Microwave Assisted Heterocyclization: A Rapid and Efficient Synthesis and Antibacterial Activity of Novel Thiazolidinones

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Abstract As a target to synthesize various Thiazolidinone derivatives, 2-Amino-4-(coumarin-3-yl)-thiazole has been prepared by the reactions of 3-Bromo acetyl coumarin with thiourea. 3-Bromo acetyl coumarin was prepared from 3-Acetyl coumarin. The resulting compound 2-amino-4-(coumarin-3-yl)- thiazole was treated with different Aldehydes to give the intermediate Schiff base, which on further reaction with Thioglycolic acid and Thiolactic acid to give titled compound Thiazolidinone. The structures of the compounds have been confirmed by elemental analysis and spectral analysis. The antibacterial activity of the compounds has also been screened against *Staphylococcus aureus* and *Escherichia coli*.

Key words Schiff Base, Thiazolidinone, Antibacterial activity.

Introduction

A survey of literature reveals that Thiazolo Coumarins possess a broad spectrum of biological importance. Thiazolo Coumarin derivatives are well known biologically active compounds. Schiff bases from 2-Amino-4-(coumarin-3-yl)-thiazole and various Aldehydes are reported to have significant antibacterial activity. These derivatives have been reported as bacteriostatic¹ and fungisidic². Schiff Base gives good antimicrobial activity and pharmacological applications³ and it can be prepared by the acid catalyzed reaction of amines & Ketones or Aldehydes. It gives a good fungicidal activity⁴. 4-Thiazolidinones give good pharmacological properties⁵. 4-Thiazolidinones are known to exhibit antitubercular⁶, antibacterial⁷, anticonvulsant⁸, antifungal⁹, and antithyroid activities.

The application of microwave irradiation (MWI) to organic synthesis has been the focus of considerable attention in recent years and is becoming an increasingly popular technology¹⁰. The salient features of the microwave approach are rapid reaction rates, cleaner reaction conditions and enhancements in chemical yields¹¹⁻¹².

Under the framework of "Green Chemistry" we have developed an environmentally benign synthesis of Thiazolidinones. Further attractions of this method are that it allows reactions in open vessels (thus avoiding the risk of high pressure development) and synthesis on preparative scale¹³. Herein we wish to report a facile microwave synthesis of Thiazolidinone from 2-Amino-4-(coumarin-3-yl)-thiazole and various aldehydes using DMF as a reaction mediator.

Different Aldehydes were condensed with 2-Amino-4-(coumarin-3-yl)-thiazole to yield Schiff base. The Schiff bases were further reacted with Thioglycolic acid and Thiolactic acid to yield Thiazolidinone derivatives [A] & [B].

Experimental

All the melting points were determined on a PMP-DM scientific melting point apparatus and are uncorrected. IR spectra were recorded with KBr on Shimadzu FT-IR 8300 spectrophotometer. Reactions were carried out in a "QPro-M Modified Microwave System" made in CANADA.

Preparation of 2-(3-hydroxy-4-methoxy phenyl)-3-[4-(coumarin-3-yl)-thiazole-2-yl]-4-thiazolidinone [A]:

The (Schiff base), 2-N-(3-methoxy-4-hydroxy benzylidene) imino-4-(coumarin-3-yl)-thiazole (0.01 mole, 3.78 g) in DMF was taken in R.B.F. To it thioglycolic acid (0.01 mole, 0.92 g) was added slowly. Then it was placed inside a microwave oven for about 3.0 minutes. It was then diluted with ice-cold water. The solid product formed was filtered, dried and recrystallised from Ethanol. Other substituted Thiazolidinones were prepared in a similar manner. Data for various substituted Thiazolidinones are given in Table-1.

Preparation of 2-(3-hydroxy-4-methoxy phenyl)-5-methyl-3-[4-(coumarin-3-yl)-thiazole-2-yl]-4-thiazolidinone [B]:

The (Schiff base), 2-N-(3-methoxy-4-hydroxy benzylidene) imino-4-(coumarin-3-yl)-thiazole (0.01 mole, 3.78 g) in DMF was taken in R.B.F. To it thiolactic acid (0.01 mole, 1.06 g) was added slowly. Then it was placed inside a microwave oven for about 3.0 minutes. It was then diluted with ice cold water. The solid product formed was filtered, dried and recrystallised from Ethanol. Other substituted Thiazolidinones were prepared in a similar manner. Data for different substituted Thiazolidinones are given in Table-2.

Table 1 PHYSICAL & ANALYTICAL DATA OF THE COMPOUNDS [A]

No.	R	M.F. (M.W.)	YIELD (%)	M.P. (°C)	% ANALYSIS CALC.(FOUND)		
					C	H	N
BN-1	3 -OCH ₃ , 4 -OH	C ₂₂ H ₁₆ N ₂ O ₃ S ₂ (452.0)	90	118	58.40 (58.42)	3.53 (3.51)	6.19 (6.23)
BN-2	2 -NO ₂	C ₂₁ H ₁₃ N ₃ O ₅ S ₂ (451.0)	84	168	55.87 (55.90)	2.88 (2.86)	9.31 (9.34)
BN-3	2 -Cl	C ₂₁ H ₁₃ N ₂ O ₃ S ₂ Cl (440.5)	82	126	57.20 (57.18)	2.95 (2.93)	6.35 (6.33)
BN-4	4 -Cl	C ₂₁ H ₁₃ N ₂ O ₃ S ₂ Cl (440.5)	80	133	57.20 (57.24)	2.95 (2.97)	6.35 (6.39)
BN-5	2, 4 -(Cl) ₂	C ₂₁ H ₁₂ N ₂ O ₃ S ₂ Cl ₂ (475.0)	81	135	53.05 (53.03)	2.52 (2.54)	5.89 (5.94)
BN-6	2 -OCH ₃	C ₂₂ H ₁₆ N ₂ O ₄ S ₂ (436.0)	86	165	60.55 (60.57)	3.66 (3.68)	6.42 (6.45)
BN-7	4 -OCH ₃	C ₂₂ H ₁₆ N ₂ O ₄ S ₂ (436.0)	85	156	60.55 (60.58)	3.66 (3.63)	6.42 (6.40)
BN-8	3, 4, 5 -(OCH ₃) ₃	C ₂₄ H ₂₀ N ₂ O ₆ S ₂ (496.0)	90	97	58.06 (58.10)	4.03 (4.06)	5.64 (5.62)
BN-9	4 -N(CH ₃) ₂	C ₂₃ H ₁₉ N ₃ O ₃ S ₂ (449.0)	84	151	61.46 (61.49)	4.23 (4.26)	9.35 (9.39)
BN-10	2 -OH	C ₂₁ H ₁₄ N ₂ O ₄ S ₂ (422.0)	87	144	59.71 (59.68)	3.31 (3.35)	6.63 (6.60)

Table 2 PHYSICAL & ANALYTICAL DATA OF THE COMPOUNDS [B]

NO.	R	M.F. (M.W.)	YIELD (%)	M.P. (°C)	% ANALYSIS CALC.(FOUND)		
					C	H	N
BN-11	3 -OCH ₃ , 4 -OH	C ₂₃ H ₁₈ N ₂ O ₅ S ₂ (466.0)	85	161	59.22 (59.26)	3.86 (3.88)	6.00 (6.04)
BN-12	2 -NO ₂	C ₂₂ H ₁₅ N ₃ O ₅ S ₂ (465.0)	80	186	56.77 (56.80)	3.22 (3.24)	9.03 (9.00)
BN-13	2 -Cl	C ₂₂ H ₁₅ N ₂ O ₅ S ₂ Cl (454.5)	75	158	58.08 (58.06)	3.30 (3.31)	6.16 (6.20)
BN-14	4 -Cl	C ₂₂ H ₁₅ N ₂ O ₅ S ₂ Cl (454.5)	74	164	58.08 (58.11)	3.30 (3.28)	6.16 (6.18)
BN-15	2 , 4 -(Cl) ₂	C ₂₂ H ₁₄ N ₂ O ₅ S ₂ Cl ₂ (489.0)	78	167	53.98 (53.94)	2.86 (2.89)	5.72 (5.74)
BN-16	2 -OCH ₃	C ₂₃ H ₁₈ N ₂ O ₄ S ₂ (450.0)	73	127	61.33 (61.29)	4.00 (3.98)	6.22 (6.24)
BN-17	4 -OCH ₃	C ₂₃ H ₁₈ N ₂ O ₄ S ₂ (450.0)	77	117	61.33 (61.36)	4.00 (4.04)	6.22 (6.20)
BN-18	3 , 4 , 5 -(OCH ₃) ₃	C ₂₅ H ₂₂ N ₂ O ₆ S ₂ (510.0)	85	153	58.82 (58.84)	4.31 (4.29)	5.49 (5.53)
BN-19	4 -N(CH ₃) ₂	C ₂₄ H ₂₁ N ₃ O ₅ S ₂ (463.0)	86	170	62.20 (62.22)	4.53 (4.56)	9.07 (9.09)
BN-20	2 -OH	C ₂₂ H ₁₆ N ₂ O ₄ S ₂ (436.0)	88	148	60.55 (60.57)	3.66 (3.69)	6.42 (6.43)

Results and Discussion

Structures of compounds synthesized have been elucidated by elemental analysis & IR measurements. 4-Thiazolidinone compound shows IR absorption bands at 1330 - 1310 cm⁻¹ (Ar-CH₃), 800 - 600 cm⁻¹ (C-S stretching), 1720 - 1700 cm⁻¹ (C=O stretching) and 1360 - 1310 cm⁻¹ (C-N stretching), 1690 - 1640 cm⁻¹ (C=N).

ANTIBACTERIAL ACTIVITY:

This part deals with the *in-vitro* screening of newly synthesized compounds for their antimicrobial activity for filter paper disc method at a concentration of 50 µg; the species, *Staphylococcus aureus* and *Escherichia coli* have been taken for the antibacterial activity. The compounds possess moderate to good activity against all stains in comparison with ampicillin, penicillin and tetracycline against *Escherichia coli* and *Staphylococcus aureus*. (Table-3)

TABLE – 3 ANTIBACTERIAL ACTIVITY OF NEWLY SYNTHESISED COMPOUNDS

No.	ZONE OF INHIBITION (mm)		No.	ZONE OF INHIBITION (mm)	
	S.aureus.	E.coli.		S.aureus.	E.coli.
BN-1	11.0	9.0	BN-11	13.0	11.0
BN-2	9.0	8.0	BN-12	9.0	8.0
BN-3	9.0	7.0	BN-13	6.0	8.0

Contd..

No.	ZONE OF INHIBITION (mm)		No.	ZONE OF INHIBITION (mm)	
	S.aureus.	E.coli.		S.aureus.	E.coli.
BN-4	7.0	8.0	BN-14	8.0	9.0
BN-5	10.0	11.0	BN-15	12.0	9.0
BN-6	9.0	10.0	BN-16	7.0	6.0
BN-7	11.0	10.0	BN-17	9.0	11.0
BN-8	13.0	11.0	BN-18	8.0	10.0
BN-9	12.0	10.0	BN-19	9.0	7.0
BN-10	8.0	6.0	BN-20	10.0	9.0

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