INVESTIGATION OF THE REACTIVITY OF THE 2,3,6,7-TETRAHYDRO-7-PHENOXYMETHYL-4*H*-OXAZOLO[3,2-a]TRIAZIN-2-ONE-4-THIONE

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Abstract : A structural investigation of the reactivity of the 2,3,6,7-tetrahydro-7-phenoxymethyl-4*H*-oxazolo[3,2-a]triazin-2-one-4-thione **A** is presented. Depending on the experimental conditions the methylation of **A** gave different methylated compounds. The treatment of **A** with hydrogen peroxide in alkaline medium readily afforded 4*H*-oxazolo[3,2-a]triazin-2,4-dione **A'**.

Introduction

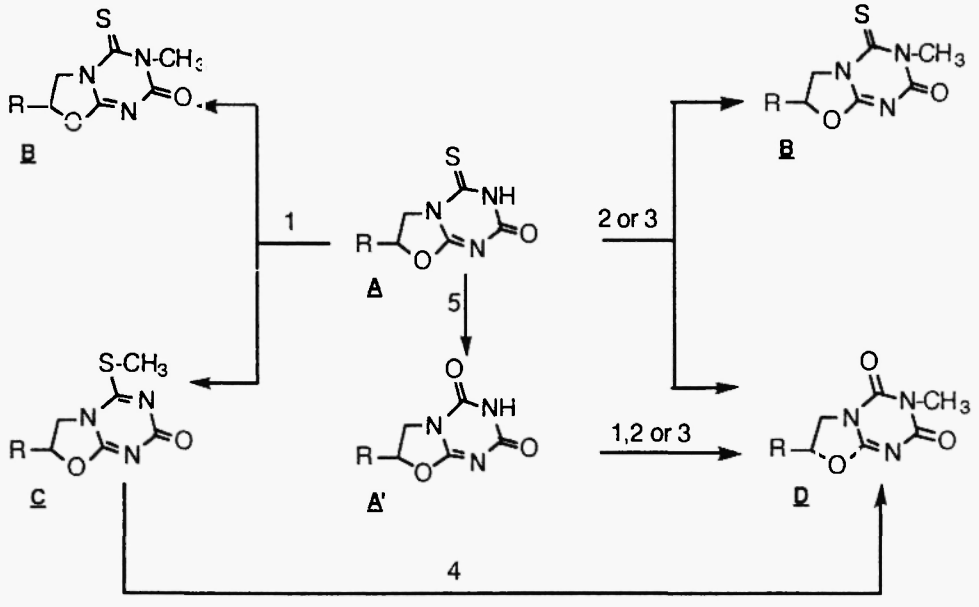
In connection with our work designed to produce new heterocyclic compounds usefull as 5-HT_2 inhibitors we previously reported the synthesis of 2,3,6,7-tetrahydro-4*H*-oxazolo[3,2-a]triazin-2-one-4-thiones [1]. We have begun to explore their reactivity with a variety of electrophiles with the goal of developing N-substituted triazines. We reported here preliminary results concerning the methylation of the 2,3,6,7-tetrahydro-7-phenoxymethyl-4*H*-oxazolo[3,2-a]triazin-2-one-4-thione **A** using either N,N-dimethyl formamide dimethylacetal (DMFDMA)[2] or diazomethane[3] as methylation agents. The structural determinations were partially supported by spectral analyses [4,5] and related to a mass spectrometry fragmentation study. In a second stage we developed an oxidation pathway leading to the corresponding 2,3,6,7-tetrahydro-7-phenoxymethyl-4*H*-oxazolo[3,2-a]triazin-2,4-dione **A'** [6].

Results

N-methylation is usually achieved by the action of either methyl iodide or dimethylsulfate in solvent in the presence of an appropriate base [7]. In an other hand,

diazomethane [8], trimethylphosphate [9] and DMFDMA[10-12] have been frequently used as methylating agents for chromatographic derivatization purpose. In order to develop an efficient methylation procedure applied to the 2,3,6,7-tetrahydro-7-phenoxymethyl-4*H*-oxazolo[3,2-a]triazin-2-one-4-thione **A** we selected diazomethane and DMFDMA as methylation reagents.

Scheme 1 : R = phenoxymethyl



1 : CH_2N_2, toluene, 25 °C ; 2 : CH_2N_2, methanol, 25 °C ; 3 : DMFDMA, toluene, 110°C,2h ; 4 : Methanol, 65°C ; 5 : H_2O_2 /NaOH, 0°C

The methylation of **A** with diazomethane was first conducted in toluene at 25°C. It provided a mixture of the 2,3,6,7-tetrahydro-3-methyl-7-phenoxymethyl-4*H*-oxazolo[3,2-a]triazin-2-one-4-thione **B** with the 2,3,6,7-tetrahydro-4-thiomethyl-7-phenoxymethyl-4*H*-oxazolo[3,2-a]triazin-2-one **C** (Scheme 1). The structure of **A** may induce a tautomeric equilibrium that could explain the formation of **B** and **C**, the methylation of **A** as a thione tautomer producing the N-Me derivative and the methylation of the iminothiol tautomer giving the S-Me derivative. When conducted in methanol at 25 °C, the methylation with diazomethane led to a mixture of **B** (65% as quantified by HPLC) with the 2,3,6,7-tetrahydro-3-methyl-7-phenoxymethyl-4*H*-oxazolo[3,2-a]triazin-2,4-dione **D** (35%).

Similarly, the methylation of **A** with DMFDMA in toluene at 110°C gave finally **B** and **D**. As DMFDMA is susceptible to produce methanol when heated[13], we investigated the behaviour of **C** in boiling methanol. By heating **C** two hours in methanol at 65°C we

noticed a complete transformation into **D**. Consequently, we modified the heating time used for the DMFDMA methylation of **A** in order to isolate only **B** and **C.** We never succeeded to avoid the formation of **D**, indicating a slight stability of the iminothiomethyl compound **C**.

This last result was confirmed by an analytical study by mass spectrometry performed with the three methylated compounds **B**, **C** and **D**. For **B** a CH_3NCS elimination from the molecular ion occured first, leading to the intense ion **a** (m/z 218). This fragmentation was followed by the elimination of a C_6H_5O radical leading to **c** (m/z 125). For **D** we observed a comparable fragmentation pathway as for **B**, but inverted. Moreover, the peak **a** resulting from the CH_3NCO elimination was weaker in **D** than its counterpart in **B**. Up to m/z 125 we remarked the great similarity of the two spectra, meaning that the resulting ion **c** could present the same structure in the two cases. On the contrary, the EI mass spectrum of **C** was completely different. The main fragmentation way involved the SCH_3 elimination giving **d** (m/z 244). This confirmed the great lability of the thiomethyl moiety, consistent with the observed chemical behaviour of **C**.

Finally, we studied the reaction of **A** with hydrogen peroxide in basic medium[14]. It led to the 2,3,6,7-tetrahydro-7-phenoxymethyl-4*H*-oxazolo[3,2-a]triazin-2,4-one **A'** already obtained through an alternative way[15]. As expected, the methylation of **A'** using either DMFDMA or diazomethane gave the 2,3,6,7-tetrahydro-3-methyl-7-phenoxymethyl-4*H*-oxazolo[3,2-a]triazin-2,4-dione **D**.

Conclusion

The reactivity of 2,3,6,7-tetrahydro-7-phenoxymethyl-4*H*-oxazolo[3,2-a]triazin-2-one-4-thione **A** was investigated. Depending on the experimental conditions, the methylation of **A** gave different methylated compounds. Whereas the formation of the isomeric N- and S-methylated compounds can be related to the normal reactivity of **A,** the formation of a desulfurized methylated compound seems to be related to the methanolysis of the S-methylated isomer. The great lability of the thiomethyl moiety was confirmed by an analytical study using mass spectrometry.

References and notes

(1) C. Jarry, I. Forfar, J. Thomas, J.M. Leger and M. Laguerre, Heterocycles, 36, 2465 (1993)

(2) *General procedure for the reaction of **A** and **A'** with DMFDMA as reagent*
A solution of 0.01 mole of compound **A** (or **A'**) in 50 mL of dry toluene with 0.04 mole of DMFDMA was refluxed under protection from moisture. After 2 hours the solvent and the excess of reagent were distilled under reduced pressure leading to a mixture of methylated products. From **A** the mixture was chromatographied over silica gel first with chloroform as eluent leading to **B** and then

with chloroform/methanol (9/1, v/v) giving **D**. From **A'**, **D** precipitated during the reaction and it was recrystailized from methanol

(3) *General procedure for the reaction of **A** and **A'** with diazomethane as reagent*
Methyiation was performed using the Aldrich "diazomethane-generation apparatus", according to the procedure described by Fales[16]. Diazomethane was generated from 0.3 g of N-methyi-N-nitroso-p-toluenesulfonamide by action of 0.2 mL of a 5N sodium hydroxide solution and reacted with **A** or **A'** (0.094 mmole in 0.5 mL of methanol or toluene) during 30 min at 25°C. From **A**, the mixture was chromatographied as it was presented precedently. From **A'**, **D** precipitated during the reaction and it was recrystailized from methanol.

(4) Spectral and analytical data of compounds **B**, **C**, **D**, and **A'**
2,3,6,7-Tetrahydro-3-methyl-7-phenoxymethyl-4*H*-oxazolo[3,2-a]triazin-2-one-4-thione **B**
Yield : 51% ; mp : 132 °C [lit [1]: 130°C]
2,3,6,7-Tetrahydro-4-thiomethyl-7-phenoxymethyl-4*H*-oxazolo[3,2-a]triazin-2-one **C**
Yield : 31% ; mp : 192 °C ; ir (KBr) : ν C=O 1640 , C=N 1610 cm^{-1} ; ^1H nmr (chloroform d) δ ppm: 7.30 and 6.96 (2m, 5H, Ar-*H*), 5.35 (m, 1H, C*H*), 4.34 (m, 2H, OCH_2), 4.30 (dd, 1H, J = 9.2, 12.5 Hz, CH_{2a}N), 3.99 (dd, 1H, J = 6.2, 12.5, CH_{2b}N), 2.55 (s, 3H, SCH_3) ; ^{13}C nmr (chloroform d) δ ppm: 165.1 (S-*C* =N), 162.3 (*C* =O), 161.6 (*C* =N), 157.5, 129.6, 122.0, 114.7 (*C* ar), 77.6 (*C* -7), 67.1 (OCH_2), 45.4 (*C* -6), 13.3 (CH_3)
Anal. Calcd for $C_{13}H_{13}N_3SO_3$: C, 53.60; H, 4.47; N, 14.43; S, 11.00. Found : C, 53.72; H, 4.51; N, 14.25; S, 10.91.
2,3,6,7-tetrahydro-3-methyl-7-phenoxymethyl-4*H*-oxazolo [3,2-a]triazin-2,4-dione **D**
Yield : 15% ; mp : 177°C [lit. [10] 176°C]

(5) *General procedure for the reaction of **A** with hydrogen peroxide*
0.01 Mole of compound **A** was dissolved in 80 mL of 0.25 M sodium hydroxide, With good stirring, 30% hydrogen peroxide (20 mL) was added dropwise at 0°C. The solution was stirred at 0°C for an additional 45 minutes. The slightly turbid solution was allowed to warm to room temperature and then acidified to pH 4 by the addition of 1M hydrochloric acid . The acidic mixture was chilled and the precipitate separated by filtration. **A'** was recrystailized from methanol.

(6) 2,3,6,7-tetrahydro-7-phenoxymethyl-4*H*-oxazolo [3,2-a]triazin-2,4-dione **A'**
Yield : 71% ; mp : 218°C [lit. [10] 218°C]

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