

Oxadiazole Condensed Ring Systems, II [1]: Synthesis of New 2-Aryl-1,3,4-oxadiazolo[3,2-a]- s-triazine-5,7(6*H*)-diones

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Summary. The syntheses of 1,3,4-oxadiazolo[3,2-a]-s-triazine-5,7(6*H*)-diones **4** through the condensation of 2-amino-5-aryl-1,3,4-oxadiazoles **1** with ethoxycarbonyl isocyanate **2** is described. Methylation of **4b** with trimethyl phosphate yielded the N-methyl derivative **5**.

Keywords. 2-Amino-1,3,4-oxadiazoles; Ethoxycarbonyl isocyanate; 1,3,4-Oxadiazolo[3,2-a]-s-triazine-5,7(6*H*)-diones.

Kondensierte Ringsysteme des Oxadiazols, 2. Mitt. [1]:

Synthese von neuen 2-Aryl-1,3,4-oxadiazolo[3,2-a]-s-triazin-5,7(6*H*)-dionen

Zusammenfassung. Die Synthese von 1,3,4-Oxadiazolo[3,2-a]-s-triazin-5,7(6*H*)-dionen **4** durch Kondensation von 2-Amino-5-aryl-1,3,4-oxadiazolen **1** mit Ethoxycarbonylisocyanat **2** wird beschrieben. Die Methylierung von **4b** mit Trimethylphosphat gibt das N-Methyl-Derivat **5**.

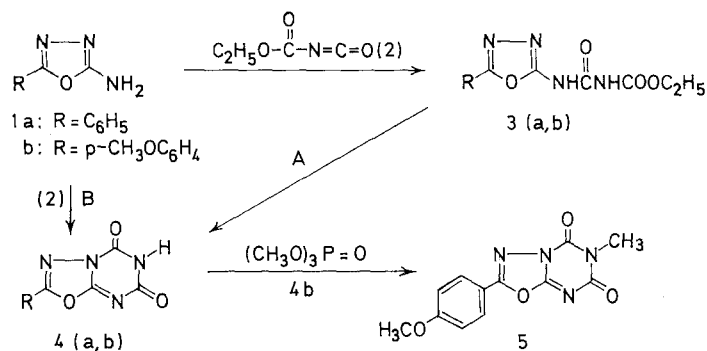
Introduction

Previously we have described the synthesis of some 5*H*-1,3,4-oxadiazolo[3,2-a]pyrimidin-5-ones as antimicrobial agents. However, test results on a variety of microbes were not encouraging [1]. Looking for more advantageous structural modifications, we become interested in the isosteric 1,3,4-oxadiazolo[3,2-a]-s-triazine-5,7(6*H*)-diones. To our knowledge, only few routes leading to the 5- or 7-thione analogs have been reported in the literature [2–4]. Such compounds showed herbicidal and fungicidal activities.

Results and Discussion

In the present work it was of interest to investigate the reaction of 2-aminooxadiazole **1** with ethoxycarbonyl isocyanate (**2**) as a possible facile route to the desired bicyclic system. When 2-amino-5-aryl-1,3,4-oxadiazoles **1** were allowed to react with ethoxycarbonyl isocyanate (**2**) at room temperature, the respective N-(5-aryl-1,3,4-oxadiazol-2-yl)-N'-ethoxycarbonyl-ureas **3** were obtained in good yields. These in-

intermediates **3** were readily cyclized in boiling chlorobenzene to the corresponding 2-aryl-1,3,4-oxadiazolo[3,2-a]-s-triazine-5,7(6*H*)-diones **4** in good yields (method A). The latter compounds could be prepared in nearly identical yields, upon condensing **1** with **2** in boiling chlorobenzene (method B). Treatment of **4b** with trimethyl phosphate afforded its 6-methyl derivative **5**. The appearance of strong $C_5=O$ and $C_7=O$ absorptions in the IR spectra of **5** confirmed the diacyl imide structure, $O=C-N-C=O$, within the triazine ring. This would favour N- and not O-methylation [5].



Based on Gehlen's findings [6] concerning the reaction of primary amines with 1,3,4-oxadiazolo[3,2-a]pyrimidinone, we have reacted the oxadiazolotriazinone **4b** with *m*-toluidine under identical reaction conditions. Unexpectedly, *N,N'*-di(3-tolyl)urea was obtained instead of the *s*-triazolo[1,5-a]-*s*-triazine. The assigned structure was confirmed by IR, ¹H-NMR and microanalytical data. We have recently reported an analogous result where *m*-toluidine reacted with 2-phenyl-5*H*-1,3,4-oxadiazolo[3,2-a]pyrimidin-5-one giving 2-phenyl-*N,N'*-(3-tolyl)propane-diamid [1].

Compounds **3a** and **4a** were screened for antimicrobial activity against five *Escherichia coli*, five *Klebsiella pneumonia*, three *Pseudomonas aeruginosa*, and two *Candida albicans* strains, using the disc method; however, they were inactive [7].

Experimental Part

Melting points were determined in open-glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer 421 spectrophotometer using samples in potassium bromide disks. ¹H-NMR spectra were recorded on a Varian EM 360 using tetramethylsilane as the internal standard. Microanalyses were carried out at the microanalytical unit, Faculty of Science, Cairo University.

N-Ethoxycarbonyl-*N'*-(5-phenyl-1,3,4-oxadiazol-2-yl)urea (**3a**)

Ethoxycarbonyl isocyanate (**2**) (0.3 g, 3 mmol) was added to a stirred solution of **1a** (0.48 g, 3 mmol) in dry chloroform (20 ml). After stirring under dry conditions for 2 h at room temperature, the excess chloroform was removed under vacuum and the solid residue was treated with petroleum ether and few drops of ethanol. The product was filtered and dried, yield 0.65 g (78.4%), m.p. 152–154° (aqueous ethanol). Anal. calcd. for C₁₂H₁₂N₄O₄: C 52.2, H 4.4, N 20.3; found: C 52.5, H 5.0, N 20.0.

N-Ethoxycarbonyl-*N'*-[5-(4-methoxyphenyl)-1,3,4-oxadiazol-2-yl]-urea (**3b**)

This was likewise prepared from **1b** (0.38 g, 2 mmol) and **2** (0.2 g, 2 mmol), yield 0.52 g (85%), m.p. 180° (aqueous ethanol). IR: 3 300–2 900 cm^{-1} (CO-ester), 1 740 s (CO), 1 600 s, 1 550 m, 1 500 m cm^{-1} . $^1\text{H-NMR}$ ($\text{CDCl}_3/\text{CF}_3\text{COOH}$): 1.35 (t, $J=7$ Hz, CH_3 -ethyl ester), 3.95 (s, OCH_3), 4.4 (q, $J=7$ Hz, CH_2 -ethyl ester), 7.05 (d, 2 *ArH*), 8.1 (d, 2 *ArH*). Anal. calcd. for $\text{C}_{13}\text{H}_{14}\text{N}_4\text{O}_5$: C 51.0, H 4.6, N 18.3; found: C 51.2, H 4.4, N 18.5.

2-Aryl-1,3,4-oxadiazolo[3,2-a]-s-triazine-5,7(6H)-diones (4)

Method A. The appropriate *N,N'*-disubstituted urea **3** (3 mmol) was refluxed in chlorobenzene (10 ml) for 1 h, during which the colorless crystalline product separated out. After cooling, the product was filtered and dried.

Method B. Equimolar quantities of the appropriate oxadiazole **1** and **2** (3 mmol) were refluxed in chlorobenzene (5 ml) for 2 h. After cooling, the product was filtered, washed with benzene and dried.

2-Phenyl-1,3,4-oxadiazolo[3,2-a]-s-triazine-5,7(6H)-dione (4a). A: yield (45%). B: yield (48%), m.p. 280° (aqueous dimethyl formamide). $^1\text{H-NMR}$ ($\text{DMSO}-d_6$): 7.2–7.8 (m, 5 *ArH*). Anal. calcd. for $\text{C}_{10}\text{H}_6\text{N}_4\text{O}_3$: N 24.3; found: N 24.6.

2-(4-Methoxyphenyl)-1,3,4-oxadiazolo[3,2-a]-s-triazine-5,7(6H)-dione (4b). A: yield (49.0%), B: yield (65%), m.p. 260° (aqueous dimethyl formamide). IR: 3 400–2 900 cm^{-1} , 1 650 s (CO), 1 600 s, 1 500 m cm^{-1} . $^1\text{H-NMR}$ ($\text{DMSO}-d_6$): 4.0 (s, OCH_3), 7.1 (d, 2 *ArH*), 8.1 (d, 2 *ArH*). Anal. calcd. for $\text{C}_{11}\text{H}_8\text{N}_4\text{O}_4$: C 50.8, H 3.1, N 21.5; found: C 50.5, H 2.9, N 21.3.

2-(4-Methoxyphenyl)-6-methyl-1,3,4-oxadiazolo[3,2-a]-s-triazine-5,7(6H)-dione (5)

3b (0.52 g, 2 mmol) was refluxed with trimethyl phosphate (5 ml) in the presence of anhydrous potassium carbonate (0.2 g) for 30 min. After cooling, water was added and the separated product was filtered, washed with water and dried, yield 0.1 g (18%); m.p. 218° (ethanol). IR: 3 400, 2 900 w, 1 780 s–1 690 s ($\text{C}_5=\text{O}$ and $\text{C}_7=\text{O}$), 1 615 m, 1 590 m, 1 550 m, 1 490 w, 1 460 w cm^{-1} . $^1\text{H-NMR}$ (CF_3COOH): 3.5 (s, NCH_3), 4.0 (s, OCH_3), 7.2 (d, 2 *ArH*), 8.1 (d, 2 *ArH*). Anal. calcd. for $\text{C}_{12}\text{H}_{10}\text{N}_4\text{O}_4$: C 52.6, H 3.7, N 20.4; found: C 52.3, H 4.1, N 20.5.

N,N'-Di(3-tolyl)urea

3b (0.61 g, 2 mmol) was refluxed with *m*-toluidine (5 ml) for 4 h, after cooling and addition of ether, the product was filtered and dried, yield 0.8 g (83.3%), m.p. 192–194° (aqueous ethanol). IR: 3 400–2 600 cm^{-1} , 1 780 m, 1 650 s (CO), 1 600 s, 1 550 s cm^{-1} . $^1\text{H-NMR}$ (CDCl_3): 2.4 (s, 6 H, 2 CH_3), 6.9–7.6 (m, 8-*ArH*). Anal. calcd. for $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}$: C 75.0, H 6.7, N 11.7; found: C 75.4, H 6.9, N 11.7.

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