Indian Journal of Chemistry
Vol. 47B, April 2008, pp. 633-636

Note

Synthesis and antimicrobial activity of 2-(2′-arylidene-hydrazino-acetyl-amino)-4-phenyl-1,3-thiazoles and 2-[2′-{4″-substituted-aryl-3″-chloro-2″-oxo-azetidine}-acetyl-amino]-4-phenyl-1,3-thiazoles

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Received 13 September 2007; accepted (revised) 5 February 2008

As a part of systematic investigation of synthesis and biological activity, several new 2-(2′-substituted-arylidene-hydrazino-acetyl-amino)-4-phenyl-1,3-thiazoles, **3** and 2-[2′-{4″-substituted-aryl-3″-chloro-2″-oxo-azetidine}-acetyl-amino]-4-phenyl-1,3-thiazoles, **4** have been synthesized from 2-(2′-hydrazino-acetyl)-amino-4-phenyl-1,3-thiazole, **2** using 2-amino-4-phenyl-1,3-thiazole as the starting material. All the synthesized products are evaluated for their antifungal activity against *Aspergillus niger, Aspergillus flavus, Fusarium oxisporium* and *Trichoderma viride* and antibacterial activity against *Bacillus substilis, Eschericha coli. Klebsiella pneumoneae* and *Staphylococcus aureus* respectively. The structures of all the synthesized compounds have been determined by their spectral and microanalytical data.

Keywords: 2-Amino-4-phenyl-1,3-thiazole, arylidenes, 2-oxo-azetidines, antimicrobial activity

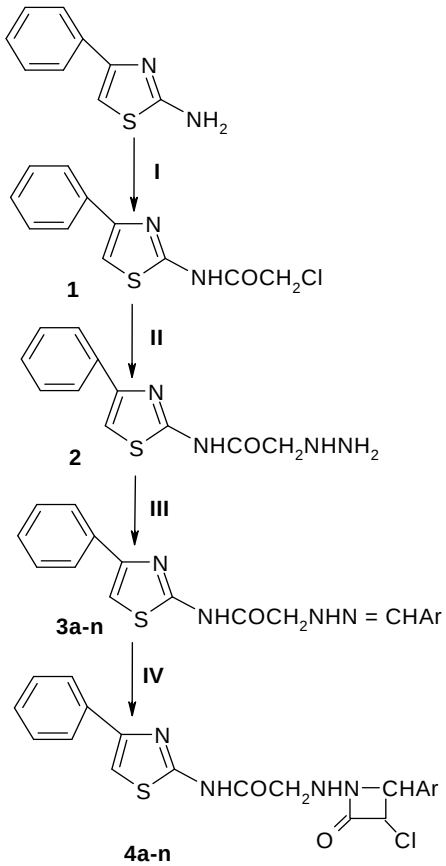
Thiazole derivatives are known to exhibit anaesthetic[1], antitubercular[2], antibacterial, antifungal[3], analgesic[4] and anticancer[5] activity. The β-lactam drugs are still the most prescribed antibiotics used in medicine. Recently 2-azetidines have been assessed for good antidegenerative[6], antiparkinsonian[7], anti-inflammatory[8], antibacterial[9] and antitubercular[10] activity. It also functions as an enzyme inhibitors and are effective on the central nervous system[11]. Moreover much interest has been focused on biological activity of thiazole derivatives. By considering the above arguments, several new thiazolo-azetidinones products have been synthesized in order to study their biodynamic behaviour[12]. The present paper reports the synthesis of 2-(2′-arylidene-hydrazino-acetyl-amino)-4-phenyl-1, 3-thiazoles, **3a-n** and 2-[2′-{4″-substituted aryl-3″-chloro-2″-oxo-azetidine}-acetyl-amino]-4-phenyl-1,3-thiazoles, **4a-n** by appropriate methods. All the synthesized compounds have been screened for their antifungal activity against *A. niger, A. flavus, F. oxisporium* and *T. viride* and antibacterial activity against *B. substilis, E. coli, S. aureus* and *K. pneumoneae* respectively[13-17].

2-Amino-4-phenyl-1,3-thiazole on reaction with chloroacetyl chloride yielded 2-(2′-chloroacetyl)-amino-4-phenyl-1,3-thiazole, **1** which on amination with hydrazine hydrate afforded 2-(2′-hydrazino-acetyl)-amino-4-phenyl-1,3-thiazole **2**. The compound **2** on condensation with various selected aromatic aldehydes yielded 2-(2′-arylidene-hydrazino-acetyl)-amino-4-phenyl-1,3-thiazoles **3a-n**. The compounds **3a-n** on treatment with chloroacetyl chloride in the presence of triethyl amine afforded 2-[2′-{4″-substituted aryl-3″-chloro-2″-oxo-azetidine}-acetyl-amino]-4-phenyl-1,3-thiazoles, **4a-n (Scheme I)**. Their structures have been elucidated on the basis of their spectral and microanalytical data. All the synthesized products were evaluated for their antifungal activity against *A. niger, A. flavus, F. oxisporium* and *T. viride* and antibacterial activity against *B. substilis, E. coli. K. pneumoneae* and *S. aureus* respectively.

Experimental Section

Melting points were taken in open capillaries and are uncorrected. Purity of compounds was monitored on silica gel G coated TLC plates. IR spectra were recorded on a Schimadzu 8201 PC spectrophotometer in KBr, ^{1}H NMR spectra on a Brucker DRX 300 spectrometer in $CDCl_3$ at 300 MHz using TMS as an internal standard and mass spectra on a Jeol SX-102 (FAB) instrument. Elemental analyses were performed on a Carlo Erba-1108 instrument. The analytical data of all the compounds were highly satisfactory. The reagent grade chemicals were purchased from the commercial sources and purified by either distillation or recrystallization before use.

2-(2′-Chloroacetyl)-amino-4-phenyl-1,3-thiazole 1: The compound 2-amino-4-phenyl-1,3-thiazole (0.20 mole, 35.20 g) dissolved in acetic acid (100 mL) saturated with sodium acetate, chloroacetyl chloride (0.20 mole, 19.69 g) was added drop wise in ice-bath[2] (to avoid the vigorous reaction) followed by stirring for about 1 hr. A light pale yellow coloured product



3,4	Ar	3,4	Ar	3,4	Ar
a	C_6H_5	**f**	$3\text{-}BrC_6H_4$	**k**	$2\text{-}NO_2C_6H_4$
b	$2\text{-}ClC_6H_4$	**g**	$4\text{-}BrC_6H_4$	**l**	$3\text{-}NO_2C_6H_4$
c	$3\text{-}ClC_6H_4$	**h**	$2\text{-}OCH_3C_6H_4$	**m**	$4\text{-}NO_2C_6H_4$
d	$4\text{-}ClC_6H_4$	**i**	$3\text{-}OCH_3C_6H_4$	**n**	$4.4'(CH_3)_2NC_6H_4$
e	$2\text{-}BrC_6H_4$	**j**	$4\text{-}OCH_3C_6H_4$		

Reagents : (I) $ClCOCH_2Cl$, (II) $NH_2NH_2.H_2O$, (III) $ArCHO/CH_3COOH$, (IV) $ClCOCH_2Cl$/TEA.

Scheme I

was separated out which was filtered, washed with water, purified over the column chromatography and recrystallised from chloroform to give compound **1**. Yield 79%, m.p. 171-73ºC; IR: 3352 (-NH), 1665 (>C=O), 2963 (-CH_2), 2847 (-CH of thiazole), 1409 (-C=N), 1188, 1072, 686 (C-S-C), 3023, 1597, 742 (aromatic ring), 776 cm^{-1} (C-Cl); ^1H NMR:δ 6.89-7.78 (m, 5H, Ar-H), 6.58 (s, 1H, C-5 of thiazole), 8.15 (s, 1H, -NH), 4.35 (s, 2H, -CH_2); *m/z*: 252 (M^+), 216, 203, 175,160, 134, 133,77, 56, 49, 41, 40, 36.

2-(2′-Hydrazinoacetyl)-amino-4-phenyl-1,3-thiazole 2: The compound **1** (0.10 mole, 25.26 g) and hydrazine hydrate (0.10 mole, 4.90 g) in methanol (100 mL) was refluxed[13] on a water-bath for about 10 hr. It was filtered, cooled, purified over the column chromatography and recrystallised from methanol to give compound **2**. Yield 82%, m.p. 149-51ºC; IR: 3356 (-NH), 3396, 3278 (-NH_2), 1669 (>C=O), 2967 (-CH_2), 2848 cm^{-1} (-CH of thiazole), 1186, 1073, 688 (C-S-C), 1413 (-C=N), 3028, 1599, 738 cm^{-1} aromatic ring); ^1H NMR: δ 6.90-7.76 (m, 5H, Ar-H), 6.55 (s, 1H, C-5 of thiazole), 8.15 (s, 1H, -NHCO), 4.79 (s, 2H, -NH_2), 7.88 (s, 1H, -NH), 4.34 (s, 2H, -CH_2); *m/z* : 248 (M^+), 232, 217, 216, 203, 175, 134, 133, 77, 57, 56,45, 42, 41, 40, 32, 31, 16.

2-(2′-Arylidene-hydrazino-acetyl)-amino-4-phenyl-1,3-thiazole 3a: The compound **2** (0.007 mole, 1.736 g) and benzaldehyde (0.007 mole, 0.70 g) in methanol (40 mL) with 3-4 drops acetic acid was refluxed[13] on a water-bath for about 3 hr. The solvent was distilled off under reduced pressure and the solid thus obtained was purified over the column chromatography and recrystallised from ethanol to give compound **3a**. Yield 87%, m.p. 172-74ºC; IR: 3349 (-NH), 1662 (>C=O), 1543 (-N=CH), 2963 (-CH_2), 2843 (-CH of thiazole), 1188, 1076, 691 (C-S-C), 1416 (C=N), 3025, 1596, 736 cm^{-1} aromatic ring); ^1H NMR: :δ 6.88-7.72 (m, 10H, Ar-H), 4.86 (s, 1H, -N=CH), 6.59 (s, 1H, C-5 of thiazole), 8.16 (s, 1H,-NHCO), 7.83 (s, 1H, -NH), 4.32 (s, 2H, -CH_2); *m/z* : 336 (M^+), 256, 232, 217, 203, 175, 133, 119, 99, 77, 57, 56, 43, 41, 40, 15 (**Chart 1**).

Other compounds **3b-n** were synthesized in the similar manner using compound **2** and various selected aromatic aldehydes. Characterization data are presented in **Table I**.

2-[2′-{4′′-substituted aryl-3′′-chloro-2′′-oxo-azetidine}-acetyl amino]-4-phenyl-1,3-thiazole 4a: The compound **3a** (0.005 mole, 1.681 g) and triethylamine (0.005 mole, 0.696 g) in ethanol (30 mL) with chloroacetyl chloride (0.005 mole, 0.398 g) was first stirred for about 3 hr followed by refluxing[13] on a water-bath for about 14 hr. The solvent was distilled under reduced pressure and the solid thus obtained was purified by column chromatography using $CHCl_3$: MeOH (8:2 v/v) as eluant and recrystallised from ethanol to give compound **4a**. Yield 70%, m.p. 181-83ºC; IR: 3352 (-NH), 1663 (>C=O), 2964 (-CH_2), 1773 (>C=O, cyclic), 2846 (-CH of thiazole), 1418 (-C=N), 768 (CH-Cl), 1192, 1080, 687 (C-S-C), 3024, 1593, 731 cm^{-1} (aromatic ring); ^1H NMR: δ 6.92-7.74 (m, 10H,

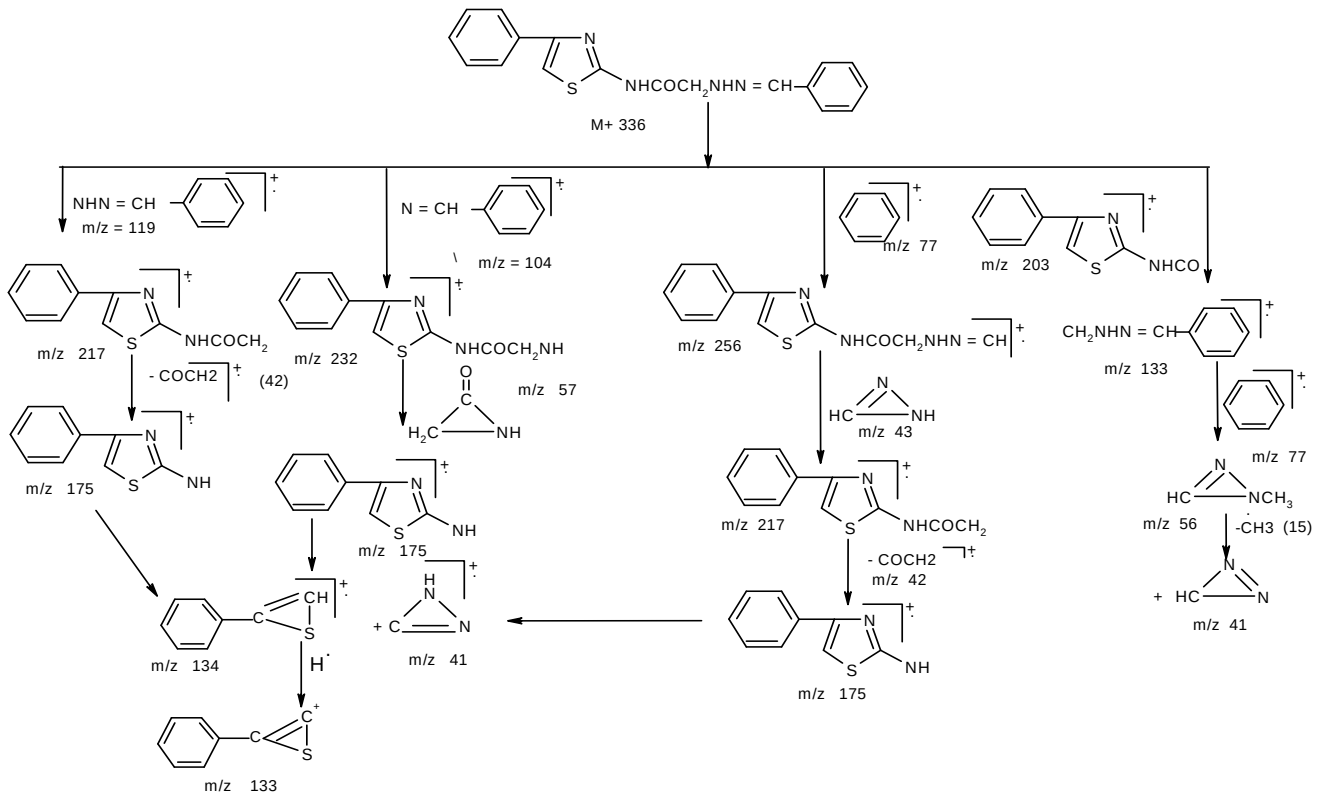


Chart 1 : Mass spectral fragmentation pattern of 2-[2'-arylidene-hydrazino-acetyl]-amino-4-phenyl-1,3-thiazole, **3a**

Ar-H), 6.58 (s, 1H, C-5 of thiazole), 8.16 (s, 1H, -NHCO), 7.79 (s, 1H, -NHN), 4.17 (d, *J* = 5.00, Hz, 1H, N-CH-Ar), 5.14 (d, *J* = 5.00, Hz, 1H, -CHCl), 4.34 (s, 2H, $-CH_2$); *m/z*: 412 (M^+), 384,232, 217, 209, 208, 203, 195, 181, 180, 175, 167, 152, 134, 133, 41(**Chart 2**).

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

Table I —- Characterization data of compounds **3b-n** and **4b-n**

Compd	Ar	Yield (%)	m.p. (°C)	Mole. formula
3c	3-ClC_6H_4	88	192-94	$C_{18}H_{15}N_4OSCl$
3d	4-ClC_6H_4	91	199-201	$C_{18}H_{15}N_4OSCl$
3e	2-BrC_6H_4	86	218-20	$C_{18}H_{15}N_4OSBr$
3f	3-BrC_6H_4	84	222-24	$C_{18}H_{15}N_4OSBr$
3g	4-BrC_6H_4	92	226-28	$C_{18}H_{15}N_4OSBr$
3h	2-$OCH_3C_6H_4$	93	232-34	$C_{19}H_{18}N_4O_2S$
3i	3-$OCH_3C_6H_4$	90	230-32	$C_{19}H_{18}N_4O_2S$
3j	4-$OCH_3C_6H_4$	87	228-30	$C_{19}H_{18}N_4O_2S$
3k	2-$NO_2C_6H_4$	86	167-69	$C_{18}H_{15}N_5O_3S$
3l	3-$NO_2C_6H_4$	88	171-73	$C_{18}H_{15}N_5O_3S$
3m	4-$NO_2C_6H_4$	85	178-80	$C_{18}H_{15}N_5O_3S$
3n	4.4′$(CH_3)_2NC_6H_4$	92	159-61	$C_{20}H_{21}N_5OS$
4b	2-ClC_6H_4	84	230-32	$C_{20}H_{16}N_4O_2SCl_2$
4c	3-ClC_6H_4	76	214-16	$C_{20}H_{16}N_4O_2SCl_2$
4d	4-ClC_6H_4	81	213-15	$C_{20}H_{16}N_4O_2SCl_2$
4e	2-BrC_6H_4	69	207-09	$C_{20}H_{16}N_4O_2SClBr$
4f	3-BrC_6H_4	63	204-06	$C_{20}H_{16}N_4O_2SClBr$
4g	4-BrC_6H_4	67	207-09	$C_{20}H_{16}N_4O_2SClBr$
4h	2-$OCH_3C_6H_4$	73	206-08	$C_{21}H_{19}N_4O_3SCl$
4i	3-$OCH_3C_6H_4$	71	187-89	$C_{21}H_{19}N_4O_3SCl$
4j	4-$OCH_3C_6H_4$	78	194-96	$C_{21}H_{19}N_4O_3SCl$
4k	2-$NO_2C_6H_4$	83	184-86	$C_{20}H_{16}N_5O_4SCl$
4l	3-$NO_2C_6H_4$	89	158-60	$C_{20}H_{16}N_5O_4SCl$
4m	4-$NO_2C_6H_4$	82	164-66	$C_{20}H_{16}N_5O_4SCl$
4n	4.4′$(CH_3)_2NC_6H4$	68	174-76	$C_{22}H_{22}N_5O_2SCl$

Antimicrobial activity

All the synthesized compounds **1, 2, 3 a-n** and **4 a-n** have been screened *in vitro* for their antifungal activity against *A. niger* (An)*, A. flavus* (Af)*, F. oxisporium* (Fo) and *T. viride* (Tv) at two concentrations (50 and 100 ppm) and antibacterial activity against *B. substilis* (Bs)*, E. coli* (Ec)*, S. aureus* (Sa) and *K. pneumoneae* (Kp) at two concentrations (50 and 100 ppm) by filter paper disc method. Standard fungicide griseofulvin and antibacterial streptomycin were also screened under the similar conditions for comparison. The following compounds were found active against the tested fungi: **4c** (An), **4d** (An, Tv), **4e** (An, Af), **4f**

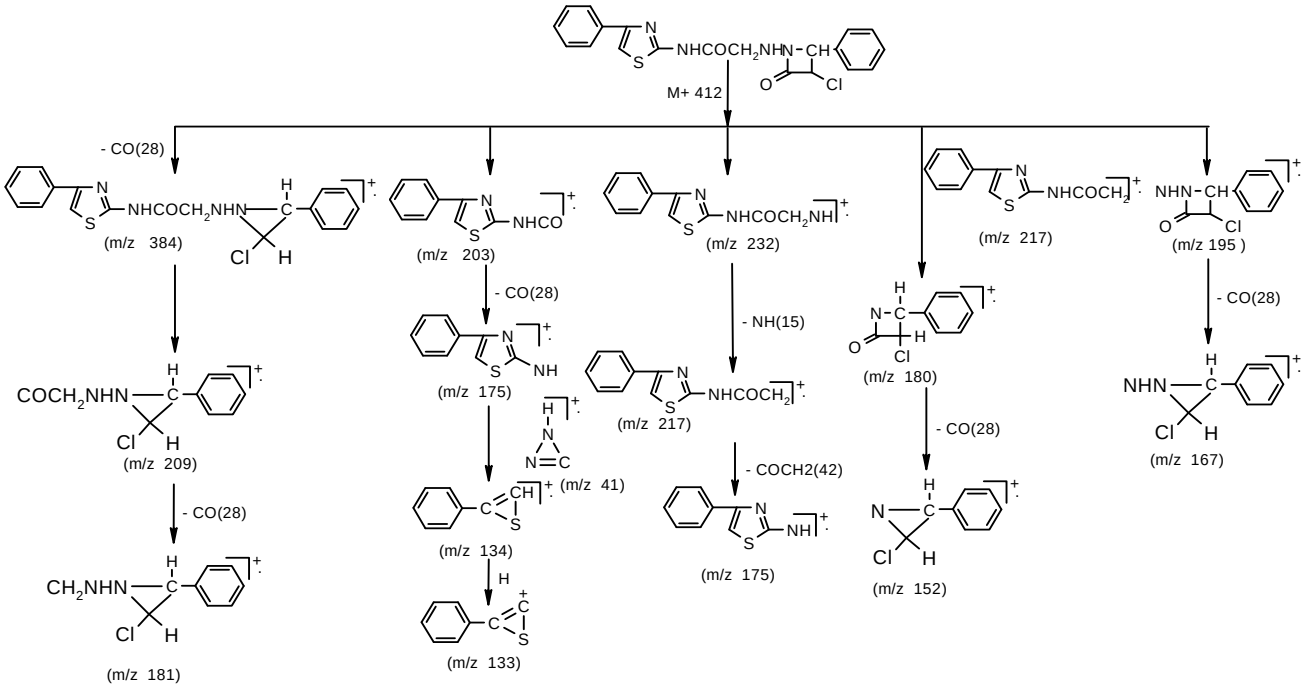


Chart-2 : Mass spectral fragmentation pattern of 2-[2'-(4"-aryl-3"-chloro-2-oxo-azetidine)-acetyl-amino]-4-phenyl-1,3-thiazole, **4a.**

(An, Af, Fo, Tv), **4g** (An, Af, Tv) and bacteria : **4b** (Bs), **4c** (Bs), **4d** (Ec), **4e** (Bs, Kp, Sa), **4f** (Bs, Kp), **4g** (Bs, Sa) respectively.

Acknowledgement

The authors are thankful to SAIF, CDRI, Lucknow for providing spectral and analytical data of the compounds. We are also grateful to Dr. Mrs. Archana Tiwari, Department of Biotechnology, Dr. H. S. Gour University for providing help in carrying out the antimicrobial screening. We are also grateful to Head, Department of Chemistry, for giving the facilities to carryout the work.

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