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Microwave Assisted Synthesis of Novel Azetidin-2-one and Thiazolidin-4-one Derivatives of Triazolyl Thiophene

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N-[3-(4-Amino-5-mercapto-4*H*-[1,2,4]triazol-3-yl)-4,5-dimethyl-thiophen-2-yl]-acetamide **(Ia)** and N-[3-(4-amino-5-mercapto-4*H*-[1,2,4]triazol-3-yl)-4,5-dimethyl thiophen-2-yl]-benzamide **(Ib)** were condensed with different aromatic aldehydes to yield Schiff bases **(IIa–j; IIIa–j)**. The Schiff bases on cyclization with chloroacetyl chloride in presence of triethyl amine furnished azetidin-2-ones **(IVa–j; Va–j)**. The Schiff bases on cyclization with mercaptoacetic acid offered thiazolidin-4-ones **(VIa–j; VIIa–j)**. The compounds thus synthesized in good yields by microwave irradiation method and were characterized by their TLC, chemical analysis and spectral data. The title compounds were subjected to antimicrobial and antitubercular activities.

Key Words: Synthesis, Microwave irradiation, Azetidin-2-one and Thiazolidin-4-one derivatives.

INTRODUCTION

In the past few years, many azetidin-2-one derivatives have been found to possess significant antibacterial[1] activity. Thiazolidin-4-ones are reported for antibacterial[2] and antitubercular[3, 4] activites. Thiophenes exhibit a wide range of biological activities[4] like antioxidants, antiinvasive, antiviral, etc. Schiff bases of triazoles have been reported to possess various pharmacological activities such as antibacterial[5], antifungal[5] activities. Microwave assisted reactions[6] using dry media[7] have attracted much interest because of the simplicity in operation, greater selectivity and rapid synthesis of a variety of heterocyclic compounds[8]. Keeping this in mind, it was worth while to develop rapid syntheses of title compounds under solvent-free conditions using microwave assisted organic reaction enhancement method.

EXPERIMENTAL

The melting points were recorded on electrothermal apparatus and are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer-983 and ^{1}H NMR spectra on Bruker-Avance 300 MHz instrument using $CDCl_3$ as solvent

(chemical shifts in δ ppm), using TMS as internal standard. Mass spectra were charted on Finning LCQ mass spectrometer. Microwave irradiations were carried out in Padmini Essentia oven, model Brownie, at 2450 MHz. Elemental analyses were performed on a Heracus CHN rapid analyser.

N-[3-(4-Amino-5-mercapto-4*H*-[1,2,4]triazol-3-yl)-4,5-dimethyl-thiophen-2-yl]-acetamide **(Ia)** and N-[3-(4-amino-5-mercapto-4*H*-[1,2,4]triazol-3-yl)-4,5-dimethyl-thiophen-2-yl]-benzamide **(Ib)** were prepared as per literature method[9, 10].

N-{3-[4-Benzylideneamino)-5-mercapto-4*H*[1,2,4]triazol-3-yl]-4,5-dimethyl-thiophen-2-yl}acetamide (IIa)

Compound **Ia** (0.01 mol), a pinch of *p*-toluene sulphonic acid and appropriate aromatic aldehyde (0.01 mol) were mixed. Acidic alumina[11] was added to the above mixture at room temperature. The reaction mixture was adsorbed, dried and kept inside the alumina bath[12] and irradiated for 40–80 s. The mixtrue was cooled and the product was extracted with dry methanol and poured on to crushed ice. The solid thus separated was filtered, washed thoroughly with water and recrystallized from aqueous ethanol. Other Schiff bases for **Ia** and **1b** series were obtained in a similar manner.

N-{3-[4-(3-Chloro-2-oxo-4-phenyl-azetidin-1-yl)-5-mercapto-4*H*-[1,2,4] triazol-3-yl]-4,5-dimethyl-thiophen-2-yl}acetamide (IVa)

Schiff base **(IIa)** (0.01 mol) was mixed with triethylamine (2.80 mL, 0.02 mol) and chloroacetyl chloride (1.60 mL, 0.02 mol) was added dropwise over a period of 30 min. Acidic alumina was added to the above solution at room temperature. The reaction mixture was adsorbed, dried and kept inside the alumina bath and irradiated for 40–80 s. The mixture was cooled and the product was extracted with absolute ethanol and poured on to crushed ice. The solid thus separated was filtered, washed thoroughly with water and recrystallized from aqueous ethanol. The product **(IVa)** obtained was filtered, washed with water and crystallized. Other azetidine-2-ones for **Ia** and **1b** series were obtained in a similar manner.

N-{3-[5-Mercapto-4-(4-oxo-2-phenyl-thiazolidin-3-yl)-4*H*-[1,2,4]triazol-3-yl]-4,5-dimethyl-thiophen-2-yl}acetamide (VIa)

Schiff base **(IIa)** (0.01 mol) was added to mercaptoacetic acid (1.40 mL, 0.02 mol) anhydrous aluminium chloride (0.05 g). Acidic alumina was added to the above solution at room temperature. The reaction mixture was mixed, adsorbed, dried and kept inside the alumina bath and irradiated for 40–80 s. The reaction mixture was then cooled and triturated with an excess of 10% sodium bicarbonate solution. The product obtained was filtered, washed several times with water and crystallized with isopropanol. Other thiazolidin-4-ones for **Ia** and **1b** series were obtained in a similar manner.

Antimicrobial activity: All the compounds were screened for antibacterial activity against *S. aureus* and *E. coli* by paper disc technique[13]. Gentamycin was used as standard. The antifungal activity of all the compounds was evaluated against *C. albicans* using the same technique. Nystatin was used as standard. The concentration of the test compound used was 100 μg.

Antitubercular activity: The title compounds were tested *in vitro* for their antitubercular activity against *M. tuberculosis* $H_{37}Rv$. The antitubercular evaluation of compounds was carried out at "Tuberculosis Antimicrobial Acquisition and Coordinating Facility (TAACF)", USA. Primary screening of the compounds for antitubercular activity was conducted using the CABTEC 460 radiometric system. Compounds demonstrating at least > 90% inhibition in the primary screening were retested at lower concentration against *M. tuberculosis* $H_{37}Rv$ to determine the actual minimum inhibitory concentration (MIC) in CABTEC 460. The data were compared with the standard drug Rifampin at 0.03 μg/mL concentration, which showed 97% inhibition.

RESULTS AND DISCUSSION

Looking at SAR, marked inhibition in bacteria was observed in the compounds bearing Ar = 2-C_6H_4Cl, 2-C_6H_4OH, 3-$C_6H_4NO_2$ substituents whereas others showed moderate to least activity. Fungicidal screening data also revealed that compounds bearing Ar = 2-C_6H_4Cl, 2-C_6H_4OH, 3-$C_6H_4NO_2$ substituent imparted maximum activity. Compounds Ar = 2-C_6H_4Cl, 2-C_6H_4OH, 3-$C_6H_4NO_2$ were most active against *M. tuberculosis* $H_{37}Rv$ (> 90% inhibition) that will be retested at lower concentration to determine the actual minimum inhibitory concentration (MIC). Other compounds, *viz*, Ar = 4-$N(CH_3)_2C_6H_4$, 2-BrC_6H_4, 4-OHC_6H_4 were moderately active against *M. tuberculosis* $H_{37}Rv$ strain (> 50% inhibition). The physical data of title compounds given in Tables 1 and 2 indicates different substitutents present.

The title compounds of the above scheme were confirmed by the following H^1 NMR spectra.

(Ia) δ 2.0 (s, 2H, NH_2), δ 2.1 (s, 3H, CH_3), δ 2.2 (s, 3H, CH_3), δ 2.4 (s, 3H, CH_3), δ 3.0 (s, 1H, SH), δ 8.0 (s, 1H, NH).

(Ib) δ 2.0 (s, 2H, NH_2), δ 2.2 (s, 3H, CH_3), δ 2.4 (s, 3H, CH_3), δ 3.0 (s, 1H, SH), δ 7.4–7.9 (M, 5H, ArH), δ 8.0 (s, 1H, NH).

(IIa) δ 2.1 (s, 3H, CH_3), δ 2.2 (s, 3H, CH_3), δ 2.4 (s, 3H, CH_3), δ 3.0 (s, 1H, SH), δ 7.3–7.6 (M, 5H, ArH), δ 8.0 (s, 1H, NH), δ 8.1 (s, 1H, CH=N).

(IIIa) δ 2.2 (s, 3H, CH_3), δ 2.4 (s, 3H, CH_3), δ 3.0 (s, 1H, SH), δ 7.3–7.9 (M, 10H, ArH), δ 8.0 (s, 1H, NH), δ 8.1 (s, 1H, CH=N).

(IVa) δ 2.1 (s, 3H, CH_3), δ 2.2 (s, 3H, CH_3), δ 2.4 (s, 3H, CH_3), δ 3.0 (s, 1H, SH), δ 5.0 (s, 1H, CH-lactam ring), δ 5.4 (s, 1H, CH-lactam ring), δ 7.1–7.3 (m, 5H, ArH), δ 8.0 (s, 1H, NH).

(Va) δ 2.2 (s, 3H, CH_3), δ 2.4 (s, 3H, CH_3), δ 3.0 (s, 1H, SH), δ 5.0 (s, 1H, CH-lactam ring), δ 5.4 (s, 1H, CH-lactam ring), δ 7.1–7.9 (m, 10H, ArH), δ 8.0 (s, 1H, NH).

(VIa) δ 2.1 (s, 3H, CH_3), δ 2.2 (s, 3H, CH_3), δ 2.4 (s, 3H, CH_3), δ 3.0 (s, 1H, SH), δ 3.3 (s, 2H, CH_2-thiazolidine), δ 5.9 (s, 1H, CH-thiazolidine), δ 7.0–7.1 (m, 5H, ArH), δ 8.0 (s, 1H, NH).

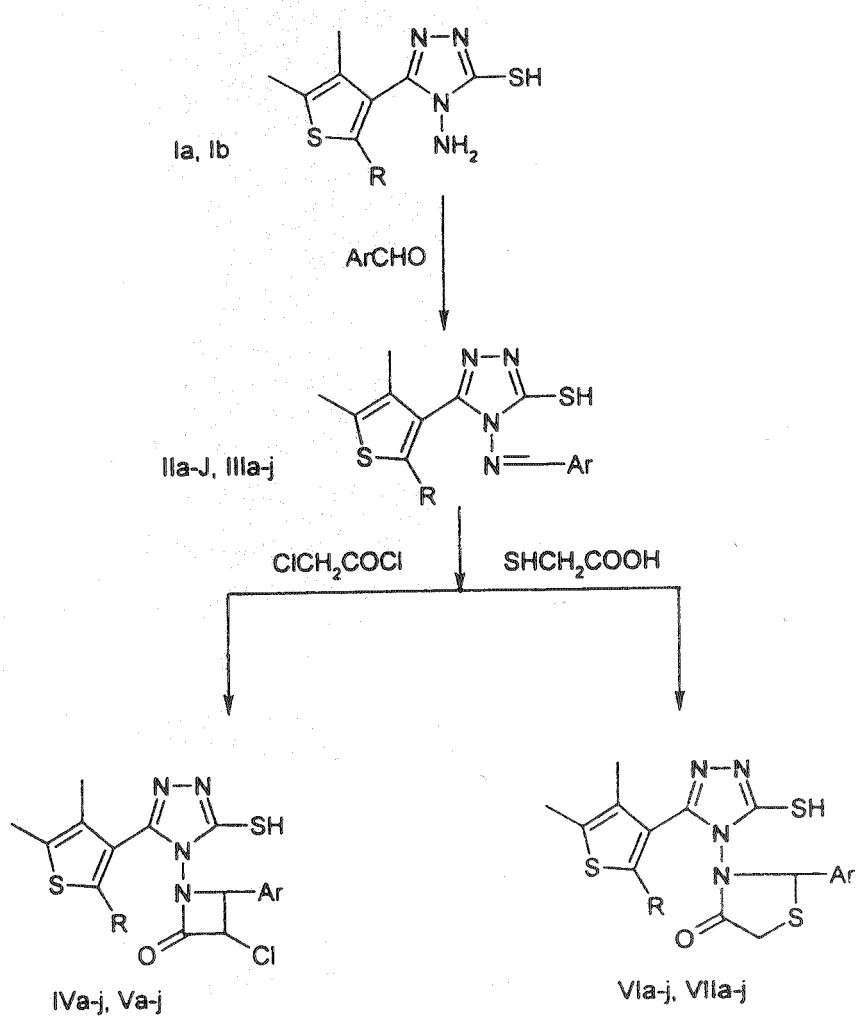
(VIIa) δ 2.2 (s, 3H, CH_3), δ 2.4 (s, 3H, CH_3), δ 3.0 (s, 1H, SH), δ 3.3 (s, 2H, CH_2-thiazolidine), δ 5.9 (s, 1H, CH-thiazolidine), δ 7.0–7.9 (m, 10H, ArH), δ 8.0 (s, 1H, NH).

TABLE-1
PHYSICAL DATA OF THE TITLE COMPOUNDS

S.No.	m.f.	m.p. (°C)	m.w.	Yield (%)	% Carbon		% Nitrogen	
					Calcd.	Found	Calcd.	Found
Ia	$C_{10}H_{13}N_5OS_2$	187	283	77	42.40	42.42	24.73	24.67
Ib	$C_{15}H_{15}N_5OS_2$	192	345	84	52.17	52.02	20.28	20.45
IIa	$C_{17}H_{17}N_5OS_2$	231	371	86	54.98	54.70	18.86	18.79
IIb	$C_{17}H_{16}N_5OS_2Cl$	241	405	84	50.37	50.45	17.28	17.46
IIc	$C_{17}H_{16}N_5OS_2Cl$	251	405	85	50.37	50.25	17.28	17.16
IId	$C_{17}H_{17}N_5O_2S_2$	231	387	82	52.71	52.53	18.08	18.23
IIe	$C_{19}H_{22}N_6OS_2$	262	414	89	55.07	55.17	20.28	20.42
IIf	$C_{17}H_{16}N_5OS_2Br$	247	449	87	45.43	45.36	15.59	15.48
IIIa	$C_{22}H_{19}N_5OS_2$	289	433	84	60.96	60.78	16.16	16.27
IIIb	$C_{22}H_{18}N_5OS_2Cl$	268	467	89	56.53	56.47	14.98	14.85
IIIc	$C_{22}H_{18}N_5OS_2Cl$	269	467	81	56.53	56.41	14.98	14.75
IIId	$C_{22}H_{19}N_5O_2S_2$	274	449	85	58.79	58.62	15.59	15.82
IIIe	$C_{24}H_{24}N_6OS_2$	272	476	84	60.50	60.43	17.64	17.74
IIIf	$C_{22}H_{18}N_5OS_2Br$	230	511	85	51.66	51.48	13.69	13.56
IVa	$C_{19}H_{18}N_5O_2S_2Cl$	285	447	86	51.00	51.16	15.65	15.42
IVb	$C_{19}H_{17}N_5O_2S_2Cl_2$	269	481	82	47.40	47.38	14.55	14.53
IVc	$C_{19}H_{17}N_5O_2S_2Cl_2$	247	481	87	47.40	47.65	14.55	14.74
IVd	$C_{19}H_{18}N_5O_3S_2Cl$	263	463	88	49.24	49.16	15.11	15.26
IVe	$C_{21}H_{23}N_6O_2S_2Cl$	246	490	80	51.42	51.24	17.14	17.32
IVf	$C_{19}H_{17}N_5O_2S_2ClBr$	276	525	79	43.42	43.21	13.33	13.41
Va	$C_{24}H_{20}N_5O_2S_2Cl$	241	509	78	56.58	56.31	13.75	13.58
Vb	$C_{24}H_{19}N_5O_2S_2Cl_2$	251	543	89	53.03	53.26	12.89	12.97
Vc	$C_{24}H_{19}N_5O_2S_2Cl_2$	287	543	85	53.03	53.14	12.89	12.69
Vd	$C_{24}H_{20}N_5O_3S_2Cl$	298	525	84	54.25	54.36	13.33	13.48
Ve	$C_{26}H_{25}N_6O_2S_2Cl$	283	552	86	56.52	56.42	15.21	15.47
Vf	$C_{24}H_{19}N_5O_2S_2ClBr$	276	587	85	49.06	49.13	11.92	11.75
VIa	$C_{19}H_{19}N_5O_2S_3$	243	445	82	51.23	51.37	15.73	15.56
VIb	$C_{19}H_{18}N_5O_2S_3Cl$	254	479	81	47.59	47.40	14.61	14.46
VIc	$C_{19}H_{18}N_5O_2S_3Cl$	268	479	83	47.59	47.62	14.61	14.49
VId	$C_{19}H_{19}N_5O_3S_3$	281	461	84	49.45	49.21	15.18	15.23
VIe	$C_{21}H_{24}N_6O_3S_3$	264	490	82	51.42	51.30	17.14	17.24
VIf	$C_{19}H_{18}N_5O_2S_3Br$	293	523	81	43.59	43.43	13.38	13.67
VIIa	$C_{24}H_{21}N_5O_2S_3$	246	507	84	56.80	56.67	13.80	13.59
VIIb	$C_{24}H_{20}N_5O_2S_3Cl$	254	541	82	53.23	53.47	12.93	12.78
VIIc	$C_{24}H_{20}N_5O_2S_3Cl$	234	541	85	53.23	53.14	12.93	12.72
VIId	$C_{24}H_{21}N_5O_3S_3$	265	523	84	55.06	55.21	13.38	13.65
VIIe	$C_{26}H_{26}N_6O_3S_3$	249	566	87	55.12	55.02	14.84	14.67
VIIf	$C_{25}H_{20}N_5O_2S_3Br$	284	597	87	50.25	50.46	11.72	11.54

TABLE-2

Compd.	R	Ar	Compd.	R	Ar
Ia	$NHCOCH_3$	—	IVj	$NHCOCH_3$	$2OCH_3C_6H_4$
Ib	$NHCOC_6H_5$	—	Va	$NHCOC_6H_5$	C_6H_5
IIa	$NHCOCH_3$	C_6H_5	Vb	$NHCOC_6H_5$	$4ClC_6H_4$
IIb	$NHCOCH_3$	$4ClC_6H_4$	Vc	$NHCOC_6H_5$	$2ClC_6H_4$
IIc	$NHCOCH_3$	$2ClC_6H_4$	Vd	$NHCOC_6H_5$	$2OHC_6H_4$
IId	$NHCOCH_3$	$2OHC_6H_4$	Ve	$NHCOC_6H_5$	$4N(CH_3)_2C_6H_4$
IIe	$NHCOCH_3$	$4N(CH_3)_2C_6H_4$	Vf	$NHCOC_6H_5$	$2BrC_6H_4$
IIf	$NHCOCH_3$	$2BrC_6H_4$	Vg	$NHCOC_6H_5$	$4BrC_6H_4$
IIg	$NHCOCH_3$	$4BrC_6H_4$	Vh	$NHCOC_6H_5$	$3NO_2C_6H_4$
IIh	$NHCOCH_3$	$3NO_2C_6H_4$	Vi	$NHCOC_6H_5$	$2,4,6(OCH_3)_3C_6H_2$
IIi	$NHCOCH_3$	$2,4,6(OCH_3)_3C_6H_2$	Vj	$NHCOC_6H_5$	$2OCH_3C_6H_4$
IIj	$NHCOCH_3$	$2OCH_3C_6H_2$	VIa	$NHCOCH_3$	C_6H_5
IIIa	$NHCOC_6H_5$	C_6H_5	VIb	$NHCOCH_3$	$4ClC_6H_4$
IIIb	$NHCOC_6H_5$	$4ClC_6H_4$	VIc	$NHCOCH_3$	$2ClC_6H_4$
IIIc	$NHCOC_6H_5$	$2ClC_6H_4$	VId	$NHCOCH_3$	$2OHC_6H_4$
IIId	$NHCOC_6H_5$	$2OHC_6H_4$	VIe	$NHCOCH_3$	$4N(CH_3)_2C_6H_4$
IIIe	$NHCOC_6H_5$	$4N(CH_3)_2C_6H_4$	VIf	$NHCOCH_3$	$2BrC_6H_4$
IIIf	$NHCOC_6H_5$	$2BrC_6H_4$	VIg	$NHCOCH_3$	$4BrC_6H_4$
IIIg	$NHCOC_6H_5$	$4BrC_6H_4$	VIh	$NHCOCH_3$	$3NO_2C_6H_4$
IIIh	$NHCOC_6H_5$	$3NO_2C_6H_4$	VIi	$NHCOCH_3$	$2,4,6(OCH_3)_3C_6H_2$
IIIi	$NHCOC_6H_5$	$2,4,6(OCH_3)_3C_6H_2$	VIj	$NHCOCH_3$	$2OCH_3C_6H_4$
IIIj	$NHCOC_6H_5$	$2OCH_3C_6H_4$	VIIa	$NHCOC_6H_5$	C_6H_5
IVa	$NHCOCH_3$	C_6H_5	VIIb	$NHCOC_6H_5$	$4ClC_6H_4$
IVb	$NHCOCH_3$	$4ClC_6H_4$	VIIc	$NHCOC_6H_5$	$2ClC_6H_4$
IVc	$NHCOCH_3$	$2ClC_6H_4$	VIId	$NHCOC_6H_5$	$2OHC_6H_4$
IVd	$NHCOCH_3$	$2OHC_6H_4$	VIIe	$NHCOC_6H_5$	$4N(CH_3)_2C_6H_4$
IVe	$NHCOCH_3$	$4N(CH_3)_2C_6H_4$	VIIf	$NHCOC_6H_5$	$2BrC_6H_4$
IVf	$NHCOCH_3$	$2BrC_6H_4$	VIIg	$NHCOC_6H_5$	$4BrC_6H_4$
IVg	$NHCOCH_3$	$4BrC_6H_4$	VIIh	$NHCOC_6H_5$	$3NO_2C_6H_4$
IVh	$NHCOCH_3$	$3NO_2C_6H_4$	VIIi	$NHCOC_6H_5$	$2,4,6(OCH_3)_3C_6H_2$
IVi	$NHCOCH_3$	$2,4,6(OCH_3)_3C_6H_2$	VIIj	$NHCOC_6H_5$	$2OCH_3C_6H_4$



Scheme-1

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