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Synthesis of new tetrazole and triazole substituted pyroglutamic acid and proline derivatives

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Abstract—Racemic 4-(substituted-1*H*-1,2,3-triazol-1-yl), 4-aryl and 4-(arylmethyl)tetrazolyl-pyroglutamic and proline derivatives were synthesized from dimethyl-2,4-dibromoglutaryle **1** in good yield using mild reaction conditions. The key step for the preparation of the triazole substituted molecule was the 1,3-dipolar cycloaddition of an acetylenic compound with an azido derivative. The tetrazole derivatives were prepared by the selective N2-alkylation of 5-substituted tetrazoles with **1**.

Unnatural, non-proteinogenic α-amino acids are important derivatives in different areas of chemistry, biology and material sciences.[1] They have a wide range of biological activities and hence are significant in medicinal chemistry. The replacement of natural amino acids by non-proteinogenic derivatives in peptides has become an important goal in medicinal chemistry because this substitution may influence their biological properties.[2] The synthesis of proline peptidomimetics that mimic natural dipeptides is very attractive.[3] The proline residue plays an important role in protein secondary structure, and in many biological processes such as protein folding and protein recognition.[4] The development of new methodologies directed towards the preparation of cyclic α-amino acids is a very attractive field in organic synthesis.[5]

Among the heterocyclic substituents which are currently studied, the 1*H*-tetrazoles and 1*H*-1,2,3-triazoles ring systems are important structural features found in natural products and drugs. The 1*H*-1,2,3-triazole heterocyclic entity is an interesting moiety in terms of biological properties such as antibacterial,[6] anti-HIV[7] and antiallergic agents.[8] Triazoles are also found in herbicides.[9] Indeed, the 1,2,3-triazole moiety is present in a number of drugs such as the β-lactam antibiotic cephalosporine Cefatrizine. The tetrazole substituted proline such as LY300020 (Fig. 1), known for its relatively potent, highly selective systemically-active AMPA receptor agonist has been reported.[10] To our knowledge, triazole substituted prolines have not been synthesized so far. Few examples in the literature describe 1*H*-1,2,3-triazole-α-amino acids.[11] Furthermore, since the discovery of L-glutamate as a major excitatory amino acid (EAA) neurotransmitter in the central nervous system,[12] several modified structures were prepared.[13]

In order to study the effects of the substituents on glutamic acid in the neuroexcitatory activity, we decided to prepare triazole or tetrazole substituted pyroglutamic acid and proline derivatives (Fig. 2).

The general strategy relied on the successive alkylation[14] of a dibromo diester derivative of glutaric acid.

The substituents we considered were 4,5-substituted-1*H*-1,2,3-triazoles. The synthetic strategy relied on the

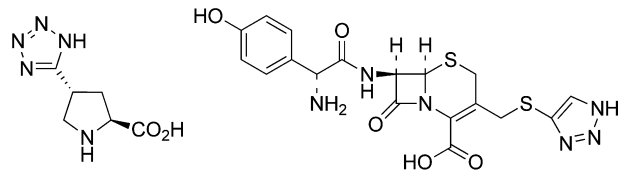

Figure 1.

Keywords: Proline; Heterocycles; Triazole; Tetrazole; Alkylation.
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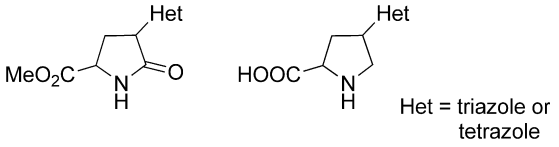


Figure 2.

double substitution of dimethyl-2,4-dibromoglutarate **1**[15] successively with sodium azide, followed by a 1,3-dipolar cycloaddition with an acetylenic compound, and again with sodium azide (Scheme 1).

According to the synthetic approach described in Scheme 1, we initially studied the reaction of an equimolar quantity of sodium azide with dimethyl-2,4-dibromoglutarate **1**, easily obtained from glutaryl dichloride. This reaction, carried out in acetone in the presence of 1.1 equiv of sodium azide, led to a 3/1 ratio of a mixture of the monosubstituted product **2** and the disubstituted product. Compound **2** was separated from the disusbstituted product by column chromatography.

Huisgen's 1,3-dipolar cycloaddition reaction between alkynes and azides is the earliest known method for the synthesis of 1,2,3-triazoles,[16] and is one of the prototype reactions in click chemistry.[17] Click chemistry is a modular approach that uses the most practical and reliable chemical transformations and has found several applications in organic chemistry,[18] drug discovery,[19] bioconjugations,[20] material sciences[21] and polymer synthesis.[22] The traditional method for synthesis of triazoles requires elevated temperatures and this non-catalyzed reaction is generally poorly regioselective, and gives a mixture of 1,4- and 1,5-disubstituted triazoles. Recently, Sharpless and co-workers have reported a high yielding synthesis of triazoles using a Cu(I) catalyst with an excellent 1,4-regioselectivity.[23] The reaction tolerates a wide variety of functional groups and is insensitive to water and oxygen. In our case, since the cycloaddition leading to **3** was performed with a symmetrical alkyne, uncatalyzed thermal conditions were used.[24] Only one product was obtained and isolated in a quantitative yield.

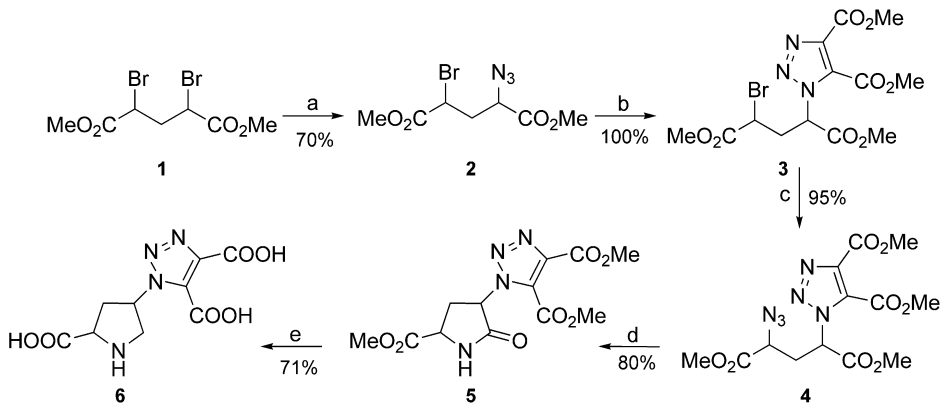
The triazole derivative **3** was then reacted with 3 equiv of sodium azide in acetone to give **4** in 95% yield. Reduction of **4** by catalytic hydrogenation over Pd/C in methanol,[25] led to the corresponding substituted pyroglutamic acid **5** via an intramolecular aminolysis. Lactam **5** was selectively reduced with BH_3 in THF at -10 °C[26] and acid hydrolysis (6 N HCl, 60 °C, 12 h) followed by neutralization with propylene oxide yielded the fully deprotected (±)-4-(4,5-substituted-1*H*-1,2,3-triazol-1-yl)proline derivative **6**. ^{1}H NMR showed that in all cases a 1/1 mixture of the two possible diastereoisomers was obtained.

In another set of reactions, tetrazole proline derivatives were obtained by double substitution of dimethyl-2,4-dibromoglutarate successively by substituted tetrazoles and sodium azide (Scheme 2).

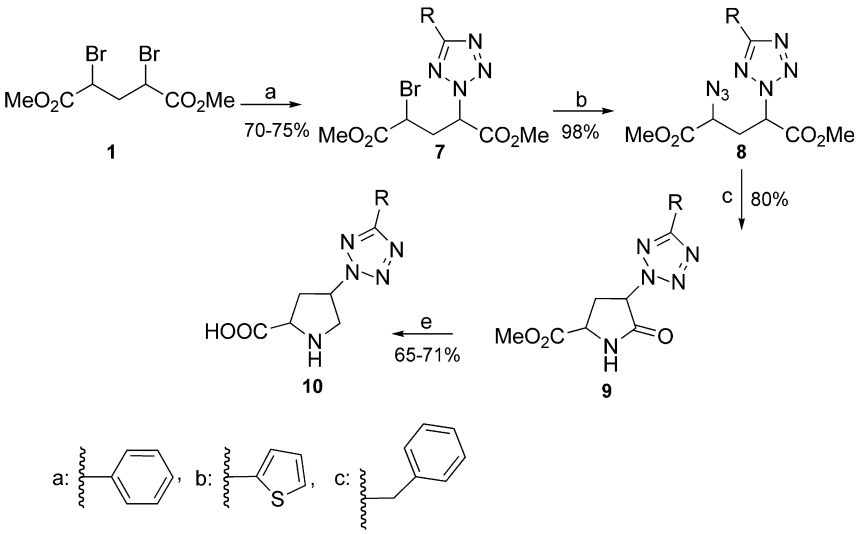
According to the synthetic approach described in Scheme 2, we initially studied the reaction of an equimolar quantity of tetrazole with dimethyl-2,4-dibromoglutarate **1**. This reaction, carried out in acetone in the presence of 1.5 equiv of triethylamine, led to the formation of the monosubstituted compound **7** as the sole product.[27]

For the preparation of 5-substituted tetrazoles, we extended the method described by Koguro[28] based on the reaction of variously substituted nitriles with sodium azide in the presence of an amine salt in toluene. The tetrazole ring is a system of the azapyrrole type and therefore two tautomeric forms can exist. During our synthesis, we obtained in all cases only one of the two N-regioisomers, as detected by ^{1}H NMR spectroscopy. All the 5-aryltetrazoles and the 5-(arylmethyl)tetrazoles obtained were N2-isomers.[29] The 2-bromo-5-tetrazolylglutarate derivatives **7a**–**c** were purified by column chromatography and isolated in good yields. In the absence of triethylamine, the 5-aryl- and 5-(arylmethyl)tetrazoles were inert towards the dibromo derivative.

The bromo derivatives **7a**–**c** were treated with 3 equiv of sodium azide in acetone to give **8a**–**c** as a mixture of diastereoisomers rising from successive non-stereocontrolled S_N2 reactions. Reduction of **8a**–**c** by catalytic



Scheme 1. Reagents and conditions: (a) NaN_3, acetone, rt; (b) acetylene; (c) NaN_3, acetone, rt; (d) 5% Pd/C, MeOH, H_2 (1 atm), rt; (e) (i) BH_3·THF, THF, -10 °C, (ii) 6 N HCl, propylene oxide, CH_2Cl_2.



Scheme 2. Reagents and conditions: (a) substituted tetrazole, NEt_3, acetone, rt; (b) NaN_3, acetone, rt; (c) 5% Pd/C, MeOH, H_2 (1 atm), rt; (d) (i) BH_3·THF, THF, −10 °C, (ii) 6 N HCl, propylene oxide, CH_2Cl_2.

hydrogenation over Pd/C in methanol[25] led to the corresponding substituted pyroglutamic acids **9a–c** by an intramolecular aminolysis.

Lactams **9a–c** were reduced with BH_3 in THF at −10 °C.[26] Subsequent acid hydrolysis (6 N HCl, 60 °C, 12 h) and neutralization with propylene oxide yielded the (±)-4-(5-aryltetrazolyl)- and (±)-4-[5-(arylmethyl)-tetrazolyl]proline.

The present study describes an efficient synthesis of racemic 4-(4,5-dicarboxy-1*H*-1,2,3-triazol-1-yl)proline and 4-(5-aryltetrazolyl)- and 4-[5-(arylmethyl)tetrazolyl]proline starting from dimethyl-2,4-dibromoglutarate. The 4,5-substituted-1*H*-1,2,3-triazol-1-yl were selectively synthesized in position 4 of the proline by 1,3-dipolar cycloaddition of acetylenic compounds on dimethyl-2-azido-4-bromoglutarate followed by hydride reduction. The 5-aryltetrazoles and the 5-(arylmethyl)tetrazoles were selectively introduced in the 4-position of the pyrrolidine ring in good chemical yields. While double substitutions of **1** with one nucleophile to give cyclic compounds have been reported,[15] to the best of our knowledge these are the first examples of successive substitutions with two different nucleophiles on a dibromoglutaric acid derivative. Generalization of this method is currently under investigation in our laboratory.

Acknowledgments

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