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Novel Syntheses of Some 1, 2, 4-Triazoles as Potent Bacteriocidal Agents

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Abstract: A facile syntheses of 4-aryl-5-(isomeric pyridoyl)-3*H*-1, 2, 4-triazoles as potent bacteriocidal agents are described. The newly synthesized compounds were characterized by spectral and elemental analyses. Some compounds were screened for their antibacterial activity against *S. aureus, E. coli, B. subtilis* and *P.aeruginosa.* All compounds carrying 1, 2, 4- triazole moiety showed significant biological activity.

Keywords: 1, 2, 4-Triazoles, 4-Methylphenyl isothiocyanate, Cyclization, Antibacterial activity.

Introduction

The chemistry of heterocyclic compounds continuous to be an explore field in the organic chemistry. The importance of 1,2,4-triazole derivative lies in the field that these have occupied an unique position in heterocyclic chemistry due to their antimicrobial activity[1-3]. 2,4-Dihydro-4-(4-methylphenyl)-5-(isomeric pyridyl)-3*H*-1,2,4-triazoles have been obtained by treating 1-(4-methylphenyl)-(isomeric pyridoyl) thiosemicarbazides and 2 M sodium hydroxide solution through the cyclization reaction. In views of these observations and in continuation of our earlier work[4-8] on the syntheses of some 1,2,4-&1,2,3-triazole derivatives, we now report the syntheses of some more triazoles derived from 1-(4-methylphenyl)–(isomeric pyridoyl) thiosemicarbazides and their antibacterial activities.

Experimental

Melting and boiling points were determined on a Gallen Kamp apparatus in open capillaries and are uncorrected. IR spectra (KBr in cm^{-1}) were recorded on a Jasco FT-IR 5300 spectrophotometer and PMR spectra (DMSO-d6) on an EM 390 spectrometer using TMS as an internal standard (chemical shift in δ ppm). Purity of the compounds was checked by TLC using silica gel G. All compounds showed satisfactory elemental analyses.

*4-Methylphenyl isothiocyanate (**1**)*

A mixture of 4-methylphenyl amine (0.01 mol), carbon disulfide (0.01 mol) and methanol (50 mL) was cooled to 15 ^{0}C. Ammonia (0.01 mol) was added drop wise to the reaction mixture with continuous stirring. The mixture was allowed to stand overnight. Water was added to the mixture (350 mL). An aqueous solution of lead nitrate (0.01 mol) was slowly added to the solution. The mixture was then steam distilled to yield 4-methylphenyl isothiocyanate **(1)**. The IR (KBr) of the isolated 4-methylphenyl isothiocyanate indicates a prominent characteristic band at 2071 cm^{-1} attributed to an N=C=S group (yield 70%).

*1-(4-Methylphenyl-(isomeric pyridoyl) thiosemicarbazides (**2a-c**)*

Pyridine carboxylic acid hydrazides **(a-c)** (0.01 mol) were reacted with 4-methylphenyl isothiocyanate (0.01 mol) in the presence of absolute ethanol (50 mL); was refluxed for 1.5 hours. On cooling the mixture to room temperature, a white solid appeared. The crude solid was filtered, washed with water and recrystallized from appropriate solvent to give compounds **(2a-c)** yield (70-85%).

*2,4-Dihydro-4-(4-methylphenyl)-5-(isomeric pyridyl) -3H-1,2,4-triazoles (**3a-c**)*

General procedure

A mixture of compounds **(2a-c)** (0.01 mol) and 2 M sodium hydroxide solution (30 mL) was refluxed for the period of 40 minutes. The resulting solution was cooled and poured on crushed ice. The solid separated was filtered, washed with water and recrystallized from ethanol-water to give compounds (**3a-c)** yield (75-85%).

3a: Yield 85%, m.p. 235 ^{0}C, Anal.Calc. for $C_{14}H_{12}N_4S$: C, 63.02; H, 4.61; N, 11.81%; Found: C, 63.22; H, 4.41; N, 11.91%. IR (KBr): 1588 (C=N), 1510 (C-N), 730,715 (monosubstituted benzene) and 690 cm^{-1}(C-S); PMR: δ2.35 (3H,s,CH_3); 3.32(1H,bs,SH); 7.12(2H,m,Aromatic-H); 7.31(2H,m, Aromatic-H); 7.39 (1H,m,Pyridyl-H), 7.78(1H,m, Pyridyl-H), 7.88(1H,m,Pyridyl-H) and 8.42 ppm (1H,m,Pyridyl-H); MS : *m/z* 265 (M^+) other peaks were observed at 263,207,163,107,95,81 and 53 .

3b: Yield 75%, m.p. 235 ^{0}C, Anal.Calc. for $C_{14}H_{12}N_4S$: C, 63.08; H, 4.58; N, 11.88%; Found: C, 63.20; H, 4.39; N, 11.86%. IR (KBr): 1587 (C=N), 1511 (C-N), 732,712 (monosubstituted benzene) and 699 cm^{-1}(C-S) ; PMR: δ2.35 (3H,s,CH_3); 3.26 (1H,bs, SH); 7.21 (2H,d,Aromatic-H); 7.29 (2H,d, Aromatic-H); 7.38 (1H,m,Pyridyl-H), 7.66 (1H,m,Pyridyl-H), 8.45 (1H,dd,Pyridyl-H) and 8.55 ppm (1H,m,Pyridyl-H); MS : *m/z* 265 (M^+) other peaks were observed at 263,207,163,107,95,81 and 53 .

3c: Yield 85%, m.p. 235 ^{0}C, Anal.Calc. for $C_{14}H_{12}N_4S$: C, 63.05; H, 4.62; N, 11.83%; Found: C, 63.18; H, 4.37; N, 11.87%. IR (KBr): 1586 (C=N), 1515 (C-N), 735,710 (monosubstituted benzene) and 688 cm^{-1}(C-S); PMR: δ 2.28 (3H,s,CH_3); 6.40 (1H,bs, SH); 7.10 (2H,d,Aromatic-H); 7.31(2H,d,Aromatic-H);7.65(2H,m,Pyridyl-H) and 8.82 ppm (2H,m,Pyridyl-H); MS:*m/z* 269 (M^+) other peaks were observed at 266,210,209,162,105,92,79,59 and 51 .

Antibacterial activity

The antibacterial activity of three compounds was studied by employing filter paper disc method[9-12]. Representative organisms selected for evaluation of antibacterial activity were *S. aureus, E.coli, B.subtilis* and *P.aeruginosa*. The antibacterial activity of each compound was evaluated at 100 µg mL^{-1}and 10 µg mL^{-1} concentrations. The compounds were tested as a solution or suspension in DMF. An important and useful drug ampicillin was also tested under similar conditions, with view to compare the results.

Ampicillin is a *beta*-lactam antibiotic[13] that has been used extensively to treat bacterial infections since 1961. Ampicillin is designated chemically as (2S, 5R, 6R)-6-([(2R)-2-amino-2-phenylacetyl] amino)-3, 3-dimethyl-7-oxo-4-thia-1-azabicyclo [3.2.0] heptane-2-carboxylicacid. Ampicillin is able to penetrate gram-positive and some gram-negative bacteria[14]. Ampicillin acts as a competitive inhibitor of enzyme transpeptidase.

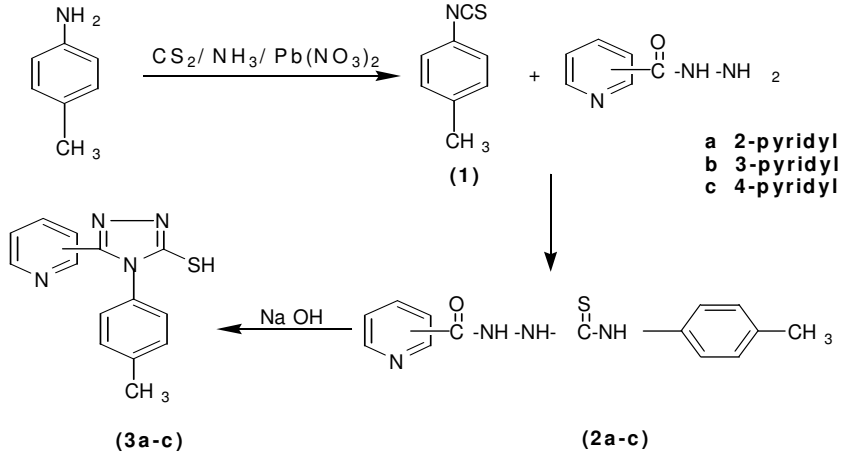
The results indicate that all three compounds showed good activity. (Table 1) All three compounds showed very good activity against *S. aureus, E.coli, B.subtilis and P.aeruginosa*. From the above observation it is clear that the 1, 2, 4-triazole derivatives are more active and play a prominent role in the biological activity.

Table 1. Evaluation of antibacterial activity of the compounds.

Compd.	Zone of Inhibition /mm							
	S. aureus		*E. coli*		*B. subtilis*		*P.aeruginosa*	
	100 µg mL^{-1}	10 µg mL^{-1}	100 µg mL^{-1}	10 µg mL^{-1}	100 µg mL^{-1}	10 µg mL^{-1}	100 µg mL^{-1}	10 µg mL^{-1}
3a	15	14	16	14	15	13	16	13
3b	17	14	14	13	15	13	16	14
3c	16	15	13	13	17	13	15	13
Standard (Ampicillin)	27	21	24	20	24	20	24	20
Control	00	00	00	00	00	00	00	00

Results and Discussion

In the present work, compound 1-(4-methylphenyl) –(isomeric pyridoyl) thiosemicarbazides **(2)** required as starting material was obtain in one-pot reaction by condensing 4-methylphenyl isothiocyanate **(1)** with Acid hydrazide. The required 4-methylphenyl isothiocyanate **(1)** was prepared from the treatment of 4-methyl aniline with carbon disulfide and ammonia in methanol and then reacted with lead nitrate. 1-(4-Methylphenyl)-(isomeric pyridoyl) thiosemicarbazides **(2)** was converted to the corresponding 2, 4-Dihydro-4-(4-methylphenyl)-5-(isomeric pyridyl)-3*H*-1, 2, 4-triazoles **(3)** by acid/base catalyzed intramolecular dehydrative cyclization reaction. (Scheme 1)



Scheme 1.

Conclusion

In conclusion, a group of 1, 2, 4-triazole derivatives were synthesized and characterized. All these compounds containing 1, 2, 4-triazole moiety is more active and plays a prominent role in biological activity. The structure of all the compounds are confirmed by IR, PMR & MS spectral data and are further supported by correct elemental analysis.

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