Pergamon

Tetrahedron Letters, Vol. 37, No. 50, pp. 9043-9046, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01972-7

A New Simple and Quantitative Synthesis of α-Aminoacid-N-Carboxyanhydrides (oxazolidines-2,5-dione)

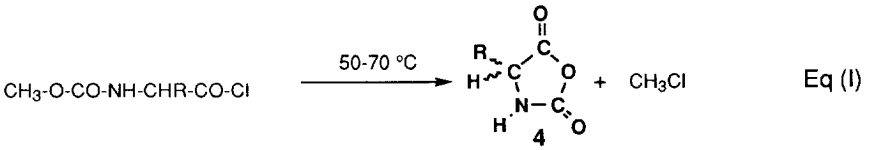
Hélène Collet*, Catherine Bied, Louis Mion, Jacques Taillades, Auguste Commeyras.

Laboratoire "Organisation moléculaire . Evolution et matériaux fluorés", associé au CNRS

Université de Montpellier II. Place E. Bataillon F-34095 Montpellier Cédex 5, France

Abstract: Nitrosation of chiral N-carbamoylaminoacids with a mixture of NO and O_2 gives, with the same configuration and in quantitative yield the corresponding α-aminoacid-N-carboxyanhydrides (NCA), well known precursors of peptides. The by products of this reaction are N_2 and H_2O.

After the discovery by Leuchs[1] in 1906 of α-aminoacid-N-carboxyanhydrides (oxazolidines-2,5-dione) (NCA) **4** (Eq I), two new routes were proposed to obtain these products, one by Curtius [2] (Eq II), the other by Fuchs-Farthing[3] (Eq III).



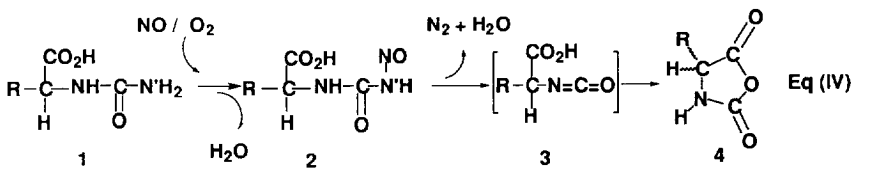
Eq (I)

CH_3CH_2-O-CO-$CHRCO_2H$ + NH_2-NH_2 ⟶ $N_3COCHRCO_2H$ ⟶ **4** Eq (II)

H_2N-CHR-CO_2H + $COCl_2$ ⟶ [Cl-CO-NH-$CHRCO_2H$] ⟶ **4** Eq (III)

Because of the large interest of the chemistry of these compounds in peptide synthesis, many authors tried to optimise these routes. Various parameters have been studied : the influence of the nature of the substituent on the oxy carbonyl group[4,5], the substitution of the halogen atom by other living groups such as $(CH_3)_3Si$-O or t-Bu$(CH_3)_2Si$-O[4,5], the use of less toxic halogenating reactants than phosgene such as oxalyl chloride, trichloromethylchloroformate, bis trichloromethylcarbamate[4,6,7]. In spite of these efforts, the syntheses described until now lead to several by-products.

In this paper, we describe a new and efficient route to NCA, which uses mild conditions, works quantitatively and liberates only H_2O and N_2 as by products (Eq IV) :



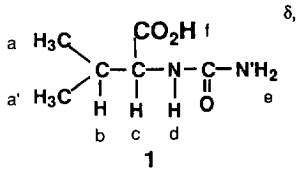
Eq (IV)

N-carbamoyl-valine **1** [13] reacts with the nitrosating system NO/O_2 to yield the N'-nitroso-N-carbamoyl-valine **2** which decomposes into α-isocyanatoacid **3** which cyclises into NCA **4**.

Alone, NO is not a nitrosating agent of **1**. It becomes able to nitrosate **1** in presence of dioxygen in different anhydrous solvents such as dioxan, acetonitrile, dimethyl sulfoxyde. This result is consistent with the general chemistry of nitric oxide [8-11].

We have used a mixture of NO/O_2 in a 1 / 0.25 ratio. In using three equivalents of this nitrosating mixture and one equivalent of **1** at 20°C, the nitrosation step was quantitative and almost instantaneous. The following decomposition step of **2** into **4** was then achieved in about 30 mn ; this evolution is accelerated when temperature is increased.

These results were obtained by monitoring the reaction directly in NMR tubes. In a typical experiment, 4 mg of D,L N-carbamoyl-valine are dissolved in 0.5 mL of DMSO-d_6 giving the following ^1H NMR data (250 MHz in DMSO-d_6):

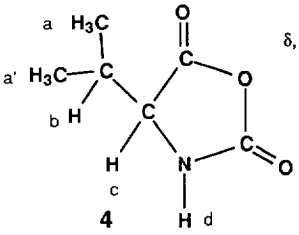


1

δ, ppm/TMS

0.78 (d, J_{ab}=7 Hz,3H,CH_3a)
0.82 (d, $J_{a'b}$ =7 Hz, 3H, CH_3a')
1.93 (m, 1H, Hb)
3.95 (dd, J_{bc} =5 Hz, J_{cd}, 9 Hz, 1H, Hc)
5.55 (s, 2H, N'H_2e)
6.11 (d, J_{cd} = 9 Hz, 1H, NHd)
12.45 (s, 1H, Hf)

After addition of the nitrosating mixture in the above conditions, a new spectrum (described below) was obtained and its evolution was followed during 30 mn at 20°C or 10 mn at 50°C. At the end of these periods, the observed signals on the spectrum correspond to those of D,L -valine-NCA spectrum (compared to authentic sample[6]) :

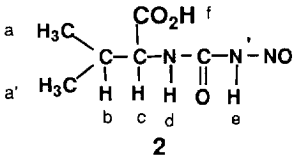


4

δ, ppm/TMS

0.84 (d, J =7 Hz, 3H, CH_3a)
0.98 (d, J =7 Hz, 3H, CH_3a')
2.14 (m, 1H, Hb)
4.35 (dd, J_{bc} = 4 Hz, J_{cd} = 1 Hz, 1H,Hc)
9.14 (dd, J_{cd} =1 Hz, 1H, Hd)

By comparison of the spectrum obtained and that of valine-NCA, we have determined the NMR data corresponding to an intermediate which can be considered as the D,L N'-nitroso-N-carbamoyl-valine **2** :



2

δ, ppm/TMS

0.86 (d, J_{ab} = 7 Hz, 3H, CH_3 a)
0.96 (d, $J_{a'b}$ =7 Hz, 3H, CH_3 a')
2.00 (m, 1H, Hb)
4.00 (dd, J_{cd} = 8.5 Hz, J_{bc} = 5 Hz, 1H, Hc)
5.6 (s, 1H, He)
6.18 (d, J_{cd} =8.5 Hz, 1H, Hd)

Effectively, we noted particularly in this spectrum three signals corresponding each of them to one proton: at 5.6 ppm a broad singlet attributed to H(e), at 6.18 ppm a doublet with a coupling constant J=8.5 Hz attributed to H(d), and the third one at 4.00 ppm which is corresponding to H(c). By irradiating H(c), we noted the disappearance of the coupling constant of the proton H(d) at 6.18 ppm.

These results show clearly that the nitrosation of the N-carbamoyl-aminoacid is regiospecific in N', unlike what could be expected referring to the nitrosation of monoalkylureas, which leads to stable N-alkyl-N-nitrosoureas [12].

When the reaction is performed in an aqueous organic solvent (CH_3CN-H_2O), the intermediate **2** cannot be detected, but the NCA is always quantitatively formed. Its stability depends on the proportion of water present in the reaction medium.

More surprising is the ease of this reaction when performed by reacting the solid N-carbamoyl-valine with the gaseous mixture NO/O_2, without any solvent. Under helium atmosphere, at room temperature, with the same stoechiometry as above, the nitrosation of the N-carbamoyl-valine leads quantitatively to valine-NCA , at more or less the same rate than in presence of a solvent. The analysis by mass spectrometry of the reaction gas atmosphere, at the end of the reaction, shows the formation of N_2 and H_2O in the reaction pathway.

Finally, the synthesis of NCA **4** from N-carbamoyl-aminoacid **1** occurs in the two following steps shown in Eq (IV) : nitrosation and decomposition occuring probably through the α-isocyanato-acid intermediate **3**. Such a mechanism can be related with two other reactions. The first one concernes the well known decomposition of chloroethylnitrosourea leading to an isocyanato group [13], and the second one is the last step of the synthesis of hydantoïne which consists into the cyclisation of an α-isocyanatoamide intermediate [8].

Moreover, this reaction has been performed with other aminoacids that is to say glycine, alanine, phenylalanine, methionine, leucine with the same quantitative yield. With methionine, less than 20 % of the product was oxidised on sulfur.

When we used chiral N-carbamoyl-(L)-valine as the starting material, pure (L)-valine was recovered after hydrolysis. This result shows that the formation of NCA occurs without any racemization.

References

1 H.Leuchs, *Ber. Dtsch. Chem. Ges.*, **1906**, *39*, 857-859

2 T. Curtius, H. Hochschwender, H. Meier, W.Lehmann, A. Benkeiser, M. Shenk, W. Nirbatz, J. Gaier, W. Mühlhäusser, *J. Prakt. Chem.*, **1930**, *125*, 211-302

3 (a) A. C. Farthing, R. J. W Reynolds, *Nature* (London), **1950**, *165*, 647

(b) D. Coleman, A. C. Farthing, *J. Chem. Soc.*, **1951**, 3218-3222

4 H. R. Kricheldorf, α-Aminoacid-N-Carboxy-Anhydrides and Related Heterocycles, Springer-Verlag Berlin 1987.

5 S. Mobashery, M. Johnston, *J. Org. Chem.*, **1985**, *50*, 2200-2202.

6 W. H. Daly, D. Poche, *Tetrahedron. Lett.*, **1988**, *29*, 5859-5862.

7 R. Wilder, S. Mobashery, *J. Org. Chem.*, **1992**, *57*, 2755-2756

8 J. Taillades, I. Beuzelin, L. Garrel, V. Tabacik, A. Commeyras, submitted to *Origin of life and evolution of the biosphere*.

9 "NITROSATION", D.L.H. Williams, Cambridge University Press, **1988**, 24-28.

10 M. Fontecave, J-L, Pierre, *Bull. Soc. Chim. Fr.*, **1994**, *131*, 620-631.

11 L. Bohé, X. Lusinchi, *Les Cahiers Imabio*, **1994**, *13*, 15-26.

12 J.K. Snyder, L.M. Stock, *J. Org. Chem.*, **1980**, *45*, 886-891.

13 H. Süly-Vargha, J. Bodi, M.Meszaros, K. Medzihradszky, *J. Med. Chem.*, **1988**, *31*, 1492-1495.

(*Received in France* 2 *July* 1996; *accepted* 1 *October* 1996)