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HALOCYCLIZATION OF 3-ALLYLTHIO-5H-[1,2,4]TRIAZINO[5,6-*b*]INDOLE

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The synthesis of 3-allylthio-5H-[1,2,4]triazino[5,6-b]indole has been carried out by the reaction of 3-mercapto-5H-[1,2,4]triazino[5,6-b]indole with allyl bromide in the NaOH–H_2O–DMSO system and in a one-pot synthesis from isatin-β-thiosemicarbazide. Halocyclization of allylthio-5H-[1,2,4]-triazino[5,6-b]indole synthesized the 3-halomethyl-3,10-dihydro-2H-[1,3]thiazolo[3',2':2,3][1,2,4]-triazino[5,6-b]indolium halides.

Keywords: 3-allylthio-5H-[1,2,4]triazino[5,6-*b*]indole, 3-halomethyl-3,10-dihydro-2H-[1,3]thiazolo-[3',2':2,3][1,2,4]triazino[5,6-*b*]indolium halides, phase-transfer catalysis, *one-pot* synthesis.

Derivatives of [1,2,4]triazino[5,6-*b*]indoles possess high biological activity and a wide spectrum of antifungal [1, 2] and antihypoxic activity [3], they are used in prophylaxis and treatment of an extensive index of viruses and have for a long time attracted attention in connection with the search for new antimicrobial and anticancer agents [4].

In the literature [3, 5] there is information on the synthesis of 3-allylthio-5H-[1,2,4]triazino[5,6-*b*]indole (**1**, yield 45%) by the alkylation of 3-mercapto-5H-[1,2,4]triazino[5,6-*b*]indole (**2**) with an allyl halide in aqueous NaOH solution. However only the UV spectral data were cited in these papers.

In the present work we have synthesized compound **1** in high yield (87%) by the reaction of compound **2** with allyl bromide in a mixture of NaOH–H_2O–DMSO. Compound **1** was also obtained by a *one-pot* synthesis from isatin-β-thiosemicarbazone (**3**) in water without isolating compound **2**. The essence of this method is that compound **3** is boiled in aqueous alkali (cyclization with formation of compound **2**) and then allyl bromide and triethylbenzylammonium chloride (TEBAC) as phase-transfer catalyst are added to the reaction mixture.

We have found that 3-bromomethyl-3,10-dihydro-2H-[1,3]thiazolo[3',2':2,3][1,2,4]triazino[5,6-*b*]-indolium bromide (**4a**) was formed on reaction of compound **1** with bromine in DMF.

3-Iodomethyl-3,10-dihydro-2H-[1,3]thiazolo[3',2':2,3][1,2,4]triazino[5,6-*b*]indolium triiodide was formed by the interaction of compound **1** with iodine in chloroform, and was converted to the monoiodide **4b** by treatment with NaI in acetone. Halocyclization of 3-allylthio-5-phenyl-1,2,4-triazine also occurs with formation of the dihydrothiazolo[3,2-*b*][1,2,4]triazinium system [6].

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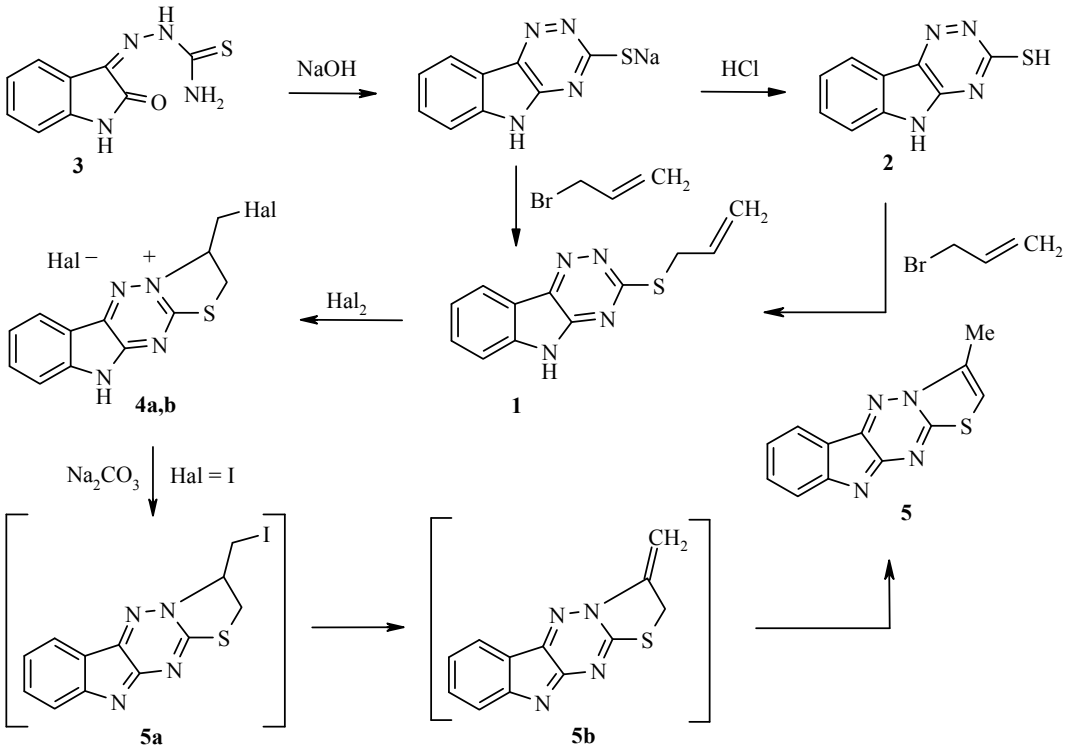

4 a Hal = Br, **b** Hal = I

In the ^{1}H NMR spectra of compounds **4a**,**b**, in contrast to that of compound **1**, the signals of the protons of the SCH_2 group are nonequivalent and form two sets of multiplets in the regions 3.60-3.90 and 4.10-4.40 ppm.

3-Methyl[1,3]thiazolo[3',2':2,3][1,2,4]triazino[5,6-*b*]indole (**5**) was formed on addition of aqueous Na_2CO_3 solution to the iodide **4b**. Evidently the reaction proceeds with the intermediate formation of compounds **5a** and **5b**. We had previously prepared compound **5** from 3-propargylthio-5H-[1,2,4]triazino-[5,6-*b*]indole [7]. The ^{1}H NMR spectra and melting points of compound **5** prepared by the different methods were identical. Mixed melting points showed no depression.

EXPERIMENTAL

^{1}H NMR spectra of DMSO-d_6 solutions with TMS as internal standard were recorded on a Bruker DRX-400 (400 MHz) instrument. Mass spectra were measured on a Hewlett Packard GC/MS-IBM instrument with a HP-5890 gas chromatograph series II, an HP-5972 mass-selective detector, EI ionization, and an ionization energy of 70eV.

3-Allylthio-5H-[1,2,4]triazino[5,6-*b*]indole (1). A. NaOH (0.160 g, 4 mmol) in water (3 ml) and allyl bromide (0.490 g, 4 mmol) were added to a solution of compound **2** (0.810 g, 4 mmol) in DMSO (10 ml) and the mixture was stirred for 2 h. The yellow precipitate was filtered off and dried. Yield 0.844 g (87%); mp 250°C (DMF) (mp 280°C [5]). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 3.97 (2H, d, *J* = 6.81, SCH_2); 5.17 (1H, dd, *J* = 10.0, *J* = 1.7, $=CH_2$); 5.41 (1H, dd, *J* = 1.7, *J* = 17.0, $=CH_2$); 6.05 (1H, m, CH=); 7.43, 7.58, 7.67, 8.31 (4H, m, H Ar). Mass spectrum, *m/z* (I_{rel}, %): 242 $[M]^+$ (17), 227 $[M-5]^+$ (100), 209 $[M-33]^+$ (33), 146 $[M-93]^+$ (83).

B. Isatin-β-thiosemicarbazide (1.700 g, 7.7 mmol) in 0.1 N NaOH (40 ml) was boiled for 3 h, allyl bromide (0.64 ml, 7.7 mmol) and TEBAC (10 mg) were then added and the mixture was stirred at room temperature. The yellow precipitate was filtered off, washed with water, and dried. Yield 0.467 g (25%).

3-Bromomethyl-3,10-dihydro-2H-[1,3]thiazolo[3',2':2,3][1,2,4]triazino[5,6-*b*]indolium Bromide (4a). A solution of bromine (0.052 ml, 1 mmol) in DMF (5 ml) was added to a solution of compound **1** (0.121 g, 0.5 mmol) in DMF (5 ml). After 48 h the yellow precipitate was filtered off. Yield 0.094 g (47%); mp 298°C (dec.). ^{1}H NMR spectrum, δ, ppm: 3.86 (1H, m, SCH_2); 4.20 (2H, m, CH_2Br); 4.29 (1H, m, SCH_2); 5.78 (1H, m, H-3); 7.62, 7.77, 7.92, 8.32 (4H, m, H Ar). Found, %: C 35.61; H 2.51; Br 39.91; N 13.93. $C_{12}H_{10}Br_2N_4S$. Calculated, %: C 35.84; H 2.51; Br 39.74; N 13.93.

3-Iodomethyl-3,10-dihydro-2H-[1,3]thiazolo[3',2':2,3][1,2,4]triazino[5,6-*b*]indolium Iodide (4b). A solution of iodine (0.127g, 0.5 mmol) in chloroform (5 ml) was added to a solution of compound **1** (0.121 g, 0.5 mmol) in chloroform (5 ml). After 48 h the chloroform was evaporated, the residue was dissolved in acetone, and NaI (50 mg) was added. After 24 h the precipitate was filtered off and dried. Yield 0.82 g (33%); mp 168°C (dec.). ^{1}H NMR spectrum, δ, ppm: 3.72 (1H, m, SCH_2); 3.91 (2H, m, CH_2); 4.17 (1H, m, SCH_2); 5,46 (1H, m, H-3); 7.59, 7.75, 7.89, 8.31 (4H, m, H Ar). Found, %: C 29.05; H 2.01; I 51.48; N 11.10. $C_{12}H_{10}I_2N_4S$. Calculated, %: C 29.05; H 2.03; I 51.16; N 11.29.

3-Methyl[1,3]thiazolo[3',2':2,3][1,2,4]triazino[5,6-*b*]indole (5). Na_2CO_3 (20 mg, 0.240 mmol) in water (3 ml) was added to a solution of compound **4b** (0.070 g, 0.14 mmol) in DMF (5 ml). Needle-like crystals were filtered off after 48 h. Yield 0.015 g (50%); mp 139°C (mp 140°C [7]). ^{1}H NMR spectrum, δ, ppm: 2.64 (3H, s, CH_3); 7.47 (1H, s, SCH=); 7.33, 7.69, 8.23 (4H, m, H Ar).

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