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Note

Synthesis of 5-arylidene-2-aryl-3-(benzotriazoloacetamidyl)-1,3-thiazolidin-4-ones as analegesic and antimicrobial agents

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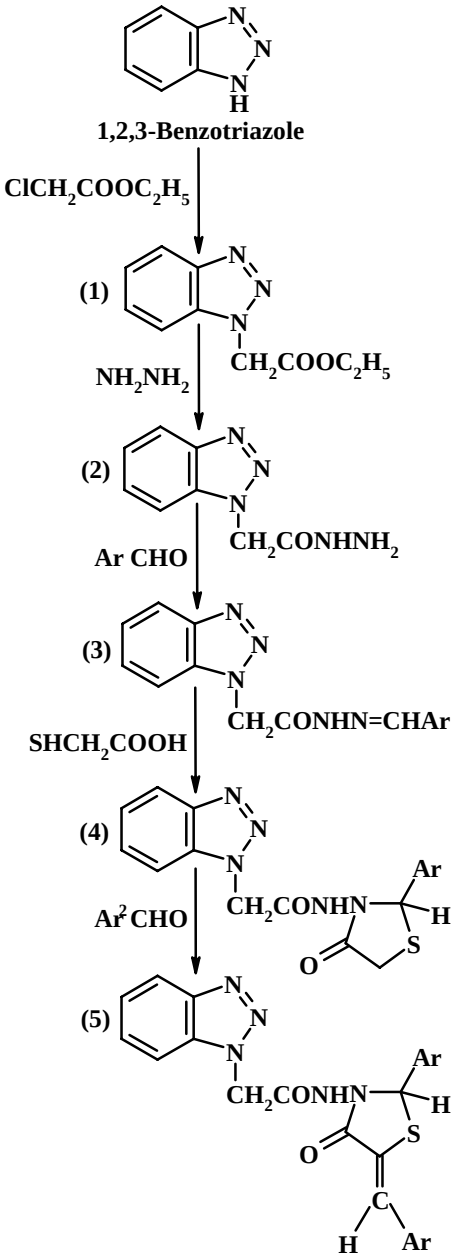
Benzotriazole on reaction with ethyl chloroacetate affords **1**, which on treatment with hydrazine hydrate yields **2**. Condensation of N^1(acetohydrazido)benzotriazole **2** with various carbonyls gives arylidene acetohydrazido benzotriazoles **3** which on cycloaddition with mercaptoacetic acid yields the corresponding 4-thiazolidinones **4**. which on reaction with various carbonyl compounds afford 5-arylidene-2-aryl-benzotriazoloacetamidyl-1,3-thiazolidin-4-ones **5**.

Key words: Thiazolidinon-arylidenes, analgesic agents, antimicrobial agents, benzotriazole, ethyl chloroacetate

IPC: **Int.Cl.**[7] **C 07 D**

Benzotriazole derivatives possess potent biological activities[1,2]. 4-Oxo-thiazolidines and their 5-arylidene derivatives are well known for their versatile pharmacological activities[3-8] such as hypnotic, anaesthetic, antifungal, analgesic, antiviral, antithyroid, anticonvulsant, CNS stimulant, antimicrobial, antiinflammatory, etc. All the compounds have been screened for their analgesic activity by the Eddy and Leimbach method using techno heated plate analgesic apparatus and antimicrobial activity by the filter paper disc technique.

Benzotriazole on *N*-estrification with ethyl chloroacetate in methanol gave ethyl ethanoate benzotriazole **1** which on amination[4,5] in methanol with hydrazine afforded acetohydrazido benzotriazole **2**. The compound **2** on condensation[4-6] with various substituted carbonyls yielded arylidene acetohydrazido benzotriazole **3** which on cycloaddition with mercaptoacetic acid in presence of anhydrous $ZnCl_2$ furnished 2-aryl-3-benzotriazolo acetamidyl-1,3-thiazolidin-4-ones **4**. Compounds **4** on application of the Knoevengel reaction with various substituted aryl carbonyls using sodium ethoxide yielded 5-arylidene-2-aryl-3-benzotriazoloacetamidyl-1,3-thiazolidin-4-ones **5 (Scheme I)**. The purity of the compounds was monitored by TLC and the structures of the products were confirmed by spectral and chemical evidences **(Table I)**.



Ar = -ClC_6H_4/-$CH_3C_6H_4$/-$NO_2C_6H_4$/-BrC_6H_4

Scheme I

Table I — Analytical data of the compounds **3,4** and **5b-j**

Compd	Ar group	Yield (%)	m.p. ºC	Mol. Formula	Calcd (Found) %		
					C	H	N
3b	2-$CH_3C_6H_4$	69	118-20	$C_{16}H_{15}N_5O$	65.52 (65.11	5.11 4.97	23.89 23.70)
3c	3-$CH_3C_6H_4$	71	128-29	$C_{16}H_{15}N_5O$	65.52 (65.15	5.11 4.99	23.98 23.72)
3d	4-$CH_3C_6H_4$	75	115-16	$C_{16}H_{15}N_5O$	65.52 (65.41	5.11 5.12	23.89 23.65)
3e	2-$NO_2C_6H_4$	73	116-18	$C_{15}H_{12}N_6O_3$	55.55 (55.41	3.70 3.58	25.93 25.75)
3f	3-$NO_2C_6H_4$	68	128-30	$C_{15}H_{12}N_6O_3$	55.55 (55.49	3.70 3.39	25.93 25.70)
3g	4-$NO_2C_6H_4$	72	119-20	$C_{15}H_{12}N_6O_3$	55.55 (55.42	3.70 3.68	25.93 25.92)
3h	2-BrC_6H_4	78	137-39	$C_{15}H_{12}N_5OBr$	50.42 (50.10	3.36 3.15	19.61 19.48)
3i	3-BrC_6H_4	75	140-41	$C_{15}H_{12}N_5OBr$	50.42 (50.15	3.36 3.11	19.61 19.44)
3j	4-BrC_6H_4	76	133-34	$C_{15}H_{12}N_5OBr$	50.42 (50.19	3.36 3.19	19.61 19.40)
4b	2-$CH_3C_6H_4$	60	130-33	$C_{18}H_{17}N_5O_2S$	58.85 (58.53	4.63 4.53	19.07 18.95)
4c	3-$CH_3C_6H_4$	65	135-37	$C_{18}H_{17}N_5O_2S$	58.85 (58.50	4.63 4.55	19.07 18.99)
4d	4-$CH_3C_6H_4$	70	124-26	$C_{18}H_{17}N_5O_2S$	58.85 (58.45	4.63 4.49	19.07 18.91)
4e	2-$NO_2C_6H_4$	66	128-30	$C_{17}H_{14}N_6O_4S$	51.25 (51.01	3.51 3.47	21.10 21.10)
4f	3-$NO_2C_6H_4$	64	139-40	$C_{17}H_{14}N_6O_4S$	51.25 (51.98	3.15 3.36	21.10 20.88)
4g	4-$NO_2C_6H_4$	61	130-32	$C_{17}H_{14}N_6O_4S$	51.25 (50.88	3.51 3.49	21.10 21.00)
4h	2-BrC_6H_4	79	140-42	$C_{17}H_{14}N_5O_2SBr$	47.33 (47.31	3.25 3.20	16.24 16.91)
4i	3-BrC_6H_4	69	153-55	$C_{17}H_{14}N_5O_2SBr$	47.33 (47.15	3.25 3.10	16.24 16.18)
4j	4-BrC_6H_4	72	146-47	$C_{17}H_{14}N_5O_2SBr$	47.33 (47.09	3.25 3.05	16.24 16.20)
5b	2-$CH_3C_6H_4$	65	101-02	$C_{26}H_{23}N_5O_2S$	66.52 (66.38	4.90 4.85	14.93 14.83)
5c	3-$CH_3C_6H_4$	68	104-05	$C_{26}H_{23}N_5O_2S$	66.52 (66.50	4.90 4.81	14.93 14.80)
5d	4-$CH_3C_6H_4$	69	97-98	$C_{26}H_{23}N_5O_2S$	66.52 (66.49	4.90 4.80	14.93 14.81)
5e	2-$NO_2C_6H_4$	61	105-07	$C_{24}H_{17}N_7O_6S$	54.23 (54.10	3.20 3.00	18.45 18.35)
5f	3-$NO_2C_6H_4$	61	114-15	$C_{24}H_{17}N_7O_6S$	54.23 (54.15	3.20 3.09	18.45 18.30)
5g	4-$NO_2C_6H_4$	63	102-04	$C_{24}H_{17}N_7O_6S$	54.23 (54.12	3.20 3.15	18.45 18.39)
5h	2-BrC_6H_4	72	115-17	$C_{24}H_{17}N_5O_2SBr_2$	48.28 (48.02	2.84 2.65	11.72 11.58)
5i	3-BrC_6H_4	65	120-22	$C_{24}H_{17}N_5O_2SBr_2$	48.28 (47.92	2.84 2.77	11.72 11.55)
5j	4-BrC_6H_4	69	105-07	$C_{24}H_{17}N_5O_2SBr_2$	48.28 (48.05	2.84 2.67	11.72 11.62)

Biological Activity

Analgesic activity: The synthesized compounds were tested for their analgesic activity in albino rats (weighing 70-110 g) by Eddy and Leimbach method[9] at an oral dose 25mg/kg b.w. Acetylsalicylic acid (ASA) was employed as a standard drug. The synthesized compounds **5h, 5i** and **5j** were found to show 141.93, 142.85 and 141.26% analgesic activity respectively **(Table II)**.

Antimicrobial activity*:* The compounds were screened for their antifungal activity against *R. oryzae, A nigar, C panical* and *C. albicans* by paper disc technique[10-12] at two concentrations (100 and 500 ppm) and antibacterial activity against *B. substilis, S. typhimurium, E. coli* and *B. anthracis* at two concentrations (50 and 100 ppm). Standard antifungal griseofulvin and antibacterial streptomycin were also screened under similar conditions for comparison.

Table II — Analgesic activity of the compounds **1,2, 3a-j, 4a-j** and **5a-j**

Compd	Reaction time in seconds				PAS after 45 min
	Before drug administration	After drug administration			
		15 min	30 min	45 min	
1	6.0 ± 0.03	7.0 ± 0.03	7.1 ± 0.02	7.2 ± 0.02	1200
2	4.5 ± 0.02	5.5 ± 0.02	5.7 ± 0.03	6.0 ± 0.02	133.33
3a	4.8 ± 0.03	5.3 ± 0.02	5.3 ± 0.02	5.7 ± 0.03	118.78
3b	5.0 ± 0.03	5.2 ± 0.03	5.8 ± 0.02	6.1 ± 0.02	122.00
3c	5.2 ± 0.02	5.4 ± 0.03	5.9 ± 0.02	6.2 ± 0.01	119.23
3d	5.8 ± 0.02	6.0 ± 0.02	6.0 ± 0.02	6.5 ± 0.02	112.06
3e	6.2 ± 0.02	6.3 ± 0.03	6.3 ± 0.02	6.7 ± 0.02	108.06
3f	6.3 ± 0.02	6.4 ± 0.03	6.6 ± 0.01	6.7 ± 0.04	106.03
3g	6.5 ± 0.03	6.6 ± 0.02	6.8 ± 0.02	7.0 ± 0.02	107.69
3h	6.3 ± 0.02	6.3 ±0.03	6.4 ± 0.03	6.9 ± 0.01	109.52
3i	6.3 ± 0.02	6.4 ± 0.03	6.6 ± 0.01	6.7 ± 0.04	106.34
3j	6.8 ± 0.04	7.1 ± 0.03	7.2 ± 0.02	7.5 ± 0.02	110.29
4a	5.0 ± 0.03	5.2 ± 0.01	5.8 ± 0.02	6.1 ± 0.01	124.00
4b	5.3 ± 0.03	5.5 ± 0.02	6.0 ± 0.01	6.3 ± 0.03	118.86
4c	5.2 ± 0.01	5.4 ± 0.02	6.0 ± 0.02	6.5 ± 0.03	125.00
4d	5.8 ± 0.02	6.1 ± 0.02	6.3 ± 0.02	6.9 ± 0.03	118.96
4e	5.7 ± 0.02	6.2 ± 0.02	6.5 ± 0.02	6.7 ±0.03	117.54
4f	6.0 ± 0.02	6.2 ± 0.02	6.3 ± 0.02	6.8 ± 0.03	113.33
4g	5.5 ± 0.03	6.0 ± 0.02	6.5 ± 0.03	7.0 ± 0.03	127.27
4h	6.3 ± 0.01	7.0 ± 0.02	8.0 ± 0.03	8.2 ± 0.03	130.15
4i	6.8 ± 0.03	7.6 ±0.02	8.0 ± 0.02	8.5 ± 0.02	125.00
4j	6.8 ± 0.02	7.1 ±0.03	8.2 ± 0.03	8.3 ± 0.03	122.05
5a	5.4 ± 0.03	5.8 ± 0.03	6.0 ± 0.02	6.5 ± 0.01	120.37
5b	5.4 ± 0.02	5.8 ± 0.01	6.3 ± 0.02	6.7 ± 0.03	124.07
5c	5.4 ± 0.03	5.8 ± 0.03	6.6 ± 0.03	6.8 ± 0.04	125.92
5d	5.6 ± 0.02	6.1 ± 0.03	6.6 ± 0.03	7.1 ± 0.02	126.78
5e	6.0 ± 0.03	6.6 ± 0.03	7.1 ± 0.03	7.6 ± 0.02	126.66
5f	5.9 ± 0.03	6.6 ± 0.02	7.0 ± 0.03	7.5 ± 0.04	126.11
5g	5.5 ± 0.03	6.3 ± 0.02	6.9 ± 0.03	7.0 ± 0.03	127.27
5h	6.2 ± 0.02	7.8 ± 0.03	8.4 ± 0.02	8.8 ± 0.02	141.93
5i	6.3 ± 0.02	7.5 ± 0.01	8.8 ± 0.03	9.0 ± 0.04	142.85
5j	6.3 ± 0.03	7.8 ± 0.01	8.6 ± 0.03	8.9 ± 0.01	141.26
ASA std	6.0 ± 0.02	6.9 ±0.03	7.6 ± 0.03	8.6 ± 0.02	143.33

PAS: Percent Analgia Sease

Results are presented in **Tables III** and **IV,** respectively.

Experimental Section

Melting points were taken in open capillary tube. IR spectra (KBr in cm^{-1}) were recorded on a Schimadzu spectrometer, ^1H NMR spectra on a Bruker WM spectrometer (200 MHz, $CDCl_3$, Chemical shift in δ, ppm) using TMS as an internal standard. The purity of the compounds was monitored by TLC.

Ethyl ethanoate benzotriazole 1. Ethyl chloroacetate (0.05 mole) was added to a solution of benzotriazole (0.05 mole) and anhydrous K_2CO_3 (3 g) in ethanol (40 mL) and the reaction mixture was refluxed for about 15 h. The solvent was removed *in vaccuo* and the residue was crystallized from $CHCl_3$ to give **1**, yield 83%, m.p. 41-42ºC; (Found: C, 58.49; H, 5.33; N, 20.43. $C_{10}H_{11}N_3O_2$ requires C, 58.53; H, 5.40; N, 20.50%); ^1H NMR: 1.20 (t, 3H, *J*=7Hz, $COOCH_2CH_3$), 3.60 (s, 2H, N-CH_2), 4.10 (q, 2H, *J*=7Hz, $COOCH_2CH_3$) and 7.30-7.80 (m, 4H, Ar-H).

Table III — Antifungal data of the compounds **1**, **2**, **3a-j**, **4a-j** and **5a-j**

Compd	*R. oryzae*		*A. nigar*		*C. panical*		*C. albicans*	
	100 ppm	500 ppm	100 ppm	500 ppm	100 ppm	500 ppm	100 ppm	500 ppm
1	+	++	+	++	+	++	-	-
2	+	++	++	++	+	+	++	++
3a	++	++	+	+	++	++	++	++
3b	+	+	+	++	+	+	+	++
3c	-	-	+	++	+	+	+	++
3d	+	+	+	+	++	++	+	+
3e	+	+	-	+	+	+	+	+
3f	+	+	++	++	+	++	+	+++
3g	++	++	+	+	+	+	+	+
3h	++	+++	++	++	++	++	++	++
3i	++	+++	++	+++	++	++	++	++
3j	+++	+++	++	++	++	++	+	++
4a	+	++	+	++	++	++	+	++
4b	+	++	++	++	+	++	+	+++
4c	-	+	+	++	+	++	+	++
4d	+	++	+	+	++	++	++	++
4e	-	+	++	++	+	++	+	++
4f	+	++	+	++	+	+	+	++
4g	++	++	+	+	+	+	++	++
4h	+	++	++	++	++	++	++	+++
4i	++	++	+++	+++	++	++	++	+++
4j	+++	+++	++	++	++	++	++	+++
5a	++	+++	+	++	++	++	++	+++
5b	++	++	+	++	+	+	+	+
5c	+	+	+	+	++	++	+	++
5d	+	++	+	+	++	++	++	++
5e	-	+	+	++	++	++	+	++
5f	+	++	+	++	+	+	+	++
5g	++	++	+	+	+	+	++	++
5h	++	+++	++	+++	++	+++	++	+++
5i	++	+++	++	+++	++	+++	++	+++
5j	+++	+++	++	++	++++	++++	+++	++++
GF	+++	+++	+++	+++	++++	++++	+++	++++

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

Table-IV — Antibacterial data of the compounds **1, 2, 3a-j, 4a-j and 5a-j**

Compd	*B.substilis*		*S. typhimurium*		*E. coli*		*B. anthracis*	
	50 ppm	100 ppm	50 ppm	100 ppm	50 ppm	100 ppm	50 ppm	500 ppm
1	+	++	+	++	+	++	-	-
2	+	++	++	++	+	+	++	+++
3a	++	++	++	++	++	++	++	++
3b	+	+	+	++	+	+	+	++
3c	-	-	+	++	+	++	+	++
3d	+	+	+	+	++	++	+	+
3e	+	+	-	+	+	+	+	+
3f	+	+	++	++	+	++	+	++
3g	++	++	+	+	+	+	+	++
3h	++	+++	++	++	++	++	+	++
3i	++	+++	++	+++	++	++	+	++
3j	+++	+++	++	++	++	++	+	++
4a	+	++	+	++	++	++	++	+++
4b	+	++	+	+	+	++	+	+
4c	-	+	+	++	+	+	+	++
4d	+	++	+	+	++	++	++	++
4e	-	+	++	++	+	++	+	++
4f	+	++	+	++	+	+	+	++
4g	++	++	+	+	+	+	++	++
4h	++	++	++	++	+++	+++	++	+++
4i	++	+++	+++	+++	++	++	+++	+++
4j	++	+++	++	++	+++	+++	++	+++
5a	++	+++	+	++	++	++	+++	+++
5b	++	++	+	++	+	+	+	+
5c	+	+	+	+	++	++	+	++
5d	+	++	+	+	++	++	++	++
5e	-	+	+	++	++	++	+	+
5f	+	++	+	++	+	+	+	+
5g	++	++	+	+	+	+	++	++
5h	++	++	++	++	++	+++	++	+++
5i	++	+++	++	+++	++	+++	++	+++
5j	+++	+++	++	++	+++	++++	+++	+++
SM	+++	+++	++	+++	+++	++++	+++	++++

SM = Streptomycin,, inhibition diameter in mm; (-) 4; (+) 5-11; (++) 11-17; (+++) 17-23 and (++++) 23-29

Acetohydrazido benzotriazole 2. A mixture of **1** (0.028 mole) and hydrazine hydrate (0.028 mole) in 1,4-dioxane (50 mL) was refluxed on a water-bath for about 5 hr, cooled and filtered to get compound **2**, yield 60%, m.p. 86-87ºC, (Found: C, 50.30; H, 4.70; N, 36.50. $C_8H_9N_5O$ requires C, 50.30; H, 4.70; N, 36.60%); ^{1}H NMR: 3.55 (s, 2H, N-CH_2), 4.52 (s, 2H, NH_2), 7.90 (s, 1H, CONH) and 7.40-7.85 (m, 4H, Ar-H).

Arylidene acetohydrazido benzotriazole 3a. A mixture of **2** (0.0036 mole) 3-chlorobenzaldehyde (0.0036 mole) and 4-5 drops of glacial acetic acid in ethanol (30 mL) was refluxed on a steam-bath for about 15 hr. The solvent was removed under reduced pressure to yield a product yield 58%, m.p. 77-78ºC; (Found: C, 57.20; H, 3.75; N, 22.30. $C_{15}H_{12}N_5OCl$ requires C, 57.20; H, 3.75; N, 22.30%); ^{1}H NMR: 4.50 (s, 1H, -N=CH-), 3.70 (s, 2H, N-CH_2), 8.10 (s, 1H, -CONH) and 7.20-7.90 (m, Ar-H).

Other compounds **3b-j** were prepared from **2** similarly using different carbonyl compounds. Characterization data are presented in **Table I.**

2-Aryl-3-(N^1-benzotriazolo acetamidyl)-1,3-thiazolidin-4-ones 4a. A mixture of **3a** (0.025 mole) in THF

(30 mL) and mercaptoacetic acid (0.0025 mole) with a pinch of anhydrous $ZnCl_2$ was refluxed on a water-bath for about 14 hr. The separated solid was filtered and crystallized from chloroform to yield compound **4a**, yield 60%, m.p. 187-88ºC; (Found: C, 52.20; H, 3.56; N, 18.00. $C_{17}H_{14}N_5O_2SCl$ requires C, 52.51; H, 3.60; N, 18.02%); ^{1}H NMR: 3.20 (s, 1H, -CHS-), 3.55 (s, 2H, $COCH_2S$), 3.70 (s, 2.H, $-NCH_2$), 8.05 (s, 1H, -CONH-) and 7.25-7.90 (m, 8H, Ar-H).

Other compounds **4b-j** were synthesized in the similar way using **3b-j** respectively. Characterization data are presented in **Table I.**

5-Arylidene-2-aryl-3-(N^1-benzotriazoloacetamidyl)-1,3-thiazolidin-4-ones 5a. Equimolar solution of a mixture of **4a** (0.0015 mole) and 3-chlorobenzaldehyde (0.0015 moles) in dioxane (45 mL) in the presence of C_2H_5ONa was refluxed for about 8 hr on a steam-bath and cooled. The resulting solid was filtered, dried and crystallized from ethnol to give **5a**, yield 50%, m.p. 143-44ºC; (Found: C, 56.21; H, 3.31; N, 13.60. $C_{24}H_{17}N_5O_2SCl_2$ requires C, 56.25; H, 3.32; N, 13.67%); ^{1}H NMR: 3.20 (s, 1H, -CHS-), 3.65 (s, 2H, $-N-CH_2$), 5.22 (s, 1H, >C=CH-Ar), 8.25 (s, 1H, -CONH-) and 7.20-8.00 (m, 12H, Ar-H).

Other compounds **5b-j** were synthesized in the similar way using **4b-j** respectively. Characterization data are presented in **Table I**.

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