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Transformations of 1-(2-Chloropyridyl-3)-4-ethoxycarbonyl- and 1-(2-Chloropyridyl-3)-4-ethoxycarbonylmethyl Thiosemicarbazides. Attempts to Prepare Pyrido[3,2-e]-1,2,4-thiadiazine

Božidar Koren, Branko Stanovnik*, and **Miha Tišler**

Department of Chemistry, Edvard Kardelj University,
YU-61000 Ljubljana, Yugoslavia

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2-Chloro-3-hydrazinopyridine (**2**) was converted with ethoxycarbonyl and ethoxycarbonylmethyl isothiocyanates into 1,4-disubstituted thiosemicarbazides **3** and **4**, while with phenyl isothiocyanate directly 1*H*-pyrido[3,2-e]-1,3,4-thiadiazine **7** was formed. Attempts to cyclize the thiosemicarbazides **3** and **4** into pyridothiadiazine derivatives **5** and **6** failed. In the reaction of **3** with hydrazine 2-aminothiazolo[5,4-b]pyridine (**9**) was formed, while **4** gave only the corresponding hydrazide **10**. The cyclization of the side chain occured in compound **4** by heating in aqueous hydrochloric acid to give **11**, which was further transformed with N,N-dimethylformamide dimethyl acetal (*DMFDMA*) into **12**, while with diethyl acetylene dicarboxylate the thiazolidone derivative **13** was produced.

(Keywords: 1,4-Disubstituted thiosemicarbazides; 1H-Pyrido[3,2-e]-1,3,4-thiadiazines; Thiazolinones)

Transformationen von 1-(2-Chlorpyridyl-3)-4-ethoxycarbonyl- und 1-(2-Chlorpyridyl-3)-4-ethoxycarbonylmethylthiosemicarbaziden. Versuche zur Synthese von Pyrido[3,2-e]-1,2,4-thiadiazinen

2-Chlor-3-hydrazinopyridin (**2**) wurde mit Ethoxycarbonyl- und Ethoxycarbonylmethylisothiocyanaten zu 1,4-disubstituierten Thiosemicarbaziden **3** und **4** umgesetzt, mit Phenylisothiocyanaten wurden direkt die 1*H*-Pyrido[3,2-e]-1,3,4-thiadiazine **7** erhalten. Versuche zur Cyclisierung der Thiosemicarbazide **3** und **4** zu den Pyridothiadiazinderivaten **5** und **6** gelangen nicht. Bei der Reaktion von **3** mit Hydrazin entstand 2-Aminothiazolo[5,4-b]pyridin (**9**), **4** gab nur das entsprechende Hydrazid **10**. Die Cyclisierung der Seitenkette von **4** gelang durch Erhitzen in wäßriger HCl unter Bildung von **11**, das seinerseits mit N,N-Dimethylformamiddimethylacetal (*DMFDMA*) weiter zu **12** umgesetzt wurde, währenddessen mit Diethylacetylendicarboxylat die Thiazolidonderivate **13** entstanden.

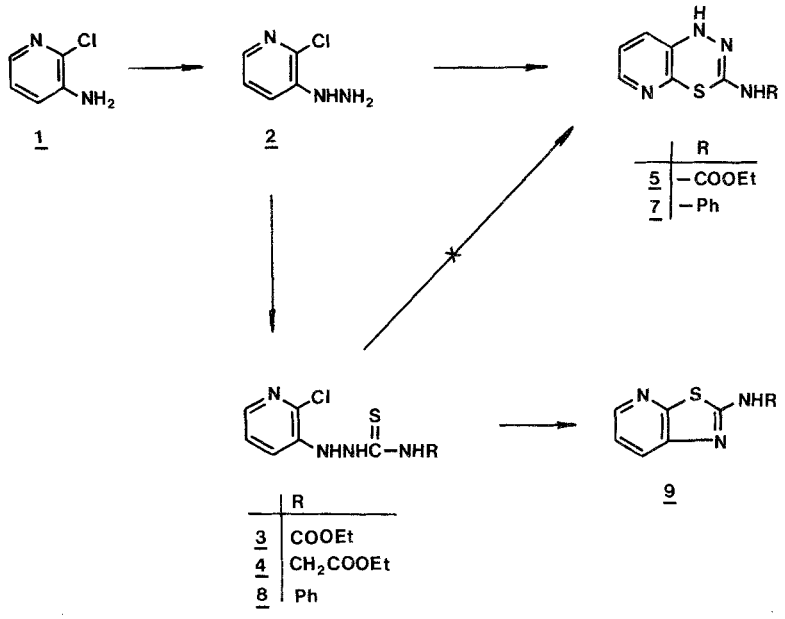
Introduction

The synthesis and reactions of condensed 1,3,4-thiadiazine systems have been of recent interest to a number of research groups [1–3]. The first synthesis of pyrido[3,2-e]-1,3,4-thiadiazine system has been acchieved by condensing N′-phenylbenzothiohydrazide and 2-chloro-3-nitropyridine [1], while an attempted synthesis to prepare derivatives of the isomeric pyrido[2,3-e]-1,3,4-thiadiazine system was unsuccessful [2]. We have observed that 4-ethoxycarbonyl-1-(3-chloropyrazinyl-2)thiosemicarbazide and 4-ethoxycarbonylmethyl-1-(3-chloropyrazinyl-2)thiosemicarbazide, prepared from 2-chloro-3-hydrazinopyrazine and ethoxycarbonyl isothiocyanate and ethoxycarbonylmethyl isothiocyanate, respectively, cyclized easily to give derivatives of the pyrazino[2,3-e]-1,3,4-thiadiazine system [3].

Results and Discussion

In the light of the above observation we have selected 2-chloro-3-hydrazinopyridine (**2**) as the starting compound for the synthesis of pyrido[3,2-e]-1,3,4-thiadiazine derivatives. In the reaction of **2** with ethoxycarbonyl isothiocyanate or ethoxycarbonylmethyl isothiocyanate the corresponding 4-ethoxycarbonyl- (**3**) and 4-ethoxycarbonylmethyl-1-(2-chloropyridyl-3)thiosemicarbazide (**4**) were formed, which did not cyclize into pyrido[3,2-e]-1,3,4-thiadiazine derivatives **5** and **6**, respectively. On the other hand, when **2** was heated in the presence of phenyl isothiocyanate in methanol a rapid conversion into 3-phenylamino-1*H*-pyrido[3,2-e]-1,3,4-thiadiazine (**7**) occured without isolation of 4-phenyl-1-(2-chloropyridyl-3)thiosemicarbazide (**8**) as an intermediate.

Some other transformations of thiosemicarbazides **3** and **4** were also performed. When **3** was heated with hydrazine hydrate in refluxing methanol for two hours, 2-aminothiazolo[5,4-b]pyridine **9** was obtained in 61% yield, identical with the compound prepared form 2-ethoxycarbonylthiazolo[5,4-b]pyridine by alkaline hydrolysis [4]. On the other hand, the thisemicarbazide **4** gave with hydrazine hydrate under essentially the same reaction conditions only the corresponding 4-carbazoylmethyl-1-(2-chloropyridyl-3)thiosemicarbazide (**10**), while on heating in aqueous hydrochloric acid at reflux for one hour cyclization of the side chain took place to give 1-(2-chloropyridyl-3)-2-(5-oxothiazolinyl-2)hydrazine (**11**). Methylation under neutral conditions with N,N-dimethylformamide dimethyl acetal (*DMFDMA*) produced 1-[methyl-(2-chloropyridyl-3)]-2-(4-dimethylaminomethylidene-5-oxothiazolinyl-2)hydrazine (**12**), indicating that N-methylation of one of the NH groups—as already observed in some other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5 | –COOEt
7 | –Ph
3 | COOEt
4 | CH_2COOEt
8 | Ph
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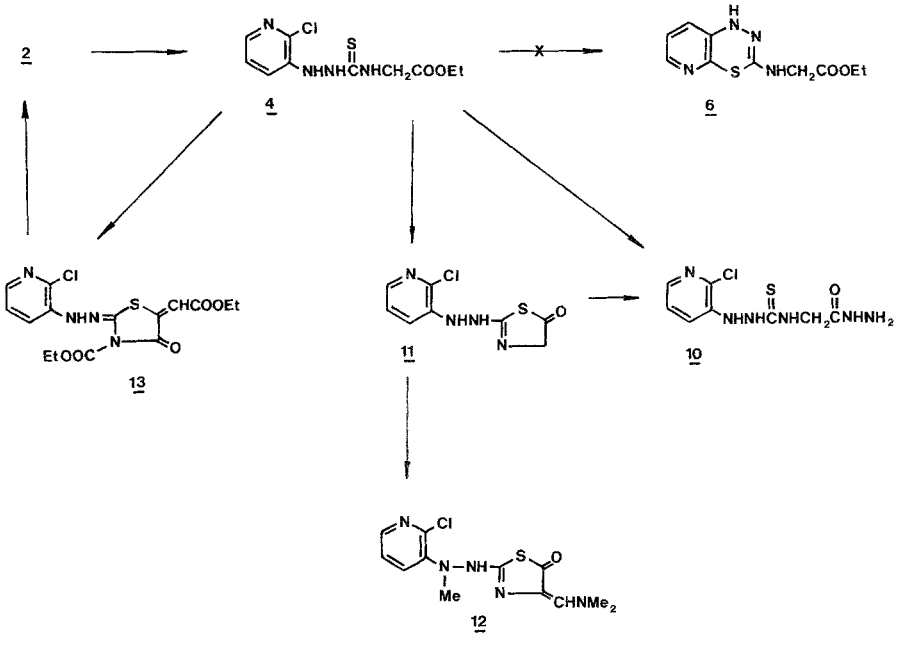
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examples [5–11]—and transformation of an active methylene group into the dimethylaminomethylidene group—as observed previously in the pyridazine series [12]—had occured. The position of the N-methylation was established on the basis of a long-range coupling constant ^3J: The coupling between $^{13}C_3$ of the pyridine ring ^{13}C—H and protons of the methyl group indicates that the methyl group must be attached at the nitrogen atom next to the pyridine ring.

By further treatment of **11** with hydrazine hydrate at room temperature the thiazolinone ring opened resulting in the formation of the hydrazide **10**.

4 reacted with diethyl acetylenedicarboxylate to give 2-(2-chloropyridyl-3)-hydrazono-3-ethoxycarbonylmethyl-5-ethoxycarbonyl-methylidene-4-thiazolidone (**13**).

Experimental

Melting points were determined on a *Kofler* hot plate m.p. apparatus. ^1H NMR spectra were recorded on a JEOL C 60 HL spectrometer and ^{13}C NMR spectra on a JEOL FX 90 Q spectrometer (*TMS* as internal standard, δ-values in ppm) and mass spectra on a Hitachi-Perkin-Elmer RMU-6L mass spectrometer. Elemental analyses (C, H, N) were obtained with a Perkin-Elmer Analyser 240 C.

2-Chloro-3-hydrazinopyridine (**2**)

To a solution of 128 mg **1** in 3 ml of aqueous hydrochloric acid (1 : 1) a solution of 69 mg of sodium nitrite in 1 ml of water was added dropwise at 0 °C. To the resulting solution 250 mg of stannous chloride was added in small portions and the mixture was stirred at 0 °C for 2 h, and than extracted with diethyl ether (5 times, 10 ml each time). The combined extracts were dried over anhydrous sodium sulphate and evaporated to give **2**. The compound is unstable and decomposes by attempted purification. It was used without further purification for the preparation of **3**, **4** and **7**.

1-(2-Chloropyridyl-3)-4-ethoxycarbonyl thiosemicarbazide (**3**)

This compound was prepared from **2** according to the general procedure described in Ref. [18] in 82% yield, m.p. 224–226 °C (from methanol). MS (*m/e*): 274 (M^+). NMR (*DMSO-d*$_6$): 1.29 (t, CH_3CH_2), 4.26 (q, CH_3CH_2), 7.43 (dd, H5′), 8.04 (dd, H4′), 8.41 (dd, H6′), 12.13 (br. s, NH), $J_{H4',H5'} = 8.5$ Hz, $J_{H4',H6'} = 1.5$ Hz, $J_{H5',H6'} = 5.4$ Hz, $J_{CH_3CH_2} = 6.9$ Hz.

$C_9H_{11}ClN_4O_2S$ (274.72). Calcd. C 39.34 H 4.03 N 20.39.
Found C 39.58 H 4.09 N 20.38.

1-(2-Chloropyridyl-3)-4-ethoxycarbonylmethyl thiosemicarbazide (**4**)

This compound was prepared from **2** according to the general procedure described in Ref. [18] in 69% yield, m.p. 194–195 °C (from methanol). MS (*m/e*) 288 (M^+). NMR (*DMSO-d*$_6$): 1.19 (t, CH_3CH_2), 4.07 (q, CH_3CH_2), 4.19 (d, $NHCH_2$), 7.06 (dd, H4′), 7.33 (dd, H5′), 7.84 (dd, H6′), 8.13 (br. s, NH), 8.40 (t,

$NHCH_2$), 9.63 (br. s, NH), $J_{H5',H6'} = 4.6$ Hz, $J_{H4',H5'} = 8.1$ Hz, $J_{H4',H6'} = 1.6$ Hz, $J_{CH_3CH_2} = 7.1$ Hz, $J_{NHCH_2} = 5.4$ Hz.

$C_{10}H_{13}ClN_4O_2S$ (288.65). Calcd. C 41.59 H 4.53 N 19.40.
Found C 41.50 H 4.46 N 19.35.

3-Phenylamino-1H-pyrido[3,2-e]1,3,4-thiadiazine (**7**)

To a mixture of 143 mg **2** in 3 ml of methanol 160 mg of phenylisothiocyanate was added and the mixture was heated under reflux for 30 min. The precipitate was, after cooling, collected by suction to give 73 mg (30%) of the product, m.p. 173–175 °C (dec.) (from ethanol). MS (*m/e*): 242 (M^+), NMR (*DMSO-d_6*): 7.14 (m, H7,H8, 3-*Ph*), 7.76 (dd, H6), 9.70 (br. s, NH), 9.86 (br. s, NH), $J_{H6,H7} = 4.4$ Hz, $J_{H6,H8} = 1.6$ Hz.

$C_{12}H_{10}N_4S$ (242.29). Calcd. C 59.48 H 4.16 N 23.12.
Found C 59.27 H 4.32 N 23.26.

2-Aminothiazolo[5,4-b]pyridine (**9**)

A mixture of 200 mg **3**, 1 ml of 80% hydrazine hydrate and 5 ml of methanol was heated under reflux for 2 h. The solvent was evaporated *in vacuo* and 2 ml of water was added to the oily residue. The precipitate was collected by suction to give 67 mg (61%) of **9**, m.p. 252–254 °C (from ethanol). Ref. [4] m.p. 252–254 °C. The IR spectrum of the compound was identical with that of an authentic sample [4].

4-Carbazoylmethyl-1-(2-chloropyridyl-3)-thiosemicarbazide (**10**)

a) To a suspension of 288 mg **4** in 5 ml of ethanol 1 ml of 80% hydrazine hydrate was added and the mixture was heated under reflux for 5 h. The solvent was evaporated *in vacuo* and the dry residue recrystallized from ethanol to give 143 mg (52%) of the product, m.p. 206–208 °C. NMR (*DMSO-d_6*): 4.01 (d, $NHCH_2$), 4.13 (br. s, NH_2), 7.01 (dd, H_4), 7.25 (dd, H5), 7.75 (dd, H6), 7.97 (br. s, NH), 8.13 (t, $NHCH_2$), 8.80 (br. s, NH), 9.49 (br. s, NH), $J_{H4',H5'} = 8.1$ Hz, $J_{H4',H6'} = 1.6$ Hz, $J_{H5',H6'} = 4.1$ Hz, $J_{NHCH_2} = 5.2$ Hz.

$C_8H_{11}ClN_6OS$ (274.74). Calcd. C 34.97 H 4.03 N 30.59.
Found C 35.35 H 4.01 N 31.02.

This compound cyclizes by heating into **11**.

b) A mixture of 242 mg **11**, 5 ml of ethanol and 1 ml of 80% hydrazine hydrate was left at room temperature for 14 h. The volatile components were evaporated *in vacuo* and the dry residue was washed with ethanol to give 180 ml (66%) of **10**. The IR spectrum of it was identical with that of the compound described under a).

1-(2-Chloropyridyl-3)-2-(5-oxadiazolinyl-2)-hydrazine (**11**)

A mixture of 100 mg **4** and 2 ml of aqueous hydrochloric acid (1 : 1) was heated under reflux for 1 h. The precipitate was, after cooling, collected by suction to give 22 mg (26%) of the product, m.p. 235 °C (dec.) (from ethanol). MS (*m/e*): 242 (M^+). NMR (*DMSO-d_6*): 4.27 (s, CH_2), 7.03 (dd, H4), 7.21 (dd, H5'), 7.80 (dd, H6'), 8.41 (br. s, NH), 10.35 (br. s, NH), $J_{H5',H6'} = 4.6$ Hz, $J_{H4',H5'} = 8.1$ Hz, $J_{H4',H6'} = 1.5$ Hz.

$C_8H_7ClN_4OS$ (242.69). Calcd. C 39.59 H 2.90 N 23.08.
Found C 40.05 H 3.33 N 23.18.

1-[Methyl-(2-chloropyridyl-3)]-2-(4-dimethylaminomethylidene-5-oxothiazolinyl-2)-hydrazine (**12**)

A mixture of 242 mg **11** and 2 ml of N,N-dimethylformamide dimethyl acetal (*DMFDMA*) was heated under reflux for 30 min. The volatile components were evaporated *in vacuo* to give 89 mg (29%) of the product, m.p. 242–244 °C (from methanol). MS (*m*/e): 311 (M^+). ^{1}H NMR (*DMSO-d*$_6$): 2.49 (s, *Me*), 3.14 (s, *Me*), 3.25 (s, *Me*), 6.69 (dd, H4), 7.05 (s, CH), 7.24 (dd, H5), 7.87 (dd, H6), 8.79 (br. s, NH), $J_{H4',H5'} = 8.1$ Hz, $J_{H4',H6'} = 1.5$ Hz, $J_{H5',H6'} = 4.6$ Hz. ^{13}C NMR (*DMSO-d*$_6$): 11.6 (q, N-*Me*); 45.6 (m, N-*Me*$_2$), 112.7 (d, C4'), 120.3 (m, C5'), 123.8 (dd, C4'), 134.7 (m, C3'), 139.4 (m), 139.6 (m), 139.7 (m) (C6',C2',CH), 147.4 (q, C2'), 165.9 (d, C5').

$C_{12}H_{14}ClN_5OS$ (311.80). Calcd. C 46.22 H 4.52 N 22.46.
Found C 46.02 H 4.80 N 22.17.

2-(2-Chloropyridyl-3)-hydrazono-3-ethoxycarbonylmethyl-5-ethoxycarbonylmethylidene-4-thiazolidone (**13**)

A mixture of 288 mg **4**, 170 mg of diethyl acetylene dicarboxylate and 3 ml of ethanol was heated under reflux for 45 min. The solvent was evaporated *in vacuo* to give 176 mg (42%) of the product, m.p. 155–156 °C (from methanol). MS (*m*/e): 412 (M^+). NMR (*DMSO-d*$_6$): 1.27 (t, CH_2*Me*), 1.34 (t, CH_2*Me*), 3.39 (s, CH_2), 4.31 (q, C**H**$_2$*Me*), 7.04 (s, CH), 7.56 (m, H4',H5'), 8.08 (dd, H6'), 10.83 (br. s, NH), $J_{H5',H6'} = 4.1$ Hz, $J_{H4',H6'} = 1.5$ Hz, $J_{CH_2Me} = 7.6$ Hz.

$C_{16}H_{17}ClN_4O_5S$ (412.86). Calcd. C 46.54 H 4.15 N 13.57.
Found C 46.46 H 4.21 N 13.43.

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