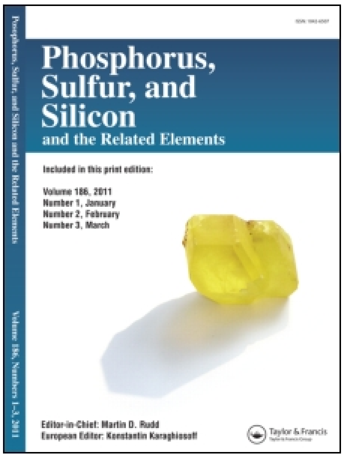

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REGIOSELECTIVE CYCLIZATION OF S-ACRYLIC ACID DERIVATIVE OF 1,2,4-BENZOTRIAZINE TO 10H-[1,3]THIAZIN0 [2,3-C][1,2,4] BENZOTRIAZIN-4-ONE

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REGIOSELECTIVE CYCLIZATION OF S-ACRYLIC ACID DERIVATIVE OF 1,2,4-BENZOTRIAZINE TO 10H-[1,3]THIAZINO [2,3-C][1,2,4] BENZOTRIAZIN-4-ONE

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3-Mercapto-1,2,4-benzotriazine was condensed with propiolic acid to afford the S-acrylic acid derivative **2**. The latter was regioselectively cyclized to 10H-[1,3] thiazino [2,3-c][1,2,4]benzotriazin-4-one **3**.

Keywords: Benzotriazine; propiolic acid; acrylic acid derivatives; regioselective cyclization

In a continuation of our interest in the synthesis of bicyclic and tricyclic heterocycles[1], we report here the utility of S-Acrylic acid derivative of 1,2,4-benzo-triazine **2** in the synthesis of a novel heterocyclic system 10H-[1,3] thiazin[2,3-c] [1,2,4] benzotriazin-4-one **3**.

Our earlier studies which make 1,2,4-benzotriazine **1** available in quantity[1b] and our continuing interest in synthetic application of acetylenic esters[2] has prompted our investigation of the cyclocondensation of **1** with propiolic acid.

Michael type addition of equimolar quantities of **1** with propiolic acid in refluxing ethanol afforded the s-substituted acrylic acid **2** in a good yield.

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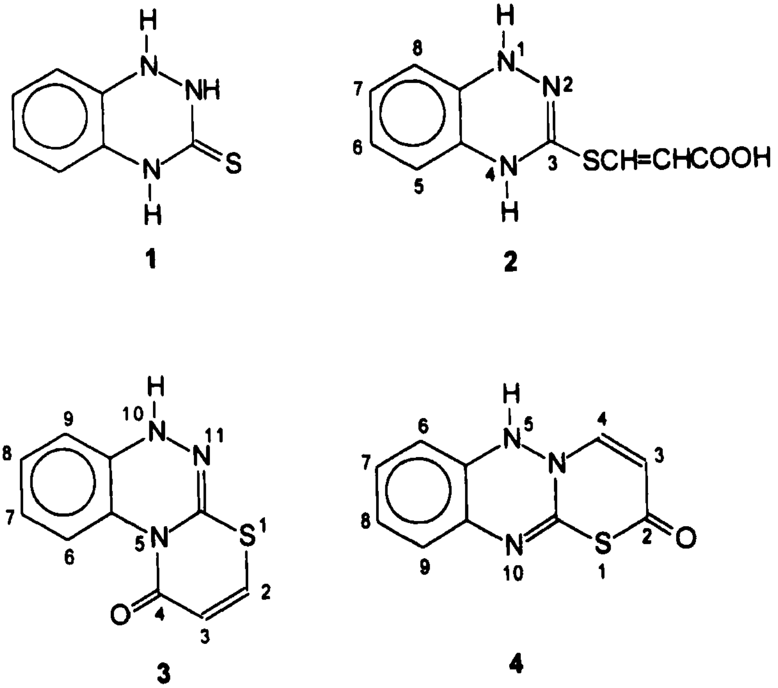
^{1}HNMR spectrum of **2** showed a broad signal which is exchangeable with D_2O at δ12.9 and two doublets around δ6 and 8.3 as well as aromatic protons. The acrylic adduct **2** was of *cis* configuration reflecting a *trans* addition to the acetylenic linkage. The two olefenic protons showed coupling constant of 10 Hz as reported for similar *cis* adducts methylpropiolate and thioamides[3]. It has been reported that in such additions, the formation of *cis* adducts (J=10 Hz) predominate over the formation of *trans* adducts (J=15.5 Hz)[3].

In spite of having *cis* configuration, which appear to favor the anticipated cyclization pathway, cyclization was not achieved under a variety of conditions namely refluxing in high boiling point solvents, sodium alkoxide and sodium hydroxide.

For further reaction, compound **2** was refluxed in $POCl_3$ to afford a single crystalline compound. The spectral data showed that a cyclization has occurred to afford a tricyclic compound **3** or **4** in good yield.



SCHEME 1

In Papers published back-to-back, our research group reported the utility of inexpensive sulfuric acid for regioselective cyclization of propynylmercapto heterocycles to condensed thiazoles[4]. Compound **2** was treated with conc. H_2SO_4 at 50°C. Subsequent aqueous work up afforded a single (tlc) compound which was identical with the compound obtained from treatment of **2** with $POCl_3$. It's ^{1}HNMR showed two doublets for olefinic protons at δ6.85 and 8.35 with J=10 Hz, indicating that cyclization had occurred to give the tricyclic compound.

Fusion of the thiazine and 1,2,4-benzotriazine nuclei can be affected in two different ways as represented by **3** and **4**. Structure **3** was chosen as, the product of regioselective cyclisation of **2**. In ^{1}HNMR of compound **2** each two aromatic protons resonate in close proximately to each other, whereas in the cyclysed product, **3**, one of them (C6) is shifted downfield relative to the other aromatic protons due to the anisotropy of the carbonyl group. This phenomenon has been noticed previously[5].

In conclusion, $POCl_3$ and H_2SO_4 can smoothly catalyse the regioselective cyclisation of S-acrylic derivative of 1,2,4-benzotriazine to the novel heterocyclic system 10H-[1,3]thiazino[2,3-c][1,2,4]benzotriazin-4-one. Sulfuric acid has an advantage over $POCl_3$ due to its price and availability.

EXPERIMENTAL SECTION

Mps were determined on a Reichert apparatus and are uncorrected. IR spectra were recorded on a Schimatzu spectrometer as KBr disc. ^{1}HNMR spectra were recorded on a Bruker (100 MHz) instrument. Mass spectra were obtained from Varian CH-7 at 70 eV.

S-Acrylic acid derivative of 1,2,4-benzotriazine 2

3-Mercapto-1,2,4-benzotriazine **1** (1.65 g, 0.01 mol) and propiolic acid (0.7 g, 0.01 mol) were dissolved in ethanol (50 mL). The reaction mixture was refluxed for 18 hrs. The progress of the reaction was monitored by TLC. The solvent was evaporated under reduced pressure. The crude was washed with water (10 mL) and crystallized from ethanol to afford **2**. Yield: 1.63 g (69%); mp: 190–91 °C; ^{1}HNMR δ(d_6-DMSO) 6.25(d, J=10 Hz, 1H, =CH), 7.2 (m, 2H, Ar), 7.5 (m, 2H, Ar), 8.3 (d, J=10 Hz, 1H, =CH), 12.95 (s, br, exchangeable with D_2O, 1H, -COOH). IR, (KBr disc), 3450, 1700, 1600, 1410, 1220, 760 cm-1, MS, m/z, M+, 235(3), 216(14), 215(16), 205(18), 204(52), 198(100), 184(27). 171(35), 164(60), 132(45), 104(66).

10H-[1,3]Thiazino[2,3-c][1,2,4] benzotriazin-4-one 3

Compound **2** (1.175 g, 0.005 mol) and $POCl_3$ (5 mL) were refluxed for 45 min. The excess of $POCl_3$ was distilled off at reduced pressure and to the crude product crushed ice was added. The precipitated solid was washed with water and crystallized from ethanol to give the title compound. Yield: 0.805 g (74%; mp: 149–50°C; ^{1}HNMR δ(d_6-DMSO) 6.85(d, J=10 Hz, 1H, =CH), 7.45 (m, 2H, Ar), 7.75 (m, 1H, Ar), 8.3 (d, J=10 Hz, 1H, =CH), 8.5 (m, 1H, Ar). IR, (KBr disc), 3100, 1700, 1600, 1590, 1480, 1450, 1380, 1150 cm^{-1}, MS, m/z, M^+, 217(2), 215(51), 199(57), 198(70). 197(100), 177(85), 163(45), 131(68), 130(31), 93(17), 88(46).

Cyclization of 2 to 3 using Conc. H_2SO_4

Compound **2** (1.175 g, 0.005 mol) was dissolved in conc. H_2SO_4 (10 mL). The reaction mixture was kept at 50°C for 2 hrs. To this mixture crushed ice was added and the solution was neutralized by NaOH. The precipitated solid was washed with water and crystallized from EtOH to afford **3**. Yield: 0.717 g (66%), mp: 148–50°C.

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