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A New Synthetic Approach Towards the Synthesis of 2-(3-Aryl-2H-1,4-benzthiazin-2-yl)-3-aryl-2H-1,4-benzothiazines

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A NEW SYNTHETIC APPROACH TOWARDS THE SYNTHESIS OF 2-(3-ARYL-2H-1,4-BENZTHIAZIN-2-YL)-3-ARYL-2H-1,4-BENZOTHIAZINES

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ABSTRACT: Synthesis of 2-(3-Aryl-2H-1,4-benzthiazin-2-yl)-3-aryl-2H-1,4-benzothiazines **(3 a-e)** from 3-aryl-5(4H)-isoxazolones **(1 a-e)** and 2-aminothiophenol **(2).**

5(4H)-Isoxazolone derivatives have been widely used as versatile synthons for the synthesis of variety of heterocycles. Earlier, 2-(3-aryl-2H-1,4-benzthiazin-2-yl)-3-aryl-2H-1,4-benzothiazines[1,2,3,4] as potential psychotropic agents have been prepared from the reaction of 2-amino thiophenol and ω-bromo acetophenone involving multiple steps. In the present communication we report here a simple and elegant method of synthesis of 2-(3-aryl-2H-1,4-benzthiazin-2-yl)-3-aryl-2H-1,4-benzothiazines by making use of isoxazolones as synthons.

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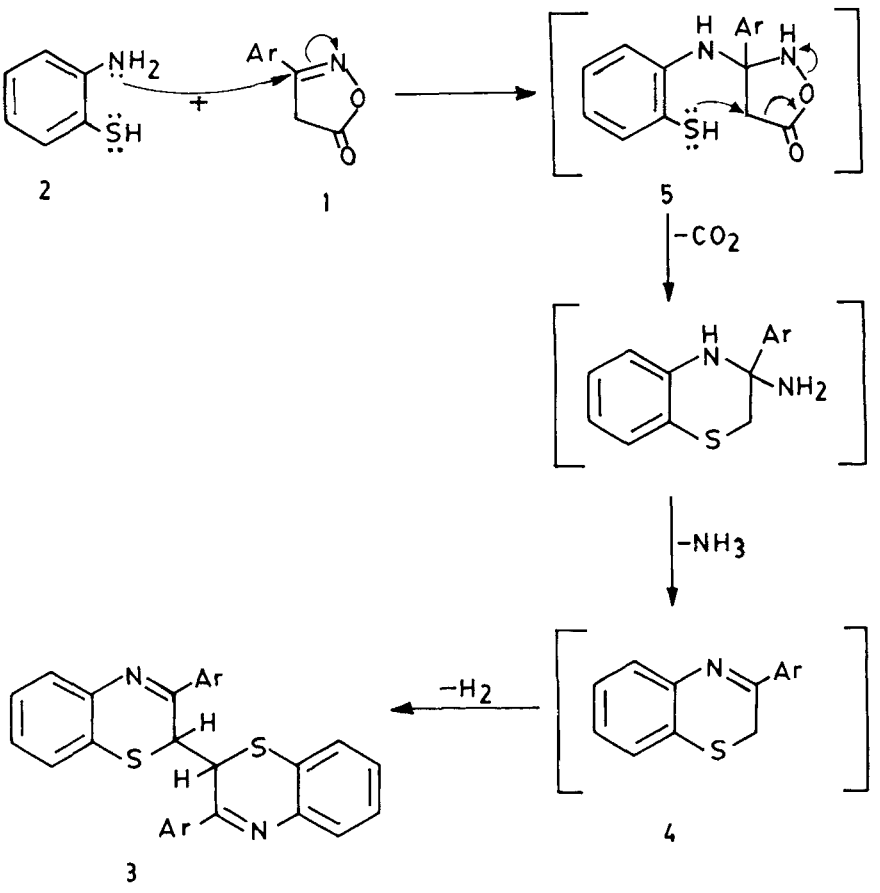
The reaction of 3-phenyl-5(4H)-isoxazolone **(1a)** with 2-aminothiophenol **(2)** in acetic acid at steambath temperature has been carried out for 4 hr. On systematic work up the resulted crystalline product **(3a)** melted at 235°C. The IR spectrum (KBr) of **3a** did not show any peak in the functional group region. ^{1}H-NMR spectrum ($CDCl_3$) exhibited two sets of peaks in 1:9 ratio at δ 4.2 and at δ 6.9-7.7. The molecular ion at m/z 448 (0.1%) in its mass spectrum and elemental analysis are corresponding to molecular formula $C_{28}H_{20}N_2S_2$. The UV absorption maxima (MeOH) for the product are observed at λ 336 nm (4.42), 260 (5.07) and 204 (5.07) corresponding to benzothiazine system. Based on the spectral and analytical data the product **3a** has been assigned 2-(3-phenyl-2H-1,4-benzthiazin-2-yl)-3-phenyl-2H-1,4-benzothiazine structure **(3a)**. The assigned structure was further confirmed by comparison with an authentic sample[1].

The reaction of 2-aminothiophenol **(2)** has been extended to other 3-aryl-5(4H)-isoxazolones **(1 b-e,** Ar=p-methylphenyl, p-methoxyphenyl, p-chlorophenyl and p-nitrophenyl) in acetic acid at steam bath temperature. The reaction followed the same course and in each case the corresponding 2-(3-aryl-2H-1,4-benzthiazin-2-yl)-3-aryl-2H-1,4-benzothiazine **(3 b-e)** was obtained. Their physical data is presented in the table. The substituent at 3-position in isoxazolone has not shown any effect on the course of reaction.

Table : Physical data of 2-(3-aryl-2H-1,4-benzthiazin-2-yl)-3-aryl-2H-1,4-benzothiazine (3 a-e)

Product No.	Ar	m.p.[a] °C	yield %	molecular[b] formula	^{1}H-NMR[c] δ ppm ($CDCl_3/C_5D_5N$)	UVλmax nm[d] (MeOH)	M^+ e
3a	phenyl	235 (234-5)[1]	75	$C_{28}H_{20}N_2S_2$	4.2 (s,1H,S-CH) 6.8-7.7 (m,9H,arom)	204,260,336	448 (0.1 %) 224 (100%)
3b	p-methyl phenyl	246 (245-6)[2]	70	$C_{30}H_{24}N_2S_2$	2.3 (s,3H,$-CH_3$) 4.5 (s,1H,S-CH) 6.9-8 (m,8H,arom)	266,341	476 (0.1%) 238 (100%)
3c	p-methoxy phenyl	223 (219-21)[3]	80	$C_{30}H_{24}N_2O_2S_2$	3.71 (s,3H,$-OCH_3$) 4.4 (s,1H,S-CH) 6.9-7.8 (m,8H,arom)	277,340,360	508 (0.1%) 238 (100%)
3d	p-chloro phenyl	232	68	$C_{28}H_{18}Cl_2N_2S_2$	4.4 (s,1H,S-CH) 6.9-7.6 (m,8H,arom)	258,338	526 (0.1%) 263 (100%)
3e	p-nitro phenyl	248 (245-7)[3]	88	$C_{28}H_{18}N_4O_4S_2$	4.5 (s,1H,S-CH) 6.9-7.9 (m,8H,arom)	254,269,359	538 (0.1%) 269 (100%)

a Uncorrected, measured with sulphuric acid bath.
b Satisfactory Micro Analytical Data obtained; C ± 0.21; H ± 0.12; N ± 0.19
c Recorded on Varian FT-80A and JEOL FX-90Q NMR Spectrometers.
d Recorded on Shimadzu 160 ultraviolet visible spectrophotometer.
e Recorded on VG Micromass 7070H and Finnigan Mat 1020B mass spectromers.



Scheme

The formation of 2-(3-aryl-2H-1,4-benzthiazine-2-yl)-3-aryl-2H-1,4-benzothiazine **(3)** from 3-aryl-5(4H)-isoxazolone **(1)** and 2-aminothiophenol **(2)** can be explained through the intermediacy of 3-aryl-2H-1,4-benzothiazine **(4)**. Nucleophilic addition of 2-aminothiophenol **(2)** across the C-N double bond of 3-aryl-5(4H)-isoxazolone **(1)** leads to addition product, 3-aryl-3-(2-thioanilino)-5(4H)-isoxazolone **(5)**.

The intra molecular nucleophilic attack by sulphhydryl sulphur on the C-4 of **5** with subsequent loss of a molecule of carbondioxide results in 3-amino-3-aryl-1,2,3,4-tetrahydro-1,4-benzothiazine which further loses ammonia molecule to give 3-aryl-2H-1,4-benzothiazine **(4).** The latter being prone to auto oxidative dimerisation in polar solvents[5], undergoes dehydrogenative dimerisation under the reaction conditions to result in the formation of **3.** This reaction constitutes a new synthetic strategy which can serve as a useful procedure for the synthesis of bis benzothiazines.

EXPERIMENTAL

General procedure for 2-(3-aryl-2H-1,4-benzthiazin-2-yl)-3-aryl-2H-1,4-benzothiazine (3 a-e)

An equimolar reaction mixture of 3-aryl-5(4H)-isoxazolone (**1 a-e,** 10 mmol) and 2-aminothiophenol (**2,** 10 mmol) dissolved in acetic acid (10 ml) was heated at steam bath temperature for ∿2 to ∿4 hr. The crystalline product 2-(3-aryl-2H-1,4-benzthiazin-2-yl)-3-aryl-2H-1,4-benzothiazine **(3 a-e)** that separated was filtered and recrystallised from suitable solvent.

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