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Sulfuric Acid: A Mild Catalyst for the Regioselective Synthesis of 2-Substituted [1,2,4]Triazolo[5,1-*b*][1,3]thiazin-7-ones

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Summary. A facile and regioselective synthesis of 2-substituted [1,2,4]triazolo[5,1-*b*][1,3]thiazin-7-ones by action of sulfuric acid on (4*H*-[1,2,4]triazol-3-ylsulfanyl)-acrylic acids is described.

Keywords. Sulfuric acid; Triazolothiazine; Regioselective cyclization.

Introduction

[1,2,4]Triazolo[5,1-*b*][1,3]thiazin-7-ones (**4**) have been first prepared by *Peter et al.* [1] by cyclization of 1,2,4-triazole-3-thiols (**1**) with diethyl ethoxy-methylenemalonate in fair to good yields. In the same year, *Heindel et al.* [2] have synthesized this heterocyclic system by condensation of 3-mercapto-1,2,4-triazole-4-amines (**2**) with methyl propionate, hydrolysis of the resulting S-acrylic esters to the corresponding S-acrylic acids (**3**), and subsequent cyclization to **4** or **5** [2]. The cyclization of **3** to **4** or **5** using thionyl chloride has also been reported as an independent synthesis [2].

Here we report a simple and efficient synthesis of **3** and the regioselective cyclization of the latter to give **4** in good to high yields.

Results and Discussion

Earlier studies which made triazoles **1** available in large quantities [3] and our continuing interest in the synthetic application of acetylenenic esters [4] prompted us to investigate the condensation of **1** with propiolic acid. A *Michael*-type addition of equimolar quantites of **1a–c** and propiolic acid in refluxing anhydrous methanol afforded 1:1 adducts identified as the S-substituted acrylic acids **3a–c** in good yields. ^{1}H NMR spectra showed a broad, D_2O exchangeable signal at about 14 ppm and, in addition, two doublets at *ca.* 6 and 8 ppm, respectively.

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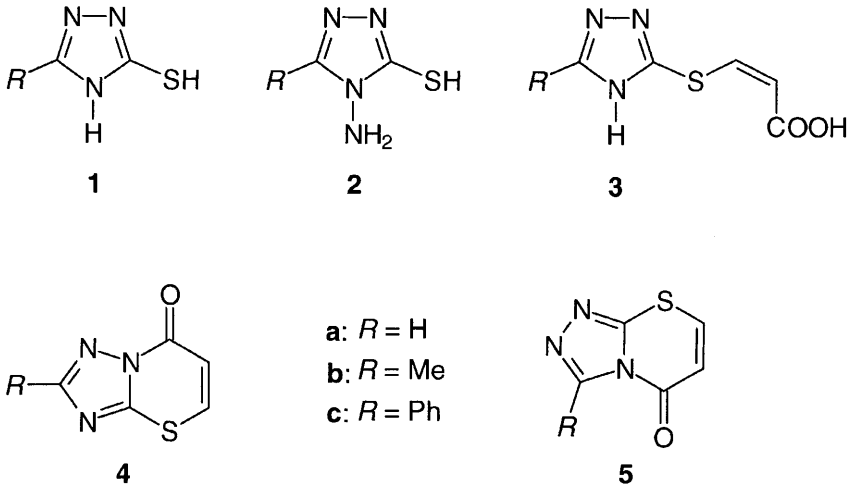

Scheme 1

The adducts **3a–c** exhibit (*Z*)-configuration, reflecting a *trans* addition of the SH group to the acetylenic bond. The two olefinic protons show coupling constant of 10 Hz as has been reported for similar (*Z*)-configured adducts of methylpropiolate and thioamides [5].

It has been reported that formation of (*Z*)-configured adducts ($J = 10.0$ Hz) predominates over that of the (*E*)-configured counterparts ($J = 15.5$ Hz) in such additions [5]. In spite of the (*Z*)-configuration, which might favour a cyclization pathway, cyclization was not observed under a variety of reaction conditions (refluxing in solvents of high boiling point and using sodium alkoxide or sodium hydroxide as catalyst). For the cyclization of **3a** *via* its acid chloride, phosphorus oxychloride was used; **4a** was obtained in moderate yield (53%).

In a recent publication [6] we have demonstrated the utility of sulfuric acid for the resioselective cyclization of propynylmercapto heterocycles to condensed thiazoles. Thus, **3a** was treated with conc. H_2SO_4 at 50°C. Subsequent aqueous work-up afforded a single compound (TLC). Its ^{1}H NMR spectra showed signals at 7.0 (d, $J = 10$Hz, 1H), 8.4 (s, 1H), and 8.6 (d, $J = 10$Hz, 1H) ppm which confirmed a cyclized product. Fusion of the triazole and the thiazine moieties could be affected in two different ways as represented by **4** and **5**. Two further S-acrylic acid derivatives (**3b**,**c**) were cyclized in order to obtain more spectroscopic information and to establish the generality of the method. The data of the corresponding products were in accordance with those of the products obtained from **3a**. To distinguish between structures **4** and **5**, one should take into account that cyclization of the acrylic acid side chain to the ring nitrogen adjacent to the substituent at C-5 of the triazolo ring would yield a carbonyl group in the *peri* position to that attachment; in the case of a methyl group at this location, one would expect a considerable anisotropic effect [2].

The ^{1}H NMR spectra of **3b** and its cyclization product show the ring methyl signal at $\delta = 2.65$ and 2.75 ppm, indicating almost no downfield shift. Thus, the cyclization product is assigned structure **4b**, and, accordingly, **4a** and **4c** are assigned to the cyclization products from **3a** and **3c**. In the case of 2,3-dimethyl-5*H*-

imidazolo[2,1-*b*][1,3]thiazin-5-one, the methyl group signal has been found at *ca.* 2.10 ppm [2].

In conclusion, sulfuric acid has been shown to smoothly catalyze the cyclization of S-acrylic acid derivatives of triazole thiols. The present method to obtain condensed 1,3-thiazines is superior to others which show drawbacks originating from an indirect route [2], low yield [1], low regioselectivity [7], and toxic reagents such as $SOCl_2$ [2].

Experimental

[1,2,4]Triazole-3-thioles (**1**) were prepared according to a known procedure [1]. Unless otherwise stated, melting points were determined on a Reichert apparatus and are uncorrected. IR spectra were recorded on a Shimatsu spectrometer using KBr discs, ^{1}H NMR spectra on a Bruker instrument at 100 MHz. Mass spectra were obtained on a Varian CH-7 spectrometer at 70 eV.

Preparation of **3a–c** *(general procedure)*

[1,2,4]Triazole-3-thioles (0.01 mol) and 0.01 mol propiolic acid were refluxed in 25 cm^3 CH_3OH for 5 h. The solvent was evaporated to dryness under reduced pressure, and the crude product was crystallized from H_2O to afford **3a–c**.

3-(4H-[1,2,4]triazol-3-ylsulfanyl)-acrylic acid (**3a**; $C_5H_5N_3SO_2$)

Yield: 78%; mp.: 209–210°C; ^{1}H NMR (*DMSO*-d_6, δ, 100 MHz): 6.15 (d, $J = 10$ Hz, 1H, CH), 8.00 (d, $J = 10$ Hz, 1H, CH), 8.6 (s, 1H, CH), 14.3 (s, br, exchangeable with D_2O, 1H, COOH) ppm; IR (KBr disc): $\nu = 3500$, 3110, 1650, 1330, 980 cm^{-1}; MS: $m/z = 171$ (M^+).

5-Methyl-3-(4H-[1,2,4]triazol-3-ylsulfanyl)-acrylic acid (**3b**; $C_6H_7N_3SO_2$)

Yield: 82%; mp.: 215–216°C; ^{1}H NMR (*DMSO*-d_6, δ, 100 MHz): 2.45 (s, 3H, Me), 6.1 (d, $J = 10$ Hz, 1H, CH), 8.00 (d, $J = 10$ Hz, CH), 13.8 (s, br, exchangeable with D_2O, 1H, COOH) ppm; IR (KBr disc): $\nu = 3100$, 1680, 1580, 1420, 1350, 900, 790 cm^{-1}; MS: $m/z = 185$ (M^+).

5-Phenyl-3-(4H-[1,2,4]triazol-3-ylsulfanyl)-acrylic acid (**3c**; $C_{11}H_9N_3SO_2$)

Yield: 81%; mp.: 244–245°C; ^{1}H NMR (*DMSO*-d_6, δ, 100 MHz): 6.2 (d, $J = 10$ Hz, 1H CH), 7.5 (s, 3H, aromatic), 7.9 (s, 2H, aromatic), 8.1 (d, $J = 10$ Hz, 1H, CH), 14.7 (s, br, exchangeable with D_2O, 1H, COOH) ppm; IR (KBr disc): $\nu = 3550$, 3110, 1680, 1590, 1320, 1210, 790 cm^{-1}; MS: $m/z = 247$ (M^+).

Preparation of **4a–c** *(general procedure)*

Compounds **3a–c** (0.005 mol) were dissolved in 5 cm^3 conc. H_2SO_4, and the reaction mixture was stirred at 50°C for 2 h. After addition of crushed ice, solution was neutralized with NaOH. The precipitated solid was filtered off, washed with 5 cm^3 H_2O, and crystallized from H_2O to afford **4a–c**.

[1,2,4]Triazolo[5,1-b][1,3]thiazin-7-one (**4a**; $C_4H_3N_3SO$)

Yield: 68%; mp.: 230–232°C; ^{1}H NMR (*DMSO*-d_6, δ, 100 MHz): 7.0 (d, $J = 10$ Hz, 1H, CH), 8.4 (d, $J = 10$ Hz, 1H, CH), 8.65 (s, 1H, CH) ppm; IR (KBr disc): $\nu = 3450$, 3010, 1700, 1500, 1280, 810 cm^{-1}; MS: $m/z = 153$ (M^+).

2-Methyl-[1,2,4]triazolo[5,1-b][1,3]thiazin-7-one (**4b**; $C_5H_5N_3SO$)

Yield: 73%; mp.: 196–197°C (Ref. [2]: 196–197°C); ^{1}H NMR (*DMSO*-d_6, δ, 100 MHz): 2.8 (s, 3H, Me), 6.7 (d, $J = 10$ Hz, 1H, CH), 8.3 (d, $J = 10$ Hz, 1H, CH) ppm; IR (KBr disc): $\nu = 3400$, 3050, 1680, 1450, 1000, 1210, 810 cm^{-1}; MS: $m/z = 167$ (M^+).

2-Phenyl-[1,2,4]triazolo[5,1-b][1,3]thiazin-7-one (**4c**; $C_{10}H_7N_3SO$)

Yield: 80%; mp.: 264–265°C; ^{1}H NMR (*DMSO*-d_6, δ, 100 MHz): 7.0 (d, $J = 10$ Hz, 1H, CH), 7.6 (m, 3H, aromatic), 8.3 (m, 2H, aromatic), 8.4 (d, $J = 10$ Hz, 1H, CH) ppm; IR (KBr disc): $\nu = 3550$, 3110, 1680, 1590, 1320, 1210, 790 cm^{-1}; MS: $m/z = 247$ (M^+).

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