INVESTIGATION OF THE REACTION OF PHENYLISOCYANATE WITH N-SUBSTITUTED 2-IMINOOXAZOLIDINES

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Abstract. The reaction of phenylisocyanate with 5-(1-aryl-4-piperazinyl)-2-phenylcarbamoyl-2-iminooxazolidines and with 5-(1-aryl-4-piperazinyl)-2,3-diphenylcarbamoyl-2-iminooxazolidines leads to the 3-phenyl-7-(1-aryl-4-piperazinyl)-2,3,6,7-tetrahydro-oxazolo[3,2-a]-1,3,5-triazin-2,4-diones. In one case the reaction could progress *via* the formation of the corresponding isomeric N,N-diphenylcarbamoyl-2-amino-2-oxazoline.

Introduction

Like bicyclic 1,3,5-triazin-2,4-diones are described as potential 5-HT_2 antagonists related to ketanserin, different methods have been developed for their preparation (1,2). One involves a cyclocondensation reaction from an aminoheterocyclic compound (3-5).

Investigating in details the reaction of 2-amino-2-oxazolines with isocyanates, we described in a previous work the synthesis and the structural assessment of 3-phenylcarbamoyl- and 2,3-diphenylcarbamoyl-2-iminooxazolidines 2 (6). Whereas the 3-phenylcarbamoyl-2-iminooxazolidines rearrange rapidely to their isomeric 2-phenylcarbamoyl-2-iminooxazolidines **1**, we noticed the stability of the 2,3-diphenylcarbamoyl-2-iminooxazolidines permitting to use them as a reagent. In this work we report the synthesis of the 3-phenyl-7-(1-aryl-4-piperazinyl)-2,3,6,7-tetrahydrooxazolo[3,2-*a*]-1,3,5-triazin-2,4-diones **4(a,b)** using the reaction of phenylisocyanate with the corresponding 2-phenylcarbamoyl- **1** or 2,3-diphenylcarbamoyl-2-iminooxazolidines **2**. By heating, we observed the irreversible rearrangement of **2** to the isomeric N,N-diphenylcarbamoyl-2-amino-2-oxazolines **3**. These compounds have been isolated as possible intermediates. They conducted to the bicyclic compounds **4** by heating with phenylisocyanate.

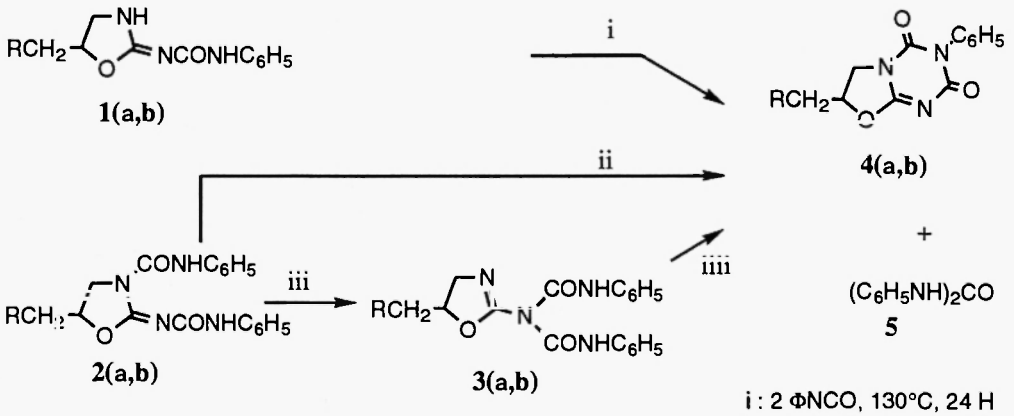
Results and discussion

The reaction of two equivalents of phenylisocyanate with the 2-phenylcarbamoyl-2-iminooxazolidines **1(a,b)** requires the heating of the two products in xylene during 24 hours (Scheme 1). N,N'-diphenylurea **5** and the 3-phenyl-2,3,6,7-tetrahydrooxazolo[3,2-a]-1,3,5-triazin-2,4-diones **4(a,b)** are obtained with a slight yield. Starting from 2,3-diphenylcarbamoyl-2-iminooxazolidines **2(a,b)**, by heating with one equivalent of phenylisocyanate in xylene during 6 hours, we isolated the corresponding **4** with good yields. N,N'-diphenylurea was obtained in parallel with **4**.

In order to investigate the mechanism of the reaction, we heated **2(a,b)** quickly up to their melting point. We observed that they rearranged to the corresponding N,N-diphenylcarbamoyl-2-amino-2-oxazolines **3(a,b)**. Then **3(a,b)** have been converted quantitatively to **4** by heating with one equivalent of phenylisocyanate in xylene during 3 hours.

However, we were unable to isolate **3** during the reaction of **1(a,b)** with phenylisocyanate. The formation of the N,N'-diphenylurea 5 could be related to a secondary reaction involving the isocyanate (7). Starting from the 5-[(4-phenyl-1-piperazinyl)methyl]-2,3-diisopropylcarbamoyl-2-iminooxazolidine (6), by heating with one equivalent of phenylisocyanate in xylene during 6 hours, we isolated **4a** with the N,N'-diisopropylurea. These results suggested that all reactions could pass through a common intermediate state, which was already noticed as the highly instable heterocyclic isocyanate (8,9). Then the triazine ring was formed through an 1,4 addition involving the phenylisocyanate (10).

Scheme 1 :



a : R = (1-phenyl-4-piperazinyl)
b : R = [1-(4-methyl)phenyl-4-(3-methyl)piperazinyl]

Structural elucidation of **3a** was accomplished on the basis of spectral data and of microanalyses.The ir spectrum closely resembles the reported spectra of 2-amino-2-oxazolines locked in the amino form by alkyl groups (11). The two C=O are quite identical and appear as a single band near 1730 cm^{-1}. The ^1H spectrum obtained at 500 Mhz shows two sharp singlets at 9.93 and 9.90 ppm assigned to the NH protons. For the 2,3-diphenylcarbamoyl-2-iminooxazolidine **2a** we reported the ^1H δ of the two NH protons at 10.76 and 7.4 ppm (6). In **3a**, the protons on the C(4) and C(5) positions in the oxazoline ring and the CH_2 protons of the lateral chain form an ABXMN system. The C(5) methine proton is found at about 4.56 ppm and the C(4)H_2 protons appear as two dd at 4.14 and 3.97 ppm. The ^{13}C nmr spectrum confirms the 2-amino-2-oxazoline structure. The most deshielded signal (155.51 ppm) is assigned to the C(2) carbon of the heterocycle, a ^3J coupling was found between the C(2) and the C(4)-H protons (^3J = 2.3 Hz). Because of the symmetry of the two substituents on the exo nitrogen atom, all δ of the carbon atoms of the two phenylcarbamoyl moieties are quite similar.

The 3-phenyl-2,3,6,7-tetrahydrooxazolo[3,2-a]-1,3,5-triazin-2,4-diones **4** have been characterized by their spectral data. The ir specta of all compounds exhibit two C=O bands near 1750 cm^{-1} and 1690 cm^{-1}. For the ^{13}C nmr spectra , the assignments of the chemical shifts of the sp^2-hybridized carbons were partially based on *Ab initio* chemical shifts calculations (5). In the ^1H nmr spectra, the C(6)H_2 and C(7)H protons on the tetrahydrooxazole ring form a characteristic ABX system, and all the NCH_2 protons appear as a large multiplet.

Experimental

Microanalyses were carried out at the Service central d'analyse CNRS, Vernaison, France. Melting points were determined with a Kofler hot-stage apparatus and were uncorrected. The ir spectra were obtained with a Bruker IF 25

spectrophotometer. Nmr data were recorded with a Bruker AC-200 and with a Bruker AMX-500 spectrometers. Chemical shifts (δ in ppm) and coupling constants (J in Hz) were measured using TMS as internal standard. Silica gel SDS 60 (70-230 mesh) was used for column chromatography.

General procedure for the preparation of 5-substituted N,N-diphenylcarbamoyl-2-amino-2-oxazolines **3(a,b)**

In a beaker, 0.01 mole of the 5-substituted 2,3-diphenylcarbamoyl-2-iminooxazolidine **2(a,b)** was heated quickly up to its melting point with stirring. After cooling the solid was recrystallized from tetrachlorethylene.

5-[(1-phenyl-4-piperazinyl)methyl]-N,N-diphenylcarbamoyl-2-amino-2-oxazoline (**3a**)

mp : 223°C ; yield : 90% ; ir (KBr) cm^{-1} : 3450, 3300 (NH) ; 1730 (C=O) ; 1690 (C=N) ; ^1H nmr 500 Mhz ($CDCl_3$), δ ppm : 9.93, 9.90 (2s, 2H, N*H*), 7.19 (m, 15H, Ar-*H*), 4.56 (m, 1H, 5-*H*), 4.14, 3.97 (2dd, 2H, 4-*H* , J=10.9, 9.1, 2.4), 3.19, 2.82, 2.63 (3m, 8H, CH_2-pip), 2.91, 2.62 (2dd, 2H, NCH_2 , J=12.7, 9.1, 3.2) ; ^{13}C ($CDCl_3$) δ ppm : 155.2 (*C*-2), 149.6, 149.1 (*C*O), 151.1, 137, 129.1, 124.4, 120, 119.9, 119.7, 116 (C_{Ar}), 76.7 (*C*-5), 59.6, 53.9, 49.1, 44.1 (NCH_2).

Anal. Calcd for $C_{28}H_{30}N_6O_3$: C, 67.47 ; H, 6.02 ; N, 16.87. Found : C, 67.27 ; H, 6.08 ; N, 16.80.

5-[(1-(4-methyl)phenyl)-4-(3-methyl)piperazinyl)methyl]-N,N-diphenylcarbamoyl-2-amino-2-oxazoline (**3b**): mp : 224°C ; yield : 83% ; ir (KBr) cm^{-1} : 3450, 3300 (NH) ; 1729 (C=O) ; 1710(C=N) ; ^1H nmr 200 Mhz ($CDCl_3$), δ ppm : 9.93, 9.91 (2s, 2H, N*H*), 7.16 (m, 14H, Ar-*H*), 4.51 (m, 1H, 5-*H*), 4.12, 3.92 (2m, 2H, 4-*H*), 2.81 (m, 9H, NCH_2), 2.25 (s, 3H, CH_3-Ar) , 0.98 (d, 3H, CH_3-pip, J=6.4) .

Anal. Calcd for $C_{30}H_{34}N_6O_3$: C, 68.44 ; H, 6.46 ; N, 15.97. Found : C, 68.39 ; H, 6.49 ; N, 15.92.

General procedures for the preparation of 3-phenyl-7-[(1-aryl-4-piperazinyl)methyl]-2,3,6,7-tetrahydrooxazolo[3,2-*a*]-1,3,5-triazin-2,4-dione (**4a,b**)

i : 0.02 mole of phenylisocyanate was added dropwise to a heated mixture of 0,01 mole of the 5-substituted 2-phenylcarbamoyl-2-iminooxazolidine**1** in dry xylene. The mixture was refluxed for 24 hours. After cooling the precipitate formed was collected and crystallized from appropriate solvent (yield in **4(a,b)** < 10%).

ii : 0.01 mole of phenylisocyanate was added dropwise to a heated solution of 0,01 mole of the 5-substituted 2,3-diphenylcarbamoyl-2-iminooxazolidine **2** in dry xylene.The solution was refluxed for 6 hours. After cooling the precipitate formed was collected and crystallized from ethanol.

3-phenyl-7-[(1-phenyl-4-piperazinyl)methyl]-2,3,6,7-tetrahydrooxazolo[3,2-*a*]-1,3,5-triazin-2,4-dione (**4a**) : mp : 283°C ; yield : 53% ; ir (KBr) cm^{-1} : 1755, 1692 (C=O) ; 1637 (C=N) ; ^1H nmr 200 Mhz (DMSO D_6), δ ppm : 7.09 (m, 10H, Ar-*H*), 5.30 (m, 1H, 7-*H*), 4.22 (t,1H, 6-*H*, J=9.6, 9.3), 3.85 (dd, 1H, 6-*H* , J=9.6, 7), 3.14, 2.88, 2.67 (3m, 10H, NCH_2) ; ^{13}C (DMSO D_6) δ ppm : 162.7 (*C*-9), 155.5 (*C*-4), 148.3 (*C*-2), 151, 135.4, 129, 128.9, 128.7, 128.3, 118.9, 115.4 (C_{Ar}), 78.8 (*C*-7), 59.6, 53.2, 48.3, 45.7 (NCH_2).

Anal. Calcd for $C_{22}H_{23}N_5O_3$: C, 65.19 ; H, 5.68 ; N, 17.28. Found : C, 65.11 ; H, 5.70; N, 17.26.

3-phenyl-7-[(1-(4-methyl)phenyl)-4-(3-methyl)piperazinyl)methyl]-2,3,6,7-tetrahydrooxazolo[3,2-*a*]-1,3,5-triazin-2,4-dione (**4b**) : mp : 230 °C ; yield : 47% ; ir (KBr) cm^{-1} : 1755, 1690 (C=O) ; 1640 (C=N) ; ^1H nmr 200 Mhz ($CDCl_3$), δ ppm : 7.14 (m, 9H, Ar-*H*), 5.15 (m, 1H, 7-*H*), 4.24, 4.10 (2dd, 2H, 6-*H*, J=10.2, 9.1, 6.8), 3.17 (m, 9H, NCH_2), 2.60 (s, 3H, CH_3-Ar), 0.97 (d, 3H, CH_3-pip, J=6.4).

Anal. Calcd for $C_{24}H_{27}N_5O_3$: C, 66.51 ; H, 6.24 ; N, 16.17. Found : C, 66.49 ; H, 6.26 ; N, 16.16.

iii : The heating of 0.01 mole of **3** with 0.01 mole of phenylisocyanate in xylene during 3 hours led quantitatively to **4**.

References

(1) Y.Wanatabe, H.Usiui, S.Kobayashi, H.Yoshiwara, T.Shibano, T.Tanaka, Y.Morishima, M.Yasuoka and M.Kanao, J.Med.Chem. 35, 189 (1992)

(2) J.L.Herndon, A.Ismaiel, S.P.Ingher, M.Teitler, and R.A.Glennon, J.Med.Chem. 35, 4903 (1992)

(3) A.Kamal and P.B.Sattur, Synthesis 892 (985)

(4) S.Purkayastha and R.P.Panzica, J.Heterocyclic Chem. 27, 743 (1990)

(5) O.Adetchessi, D.Desor, I.Forfar, C.Jarry, J.M.Leger, M.Laguerre and A.Carpy, Heterocycles in press

(6) J.J.Bosc, C.Jarry, M.Laguerre, J.Ouhabi and A.Carpy, Can.J.Chem. in press

(7) D.P.N.Satchell and R.S.Satchell,Chem.Soc.Rev. 4, 231 (1975)

(8) G.Puglisi, R.Pignatello, A.Panico, G.Mazzone, A.Corsaro, A.Caruso, M.G.Leone, M.Amico-Roxas, Eur.J.Med.Chem. 24, 277 (1989)

(9) M.Tisler and B.Stanvnik, J.Chem.Soc. Chem.Comm. 313 (1980)

(10) R.Richter and H.Ulrich, Chem.Ber. 103, 3525 (1970)

(11) J.R.Carson, G.I.Poos and H.R.Almond, J.Org.Chem. 30, 2295 (1965)

Received February 20, 1996