Int. J. Chem. Sci.: 6(2), 2008, 800-806

SYNTHESIS OF SOME THIAZOLE COMPOUNDS OF BIOLOGICAL INTEREST CONTAINING MERCAPTO GROUP

N. S. MAHAJAN*, S. R. PATTAN[a], R. L. JADHAV, N. V. PIMPODKAR and A. M. MANIKRAO[b]

Department of Pharmaceutical Chemistry, Satara College of Pharmacy,
SATARA (M. S.) INDIA
[a]Department of Medicinal Chemistry, K. L. E.'s College of Pharmacy,
BELGAUM (K. S.) INDIA
[b]Department of Pharmaceutical Chemistry, G. S. P. S. Institute of Pharmacy,
AKOLA. (M. S.) INDIA

ABSTRACT

A new series of β-(4-phenyl-2-thiazolyol) thio-alkyl/aryl substituted acetamides have been synthesized by reacting 4-phenyl-2-mercaptothiazole with appropriate N-substituted α-chloracetamides. The structures of these compounds were established on the basis of spectral data. All these compounds were screened for their antibacterial and antifungal activities. Some of these compounds have been shown promising activities.

Key words: 4-Phenyl-2-mercaptothiazoles, Chloroacetylation, Antibacterial activity, Antifungal activity

INTRODUCTION

Several physiological activities such as antibacterial, fungicidal, antispasmodic, analgesic and antitubercular of various thiazole derivatives have proved their efficacy in combating variety of diseases[1, 2]. Amongst the thiazole derivatives, 2-mercaptothiazole compounds have attracted maximum attention, as they possess known potential activity, well-built (S-C=N) toxophoric unit, relative stability, enhanced lipid solubility and hydrophilicity and non-carcinogenic nature[3]. Based on the above observations, it has been thought to synthesise various β-(4-phenyl–2-thiazolyl)-thio-N-alkyl/aryl substituted acetamides and evaluate them for antibacterial[4] and antifungal activities[5].

* Author for correspondence; E-mail: nsmahajan17@gmail.com

EXPERIMENTAL

Materials and methods

All the melting points and boiling points were determined by open capillary method in liquid paraffin bath and uncorrected. All the solvents were used after distillation. Chloroacetyl chloride was purchased from Lancaster (Germany). Aniline, morpholine, p-chloroanline, benzylamine, n-propylamine, pyrrolidine and acetophenone were purchased from S.D. Fine Chemicals, Mumbai. Liquid bromine was used after drying over conc. H_2SO_4. Silica gel G plates (3 x 8 cm) were used for TLC and spots located by iodine vapors in a chamber. Column chromatography was performed on a neutral alumina column (2.5 x 45 cm) using appropriate eluent.

The IR spectra (KBr/nujol) were recorded on PERKIN-ELMER FT-IR spectrometer and the values expressed in cm^{-1}. UV spectra were determined on Shimadzu UV – Visible recording spectrometer, UV-160 TCC 240A. ^1H NMR spectra ($CDCl_3$) were taken on Brucker AC 200 MHz FT using TMS as an internal reference compound.

Method of preparation

Prepration of △-4-thiazoline-2-thione (I)

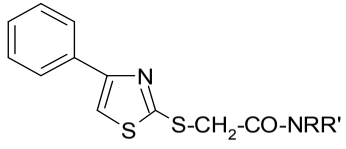
To a suspension of 24.8 g of ammonium dithiocarbamate in 50 mL of absolute ethanol, a mixture of 20.4 g of phenacyl bromide and 100 mL of absolute ethanol was added with shaking and cooling. After the initial reaction has subsided, the flask was stoppered and allowed to stand at room temperature for overnight.

Next day, the reaction mixture was refluxed for 1 hr to complete the reaction and solvent was removed under reduced pressure. The crude solid product was diluted with 200 mL of water, filtered and dried. This product was dehydrated by heating with 150 mL of benzene and collecting the water in a Dean and Stark trap. The residue, obtained by evaporating the benzene, was treated with 150 mL of 5% sodium hydroxide and filtered. The filtrate was cooled in an ice-bath and acidified with dilute hydrochloric acid. The resulting white precipitate was washed with water and dried. It was then recrystallized from aqueous ethanol.

General preparation of n- substituted –α-chloroacetamides II (a-f)

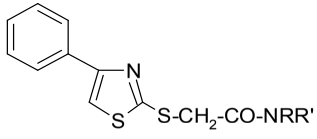
For primary amines: Appropriate amine (0.05 mol) was dissolved in a mixture of 25 mL of glacial acetic acid and 25 mL of saturated sodium acetate.

Table 1. Physicochemical data of III (a-f)



Comp.	R	R'	M. P. (°C)	Yield (%)	Nature	Mol. formula	Elemental analysis Calc (%) Found (%)		
							C	H	N
IIIa	H	Ph	136-138	69.10	Pale yellow needles	$C_{17}H_{14}N_2OS_2$	62.58 63.04	4.29 4.19	8.59 8.32
IIIb	H	p- C1Ph	132-135	68.28	Pale yellow shining needles	$C_{17}H_{13}N_2OS_2Cl$	56.59 55.88	3.61 3.90	7.77 7.55
IIIc	H	CH_2 Ph	121-123	70.08	Pale yellow shining needles	$C_{18}H_{16}N_2OS_2$	63.53 63.35	4.71 4.92	8.24 8.00
IIId	H	n-C_3H_7	78-80	58.80	Pale yellow flakes	$C_{14}H_{16}N_2OS_2$	57.53 58.11	5.48 5.56	9.59 10.08
IIIe	RR' = Pyrolidine-1-yl		142-145	55.15	Light yellow granules	$C_{15}H_{16}N_2OS_2$	59.21 60.00	5.26 5.58	9.21 9.58
IIIf	RR' = Morpholine-1-yl		165-168	54.32	Pale yellow granules	$C_{15}H_{16}N_2O_2S_2$	56.25 56.56	5.00 5.42	8.75 9.00

Table 2. Spectral data of III (a-f)



Comp.	R	R'	IR cm^{-1} KBr				^{1}H NMR (ppm) CDC1$_3$
			vNH	vCO	vC = N	ArH	
IIIa	H	Ph	3263	1659	1552	689 & 748	10.20 (s, 1H,NH) ; 7.90 (d, 1H, 5-H) ; 7.50-7.19 (m, 10H, 2XC6H5) ; 4.00 (s, 2H,S-CH2)
IIIb	H	p- ClPh	3268	1660	1550	720 & 830	10.20 (br s, 1H,NH) ; 7.90 (d, 1H, 5-H) ; 7.50-7.10 (m, 9H,Ar-H) ; 4.00 (s, 2H,S-CH2) .
IIIc	H	CH_2Ph	3310	1646	1532	705 & 725	7.85 (br s, 1H,NH) ; 7.70 (d, 1H, 5-H) ; 7.43-7.20 (m, 10H, 2xC6-H5) ; 4.50 (d, 2CH2,of Benzyl) ; 4.00 (s, 2H,S-CH2) .
IIId	H	n-C_3H_7	3442 & 3296	1639	1556	690 & 728	7.90 (d, 1H, 5-H) ; 7.51-7.32 (m, 6H,C6-H5+ NH) ; 3.92 (s, 2H,S-CH2) ; 3.25 (q, 2H,NH-CH2) ; 1.45 (sext, 2H, -CH2-of n-propyl) ; 0.81 (t, 3H, -CH3 of n-propyl)
IIIe	RR' = Pyrolidine-1-yl		-	1635	1555	689 & 728	-
IIIf	RR' = Morpholine-1-yl		-	1639	1557	685 & 730	-

Biological screening

Table 3. Antibacterial activity of compounds II (a-f).

Comp.	R	R^1	Zone of inhibition (mm)					
			P. aeuroginose		*S. aureus*		*E. coli*	
			100 (µg/mL)	**150 (µg/mL)**	**100 (µg/mL)**	**150 (µg/mL)**	**100 (µg/mL)**	**150 (µg/mL)**
IIIa	H	C_6H_5	9	9	15	17	5	6
IIIb	H	p-Cl-C_6H_5	9	12	15	16	5	8
IIIc	H	CH_2-C_6H_5	8	9	12	15	2	2
IIId	H	n-C_3H_7	5	8	13	15	5	7
IIIe	RR' = Pyrolidine-1-yl		10	14	25	27	6	8
IIIf	RR' = Morpholine-1-yl		11	15	26	29	9	10
Standard	Norfloxacin		16	22	35	45	10	15

Table 4. Antifungal activity of compounds II (a-f)

Comp.	R	R'	Zone of inhibition (mm)			
			C. albicans		*A. niger*	
			100 (µg/mL)	**150 (g/mL)**	**100 (µg/mL)**	**150 (g/mL)**
IIIa	H	C_6H_5	8	8	7	8
IIIb	H	p-Cl-C_6H_5	9	9	7	8
IIIc	H	CH_2-C_6H_5	7	8	5	5
IIId	H	n-C_3H_7	7	10	5	8
IIIe	RR'= Pyrolidine - 1-yl		22	29	25	25
IIIf	RR'= Morpholine - 1-yl		25	31	27	28
Standard	Griseofulvin		34	38	32	36

It was then cooled to 5ºC and to this cold solution, chloroacetyl chloride (0.06 mol)

was added dropwise, with stirring at 0-5ºC. Then, it was allowed to remain at room temperature. The crude product that separated was filtered, washed with 50% acetic and water. It was then recrystallised from 50% alcohol.

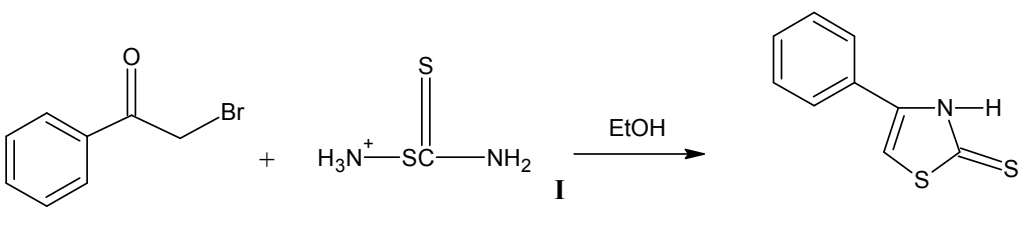
For secondary amines: Appropriate amine (0.1 mol) in 20 mL of ether was added at 0-5ºC to chloroacetyl chloride (0.12 mol), in ether, dropwise with stirring and it was left at room temperature for 1 hr. Then ether was removed under reduced pressure and crude viscous liquid was washed with petroleum ether. It was used directly in the next reaction.

General preparation of n-substituted-α-(4-phenyl-2-thiozolyl-thio) acetamides III (a-f)

To a cooled solution of metallic sodium (0.025 mole) in a absolute ethanol (50 mL), △-4-thiazoline–2-thione (0.025 mole) was added with stirring, at room temperature. Then the excess of solvent was removed and cold water was added to getaclear solution. The solution was filtered to remove suspended particles. Then 0.025 mole of N-substituted -α- chloroacetamide was added in small portions at 15-20ºC with stirring. Stirring was continued for 8 hours and the mixture was kept at room temperature overnight.

Next day, the precipitate was filtered. The residue was washed with water and dried. This dried product was purified by recrystalization from alcohol.

The physicochemical characteristics and spectral data of various compounds **III (a-f)** are reported in Table 1 and 2.

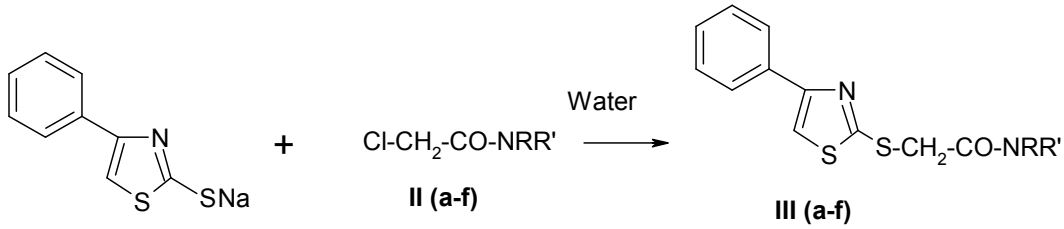


Where,

(a) R = H; R' = C_6H_5 (b) R = H; R' = p-ClC_6H_4

(c) R = H; R' = $CH_2C_6H_5$ (d) R = H; R' = n-C_3H_7

(e) RR' = Pyrolidine-1-yl (f) RR' = Morpholine –1-yl.



RESULTS AND DISCUSSION

The synthesized compounds were evaluated for both antibacterial and antifungal activities.

Compounds such as **IIIe** and **IIIf** showed reasonably promising antibacterial and antifungal activities at 100 μg/ mL and 150 μg/ mL concentrations as compared with norfloxacin and griseofulvin, respectively.

ACKNOWLEDGEMENT

The authors are grateful to Shivaji University, Kolhapur for granting fund for research. They are also thankful to Prof. M.S. Jagtap, Chairman Gourishankar Education Society, Satara, and Shri. R. J. Dias for providing all the facilities to carry out present work.

REFERENCES

1. The Chemistry of Heterocyclic Compounds, Thiazole and its Derivatives, Vol. 34, (part II), J. V. Metzer. (Ed.) John Wiley and Sons Inc, New York, (1979) pp. 436-452.
2. E. E. Block, Reactions of Organo Sulphur Compounds, New York, Academic Press, (1978) p. 13.
3. N. Lozach, Forty Years of Heterocyclic Sulphur Chemistry in Sulphur Reports, Vol. 10, 7 (1990).
4. E. Joan, Clinical Bacteriology, **4,** 226 (1975).
5. H. W. Seeley and P. J. Van Demark, Microbes in Action, A Laboratory Manual of Microbiology, Edn. II, (1975) p. 55.

Accepted : 17.03.2008