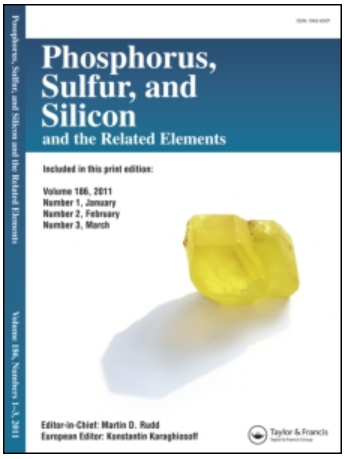

Phosphorus, Sulfur, and Silicon and the Related Elements

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Synthesis and Thermal Isomerization of Carboxylic and Phosphonic α-Aminoesters Substituted With a Triazole Ring

S. Achamlale[a]; H. Mabrouk[a]; A. Elachqar[a]; A. El Hallaoui[a]; S. El Hajji[a]; A. Alami[a]; J. Bellan[b]; M. R. Mazières[b]; J. G. Wolf[b]; M. Pierrot[c]

[a] Laboratoire de Chimie Organique, Université sidi Mohamed Ben Abdellah, Fès-Atlas, Maroc [b] Laboratoire de Synthèse et Physicochimie de Molécules d'Intérêt Biologique, Université Paul Sabatier, Toulouse, France [c] Laboratoire de Bioinorganique Structurale, Université d'Aix-Marseille, Escadrille Normandie Niemen, Marseille, France

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Laboratoire de Chimie Organique, Université sidi Mohamed Ben Abdellah, Fès-Atlas, Maroc

J. Bellan
M. R. Mazières
J. G. Wolf
Laboratoire de Synthèse et Physicochimie de Molécules d'Intérêt Biologique, Université Paul Sabatier, Toulouse, France

M. Pierrot
Laboratoire de Bioinorganique Structurale, Université d'Aix-Marseille, F.S.T. St Jérôme, Escadrille Normandie Niemen, Marseille, France

Thermal isomerization of phosphonic α-aminoesters bearing a 4,5-carboxymethyltriazole ring in α position is described. The results are analyzed by ^{31}P, ^{1}H, and ^{13}C NMR spectroscopy and X-ray crystallography. The same phenomenon is also observed in the case of carboxylic amino acids analogs. It does not occur with triazoles bearing a substituent other than carboxymethyl.

Keywords 1,2,3-triazole; α-aminoacid; aminophosphonate; thermal isomerization

INTRODUCTION

Due to their important biological activities, for example, as enzyme inhibitors,[1] antiepileptics,[2] or neuroexcitators,[3] α-amino acids are

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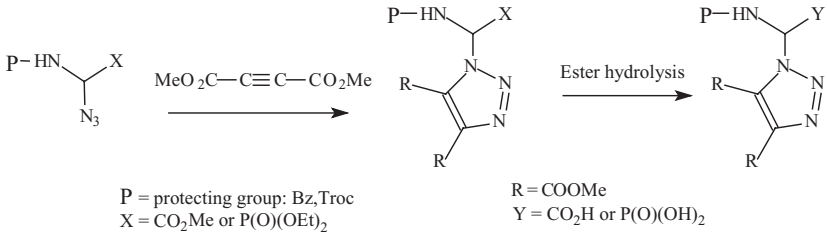
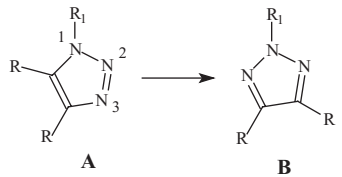
Address correspondence to J. Bellan, Laboratoire de Synthése et Physicochimie de Molécules d' Intérêt Biologique, LSPCMIB, UMR CNRS 5068, Université Paul Sabatier, F-31062 Toulouse cedex 9, France. E-mail: bellan@chimie.ups-tlse.fr

widely studied. Heterocyclic α-amino acids constitute an interesting class of compounds due to their remarkable pharmacological properties.[4] We have previously reported the synthesis of new carboxylic and phosphonic α-amino acids bearing a substituted triazole side chain.[5a] The key step of synthesis is a 1,3 dipolar cycloaddition between an *N*-protected α-azido aminoester and an acetylenic compound (Scheme 1).[5b–5j]



SCHEME 1

Hydrolysis of the ester occurs readily in basic media, whereas all the attempts to deprotect the amine function have failed. Unfortunately, cleavage of the bond between the α-carbon atom and the nitrogen atom of the triazole ring occurred prior to deprotection. During this synthesis, we observed a migration of the amino-acid moiety (R_1) on the triazole ring, from the nitrogen atom 1 to the nitrogen atom 2 (Scheme 2).

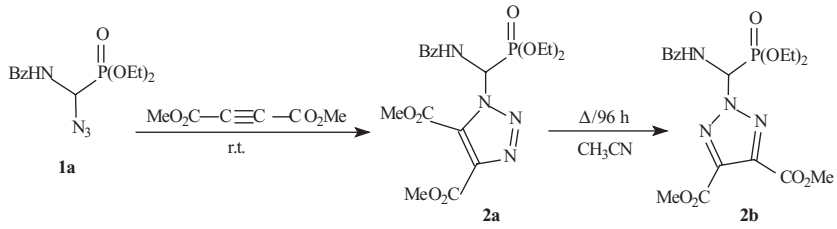


SCHEME 2

The aim of this article is to report these results and to propose a consistent mechanism.

RESULTS AND DISCUSSION

Diethyl-(2-benzoylamino-2-(4,5-dicarboxymethyl-1,2,3-triazol-1-yl)-methyl) phosphonate **2a** was prepared by a reaction of diethyl-(2-azido-2-benzoylaminomethyl) phosphonate **1a** with dimethyl acetylenedicarboxylate at room temperature (Scheme 3).



SCHEME 3

Crystallization of crude material from diethylether/dichloromethane afforded **2** as a mixture of **2a** and **2b** (ratio 90:10) according to the ^{31}P NMR spectrum, which showed two signals at $\delta = 12.8$ and 13.1 ppm.

Total and irreversible transformation of **2a** into **2b** was observed after heating the mixture (**2a**: 90%, **2b**: 10%) in acetonitrile for 96 h in the ^{31}P NMR spectrum (Figure 1).

Isomers **2a** and **2b** were characterized by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The ^{1}H NMR spectrum of **2a** showed two singlets for the protons of the methyl ester groups, whereas for **2b** only one singlet was observed. The ^{13}C NMR spectrum of compound **2b** contained one signal for the carbon atom of the CH_3 ester groups instead of two in the case of **2a**, and only one signal for the two carbonyl carbon atoms. Simplification was also observed for the quaternary carbon atoms of the triazole ring.

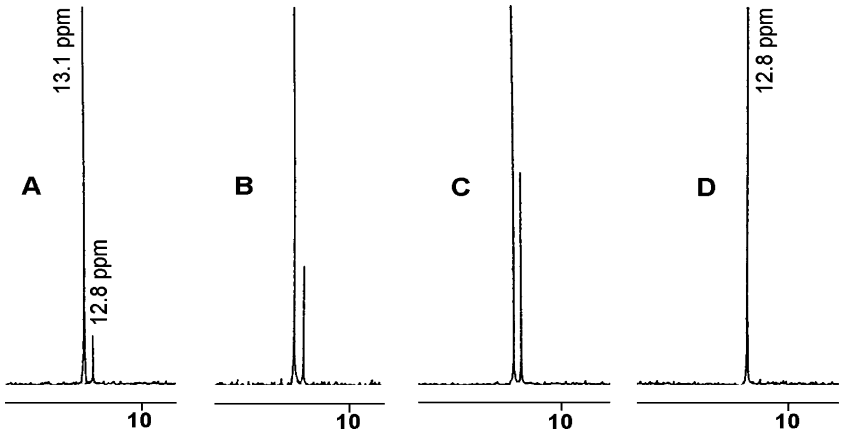
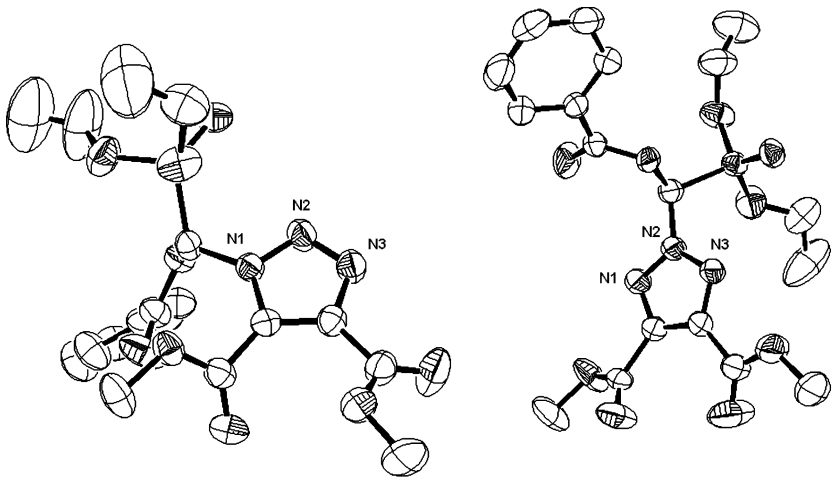


FIGURE 1 Evolution in the ^{31}P NMR spectrum (CH_3CN) during the transformation of **2a** ($\delta\,^{31}P = 13.1$ ppm) into **2b** ($\delta\,^{31}P = 12.8$ ppm). **A** (r.t.), **B** (12 h at 82°C), **C** (24 h at 82°C), **D** (96 h at 82°C).



2a **2b**

FIGURE 2 ORTEP representation of the structures of **2a** CCDA 297111 contains the supplementary crystallographic data for this article. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk./data_request/cif and **2b** (see Experimental section) obtained by single crystal X-ray diffraction.

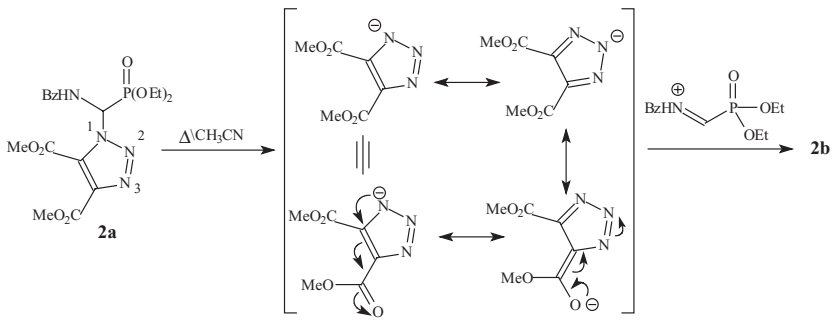
The mass spectrum of compound **2b** (FAB mode) contained two peaks at m/z = 455 $[MH]^+$ and m/z = 477 $[M+Na]^+$, which were identical with those observed for compound **2a**, indicating that the two compounds are structural isomers. NMR (^{31}P, ^{1}H, ^{13}C) and MS data led us to propose that an isomerization process occurred at the triazole ring with a migration of the diethyl-(2-benzoylaminomethyl) phosphonate group from the N-1 to the N-2 position.

This hypothesis was confirmed by X-ray diffraction of single crystals of the two isomers (Figure 2).

The thermodynamically more stable compound **2b** is the one in which the triazole ring is linked to the aminoester α-carbon atom through N-2.

Mechanism

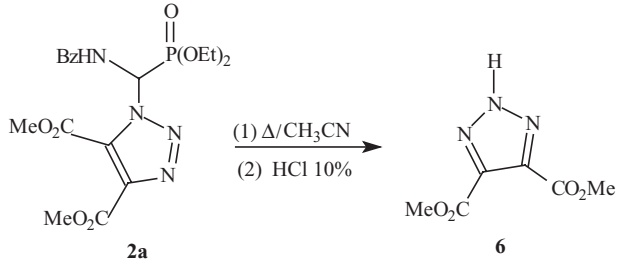
We studied this reaction in order to determine by what process the isomerization takes place. A probable mechanism involved cleavage of the exocyclic C-N-1 bond, which resulted in the formation of two charged fragments, an iminium cation and a triazolate anion. Delocalization of the negative charge on N-2 and nucleophilic attack of this nitrogen atom on the iminium ion afforded compound **2b** (Scheme 4).



SCHEME 4

Moreover, it is likely that the presence of the carboxymethyl groups favored delocalization of the negative charge on the N2 atom (Scheme 4). This mechanism seems plausible since the C(α)—N (heterocycle) bond was very weak and the rupture took place easily.

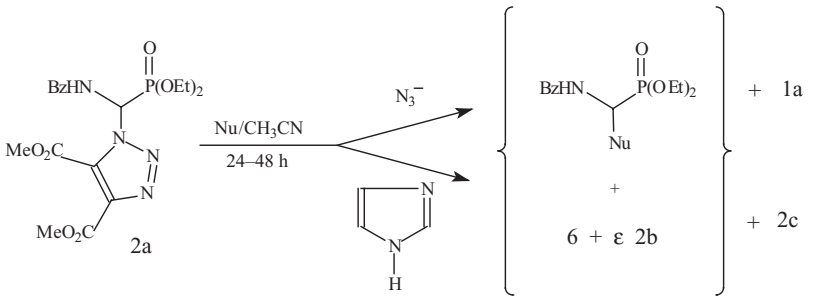
The presence of a triazolate anion is confirmed by two experiments. First, the hydrolysis of different aliquots sampled during the 96-h isomerization process by 10% aq HCl afforded the triazole **6** quantitatively (Scheme 5). In this case, the protonation of the triazolate anion was the main reaction.



SCHEME 5

In a second experiment, we introduced a nucleophile in the reaction medium. Using sodium azide (NaN_3) as a nucleophile, an attack on the iminium ion led in the case of **2a** to the formation of the diethyl-(2-azido-2-benzoylaminomethyl) phosphonate **1a** with traces of **2b**. In the same way, using imidazole as a nucleophile, we obtained diethyl (2-imidazolyl-2-benzoylaminomethyl) phosphonate **2c** and also traces of **2b** (Scheme 6).

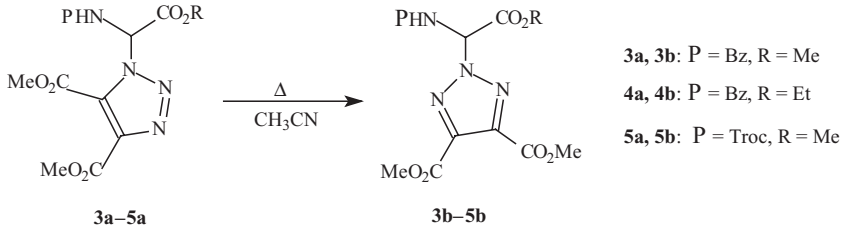
These experiments enforce the hypothesis that the isomerization mechanism is an intermolecular process. This study was extended to the



SCHEME 6

carboxylic aminoesters, and the isomerization phenomenon was found to be general if the α-substituent is a 4,5-carboxymethyl triazolyl group (Scheme 7).

Most probably, the carboxymethyl group favors delocalization of the negative charge on to the N-2 atom of the triazolate anion (Scheme 4).



SCHEME 7

In the case of aminoesters bearing a triazole ring substituted by other groups than carboxymethyl, e.g., 4-phenyltriazolyl or 4-ethoxycarbonyltriazolyl, isomerization and substitution did not occur.

Cases of isomerization of triazoles have been reported in the literature. Thus, Birkofer and Wegner[6] observed that the triazole ring carrying a trimethylsilyl group on the N1 nitrogen atom undergoes isomerization by migration of the trimethylsilyl group from the N1 to the N2 nitrogen atom. For the acetylation of these *N*-trialkylsilyltriazoles by action of acetic acid derivatives, the authors[7,8] observed at a low temperature 1-acetyltriazole and traces of 2-acetyltriazole; by heating to 150°C, an acid-catalyzed transformation of 1-acetyltriazole to 2-acetyltriazole occurred.

This phenomenon was also observed by Ykman et al.[9,10] in the synthesis of *N*-acetyltriazoles by a reaction of phosphorus ylides with

azides. The authors showed that isomerization is an intermolecular process and requires the presence of a base.

It is interesting to note that in our case, isomerization occurs in a neutral reaction medium (refluxing acetonitrile). This reaction is irreversible and complete after three days.

CONCLUSION

1,3-dipolar cycloaddition between an *N*-protected α-azido aminoester and an acetylene afforded α-aminoesters substituted with a 1,2,3-triazole ring. Thermal isomerization of these compounds in a neutral medium led to more stable[11,12] symmetric compounds in which the triazole ring was linked to the aminoester moiety by the N-2 atom.

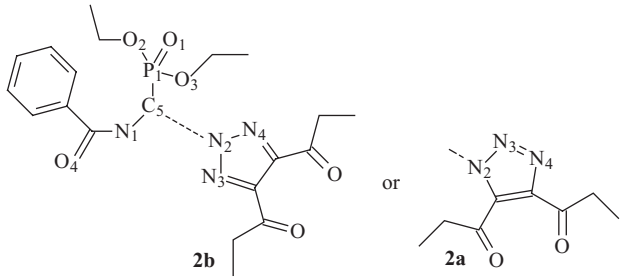
EXPERIMENTAL

^{1}H NMR spectra were recorded on a Brucker AC 250 (250 MHz) instrument, with TMS as internal reference. ^{31}P NMR spectra were recorded on a Brucker AC 80 (32.44 MHz) instrument, and ^{13}C NMR spectra were obtained with a Brucker AC 200 (62.89 MHz) instrument. Microanalyses were performed by the Ecole Nationale Supérieure de Chimie de Toulouse. Mass spectra were measured in DCI (NH_3) or FAB mode by means of a Nermag R10-10 mass spectrometer (Université Paul Sabatier, France). Melting points were obtained with an electrothermal point apparatus and are uncorrected.

X-ray structure determination was performed at r.t. (298 K) for **2a** and **2b** on a Nonius Kappa CCD diffractometer with a graphite-oriented monochromator utilizing MoKα radiation ($\lambda = 0.71073$). The structure was solved by direct methods and refined by least-squares procedures. All diagrams and calculations were performed using maXus package programs (Mac Science, Yokohama, Japan). The supplementary crystallographic data for **2a**, crystals, and data-collection parameters were deposited with the Cambridge Crystallographic Data Base (Reference: CCDC 297111).

In the case of **2b**, the structure was solved and refined to R (R_w) values 0.063 (0.108), but an uncertainty remains in the orientation of the carboxymethyl ester groups. This may be due to the simultaneous presence in the crystal of two different conformers like in Scheme 8. Nevertheless, N1-N2 isomerization is ascertained by N2 substitution.

Crystal data for **2a**: C18 H24 P1 O8 N4; M = 455.38; a = 9.1547(3) Å, b = 10.4784(3) Å, c = 12.3139(3) Å, triclinic, P-1, $\alpha = 101.241(3)^\circ$,



SCHEME 8 ORTEP III numbering scheme for selected bond length and angles.

$\beta = 102.501(2)^\circ$, $\gamma = 92.496(3)^\circ$, V = 1126.6(1) Å^3, Z = 2, crystal size $0.5 \times 0.5 \times 0.4$ mm, T = 298 K, 4121 reflections (3195 independent).

Selected bond lengths (Å): P(1)-O(1) 1.459(2), P(1)-O(2) 1.556(2), P(1)-O(3) 1.552(2), P(1)-C(5) 1.827(2), C(5)-N(1) 1.433(2), C(5)-N(2) 1.474(2); Selected bond angles (°): O(1)-P(1)-O(2) 114.4(1), O(1)-P(1)-O(3) 116.9(1), O(1)-P(1)-C(5) 117.2(1), O(2)-P(1)-C(5) 101.5(1), O(3)-P(1)-C(5) 98.7(1), O(2)-P(2)-O(3) 105.8(1).

Crystal data for **2b**: C18 H24 P1 O8 N4; M = 455.38; a = 9.5288(5) Å, b = 10.7523(5) Å, c = 11.4961(5) Å, triclinic, P-1, $\alpha = 72.891(2)^\circ$, $\beta = 89.491(2)^\circ$, $\gamma = 76.695(2)^\circ$, V = 1093.3(1) Å^3, Z = 2, crystal size $0.5 \times 0.5 \times 0.4$ mm, T = 298 K, 3985 reflections (3199 independent). The corresponding CIF file may be obtained from the authors.

Selected bond lengths (Å): P(1)-O(1) 1.454(1), P(1)-O(2) 1.562(1), P(1)-O(3) 1.548(1), P(1)-C(5) 1.829(2), C(5)-N(1) 1.428(2), C(5)-N(2) 1.464(2); selected bond angles (°): O(1)-P(1)-O(2) 114.4(1), O(1)-P(1)-O(3) 118.1(1), O(1)-P(1)-C(5) 114.4(1), O(2)-P(1)-C(5) 101.7(1), O(3)-P(1)-C(5) 102.3(1), O(2)-P(1)-O(3) 105.8(1).

General Procedure of Isomerization

Cycloadduct **2a–5a** (5 mmol) was dissolved in 30 mL acetonitrile and refluxed at 82°C for 3 days. After completion of the reaction, the solvent was evaporated, and the compound recrystallized from a petroleum ether/dichloromethane mixture.

2a: m.p. 114–116°C. ^{31}P NMR ($CDCl_3$): δ 13.1. ^{1}H NMR ($CDCl_3$): δ 1.18 (t, J = 7.0 Hz, 3H, $POCH_2C\underline{H}_3$), 1.30 (t, J = 7.0 Hz, 3H, $POCH_2C\underline{H}_3$), 3.90 (s, 3H, $C\underline{H}_3OC$), 4.02 (s, 3H, $C\underline{H}_3OC$), 4.00–4.38 (m, 4H), 7.41 (dd, $^3J_{HH}$ = 10.0 Hz, $^2J_{HP}$ = 16.7 Hz, 1H, C<u>H</u>P), 7.48–7.87 (m, 5H, C_6H_5),

8.48 (br. s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 16.6 ($^3J_{PC}$ = 4.7 Hz), 16.8 ($^3J_{PC}$ = 4.7 Hz), 53.5, 54.7, 61.4 ($^1J_{PC}$ = 180.2 Hz), 65.4 ($^2J_{PC}$ = 6.6 Hz), 65.8 ($^2J_{PC}$ = 6.6 Hz), 129.0, 129.7, 133.3, 133.7, 132.2, 140.6, 160.0, 161.3, 168.6. Anal. calced. for $C_{18}H_{23}N_4O_8P$, C 47.58, H 5.10, N 12.33; found: C 47.33, H 5.17, N 12.21%.

2b: m.p. 112–113°C. ^{31}P NMR ($CDCl_3$): δ 12.8. ^{1}H NMR ($CDCl_3$): δ 1.18 (t, J = 7.0 Hz, 3H, $POCH_2C\underline{H}_3$), 1.30 (t, J = 7.0 Hz, 3H, $POCH_2C\underline{H}_3$), 3.90 (s, 6H, $OC\underline{H}_3$), 4.00–4.38 (m, 4H, $POC\underline{H}_2CH_3$), 7.14 (dd, $^3J_{HH}$ = 9.7 Hz, $^2J_{HP}$ = 16.1 Hz, 1H, C<u>H</u>-P), 7.48–7.87 (m, 5H, arom.), 8.63 (br s, NH). ^{13}C NMR ($CDCl_3$): δ 16.6 ($^3J_{PC}$ = 5.4 Hz), 16.9 ($^3J_{PC}$ = 5.4 Hz), 53.6, 65.5 ($^2J_{PC}$ = 6.5 Hz), 65.9 ($^2J_{PC}$ = 6.5 Hz), 66.6 ($^1J_{PC}$ = 179.8 Hz), 129.0, 129.6, 133.4, 133.7, 141.3, 161.1, 168.7. MS (FAB/glycerol) m/z: 455 $[M+H]^+$, 477 $[M+Na]^+$.

2c: Rf = 0.3 (ether-methanol 95/5). ^{1}H NMR ($CDCl_3$) δ: 1.05 (t, J = 7.0 Hz, 3H, $POCH_2C\underline{H}_3$); 1.25 (t, J = 7.0 Hz, 3H, $POCH_2C\underline{H}_3$); 3.70–4.15 (m, 4H, $POC\underline{H}_2$); 6.60 (dd, $^2J_{PH}$ = 17.3 Hz, $^3J_{HH}$ = 9.7 Hz, 1H, C<u>H</u>-P); 6.97 (s, 1H, H_{imide}); 7.30 (s, 1H, H_{imide}); 7.32–7.46 (m, 3H, H arom.); 7.80 (m, 2H, H arom.); 7.83 (s, 1H, H_{imide}); 8.48 (m, 1H, NH). MS (FAB/glycerol) m/z: 338 $[M + H]^+$.

3a: m.p. 109–110°C. ^{1}H NMR ($CDCl_3$): δ 3.77 (s, 3H, CH_3O), 3.88 (s, 3H, CH_3O), 3.98 (s, 3H, CH_3O), 7.33–7.78 (m, 5H, C_6H_5), 7.69 (d, J = 10.0 Hz, 1H, CH), 8.01 (d, J = 10.0 Hz, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 52.9, 53.8, 54.2, 64.7, 127.5, 128.8, 129.8, 131.9, 132.8, 140.0, 159.2, 160.2, 165.5, 166.7. Anal. calcd. for $C_{16}H_{16}N_4O_7$, C 51.07, H 4.26, N 14.89; found: C 51.10, H 4.09, N 14.55%.

3b: m.p. 124–125°C. ^{1}H NMR ($CDCl_3$): δ 3.86 (s, 3H, OCH_3), 3.96 (s, 6H, OCH_3), 7.33–7.78 (m, 5H, C_6H_5), 7.69 (d, J = 10.0 Hz, 1H, CH), 8.01 (d, J = 10.0 Hz, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 53.0, 54.4, 68.9, 127.6, 128.8, 131.8 , 132.9, 140.6, 160.0, 165.0, 166.7. MS (DCI/NH_3) m/z: 377 $[M+H]^+$, 394 $[M+NH_4]^+$.

4a: m.p. 88–90°C. ^{1}H NMR ($CDCl_3$): δ 1.23 (t, J = 7.0 Hz, 3H, $C\underline{H}_3CH_2$), 3.95 (s, 3H, CH_3O), 4.04 (s, 3H, CH_3O), 4.29 (q, J = 7.0 Hz, 2H, $CH_3C\underline{H}_2$), 7.32–7.82 (m, 5H, C_6H_5), 7.68 (d, J = 10.0 Hz, 1H, CH), 8.01 (d, J = 10.0 Hz, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 14.0, 52.9, 53.9, 64.0, 64.7, 127.5, 128.9, 129.9, 132.0, 140.0, 142.8, 159.4, 160.2, 164.8, 166.7. Anal. calcd. for $C_{17}H_{18}N_4O_7$ C 52.31, H 4.62, N 14.36; found: C 52.10, H 4.59, N 14.55%.

4b: m.p. 80–82°C. ^{1}H NMR ($CDCl_3$): δ 1.23 (t, J = 7.0 Hz, 3H, $C\underline{H}_3CH_3O$), 3.98 (s, 6H, CH_3O), 4.29 (q, J = 7.0 Hz, 2H, $CH_3C\underline{H}_2O$), 7.32–7.89 (m, 5H, C_6H_5), 7.68 (d, J = 10.0 Hz, 1H, CH), 8.01

(d, $J = 10.0$ Hz, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 13.9, 53.1, 64.1, 71.8, 127.4, 128.8, 131.9, 132.9, 140.6, 160.0, 164.4, 167.1. M S (FAB/thioglycerol) m/z: 391 $[M+H]^+$, 413 $[M+Na]^+$, 781 $[2M+H]^+$.

5a: m.p. 134–136°C. ^{1}H NMR ($CDCl_3$): δ 3.61 (s, 3H, CH_3O), 3.94 (s, 3H, CH_3O), 3.99 (s, 3H, CH_3O), $\delta_A = 4.64$, $\delta_B = 4{,}76$ ($J_{AB} = 12.0$ Hz, 2H, CCl_3CH_2), 6.90 (d, $J = 8.0$ Hz, 1H, CH), 7.31 (d, $J = 8$ Hz, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 53.0, 53.9, 54.5, 66.7, 74.8, 94.6, 140.4, 153.5, 159.1, 159.9, 160.1, 164.6. Anal. calcd. for $C_{12}H_{13}Cl_3N_4O_8$, C 32.29, H 2.92, N 12.56; found: C 32.05, H 2.96, N 12.55%.

5b: m.p. 144–146°C. ^{1}H NMR ($CDCl_3$): δ 3.62 (s, 3H, CH_3O), 3.95 (s, 6H, CH_3O), $\delta_A = 4.66$, $\delta_B = 4{,}78$ ($J_{AB} = 12$ Hz, 2H, CCl_3CH_2), 6.93 (d, $J = 8.0$ Hz, 1H, CH), 7.20 (d, $J = 8.0$ Hz, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 53.1, 54.6, 70.6, 75.2, 94.5, 140.8, 153.2, 159.9, 164.1. MS (FAB/thioglycerol) m/z: 447 $[M+H]^+$, 469 $[M+Na]^+$.

6: m.p. 131°C. ^{1}H NMR ($CDCl_3$): δ 3.46 (s, 6H). ^{13}C NMR ($CDCl_3$): δ 52.3, 137.7, 133.7, 160.2. Anal. calcd. for $C_6H_7N_3O_4$, C 38.92, H 3.78, N 22.70; found: C 38.20, H 3.01, N 22.13%.

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