplet signal appeared at 1.4-1.8 \(\delta\) corresponds four alicyclic protons. The \(^31\)P NMR information about compound A which has been confirmed the presence of P in (N-P) 5,6,7,8-tetrahydrocarbazole-9-phosphonyl dichloride at -1.11 ppm (Fig 3). The mass spectrum of compound A have shown in Fig 4. The observed molecular ion peak m/z 290.1 (M+2). Calculated mass value of 5,6,7,8-tetrahydrocarbazole-9-phosphonyl dichloride was found m/z 288.1.

SPECTRAL ANALYSIS

Compound A

![FTIR spectrum of 5,6,7,8-tetrahydrocarbazole-9-phosphonyl dichloride.](image)

Figure 1. FTIR spectrum of 5,6,7,8-tetrahydrocarbazole-9-phosphonyl dichloride.
Figure 2. $^1$H NMR spectrum of 5,6,7,8-tetrahydrocarbazole-9-phosphonyl dichloride.

Figure 3. $^{31}$P NMR spectrum of 5,6,7,8-tetrahydrocarbazole-9-phosphonyl dichloride.

Figure 4. Mass spectrum of 5,6,7,8-tetrahydrocarbazole-9-phosphonyl dichloride.
Compound B

Figure 5. FTIR spectrum of 5,6-dihydrobenzo [α]carbazole-11-phosphonyl dichloride.

Figure 6. ¹H NMR spectrum of 5,6-dihydrobenzo [α]carbazole-11-phosphonyl dichloride.

Figure 7. ³¹P NMR spectrum of 5,6-dihydrobenzo [α]carbazole-11-phosphonyl dichloride.
Figure 8. Mass spectrum of 5,6-dihydrobenzo [α]carbazole-11-phosphonyl dichloride.

Figure 9. FTIR spectrum of 2,3-dihydrocyclopenta[b]indole-4(1H)-phosphonyl dichloride.

Figure 10. ^1H NMR spectrum of 2,3-dihydrocyclopenta[b]indole-4(1H)-phosphonyl dichloride.

- C=H-3069 cm\(^{-1}\)
- C-H-2853 cm\(^{-1}\)
- C=C-1479 cm\(^{-1}\)
- C-C-1172 cm\(^{-1}\)
- P=O-1387 cm\(^{-1}\)
- N-P-1244 cm\(^{-1}\)
- P-Cl-587 cm\(^{-1}\)

\(a=2.4-2.5\) (m,4H)
\(b=1.2-1.8\) (t,2H)
\(c=7.26\) (2d,2H)
\(d=7.54\) (m,2H)
Figure 11. $^{31}$P NMR spectrum of 2,3-dihydrocyclopenta[b]indole-4(1H)-phosphonyl dichloride.

Figure 12. Mass spectrum of 2,3-dihydrocyclopenta[b]indole-4(1H)-phosphonyl dichloride.

Antibacterial analysis

Compounds: A (mcnp1), B (mcnp2) & C (mcnp3)

![Staphylococcus aureus](image1)

![Escherichia coli](image2)

Figure 13. Zone of inhibition for synthesized compounds.
5,6-DIHYDROBENZO[A]CARBAZOLE-11-PHOSPHONYL DICHLORIDE
The FTIR spectrum of compound B have shown in Fig 5 was confirmed by the disappearance of N-H stretching and appearance of N-P and P=O stretching at 1244 cm\(^{-1}\) and 1387 cm\(^{-1}\) respectively. P-Cl stretching shown around 536 cm\(^{-1}\). \(^1\)H NMR (Fig 6) spectrum a two-doublet peak appeared at 7.24-7.26 δ corresponds to two protons. The aromatic protons observed at 7.35-7.37 δ. The doublet signal appeared at 2.61-2.63 δ corresponds to two alicyclic protons. The \(^3\)P NMR information about 5,6-dihydrobenzo[a]carbazole-11-phosphonyl dichloride which has been confirmed the presence of P in (N-P) compound B at -1.07 ppm (Fig 7). The mass spectrum of 5,6-dihydrobenzo[a]carbazole-11-phosphonyl dichloride have shown in Fig 8. The observed molecular ion peak m/z 341.2 (M+4). Calculated mass value of compound B was found m/z 337.1.

2,3-DIHYDROCYCLOPENTA[B]INDOLE-4(1H)-PHOSPHONYL DICHLORIDE
The FTIR spectrum of 2,3-dihydrocyclopenta[b]indole-4(1H)-phosphonyl dichloride have shown in Fig 9 was confirmed by the disappearance of N-H stretching and appearance of N-P and P=O stretching at 1244 cm\(^{-1}\) and 1387 cm\(^{-1}\) respectively. P-Cl stretching shown around 587 cm\(^{-1}\). \(^1\)H NMR (Fig 10) spectrum a two-doublet peak appeared at 2.4-2.5 δ corresponds to four protons. The aromatic protons observed at 7.26 δ. The doublet signal appeared at 1.2-1.8 δ corresponds to two alicyclic protons. The \(^3\)P NMR information about compound C which has been confirmed the presence of P in (N-P) 2,3-dihydrocyclopenta[b]indole-4(1H)-phosphonyl dichloride at -1.15 ppm (Fig 11). The mass spectrum of compound C have shown in Fig 12. The observed molecular ion peak m/z 279.2 (M+4). Calculated mass value of 2,3-dihydrocyclopenta[b]indole-4(1H)-phosphonyl dichloride was found m/z 275.0.

**ANTIBACTERIAL AND ANTIFUNGAL ACTIVITY**
The results of antibacterial activity for synthesized compounds A, B & C have shown in Table 1. The zone of inhibition was indicated the nature of antibacterial activity. The synthesized compounds were subjected to *Staphylococcus aureus* and *Escherichia coli*. The antifungal activity of various synthesized compounds A, B & C have done using zone of inhibition in mm, the result shows no antifungal activity.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>ZONE OF INHIBITION</th>
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<tr>
<td></td>
<td>Gram Positive Staphylococcus aureus</td>
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<tr>
<td></td>
<td>Mm</td>
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<tr>
<td>Ciprofloxacin</td>
<td>20</td>
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<tr>
<td>A</td>
<td>5</td>
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<tr>
<td>B</td>
<td>5</td>
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<td>C</td>
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**CONCLUSION**
The expected organophosphonyl carbazole derivatives were synthesized by POCl\(_3\) at 0º C various carbazole derivatives reactant with suitable solvent such as Tetrahydrofuran. The solvent selected must be suitable for reaction condition and temperature. The formation various compounds were identified using thin layer chromatography. All the synthesized compounds have been characterized various spectral techniques viz UV-visible, FTIR, \(^1\)H NMR, \(^13\)C NMR, \(^31\)P NMR and Mass spectroscopy. All the synthesized compounds were subjected to antimicrobial activity. The synthesized compounds A, B & C found to have excellent bacterial activity. Among all the synthesized compounds A, B & C compound C found to have exhibit excellent bacterial activity than other compounds. The antifungal activity of various synthesized compounds A, B & C have done using zone of inhibition in mm, the result shows no antifungal activity.

**CONFLICT OF INTEREST**
The authors don’t have any conflict of interest from this article.

**REFERENCES**


