Synthesis and Spectral Characterization of Derivatives of Benzotriazole and Piperidine

Selvarathy Grace P a, Ravindran Durainayagam B b* and Pon Matheswari P b.

a,b Department of Chemistry, Pope’s College (Autonomous), Affiliated to Manonmaniam Sundaranar University, Tirunelveli-12, Tamil Nadu, INDIA. email: selvarathigrace@gmail.com.

(Received on: January 30, 2018)

ABSTRACT

The heterocyclic systems containing benzotriazole and piperidine moieties have huge applications because of their diverse biological activities. Also they have numerous commercial applications. Here we report a series of novel benzotriazole and piperidine derivatives synthesized from bromo derivatives of mesitylene and durene by conventional method. Ethanol is used as solvent of the reaction. The synthesized compounds were isolated and purity was checked by TLC method. The structures of synthesized compounds were confirmed by FT-IR, 1H NMR and 13C NMR. All the compounds were evaluated for anti-microbial activity.

Keywords: Benzotriazole, piperidine, spectral characterization and anti-microbial activity.

1. INTRODUCTION

Heterocycles constitute a wide classification of natural and synthetic compounds. Majority of organic compounds found in natural product are heterocyclic in nature. These compounds found in natural products had been known for centuries for their medicinal nature and also their toxicity- indeed it was an extract of the hemlock that contains piperidine alkaloid was used to cause the death of the great Philosopher Socrates. Chlorophyll the green photosynthetic pigment in plant, hemoglobin the oxygen carrier in RBC, DNA and RNA the most important biological molecules are some of the heterocyclic compounds associated with our life.

Heterocyclic compounds possess a broad range of high profile biological activities such as antifungal, antibacterial, anti-inflammatory, anticancer, antioxidant,
anticonvulsant, anti-allergic, and herbicidal activity. A number of their derivatives have found diverse uses in synthetic, analytical, agrochemical, and photographic chemistry.

Among the N-heterocycles derivatives of azole and piperidine find numerous applications. Several pharmacologically active drug candidates bear the ubiquitous piperidine nucleus. Apart from the curative area they show applications in commercial field for the synthesis of additives in rubber industry as radical scavengers to inhibit photo oxidative degradation of polymers, a structural probe for biological studies etc. Benzotriazole is a class of azole compounds showing potential biological applications in medicine and also as an effective corrosion inhibitor.

The multifaceted applications of piperidine and benzotriazole compounds prompted us to synthesize novel derivatives of the titled compounds.

2. MATERIAL AND METHODS

Chemicals used for the synthesis were of AR grade of Merck, S.D.Fine and Aldrich. The melting points were recorded in open capillary in paraffin bath and are uncorrected. FT - IR spectra were recorded on a Jasco FT-IR-4600 Spectrophotometer (KBr, $\nu_{max}$ in cm$^{-1}$). $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker AVV 300 instrument (300 MHz) CDCl$_3$-d3 as solvent. Chemical Shifts are given in parts per million (ppm). The reactions were monitored by TLC and visualized the spot in iodine chamber.

3. EXPERIMENTAL METHODS

Compounds such as mesitylene and durene as starting material were used for the synthesis of bromomethyl mesitylenes and bromomethyl durenes following available literature procedure. Using the above compounds derivatives of benzotriazole (Bt) and piperidine (pip) were synthesized. The structural identities were confirmed on the basis of spectral data.

3.1 Procedures for the synthesis of benzotriazole derivative (2a-2e)

In a 100 ml round bottom flask metallic sodium (1 mmol) and 10ml ethanol were added, stirred well and then added benzotriazole (1mmol). This mixture was stirred well for about 10 minutes. To the above mixture monobromomethyl mesitylene 1a (1 mmol) dissolved in ethanol was added refluxed for about 4 hour at 333K. The mixture was then slowly cooled; the solid product obtained was thoroughly washed with water to remove sodium bromide completely. The product was dissolved in chloroform and evaporated slowly to get the final product 2a. Similarly, 2b-2e were synthesized from 1b-1e. Using the above procedure, synthesis of piperidine derivatives 3a-3m was carried out. All the synthesized compounds were recrystallized by using chloroform.

Reaction scheme 1

Reaction scheme 2
Reaction scheme 3

\[
\begin{align*}
3a & : R = \text{H} \\
3c & : R = 2\text{-CH}_3 \\
3d & : R = 4\text{-Bz}
\end{align*}
\]

Reaction scheme: 4

\[
\begin{align*}
3e-3i & : R = \text{H} \\
3f & : R = 2\text{-CH}_3 \\
3g & : R = 3\text{-CH}_3 \\
3h & : R = 4\text{-CH}_3 \\
3i & : R = 4\text{-Bz}
\end{align*}
\]
3.2 SPECTRAL ANALYSIS OF SYNTHESIZED COMPOUNDS

3.2.1 FT-IR

The synthesis of the novel compounds (2a-2e and 3a-3m) are described in the above reaction schemes. The identities of the newly synthesized compounds have been established on the basis of their FT-IR, $^1$H NMR and $^{13}$C NMR. In compound 3a-e aromatic stretch, appears in the region 2910-2974 cm$^{-1}$. Aromatic bent is seen around 1606-1638 cm$^{-1}$C stretch signals appear at 1449-1491cm$^{-1}$. Alkyl stretch and alkyl bend appear around 2769-2914cm$^{-1}$ and 1316-1384cm$^{-1}$ respectively.

3.2.2 $^1$H NMR and $^{13}$C NMR

(2a) was synthesized by reaction between Bt and 1a. Pale yellow. M.Pt°C: 85. $^1$H NMR (CDCl$_3$): δ ppm 8.05-6.93 (m, 4H, Bt H, 2H, Ar H), 5.95-5.85 (m, 2H, N-CH$_2$), 2.49-1.86 (m, 9H, –CH$_3$).

(2b) was synthesized by reaction between Bt and 1b. White. M.Pt°C: 163.4. $^1$H NMR (CDCl$_3$): δ ppm 8.04-6.98 (m, 8H, Bt H, 1H, Ar H), 5.86 (s, 4H, N-CH$_2$), 2.60-1.75 (m, 9H –CH$_3$).

(2c) was synthesized by reaction between Bt and 1c. White. M.Pt°C: 140.6. $^1$H NMR (CDCl$_3$): δ ppm 8.06-7.08 (m, 12H, Bt H), 5.86 (s, 6H, N-CH$_2$), 2.56-1.80 (m, 9H, –CH$_3$). $^{13}$C NMR (300 MHz CDCl$_3$): δ ppm: CH$_3$-17.06, N-CH$_2$- 21.77, 22.56, 31.28, 52.10 and 64.50, Ar carbon 123.12, 130.0, 120.1, 144.26 and 146.16. Aromatic bent is seen around 1606 cm$^{-1}$.

(2d) was synthesized by reaction between Bt and 1d. White. M.Pt°C: 198.8. $^1$H NMR (CDCl$_3$): δ ppm 8.0-6.90 (m, 4H, Bt H, 1H, Ar H), 5.98-5.90 (m, 2H, N-CH$_2$), 2.5-1.8 (m, 12H –CH$_3$).

(2e) was synthesized by reaction between Bt and 1e. White. M.Pt°C: 235. $^1$H NMR (CDCl$_3$): δ ppm 8.07-7.02 (m, 8H, Bt H), 5.92 (s, 4H, N-CH$_2$), 2.49-1.73 (m, 12H –CH$_3$). $^{13}$C NMR (300 MHz CDCl$_3$): δ ppm: CH$_3$-16.9, N-CH$_2$- 48.56, 55.33, Bt Carbon- 109.70, 109.79, 118.10, 120.1, 144.26 and 146.16, Ar carbon- 123.8, 126.18, 127.34, 135.14 and 135.45.

(3a) was synthesized by reaction between Piperidine and 1a. White. M.Pt°C: 174.1. $^1$H NMR (CDCl$_3$): δ ppm 6.90, 6.83 (d, 2H, Ar H), 3.53-3.36 (m, 2H, N-CH$_2$Ar), 2.39-1.18 (m, 9H –CH$_3$) and piperidine, 10H).

(3b) was synthesized by reaction between piperidine and 1b. Pale yellow. M.Pt°C: 101. $^1$H NMR (CDCl$_3$): δ ppm 6.80 (s, 1H, Ar H), 3.46-3.34 (m, 4H, N-CH$_2$Ar), 2.53-1.41 (m, 9H –CH$_3$, 20H, Pip H). $^{13}$CNMR (300 MHz CDCl$_3$): δ ppm: CH$_3$-15.75, N-CH$_2$-57.06, Pip Carbon-24.65,26.28 and 54.20, Ar Carbon-129.62,133.26, 136.42 and 138.89.

(3c) was synthesized by reaction between 2-methyl piperidine and 1a. Orange. M.Pt°C: 201. $^1$H NMR (CDCl$_3$): δ ppm 6.9 (s,2H, Ar H), 3.97 (s, 2H, N-CH$_2$), 2.50-1.16 (m, 3H –CH$_3$, 9H, Pip H, 3H, Pip-CH$_3$). $^{13}$CNMR (300 MHz CDCl$_3$): δ ppm: CH$_3$-18.05, 20.94, 21.35 and 22.40, N-CH$_2$-51.57, Pip carbon-21.77, 22.56, 31.28, 52.10 and 64.50, Ar carbon-123.12, 130.0, 130.06 and 143.04.

(3d) was synthesized by reaction between 4-benzyl piperidine and 1a. Orange. M.Pt°C: 43.5.¹H NMR (CDCl3): δ ppm 7.34-6.86 (m, 7H, Ar H), 3.42 (s, 2H, N-CH2), 2.84-2.80 (m,2H,Bz-CH2) 2.56-1.22 (m, 9H –CH3 and 8H, Pip H).¹³C NMR (300 MHz CDCl3): δ ppm: CH3-19.69 and 32.20, N-CH2-53.2, Benzyl-CH2-42.92, pip carbon-20.53, 37.85 and 55.87, Ar carbon-125.3, 127.74, 128.42, 128.73, 132.05, 135.71, 137.72 and 140.61.

(3e) was synthesized by reaction between piperidine and 1d. White. M.Pt°C: 206. ¹H NMR (CDCl3): δ ppm 6.894 (s, 1H, Ar H), 3.451(s, 2H, N-CH2Ar), 2.389 -1.401 (m, 12H –CH3, 10H, Pip H).¹³C NMR (300 MHz CDCl3): δ ppm: CH3-15.19,20.56, N-CH2-57.06, Pip carbon-24.64, 26.33 and 54.19, Ar carbon-130.35, 131.62, 133.29 and 134.27.

(3f) was synthesized by reaction between 2-methyl piperidine and 1d. White. M.Pt°C: 45.2. ¹H NMR (CDCl3): δ ppm 6.92 (s,1H, Ar H), 3.45-3.41 (s, 2H, N-CH2), 2.33-0.88 (m, 12H –CH3, 9H, Pip H, 3H, Pip-CH3).

(3g) was synthesized by reaction between 3-methyl piperidine and 1d. White. M.Pt°C: 50.3. ¹H NMR (CDCl3): δ ppm 6.94 (s, 1H, Ar H), 3.20-3.43 (m, 2H, N-CH2), 2.30-0.85 (m, 12H –CH3, 9H, Pip H, 3H, Pip-CH3).

(3h) was synthesized by reaction between 4-methyl piperidine and 1d. Yellow. M.Pt°C: 45.6.¹H NMR (CDCl3): δ ppm 6.90 (s, 1H, Ar H), 3.49-3.44 (m, 2H, N-CH2), 2.29-0.89 (m, 12H –CH3, 9H, Pip H, 3H, Pip-CH3).

(3i) was synthesized by reaction between 4-benzyl piperidine and 1d. White. M.Pt°C: 106.8. ¹H NMR (CDCl3): δ ppm 7.13, 7.11 (m, 1H, Ar H), 3.47-3.30 (m, 2H, N-CH2), 2.77-1.52 (d, 2H, Bz-CH2, 12H –CH3, 9H, Pip H).

(3j) was synthesized by reaction between 2-methyl piperidine and 1e. White. M.Pt°C: 120.6. ¹H NMR (CDCl3): δ ppm3.49-3.31 (m, 4H, N-CH2), 2.60-1.27 (s, 12H, -CH3, 18H, PipH, 6H, Pip-CH3).¹³C NMR (300 MHzCDCl3): δ ppm: CH3-15.85 and 16.57, N-CH2-57.99, Pip carbon-17.95, 23.50, 49.74, 52.52 and 69.40, Ar carbon-132.94 and 133.9.

(3k) was synthesized by reaction between 3-methyl piperidine and 1e. White. M.Pt°C: 162.2. ¹H NMR (CDCl3): δ ppm3.52-3.43(s, 4H, N-CH2), 2.77-0.95 (m, 12H, -CH3, 18H, PipH, 6H, Pip-CH3).¹³C NMR (300 MHzCDCl3): δ ppm: CH3-16.22 and 19.31, N-CH2-53.21, pip carbon-25.36, 30.85, 32.86,56.95 and 61.41, Ar carbon- 131.75, 133.75.

(3l) was synthesized by reaction between 4-methyl piperidine and 1e. White. M.Pt°C: 77.5. ¹H NMR (CDCl3): δ ppm3.55-3.46(m, 4H, N-CH2), 2.84-0.89 (m, 12H, -CH3, 18H, PipH, 6H, Pip-CH3).¹³C NMR (300 MHzCDCl3): δ ppm: CH3-15.83 and 16.28, N-CH2-56.71, pip carbon- 21.56, 30.61 and 53.20, Ar carbon- 131.50 and 133.78.

(3m) was synthesized by reaction between 4-benzyl piperidine and 1e. Pale yellow. M.Pt°C: 86. ¹H NMR (CDCl3): δ ppm7.11-7.29 (m, 10H, ArH), 3.41-3.47 (m, 4H, N-CH2), 2.81-1.53 (s, 4H, Bz-CH2 12H,-CH3, 18H, Pip H).¹¹CNMR (300 MHzCDCl3): δ ppm: CH3-16.35, N-CH2- 53.6, Benzyl CH2-43.47, pip carbon-32.2, 37.66 and 58.27, Ar carbon 128.25, 129.74, 133.60, 134.4 and 138.7
4. RESULT AND DISCUSSION

The newly synthesized compounds of the series (2a-2e and 3a-3m) were characterized on the basis of FT-IR, \(^1\)H NMR and \(^{13}\)C NMR spectral data. The compounds (2a-2e) possess two motifs benzotriazole and methylated benzene connected by methylene group through N1 of benzotriazole ring. The compounds (3a-m) also possess two motifs piperidine and methylated benzene.

In the IR spectra of benzotriazole a strong broad band appears in the region 3248 cm\(^{-1}\) corresponding to the N-H stretching frequency. This band is completely absent in the 2a-2e series indicating the involvement of N-H of benzotriazole ring in bond formation. The N-H stretch that occurs in 3350 cm\(^{-1}\) in the piperidine molecule is absent in the series (3a-3m) indicating the formation of new product.

In \(^1\)H NMR spectra of the compounds (2a-2e) four signals corresponding to the protons of benzotriazole ring, methylated benzene ring, methyl and methylene group are observed. The protons of the benzotriazole and benzene ring appear as multiplet in the region 8.07-6.9 ppm. In 2c and 2e, there is no aromatic proton. The newly formed N-CH\(_2\) bond has its proton signal deshielded around 5.98-5.85 ppm \(^{18}\). The methyl protons are observed in the region 2.6-1.8 ppm.

\(^{13}\)C NMR of the compounds (2a-2e) show chemical shift between \(\delta\) 16-146 ppm. The signal of N-CH\(_2\) carbon is seen between 47 and 55 ppm. The carbon of benzene ring and benzotriazole ring appear between 109 and 146 ppm.

In the \(^1\)H NMR of the piperidine derivatives (3a-3m) signals corresponding to piperidine ring, methylated benzene ring, methyl and methylene group are observed. Distinct peak for the benzene ring is observed around 6.9 ppm in most of the derivatives. In 3a, 3b and 3e the signals of piperidine ring protons appear around 2.53-1.18 ppm \(^{19,20}\). In methyl substituted piperidines (3c, 3f, 3g, 3h 3j-3l) the signals due to the protons of piperidine and methyl are merged and overlapped and appear as multiplet in the region 2.5 to 0.88 ppm. The N-CH\(_2\) signal is observed in 3.97-3.20 ppm. The -CH\(_2\) proton of benzyl in (3d, 3i, 3m) is seen in 2.77-2.8 ppm.

\(^{13}\)C NMR of the compounds (3a-3m) show chemical shift between \(\delta\) 15-143 ppm. The signal of methyl has signal from 15-20 ppm. The signal of N-CH\(_2\)carbon is seen between 51 and 57. The piperidine ring carbons appear from 17-69 ppm. In the piperidine ring the carbon ortho to nitrogen is deshielded than the meta and para carbon. Also in methylated benzene rings, the carbon attached to N-CH\(_2\) is deshielded.

4.1 Anti-microbial activity

All the synthesized compounds were tested for their antimicrobial activity. The agar well diffusion method was used for antibacterial assay against two gram-positive bacteria \(S.aureus, B. subtilis\) and two gram-negative bacteria, \(E.coli\) and \(P.aeruginosa\). For antifungal screening Kirby-bauer method was used against fungi \(Candida albicans\) and \(Aspergillus niger\). 1mg/ml concentration of the test samples was employed. The compounds, which were found
to be active in preliminary screening, were tested on further dilution. Among all the compounds benzotriazole derivative (2d) was found to be more active against all the bacteria and fungi with high zone of inhibition.

Fig: 1 Preliminary screening against the bacteria (a) S.aureus, (b) B. subtilis, (c) E.coli and (d) P.aeruginosa for 2c, 2d, 3b and 3e

Fig: 2 Screening on dilution against (a) S.aureus, (b) B. subtilis, (c) E.coli and (d) P.aeruginosa for 2d
5. CONCLUSION

In this paper a series of novel benzotriazole and piperidine derivative were synthesized and their chemical structures were confirmed by FT-IR, 1H NMR and 13C NMR spectroscopy technique. All the compounds were screened for anti-microbial activity against four bacteria and two fungi. Among the compounds tested, benzotriazole derivative 2d showed good anti-microbial activity. All the synthesized compounds are currently under the investigation of single crystal XRD study.

REFERENCES