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Synthesis and Biological Activities of 2-Substituted-5-(β-Pyridyl)-2,3-dihydro-1,2,4-triazolo[3.4-b]-1,3,4-thiadiazoles

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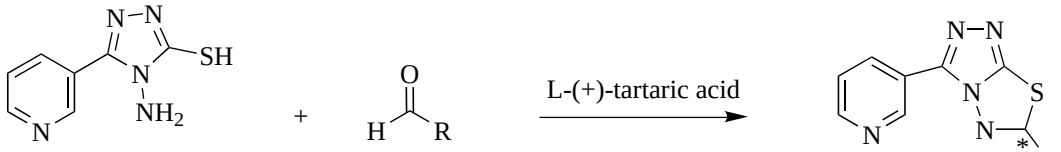
Abstract

Seven 2-substituted-5-(β-pyridyl)-2,3-dihydro-1,2,4-triazolo[3.4-b]-1,3,4-thiadiazoles have been synthesized by the Mannich reaction of 3-pyridyl-4amino-5-mercapto-1,2,4-triazole with aromatic aldehydes and furaldehyde in the presence of a catalytic amount of tartaric acid. All of them were screened for antibacterial activity and five of them showed significant activities.



1 **3**

Keywords: Triazolo[3.4-b]-1,3,4-thiadiazoles, L-(+)-tartaric acid, Mannich reaction, biological activities.

Introduction

Triazoles and their fused heterocyclic derivatives have been reported to possess significant antifungal, antibacterial and insecticidal properties [1-3]. Recently, some new triazole derivatives have been synthesized as possible antidepresants [4] and plant growth regulators [5]. Mannich base derivatives also possess antimicrobial [6] and anticancer [7] properties.

Prompted by these observations and in continuation of our studies on condensed heterocycles [8-9], we have studied the intramolecular Mannich reaction of 3-(β-pyridyl)-4-amino-5-mercapto-1,2,4-triazole, We have synthesized a series of 2-substituted-5-(β-pyridyl)-2,3-dihydro-1,2,4-triazolo-[3,4-b]-1,3,4-thiadiazoles and screened them for their anti-bacterial activity for the first time.

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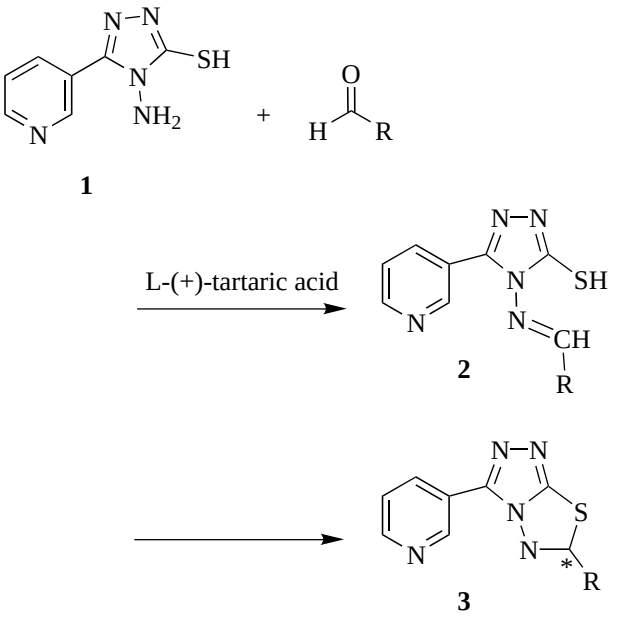
Results and Discussion

The 3-pyridyl-4-amino-5-mercapto-1,2,4-triazoles (**1**) required were prepared according to the literature [10]. Compounds (**1**) have two reactive centers (the SH and NH2 groups). We have observed that heating an aromatic aldehyde with 3-(β-pyridyl)-4-amino-5-mercapto-1,2,4-triazole (**1**) in the presence of a catalytic amount of L(+)-tartaric acid for 5 h at 45 up to 70 °C leads to condensation products. Ring closure of the corresponding Schiff bases with the SH groups gives the chiral Mannich bases in 53-95 % yield, as shown in Scheme 1.



Scheme 1.

Compounds **3a-g** were characterized by elemental analysis, IR, ^{1}H-NMR and MS data. By our method the Mannich bases **3a-g** could be prepared from substituted benzaldehydes and furfuraldehyde. However, the method failed to give the Mannich base product when o-methoxybenzaldehyde was used as aromatic aldehyde. The reaction can proceed smoothly under the action of a catalytic amount of acid. Obviously optically active Mannich base was obtained when using L(+)-tartaric acid. Only the racemic compounds were obtained when using H_2SO_4 and HCl. The structure **3** finds further support from its insolubility in dilute, aqueous NaOH or $NaHCO_3$ (10%) solutions.

In the IR spectra SH absorption (around 2600 cm^{-1}) was not observed in the case of **3a-g**, which provided the additional evidence for the second step reaction leading to the products of the assigned structure.

The ^{1}H-NMR spectra of **3a-g** also conform with the assigned structures. The NH proton singlet appeared at δ 7.5-5.8 ppm. The signals of the aromatic protons of the pyridyl system and the aryl ring overlapped with each other and appeared as a multiplet at δ 6.9-10.19 ppm. Comparison of the ^{1}H-NMR spectra with that of compound **1**, the chemical shifts of the NH and CH protons of **3a-g**, showed low field shifts. This can be explained by the strong deshielding effect of the structure in **3a-g**.

Mass spectra of a large number of similar heterocyclic compound have been reported, but the mass spectra of this kind of Mannich base have not been reported in the literature to our knowledge. The predominant fragmentation in the mass spectra of compounds **3a-g** involves expulsion of RCN from the molecular ion, resulting in the formation of ions at m/e 178 as the strongest spectral line for all products.

Conclusions

Compounds **3a-g** were synthesised and tested for their antibacterial activities against *B. Bob.*, *S. Aur.* and *E. Coli*. at 500 and 100 ppm concentrations. The results show that **3a**, **3b**, **3d** and **3e** have particularly significant activities. Detailed results will be described elsewhere. The determination of enantiomeric purity and the absolute configuration of the dominant enantiomeric products will be our further interests.

Experimental Part

Melting points were determined using an x4 apparatus and are uncorrected. IR spectra were recorded on a PERKIN-ELMER 983 spectrophotometer as KBr pellet. The ^{1}H-NMR spectra were determined on an AC-100 spectrometer in (D_6)DMSO, chemical shifts δ in ppm are relative to TMS. Elementary analyses were done with a PE-2400 elementary analysis instrument. Mass spectra were determined on

a HP-5989 A instrument at 70 eV. Optical rotation was measured with a wzz-1 instrument. 3-(β-pyridyl)-4-amino-5-mercapto-1,2,4-triazole (**1**) was synthesized by the literature method [10]

*Mannich base **3a-g**: General procedure for the preparation of 2-substituted-5-(β-pyridyl)-2,3-dihydro-1,2,4-triazolo[3.4-b]-1,3,4-thiadiazoles.*

The 3-(β-pyridyl)-4-amino-5-mercapto-1,2,4-triazole (**1**) (0.01 mol) was dissolved in absolute EtOH (10 mL). Then the aromatic aldehyde (0.01 mol) was added, followed by the addition of L(+)-tartaric acid (0.25 g). The mixture was stirred at 45 °C for 1 h, then at 70 °C for 4-5 h and cooled. The Mannich bases **3a-g** were collected by filtration and washed with water. The pure product was obtained by recrystallization from absolute EtOH or a mixture of EtOH-$CH_3COOC_2H_5$ (3:1).

*2-Phenyl-5-(β-pyridyl)-2,3-dihydro-1,2,4-triazolo[3.4-b]-1,3,4-thiadiazole (**3a**)*

Pale yellow powder was obtained in 93.6 % yield. M.p. 218-219.5 °C. Anal. Calc. for $C_{11}H_{11}N_5S$: C 59.77; H 3.94; N 24.89. Found: C 59.89; H 3.88; N 25.05. $[\alpha]_D^{20}$ = +6.7 ° (C = 0.0042 g/mL in DMSO). ^{1}H-NMR: 7.62 (5H, s, Ph-H), 7.85-9.82 (4H, m, Py-H), 3.48 (1H, s, CH). IR: 3220(NH), 3080, 3040 (Ar-H), 1600, 1589, 1548, 1462 (C=N, C=C). 1294 (N-N=C), 697 (C-S-C). m/e: 281 (M^+, 7.97), 204 (0.63), 178 (100), 149 (2.65), 119 (28.55), 105 (28.25), 92 (7.88), 77 (15.62).

*2-(p-Chlorophenyl)-5-(β-pyridyl)-2,3-dihydro-1,2,4-triazolo[3.4-b]-1,3,4-thiadiazole (**3b**)*

Yellow powder was obtained in 89% yield. M.p. 246.5-248 °C. Anal. Calc. for $C_{14}H_{10}N_5ClS$: C 53.24; H 3.19; N 22.18. Found: C 53.15; H 3.23; N 22.31. $[\alpha]_D^{20}$ =+5.01 ° (C = 0.0036 g/mL in DMSO). ^{1}H-NMR: 5.80 (1H, s, NH), 9.89-7.88 (4H, m, Py-H), 7.68-7.52 (4H, m, Ar-H), 3.32 (1H, s, CH). IR: 3250 (NH), 3060 (Ar-H), 2921 (C-H), 1592, 1554, 1482, 1461 (C=N, C=C), 1284 (N-N=C), 690 (C-S-C). m/e: 315 (M^+, 4.58), 210 (4.47), 178 (100), 149 (10.43), 119 (31.13), 105 (37.44).

*2-(p-Nitrophenyl)-5-(β-pyridyl)-2,3-dihydro-1,2,4-triazolo[3.4-b]-1,3,4-thiadiazole (**3c**)*

Orange yellow powder was obtained in 95 % yield. M.p. 245-246.5 °C. Anal. Calc. for $C_{14}H_{10}N_6SO_2$: C 51.52; H 3.09; N 25.76. Found: C 51.50; H 3.14; N 25.88. $[\alpha]_D^{20}$ = + 5. 87 ° (C = 0.0017 g/mL in DMSO). ^{1}H-NMR: 7.53 (1H, s, NH), 10.19-7.58 (4H, m, Py-H), 8.10-8.43 (4H, m, Ar-H), 3.30 (1H, s, CH). IR: 3340 (NH), 3045 (Ar-H), 2955 (C-H), 1601, 1590, 1534, 1483 (C=N, C=C), 1283 (N-N=C), 692 (C-S-C). m/e: 326 (M^+, 4.66), 178 (100), 148 (9.50), 119 (30.34), 105 (31.63).

*2-(p-Methoxyphenyl)-5-(β-pyridyl)-2,3-dihydro-1,2,4-triazolo[3.4-b]-1,3,4-thiadiazole (**3d**)*

Pale yellow powder was obtained in 67.5 % yield. M.p. 219-220 °C. Anal. Calc. for $C_{15}H_{13}N_5SO$: C 57.86; H 4.21; N 22.49. Found: C 57.75; H 4.26; N 22.62. $[\alpha]_D^{20}$ = +4.63 ° (C = 0.0043 g/mL in DMSO). ^{1}H-NMR: 7.07(1H, s, NH), 9.91-7.51(4H, m, Py-H), 7.90, 7.51 (4H, m, Ar-H), 3.33 (3H, s, OCH3). IR: 3140 (NH), 3061 (Ar-H), 1635, 1604, 1565, 1482 (C=N, C=C), 1287 (N-N=C), 699 (C-S-C). m/e: 311 (M^+, 6.96), 178 (91.40), 133 (100), 119 (21.55), 105 (25.45), 97 (16.93).

*2-(4'-Hydroxy-3'- methoxyphenyl)-5-(β-pyridyl)-2,3-dihydro-1,2,4-triazolo [3.4- b] - 1, 3, 4- thiadiazole (**3e**)*

Pale yellow powder was obtained in 57.9 % yield. M.p. 215-217 °C. Anal. Calc. for $C_{15}H_{13}N_5SO_2$: C 55.03; H 4.00; N 21.39. Found: C 55.16; H 3.91; N 21.24. $[\alpha]_D^{20}$ = -28.8 ° (C = 0.000868 g/mL in EtOH). ^{1}H-NMR: 6.98 (1H, s, NH), 9.50-8.21 (4H, m, Py-H), 10.06 (1H, s, OH), 7.29-7.59 (3H, m, Ar-H), 3.82 (1H, s, CH), 3.31 (3H, s, OCH3). IR: 3230 (NH), 3080, 3050 (Ar-H), 1598, 1554, 1511, 1461 (C=N, C=C). 1297 (N-N=C), 694 (C-S-C). m/e: 327 (M^+, 5.89), 295 (0.64), 207 (0.54), 178 (69.93), 149 (100), 134 (63.94), 119 (20.73).

*2-(o-Hydroxyphenyl)-5-(β-pyridyl)-2,3-dihydro-1,2,4-triazolo[3.4-b]-1,3,4-thiadiazole (**3f**)*

Pale yellow powder was obtained in 53.5 % yield. M.p. 236-238 °C. Anal. Calc. for $C_{14}H_{11}N_5SO$: C 56.55; H 3.73; N 23.56. Found: C 56.39; H 3.81; N 23.79. $[\alpha]_D^{20}$ = -9.4 ° (C = 0.001065 g/mL in absolute EtOH). ^{1}H-NMR: 10.19 (1H, s, OH), 9.12-7.66 (4H, m, Py-H), 7.61-6.98 (4H, m, Ar-H), 3. 03 (1H, s, CH). IR: 3360 (NH), 3060 (Ar-H), 1617, 1599, 1511, 1462 (C=N, C=C). 1291(N-N=C), 691(C-S-C). m/e: 297 (M^+, 6.42), 193 (0.66), 178 (100), 137 (1.18), 119 (46.58), 105 (29.68), 91 (19.71), 78 (12.26).

*2-(a-Furyl)-5-(β-pyridyl)-2,3-dihydro-1,2,4-triazolo[3.4-b]-1,3,4-thiadiazole (**3g**)*

Greyish-yellow powder was obtained in 79.3 % yield. M.p. 232.5-234 °C. Anal. Calc. for $C_{12}H_9N_5SO$: C 53.12; H 3.34; N 25.82. Found: C 53.28; H 3.26; N 25.63. $[\alpha]_D^{20}$ = +7.7 ° (C = 0.0013 g/mL, absolute EtOH). ^{1}H-NMR: 10.12-7.95 (4H, m, Py-H), 7.67-6.55 (3H, m, furan), 3.11 (1H, s, CH). IR: 3160 (NH), 3055 (Py-H), 1599, 1516, 1462, 1413 (C=N, C=C), 1300 (N-N=C), 695 (C-S-C). m/e: 271 (M^+, 19.12), 193 (2.41), 178 (100), 162 (1.77), 149 (2.77), 119 (35.31), 105 (30.58), 78 (10.85).

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Supporting samples are available from MDPI: **3a**, MDPI 559; **3b**, MDPI 560; **3e**, MDPI 561.