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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 pharmocological activites such as antimicrobial, analgesic, anti-inflammatory, anticancer and antioxidant properties[1-4]. In addition, they are used in photosensitive materials[5], as corrosion inhibitors[6] 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 importance[7-12]. 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 thienyl moiety has been discussed[13].

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 group[14] 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

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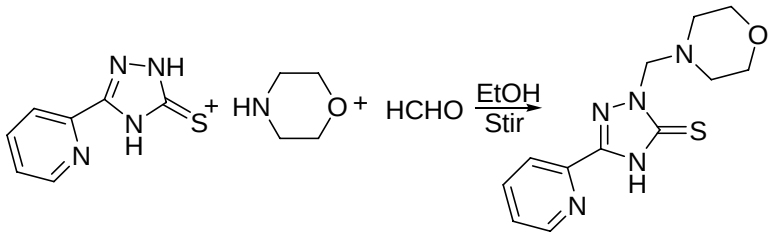
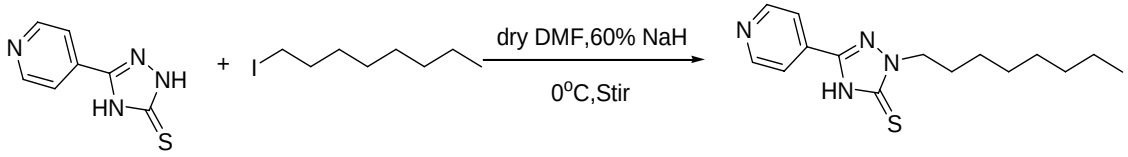
have aimed at synthesizing two types of derivatives of 3-substituted-1H-1,2,4-triazole-5(4H)-thiones, namely Mannich base and alkylated triazole. We also studied the antioxidant activity of six triazoles, bearing biologically active rings such as pyridinyl, pyrazinyl, pyrimidinyl and quinolinyl moieties. The antioxidant activity was evaluated by DPPH method using ascorbic acid as standard.

Mannich bases[13] of 1,2,4-triazole have been found to posses 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[15]. 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

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

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 moiety 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

S. No.	Name	Molecular formula	Yield (%)	M.P. (^oC)	Elemantal analysis found (calcd.)		
					C	H	N
1	1-(morpholinomethyl)-3-(pyridine-2-yl)-1H-1,2,4-triazole-5(4H)-thione	$C_{12}H_{15}N_5OS$	85	190	51.95 (51.97)	5.41 (5.45)	25.22 (25.25)
2	1-(morpholinomethyl)-3-(pyridine-3-yl)-1H-1,2,4-triazole-5(4H)-thione	$C_{12}H_{15}N_5OS$	80	225	51.94 (51.97)	5.48 (5.45)	25.23 (25.25)
3	1-(morpholinomethyl)-3-(pyridine-4-yl)-1H-1,2,4-triazole-5(4H)-thione	$C_{12}H_{15}N_5OS$	78	238	51.99 (51.97)	5.44 (5.45)	25.21 (25.25)
4	1-octyl-3-(pyridine-2-yl)-1H-1,2,4-triazole-5(4H)-thione	$C_{15}H_{22}N_4S$	80	90-95	62.01 (62.03)	7.61 (7.64)	19.31 (19.29)
5	1-octyl-3-(pyridine-3-yl)-1H-1,2,4-triazole-5(4H)-thione	$C_{15}H_{22}N_4S$	55	80-85	62.05 (62.03)	7.62 (7.64)	19.32 (19.29)
6	1-octyl-3-(pyridine-4-yl)-1H-1,2,4-triazole-5(4H)-thione	$C_{15}H_{22}N_4S$	78	95-100	62.07 (62.03)	7.60 (7.64)	19.26 (19.29)
7	1-hexyl-3-(pyridine-2-yl)-1H-1,2,4-triazole-5(4H)-thione	$C_{13}H_{18}N_4S$	78	140-45	59.49 (59.51)	6.88 (6.91)	21.33 (21.35)
8	1-hexyl-3-(pyridine-3-yl)-1H-1,2,4-triazole-5(4H)-thione	$C_{13}H_{18}N_4S$	57	120-25	59.53 (59.51)	6.93 (6.91)	21.31 (21.35)
9	1-hexyl-3-(pyridine-4-yl)-1H-1,2,4-triazole-5(4H)-thione	$C_{13}H_{18}N_4S$	75	142-48	59.48 (59.51)	6.89 (6.91)	21.38 (21.35)

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) δ: 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) δ: 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) δ: 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) δ: 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), 2854-2955 (C-H str.), 1333-1471 (C-H bend.), 722 (long chain band); ^{1}H NMR (DMSO) δ: 0.87 (t, 3H, CH_3- octyl), 1.28 (m, 8H, -$(CH_2)_4$- 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) δ: 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) δ: 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-CH_2- hexyl), 6.8-8.0 (m, 4H, ArH), 12.6 (s, NH); ^{13}C NMR (DMSO-d_6) 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 IC_{50} value of 49 µg/mL[16]. 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 activites, 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

S. No.	Compound	Antioxidant activity (IC_{50} in µg/mL)
1	3-(pyridin-2-yl)-1H-1,2,4-triazole-5(4H)-thione	64.9
2	3-(pyridin-3-yl)-1H-1,2,4-triazole-5(4H)-thione	48.5
3	3-(pyridin-4-yl)-1H-1,2,4-triazole-5(4H)-thione	42.6
4	3-(pyrimidin-2-yl)-1H-1,2,4-triazole-5(4H)-thione	85.2
5	3-(pyrazin-2-yl)-1H-1,2,4-triazole-5(4H)-thione	134.5
6	3-(quinolin-2-yl)-1H-1,2,4-triazole-5(4H)-thione	56.2
7	Ascorbic acid	49

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