Monatshefte für Chemie 121, 281–287 (1990)

Monatshefte für Chemie
Chemical Monthly

Heterocyclic Synthesis with 3-Cyano-2(1*H*)pyridinethione: Synthesis of 3-Oxo-2,3-dihydroisothiazolo[5,4-b]pyridine and Related Compounds [1]

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Summary. 3-Carbethoxy-4,6-diphenyl-2-pyrridine sulfonamide (**5**), can be cyclized to 3-oxo-2,3-dihydro-4,6-diphenylisothiazolo[5,4-b]pyridine-1,1-dioxide (**2**). Oxidation of pyridinethione **6** with Cl_2/H_2O gave the sulfonyl chloride derivative **7**, which can be ammonolyzed to 3-amino-4,6-diphenylisothiazolo[5,4-b]pyridine-1,1-dioxide (**8**), and 3-cyano-4,6-diphenylpyridine-2-sulfonamide (**9**). Hydrolysis of **6** gave 3-carboxamido-2(1*H*)pyridinethione (**12**) which can be oxidized with iodine to 3-oxo-4,6-diphenyl-2,3-dihydroisothiazolo[5,4-b]pyridine (**13**). 3-Methyl-4,6-diphenylisothiazolo[5,4-b]pyridine-1,1-dioxide (**17**) was also prepared from **6**.

Keywords. 2-Amino-4,6-diphenylethyl nicotinate; 3-Cyano-4,6-diphenyl-2-mercaptopyridine.

Heterocyclensynthese mit 3-Cyano-2(1*H*)pyridinthion: Synthese von 3-Oxo-2,3-dihydroisothiazolo-[5,4-b]pyridin und verwandten Verbindungen

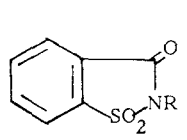
Zusammenfassung. 3-Carbethoxy-4,6-diphenyl-2-pyridinsulfonamid (**5**) kann zu 3-Oxo-2,3-dihydro-4,6-diphenylisothiazolo[5,4-b]pyridin-1,1-dioxid (**2**) cyclisiert werden. Die Oxidation des Pyridinthions **6** mit Cl_2/H_2O ergab das Sulfonylchlorid-Derivat **7**, das mit Ammoniak zu 3-Amino-4,6-diphenylisothiazolo[5,4-b]pyridin-1,1-dioxid (**8**) und 3-Cyano-4,6-diphenylpyridin-2-sulfonamid (**9**) umgesetzt werden kann. Die Hydrolyse von **6** ergab 3-Carboxamido-2(1*H*)pyridinthion (**12**), das mit Jod zu 3-Oxo-4,6-diphenyl-2,3-dihydroisothiazolo[5,4-b]pyridin (**13**) oxidiert wurde. 3-Methyl-4,6-diphenyl-isothiazolo[5,4-b]pyridin-1,1-dioxid (**17**) wurde ebenfalls aus **6** hergestellt.

Introduction

The considerable biological activity of 1,2-benzisothiazole-3(2*H*)-one 1,1-dioxide (**1**) as fungicide, antiviral and antibacterial agent [2] has prompted considerable interest in synthesis and chemistry of these compounds. As a part of a programme directed for developing new compounds for utility as antischitosomal agent we became interested in synthesizing derivatives of **1** in which the benzene ring is replaced by a nitrogen heteroaromatic ring.

Results and Discussion

The precursors 2-amino-4,6-diphenylethyl nicotinate (**3**) and 3-cyano-4,6-diphenyl-2-mercapto pyridine (**6**) were synthesized following the literature procedure [3]. The 2-NH_2 group of **3** can be replaced, thus on treatment with nitrous acid in presence of cold saturated solution of SO_2 in acetic acid containing copper(II)



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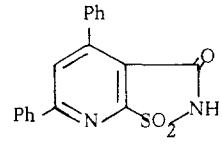

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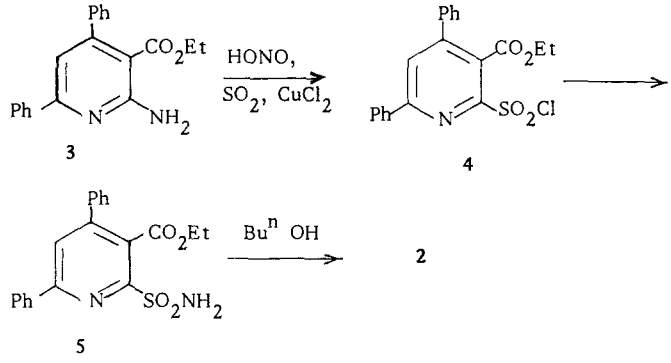
chloride dihydrate [4], it gives the sulfonyl chloride derivative **4**, which on direct ammonolysis with ammonium hydroxide afforded the sulfonamide derivative **5** in 50% yield. The structure of **5** was established based on the IR spectrum which showed absorption bands at 3 400–3 300 cm^{-1} (νNH_2), at 1 700 cm^{-1} ($\nu C=O$ ester), and at 1 320, 1 150 cm^{-1} typical for a SO_2 group. The sulfonamide **5** was cyclized in boiling butanol to give 3-oxo-2,3-dihydro-4,6-diphenylisothiazolo[5,4-b]pyridine-1,1-dioxide (**2**). The ^1H NMR of **2** showed the presence of an 11 H multiplet centered at δ 8.00–7.66 due to the aromatic protons, and a broad weak singlet at δ 11.00 due to the NH proton.

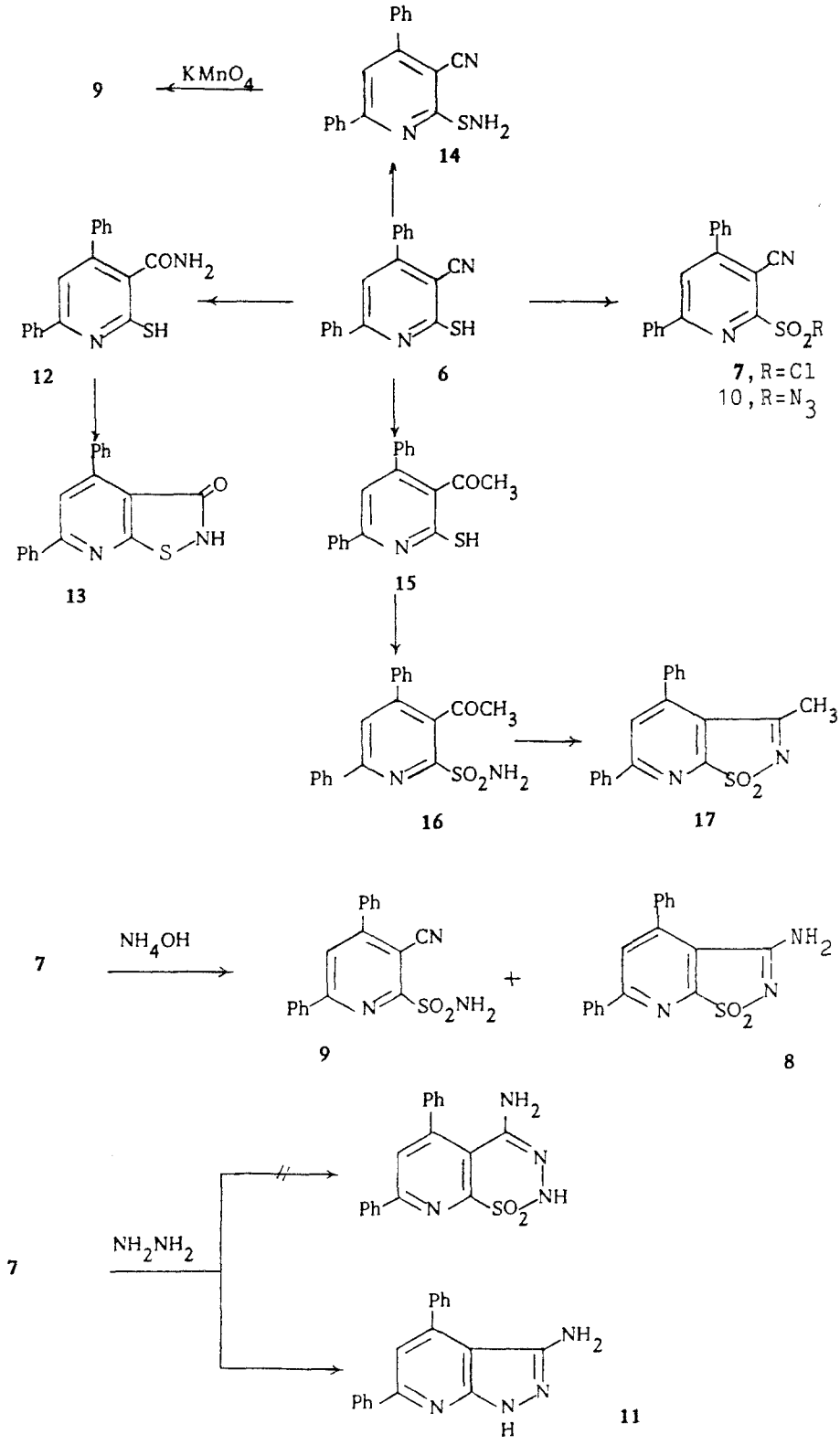


3 4 2 5

Since this synthesis was successful, it was of interest to synthesize substituted isothiazolo[5,4-b]pyridine-1,1-dioxide derivatives. It has been found that when **6** was treated with chlorine gas in presence of 10% acetic acid at 0°C the corresponding sulfonyl chloride **7** was obtained, which on direct ammonolysis with NH_4OH [5] afforded 3-amino-4,6-diphenylisothiazolo[5,4-b]pyridine-1,1-dioxide (**8**) and 3-cyano-4,6-diphenylpyridine-2-sulfonamide (**9**).

On treatment with sodium azide in aqueous acetone the sulfonyl chloride **7** was readily converted into the corresponding sulfonyl azide **10** [6].

Similarly, treatment of **7** with anhydrous hydrazine gave 3-amino-4,6-diphenylpyrazolo[3,4-b]pyridine (**11**) instead of pyridothiadiazine-1,1-dioxide [7]. The formation of **11** is the consequence of nucleophilic attack on the C-2 by the chlorine atom followed by hydrazine attack. The IR revealed the presence of an NH_2 group


9
KMnO4
14
12
6
7, R=Cl
10, R=N3
13
15
16
17
7
NH4OH
9
8
7
NH2NH2
11

(3 400–3 100 cm^{-1}), no bands due to either the cyano group or the sulfone group were detectable.

Schaper [8] has reported the synthesis of 3-oxo-2,3-dihydroisothiazolo[5,4-b]pyridines by oxidation reactions of 3-carboxamido-2(1*H*)pyridinethione. We have prepared 3-carboxamido-4,6-diphenyl-2(1*H*)pyridinethione (**12**) using acidic hydrolysis of **6** [9]. Compound **12** was treated with iodine in benzene at reflux temperature, 3-oxo-2,3-dihydroisothiazolo[5,4-b]pyridine (**13**) was obtained in 60% yield. The structure of **13** was confirmed by ir by the presence of bands at 3 400, 1 650, and 1 100 cm^{-1} due to (NH), (C=O), and (−S−) groups.

The amination of **6** was investigated, thus treatment of **6** with sodium hypochlorite followed by ammonium hydroxide gave 2-sulfenamide derivative **14**, which can be oxidize by potassium permanganate giving the corresponding sulfonamide **9**.

On the other hand, the reaction of **6** with methylmagnesium iodide afforded 3-acetyl derivative **15** [10]. When **15** was treated with chlorine gas in acetic acid at 0°C it gave the corresponding sulfonyl chloride, which on direct ammonolysis with ammonium hydroxide afforded the sulfonamide derivative **16** in 50% yield.

The sulfonamide **16** was cyclized in boiling acetic anhydride giving 3-methyl-4,6-diphenylisothiazolo[5,4-b]pyridine-1,1-dioxide (**17**). The structure of **17** was confirmed by ir, the presence of a bands at 1 370, 1 200 cm^{-1} being typical of an SO_2 group. No C=O band was observed in the ir spectrum of compound **17**. The ^{1}H NMR spectrum exhibited lines at δ 8.20–7.4 (m, 11 H, aromatic protons), and 2.5 (s, 3 H, CH_3).

Extension of the synthetic scope of these reactions are under study.

Experimental Part

Melting points are uncorrected. ^{1}H NMR spectra were determined in *DMSO-d_6* on a Varian 60 MH_2 spectrometer with *TMS* as internal standard and chemical shifts are expressed as (ppm). IR spectra were obtained in a Pye Unicam Sp-1100 spectrophotometer (KBr). Analytical data were performed by the Microanalytical centre, Cairo University.

3-Carbethoxy-4,6-diphenyl-2-pyridinesulfonamide (**5**)

2-Amino-4,6-diphenylethyl nicotinate (**3**) (3.18 g, 10 mmol) in acetic acid (20 ml) and concentrated HCl (10 ml) was treated with sodium nitrite (1.16 g) at 0°C and the diazonium salt solution poured all at once into a cold saturated solution of SO_2 in acetic acid (15 ml) containing copper(II) chloride dihydrate (1 g). The solid product obtained was filtered off and washed with water to give the sulfonyl chloride **4**; this was added to ammonium hydroxide (150 ml). The reaction mixture was stirred at 5–10°C for 2 h, the resulting solution was concentrated to half of its volume and neutralized with hydrochloric acid to precipitate **5** (see Table 1).

3-Oxo-2,3-dihydro-4,6-diphenylisothiazolo[5,4-b]pyridine-1,1-dioxide (**2**)

Compound **5** (3.82 g, 10 mmol) was refluxed in butyl alcohol (30 ml) for 3 h, excess solvent was removed and the residue set aside for 24 h. Then solid **2** was collected by filtration.

Table 1. Analytical and spectral data

Compound	M.p. °C Solvent of cryst.*	IR cm^{-1}	^1H NMR (ppm)	Yield %	Formula *m/e*	Analysis % Calc./Found	
						C	H
2	125 *E*	3 300 (NH), 3 200 (OH), 1 700 (C=O), 1 350, 1 100 (SO_2)	11 (br, 1 H, NH), 8.00–7.66 (m, 11 H, *Ar*)	57	$C_{18}H_{12}N_2O_3S$ 336.36	64.27 64.20	3.59 3.40
5	220 *E*	3 400–3 300 (NH_2), 1 700 (C=O, ester), 1 320, 1 150 (SO_2)	8.30–7.40 (m, 11 H, *Ar*), 6.3 (br, 2 H, NH_2), 4.4 (9, 2 H, CH_2), 2.8 (s, 3 H, CH_3)	37	$C_{20}H_{18}N_2O_4S$ 382.42	62.81 62.80	4.74 4.90
8	176 *E*	3 300–3 250 (NH_2), 1 320, 1 150 (SO_2)	–	60	$C_{18}H_{13}N_3O_2S$ 335.36	64.46 64.29	3.90 4.10
9	220 *DMF*	3 100 (NH), 2 200 (CN), 1 320, 1 150 (SO_2)	8.20–7.40 (m, 11 H, *Ar*), 6.2 (br, 2 H, NH_2)	31	$C_{18}H_{13}N_3O_2S$ 335.36	64.46 64.60	3.90 4.20
10	170 *E*	2 220 (CN), 2 175 (N_3), 1 350, 1 150 (SO_2)	–	28	$C_{18}H_{11}N_5O_2S$ 361.37	59.82 60.20	3.06 3.20
11	210 *E*	3 400–3 100 (NH_2), 1 610 (C=N)	8.32–7.27 (m, 12 H, *Ar*), 4.5 (br, 2 H, NH_2)	60	$C_{18}H_{14}N_4$ 286.32	75.50 75.60	4.92 5.00
12	140 *E*	3 400 (NH_2), 1 660 (C=O), 1 100 (−S−)	8.50–7.40 (m, 11 H, *Ar*), 6.20 (br, 2 H, NH_2), 3.73 (m, 1 H, SH)	82	$C_{18}H_{14}N_2OS$ 306.37	70.56 70.30	4.60 4.30
13	250 *M*	3 200 (NH), 1 650 (C=O), 1 100 (−S−)	9.8 (br, 1 H, NH), 8.20–7.6 (m, 11 H, *Ar*)	60	$C_{18}H_{12}N_2OS$ 304.36	71.02 71.10	3.97 3.80
14	220 *E*	3 200 (NH_2), 2 210 (CN), 1 600 (C=N)	8.3–7.5 (m, 11 H, *Ar*), 6.10 (br, 2 H, NH_2)	55	$C_{18}H_{13}N_3S$ 303.36	71.26 71.10	4.31 4.20
16	135 *E*	3 400–3 300 (NH_2), 1 650 (C=O), 1 320, 1 150 (SO_2)	8.10–7.6 (m, 11 H, *Ar*), 6.00 (br, 2 H, NH_2), 2.7 (s, 3 H, CH_3)	51	$C_{19}H_{16}N_2O_2S$ 352.40	64.75 64.20	4.57 4.30
17	190 *B/P*	1 370, 1 200 (SO_2)	8.20–7.4 (m, 11 H, *Ar*), 2.5 (s, 3 H, CH_3)	50	$C_{19}H_{14}N_2O_2S$ 334.38	68.24 68.70	4.21 4.10

* *B* Benzene, *E* Ethanol, *M* Methanol, *P* Petrolether (40–60°), *DMF* dimethylformamide

3-Amino-4,6-diphenylisothiazolo[5,4-b]pyridine-1,1-dioxide (**8**) *and 3-cyano-4,6-diphenylpyridine-2-sulfonamide* (**9**)

In a solution of 3-cyano-4,6-diphenyl-2(1*H*)pyridinethione (**6**) (2.88 g, 10 mmol) in acetic acid (100 ml, 10%), chlorine gas was bubbled at 0°C. A white precipitate started forming. After 1 h the precipitate was filtered, washed with water several times, and dried to give 2-sulfonylchloride derivative **7**; this was added to conc. NH_4OH (100 ml). The reaction mixture was heated on a steam bath for 4 h, the volume was reduced to the half and neutralized with 6 *N* HCl to give a solid product. The solid product was washed with water, dried, and then treated with acetic acid. It was divided into two parts: an acetic acid soluble part and an acetic acid insoluble part. The acetic acid solution was concentrated to obtain **8**. The acetic acid insoluble part afforded **9**.

3-Cyano-4,6-diphenylpyridine-2-sulfonylazide (**10**)

Sodium azide (1.3 g, 20 mmol) in water (10 ml) was added to a stirred solution of **7** (3.55 g, 10 mmol) in acetone (50 ml) and the solution was stirred at room temperature for further 10 h. It was evaporated in vacuo to one third of its volume and water (200 ml) was added. The precipitate of **10** was filtered, washed with water and dried.

3-Amino-4,6-diphenylpyrazolo[3,4-b]pyridine (**11**)

To a solution of **7** (3.55 g, 10 mmol) in absolute ethanol (30 ml) was added anhydrous hydrazine (10 mmol). The solution was heated under reflux for 6 h. It was evaporated to one-third of its volume. Then **11** precipitated from the solution.

3-Carboxamido-4,6-diphenyl-2(1H)pyridinethione (**12**)

Compound **6** (2.88 g, 10 mmol) was dissolved in conc. H_2SO_4 (30 ml) and heated on a steam bath for 3 h. The solution was cooled to room temperature and poured over crushed ice (200 g). The precipitate of **12** was filtered and dried.

3-Oxo-2,3-dihydro-4,6-diphenylisothiazolo[5,4-b]pyridine (**13**)

To a solution of **12** (1 g, 3.2 mmol) in benzene (20 ml) was added a solution of iodine (1.27 g, 5 mmol) in benzene (10 ml) and the solution was heated under reflux for 5 h. Then excess iodine was destroyed with a saturated solution of potassium hydroxide and precipitated **13** was filtered.

3-Cyano-4,6-diphenylpyridine-2-sulfenamide **14**

6 (2.88 g, 10 mmol) was added to a solution of sodium hypochlorite (20 ml, 5 mmol). The reaction mixture was stirred at 30°C for 3 h. Ammonium hydroxide (50 ml) was added to the reaction mixture, the mixture was stirred for an additional hour at room temperature, the precipitate of **14** was filtered and washed with water several times.

Oxidation of **14**

To a solution of **14** (3.03 g, 10 mmol) in acetone (20 ml) was added a solution of potassium permanganate (3.28 g, 20 mmol) in water (60 ml) portion-wise and the solution was stirred at room temperature for 12 h. The excess permanganate was destroyed with sulfur dioxide and the solution filtered to remove the precipitated manganese dioxide. The aqueous solution was made strongly alkaline with sodium hydroxide pellets (2 g) and then extracted with chloroform (3 × 20 ml). Evaporation of the dried (Na_2SO_4) chloroform extract gave **9** (1.89 g, 56%). The compound had a melting point and spectral properties identical to those of a sample obtained in the previous experiment.

3-Acetyl-4,6-diphenylpyridine-2-sulfonamide (**16**)

To a cold solution of 3-acetyl-4,6-diphenyl-2(1*H*)pyridinethione (**15**) (3.05 g, 10 mmol) in dilute acetic acid (100 ml, 10%) chlorine gas was bubbled at 0°C. A white precipitate started forming. After 1 h the precipitate was filtered, washed with water several times and dried; this 2-sulfonyl chloride derivative was added to conc. ammonium hydroxide (100 ml). The reaction mixture was heated on a steam bath for 3 h and then neutralized with hydrochloric acid to give **16**.

3-Methyl-4,6-diphenylisothiazolo[5,4-b]pyridine-1,1-dioxide (**17**)

A solution of **16** (3.52 g, 10 mmol) in acetic anhydride (20 ml) was heated under reflux for 3 h. The reaction mixture was cooled and a saturated solution of sodium bicarbonate was added. Solid **17** was separated by filtration.

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Received October 3, 1989. Accepted November 4, 1989