Asian Journal of Chemistry Vol. 20, No. 8 (2008), 6468-6472

Synthesis of Some S-Mannich Bases of 1-[3-Substituted aminomethylsulfanyl-5-(6-aryl-imidazo-[2,1-B]thiazol-3-ylmethyl)-[1,2,4]triazol-4-yl]propan-2-ones

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In this paper, the synthesis of a series of novel S-Mannich bases of 1-[3-Substituted aminomethylsulfanyl-5-(6-aryl-imidazo[2,1-b]thiazol-3-ylmethyl)-[1,2,4]triazol-4-yl]-propan-2-ones are reported. The structures of the synthesized compounds were characterized by elemental and spectral studies.

Key Words: Synthesis, S-Mannich Bases, Substituted triazoles.

INTRODUCTION

The azole antitubercular may be regarded as a new class providing truly effective drugs, which are reported to inhibit bacteria by blocking the biosynthesis of certain bacterial lipids and/or by additional mechanisms[1,2]. Triazole and thiazole derivatives[3-7] represents a novel emerging major chemical group as antimicrobial agent. Triazoles, in particular, substituted-1,2,4-triazoles and the open-chain thiosemicarbazide counterparts of 1,2,4-triazole, are among the various heterocycles that have received the most attention during the last two decades as potential antimicrobial agents[8-11]. Substitutions including thio[12] alkylthio and alkenylthio[13] derivatives have been carried out primarily at the 3-position of the 1,2,4-triazole ring, as potential antimicrobial and antimycobacterial agents those will overcome the above mentioned resistance problems. Thiazole moiety has already been reported for its antimicrobial activity[14,15]. Recently, environmentally benign synthetic methods have received considerable attention and solvent free protocols are reported[16-18]. Thus, in this paper the microwave irradiation synthesis of new 1,2,4-triazole derivatives clubbed with thiazole moiety are reported.

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EXPERIMENTAL

The melting points were recorded on electrothermal apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker Avance 300 MHz instrument using $CDCl_3$ as solvent using TMS as internal standard; the chemical shifts (δ) are reported in ppm and coupling constants (*J*) are given in Hz. Microwave irradiation was carried out in Raga Scientific Microwave Systems, Model RG31L at 2450 MHz. Elemental analyses were performed on a Heracus CHN-Rapid Analyzer. Analyses indicated by the symbols of the elements of functions were within ±/0.4 % of the theoretical values. The purity of the compounds was checked on Merck pre-coated silica gel 60 F-254.

N-[3-Mercapto-5-(6-aryl-imidazo[2,1-b]thiazol-3-ylmethyl)-[1,2,4]-triazol-4-yl]acetamide (II a-d): Acetic anhydride (1 mmol) in pyridine (10 mL) was added dropwise, with constant stirring to 4-amino-5-(6-aryl-imidazo[2,1-b]thiazol-3-ylmethyl)-4*H*-[1,2,4]triazole-3-thiol(**I a-d**) (0.01 mol) in 20 mL of pyridine at 0 ºC. The mixture after standing overnight was refluxed, for 5-6 h. It was cooled and then poured on ice-cold water, acidified with hydrochloric acid. The solid thus separated was filtered, washed thoroughly with water and crystallized from absolute alcohol.

1-[3-Substituted aminomethylsulfanyl-5-(6-aryl-imidazo[2,1-b]-thiazol-3-ylmethyl)-[1,2,4]triazol-4-yl]propan-2-one (III a-l): A solution of N-[3-mercapto-5-(6-aryl-imidazo[2,1-b]thiazol-3-ylmethyl)-[1,2,4]-triazol-4-yl]-acetamide (**II a-d**) (1 mmol) and 0.4 g (0.01 mol) of NaOH in 30 mL of ethanol was refluxed for 0.5 h. To this solution, N-substituted amine (1 mmol) was added dropwise to the mixture. Reaction mixture was refluxed for 4-5 h. The mixture was cooled and poured on ice. The solid thus separated was filtered, washed thoroughly with water and crystallized from ethanol. The physical data of the synthesized compounds are given in Table-1.

N-(3-((Diethylamino)methylthio)-5-((6-phenylimidazo[2,1-b]thiazol-3-yl)methyl)-4*H*-1,2,4-triazol-4-yl)acetamide (IIIa): ^{1}H NMR (300 MHz DMSO), δ (ppm): 1.21 (t, 6H, CH_2-CH_3), 2.36 (q, 4H, CH_2-CH_3) 2.89 (s, 3H, CH_3), 4.12 (s, 2H, S-CH_2), 4.72 (s, 2H, -CH_2-), 6.47 (s, 1H, thiazole), 7.13 (s, 1H, imidazole), 7.26-7.58 (m, 5H, ArH), 9.83 (s, 1H, SH).

N-(3-((6-Phenylimidazo[2,1-b]thiazol-3-yl)methylthio)-5-((piperidin-1-yl)methyl)-4*H*-1,2,4-triazol-4-yl)acetamide (IIIb): ^{1}H NMR (300 MHz DMSO), δ (ppm): 1.34-2.48 (m, 10H, piperidine), 2.94 (s, 3H, CH_3), 4.17 (s, 2H, S-CH_2), 4.73 (s, 2H, -CH_2-), 6.48 (s, 1H, thiazole), 7.15 (s, 1H, imidazole), 7.33-7.62 (m, 5H, ArH), 9.82 (s, 1H, SH).

N-(3-((Diethylamino)methylthio)-5-((6-*p*-tolylimidazo[2,1-b]thiazol-3-yl)methyl)-4*H*-1,2,4-triazol-4-yl)acetamide (IIId): ^{1}H NMR (300 MHz DMSO), δ (ppm): 1.28 (t, 6H, CH_2-CH_3), 2.32 (q, 4H, CH_2-CH_3) 2.81 (s, 6H, CH_3), 4.12 (s, 2H, S-CH_2), 4.65 (s, 2H, -CH_2-), 6.47 (s, 1H, thiazole), 7.15 (s, 1H, imidazole), 7.34-7.52 (m, 4H, ArH), 9.87 (s, 1H, SH).

TABLE-1
ANALYTICAL DATA OF 1-[3-SUBSTITUTEDAMINO-METHYLSULFANYL-5-(6-ARYL-IMIDAZO [2,1-B]THIAZOL-3- YLMETHYL)-[1,2,4]TRIAZOL-4-YL]-PROPAN-2-ONES (**III a-l**)

Compd. (m.f.)	R	R′	R″	m.w. (m.p. ºC)	Elemental analysis %: Calcd. (Found)		
					C	H	N
III a ($C_{22}H_{26}N_6OS_2$)	-H	$-C_2H_5$	$-C_2H_5$	455 (214)	58.12 (58.31)	5.76 (5.58)	18.49 (18.63)
III b ($C_{23}H_{26}N_6OS_2$)	-H	Piperidine		467 (235)	59.20 (59.34)	5.62 (5.72)	18.01 (18.23)
III c ($C_{22}H_{24}N_6O_2S_2$)	-H	Morpholine		469 (228)	56.39 (56.51)	5.16 (5.30)	17.93 (17.79)
III d ($C_{23}H_{28}N_6OS_2$)	$-CH_3$	$-C_2H_5$	$-C_2H_5$	469 (221)	58.95 (58.78)	6.02 (6.26)	17.93 (17.78)
III e ($C_{24}H_{28}N_6OS_2$)	$-CH_3$	Piperidine		481 (220)	59.97 (59.84)	5.87 (5.74)	17.48 (17.62)
III f ($C_{23}H_{26}N_6O_2S_2$)	$-CH_3$	Morpholine		483 (246)	57.24 (57.35)	5.43 (5.57)	17.41 (17.58)
III g ($C_{23}H_{28}N_6O_2S_2$)	OCH_3	$-C_2H_5$	$-C_2H_5$	485 (251)	57.00 (57.17)	5.82 (5.93)	17.34 (17.47)
III h ($C_{24}H_{28}N_6O_2S_2$)	OCH_3	Piperidine		497 (247)	58.04 (58.24)	5.68 (5.84)	16.92 (16.77)
III i ($C_{23}H_{26}N_6O_3S_2$)	OCH_3	Morpholine		499 (239)	55.40 (55.64)	5.26 (5.31)	16.85 (16.73)
III j ($C_{22}H_{25}N_7O_3S_2$)	$-NO_2$	$-C_2H_5$	$-C_2H_5$	500 (230)	52.89 (52.76)	5.04 (5.25)	19.62 (19.82)
III k ($C_{23}H_{25}N_7O_3S_2$)	$-NO_2$	Piperidine		512 (237)	53.99 (53.74)	4.93 (4.75)	19.16 (19.02)
III l ($C_{22}H_{23}N_7O_4S_2$)	$-NO_2$	Morpholine		514 (246)	51.45 (51.67)	4.51 (4.63)	19.09 (19.17)

N-(3-((Piperidin-1-yl)methylthio)-5-((6-*p*-tolylimidazo[2,1-b]thiazol-3-yl)methyl)-4*H*-1,2,4-triazol-4-yl)acetamide (IIIe): ^{1}H NMR (300 MHz DMSO), δ (ppm): 1.32-2.47 (m, 10H, piperidine), 2.86 (s, 6H, CH_3), 4.12 (s, 2H, S-CH_2), 4.63 (s, 2H, -CH_2-), 6.69 (s, 1H, thiazole), 7.12 (s, 1H, imidazole), 7.31-7.57 (m, 4H, ArH), 9.89 (s, 1H, SH).

N-(3-(Morpholinomethylthio)-5-((6-*p*-tolylimidazo[2,1-b]thiazol-3-yl)methyl)-4*H*-1,2,4-triazol-4-yl)acetamide (IIIf): ^{1}H NMR (300 MHz DMSO), δ (ppm): 1.24-1.37 (m, 6H, morpholine), 2.13-2.17 (m, 2H, morpholine), 2.89 (s, 6H, CH_3), 4.12 (s, 2H, S-CH_2), 4.61 (s, 2H, -CH_2-), 6.62 (s, 1H, thiazole), 7.18 (s, 1H, imidazole), 7.30-7.53 (m, 4H, ArH), 9.81 (s, 1H, SH).

N-(3-((Diethylamino)methylthio)-5-((6-(4-methoxyphenyl)imidazo-[2,1-b]thiazol-3-yl)methyl)-4*H*-1,2,4-triazol-4-yl)acetamide (IIIg): ^{1}H NMR (300 MHz DMSO), δ (ppm): 1.23 (t, 6H, CH_2-CH_3), 2.38 (q, 4H, CH_2-CH_3) 2.82 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 4.12 (s, 2H, S-CH_2), 4.69

(s, 2H, -CH_2-), 6.48 (s, 1H, thiazole), 7.10 (s, 1H, imidazole), 7.31-7.56 (m, 4H, ArH), 9.84 (s, 1H, SH).

N-(3-((Piperidin-1-yl)methylthio)-5-((6-(4-methoxyphenyl)imidazo-[2,1-b]thiazol-3-yl)methyl)-4*H*-1,2,4-triazol-4-yl)acetamide (IIIh): ^{1}H NMR (300 MHz DMSO), δ (ppm): 1.31-2.49 (m, 10H, piperidine), 2.80 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 4.12 (s, 2H, S-CH_2), 4.72 (s, 2H, -CH_2-), 6.49 (s, 1H, thiazole), 6.92 (s, 1H, imidazole), 7.28-7.46 (m, 4H, ArH), 9.86 (s, 1H, SH).

N-((6-(4-Methoxyphenyl)imidazo[2,1-b]thiazol-3-yl)methyl)-5-morpholinomethylthio)-4*H*-1,2,4-triazol-4-yl)acetamide (IIIi): ^{1}H NMR (300 MHz DMSO), δ (ppm): 1.27-1.31 (m, 6H, morpholine), 2.24-2.29 (m, 2H, morpholine), 2.74 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 4.12 (s, 2H, S-CH_2), 4.74 (s, 2H, -CH_2-), 6.50 (s, 1H, thiazole), 6.97 (s, 1H, imidazole), 7.21-7.57 (m, 4H, ArH), 9.71 (s, 1H, SH).

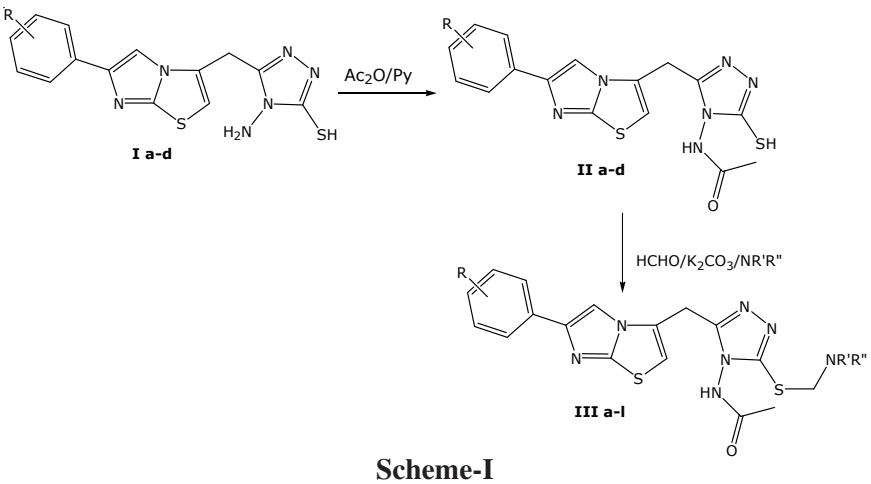
N-(3-((Diethylamino)methylthio)-5-((6-(4-nitrophenyl)imidazo[2,1-b]-thiazol-3-yl)methyl)-4*H*-1,2,4-triazol-4-yl)acetamide (IIIj): ^{1}H NMR (300 MHz DMSO), δ (ppm): 1.26 (t, 6H, CH_2-CH_3), 2.36 (q, 4H, CH_2-CH_3) 2.78 (s, 3H, CH_3), 4.12 (s, 2H, S-CH_2), 4.77 (s, 2H, -CH_2-), 6.64 (s, 1H, thiazole), 6.95 (s, 1H, imidazole), 7.27-7.43 (m, 4H, ArH), 9.75 (s, 1H, SH).

N-(3-((Piperidin-1-yl)methylthio)-5-((6-(4-nitrophenyl)imidazo-[2,1-b]thiazol-3-yl)methyl)-4*H*-1,2,4-triazol-4-yl)acetamide (IIIk): ^{1}H NMR (300 MHz DMSO), δ (ppm): 1.37-2.40 (m, 10H, piperidine), 2.89 (s, 3H, CH_3), 4.12 (s, 2H, S-CH_2), 4.81 (s, 2H, -CH_2-), 6.67 (s, 1H, thiazole), 6.95 (s, 1H, imidazole), 7.21-7.49 (m, 4H, ArH), 9.70 (s, 1H, SH).1.26 (t, 6H, CH_2-CH_3), 2.36 (q, 4H, CH_2-CH_3) 2.78 (s, 3H, CH_3), 4.12 (s, 2H, S-CH_2), 4.77 (s, 2H, -CH_2-), 6.64 (s, 1H, thiazole), 6.95 (s, 1H, imidazole), 7.27-7.43 (m, 4H, ArH), 9.75 (s, 1H, SH).

N-(3-(Morpholinomethylthio)-5-((6-(4-nitrophenyl)imidazo[2,1-b]-thiazol-3-yl)methyl)-4*H*-1,2,4-triazol-4-yl)acetamide (IIIl): ^{1}H NMR (300 MHz DMSO), δ (ppm): 1.25-1.29 (m, 6H, morpholine), 2.18-2.21 (m, 2H, morpholine), 2.92 (s, 3H, CH_3), 4.12 (s, 2H, S-CH_2), 4.84 (s, 2H, -CH_2-), 6.42 (s, 1H, thiazole), 7.16 (s, 1H, imidazole), 7.34-7.59 (m, 4H, ArH), 9.73 (s, 1H, SH).

RESULTS AND DISCUSSION

N-[3-mercapto-5-(6-aryl-imidazo[2,1-b]thiazol-3-ylmethyl)-[1,2,4]-triazol-4-yl]-acetamides (**II a-d**) were prepared by acetylation of 4-amino-5-(6-aryl-imidazo[2,1-b]thiazol-3-ylmethyl)-4*H*-[1,2,4]triazole-3-thiols using acetic anhydride in the presence of pyridine. Thus obtained intermediates were subjected to Mannich reactions using different secondary amines in the presence of the base and formaldehyde to afford 1-[3-substituted aminomethylsulfanyl-5-(6-aryl-imidazo[2,1-b]thiazol-3-ylmethyl)-[1,2,4]-triazol-4-yl]-propan-2-ones (**III a-l**) (**Scheme-I**).



Scheme-I

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(*Received*: 22 February 2008; *Accepted*: 17 July 2008) AJC-6706