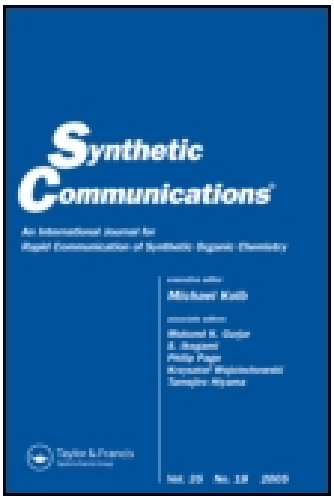

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A Convenient Method of Protection and Mild Deprotection of α-Aminoacids

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SYNTHETIC COMMUNICATIONS, 23(15), 2101-2111 (1993)

A CONVENIENT METHOD OF PROTECTION AND MILD DEPROTECTION OF α–AMINOACID GROUP FOR THE SYNTHESIS OF FUNCTIONAL α-AMINOACIDS.

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Jérôme Rudelle [2], Jean-Louis Bonnemain [2].

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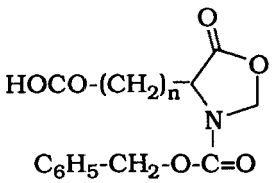
Abstract :
Functionalisation of β or γ carboxyl group of aspartic and glutamic acids with labile substituents was performed *via* the use of N-trichloroethoxycarbonyl-5-oxazolidinone as protective group.

The purpose of this work was regioselective functionalisation with aromatic amines, benzylic alcohols and phenols of β or γ carboxyl group of aspartic and glutamic acids. So as to do this, we have tried to use classical methods for masking carboxyl and amino functions employed in peptide synthesis (1,2). Unfortunately, on account of new bonds fragility, these classical methods revealed inadequate : when we have restored α-aminoacid function, we have also observed the breaking of the new bond or modifications on the functional group.

* To whom correspondence should be addressed.

In order to avoid these drawbacks, we have decided to work with a mixed protective group, releasing α-aminoacid function in one step. For this purpose, we have synthesised at first N-benzyloxycarbonyl-5-oxazolidinones :

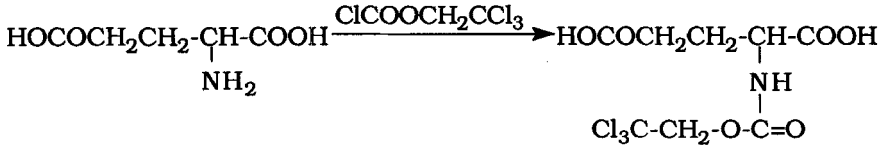


(3,4)

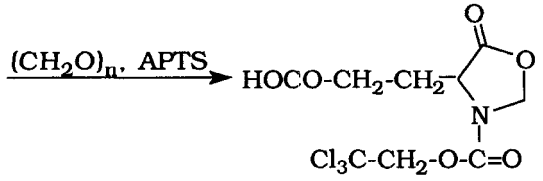
Then, when the carboxyl group was functionalized, the α-aminoacid function was restored by catalytic hydrogenation : this usual way in peptide synthesis was still too drastic in our case.

Finally, we have resolved our problem by changing benzyl group in the above structure by trichlorethyl group, the unmasking being made with zinc in acetic acid/water in well defined conditions (see experimental part).

A typical procedure is as follows :

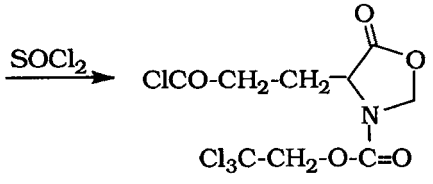


1b, Rdt = 86%



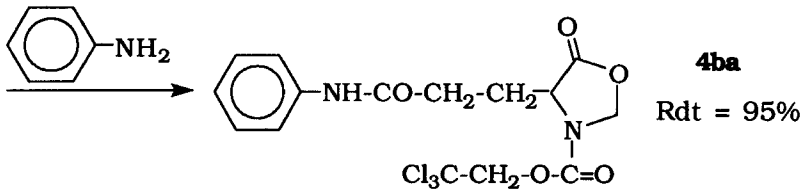
2b

Rdt = 70%

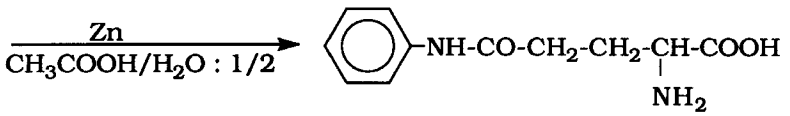


3b

Rdt = 95%



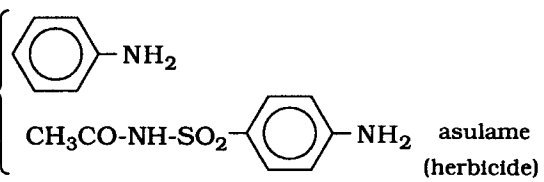
4ba
Rdt = 95%



6ba , Rdt = 80%

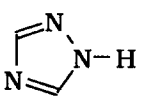
By this mean, we have branched the following molecules on aspartic and glutamic acids :

Primary amines

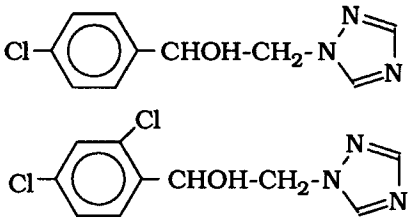


asulame
(herbicide)

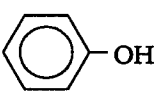
Secondary amine



Benzylic alcohols



Phenol



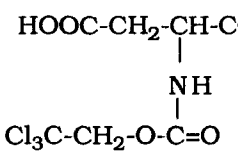
EXPERIMENTAL

Preparation of derivatives 1

Procedure : A solution of 0.375 mol (31.5g) of $NaHCO_3$ in water (125 ml) was poured in a 500 ml three-necked flask equipped with a mechanical stirrer, a

thermometer, a reflux condenser and an isobar dropping funnel. To this solution, 0.1 mol (13.3g) of aspartic acid or 0.1 mol (14.7g) of glutamic acid was slowly added at room temperature with moderate stirring. The reaction was endothermic and the temperature was reduced (10°C). Then 0.11 mol (23.3g) of 2,2,2-trichloroethylchloroformate was added dropwise and the temperature arose to 35°C. The resulting stirred solution was heated at 40-45°C during 6h, then was maintained at 20°C during 15h. The aqueous phase was washed by ether (30ml), then acidified dropwise by a solution of HCl 5M (Red Congo turned in blue) and extracted by ethylacetate (3 x 50 ml). The combined extracts were dried ($MgSO_4$). After removal of the solvents, the product was obtained as an yellow oil.

Products 1 :

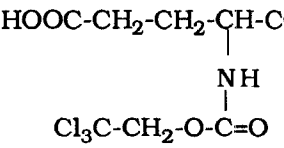


1a

Oil ; Yield = 78 %.

^1H NMR (δppm, acetone d_6) : 2.7-3.3 (m, 2H, CH_2CH) ; 4.4-5.1 (m, 3H, CH, CH_2CCl_3) ; 6.95 (d, J 8.6Hz, 1H, NH) ; 10.53 (s, 2H, OH).

^{13}C NMR (δppm, acetone d_6) : 36.5 ; 51.2 ; 75.2 ; 96.5 ; 155.3 ; 173.0 ; 173.4.



1b

Oil ;Yield = 86 %.

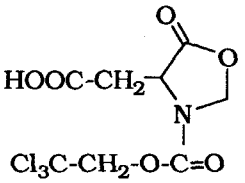
^1H NMR (δppm, acetone d_6) : 1.55-2.75 (m, 4H, CH_2CH_2) ; 4.15-4.55 (m, 1H, CH) ; 4.70 (s, 2H, CH_2CCl_3) ; 6.65 (d, J 8Hz, 1H, NH) ; 10.6 (s, 2H, OH).

Preparation of oxazolidinones 2

Procedure : A solution of a derivative **1** (0.04 mol) in toluene (200 ml) was poured in a 500ml two necked flask fitted with a Dean-Stark apparatus and a reflux condenser. 0.08 mol (2.4g) of polyoxymethylene, then 0.0024 mol (0.46g) of p-toluenesulfonic acid were added. The mixture was refluxed during about 3h, until the end of the azeotropic separation. After cooling, ethylacetate (50ml) was added. The organic phase was separated, washed with an aqueous solution of K_2CO_3 0.3M (4ml), then with water (3 x 5 ml). After drying ($MgSO_4$), the solvents were removed. The product **2a** was an oil, whereas **2b** was appeared as white crystals ; this material was purified by trituration with anhydrous ether

(5 ml), then by adding petroleum ether (5ml). The crystals were filtered and dried over P_2O_5 in vacuo.

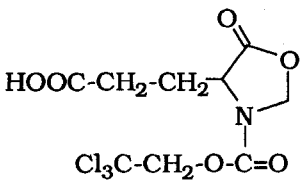
Products 2 :



2a

Oil ; Yield = 94%.
^1H NMR (δppm, acetone d_6) : 3.08 and 3.3 (2dd, J_{AB} 18.1Hz, J_{AX} 4.2Hz, J_{BX} 2.9Hz, 2H, CCH_2C) ; 4.4-4.65 (m, 1H, CH) ; 4.7-5.2 (s, 2H, CH_2CCl_3) ; 5.2-5.8 (m, 2H, NCH_2O) ; 10.3 (s, 1H, OH).

^{13}C NMR (δppm, acetone d_6) : 52.8 ; 62.2 ; 75.8 ; 79.4 ; 96.6 ; 152.1 ; 172.2 ; 172.7.



2b

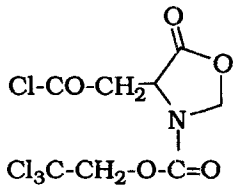
White crystals, F 116°C ; Yield = 85%.
^1H NMR (δppm, acetone d_6) : 2.15-2.65 (m, 4H, CH_2CH_2) ; 4.51 (t, J 5.7Hz, 1H, CH) ; 4.82 and 4.92 (2d, J_{AB} 12.2Hz, 2H, CH_2CCl_3) ; 5.38 and 5.58 (2d, J_{AB} 4.3Hz, 2H, NCH_2O) ; 10.32 (s, 1H, OH).

^{13}C NMR (δppm, acetone d_6) : 26.8 ; 29.7 ; 55.2 ; 75.8 ; 78.7 ; 96.3 ; 152.4 ; 172.5 ; 174.5.

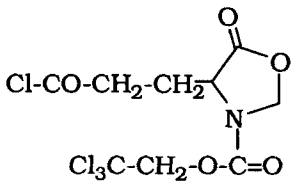
Preparation of acid chlorides 3

Procedure : Under a well ventilated hood, a solution of 0.01 mol of oxazolidinone **2** and 0.05 mol of thionyl chloride (3.7ml) in distillated CCl_4 (2 ml) was poured in a 50ml flask equipped with a thermometer and a reflux condenser bearing a gas meter. Just after the mixing of reagents, gas was evolved and the mixture was heated to reflux with the assistance of a water-bath, until no more gas evolved. After removal of the solvent, the chloride was treated with distillated CH_2Cl_2 (2 x 15 ml) and this solution was evaporated (elimination of traces of hydrogen chloride and sulfur dioxide). The crude chlorides **3a** and **3b** were employed without an other purification.

Products 3 :



3a

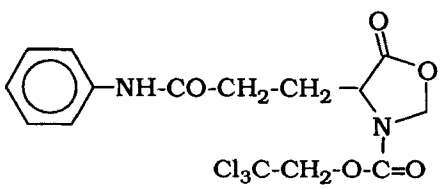


3b

Preparation of amides 4

Procedure : The derivative **3** was dissolved in CH_2Cl_2 (50 ml) and placed in a 100 ml three-necked flask flame dried under nitrogen stream. The reagent (0.095 mol) was added in small portions, at room temperature, alternatively with pyridine (0.8 ml). The reaction was exothermic (the temperature arose to 28-30°C). The mixture was heated at 40°C during 3h, and allowed to cool at room temperature during 15h, then it was diluted with CH_2Cl_2 (20 ml). The mixture was washed with water (15 ml), $NaHCO_3$ saturated solution (15 ml) (except in the case of reaction with asulame) and water (2 x 15 ml). The organic phase was dried ($MgSO_4$), filtered and the solvents were removed under reduced pressure.

Products 4 :

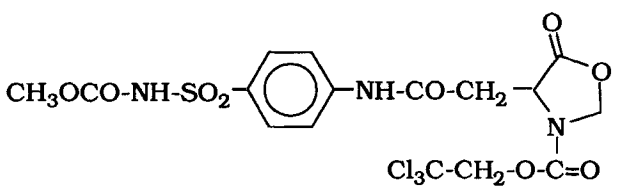


4ba

Yellow-brown oil ; Yield = 95 %.
^1H NMR (δppm, acetone d_6) : 2.1-2.75 (m, 4H, CH_2CH_2) ; 4.53 (t, 1H, CH) ; 4.79 and 4.89 (2d, J_{AB} 12.1Hz, 2H, CH_2CCl_3) ; 5.37 and 5.57 (2d, J_{AB} 4.2Hz, 2H, NCH_2O) ; 6.85-8.00 (m, 5H, C_6H_5) ; 9.21 (s, 1H, NH).

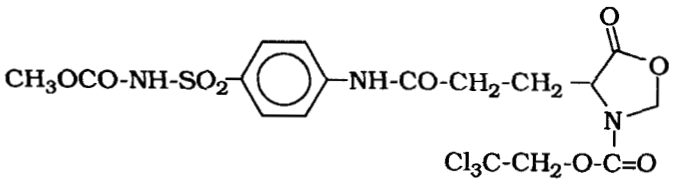
^{13}C NMR (δppm, acetone d_6) : 27.2 ; 32.7 ; 55.4 ; 75.7 ; 78.8 ; 96.3 ; 120.5 ; 129.7 ; 140.3 ; 150.7 ; 152.3 ; 170.8 ; 172.7.

IR (cm^{-1}) : 3325F (NH) ; 1805F, 1725F (C=O ester) ; 1670F (C=O amide) ;1600m, 1500m, 755m, 705m (C_6H_5).



4ab

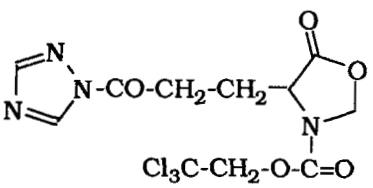
Reddish-yellow oil ; Yield = 80%.
^{1}H NMR (δppm, DCl/D_2O) : 3.2-3.4 (m, 2H, $COCH_2$) ; 3.65 (s, 3H, CH_3O) ; 4.57 (t, J 4.75Hz,1H, CH) ; 4.80 and 4.90 (2d, J_{AB} 12.1Hz, 2H, CH_2CCl_3) ; 5.40 and 5.60 (2d, J_{AB} 4.3Hz, 2H, NCH_2O) ; 7.85 and 7.94 (2d, J_{AB} 9.4Hz, 4H, C_6H_4) ; 9.00 (s, 1H, NH) ; 9.53 (s, 1H, NH).



4bb

Yellow-brown crystals, F 100°C ; Yield = 85%.
^{1}H NMR (δppm, acetone d_6) : 2.15-2.85 (m, 4H, CH_2CH_2) ; 3.65 (s, 3H, CH_3O) ; 4.57 (t, J 4.5Hz, 1H,CH) ; 4.80 and 4.90 (2d, J_{AB} 12.1Hz, 2H, CH_2CCl_3) ; 5.40 and 5.60 (2d, J_{AB} 4.3Hz, 2H, NCH_2O) ; 7.85 and 7.94 (2d, J_{AB} 9.4Hz, 4H, C_6H_4) ; 9.00 (s, 1H, NH) ; 9.53 (s, 1H, NH).

^{13}C NMR (δppm, acetone d_6) : 26.6 ; 32.8 ; 53.5 ; 55.1; 75.7 ; 78.7 ; 96.2 ; 119.7 ; 130.2 ; 134.3 ; 144.8 ; 152.3 ; 152.6 ; 171.7 ; 172.7.



4bc

Yellow-brown oil ; Yield = 90%.
^{1}H NMR (δppm, acetone d_6) : 2.15-2.65 (m, 2H, $COCCH_2$) ; 3.05-3.55 (m, 2H, $COCH_2$) ; 4.66 (t, J 6.3Hz, 1H, CH) ; 4.87 (s, 2H, CH_2CCl_3) ; 5.47 and 5.65 (2d, J_{AB} 4.5Hz, 2H, NCH_2O) ; 8.10 (s, 1H, H_3 triazole) ; 9.05 (s, 1H, H_5 triazole).

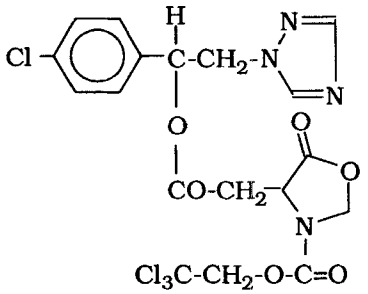
^{13}C NMR (δppm, acetone d_6) : 25.8 ; 31.0 ; 55.1 ; 75.8 ; 78.9 ; 96.2 ; 144.9 ; 152.7 ; 154.2 ; 171.0 ; 172.7.

IR (cm^{-1}) : 1805F, 1755F, 1730F (C=O) ; 1495m, 755m, 710m (C_6H_5).

Preparation of esters 5

Procedure : We have employed the same process that this described for the preparation of **4**.

Products 5 :

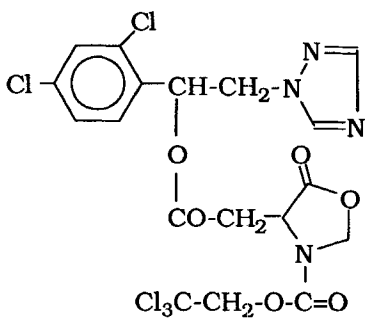


2 diastereoisomers

5aa

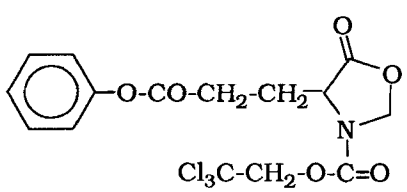
Yellow-brown oil ; Yield = 79 %.
^{1}H NMR (δppm, acetone d_6) : 2.9-3.6 (m, 2H, CH_2CO) ; 4.4-5.5 (m, 7H, CH_2CCl_3, CH_2N, CHCO) ; 6.1-6.4 (m, 1H, Aryl-CH) ; 7.35 and 7.45 (2s, 4H, C_6H_4Cl) ; 7.84 (s, 1H, H_3 triazole) ; 8.25 and 8.28 (2s, 1H, H_5 triazole).

^{13}C NMR (δppm, acetone d_6) : 53.9 ; 54.1 ; 55.3 ; 57.5 ; 62.1 ; 75.7 ; 76.0 ; 79.3 (CH_2) ; 72.3 (CHN) ; 74.9 ; 75.1 (CHO) ; 129.6 ; 129.7 ; 129.9 ; 130.1 (aryl-CH) ; 145.7 ; 150.9 ; 152.5 ; 152.9 (CH triazole) ; 96.5 ; 135.4 ; 136.5 ; 136.8 ; 142.1 ; 152.0 ; 170.2 ; 172.2 (quaternary C).



5 ab

Yellow-brown oil ; Yield = 85 %.
^{1}H NMR (δppm, acetone d_6) : 3.0-3.8 (m, 2H, CH_2CO) ; 4.4-5.6 (m, 7H, CH_2CCl_3, CH_2N, CHCO) ; 6.2-6.6 (m, 1H, aryl-CH) ; 6.9-7.6 (m, 3H, C_6H_3) ; 7.7 (s, 1H, H_3 triazole) ; 8.25 (s, 1H, H_5 triazole).



5ba

Oil ; Yield = 65 %.
^{1}H NMR (δppm, acetone d_6) : 2.1-3.0 (m, 4H, CH_2CH_2) ; 4.52 (t, J 5.5Hz, 1H, CH) ; 4.76 and 4.90 (2d, J_{AB} 12.1Hz, 2H, CH_2CCl_3) ; 5.40 and 5.57 (2d, J_{AB} 4.5Hz, 2H, NCH_2O) ; 7.00-7.40 (m, 5H, C_6H_5).

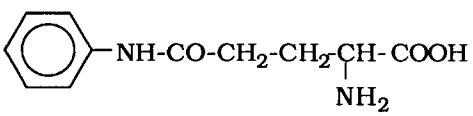
^{13}C NMR (δppm, acetone d_6) : 25.8 ; 30.5 ; 54.1 ; 75.0 ; 77.9 ; 95.3 ; 123.4 ; 125.6 ; 129.4 ; 130.8 ; 151.5 ;170.4 ; 171.5.

IR (cm^{-1}) : 1805F, 1755F, 1730F (C=O) ; 1495m, 755m, 710m (C_6H_5).

Preparation of derivatives 6

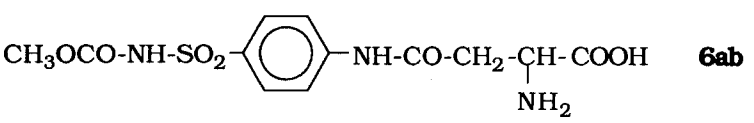
Procedure : A solution of the compound **4** (0.0018 mol) in glacial acetic acid (6 ml) was placed in a 50ml flask ; this solution was stirred with a magnetic stirrer. Water (7 ml), then zinc powder (1g), were added. The time of the reaction was deducted from the addition of zinc. When the suspension of zinc was homogen (about 2 min), water (5 ml) was slowly added and the stirring was continued at room temperature during 5 min. The mixture was filtered immediately and washed with CH_2Cl_2 (2 x 10 ml). The aqueous phase was concentrated and crystals generally appeared. They were treated with CH_3OH (25 ml), filtered and dried in vacuo (P_2O_5) or in drying vacuum stove at 100°C.

Products 6 :



6ba

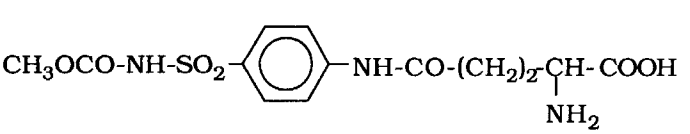
Oil ; Yield = 80 %.
^{1}H NMR (δppm, DMSO d_6/DCl/D_2O) :2.15-3.00 (m, 4H, CH_2CH_2) ; 4.00-4.60 (m, 1H, CH) ; 7.00-8.00 (m, 9H, C_6H_5, OH, NH, NH_2).



6ab

White crystals, F>260°C ; Yield = 77%.
^{1}H NMR (δppm, DCl/D_2O) : 3.3-3.6 (m, 2H, $COCH_2$) ; 3.8 (s, 3H, OCH_3) ; 4.8 (t, J 5.4Hz, 1H, CH) ; 5.80 (s, 5H, OH, NH_2, NH) ; 7.75 and 7.95 (2d, J_{AB} 9.1Hz, 4H, C_6H_4).

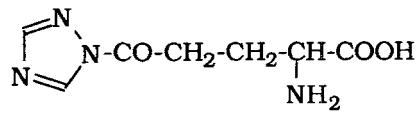
^{13}C NMR (δppm, DCl/D_2O) : 38.3 ; 52.2 ; 56.7 ; 122.8 ; 131.7 ; 135.2 ; 145.1 ; 155.6 ; 172.1 ; 173.4.



6bb

White crystals, F > 260°C ; Yield = 70%.
^{1}H NMR (δppm, DCl/D_2O) : 2.15-3.00 (m, 4H, CH_2CH_2) ; 3.65 (s, 3H, CH_3O) ; 4.38 (t, J 5.4Hz, 1H, CH) ; 6.96 (s, 5H, NH_2, NH, OH) ; 7.62 and 7.81 (2d, J_{AB} 9Hz, 4H, C_6H_4).

^{13}C NMR (δppm, DCl/D_2O) : 25.5 ; 30.5 ; 53.0 ; 55.0 ; 125.6 ; 130.6 ; 139.4 ; 153.4 ; 171.6 ; 173.6 ; 176.9.



6bc

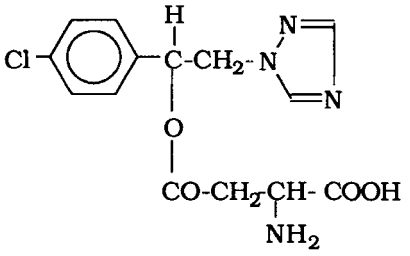
White crystals, F > 260°C ; Yield = 95%.
^{1}H NMR (δppm, DCl/D_2O) : 2.15-2.85 (m, 4H, CH_2CH_2) ; 4.24 (t, J 6.6Hz, 1H, CH) ; 5.24 (s, 3H, OH, NH_2) ; 9.16 (s,2H, H_3 and H_5 triazole).

^{13}C NMR (δppm, DCl/D_2O) : 26.0 ; 30.9 ; 53.5 ; 143.8 ; 146.5 ; 172.3 ; 177.2.

Preparation of derivatives 7

Procedure : We have employed the same process that this described for the preparation of **6**.

Products 7 :

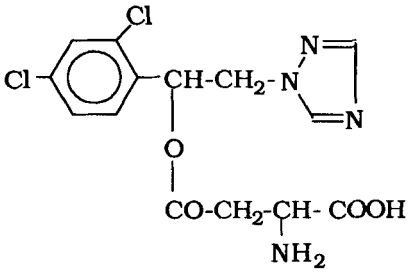


2 diastereoisomers

7aa

White crystals, F > 218°C ; Yield = 70%.
^{1}H NMR (δppm, DCl/D_2O) : 3.2-3.45 (m, 2H, CH_2CO) ; 4.53 and 4.56 (2t, J_1 5.2Hz, J_2 6.0Hz, 1H, *CH) ; 4.9-5.1 (m, 2H, CH_2N) ; 5.90 (s, 3H, OH, NH_2) ; 6.2-6.4 (m, 1H, Aryl-*CH) ; 7.41 and 7.43 (2s, 4H, C_6H_4Cl) ; 8.89 and 8.91 (2s, 1H, H_3 triazole) ; 9.84 (s, 1H, H_5 triazole).

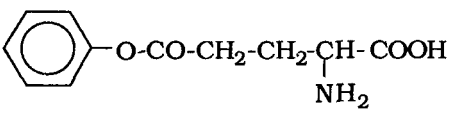
^{13}C NMR (δppm, DCl/D_2O) : 36.1 ; 36.4 ; 51.4 ; 57.7 ; 76.3 ; 130.2 ; 130.4 ; 130.5 ; 131.7 ; 135.6 ; 137.1 ; 144.4 ; 145.9 ; 172.0 ; 172.2 ; 172.3.



2 diastereoisomers

7 ab

White crystals, F > 260°C ; Yield = 65%.
^{1}H NMR (δppm, DCl/D_2O) : 3.0-3.45 (m, 2H, CH_2CO) ; 4.4-4.65 (m, 1H, CHCOO) ; 4.70-5.25 (m, 2H, CH_2N) ; 5.90 (s, 3H, OH, NH_2) ; 6.40-6.60 (m, 1H, aryl-CH) ; 7.10-7.60 (m, 3H, $C_6H_3Cl_2$) ; 8.83 and 8.85 (2s, 1H, H_3 triazole) ; 9.91 (s, 1H, H_5 triazole).



7ba

Oil ; Yield = 58%.
^{1}H NMR (δppm, acetone d_6) : 2.10-3.30 (m, 4H, CH_2CH_2) ; 4.00-4.60 (m, 1H, CH) ; 6.6-7.5 (m, 5H, C_6H_5) ; 7.60 (s, 3H, OH, NH_2).

IR (cm^{-1}) : 3300F (NH_3^+) ; 1750F, 1690F (C=O) ; 1495m (C_6H_5).

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