RJC
http://www.rasayanjournal.com

RASĀYAN *J. Chem.*
Vol.3, No.4 (2010), 721-725
ISSN: 0974-1496
CODEN: RJCABP

CONVENIENT SYNTHESIS OF 3-CHLORO-1-(4,6-DIMETHYL-BENZOTHIAZOL-2-YLAMINO)-4-ARYL-AZETIDIN-2-ONES AND THEIR ANTIBACTERIAL SCREENING

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ABSTRACT

Substituted 4,6-dimethyl-benzothiazolyl hydrazone was taken along with triethyl amine in dioxane solvent. Chloroacetyl chloride was added to this mixture and stirred. Product substituted azetidin-2-ones obtained were isolated. Five such new compounds were evaluated for their antibacterial activity.

Key words: Aryl-azetidin-2-ones, antibacterial, chloroacetyl chloride.

INTRODUCTION

Azetidin-2-ones have been assessed as antiparkinson, anti-inflammatory[1], antibacterial[2-4], antifungal[5,6], cardiovascular drugs. Most prominently prescribed antibiotics used in medicine also certain azetidin-one benzothiazole is also challenging field in heterocyclic chemistry. Hence it was thought worthwhile to undertake the studies focusing biological activities of condensed benzothiazole and azetidin-one systems, despite of its versatility of azetidin-2-one ring. This is little information available of 2-heteryl-azetidin-one. Starting from 2-hydrazino-4,6-dimethylbenzothiazole and condensing it with aldehyde respective hydrazones were obtained (Scheme-1).

These hydrazones were treated with chloroacetyl chloride (Scheme-2). Structure of the product was authenticated by elemental analysis and spectral data.

EXPERIMENTAL

Materials

All reagents and solvents for synthesis were commercially available and used without further purification. Other chemicals employed were of analytical grade.

Preparation of 3-chloro-1-(4,6-dimethyl-benzothiazol-2-ylamino)-4-aryl-azetidin-2-ones (4_{f-j})

2-Hydrazino-4,6-dimethyl-benzothiazole (**2**) was taken as starting material in ethanol and refluxed with benzaldehyde, cinnamaldehyde, 2-hydroxy-3-methoxy benzaldehyde, 4-hydroxy-3-methoxy benzaldehyde and 4-N,N-dimethyl amino benzaldehyde independently for half to one and half hour to obtain corresponding hydrazones (3_{a-e}). A mixture of hydrazone (0.001 mole), dioxane (5ml) and triethylamine (1ml) was taken into a 100 ml round bottom flask and then chloroacetyl chloride (6 ml) was added drop by drop maintaining the temperature 0-5°C. The reaction mixture was stirred at room temperature for 13 hours, it was kept overnight. Separated solid product was filtered, washed with water, dried and recrystallized from methanol.

3-Chloro-1-(4,6-dimethyl-benzothiazol-2-ylamino)-4-phenyl-azetidin-2-one (4_f): Yield 0.488 g, 68 %, mp 120°C; ir (KBr): C=N 1500, C-N 1260, broad -NH, -OH 3250, >C=O 1653 cm^{-1}. ^1H nmr ($CDCl_3$): δ

2.4 (s, 6H, Ar-CH_3), 4.1 (s, 1H, NH), 5.3 (s, 1H, -CHAr), 5.9 (s, H, CHCl), 7.2-7.9 (m, 7H, Ar-H); ms: m/z 357 (M^+). *Anal*. Calcd. for $C_{18}H_{16}N_3O_3SCl$: C, 60.50; H, 4.47; N, 11.76. Found: C, 60.11; H, 4.17; N, 11.34.

3-Chloro-1-(4,6-dimethyl-benzothiazol-2-ylamino)-4-(2-hydroxy-3-methoxy-phenyl)-azetidin-2-one (4_g): Yield 0.263 g, 65 %, mp 225°C; ir (KBr): C=N 1543, C-N 1290, broad -NH, -OH 3246, >C=O 1671 cm^{-1}. ^1H nmr ($CDCl_3$): δ 2.1 (s, 6H, Ar-CH_3), 3.5 (s, 3H, -OCH_3), 4.0 (s, 1H, NH), 4.5 (s, 1H, OH), 5.4 (s, H, CH), 6.0 (s, 1H, CHCl), 7.3-8.0 (m, 5H, Ar-H); ms: m/z 403 (M^+). *Anal*. Calcd. for $C_{19}H_{18}N_3O_3SCl$: C, 56.50; H, 4.46; N, 10.40. Found: C, 56.31; H, 4.16; N, 10.21.

3-Chloro-1-(4,6-dimethyl-benzothiazol-2-ylamino)-4-(4-hydroxy-3-methoxy-phenyl)-azetidin-2-one (4_h): Yield 0.255 g, 63 %, mp 220°C; ir (KBr): C=N 1512, C-N 1276, broad -NH, -OH 3286, >C=O 1640 cm^{-1}. ^1H nmr ($CDCl_3$): δ 2.2 (s, 6H, Ar-CH_3), 3.3 (s, 3H, -OCH_3), 3.9 (s, 1H, NH), 4.3 (s, 1H, OH), 5.2 (s, H, CH-Ar), 6.1 (s, H, CHCl), 7.2-7.8 (m, 5H, Ar-H); ms: m/z 403 (M^+). *Anal*. Calcd. for $C_{19}H_{18}N_3O_3SCl$: C, 56.50; H, 4.46; N, 10.40. Found: C, 56.23; H, 4.41; N, 10.28.

3-Chloro-1-(4,6-dimethyl-benzothiazol-2-ylamino)-4-styryl-azetidin-2-one (4_i): Yield 0.493 g, 65%, mp 147°C; ir (KBr): C=N 1500, C-N 1246, >C=O 1650 cm^{-1}. ^1H nmr ($CDCl_3$): δ 2-2.4 (s, 6H, Ar-CH_3), 3.7 (s, 1H, NH), 4-4.3 (d, 2H, CH=CH), 5.4 (s, 1H, CH-Ar), 6.0 (s, 1H, CHCl), 7.1-7.8 (m, 7H, Ar-H); ms: m/z 383 (M^+). *Anal*. Calcd. for $C_{20}H_{18}N_3OSCl$: C, 62.58; H, 4.69; N, 10.95. Found: C, 62.21; H, 4.32; N, 10.74.

3-Chloro-1-(4,6-dimethyl-benzothiazol-2-ylamino)-4-(4-dimethylamino-phenyl)-azetidin-2-one (4_j): Yield 0.530 g, 67 %, mp 157°C; ir (KBr): C=N 1527, C-N 1230, Aromatic stretch 1527, 1363, >C=O 1610 cm^{-1}. ^1H nmr ($CDCl_3$): δ 2.39 (s, 3H, Ar-CH_3), 2.52 (s, 6H, N-CH_3), 5.45 (s, 1H, Ar-CH), 6.0 (s, 1H, CHCl), 7-7.5 (Ar-H); ms: m/z 400 (M^+). *Anal*. Calcd. for $C_{20}H_{21}N_4OSCl$: C, 59.92; H, 5.24; N, 13.98. Found: C, 59.80; H, 5.08; N, 13.31.

RESULTS AND DISCUSSION

Starting material for the synthesis is 2-hydrazino-4,6-dimethyl-benzothiazole (2) which was prepared by following the method suggested by MVD[7]. This was condensed with different aldehydes, were allowed to react with chloroacetyl chloride. The products obtaind (4_{f-j}) are 3-chloro-1-(4,6-dimethylbenzothiazol-2-ylamino)-4-aryl-azetidin-2-ones (scheme 2). The IR spectra show absorption bands at 3250-3350 cm^{-1} due to cyclic >C=O stretching. The absorption band due to four membered cyclic >C=O stretching appears at lower frequency due to cyclic >C=O stretching appears at lower frequency because of the presence of intramolecular hydrogen bonding (Fig. 1).

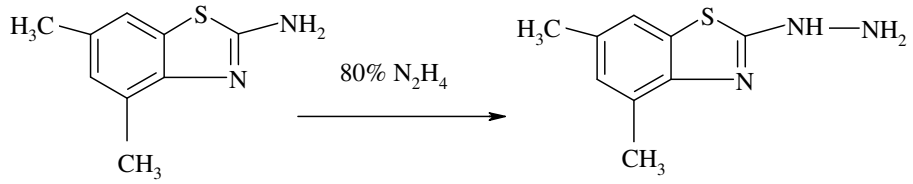
Evaluation of antimicrobial screening:

Nutrient medium was sterilized in autoclave at 121°C. A suitable dilution growth culture of the test bacteria was spread over media and was allowed to cool at room temperature for 0.5 hrs. A filter paper disc 6 mm diameter, commercially used loaded with the compound of appropriate dilution in DMF was applied with sterile forceps. After 24 hours of incubation, the degree of sensitivity was determined by measuring growth inhibition zones around the disc. The antimicrobial activity of these compounds was examined by the study of growth inhibition pattern of the microbes on media containing these compounds 1 to 6 by paper disc method. The microbes selected were Xanthomonas, Erwinia and E-coli using amphicilin as standard. The antimicrobial screening data of the compounds have been incorporated in the Table-1.

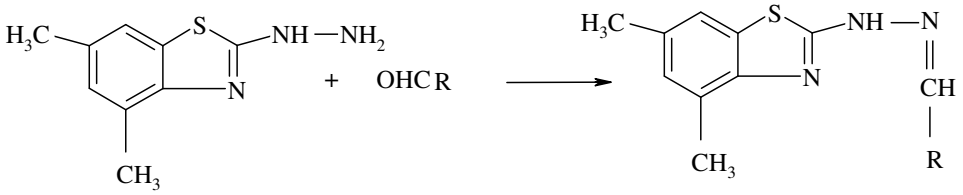
CONCLUSION

The maximum activity was shown by 3-chloro-1-(4,6-dimethyl-benzothiazol-2-ylamino)-4-(4-hydroxy-3-methoxyphenyl)-azetidin-2-one. Whereas minimum activity was shown by 3-chloro-1-(4,6-dimethyl-benzothiazol-2-ylamino)-4-(4-dimethylaminophenyl)-azetidin-2-one against Xanthomonas.

As far as activity against Erwinia, maximum activity was shown by 3-chloro-1-(4,6-dimethyl-benzothiazol-2-ylamino)-4-(4-hydroxy-3-methoxyphenyl)-azetidin-2-one, and minimum activity by 2-hydroxy-3-methoxy substituted compound and 4-styryl. Surprisingly styryl compound which showed minimum activity with Erwinia, showed maximum activity with E-coli.



(1) (2)

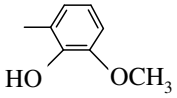


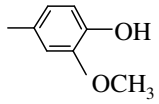
(3a-e)

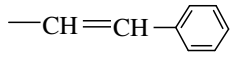
Benzothiazolyl hydrazone

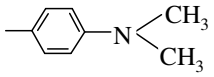
Where R=

a) 

b) 

c) 

d) 

e) 

Scheme-1

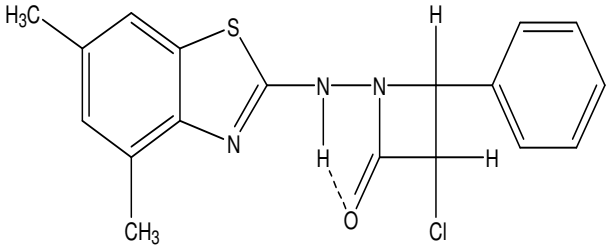
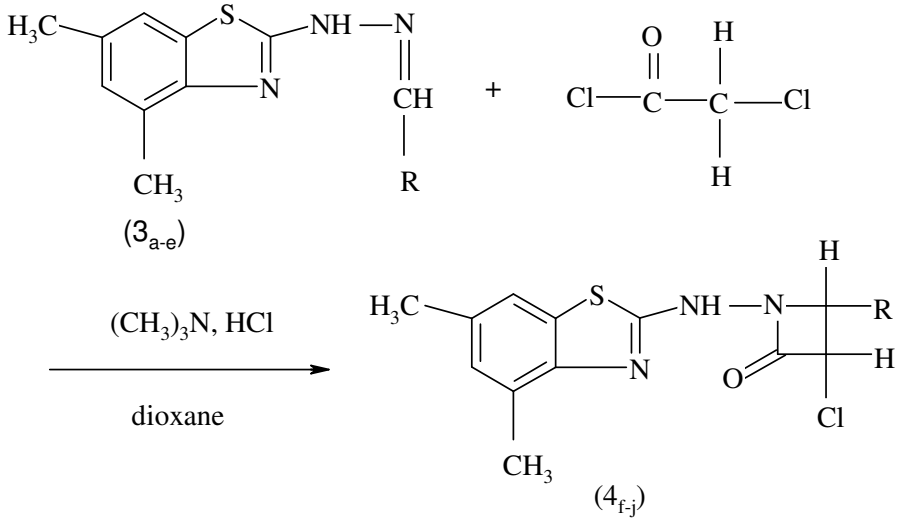
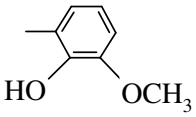


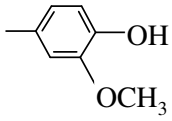
Fig.-1

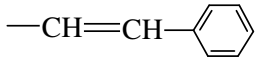


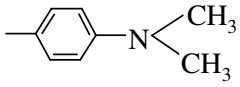
Where R=

f) 

g) 

h) 

i) 

j) 

Scheme-2

Table-1: Evaluation of antibacterial activity of (4_{f-j})

Sr. No.	Compound	Antimicrobial Activity (Zone of inhibition in mm)		
		Xanthomonas	Erwinia	E-Coli
1	3-chloro-1-(4,6-dimethyl-benzothiazol-2-ylamino)- 4-phenyl-azetidin-2-one	11	13	09
2	3-chloro-1-(4,6-dimethyl-benzothiazol-2-ylamino)-4-(2-hydroxy-3-methoxy-phenyl)-azetidin-2-one	14	08	--
3	3-chloro-1-(4,6-dimethyl-benzothiazol-2-ylamino)-4-(4-hydroxy-3-methoxy-phenyl)-azetidin-2-one	20	16	07

4	3-chloro-1-(4,6-dimethyl-benzothiazol-2-ylamino)- 4-styryl-azetidin-2-one	12	08	20
5	3-chloro-1-(4,6-dimethyl-benzothiazol-2-ylamino)-4-(4-dimethyl amino phenyl)-azetidin-2-one	10	09	10
6	Ampicillin (1mg/ml)	18	16	08

-- No activity

ACKNOWLEDGEMENTS

We express our gratitude to Principal Dr.G.M.Kalamse, Science College, Nanded and Principal, Pratibha Niketan College, Nanded for encouragement.

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[RJC-669/2010]