Simple and Effective Method for Substitution Triazole Rings of Amino Esters by Imidazole Group

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Abstract: *Diethyl (2-imidazolyl-2-benzoylaminomethyl) phosphonate and methyl N-benzoyl α-imidazolyl glycinate were synthesized by Simple substituting triazole rings of diethyl-(2-benzoylamino-2-(4,5-dicarboxymethyl-1,2,3-triazol-1-yl)-methyl) phosphonate and methyl 2-benzoylamino-2 (4.5-dicarboxymethyl 1,2,3-triazolyl) methylcarboxylate with imidazole.*

Keywords: Diethyl-(2-benzoylamino-2-(4,5-dicarboxymethyl-1,2,3-triazol-1-yl)-methyl) phosphonate, methyl 2-benzoylamino-2 (4.5-dicarboxymethyl 1,2,3-triazolyl) methylcarboxylate, substitution, α-amino acids.

1. Introduction

Due to their important biological activities, for example, as enzyme inhibitors, antiepileptics, or neuroexcitators [1-10], their applications make themselves currently are still in industry agrochemical (herbicides, fungicides, regulating of plant growth) in addition of their important utility in asymmetric synthesis [11]. α-amino acids are widely studied. Heterocyclic α-amino acids constitute an interesting class of compounds due to their remarkable pharmacological properties [12]. So a large number of between them isolated of plants have a very varied biologic activity [13].

Nitrogen-containing heterocyclic molecules have been considered as the privileged synthetic targets in the pharmaceutical and veterinary industries [14-17] because of their diverse biological properties and a wide variety of applications, e.g., anticancer, diuretic, anticonvulsant, anti-inflammatory and anti-hypertensive activities [18-20].
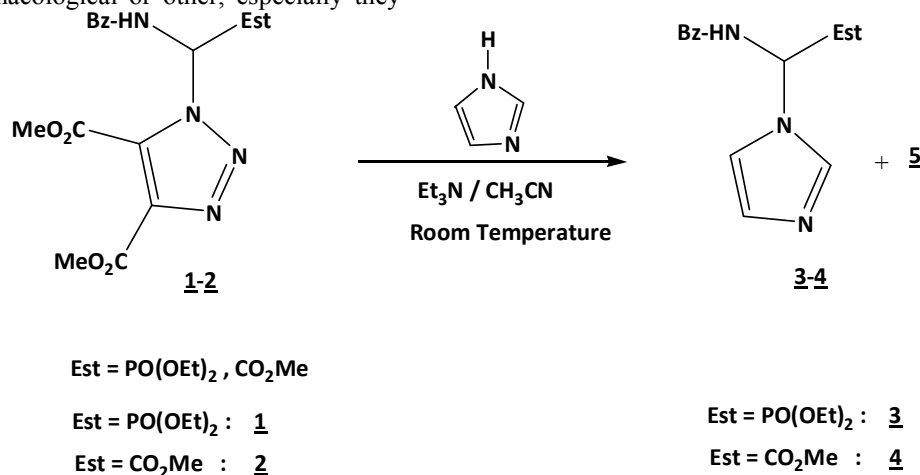
2. Results

Within the team of amino acids and peptides, several studies have been devoted to the synthesis of few α-amino esters phosphonic and carboxylic carrying a triazole ring in position α in order to study their potential applications in biological fields, pharmacological or other, especially they are analogous to histidine and its derivatives whose biological properties are well established [21-23] .

By adopting the same procedure [24-25], we set a goal substitution triazole rings of diethyl-(2-benzoylamino-2-(4,5-dicarboxymethyl-1,2,3-triazol-1-yl)-methyl) phosphonate **1** and methyl 2-benzoylamino-2 (4.5-dicarboxymethyl 1,2,3-triazolyl) methylcarboxylate **2**.

The action of the imidazole on diethyl-(2-benzoylamino-2-(4,5-dicarboxymethyl-1,2,3-triazol-1-yl)-methyl) phosphonate **1** or on methyl 2-benzoylamino-2 (4.5-dicarboxymethyl 1,2,3-triazolyl) methylcarboxylate **2** in acetonitrile in the presence of triethylamine for 48 hours at room temperature led mainly after filtering the solution and evaporating the solvent respectively the product diethyl (2-imidazolyl-2-benzoylaminomethyl) phosphonate **3** or methyl *N*-benzoyl α-imidazolyl glycinate **4** and 4.5-dicarboxymethyl 1,2,3-triazolyle **5**.

The imidazole group considered more nucleophilic than the 4,5-dicarboxymethyl-1,2,3- triazolate anion (nucleophilicity of this group is reduced by the presence of two carboxymethyl groups located in position 4 and 5 of the 1,2,3-triazole ring) attack the electrophilic site of the iminium cation, to give the product **3** or **4** (Scheme **1**).
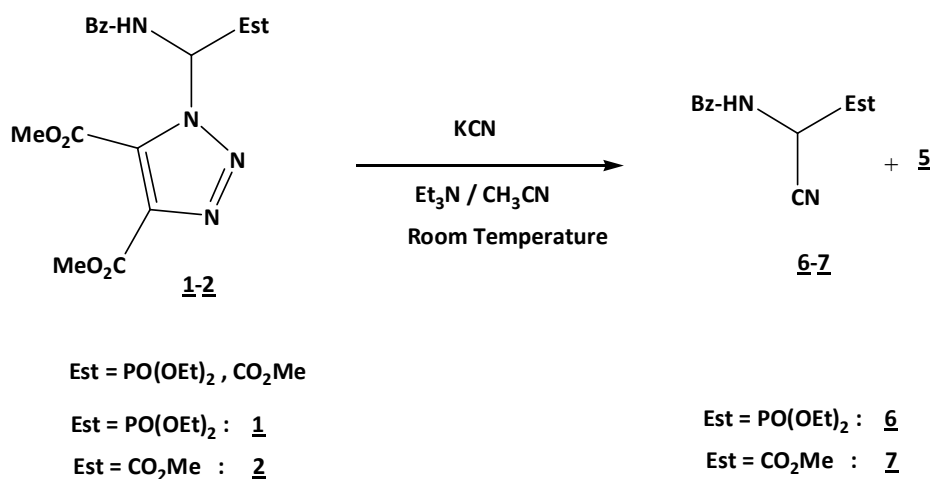

Scheme 1.

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Results are summarized in table 1.

Table 1. Synthesis of diethyl (2-imidazolyl-2-benzoylaminomethyl) phosphonate **3** and methyl *N*-benzoyl α-imidazolyl glycinate **4**.

Entry	reagent	Nu-H	Product	M.P. (°C)	Reaction Time (h)	Yield (%)
1	diethyl-(2-benzoylamino-2-(4,5-dicarboxymethyl-1,2,3-triazol-1-yl)-methyl) phosphonate **1**	imidazole	diethyl (2-imidazolyl-2-benzoylaminomethyl) phosphonate **3**	135-137	48	80
2	methyl 2-benzoylamino-2 (4.5-dicarboxymethyl 1,2,3-triazolyl) methylcarboxylate **2**		methyl N-benzoyl α-imidazolyl glycinate **4**	177-179	48	81

Following the same procedure and the same experimental protocol by replacing imidazole with potassium cyanide, potassium cyanide reacted with both triazole esters **1** and **2**, respectively, to give the products **6** and **7**.

The cyanide group considered more nucleophilic than the 4,5-dicarboxymethyl-1,2,3- triazolate anion, attack the electrophilic site of the iminium form to give respectively the diethyl (2-cyano -2-benzoylaminomethyl) phosphonate **6** or methyl *N*-benzoyl α-cyano glycinate **7** (Scheme **2**).

Bz-HN — Est

MeO$_2$C

N
N
N

MeO$_2$C   **1-2**

KCN

Et$_3$N / CH$_3$CN

Room Temperature

Bz-HN — Est

CN

6-7

+ **5**

Est = PO(OEt)$_2$, CO$_2$Me

Est = PO(OEt)$_2$:   **1**

Est = CO$_2$Me   :   **2**

Est = PO(OEt)$_2$:   **6**

Est = CO$_2$Me   :   **7**

Results are summarized in table 2.

Table 2. Synthesis of diethyl (2-cyano-2-benzoylaminomethyl) phosphonate **6** and methyl *N*-benzoyl α-cyano glycinate **7**.

Entry	Reagent	Nu-H	Product	Reaction Time (h)	Yield (%)
3	diethyl-(2-benzoylamino-2-(4,5-dicarboxymethyl-1,2,3-triazol-1-yl)-methyl) phosphonate **1**	Potassium cyanide	diethyl (2-cyano -2-benzoylaminomethyl) phosphonate **6**	48	86
4	methyl 2-benzoylamino-2 (4.5-dicarboxymethyl 1,2,3-triazolyl) methylcarboxylate **2**		methyl N-benzoyl α-cyano glycinate **7**	48	88

3. Conclusion

In summary, this method provides a convenient method and easy procedure for the preparation of diethyl (2-imidazolyl-2-benzoylaminomethyl) phosphonate **3**, methyl *N*-benzoyl α-imidazolyl glycinate **4**, diethyl (2-cyano-2-benzoylaminomethyl) phosphonate **6** and methyl *N*-benzoyl α-cyano glycinate **7** starting from the appropriate triazole amino esters **1** et **2**. The Simple substituting triazole rings by the imidazole or cyanide groups occurred under very mild conditions and led to desired products with good yields.

4. Experimental

4.1 General

^{1}HNMRspectra were recorded on a Brucker AC250 (250 MHz) instrument, with TMS as internal reference. ^{31}P NMR spectra were recorded on a Brucker AC 80 (32.44 MHz)

instrument, and 13C 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 (NH3) or FAB mode by means of a Nermag R10-10 mass spectrometer (Universit´e Paul Sabatier, France). Melting points were obtained with an electrothermal point apparatus and are uncorrected.

4.2 Typical Procedure

To a stirred solution of 100 mg of diethyl-(2-benzoylamino-2-(4,5-dicarboxymethyl-1,2,3-triazol-1-yl)-methyl) phosphonate **1** (0.22 mmol) and 100 mg of methyl 2-benzoylamino-2 (4.5-dicarboxymethyl 1,2,3-triazolyl) methylcarboxylate **2** (0.26 mmol) and 18 mg of imidazole (0.26 mmol), in 0.22 mmol (9ml) acetonitrile. The mixture was stirred at room temperature for 48 hours and the reaction was followed by TLC (Kiesegel Merck 60F524). The solvent was evaporated under reduced pressure. The residue was quenched with saturated aqueous solution of ammonium chloride (20 ml) and extracted with dichloromethane (20 ml × 3). The organic phase was dried in sodium sulfate (Na_2SO_4) and the solvent was removed under reduced pressure. The product was purified wherever necessary by column chromatography on silica gel.

4.3 Diethyl (2-imidazolyl-2-benzoylaminomethyl) phosphonate 3.

Yield = 80 %. Mp = 135-137°C (ether/ hexane). Rf = 0.3 (ether-methanol 95/5). ^{1}H NMR (CDCl3) δ: 1.05 (t, J = 7.0 Hz, 3H, $POCH_2CH_3$); 1.25 (t, J = 7.0 Hz, 3H, $POCH_2CH_3$); 3.70–4.15 (m, 4H, $POCH_2$); 6.60 (dd, [2]JPH = 17.3 Hz, [3]JHH = 9.7 Hz, 1H, CH-P); 6.97 (s, 1H, Himide); 7.30 (s, 1H, Himide); 7.32–7.46 (m, 3H, Harom.); 7.80 (m, 2H, H arom.); 7.83 (s, 1H, Himide); 8.48 (m, 1H, NH). MS (FAB/glycerol) m/z: 338 [M + H]$^+$. $C_{15}H_{20}N_3O_4P$.

3.4 methyl N-benzoyl α-imidazolyl glycinate 4.

Yield = 81 %. Mp = 177-179(ethyl acetate). ^{1}H NMR (DMSO-d6), δ: 3.76 (s, 3H, OCH_3); 6.91 (d, 1H, H$_\alpha$, J=8.60Hz); 6.97 (s, 1H, H$_{imidaz}$); 7.38 (s, 1H, H$_{2imidaz}$); 7.50-7.70 (m, 3H, H$_{arom}$); 7.95 (m, 3H, 2H$_{arom}$+1H$_{imidaz}$). SM (FAB$^+$) : 260 [M+H]$^+$. $C_{13}H_{13}N_3O_3$.

1. Acknowledgements

References

[1] W. S. Knowles, Acc. Chem. Res., 106 (**1983**).
[2] a-A. Osborn, J. F. Jardine, J. F. Young, and G. Wilkinson, J. Chem. Soc., 1711 (**1966**). b- Amy K. Styring , Rebecca A. Fraser, Amy Bogaard , Richard P. Evershed. Phytochemistry 97 (**2014**) 20–29.
[3] a-H. Kagan, Pure Appl. Chem., 43, 401 (**1975**). b- Babu A. Manjasetty, Mark R. Chance, Stephen K. Burley , Santosh Panjikar , Steven C. Almo. Biotechnology Reports 3 (**2014**) 73–85.
[4] a-Costantino, G., Marinozzi,M., Camaioni, E., Natalini, B., Sarichelou, I., Micheli, F., Cavanni, P., Faedo, S., Noe, C., Morini, F., Pelliciari, R., **2004**. Ilfarmaco 59, 93. b- Liu, H.; Thomas, E. J. Tetrahedron Lett. **2013**, 54, 3150e3153
[5] a-Jorgensen, C.G., Osborne, H.B., Nielsen, B., Kehler, J., Clausen, R.P., Krogsgaard-Larsena, P., Madsena, U., **2007**. Bioorg. Med. Chem. 15, 3524. b- Graupner, K.; Scherlach, K.; Bretschneider, T.; Lackner, G.; Roth, M.; Gross, H.; Hertweck, C. Angew. Chem. **2012**, 124, 13350e13354.
[6] Samel, M.; Tõnismägi, K.; Rönnholm, G.; Vija, H.; Siigur, J.; Kalkkinen, N.; Siigur, E. L-Amino acid oxidase from Naja naja oxiana venom. Comp. Biochem. Physiol. B **2008**, 149, 572–580.
[7] Eddy, N.O. Experimental and theoretical studies on some amino acids and their potential activity as inhibitors for the corrosion of mild steel, part 2. J. Adv. Res. **2011**, 2, 35–47.
[8] Sant'Ana, C.D.; Menaldo, D.L.; Costa, T.R.; Godoy, H.; Muller, V.D.M.; Aquino, V.H.; Albuquerque, S.; Sampaio, S.V.; Monteiro, M.C.; Stábeli, R.G.; et al. Antiviral and antiparasite properties of an L-amino acid oxidase from the snake Bothrops jararaca: Cloning and identification of a complete cDNA sequence. Biochem. Pharmacol. **2008**, 76, 279–288.
[9] a-Stábeli, R.G.; Sant'Ana, C.D.; Ribeiro, P.H.; Costa, T.R.; Ticli, F.K.; Pires, M.G.; Nomizob, A.; Albuquerque, S.; Malta-Neto, N.R.; Marins, M.; et al. Cytotoxic L-amino acid oxidase from Bothrops moojeni: Biochemical and functional characterization. Int. J. Biol. Macromol. **2007**, 41,
[10] 132–140. b-Little, M. J.; Vederas, J. C. Med. Chem. Commun. **2012**, 3, 971e975.
[11] Samel, M.; Vija, H.; Rönnholm, G.; Siigur, J.; Kalkkinen, N.; Siigur, E. Isolation and characterization of an apoptotic and platelet aggregation inhibiting L-amino acid oxidase from Vipera berus berus (common viper) venom. Biochim. Biophys. Acta **2006**, 1764, 707–714.
[12] Saravanan, P.; Corey, E.J. A short, stereocontrolled, and practical synthesis of alpha-methylomuralide, a potent inhibitor of proteasome function. J. Org. Chem. **2003**, 68, 2760–2764.
[13] (a) V. Kukhar, V. Soloshonok, and V. Solodenko, Phosphorus, Sulfur , and Silicon, 92, 239 (**1994**); (b) I. Lefevre and S. Evans, Phosphorus, Sulfur , and Silicon, 144–146, 397 (**1999**); (c) H. J. Cristau, J.M. Lambert, and J. L. Pirat, Phosphorus, Sulfur , and Silicon, 151, 51 (**1998**); (d) B. Boduszek, Phosphorus, Sulfur , and Silicon, 113, 209 (**1996**); (e) P. Murray, I. Starkey, and J. Davies, Tetrahedron Lett., 39, 6721 (**1998**); (f) D. Kim, N. Lee, Y. Kim, K. Chang, G. Im, W. Choi, et al., Bioorg. Med. Chem. Lett., 7, 419 (**1999**); (g) P. M. Ferreira, H. L. Maia, and L .S. Monteiro, Tetrahedron Lett., 40, 4099 (**1999**); (h) M.Welch and R. Phillips, Bioorg. Med. Chem. Lett., 9, 637 (**1999**); (i) H. Pajouhesh and K. Curry, Tetrahedron Asymmetry, 9, 2757 (**1998**).

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[14] Schenk, S.U., Werner, D., **1991**. Photochemistry 30, 467.

[15] Katritzky, A.R., Rees, C.W., Scriven, E.F.V., **1996**. Comprehensive Heterocyclic Chemistry, vol. II. Pergamon, Oxford.

[16] Undheim, K., Benneche, T., **1999**. In: Gilchrist, T.L., Gribble, G.W. (Eds.), Advances in Heterocyclic Chemistry, vol. 11. Pergamon, Oxford, p. 21.

[17] Joule, J.A.,Mills, K., **2000**. Heterocyclic Chemistry. Blackwell Science, Oxford.

[18] Katritzky, A.R., Pozharskii, A.F., 2003. Handbook of Heterocyclic Chemistry. Pergamon, Oxford.

[19] Chan, J.H., Hong, J.S., Kuyper, L.F., Jones, M.L., Baccanari, D.P., Tansik, R.L., Boytos, C.M., Rudolph, S.K., Brown, A.D., **1997**. J. Heterocycl. Chem. 34, 145.

[20] Gackenheimer, S.L., Schaus, J.M., Gehlert, D.R., **1996**. J. Pharmacol. Exp. Ther. 732, 113.

[21] Dempcy, R.O., Skibo, E.B., **1991**. Biochemistry 30, 8480.

[22] a-A. Elachqar, A. El Hallaoui, M. L. Roumestant, Ph. Viallefont; Synthetic Comm. **1994**, <u>24</u>, 1279. b- S. Achamlale, A. Elachqar, A. El Hallaoui, S. El Hajji, M. L. Roumestant, Ph. Viallefont. Amino Acids **1997**, 257.

[23] S. El Hajji, A El Hallaoui, A. Atmani, M. L. Roumestant, Ph. Viallefont; Synthetic Comm. **1991**, 21, 2383.

[24] a-F. Zaid, S. El Hajji, A. El Hallaoui, A. Elachqar, A. Kerbal, M. L. Roumestant, Ph. Viallefont; Prep. Biochem. & Biotechnol. **1998**, <u>28,</u> 137. b- F. ZAÏD, S. El Hajji, A. El Hallaoui, A. Elachqar, A. Alami, M. L. Roumestant, Ph. Viallefont ; Prep. Biochem. & Biotechnol. **1998**, <u>28</u>, 155.

[25] Achamlale, S., Elachqar, A., El Hallaoui, A., El Hajji, S, A. Alami, Roumestant, ML., Viallefont, Ph., Phosphorus, Sulfure and Silicon, **1998**, <u>140</u>, 103.

[26] Achamlale, S., Elachqar, A., El Hallaoui, A., El Hajji, S., Alami, A., Roumestant, ML., Viallefont, Ph. *Amino Acids*, **1999**, 17, 149-163.

Paper ID: SEP14445

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