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Synthesis and antimicrobial activity of some new 2-[2", 3"-dinitrophenyl]-3-(substituted aryl)-3,3a-dihydrobenzimidazo [2, 1-a] pyrazolo [3,4-d] thiazoles derivatives

J.P. Sen and S.D. Srivastava
Synthetic Organic Chemistry Laboratory, Department of Chemistry,
Dr. H.S. Gour Central University, Sagar (M.P)

ABSTRACT

A series of several new 2-substituted phenyl-3-substituted aryl 3,3a-dihydrobenzimidazo [2,1-a] pyrazolo [3,4-d] thiazoles (2) have been synthesized from 2-arylidene benzimidazo [2,1-b] thiazolidine-3-ones (1) using 2-mercapto-benzimidazole as the starting material. All the synthesized products were evaluated for their antibacterial activity against *Escherichia coli, Klebsiella pneumoniae* and *Staphylococcus aureus* and antifungal activity against *Aspergillus niger, Aspergillus flavus, Fusarium oxisporum* and *Trichoderma viride*. The structures of all the synthesized compounds have been established on the basis of their spectral and chemical methods.

Keywords: 2-mercaptobenzimidazole, dihydropyrazolo, thiazole, antimicrobial activity

INTRODUCTION

In the past years, the literature is enriched with progressive findings about the synthesis and pharmacological action of fused heterocycles. Benzimidazoles constitute an important class of heterocyclic compounds possessing a wide spectrum of biological activities. The benzimidazole nucleus is associated with diverse type of pharmacological activities [1] such as antibacterial, insecticidal, and fungicidal. In the recent years N and S-substituted derivatives in the heterocycle ring have received much attention because of many chemotherapeutic properties. Therefore, efforts are being made by several research workers to synthesize various substituted azoles with bridgehead nitrogen and to exploit their potentially useful biological properties [2,3]. Imidazole and pyrazole condensed heterocycles [4,5] are of their great therapeutic index [6,7,8]. Benzimidazole and their derivatives have been demonstrated to inhibit antiviral [9] activity. In continuation of our earlier work on the synthesis of condensed heterocyclic systems and in view of the broad spectrum antimicrobial [10, 11] activity of benzimidazole it was thought to synthesize various bridgehead nitrogen atom with substitution at 1 and 2 positions in benzimidazole and to evaluate their antibacterial and antifungal activities.

MATERIALS AND METHODS

Melting points were taken in an open capillary tube. IR spectra (KBr) were recorded on Shimadzu 8201 PC spectrophotometer (ν_{max} in cm^{-1}) and ^{1}HNMR spectra in $CDCl_3$ at 300 MHz on Bruker DRX 300 spectrometer using TMS as an internal standard (Chemical shifts in δ, ppm). *2-Arylidene benzimidazo [2,1-b] thiazolidin-3-ones* 1a.

A mixture of 2-mercaptobenzimidazole (2gm, 0.013 mole), ethyl chloroacetate (1.633 gm, 0.013 mole) and benzaldehyde (1.414 gm, 0.013 mole) in acetic anhydride (20 ml) and glacial acetic acid (30 ml) was refluxed on a water bath for about 12 hrs, concentrated and cooled. The solid thus obtained was purified over the column of silica gel using $CHCl_3$ as an eluant. The product was crystallized from methanol to give compound **1**, yield 88%, m.p. 248-50. (Anal. calcd for

$C_{16}H_{10}N_2OS$: C, 69.06; H, 3.59; N, 10.07 : Found : C, 69.04; H, 3.57; N 10.04%); IR : 3054, 3040, 2985, 1610, 1598, 1470, 1455, 1258, 1182, 742 and 715 (benzimidazole with aromatic ring), 1730 (C=0, cyclic), 1589 and 1542, 680 (C-S-C), ^{1}HNMR : 5.14 (s, 1H,-C=CH-Ar), 7.28-7.85 (m, 9H, Ar-H).

Other compounds 1b-k were synthesized similarly from 2-mercaptobenzi-midazole using different aromatic aldehydes. Characterization data are presented in Table 1. *2-(2', 4'-Dinitrophenyl)-3-(substitutedaryl) -3, 3a-dihydro benzimidazo [2,1-b] pyrazolo-[3,4-d] thiazoles,* 2a.

A mixture of 1a [1.70 gm, 0.003 mole], 2, 4 DNP (0.735 gm, 0.003 mole) and anhydrous sodium acetate (0.304 gm, 0.003 mole) in glacial acetic acid (40 ml) was heated under reflux condition on a water both for about 18 hrs, concentrated and cooled. The residue thus obtained was purified over the column of silica gel using $CHCl_3$ as in eluant. The product was crystallized from methanol to give compound 2a, yield 75%, mp 226-28^0 (Anal.calcd for $C_{22}H_{14}N_6O_4S$: C, 57.64; H, 3.05; N, 18.34; Found C, 57.62; H, 3.02; N, 18.33%). IR : 3059, 3045, 2997, 1608, 1592, 1470, 1453, 1254, 1186, 732 and 710 (benzimidazole with aromatic ring), 920, 880, 840 (1,2,3-trisubstituted benzene ring), 680 (C-S-C), 1620 (C=N), 1518, 1343 (-NO_2 group), 1549, 1508 (C-N-C). ^{1}HNMR : 6.93 (1H, d, J = 9Hz, C_{3a}-H), 8.33 (1 H, d, J = 9 Hz, C_3-H), 9.18 (1H, d, J = 2.5 Hz, C_3-H of 2, 4-DNP), 7.06-7.92 (m, 12H, Ar-H).

Other compounds 2b-k and 3a-k were synthesized similarly from 1b-k using 2,4-DNP, and 1a-k using phenylhydrazine respectively. Characterization data are presented in Table 1.

RESULTS AND DISCUSSION

2-Mercaptobenzimidazole [12] on condensation with ethyl chloroacetate and various aromatic aldehydes in the presence of anhydrous sodium acetate, acetic anhydride and glacial acetic acid afforded 2-substitutedarylidene benzimidazo [2,1-b] thiazolidin-3-ones **1** which on further condensation with 2,4 DNP or phenyl hydrazine yielded the cyclized products, 2-(2', 4'-dinitrophenyl/phenyl)-3-substituted phenyl-3, 3a-dihydrobenzimidazo [2, 1-a] pyrazolo [3, 4-d] thiazoles **2** (**Scheme 1**). The structure of 2 was supported by their chemical and spectral data. The appearance of two doublets at δ 6.98 and δ8.29 (J = 9Hz) respectively for the protons at 3a and 3 positions corroborated the cyclic structure and cis configuration. [2,13]

The compounds were screened for their antifungal activity against *Aspergillus niger, Aspergillus flavus, Fusarium oxisporium* and *Trichoderma viride* by filter paper disc technique[14] at two concentrations (100 and 500 ppm) and antibacterial activity against *Escherichia coli, Klebsiella pneumoniae* and *Staphylococcus aureus* at two concentrations (50 and 100 ppm) by filter paper disc technique. Standard antifungal griseofulvin and antibacterial streptomycin were also screened under the similar conditions for comparison. Results are presented in Table-2 and 3 respectively.

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Table 1. Characterization data of compounds (1b-k), (2b-k) and (3a-k)

Comp.	Ar	Yield (%)	m.p. (°C)	Mol. Formula	Calcd (Found) %		
					C	H	N
1b	2-BrC_6H_4	75	245-247	$C_{16}H_9N_2OSBr$	53.79 (53.74)	2.52 (2.49)	7.84 (7.82)
1c	3-BrC_6H_4	78	226-228	$C_{16}H_9N_2OSBr$	53.79 (53.78)	2.52 (2.50)	7.84 (7.81)
1d	4-BrC_6H_4	76	239-240	$C_{16}H_9N_2OSBr$	53.79 (53.76)	2.52 (2.51)	7.84 (7.82)
1e	2-ClC_6H_4	77	278-280	$C_{16}H_9N_2OSCl$	61.44 (61.41)	2.85 (2.86)	8.96 (8.93)
1f	3-ClC_6H_4	75	250-252	$C_{16}H_9N_2OSCl$	61.44 (61.42)	2.85 (2.84)	8.96 (8.94)
1g	4-ClC_6H_4	78	251-253	$C_{16}H_9N_2OSCl$	61.44 (61.40)	2.85 (2.83)	8.96 (8.95)
1h	2-$NO_2C_6H_4$	80	235-237	$C_{16}H_9N_3O_3S$	59.44 (59.43)	2.75 (2.72)	13.00 (12.98)
1i	3-$NO_2C_6H_4$	82	237-240	$C_{16}H_9N_3O_3S$	59.44 (59.42)	2.75 (2.74)	13.00 (12.99)
1j	4-$NO_2C_6H_4$	81	238-240	$C_{16}H_9N_3O_3S$	59.44 (59.43)	2.75 (2.71)	13.00 (12.97)
1k	4,4'-$N(CH_3)_2C_6H_4$	88	264-266	$C_{18}H_{15}N_3OS$	67.28 (67.25)	4.67 (4.65)	13.08 (13.06)
2b	2-BrC_6H_4	80	271-273	$C_{22}H_{13}N_6O_4SBr$	49.17 (49.14)	2.42 (2.40)	15.64 (15.61)
2c	3-BrC_6H_4	81	272-275	$C_{22}H_{13}N_6O_4SBr$	49.17 (49.15)	2.42 (2.41)	15.64 (15.60)
2d	4-BrC_6H_4	82	274-276	$C_{22}H_{13}N_6O_4SBr$	49.17. (49.13)	2.42 (2.39)	15.64 (15.62)
2e	2-ClC_6H_4	84	258-259	$C_{22}H_{13}N_6O_4SCl$	53.60 (53.58)	2.63 (2.61)	17.05 (17.02)
2f	3-ClC_6H_4	83	260-262	$C_{22}H_{13}N_6O_4SCl$	53.60 (53.57)	2.63 (2.60)	17.05 (17.03)
2g	4-ClC_6H_4	82	260-263	$C_{22}H_{13}N_6O_4SCl$	53.60 (53.58)	2.63 (2.61)	17.05 (17.01)
2h	2-$NO_2C_6H_4$	80	190-193	$C_{22}H_{13}N_7O_6S$	52.48 (52.45)	2.58 (2.56)	19.48 (19.45)
2i	3-$NO_2C_6H_4$	81	192-194	$C_{22}H_{13}N_7O_6S$	52.48 (52.44)	2.58 (2.55)	19.48 (19.44)
2j	4-$NO_2C_6H_4$	82	193-195	$C_{22}H_{13}N_7O_6S$	52.48 (52.40)	2.58 (2.54)	19.48 (19.46)
2k	4,4'-$N(CH_3)_2C_6H_4$	84	213-215	$C_{24}H_{19}N_7O_4S$	57.48 (57.46)	3.79 (3.76)	19.56 (19.53)
3a	C_6H_5CHO	84	242-244	$C_{22}H_{16}N_4S$	74.74 (74.71)	4.35 (4.32)	15.22 (15.20)
3b	2-BrC_6H_4	80	252-255	$C_{22}H_{15}N_4SBr$	59.07 (59.05)	3.36 (3.33)	12.53 (12.51)
3c	3-BrC_6H_4	81	254-256	$C_{22}H_{15}N_4SBr$	59.07 (59.05)	3.36 (3.32)	12.53 (12.49)
3d	4-BrC_6H_4	82	257-258	$C_{22}H_{15}N_4SBr$	59.07 (59.04)	3.36 (3.34)	12.53 (12.50)
3e	2-ClC_6H_4	78	190-192	$C_{22}H_{15}N_4SCl$	65.59 (65.55)	3.73 (3.70)	13.91 (13.89)
3f	3-ClC_6H_4	76	191-194	$C_{22}H_{15}N_4SCl$	65.59 (65.57)	3.73 (3.71)	13.91 (13.88)
3g	4-ClC_6H_4	79	192-194	$C_{22}H_{15}N_4SCl$	65.59 (65.56)	3.73 (3.72)	13.91 (13.90)
3h	2-$NO_2C_6H_4$	76	198-200	$C_{22}H_{15}N_5O_2S$	63.92 (63.90)	3.63 (3.61)	16.95 (16.92)
3i	3-$NO_2C_6H_4$	78	201-203	$C_{22}H_{15}N_5O_2S$	63.92 (63.90)	3.63 (3.61)	16.95 (16.91)
3j	4-$NO_2C_6H_4$	77	202-204	$C_{22}H_{15}N_5O_2S$	63.92 (63.89)	3.63 (3.60)	16.95 (16.94)
3k	4,4'-$N(CH_3)_2C_6H_4$	82	205-208	$C_{24}H_{21}N_5S$	70.07 (70.06)	5.11 (5.09)	17.03 (17.01)

Table 2. Antifungal data of compounds (1a-k), (2a-k) and (3a-k)

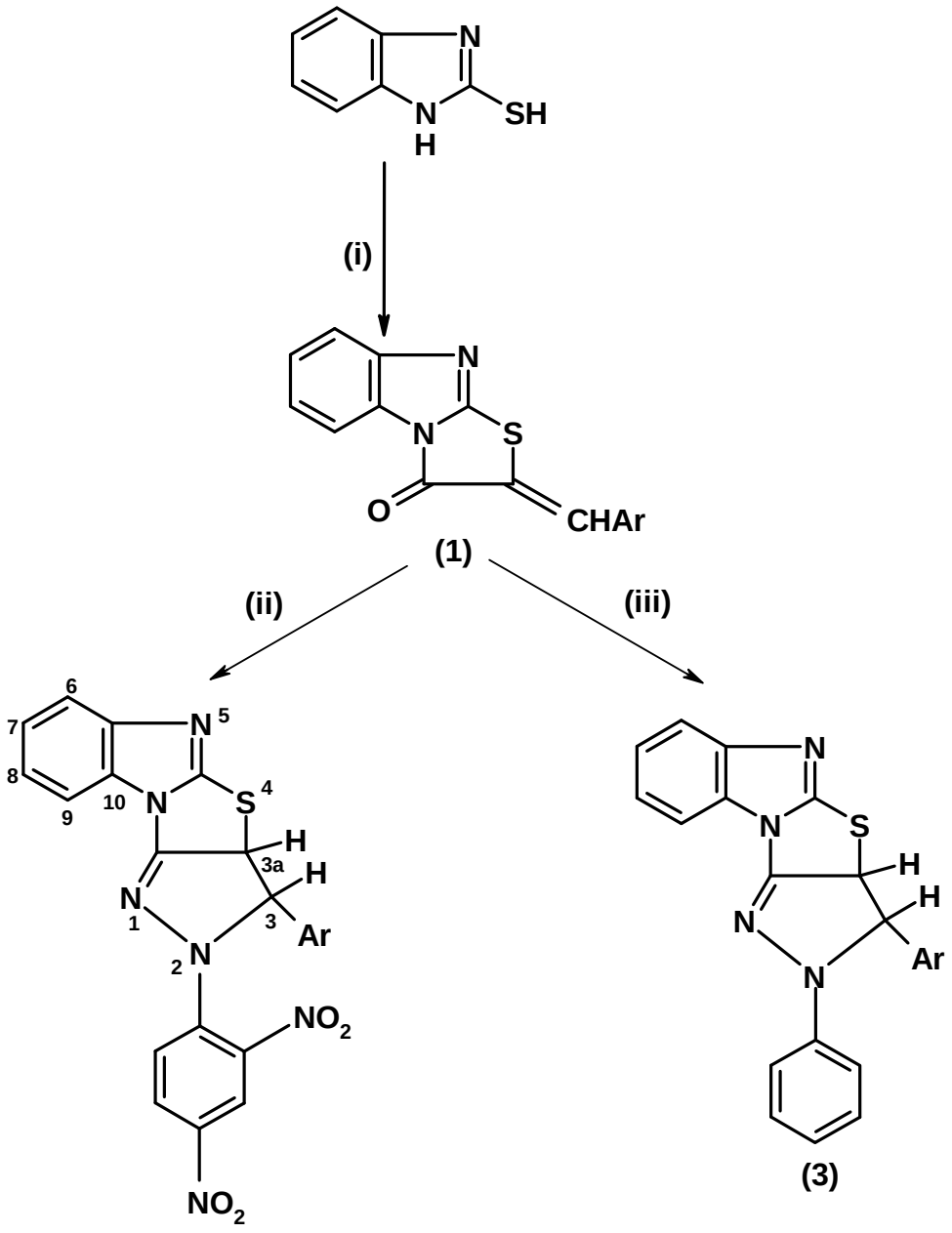
Comp.	*A. niger*		*A. flavus*		*F. oxisporum*		*T. viride*	
	100 ppm	**500 ppm**	**100 ppm**	**500 ppm**	**100 ppm**	**500 ppm**	**100 ppm**	**500 ppm**
1a	+	++	-	-	+	++	++	++
1b	+++	++++	++	+++	+++	++++	+++	+++
1c	++	+++	++	+++	++	++	++	+++
1d	+++	+++	+	++	+++	+++	++	+++
1e	+	+	+	+	+	+	+	++
1f	++	++	-	+	-	-	+	+
1g	++	++	+	++	-	-	+	+
1h	-	+	+	++	++	++	+	++
1i	+	+	+	+	-	+	-	+
1j	++	++	++	+++	+	++	+	++
1k	++	++	+	+	+	+	-	-
2a	+	+	+	++	+	+	+	+
2b	++	++	+++	++++	++	++	+++	+++
2c	++	++	+++	+++	++	++	+++	++++
2d	+	+	+	++	++	++	++	++
2e	+	++	-	-	-	+	-	+
2f	++	++	+	+	+	+	+	++
2g	+	+	-	+	-	-	+	++
2h	++	++	-	-	+	+	+	++
2i	+	+	+	-	-	-	++	+++
2j	+	+	-	+	+	+	+	+
2k	+	++	+	+	+	++	-	+
3a	+	++	+	+	+	+	+	+
3b	+++	+++	++	++	+	++	+++	+++
3c	++	++	+++	++++	+++	++++	++	+++
3d	++	++	+	++	+++	+++	+++	+++
3e	++	++	-	+	-	+	-	-
3f	+	+	+	+	+	+	+	-
3g	-	-	+	+	+	+	+	+
3h	+	++	+	+	+	++	++	++
3i	+	++	+	+	+	++	+	++
3j	+	+	-	-	-	+	-	+
3k	-	-	-	-	+	+	++	++
GF	+++	++++	+++	++++	+++	++++	+++	++++

GF = Griseofulvin, inhibition diameter in mm; (-) 5; (+) 5-11; (++) 11-15; (+++) 15-19 and (++++) 19-24.

Table 3. Antibacterial data of the compounds (1a-k), (2a-k) and (3a-k)

Comp.	*E. coli*		*K. pneumoniae*		*S. aureus*	
	50ppm	**100ppm**	**50ppm**	**100ppm**	**50ppm**	**100ppm**
1a	++	++	+	+	++	+
1b	+++	++++	++	+++	+++	+++
1c	++	+++	+++	++++	++	+++
1d	+++	+++	++	+++	+++	++++
1e	++	++	+	+	+	++
1f	+	+	+	++	+	++
1g	++	+++	++	++	++	+++
1h	+	++	-	+	+	++
1i	++	++	-	-	++	++
1j	-	+	-	+	+	++
1k	+	+	+	++	+	++
2a	+	++	+	++	++	+++
2b	++	+++	+	++	+	+
2c	+++	++++	++	++++	+	++
2d	++	++	+	+	+	+
2e	++	+++	-	-	+	++
2f	++	++	-	-	+	+
2g	+	++	-	-	+	++
2h	++	++	-	+	++	+++
2i	-	+	-	+	+	-
2j	+	++	+	++	+	+
2k	+	+	+	++	+	+
3a	+++	++++	+	++	+	++
3b	+++	++++	+++	+++	++	+++
3c	+++	+++	++	++	++	+++
3d	+++	++++	+	++	+	++
3e	++	++	+	++	+	++
3f	+	+	-	+	+	++
3g	++	++	+	+	-	-
3h	+	+	-	-	+	+
3i	+	+	+	++	+	++
3j	++	+++	+	+	+	+
3k	+	++	-	+	-	+
SM	+++	++++	+++	++++	+++	++++

SM = Streptomycin, inhibition diameter in mm; (-) 4; (+) 4-11, (++) 11-17; (+++) 17-23 and (++++) 23-29.



(i) $ClCH_2COOEt$, Ar-CHO, AcONa, gl AcOH

(ii) 2, 4-DNP

(iii) $PhNHNH_2$

Ar = Various sub. aldehydes

Scheme-I