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Regioselective Annelation of 3-(Prop-2-ynylsulfanyl)-1,2,4-benzotriazine to Thiazolo[2,3-*c*][1,2,4]benzotriazine

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Summary. Thiosemicarbazide reacted with 1,2-diaminobenzene to give 1,2-dihydro-3-thioxo-1,2,4-benzotriazine (**1**) in fairly good yield in a solvent free reaction under microwave irradiation. **1** was condensed with prop-2-ynyl bromide in the presence of sodium methoxide to afford the corresponding 3-(prop-2-ynylsulfanyl)-1,2,4-benzotriazine (**5**). Transformation of **5** to 3-methylidene-2,3-dihydro-9*H*-thiazolo[2,3-*c*][1,2,4]benzotriazine (**6**) was performed in the presence of a palladium salt.

Keywords. Regioselectivity; Annelation; Thiazolo benzotriazine; Microwave irradiation.

Regioselektive Anellierung von 3-(prop-2-inylsulfanyl)-1,2,4-benzotriazin zu Thiazolo[2,3-*c*][1,2,4]benzotriazin

Zusammenfassung. Thiosemicarbazid reagierte mit 1,2-Diaminobenzol ohne Lösungsmittel und unter Bestrahlung mit Mikrowellen in guter Ausbeute zu 1,2-Dihydro-3-thioxo-1,2,4-benzotriazin (**1**), welches in Gegenwart von Natriummethoxid mit Prop-2-inylbromid zum entsprechenden 3-(Prop-2-inylsulfanyl)-1,2,4-benzotriazin (**5**) kondensiert wurde. Die Umsetzung von **5** zu Methyliden-2,3-dihydro-9*H*-thiazolo[2,3-*c*] [1,2,4]benzotriazin (**6**) gelang unter Palladiumkatalyse.

Introduction

Many efforts have been devoted to the preparation of thiazolo-1,2,4-triazines [1–5] and selenazolo-1,2,4-triazines [6–7] using catalyzed intramolecular functionalization of an acetylenic moiety. However, the related thiazolo-1,2,4-benzotriazines have been largely overlooked. A literature survey disclosed only one reference concerned with the synthesis of thiazolo-1,2,4-benzotriazines [8]. *Pujari* and his co-workers [8] correctly reported that 1,2-dihydro-3-thioxo-1,2,4-benzotriazine (**1**) yields ketone **2** upon condensation with α-halogeno ketones. Treatment of **2** with polyphosphoric acid includes a cyclization leading to a single compound (TLC) to which structure **3** has been assigned by analogy reasons. However, cyclization of **2** can afford regioisomer **4** too. Spectroscopic data were not of much help in deciding in favour of either angular product **3** or linear product **4**.

In continuation of our earlier studies on the orientation of cyclization in unsymmetrical triazines with bifunctional groups [2–7] we now wish to report on

the reaction of **1** with prop-2-ynyl bromide. It has been found that condensation of thiosemicarbazide with 1,2-diaminobenzene yielded 46% of **1** in 5 h under conventional heating [8]. Microwave irradiation has recently found application in organic synthesis due to its ability to reduce reaction times dramatically [9]. Dry media techniques employing microwave heating have attracted much attention [10, 11] since there is no need to use either sealed tubes or closed and transparent teflon vessels. We found that the condensation of thiosemicarbazide with 1,2-diaminobenzene without any solvent under microwave irradiation results in the rapid formation of **1** in fairly good yield.

Results and Discussion

Compound **1** was condensed with prop-2-ynyl bromide in the presence of sodium methoxide at ambient temperature to obtain the corresponding 3-(prop-2-ynylsulfanyl)-1,2,4-benzotriazine **5**. In the ^{1}H NMR spectrum of this compound, the methylene protons appear as a doublet and the acetylenic proton as a triplet due to long range coupling.

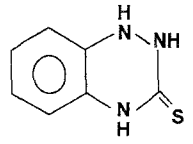
Pd catalyzed cyclization enjoys widespread application in organic synthesis [12]. We have recently described the use of Pd salts for the implementation of sequential carbomethylation anion capture [13–15] and the catalyzed intramolecular cyclization and functionalization of acetylenes [3, 5, 7, 16]. Armed with these experiences, compound **5** was refluxed with a catalytic amount of $Pd[Cl_2(PhCN)_2]$ in a mixture of acetonitrile and methanol (1:1) for 4 h. After evaporation of the solvent the crude material was subjected directly to column chromatography to obtain a crystalline compound as the major product.

Analytical and spectroscopic data suggested a direct nucleophilic addition of amide to acetylene to afford either **6** or **7**. The mass spectrum of the cyclized compound showed the same parent peak as the starting material. The methylidene thiazoline structure of **6** or **7** was indicated by the presence of endocyclic ($\delta = 4.6$ ppm) and exocyclic ($\delta = 4.9$ ppm, $J = 1.8$ Hz; $\delta = 5.42$ ppm, $J = 1.8$ Hz) methylene protons in the ^{1}H NMR spectrum. The large difference in the ^{1}H chemical shifts of the exomethylene protons may be due to the anisotropy of the benzene ring, and the deshielded resonance was assigned to the methylene proton *syn* to the aromatic moiety. Moreover, in structure **5** each two aromatic protons resonate in close proximity to each other, whereas in the cyclized product H_a is shifted downfield relative to the other aromatic protons, thus confirming structure **6**.

When **6** was refluxed in NaOMe/MeOH, a single compound was isolated and identified as 9*H*-3-methylthiazolo[2,3-*c*]triazine (**3**). This process of aromatization has been noticed previously [3, 7]. Orientation of the selective cyclization of **5** to either **6** or **7** was also ascertained by an NOE experiment performed with **3** indicating spatial proximity between the methyl group and H_a (benzene ring) as well as the methyl group and the CH group of the thiazole ring.

When **5** was refluxed in sodium methoxide in MeOH for 4 h a solid was isolated which was identified as **3**. The same result was obtained when **5** was refluxed in triethylamine and methanol.

Whereas a wealth of methods exist for the synthesis of thiazolo-1,2,4-triazines from the corresponding prop-2-ynylsulfanyl derivative using base [1, 2] and Pd salt [1, 3, 5, 7]. The simple transformation of prop-2-ynylsulfanyl-1,2,4-triazines to the corresponding thiazolotriazines by acid catalysis has not been reported. When **5** was treated with conc. H_2SO_4 at 50°C, **3** was obtained in high yield after aqueous workup. The same result was obtained when **5** was treated with mercury(II) acetate in glacial acetic acid.



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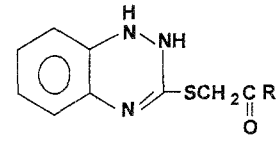

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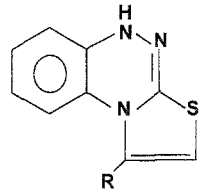

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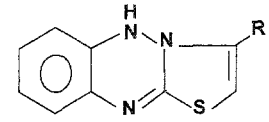

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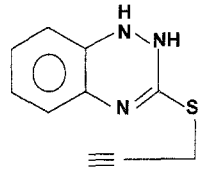

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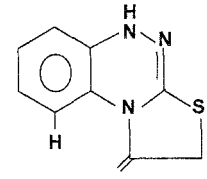

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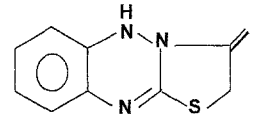

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Experimental

Melting points (uncorrected) were obtained on a Büchi 530. ^{1}H NMR spectra were recorded on a Bruker A 80 spectrometer in *DMSO*-d_6 serving as solvent and internal standard. IR spectra were recorded on a Perkin-Elmer model 883 (KBr discs), and mass spectra were obtained on a Finnigan-Mat model 8430 and a Varian-Mat CH-7 instrument at 70 eV.

1,2-Dihydro-3-thioxo-1,2,4-benzotriazine (**1**)

A mixture of 1,2-diaminobenzene (0.648 g, 0.006 mol) and thiosemicarbazide (0.546 g, 0.006 mol) contained in an *Erlenmeyer* flask (50 ml) was placed in a microwave oven (Westinghouse) and irradiated for 5–6 min with a power of 490 W. The reaction mixture was allowed to cool to room temperature. The crude product was crystallized from MeOH to afford **1**.

Yield: 0.693 g (70%), Ref. [8]: 48%; m.p.: 290–291°C, Ref. [8]: 290°C; IR: ν = 3050–3060 (NH broad), 1216 (C = S str)cm^{-1}; ^{1}H NMR: δ = 7.1–7.6 (m, 4H, C_6H_4) ppm, NH protons not observed; MS: m/z% 165 (M^+, 12), 164 (62), 76 (100).

3-(Prop-2-ynylsulfanyl)-1,2,4-benzotriazine (**5**)

Sodium methoxide (0.5 g, 0.092 mol) was dissolved in MeOH (50 ml). To this solution, compound **1** (0.82 g, 0.05 mol) was added. Under nitrogen, prop-2-ynl bromide (0.06 g, 0.0504 mol) was added dropwise at room temperature. The reaction mixture was stirred at ambient temperature for 4 h. The solvent was evaporated, and the solid was washed with water thoroughly and recrystallized from MeOH to afford **5**.

Yield: 0.908 g (90%); m.p.: 143–145°C; IR: ν = 3285 (≡ CH), 1679, 1621, 1508, 1440, 927, 826, 743 cm^{-1}; ^{1}H NMR: δ = 3.1 (t, J = 2.60 Hz, 1H, C ≡ CH), 4.1 (d, J = 2.60 Hz 2H, CH_2), 7.01–7.25 (m, 2H, C_6H_4), 7.31–7.58 (m, 2H, C_6H_4) ppm, NH protons not observed; MS: m/z(%) 203 (M^+,8), 188 (100), 155 (9), 143 (18), 102 (10).

9H-3-Methylidene-2,3-dihydrothiazolo[2,3-c][1,2,4]benzotriazine (**6**)

Compound **5** (1 g, 0.005 mol) was refluxed for 4 h in a mixture of 50 ml CH_3CN:MeOH = 1:1 containing 0.1 g [$PdCl_2$(*ph*$CN)_2$]. After evaporation of the solvent, the crude product was subjected directly to column chromatography. Elution with hexane-ethyl acetate (7:5) afforded **6** as the major product.

Yield: 0.6 g (60%); m.p.: 97–98°C; IR: ν = 3419, 3064, 2932, 1646, 1612 (C = C), 1375, 922 cm^{-1}; ^{1}H NMR: δ = 4.65(S, 2H, CH_2), 4.90 (d, J = 1.8Hz, 1H, exomethylene), 5.42 (d, J = 1.8 Hz, 1H, exomethylene), 5.42 (d, J = 1.8 Hz, 1H, exomethylene), 7.13–7.25 (m, 2H, C_6H_4), 7.48 (m, 1H, C_6H_4), 7.86 (m, 1H, C_6H_4) ppm, NH proton not observed; MS: m/z = 203 (M^+).

9H-3-Methylthiazolo[2,3-c][1,2,4]benzotriazine (**3**, R = Me)

Compound **6** (0.3 g, 0.014 mol) was refluxed in a solution of NaOMe (0.08 g, 0.016 mol) in MeOH (50 ml) for 20 min. The solvent was evaporated and the obtained solid was washed with water and crystallized from MeOH to afford **3**.

Yield: 0.27 g (90%); m.p.: 130 - 132°C; IR: ν = 3419, 2950, 1931, 1625, 1308, 809, 735 cm^{-1}; ^{1}H NMR: δ = 2.35 (s, 3H, Me), 6.83 (s, 1H, CH of thiazolo ring), 7.10–7.39 (m, 2H, C_6H_4), 7.58 cm^{-1}; 7.76 (m, 1H, C_6H_4), 7.86–8.03 (m, 1H, *ortho* proton, C_6H_4)ppm, NH proton not observed; the sample was degased prior to the NOE experiment; MS: m/z(%) = 203 (5), 187 (100), 155 (42), 149 (45), 122 (50), 41 (35).

Base catalyzed transformation of **5** *to* (**3** R = Me)

Compound **5** (0.5 g, 0.024 mol) was refluxed in a solution of NaOMe (1 g, 0.048 mol) in MeOH (50 ml) for 5 h. The solvent was evaporated, and the obtained solid was washed thoroughly with water and recrystallized from MeOH to afford **3**, (0.44 g (88%), m.p.: 131–132°C).

Acid catalyzed transformation of **5** *to* **3** (R =Me)

Compound **5** (0.5 g, 0.024 mol) was treated with conc.H_2SO_4 (20 ml) at 50°C for 1 h. This solution was poured onto crushed ice, and sodium hydroxide solution was added till *pH* 8 was reached. The obtained solid was filtered off, washed with water, and crystallized from MeOH to afford **3** (0.25 g (50%), m.p.: 129–130°C).

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