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R E S E A E C H A R T I C L E

Synthesis of the new carboxylic α,α-diamino acid: Benzoylamino-(2-methyl-quinolin-4-ylamino) acetic acid

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A B S T R A C T

After the obtaining of the *N*-protected methyl α,α-diamino ester via *N*-alkylation reaction between methyl α-bromo glycinate *N*-benzoylated and 2-methyl quinolin-4-amine, the synthesis of benzoylamino-(2-methyl-quinolin-4-ylamino) acetic acid in high yield through alkaline hydrolysis reaction of methyl 2-benzamido-2-(2-methylquinolin-4-ylamino) acetate was performed via cleavage of the protecting group. The structure of these products were established on the basis of NMR spectroscopy (^{1}H, ^{13}C), and MS data.

Keywords: *N*-alkylation, α,α-Diamino ester, α,α-diamino acid, methyl α-bromo glycinate, alkaline hydrolysis reaction.

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C O N T E N T S

1. Introduction

Heterocyclic α-amino acids play a predominant role in medicinal chemistry because of the large activity spectrum they present. The synthesis of new α-carboxylic amino esters containing heterocyclic systems occupies an important place in the realm of synthetic organic chemistry [1–3] and they are the fundamental units of life because of their wide utility of such compounds as components of proteins, peptides, and as starting materials for the synthesis of naturally occurring biologically active compounds [4–6]. Recently, heterocyclic α-amino acids have shown biological properties including antibacterial activity [7]. In view of these observations and in continuation of our previous work in heterocyclic chemistry [8,9], we focused in the present study on the synthesis of new carboxylic α,α-diamino acid

derivative with the aim to have access to new active biomolecule with a good yield.

2. Experimental

Typical procedure for N-alkylation

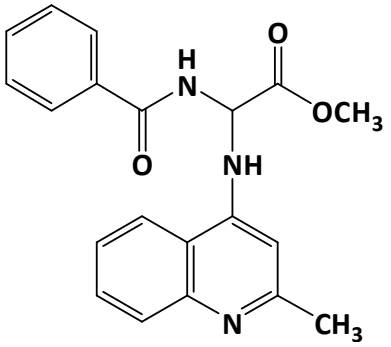
To a stirred solution of 2.86 mmol of 2-methyl quinolin-4-amine and 3.12 mmol of diisopropylethylamine in 10 mL of dry acetone, 2.6 mmol of methyl α-bromo glycinate were added. The mixture was stirred at room temperature and the reaction was followed by TLC (Kiesegel Merck 60F524). The solvent was evaporated 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 by column chromatography on silica gel using ether/hexane as eluant to afford pure *N*-alkylated product.

3.2. Deprotection of acid function: Synthesis of N-benzoylated α,α-diamino acid derivative 4

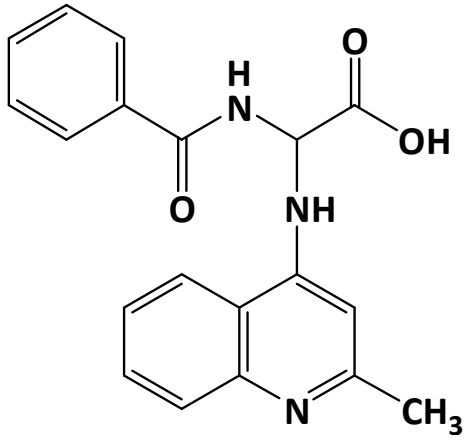
To a solution of the methyl 2-benzamido-2-(2-methylquinolin-4-ylamino) acetate (1 mmole) in 10 mL of dioxane/water mixture (8/2), one adds 1.5 mmole of NaOH (0,5N) with stirring and at 0°C. The stirring is maintained at room temperature until disappearance of the starting material. The reaction is always followed by TLC. The solvent is then evaporated and the pH of the aqueous phase is adjusted to 6 using a solution of sulfuric acid or hydrochloric acid (0,5N). One extracts with ethyl acetate and the organic layers recovered, are dried and concentrated under vacuum. The product is recrystallized from ethyl acetate.

***3.3. Methyl 2-benzamido-2-(2-methylquinolin-4-ylamino) acetate* 3**:

yield: 46%; m.p.: 158–160 °C (ether/hexane); R_f: 0.6 (ether);^{1}H NMR ($CDCl_3$): δppm: 3.57 (3H, s, CH_3); 3.88 (s, 3H,OCH_3); 4.9 (br s, 1H, NH); 5.8 (d, 1H, J = 9.0 Hz, H_α); 6.2 (br s, 1H, Ar); 6.7–7.9 (3 m, 10H, Ar + NH_{amid}).^{13}C NMR($CDCl_3$): δppm: 24.13 (CH_3); 53.08 (OCH_3); 56.98 (–CH–);78.69, 109.23, 116.34, 120, 125.33,127.25, 128.77, 132.38, 133,149.12, 149.23, 159.77, (C_6H_5 aromatic carbons); 168.58, 171(2CO) M.S-E.I: m/z = 349.1 [M]; $C_{20}H_{19}N_3O_3$.



***3.4. Benzoylamino-(2-methyl-quinolin-4-ylamino)acetic acid* 4**: yield: 86%; R_f: 0.72 (ether); ^{1}H NMR ($CDCl_3$): δppm: 3.48 (3H, s, CH_3); 5.0 (br s, 1H, NH); 5.74 (d, 1H, J = 9.0 Hz, H_α); 6.75–8.1 (3 m, 11H, Ar + NH_{amid}); 10.98 (s, 1H, H_{acid}).^{13}C NMR($CDCl_3$): δppm: 25.22 (CH_3); 57.04 (-CH-); 78.52, 110.08, 116.78, 120.26, 125.85,127.34, 129.16,132.45, 133.18,149.09, 149.27, 159.92, (C_6H_5 aromatic carbons); 168.64, 171.14 (2CO) M.S-E.I: m/z = 335.1 [M]; $C_{19}H_{17}N_3O_3$.



3. Results and Discussions

Synthesis of new racemic α,α-carboxylic diamino ester:

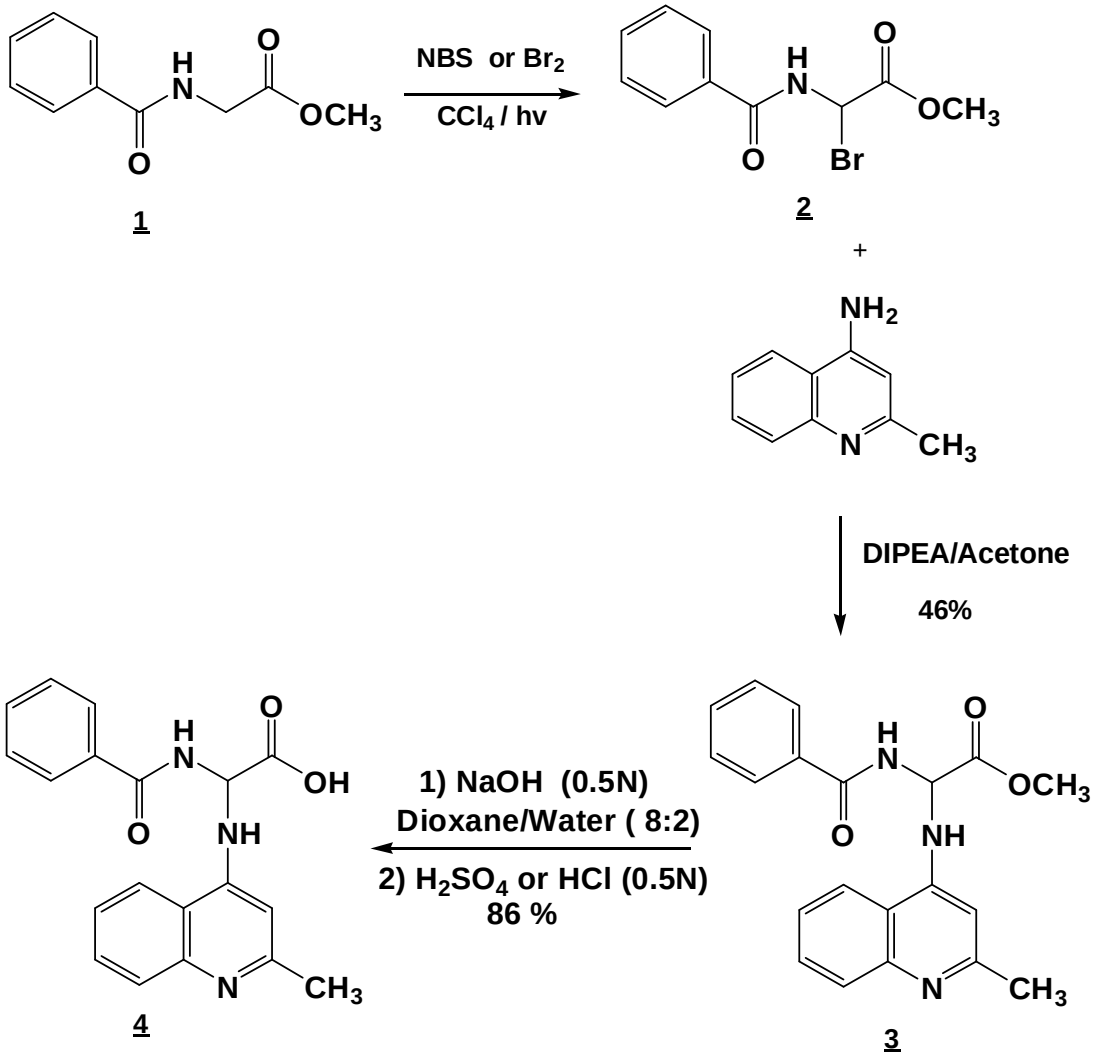
As shown in Scheme 1, The product **3** was obtained with a satisfactory chemical yield by *N*-alkylation of 2-methyl quinolin-4-amine with methyl α-bromo glycinate *N*-benzoylated **2** in dry acetone for 48 hours at room temperature in the presence of diisopropylethylamine (DIPEA) and was characterized by MS, ^{1}H-NMR and ^{13}C-NMR spectroscopy.

Synthesis of new racemic α,α-carboxylic diamino acid:

In continuation of our research interest in amino acids [8,9], we will present in this paragraph, our results concerning the synthesis of new α,α-diamino acid derivative, as benzoylamino-(2-methyl-quinolin-4-ylamino) acetic acid through alkaline hydrolysis reaction of methyl 2-benzamido-2-(2-methylquinolin-4-ylamino)acetate **3**. After the obtaining of the *N*-protected methyl α,α-diamino ester **3**, we proceeded to the cleavage of the protecting group to obtain the corresponding α,α-diamino acid **4**. The hydrolysis reaction of the methyl 2-benzamido-2-(2-methylquinolin-4-ylamino) acetate **3** in a basic medium is carried out for approximately 30 minutes and leads, after acidification of the reaction medium with sulfuric acid or hydrochloric acid, to the benzoylamino-(2-methyl-quinolin-4-ylamino) acetic acid **4** in high yield (scheme 1).

4. Conclusion

α-Amino acids possess a broad range of applications ranging from agrochemistry to medicine. We developed a simple and environmentally benign method for the preparation of new carboxylic α,α-diamino acid. The nucleophilic substitution of methyl α-bromo glycinate with 2-methyl quinolin-4-amine occurred under very mild conditions and led after about 48 hours to the desired product with a satisfactory yield. The synthesis of benzoylamino-(2-methyl-quinolin-4-ylamino) acetic acid in high yield through alkaline hydrolysis reaction of methyl 2-benzamido-2-(2-methylquinolin-4-ylamino) acetate was carried out by cleavage of the protecting group.



Scheme 1: Synthesis of benzoylamino-(2-methyl-quinolin-4-ylamino) acetic acid 4

5. Acknowledgements

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