SYNTHESIS OF NOVEL 1,2,4,5-OXATRIAZINAN-3,6-DIONES AND 6-THIOXO-1,2,4,5-OXATRIAZINAN-3-ONES

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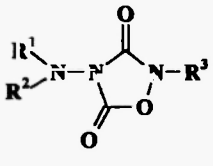
Abstract: The novel title compounds **2A/B** are readily prepared by cyclic (thio)carbonylation of 1,4-disubstituted 4-hydroxysemicarbazides (**3**) with either diphosgene or thiophosgene.

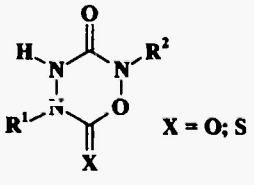
INTRODUCTION

Recently [1] we reported on the first synthesis of 4-aminosubstituted 1,2,4-oxadiazolidin-3,5-diones (**1**) by the reaction of 1,1,4-trisubstituted 4-hydroxysemicarbazides with methyl chloroformate. In continuation of our studies directed to the chemistry of 4-hydroxysemicarbazides we now investigated the ring closing acylation of 1-monosubstituted 4-hydroxysemicarbazides **3** which we expected – based on the well known successive acylation of semicarbazides [2,3] - to furnish the novel six-membered heterocycles of type **2A/B.**

Scheme 1



1



2A/B

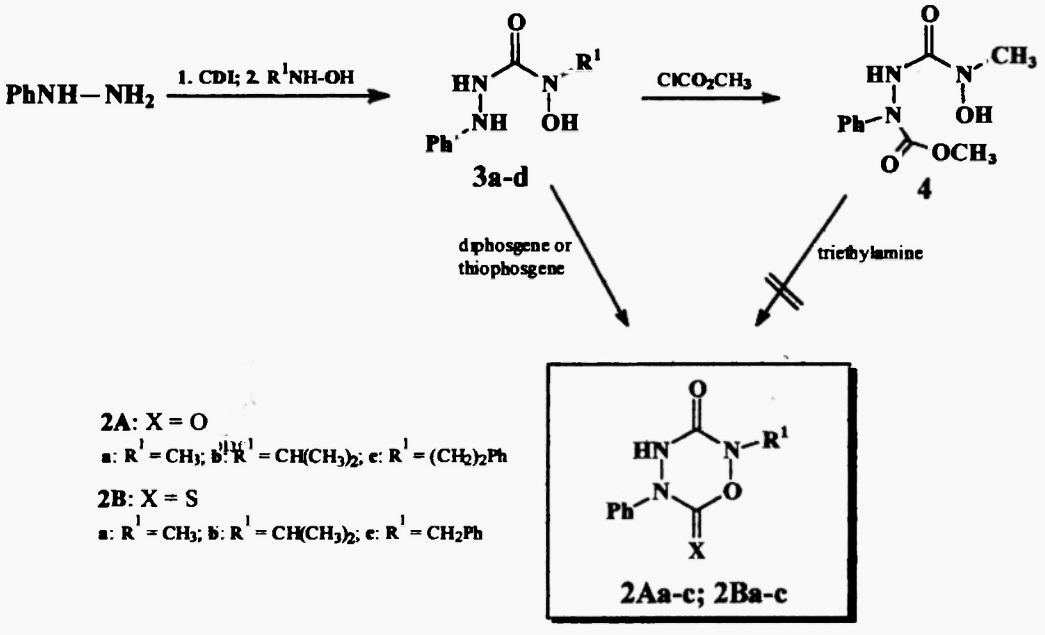
RESULTS AND DISCUSSION

As starting materials for the synthesis of **2A/B** we selected 1-phenyl-4-alkyl(aralkyl)-4-hydroxysemicarbazides **3a-d** that could easily prepared by a one-pot reaction from phenylhydrazine, 1,1'-carbonyldiimidazole and N-substituted hydroxylamines according to [1]. Initial attempts to cyclize **3a** by means of methyl chloroformate failed. Instead of the desired 1,2,4,5-oxatriazinan-3,6-dione **2Aa** the open-chained product **4** was formed that, to our surprise, resisted a base-catalyzed cyclization and was recovered unchanged.

However, when reacting **3** with diphosgene in a molar ratio of 2:1 the heterocycles **2A** could be achieved in high yields of 81-89% . Similarly, the reaction of **3** with thiophosgene produced the corresponding 6-thioxo-1,2,4,5-oxa-triazinan-3-ones **2Ba-c** in 69-71% [4].

The structure of **2A/B** which are stable compounds at ambient temperature follows unambiguously from elemental analysis, IR-, ^{1}HMR- and ^{13}C-NMR spectra (s. experimental part). The IR-spectra of **2A** show two carbonyl bands at 1751-1770 and 1627-1635 cm^{-1} which are significantly bathochromic shifted in comparison to the carbonyls of the heterocycles **1** (1820, 1750 cm^{-1}). **2Ba-c** are characterized by a carbonyl stretching vibration at 1655-1670 cm^{-1}.

Scheme 2



Conclusion

Novel 1,2,4,5-oxatriazinan-3,6-diones **2A** and 6-thioxo-1,2,4,5-oxatriazinan-3-ones **2B** which can be regarded as ring-expanded 4-amino-1,2,4-oxadiazolidin-3,5-diones **1** have been successfully prepared by cyclic carbonylation of 1,4-disubstituted 4-hydroxysemicarbazides **3**. Preliminary results from biological screening proved for **2Aa** a moderate insecticidal and herbicidal activity. Future structure-activities studies will show whether these biological activities can be improved.

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 tetramethylsilane as an internal standard and DMSO-d_6 or $CDCl_3$ as solvent. Elemental analysis were performed on a Heraeus CHN-O-Rapid. For all compounds satisfactory microanalyses were obtained (C, H, N : ± 0.4%). Column chromatography was performed on silica gel (ICN Silica 100-200, active).

General procedure for the synthesis of 3a-d

To a stirred, ice-cooled mixture of 1,1'-carbonyldiimidazole (10 mmol) in CH_2Cl_2 (30 ml) was added slowly a solution of phenylhydrazine (10 mmol) in CH_2Cl_2 (10 ml). After stirring at ambient temperature for 30 min the corresponding N-substituted hydroxylamine (10 mmol) in CH_2Cl_2 (10 ml) was added. The reaction was followed by running IR-spectra from the mixture until disappearance of the absorption at 1730 cm^{-1}. The solvent was evaporated and the residue chromatographed (THF). Fractions which were devoid of eluted imidazole (IR control) and gave a blue or purple color reaction with $FeCl_3$ were combined, evaporated and the residue recrystallized from THF/diethyl ether (8:1).

4-Hydroxy-4-methyl-1-phenylsemicarbazide (3a)

Yield 75 %; mp 147°C; IR (KBr): 3337 (OH), 3177 (NH), 1649 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ (ppm) 2.99 (s, 3H, NCH_3), 6.67-7.10 (m, 5 ArH), 7.42 (s, NH), 8.78 (s NH), 9.49 (s, OH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 38.5 (CH_3), 111.8, 117.9, 128.4, 150.1 (ArC), 161.0 (C=O).

4-Hydroxy-1-phenyl-4-(2-propyl)semicarbazide (3b)

Yield 75 %; mp 180°C; IR (KBr): 3381 (OH), 3200 (NH), 1632 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ (ppm) 1.10 (d, 6H, J = 6.60 Hz, CH_3), 4.16 (sept, 1H, J = 6.60 Hz, CH), 6.66-7.11 (m, 5 ArH), 7.45 (s, NH), 8.74 (s NH), 8.95 (s, OH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 18.3 (CH_3), 49.1 (CH), 111.8, 117.8, 128.4, 150.1 (ArC), 160.6 (C=O).

4-Hydroxy-1-phenyl-4-(2-phenylethyl)semicarbazide (3c)

Yield 62 %; mp 157°C; IR (KBr): 3300 (OH), 3200 (NH), 1627 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ (ppm) 2.83 (t, 2H, J= 8.21 Hz, CH_2Ph), 3.56 (t, 2H, J = 8.21 Hz, CH_2N), 6.66-7.32 (m, 10 ArH), 7.45 (s, NH), 8.82 (s, NH), 9.49 (s, OH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 32.2 (CH_2), 51.7 (NCH_2), 111.8, 117.9, 125.9, 128.2, 128.4, 128.5, 150.1 (ArC), 160.3 (C=O).

4-Benzyl-4-hydroxy-1-phenylsemicarbazide (3d)

Yield 68 %; mp 183°C; IR (KBr): 3308 (OH), 1620 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ (ppm) 4.55 (s, 2H, CH_2Ph), 6.70-7.32 (m, 10 ArH), 7.51 (s, NH), 8.82 (s, NH), 9.50 (s, OH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 54.4 (CH_2), 112.4, 118.3, 127.4, 128.4, 128.6, 128.8, 138.1, 150.1 (ArC), 160.8 (C=O).

4-Hydroxy-1-methoxycarbonyl-4-methyl-1-phenylsemicarbazide (4)

A solution of 3a (3 mmol) and methyl chloroformate (3.3 mmol) in 50 ml THF was refluxed for 3 h. The solvent was evaporated and the solid residue recrystallized from CH_2Cl_2/diethyl ether/petrolether.

Yield 90 %; mp 166°C; IR (KBr): 3333 (OH), 3177 (NH), 1688, 1644 (C=O) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ (ppm) 3.00 (s, 3H, NCH_3), 3.63 (s, 3H, OCH_3) 7.12-7.41 (m, 5 ArH), 9.68 (s, NH), 9.79 (s, OH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 38.0 (NCH_3), 53.0 (OCH_3), 128.2, 142.5 (ArC), 154.9, 158.9 (C=O).

General procedure for the synthesis of 2A/Ba-c

An ice-cooled solution of 3 (5 mmol) in 40 ml THF was treated dropwise with trichloromethyl chloroformate (2.5 mmol) or thiophosgene (5 mmol). After stirring at ambient temperature for 30 min the solvent was evaporated and the residue chromatographed. Elution with CH_2Cl_2/ethyl acetate 4:1 (**2Aa-c**) or CH_2Cl_2/ethyl acetate/petrolether 3:1:1 (**2Ba-c**) gave **2A/2B** as crystalline materials.

2-Methyl-5-phenyl-1,2,4,5-oxatriazinan-3,6-dione (2Aa)

Yield 81%; mp 100 °C ; IR (KBr): 3319 (NH), 1751, 1633 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ (ppm) 3.20 (s, 3H, NCH_3), 7.00 (NH), 7.25-7.81 (m, 5 ArH); ^{13}C-NMR ($CDCl_3$)): δ (ppm) 40.7 (CH_3), 118.2, 125.8, 129.1, 136.0 (ArC), 149.7, 156.7 (C=O).

5-Phenyl-2-(2-propyl)-1,2,4,5-oxatriazinan-3,6-dione (2Ab)

Yield 89%; mp 145 °C ; IR (KBr): 3322 (NH), 1772, 1628 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.28 (d, 6H, J = 6.00 Hz, CH_3), 4.00 (sept, 1H, J = 6.00 Hz, CH), 6.73 (NH), 7.20-7.80 (m, 5 ArH); ^{13}C-NMR ($CDCl_3$): δ (ppm) 17.8 (CH_3), 53.4 (CH), 118.3, 129.1, 136.0 (ArC), 149.5, 155.8 (C=O).

5-Phenyl-2-(2-phenylethyl)-1,2,4,5-oxatriazinan-3,6-dione (2Ac)

Yield 81%; mp 123 °C ; IR (KBr): 3330 (NH), 1773, 1627 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ (ppm) 2.99 (t, 2H, J = 7.00 Hz, CH_2Ph), 3.58 (t, 2H, J = 8.20 Hz, CH_2N), 7.29-7.71 (m, 10 ArH); ^{13}C-NMR (DMSO-d_6): δ (ppm) 31.3 (CH_2), 53.8 (CH_2), 117.5, 125.2, 126.2, 128.2, 128.8, 129.1, 136.0, 138.6 (ArC), 148.8, 155.9 (C=O).

2-Methyl-5-pbenyl-6-thioxo-1,2,4,5-oxatriazinan-3-one (2Ba)

Yield 71%; mp 117 °C ; IR (KBr): 3166 (NH), 1670 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ (ppm) 2.28 (s, 3H, NCH_3), 7.30-8.00 (m, 5 ArH); ^{13}C-NMR ($CDCl_3$)): δ (ppm) 41.3 (CH_3), 122.5, 128.3, 128.9, 136.3 (ArC), 161.8 (C=O), 172.4 (C=S).

5-Phenyl-2-(2-propyl)-6-thioxo-1,2,4,5-oxatriazinan-3-one (2Bb)

Yield 69%; mp 118 °C ; IR (KBr): 3203 (NH), 1625 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ (ppm) 1.28 (d, 6H, J = 6.10 Hz, CH_3), 4.08 (sept, 1H, J = 6.10 Hz, CH), 6.99 (NH), 7.35-8.00 (m, 5 ArH); ^{13}C-NMR ($CDCl_3$): δ (ppm) 17.9 (CH_3), 53.9 (CH), 122.5, 128.2, 128.9, 136.4 (ArC), 160.8 (C=O), 171.9 (C=S).

2-Benzyl-5-phenyl-6-thioxo-1,2,4,5-oxatriazinan-3-one (2Bc)

Yield 70%; mp 168 °C ; IR (KBr): 3188 (NH), 1655 (C=O) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ (ppm) 4.67 (s, 2H, CH_2Ph), 7.32-7.56 (m, 10 ArH), 8.05 (s, NH); ^{13}C-NMR ($CDCl_3$)): δ (ppm) 53.5 (CH_2), 122.4, 127.9, 128.1, 128.8, 136.2, 143.6 (ArC), 158.0 (C=O), 172.4 (C=S).

Acknowledgements:

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References and Notes

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4 It should be mentioned that the reactions must be run in the *absence* of a base, otherwise side reactions take place lowering yields of **2A/B** dramatically.

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