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Synthesis of New Racemic α-Amino Esters Carboxylic Derivatives by *S*-alkylation

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Abstract: ***New racemic methyl α-amino glycinates derivatives were synthesized by S-alkylation of aromatic thiols with methyl α-azido glycinate.***

Keywords: methyl α-azido glycinate, thiol, *S*-alkylation, α-amino acids.

1. Introduction

The synthesis of new carboxylic amino acids and their esters raises the interest of research teams around the world because of the wide spectrum of activity they have [1-4]. Indeed, these biomolecules are a class of compounds active in various areas (enzymology, medicine and pharmacology, industry, asymmetric synthesis ...)[5].

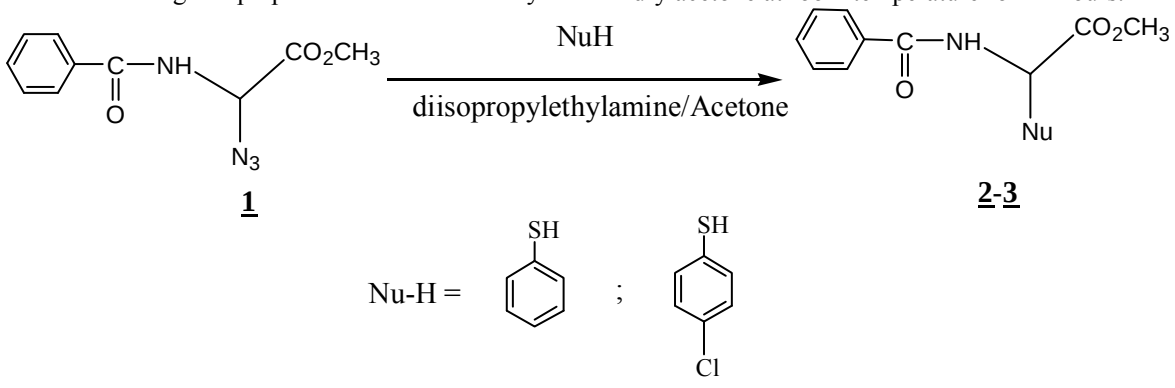
This has led to the development of numerous synthetic methods for a variety of compounds [6]. The importance of sulfur-containing compounds in biological systems as well as in atmospheric and environmental chemistry is now well established [7,8]. Since the thiol group (R-SH) could easily be oxidized, especially in the presence of light, they have been used as efficient antioxidants of organic matter ranging from polymers to living cell systems [7,8].

Different methods of alkylation were represented in literature. Among these, C–S bond formation is one of the most important transformations in organic synthesis. *S*-alkylation of thiols was broadly studied by several research teams; Literature is very rich in examples of these methods [9]. Continued our investigations on the use of organic azides [10], we reported in this paper another part of our investigations concerning the preparation of new carboxylic α-aminoesters carrying a variety of phenylsulfanyl derivatives in position α.

2. Results

Our strategy is based on the *S*-alkylation of aromatic thiols with methyl α-azido glycinate 1 (scheme 1). Azide derivative **1** was prepared using Steglich method [11] and Achamlale's procedure [12]. The title compound is stable and can be stored for an unlimited amount of time without any signs of decomposition. Methyl α-bromo glycinate also can be used and give satisfactory results; the azide **1** are used especially for their stability.

As shown in Scheme 1, the reactions of aromatic thiols (thiophenol and 4-chloro thiophenol) with azide **1** result in formation of the compounds **2**-**3**. As a first step and to optimize the different reaction conditions (choice of base, solvent ...), we conducted several test reactions. For all these tests, the reactions were followed by TLC and ^{1}H NMR. Yields are given as pure product after column chromatography on silica gel. After several attempts of reactions without base or in the presence of bases such as triethylamine (Et_3N), reaction with diisopropylethylamine (DIEPA) gave the best results. The reaction was carried out in dry acetone at room temperature for 24 hours.



Scheme 1. *S*-alkylation of different thiols, with methyl α-azido glycinate **1**

For all these test reactions, results are summarized in table 1.

Table 1: Synthesis of new α-aminoesters carrying a variety of phenylsulfanyl derivatives in position α **2**-**3**

Entry	*Nu-H*	*Product*	*M.P. (°C)*	*Reaction Time (h)*	*- DCM*	*Et_3N DCM*	*Et_3N Acetone*	*DIEPA DCM*	*DIEPA Acetone*
					Yield (%)	*Yield (%)*	*Yield (%)*	*Yield (%)*	*Yield (%)*
1	Thiophenol	Methyl 2-benzamido-2-(phenylsulfanyl)acetate **2**	76-78	24	0	23.5	41	51.5	82
2	4-chloro thiophenol	Methyl 2-benzamido-2-(4-chloro phenylsulfanyl) acetate **3**	64-66	24	0	25	43	54	86

DCM: Dichloromethane, Et_3N: Triethylamine

The products **2**-**3** were obtained in 82 to 86 % overall yield from **1** and were characterized by MS, ^1H NMR and ^{13}C NMR spectroscopy. It should be noted that the yield of pure product **3** was slightly increased, which is consistent with the presence of halogen atoms on the system thiophenol (nucleophilic agent) whose the (+M) mesomeric effect outweighs the inductive effect attractor (-I).

Comparing these results with the work done by our team [19,22]: Synthesis of new α-heterocyclic α-aminophosphonates, synthesis of α-Heterocyclic α-Aminophosphonates, Part II: Morpholine, Piperidine, Pyrrolidine, Tetrahydrofurylmethylamine, *N*-Benzyl-*N*-Methylamine, and Aniline Derivatives, Synthesis of new racemic α-heterocyclic α, α-diaminoesters and α-aminoester carboxylic we see that we have obtained almost the same results.

The methyl glycinate prepared may be protected by different protecting groups: trifluoroacetic anhydride, trichloroethoxycarbonyl chlorides, acetyl chloride and benzoyl chloride. The protection reaction is carried out in dichloromethane in the presence of triethylamine or pyridine. After column chromatography on silica gel the aminoesters *N*-protected are obtained with good yields.

3. Conclusion

In summary, this method provides a convenient method and easy procedure for the preparation of new methyl α-amino glycinates derivatives starting from the appropriate azide derivative **1**. The *S*-alkylation of different thiols (thiophenol and 4-chloro thiophenol) with compound **1** occurred under very mild conditions and led to desired products with good yields.

4. Experimental

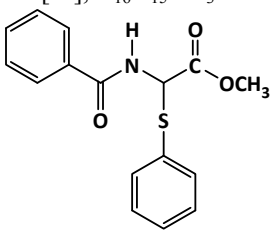
4.1 General

Melting points were determined with an Electrothermal melting point apparatus and are uncorrected. NMR spectra (^1H, ^{13}C) were recorded on a Bruker AM 300 (operating at 300.13 MHz for ^1H, at 75.47 MHz for ^{13}C) spectrometer (Centre Universitaire Régional d'Interface, Fès). NMR data are listed in ppm and are reported relative to tetra-methylsilane (^1H, ^{13}C); residual solvent peaks being used as internal standard. All reactions were followed by TLC. TLC analyses were carried out on 0.25 mm thick precoated silica gel plates (Merck Fertigplatten Kieselgel 60F254) and spots were visualised under UV light or by exposure to vaporised iodine. Mass spectra were recorded on a PolarisQ Ion Trap GC/MSn Mass Spectrometer (Centre Universitaire Régional d'Interface, Fès); methy α-azidoglycinate **1** was prepared using Steglich method [11] and Achamlale's procedure [12].

4.2 Typical procedure

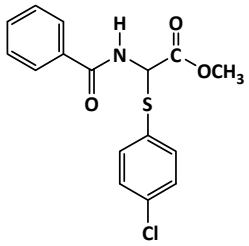
To a stirred solution of 2.86 mmoles of thiols (sulfur compounds) and 3.12 mmoles of diisopropylethylamine in 10 ml of dry acetone, 2.6 mmoles of methyl α-azido glycinate were added. The mixture was stirred at room temperature and the reaction was followed by TLC (Kiesegel Merck 60F524). The solvent 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 using ether/hexane as eluant to afford pure *S*-alkylated product.

Methyl 2-benzamido-2-(phenylsulfanyl)acetate 2. Yield = 82 %. Mp = 76-78 °C (ether/ hexane). Rf = 0.8 (ether). ^1H NMR (300 MHz, $CDCl_3$): δppm = 3.821 (s, 3H, OCH_3), 5.9 (d, 1H, *J* = 8.5 Hz, Hα), 6.9 (d, 1H, *J* = 8.5 Hz, NH), 7.36-7.8 (2m, 10H, Ar). ^{13}C NMR (75.5 MHz, $CDCl_3$): δppm = 53.05 ($\underline{C}H_3O$), 56.71 (-$\underline{C}$H-) 127.11 (2C), 128.71 (2C), 129.22 (2C), 129.65, 129.85, 132.19, 133.22, 135.74 (2C) ($\underline{C}_6H_5$ aromatic carbons), 165.76, 169.16 (2$\underline{C}$O). MS-EI: 604.4 [2M+1], 301.8 [M], $C_{16}H_{15}NO_3S$.



Methyl 2-benzamido-2-(4-chloro phenylsulfanyl) acetate 3. Yield = 86 %. Mp = 64-66 °C (ether/hexane). Rf = 0.8 (ether). ^1H NMR (300 MHz, $CDCl_3$): δppm = 3.821 (s, 3H, OCH_3), 5.9 (d, 1H, *J* = 8.40 Hz, Hα), 6.9 (d, 1H, *J* = 8.40 Hz, NH), 7.3-7.8 (2m, 9H, Ar). ^{13}C NMR (75.5 MHz, $CDCl_3$): δppm = 53.15 ($\underline{C}H_3O$), 57.02 (-$\underline{C}$H-), 127.09 (2C), 128.56, 128.78 (2C), 129.45 (2C), 132.33, 133.02, 136.17,

136.91(2C) ($\underline{C}_6H_5$ aromatic carbons), 165.74, 169.04, (2$\underline{C}$O).
MS-EI: 335.7 [M], $C_{16}H_{14}Cl\ NO_3S$.



5. Acknowledgements

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