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Synthesis and Antimicrobial Activity of Some Pyridyl and Naphthyl Substituted 1,2,4-Triazole and 1,3,4-Thiadiazole Derivatives

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Synthesis of new 1,2,4-tri and 1,3,4-thiadiazoles, bearing isomeric pyridyl and 1-naphthyl is reported using 1,4-disubstituted thiosemicarbazides in alkaline and acidic media, respectively. The methylthio and benzylthio derivatives of the synthesized triazoles are also reported. All of the synthesized compounds were characterized by their FT-IR, ^{1}H-NMR and mass spectral data. The antibacterial studies of some of the synthesized compounds against *S. aureus* and *E. coli* as MIC values are reported. None of them have important antibacterial activities.

Introduction

Fused and pendent 1,2,4-triazoles are a ubiquitous feature of many pharmaceutical and agrochemical products[1−3]. The substituted-1,2,4-triazole nucleus is particularly common, and examples can be found in marketed drugs such as fluconazole[4], terconazole[5], rizatriptan[6], alperazolame and triazolame. Some other 1,2,4-triazole and 1,3,4-thiadiazole heterocyclic entities that are very interesting components in terms of their biological properties, such as antifungal[7,8], antibacterial[9], herbicidal[10] and plant growth regulator activities, have been reported[11]. Due to these findings and as a part of our research program we are interested in preparing some new 1,2,4-triazole and their derivatives bearing isomeric pyridyl and 1-naphthyl substituents. The intramolecular dehydrative cyclization reaction of thiosemicarbazides in basic or acidic media was used for the construction of 1,2,4-triazole and 1,3,4-thiadiazole heterocycle rings, respectively. The benzyl- and methylthio derivatives of 1,2,4-triazole were synthesized by reaction of corresponding triazoles **(3a-c)** with benzyl chloride and methyl iodide, respectively. The synthesis of these compounds was accomplished as shown in the Scheme.

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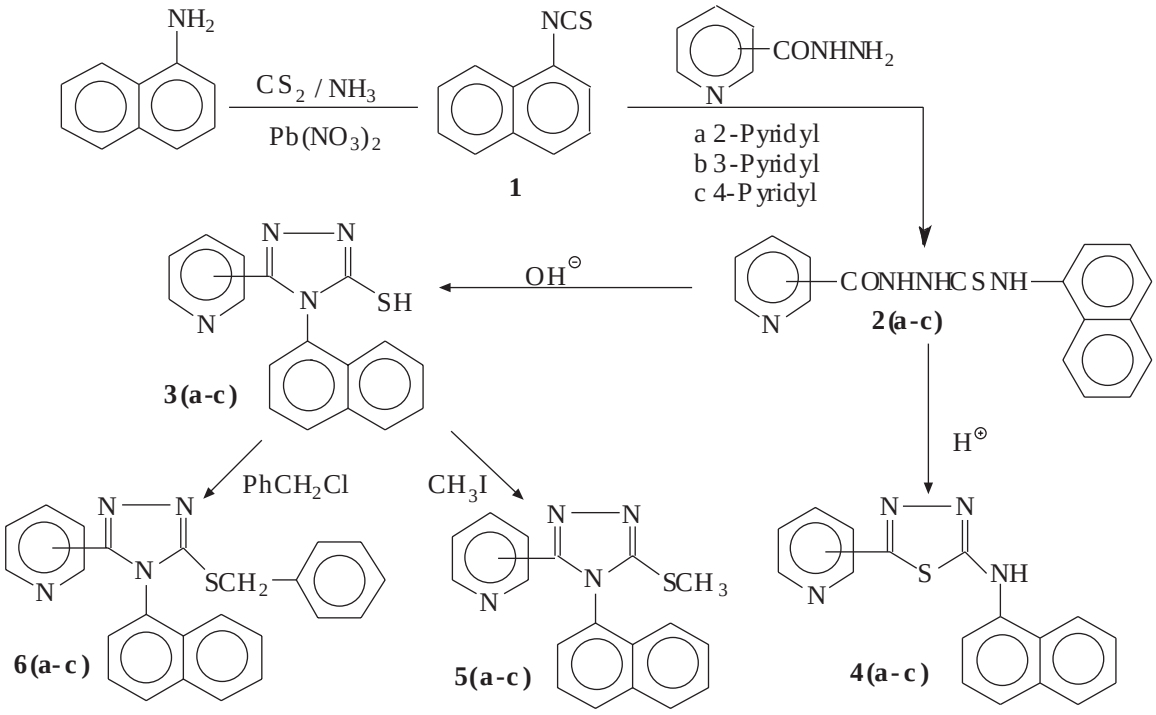

Scheme

Experimental

All chemicals were purchased from the Fluka Chemical Co. (Switzerland), the Aldrich Chemical Co. (Milwaukee, USA) or the Merck Chemical Co. (Germany). Melting points were determined using an electrothermal melting point apparatus and are uncorrected. Fourier transformer infrared spectra were recorded on a Galaxy series FT-IR 5000 spectrophotometer using KBr pellets. ^{1}H-NMR spectra were recorded on a Bruker 60 or 250 MHz instrument. The EIMS were recorded on a MAT-112-s- machine.

Synthesis of 1-naphthyl isothiocyanate (1) A mixture of 1-naphthyl amine (0.25 mol, 35.8 g), carbon disulfide (0.39 mol, 11.78 mL) and methanol (95% , 60 mL) was cooled to about 10 °C. Ammonia (33%, 6.1 mL) was added dropwise to the reaction mixture with continuous stirring. The mixture was allowed to stand overnight. The mixture was filtered and the solid was then washed with 50 mL of ether. The solid was dissolved in 250 mL of water. An aqueous solution of lead nitrate (0.25 mol, 82.7 g) was slowly added to the solution. The mixture was then steam distilled to yield **1**, m.p. 58 °C.

Synthesis of 4-(1-naphthyl)-1-(isomeric pyridyl) thiosemicarbazides (2a-c)

General procedure: related substituted pyridine carboxylic acid hydrazides (0.01 mol) were dissolved in absolute ethanol (25-50 mL). The 1-naphthyl isothiocyanate **(1)** (0.01 mol) was separately dissolved in absolute ethanol (10 mL). Then the solution of the isothiocyanate was added to the solution of hydrazide with continuous stirring. The reaction mixture was then refluxed and monitored by TLC. After consumption of the starting material, the mixture was cooled to room temperature to form a white precipitate. The crude solid was then filtered and recrystallized from the appropriate solvent to yield the compounds **(2a-c)**.

Synthesis of 4-(1-naphthyl)-5-(isomeric pyridyl) 1,2,4-triazole-3-thiole (3a-c)

General procedure: solid thiosemicarbazides **(2a-c)**(3 mmol) were added portionwise to 25 mL of

2N sodium hydroxide solution. The reaction mixture was refluxed, and the completion of the reaction was checked by TLC. The mixture was then allowed to cool to room temperature. It was filtered and then the filtrate was acidified with 2N hydrochloric acid. The precipitated solid was filtered, washed thoroughly with water, dried and recrystallized from ethanol/water (80/20).

Synthesis of 4-(1-naphthylamino)-5-(isomeric pyridyl) 1,3,4-thiadiazole (4a-c)

General procedure: each thiosemicarbazide **(2a-c)** (0.6 mmol, 0.2 g) were added portionwise to 25 mL of conc. sulfuric acid at 0 °C with continuous stirring. The reaction mixture was stirred further for 3 h at room temperature. Then it was poured into an ice-water mixture to precipitate a crude solid. The crude product was then recrystallized from a mixture of acetic acid and water (1:1 or 1:2) to furnish disubstituted 1,3,4-thiadiazole **(4a-c)**.

Synthesis of 3-methylthio-4-(1-naphthyl)-5-(isomeric pyridyl) 1,2,4-triazole (5a-c).

A mixture of the triazole **(3a-c)** (0.5 mmol), and methyl iodide (0.5 mmol) in ethanolic alkali (0.08 g KOH in 20 mL aq. EtOH) was refluxed for the time specified in Table 1. On cooling, the reaction mixture was poured into crushed ice, and a crude precipitate was obtained, which was filtered and then recrystallized from acetone.

Table 1. Reaction time, % yield and melting point of the synthesized compounds.

Comp. No. No.	Formula	Reflux Time (h)	Yield (%)	Melting Point (°C)	Mass spectral data (m/z)
1		-	63	58	———
2a	$C_{17}H_{14}N_4OS$	0.5	75	168	322 (M^+), 185, 137, 78
2b	$C_{17}H_{14}N_4OS$	1.0	67	166	322 (M^+), 216, 185, 106, 78
2c	$C_{17}H_{14}N_4OS$	*	87	200[a]	322 (M^+), 216, 185, 51
3a	$C_{17}H_{12}N_4S$	1.0	98	255	304 (M^+), 303, 271, 105, 78
3b	$C_{17}H_{12}N_4S$	3.0	70	218	304 (M^+), 303, 271, 105, 77
3c	$C_{17}H_{12}N_4S$	2.5	81	271[b]	304 (M^+), 303, 271, 186, 77
4a	$C_{17}H_{12}N_4S$	4.5	65	249	304 (M^+), 271, 200, 104, 51
4b	$C_{17}H_{12}N_4S$	5.0	60	244	304 (M^+), 271, 178, 104, 77
4c	$C_{17}H_{12}N_4S$	4.0	98	258	304 (M^+), 271, 200, 104, 78
5a	$C_{18}H_{14}N_4S$	1.5	88	149	318 (M^+), 271, 214, 141, 78
5b	$C_{18}H_{14}N_4S$	2.5	78	161	318 (M^+), 271, 167, 141, 77
5c	$C_{18}H_{14}N_4S$	2.0	83	147[c]	318 (M^+), 271, 167, 141, 77
6a	$C_{24}H_{18}N_4S$	1.0	63	141	394 (M^+), 290, 213, 167, 91
6b	$C_{24}H_{18}N_4S$	1.5	53	125	394 (M^+), 290, 213, 167, 91
6c	$C_{24}H_{18}N_4S$	1.0	58	143	394 (M^+), 290, 213, 167, 91

*In this case reflux was not required.

[a]Reported (207-208)[15] , [b] Reported (275-276)[15] and [c] Reported (140-141)[16].

Synthesis of 3-benzylthio-4-(1-naphthyl)-5-(isomeric pyridyl) 1,2,4-triazole (6a-c).

A mixture of suitable substitute-*s*-triazole **(3a-c)**(0.5 mmol), benzyl chloride (0.5 mmol) in ethanolic alkali (0.08 g KOH in 20 mL aq. EtOH) was refluxed for the time mentioned in table 1. On cooling, the reaction mixture was poured into crushed ice, to form a precipitate, which was filtered and recrystallized from acetone.

Results and Discussion

The synthesis of the title compounds **(2-6 a-c)** is illustrated in the scheme. The required isomeric pyridinecarboxylic acid hydrazides were prepared by treatment of the corresponding pyridinecarboxylic acid with hydrazine hydrate following the reported procedure[12]. 1-naphthylisothiocyanate was synthesized from 1-naphthylamine, using a modified procedure, which is already used for the synthesis of benzyl isothiocyanate[13]. The preparation of the intermediate thiosemicarbazide **(2a-c)** was carried out with the reaction of pyridinecarboxylic acid hydrazides with 1-naphthylisothiocyanate **(1)**. The isomeric substituted thiosemicarbazides **(2a-c),** when subjected to reaction with 2N sodium hydroxide, underwent intramolecular cyclization to furnish the corresponding isomeric 1,2,4-triazole-3-thioles **(3a-c)**. Compounds **(3a-c)**, when treated separately with methyl iodide or benzyl chloride, yielded methylthio **(5a-c)** or benzylthio derivatives **(6a-c)**. The substituted thiosemicarbazides **(2a-c)** in acidic medium underwent intramolecular dehydrative cyclization to form substituted 1,3,4-thiadiazoles **(4a-c)**. The purity of the isolated compounds was checked by TLC in different solvents.

The characterization of the synthesized compounds **(2-6a-c)** is based on the infrared, mass and ^{1}H-NMR spectral data (Tables 1 and 2).

The infrared spectra of **(2a-c)** showed characteristic C=C/ C=N absorptions in the region 1599-1612 cm^{-1}. The substituted thiosemicarbazides **(2a-c)** showed a peak in the region between 1676 and 1690 cm^{-1} due to carbonyl, which was eliminated by the formation of 1,2,4-triazole **(3a-c)** or 1,3,4-thiadiazole **(4a-c)** rings. The substituted-s-triazole-3-thioles **(3a-c)** showed a peak in the region 2578-2650 cm^{-1} attributed to SH. None of the triazoles **(3a-c)** showed absorption in the region 1280-1295 cm^{-1} ($\upsilon_{C=S}$). The absence of C=S and N-H and presence of S-H absorptions established that all the isolated triazoles are in their thiole rather than the thion form.

The ^{1}H-NMR spectra of the synthesized triazoles **(3a-c)** in DMSO-d_6 are listed in Table 2, in which all protons appear in the aromatic region of the spectra. The mass spectral data provided further of evidence their structure. In each case the molecular ion peak was observed at the expected m/z 304 (43-100%). Loss of thiole radical from the molecular ion radical furnished a fragment with m/z 271 (48-97%).

1,3,4-Thiadiazole **(4a-c)** structures were established using the same techniques as above. The infrared spectra of these compounds lacked carbonyl absorption; however, they exhibited absorption of N-H in the 3430-3440 cm^{-1} region. In the ^{1}H-NMR spectra of these compounds the protons were observed in the expected region. The mass spectra exhibited a molecular ion peak at m/z 304 (40-100%).

In the infrared spectra of methyl- and benzylthio derivatives **(5-6a-c)**, lack of absorbance in the region 2578-2650 cm^{-1} indicates that the compounds do not contain any S-H bond. In ^{1}H-NMR spectra, the compounds **(5a-c)** showed a singlet for 3 protons of the methyl group, and compounds **(6a-c)** exhibited a singlet for 2 protons of methylene in the benzyl group in the regions 2.6-2.8 and 4.4 ppm. respectively. In the mass spectra of the methylthio derivatives **(5a-c)** a molecular ion peak was observed at m/z 318 (10-84%). Elimination of the methylthio radical from the molecular ion gave a cation at m/z 271 (3-17%). The mass spectra of benzylthio **(6a-c)** derivatives exhibited a molecular ion peak at m/z 394 (15-22%).

Table 2. ^{1}H-NMR spectral data of the synthesized compounds.

Compd No.	^{1}H-NMR δ (ppm)
2a	7.2-8.8 (m, 11H, Ar-H), 9.9, 10.0, 10.2 (3s, 3H, 3 NH)
2b	7.2-9.2 (m, 11H, Ar-H), 9.8, 10.1, 10.8 (3s, 3H, 3 NH)
2c	7.0-8.9 (m, 11H, Ar-H), 9.8, 10.1, 11.0 (3s, 3H, 3 NH)
3a	4.4 (s, 1H, SH), 6.8-8.7 (m, 11H, Ar-H)
3b	4.5 (s, 1H, SH), 6.4-8.8 (m, 11H, Ar-H)
3c	4.0 (s, 1H, SH), 6.4-8.7 (m, 11H, Ar-H)
4a	7.9-9.8 (m, 11H, Ar-H)
4b	7.9-9.2 (m, 11H, Ar-H)
4c	7.3-9.3 (m, 11H, Ar-H), 10.5 (s, 1H, NH)
5a	2.6 (s, 3H, CH_3), 7.2-8.0 (m, 11H, Ar-H)
5b	2.6 (s, 3H, CH_3), 7.6-8.5 (m, 11H, Ar-H)
5c	2.8 (s, 3H, CH_3), 7.2-8.4 (m, 11H, Ar-H)
6a	4.4 (s, 2H, CH_2), 7.0-8.1 (m, 16H, Ar-H)
6b	4.4 (s, 2H, CH_2), 7.2-8.4 (m, 16H, Ar-H)
6c	4.4 (s, 2H, CH_2), 7.1-8.1 (m, 16H, Ar-H)

Antibacterial Activities

The anti microbial activities of the synthesized compounds were studied through applying the broth dilution method, which is one of the mostprecise and reliable methods for determining the degree of sensitivity of microbes to antibiotics[14]. The base medium used was Muller Hinton Broth (21 g/L), which turns homogeneous and clear using DMSO as solvent. The results of the antimicrobial effect of the newly synthesized compounds were reported as minimum inhibition concentration (MIC) against Gram (+) bacteria (*Staphylococcus aureus*) and Gram (-) bacteria (*Escherichia coli*). None of the synthesized compounds have important antibacterial activities. While compounds **2a, 2b, 3b** and **6a** exhibit moderate inhibitory activities at 32 μg/mL against *S. aureus* only compounds **2a** and **3b** exhibit weak inhibitory activity against *E. coli* at 64 μg/mL MIC. The other compounds had no inhibitory activity.

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