CYCLIZATION OF THIOCYANATO MALONATES WITH HYDROXYLAMINES TO 5-CARBOXYALKYL-4-OXO-THIAZOLI(DI)NES

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Abstract: Thiocyanato malonates **1a-c** were cyclized with hydroxylamine or N-substituted hydroxylamines to 5-carboxyalkyl-thiazoli(di)n-4-ones of type **2** and **4.** Carbamoylation of **2c** with isocyanates occured at the hydroxyimino group to give **3a,b**.

Introduction

Oxazolidin-4-ones and thiazolidin-4-ones bearing a (substituted) hydroxyimino group in ring position 2 have been shown to display good to excellent fungicidal [1] and insecticidal [2] activity.

Our continuing interest in the chemistry and biology of functionalized five-membered heterocycles led us now to investigate 5-carboxyalkyl-thiazoli(di)ne derivatives of type **2** and **4**.

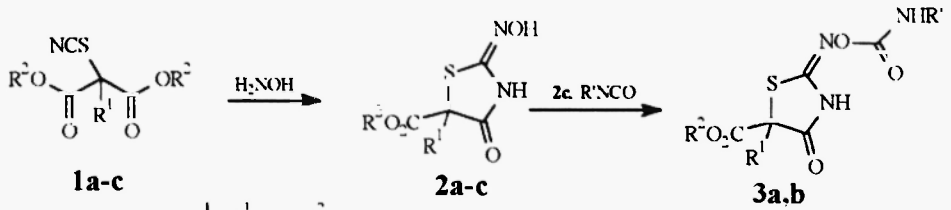
We herein describe a synthetic route to the target molecules by the reaction of thiocyanato malonates **1a-c** with hydroxylamines.

Results and discussion

Treatment of the thiocyanato malonates **1a-c** [3] with hydroxylamine hydrochloride and sodium acetate in methanol afforded **2a-c** [4] in moderate yields of 30-38%, which develop a green color with ethanolic ferric chloride due to the incorporated N-hydroxy isothiourea moiety. The IR-spectra of **2a-c** revealed absorption bands at 1738-1728, 1702-1695 (C=O) and 1655-1649 (C=N) cm^{-1}, which are in good accordance with literature data [5]. Further support for the structure of **2a-c** came from the ^{13}C-NMR-spectra with signals at δ 172.0–168.6 ppm (C4 and exocyclic C=O) and δ 148.4-146.7 ppm (C=N).

When equimolar amounts of **2c** and isocyanate were allowed to react for 6h at ambient temperature the 2-carbamoyloxyiminothiazolidin-4-ones **3a,b** were formed, the IR-spectra of which showed two strong (C=O) absorptions at 1759-1735 and 1733-1719 cm^{-1} besides a slightly bathochromic shifted (C=N) band at 1651-1633 cm^{-1} (Scheme 1).

Scheme 1



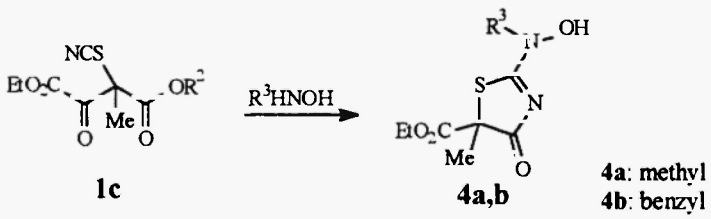
1a-c **2a-c** **3a,b**

1, 2	R^1	R^2
a	H	CH_3
b	H	C_2H_5
c	CH_3	C_2H_5

3a: R' = 3,4-Cl-phenyl
3b: R' = n-butyl

The reaction of **1c** with N-methyl- or N-benzylhydroxylamine gave the corresponding 2-(N-alkyl)-hydroxyamino-thiazoline-4-ones **4a,b** [4] in 40-43% yield (Scheme 2). Contrary to **2**, a purple colored complex resulted from **4a,b** with ethanolic ferric chloride.

Scheme 2



1c **4a,b**

4a: methyl
4b: benzyl

Experimental

Melting points were determined on a Mettler FP 62 and are uncorrected. The IR spectra were scanned on a Perkin Elmer 1600 FTIR spectrophotometer. The ^{1}H-NMR- (400 MHz) and ^{13}C-NMR-spectra (100,6 MHz) were recorded on a Bruker AMX 400 spectrometer using tetramethyl-silane as an internal standard and DMSO-d_6 as solvent. Elemental analysis were performed on a Heraeus CHN-O-Rapid. For all new compounds satisfactory microanalyses were obtained (C, H, N, S: ± 0.4%). Column chromatography was performed on silica gel (ICN Silica 100-200, active).

Starting materials:

The thiocyanato malonates **1a-c** were prepared according to literature [3].

Methyl 2-hydroxyimino-4-oxo-thiazolidine-5-carboxylate (2a)

To a stirred solution of **1a** (20 mmol) and NaOAc (22 mmol) in methanol (25 ml) was added H_2NOH x HCL (22 mmol). After 24 h the reaction mixture was rotoevaporated, the oily residue dissolved in EtOAc (50 ml) and washed with brine. The organic layer was dried over $MgSO_4$, rotoevaporated and the oil chromatographed. Elution with diethyl ether/CH_2Cl_2 (1:1) gave **2a.** Yield 30%; mp 138 °C (CH_2Cl_2 /hexane); IR (KBr): υ = 1734, 1697 (C=O), 1649 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ (ppm) 3.72 (s, 3H, OCH_3), 5.03 (s, 1H, CH), 10.60 (s, 1H, NH) 11.79 (s, 1H, OH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 49.0 (CH), 53.2 (OCH_3), 148.3 (C=N), 167.2, 168.6 (C=O).

Ethyl 2-hydroxyimino-4-oxo-thiazolidine-5-carboxylate (2b)

From **1b** according to **2a.** Yield 32%, mp 156 °C (CH_2Cl_2/hexane); IR (KBr): υ = 1738, 1695 (C=O), 1655 (C=N) cm^{-1}, ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.21 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$), 4.18 (q, 2H, *J* = 7.1 Hz $\underline{CH_2}CH_3$), 5.00 (s, 1H, CH); 10.60 (s, 1H, NH). 11.77 (s, 1H, OH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 13.7 ($CH_2\underline{CH_3}$), 49.1 (CH), 62.1 (OCH_2), 148.4 (C=N), 166.7, 168.7 (C=O).

Ethyl 2-hydroxyimino-5-methyl-4-oxo-thiazolidine-5-carboxylate (2c)

From **1c** according to **2a**, without chromatographic purification. Yield 38%, mp 138 °C (CH_2Cl_2/ hexane); IR (KBr): υ = 1728, 1702 (C=O), 1655 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.18 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$), 1.69 (s, 3H, CH_3), 4.18 (q, 2H, *J* = 7.1 Hz $\underline{CH_2}CH_3$), 10.63 (s, 1H, NH), 11.81 (s, 1H, OH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 13.6 ($CH_2\underline{CH_3}$), 21.9 (CH_3), 56.1 (C quart.), 62.2 (OCH_2), 146.7 (C=N), 168.7, 172.0 (C=O.

Ethyl 5-methyl-2-(N-methylhydroxylamino)-4-oxo-2-thiazoline-5-carboxylate (4a)

From **1c** and N-methylhydroxylamine hydrochloride according to **2a.** Yield 40%, mp 105 °C (CH_2Cl_2/ hexane); IR (KBr): υ = 1745, 1701 (C=O), 1615 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.15 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$), 1.66 (s, 3H, CH_3), 3.49 (s, 3H, NCH_3), 4.13 (q, 2H, *J* = 7.1 Hz $\underline{CH_2}CH_3$), 11.75 (s, 1H, OH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 13.7 ($CH_2\underline{CH_3}$), 22.2 (CH_3), 40.7 (CH_3N), 61.8 (OCH_2), 64.2 (C quart.), 168.7 (C=N), 178.4, 182.3 (C=O).

Ethyl 2-(N-benzylhydroxylamino)-5-methyl-4-oxo-2-thiazoline-5-carboxylate (4b)

To a stirred solution of **1c** (10 mmol) in CH_2Cl_2 (8 ml) was added N-benzylhydroxylamine (10 mmol). After 1d the mixture was rotoevaporated and the solid recrystallized. Yield 43%; mp 134 °C (EtOAc/hexane); IR (KBr): υ = 1742, 1711 (C=O), 1600 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.16 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{CH_3}$), 1.69 (s, 3H, CH_3), 4.13 (q, 2H, *J* = 7.1 Hz $\underline{CH_2}CH_3$), 5.02 (d, *J* = 15.3 Hz, 1H, $N\underline{CH_2}Ph$), 5.06 (d, *J* = 15.3 Hz, 1H, $N\underline{CH_2}Ph$), 7.32-7.42 (m, 5H, ArH), 11.75 (s, 1H, OH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 13.7 ($CH_2\underline{CH_3}$), 22.1 (CH_3), 56.6 (NCH_2Ph), 61.9

(OCH_2), 64.3 (C quart.), 127.9, 128.1, 128.5 (C tert., ArC), 134.4 (C quart., ArC), 168.6 (C=N), 179.7, 184.5 (C=O).

Ethyl 2-(3,4-dichlorophenylcarbamoyl)oxyimino-5-methyl-4-oxo-thiazolidine-5-carboxylate (3a). To a solution of **2c** (2 mmol) in THF (5ml) was added dropwise 3,4-dichlorophenylisocyanate (2 mmol, 5 ml THF), the reaction mixture stirred for 6 h, the solvent removed and the residue chromatographed with EtOAc as eluent. The oil crystallized from EtOAc by standing in the refrigerator. Yield 46%; mp 196 °C (EtOAc); IR (KBr): υ = 3354, 3160 (NH), 1759, 1733 (C=O), 1633 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.19 (t, J = 7.1 Hz, 3H, $CH_2\underline{CH_3}$), 1.78 (s, 3H, CH_3), 4.20 (q, 2H, J = 7.1 Hz $\underline{CH_2}CH_3$), 7.42-7.78 (m, 3H, ArH), 10.31 (s, 1H, NH), 12.58 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 13.6 ($CH_2\underline{CH_3}$), 21.6 (CH_3), 57.5 (C quart.), 62.1 (OCH_2), 118.6, 119.6, 130.7 (C tert., ArC), 124.5, 131.1, 138.5 (C quart., ArC), 150.7 (C=N), 155.6, 167.7, 172.3 (C=O).

Ethyl 2-(n-butylcarbamoyl)oxyimino-4-oxo-5-methyl--thiazolidine-5-carboxylate (3b)

2c was reacted with n-butylisocyanate according to **3a.** Yield 55%; mp 118°C (EtOAc); IR (KBr): υ = 3292, 3166 (NH), 1735, 1719 (C=O), 1651 (C=N) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ (ppm) 0.86 (t, J = 7.1 Hz, 3H, $CH_2\underline{CH_3}$), 1.18 (t, J = 7.1 Hz, 3H, CH_2CH_3), 1,22-1,44 (m, 4H, $2CH_2$), 1.74 (s, 3H, CH_3), 3,00-3,06 (m, 2H, NCH_2), 4.24 (q, 2H, J = 7.1 Hz $\underline{CH_2}CH_3$), 7,39 (s, 1H, NH), 12.41 (s, 1H, NH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 13.5, 13.7 ($CH_2\underline{CH_3}$), 21.6 (CH_3), 19,2, 31,2 (CH_2); 40.1 (NCH_2), 57.2 (C quart.), 62.5 (OCH_2), 153.7 (C=N), 155.0, 167.9, 172.3 (C=O).

References and Notes

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(4) It should be noted that other tautomeric forms of the thiazolidines **2**, **3** and **4** may exsist [6]

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