SYNTHESIS, CHARACTERIZATION AND ANTIOXIDANT STUDY OF A FEW 3-SUBSTITUTED 1,2,4-TRIAZOLE-5-THIONES AND THEIR DERIVATIVES

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ABSTRACT

A few derivatives of 3-substituted-1H-1,2,4-triazole-5(4H)-thiones were synthesized in good yield, by alkylation and Mannich reaction. The synthesized compounds have been characterized on the basis of IR, NMR and mass spectral data. The free radical scavenging activity of six triazolethiones were evaluated by DPPH method. Specific number of them showed moderate activity and the scavenging activity was found to be proportional to the sample concentration.

Key words: Triazolethione, Mannich base, Alkylation, Antioxidant activity.

INTRODUCTION

Triazole derivatives, which belong to an important group of heterocyclic compounds have been the subject of extensive study in the recent past. 1,2,4-Triazole and its derivatives are reported to exhibit various pharmacological activities such as antimicrobial, analgesic, anti-inflammatory, anticancer and antioxidant properties1-4. In addition, they are used in photosensitive materials5, as corrosion inhibitors6 and also in synthesis of several active heterocyclic compounds. 3-Substituted-1H-1,2,4-triazole-5(4H)-thiones, generally called triazolethiones have received considerable attention owing to their synthetic and biological importance7-12. In a recent report on the synthesis and biological evaluation of 4-substituted-5-(2-thienyl)-1,2,4-triazole-thiones, the antioxidant activity of triazoles bearing thiienyl moiety has been discussed13.

Two new synthetic routes for the synthesis of 3-substituted-1H-1,2,4-triazole-5(4H)-thiones by intermolecular cyclization have been recently developed by our research group14 with easily available starting materials, which is cost effective and required short reaction time. In view of the above mentioned findings and in continuation to our earlier research, we
have aimed at synthesizing two types of derivatives of 3-substituted-1H-1,2,4-triazole-5(4H)-thiones, namely Mannich base and alkylated triazole. We also studied the antioxidant activity of six triazoles, bearing biologically active rings such as pyridinyl, pyrazinyl, pyrimidinyl and quinolinyl moieties. The antioxidant activity was evaluated by DPPH method using ascorbic acid as standard.

Mannich bases of 1,2,4-triazole have been found to possess potential antimicrobial properties. Similarly, alkylated triazole derivatives are known for their mesomorphic property as well as piezochromic luminescent behavior, which are tunable by changing the length of alkyl groups. In the present work, a few Mannich bases of 3-substituted-1H-1,2,4-triazole-5(4H)-thiones were synthesized by stirring the corresponding triazole with 40% formaldehyde and morpholine in ethanol (Scheme 1).

![Scheme 1: Mannich base formation](image)

The octylated and hexylated triazoles were synthesized by stirring the corresponding triazoles with 1-iodooctane and 1-iodohexane, respectively in DMF, using sodium hydride as the base (Scheme 2).

![Scheme 2: Formation of octylated-1,2,4-triazole](image)

**EXPERIMENTAL**

Melting point of the synthesized compounds were determined using Toshniwal capillary melting point apparatus and are uncorrected. The IR spectra were recorded as KBr pellets using Shimadzu 8101A FTIR equipment. The NMR spectra were recorded on Bruker Avance III 500 MHz FT-NMR instrument. Mass spectra were recorded using LCMS-2020.
Shimadzu machine. CHNS analysis was carried out on a Vario-EI (Elementar) model. Purity of the compounds was checked by thin layer chromatography on silica gel plates.

**General procedure**

The starting triazoles were prepared by intermolecular cyclization of corresponding imidic acid ester and thiosemicarbazide\(^{14}\).

**Synthesis of Mannich bases of 3-substituted-1H-1,2,4-triazole-5(4H)-thiones**

A solution of 3-substituted-1H-1,2,4-triazole-5(4H)-thione (0.005 mol), 40% formaldehyde (0.005 mol) and morpholine (0.005 mol) in ethanol (20 mL) was stirred for 2 hours and kept overnight at room temperature. The colourless solid obtained was recrystallized from ethanol.

**Synthesis of 1-Octyl-3-substituted-1H-1,2,4-triazole-5(4H)-thiones**

To a solution of 3-substituted-1H-1,2,4-triazole-5(4H)-thione (0.005 mol) in dry DMF (15 mL) taken in an icebath 60% NaH (0.005 mol) was added followed by 1-iodooctane (0.005 mol) and stirred for 2 hours. Then the mixture was poured into ice-cold water to precipitate the product. The off white fluffy product was recrystallized from ethanol.

**Synthesis of 1-Hexyl-3-substituted-1H-1,2,4-triazole-5(4H)-thiones**

To a solution of 3-substituted-1H-1,2,4-triazole-5(4H)-thione (0.005 mol) in dry DMF (15 mL) taken in an ice bath added 60% NaH (0.005 mol), followed by 1-iodohexane (0.005 mol) and then stirred for 2 hrs. The reaction mixture was poured into crushed ice to precipitate fluffy solid. The product was filtered, washed and then recrystallized from ethanol.

**Antioxidant study**

The free radical scavenging activity was determined by spectrophotometric measurement of the change in absorbance of DPPH at 525 nm in DMSO. The absorbance was measured using JASCO V-550 UV-VIS spectrophotometer. Ascorbic acid was used as a standard. The antioxidant activity of six 3-substituted-1H-1,2,4-triazole-5(4H)-thiones with pyridinyl, pyrimidinyl, pyrazinyl and quinolinyl groups were evaluated. These triazoles were synthesized from aryl imidic acid ester and thiosemicarbazide\(^{14}\). The IC\(_{50}\) values (Table 2) were determined from the calibration curve in which the percentage inhibition is plotted against concentration.
RESULTS AND DISCUSSION

Three Mannich bases of triazolethiones with pyridinyl moieity were synthesized in good yield (78-85%), by stirring the corresponding triazole, 40% formaldehyde and morpholine in ethanol (Scheme 1). All the synthesized compounds (Table 1) gave satisfactory analytical data.

Table 1: Characteristic properties of derivatives of 3-substituted-1H-1,2,4-triazole-5(4H)-thiones

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Name</th>
<th>Molecular formula</th>
<th>Yield (%)</th>
<th>M.P. (°C)</th>
<th>Elemantal analysis found (calcd.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-(morpholinomethyl)-3-(pyridine-2-yl)-1H-1,2,4-triazole-5(4H)-thione</td>
<td>C_{12}H_{15}N_{5}OS</td>
<td>85</td>
<td>190</td>
<td>C 51.95 (51.97) H 5.41 (5.45) N 25.22 (25.25)</td>
</tr>
<tr>
<td>2</td>
<td>1-(morpholinomethyl)-3-(pyridine-3-yl)-1H-1,2,4-triazole-5(4H)-thione</td>
<td>C_{12}H_{15}N_{5}OS</td>
<td>80</td>
<td>225</td>
<td>C 51.94 (51.97) H 5.48 (5.45) N 25.23 (25.25)</td>
</tr>
<tr>
<td>3</td>
<td>1-(morpholinomethyl)-3-(pyridine-4-yl)-1H-1,2,4-triazole-5(4H)-thione</td>
<td>C_{12}H_{15}N_{5}OS</td>
<td>78</td>
<td>238</td>
<td>C 51.99 (51.97) H 5.44 (5.45) N 25.21 (25.25)</td>
</tr>
<tr>
<td>4</td>
<td>1-octyl-3-(pyridine-2-yl)-1H-1,2,4-triazole-5(4H)-thione</td>
<td>C_{15}H_{22}N_{4}S</td>
<td>80</td>
<td>90-95</td>
<td>C 62.01 (62.03) H 7.61 (7.64) N 19.31 (19.29)</td>
</tr>
<tr>
<td>5</td>
<td>1-octyl-3-(pyridine-3-yl)-1H-1,2,4-triazole-5(4H)-thione</td>
<td>C_{15}H_{22}N_{4}S</td>
<td>55</td>
<td>80-85</td>
<td>C 62.05 (62.03) H 7.62 (7.64) N 19.32 (19.29)</td>
</tr>
<tr>
<td>6</td>
<td>1-octyl-3-(pyridine-4-yl)-1H-1,2,4-triazole-5(4H)-thione</td>
<td>C_{15}H_{22}N_{4}S</td>
<td>78</td>
<td>95-100</td>
<td>C 62.07 (62.03) H 7.60 (7.64) N 19.26 (19.29)</td>
</tr>
<tr>
<td>7</td>
<td>1-hexyl-3-(pyridine-2-yl)-1H-1,2,4-triazole-5(4H)-thione</td>
<td>C_{13}H_{18}N_{4}S</td>
<td>78</td>
<td>140-45</td>
<td>C 59.49 (59.51) H 6.88 (6.91) N 21.33 (21.35)</td>
</tr>
<tr>
<td>8</td>
<td>1-hexyl-3-(pyridine-3-yl)-1H-1,2,4-triazole-5(4H)-thione</td>
<td>C_{13}H_{18}N_{4}S</td>
<td>57</td>
<td>120-25</td>
<td>C 59.53 (59.51) H 6.93 (6.91) N 21.31 (21.35)</td>
</tr>
<tr>
<td>9</td>
<td>1-hexyl-3-(pyridine-4-yl)-1H-1,2,4-triazole-5(4H)-thione</td>
<td>C_{13}H_{18}N_{4}S</td>
<td>75</td>
<td>142-48</td>
<td>C 59.48 (59.51) H 6.89 (6.91) N 21.38 (21.35)</td>
</tr>
</tbody>
</table>

1-Octyl-3-substituted-1H-1,2,4-triazole-5(4H)-thiones and 1-Hexyl-3-substituted-1H-1,2,4-triazole-5(4H)-thiones were synthesized from three different triazolethiones with
pyridinyl group (Scheme 2). The triazoles were stirred with 1-iodooctane and 1-iodohexane respectively, in dry DMF using sodium hydride as the base. The off-white product was fluffy solid. Except alkylated-3-(pyridine-3-yl)-triazoles (55 & 57%) others were obtained in good yield (75-80%). The melting point of triazoles got substantially lowered by 100 degrees and solubility in ethanol is increased. The product melted in a wide range of temperature indicating a mesomorphic nature. All the six alkylated triazoles (Table 1) synthesized gave satisfactory analytical data.

Spectral analysis

The IR, $^1$H NMR, $^{13}$C NMR and mass spectra of some representative compounds are given.

1-(Morpholinomethyl)-3-(pyridine-2-yl)-1H-1,2,4-triazole-5(4H)-thione

IR (KBr, cm$^{-1}$): 3448 (N-H), 3055 (Ar-H), 2848-2967 (C-H str.), 1566, 1576 (C=N), 1277 (C=S); $^1$H NMR (DMSO) $\delta$: 2.7 (t, 4H, N-CH$_2$ morpholine), 3.6 (t, 4H, O-CH$_2$ morpholine), 5.1 (s, 2H, N-CH$_2$-N), 7.6-8.7 (m, 4H, ArH); $^{13}$C NMR (DMSO-d$_6$) $\delta$: 50.2, 66.0, 67.8, 120.9, 125.5, 137.7, 144.3, 148.6, 149.7, 168.6; Mass (m/z): 279 (M+2), 179, 100.

1-(Morpholinomethyl)-3-(pyridine-3-yl)-1H-1,2,4-triazole-5(4H)-thione

IR (KBr, cm$^{-1}$): 3430 (N-H), 3050 (Ar-H), 2850-2943 (C-H str.), 1548, 1580 (C=N), 1280 (C=S); $^1$H NMR (DMSO) $\delta$: 2.7 (t, 4H, N-CH$_2$ morpholine), 3.6 (t, 4H, O-CH$_2$ morpholine), 5.0 (s, 2H, N-CH$_2$-N), 7.5-9.0 (m, 4H, ArH); $^{13}$C NMR (DMSO-d$_6$) $\delta$: 50.1, 66.1, 67.9, 121.0, 126.1, 137.9, 145.3, 148.2, 150.2, 168.4; Mass (m/z): 279 (M+2), 179, 100.

1-Octyl-3-(pyridine-2-yl)-1H-1,2,4-triazole-5(4H)-thione

IR (KBr, cm$^{-1}$): 3418 (N-H), 3071 (Ar-H), 2850-2955 (C-H str.), 1333-1471 (C-H bend.), 722 (long chain band); $^1$H NMR (DMSO) $\delta$: 0.87 (t, 3H, CH$_3$- octyl), 1.28 (m, 8H, -(CH$_2$)$_3$- octyl), 1.46 (m, 2H, -CH$_2$-CH$_2$-CH$_2$-N octyl), 1.77 (m, 2H, -CH$_2$-CH$_2$-N octyl), 3.2 (t, 2H, N-CH$_2$- octyl), 7.4-8.7 (m, 4H, ArH), 12.6 (s, NH); $^{13}$C NMR (DMSO-d$_6$) $\delta$: 14.1, 22.6, 28.7, 29.1, 29.2, 29.7, 31.6, 32.3, 119.1, 121.0, 137.6, 147.9, 148.2, 155.3, 161.4; Mass (m/z): 291 (M+1).

1-Hexyl-3-(pyridine-2-yl)-1H-1,2,4-triazole-5(4H)-thione

IR (KBr, cm$^{-1}$): 3413 (N-H), 3064 (Ar-H), 2853-2951 (C-H str.), 1333-1471 (C-H bend), 722 (long chain band); $^1$H NMR (DMSO) $\delta$: 0.86 (t, 3H, CH$_3$-hexyl), 1.3 (m, 4H, -(CH$_2$)$_2$- hexyl), 1.5 (m, 2H, -CH$_2$-CH$_2$-CH$_2$-N hexyl), 1.8 (m, 2H, -CH$_2$-CH$_2$-N hexyl), 3.3 (t,
2H, N-CH₂− hexyl), 6.8-8.0 (m, 4H, ArH), 12.6 (s, NH); ¹³C NMR (DMSO-d₆) δ: 13.0, 21.6, 27.4, 28.7, 29.2, 30.5, 32.3, 119.4, 122.6, 136.7, 148.2, 148.4, 155.3, 161.5; Mass (m/z): 263 (M + 1).

Antioxidant study

DPPH (1,1-diphenyl-2-picrylhydrazyl) method was used to evaluate antioxidant activity of six 3-substituted-1H-1,2,4-triazole-5(4H)-thiones. Of all the six compounds, those with pyridinyl and quinolinyl groups at 3 position of the triazole ring showed higher scavenging activity (Table 2). Ascorbic acid, reference antioxidant compound is known to have IC₅₀ value of 49 μg/mL¹⁶. 3-(pyridin-3-yl)-1H-1,2,4-triazole-5(4H)-thione and 3-(pyridin-4-yl)-1H-1,2,4-triazole-5(4H)-thione exhibited the highest radical scavenging activities, which were better than the reference compound. The scavanging activity of the compounds increased with increase in sample concentration.

Table 2: Antioxidant activity of 3-substituted-1H-1,2,4-triazole-5(4H)-thiones

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Compound</th>
<th>Antioxidant activity (IC₅₀ in μg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-(pyridin-2-yl)-1H-1,2,4-triazole-5(4H)-thione</td>
<td>64.9</td>
</tr>
<tr>
<td>2</td>
<td>3-(pyridin-3-yl)-1H-1,2,4-triazole-5(4H)-thione</td>
<td>48.5</td>
</tr>
<tr>
<td>3</td>
<td>3-(pyridin-4-yl)-1H-1,2,4-triazole-5(4H)-thione</td>
<td>42.6</td>
</tr>
<tr>
<td>4</td>
<td>3-(pyrimidin-2-yl)-1H-1,2,4-triazole-5(4H)-thione</td>
<td>85.2</td>
</tr>
<tr>
<td>5</td>
<td>3-(pyrazin-2-yl)-1H-1,2,4-triazole-5(4H)-thione</td>
<td>134.5</td>
</tr>
<tr>
<td>6</td>
<td>3-(quinolin-2-yl)-1H-1,2,4-triazole-5(4H)-thione</td>
<td>56.2</td>
</tr>
<tr>
<td>7</td>
<td>Ascorbic acid</td>
<td>49</td>
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</tbody>
</table>

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REFERENCES


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