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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-BENZOTHAZINES

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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. ¹H-NMR spectrum (CDCl₃) 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 C₂₈H₂₀N₂S₂. 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 sample¹.

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 formula ^b | ¹ H-NMR ^c δ ppm (CDCl ₃ /C ₂ D ₅ N) | UVλ _{max} nm ^d (MeOH) | η ^e |
|-------------|---------------------|------------------------------|------------|--|--|--|---------------------------|
| 3a | phenyl | 235 (234-5) ¹ | 75 | C ₂₈ H ₁₈ N ₂ S 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 ₂₀ N ₂ S 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 ₁₈ N ₂ O ₂ S 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 ₁₆ ClN ₂ S 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 ₁₆ N ₂ O ₄ S ₂ | 4.5 (s, 1H, S-CH) 6.9-7.9 (m, 8H, arom) | 254, 269, 359 | 538 (0.1 %) 269 (100%) |

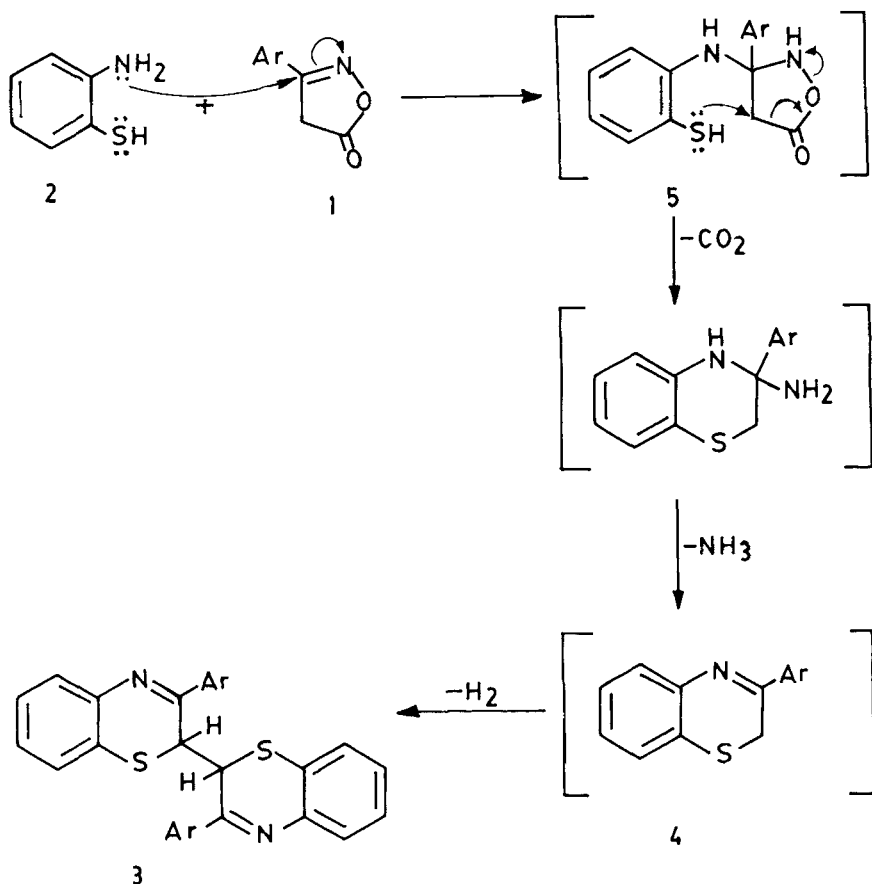
^a Uncorrected, measured with sulphuric acid bath.

^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 spectrometers.



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 solvents⁵, 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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