

PREPARATION OF INTERMEDIATES FOR ORGANIC SYNTHESIS

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Abstract

Several synthetic methods are described for the preparation of compounds such as derivatives of natural amino acids, unnatural amino acids, amino esters, oxime esters and amino amides that may serve as intermediates in the synthesis of active pharmaceutical ingredients (APIs) or drugs. The compounds described herein are produced in high yield and purity and the synthetic procedures are detailed along with the NMR spectra of the compounds and useful chemical data relating to these compounds.

Keywords: organic synthesis, natural amino acids, unnatural amino acids, amino esters, oxime esters, amino amides, active pharmaceutical intermediates (APIs).

Introduction

The chemical structure of small molecule drugs and drug candidates or active pharmaceutical ingredients often reflect the complexity of these compounds in terms of stereochemistry, functional groups, and framework. Compounds such as unnatural amino acids, derivatives of natural amino acids, amino esters, amino amides and oxime esters are most important and versatile intermediates in organic synthesis being attractive starting materials for the synthesis of various nitrogen and oxygen containing compounds, which can be used as reagents in the formation of drugs.

Unnatural amino acids are important intermediates in biosynthesis and preparation of pharmaceuticals. The unnatural amino acids are distinct from the 22 proteinogenic amino acids,

which are naturally encoded in the genome of organisms for the assembly of proteins. They can be synthetically prepared via, e.g., amine alkylation or esterification, side chain substitution, structural bond extension and isosteric replacements within the amino acid backbone. In addition, the construction of building blocks based on derivatives of natural amino acids has received much attention in the areas of peptide chemistry and pharmaceutical chemistry due to their importance in the synthesis of drugs¹. For example, γ -aminobutyric acid (4-aminobutanoic acid or GABA) is a natural compound, which is an inhibitory neurotransmitter in the developmentally mature mammalian central nervous system. This compound is mainly used as a dietary supplement. A derivative of GABA is N-methyl-4-aminobutanoic acid, which is a product of nicotine catabolism in bacteria inhibiting L-carnitine from undergoing β -oxidation in mammals².

β -aminobutyric acid (BABA) is a natural compound, which is known as neurotransmitter in animals.

R-4-amino-2-methylbutanoic acid is an intermediate in the synthesis of biaryl-substituted 4-aminobutanoic acid derivatives, which are inhibitors of enzyme neutral endopeptidase (NEP)³.

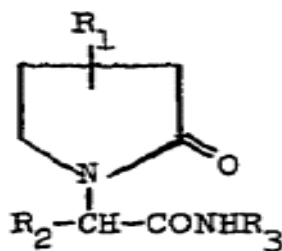
L-glutamic acid is a building block in the synthesis of α -phthalimidoglutarimide, also known as thalidomide, in which one enantiomer of the molecule causes birth defects and the other enantiomer is a drug used for treating multiple myeloma⁴.

Amino esters can be ester derivatives of natural or unnatural amino acids whereas other classes of amino esters exist such as local anesthetics or drugs including, e.g., the molecule of cocaine that has benzoyl as well as acetyl ester moieties and cyclic N-methyl amine moiety. N-acetyl-L-cysteine methyl ester is an important building block, which can be used in the preparation of benzyl mono-fluorophosphate and benzyl penta-fluorophosphate anions as physiologically stable phosphotyrosine mimetics and inhibitors of protein tyrosine phosphatases. It can also be used in the preparation of anthracene derivatives⁵.

One of the starting materials in the synthesis of the drug valsartan, used to treat high blood pressure, heart failure and diabetic kidney disease, is the amino acid ester derivative L-valine methyl ester⁶.

Amino amides are important starting materials for the synthesis of drugs. Reacting 2-aminoethanamide hydrochloride with 4-chloro-butyric acid methyl ester yields the drug piracetam, which is used for treating myoclonus and dementia⁷.

The general chemical structure indicating related racemic lactam compounds (Markush) of etiracetam⁸ is the following:

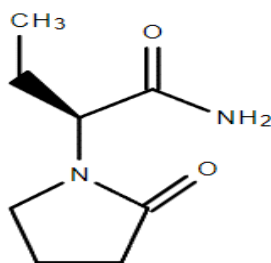


[for racemic etiracetam $R_1=H$ (no substitution on the lactam ring), $R_2=ethyl$, $R_3=H$].

Said Markush includes the compounds 2-(2-oxo-pyrrolidino)-propionamide, 5-

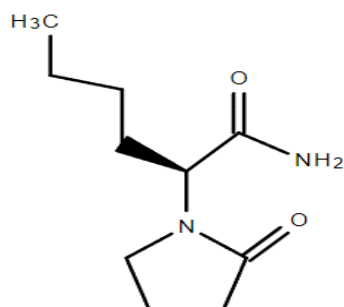
methyl-2-oxo-pyrrolidino)-acetamide, (4-methyl-2-oxo-pyrrolidino)-acetamide, (3,5-dimethyl-2-oxo-pyrrolidino)-acetamide, 2-(5-methyl-2-oxo-pyrrolidino)-butyramide and (4,5-dimethyl-2-oxo-pyrrolidino)-N,N-dimethylacetamide.

The amino amide starting material (*S*)-(+)-2-aminobutanamide hydrochloride is a building block employed in the synthesis of the drugs brivaracetam and levetiracetam⁹ used to treat epilepsy. Levetiracetam [(*S*)-2-(2-oxo-pyrrolidin-1-yl)butanamide] is the more active *S*-enantiomer of the racemic etiracetam.



Levetiracetam

Thus, aliphatic substituted or non-substituted 2-amino-pentanamide hydrochloride compounds could serve as building blocks for additional drug candidates as depicted in the following example:

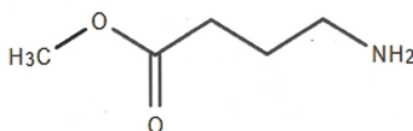


Processes for preparing 2-aminobutanamide can be carried out by passing ammonia gas to ethyl- $[\alpha]$ -bromobutyrate at 0°C and keeping it at -5°C for 10 days for completion of reaction¹⁰ or by contacting the corresponding free base with ammonia at 0°C and keeping it for three days¹¹. 5-aminopentanamide hydrochloride is a useful starting material for preparing δ -amino- γ -hydroxy-aryl alkanolic amides, which are renin inhibitors¹².

Oxime esters are important and versatile intermediates in organic synthesis that are used as, e.g., starting materials for the synthesis of various nitrogen and oxygen containing compounds such as amine and its derivatives, amides, nitriles and esters. The oxime ester moiety exists in a large number of bioactive compounds such as antibacterial, anti-inflammatory, antioxidant, insecticidal and antifungal compounds, for example, 1,5-diphenyl-1,4-pentadien-3-one oxime esters are class of compounds showing antifungal activity that may be synthesized by reacting 1,5-diphenyl-1,4-pentadien-3-one oxime with acyl chloride¹³.

Materials and methods

The starting material used in the synthesis of methyl-N-acetyl-4-aminobutanoate is methyl-4-aminobutanoate, which is the methyl ester of 4-aminobutanoic acid.



methyl-4-aminobutanoic acid

Unnatural amino acids were prepared from their precursors, which are the corresponding lactams using basic or acidic hydrolysis, e.g., barium hydroxide decahydrate solution or concentrated HCl solution respectively or by multiple-step synthesis. For example, δ -aminocaproic acid was prepared starting from N-benzoyl-2-methyl-piperidine.

The preparation of amino ester hydrochloride salts was carried out by preparing a suspension of the amino acid in dry alcohol while cooling to 0°C followed by addition of thionyl chloride and reflux.

The preparation of amide esters or amino amides was carried out by e.g., multistep synthesis, as depicted in Figure 3, for the synthesis of 4-aminopentaneamide.

Preparation of solution of gaseous ammonia dissolved in chloroform was carried out by bubbling gaseous ammonia into the solvent under cooling. The concentration of ammonia in chloroform was determined by titrating an emulsion of 11 ml aqueous solution of ammonia in chloroform with 13.5 ml of 0.85 molar HCl solution in presence of the indicator methyl orange until color was changed from brown to red. The solution's concentration was 1.05 molar.

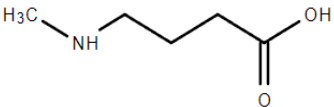
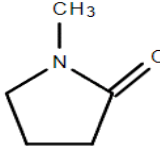
NMR spectra were taken using Bruker NMR 400 MHz spectrometer. Referring to the NMR spectra, the following abbreviations were used: s=singlet, d=doublet, t=triplet, m=multiplet, j=coupling coefficient. IR spectra were taken using Perkin Elmer VIS-NIR spectrometer of samples dissolved in chloroform.

Results and Discussion

1. Preparation of unnatural amino acids

Table 1 below details several racemic or non-chiral unnatural amino acids that were prepared along with the precursors used to obtain them and their structures. Although 4-aminobutanoic acid is a natural amino acid, it does not belong to the group of 22 proteinogenic amino acids and therefore a derivative of this acid is included in Table 1.

Table 1

Entry	Amino acid	Starting material (precursor)
1	N-methyl-4-aminobutanoic acid 	N-methyl-2-pyrrolidone 
2	4-aminopentanoic acid	5-methyl-2-pyrrolidone

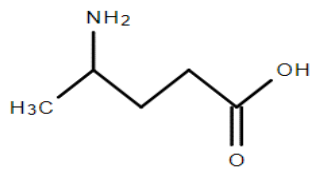
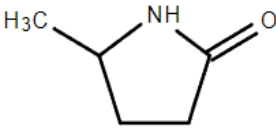
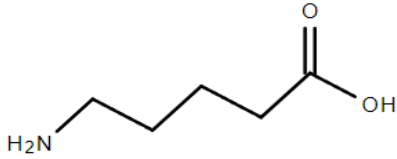
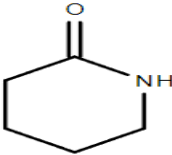
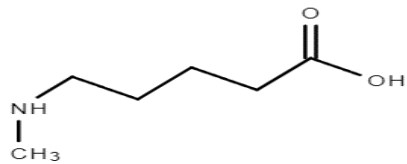
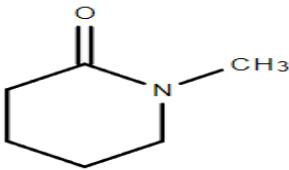
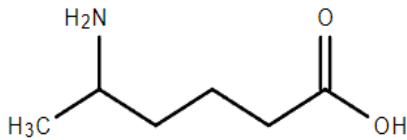
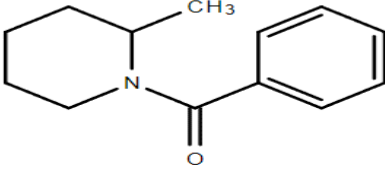
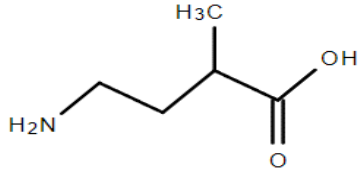
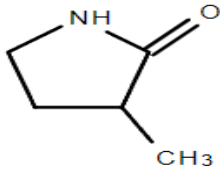
		
3	5-aminopentanoic acid 	2-piperidone 
4	N-methyl-5-aminopentanoic acid 	N-methyl-2-piperidone 
5	δ -aminocaproic acid 	N-benzoyl-2-methyl-piperidine 
6	4-amino-2-methylbutanoic acid 	3-methyl-2-pyrrolidone 

Table 2 details the NMR spectra and other data relating to the racemic or non-chiral unnatural amino acids detailed in Table 1.

Table 2

Entry	Amino acid
1	N-methyl-4-aminobutanoic acid, synthesis yield: 70%, melting point: 146°C. <u>NMR spectrum $\delta(D_2O)$</u> : 1.65 (m, 2H), 2.03 (t, 2H, J=7.5 Hz), 2.45 (s, 3H), 2.78 (t, 2H, J=8.0 Hz)
2	4-aminopentanoic acid, synthesis yield: 85%, melting point: 151°C <u>NMR spectrum $\delta(D_2O)$</u> : 1.07 (d, 3H, J=7.0 Hz), 1.85 (m, 2H), 2.28 (t, 2H, J=7.0 Hz), 3.20 (m, 1H)
3	5-aminopentanoic acid, synthesis yield: 89%, melting point: 157°C <u>NMR spectrum $\delta(D_2O)$</u> : 1.40 (m, 4H), 1.98 (t, 2H, J=6.7 Hz), 2.76 (t, 2H, J=6.8 Hz)
4	N-methyl-5-aminopentanoic acid, synthesis yield: 93%, melting point: 100°C. <u>NMR spectrum $\delta(D_2O)$</u> : 1.20-1.40 (m, 4H), 1.90 (t, 2H, J=7.0 Hz), 2.35 (s, 3H), 2.72 (t, 2H, J=7.0 Hz)
5	δ -aminocaproic acid, synthesis yield: 56% <u>NMR spectrum $\delta(D_2O)$</u> : 1.16 (d, 3H, J=6.5 Hz), 1.54 (m, 4H), 2.28 (t, 2H, J=7.0 Hz), 3.10-3.30 (m, 1H)
6	4-amino-2-methyl-butanoic acid, synthesis yield: 98%, melting point: 193-195°C. <u>NMR spectrum $\delta(D_2O)$</u> : 0.92 (d, 3H, J=7 Hz), 1.50-1.70 (m, 2H), 2.15 (m, 1H), 2.75 (t, 2H, J=7.6 Hz)

Preparation of N-methyl-4-aminobutanoic acid

5.13 grams of N-methyl-2-pyrrolidone (0.052 moles) were dissolved in 55 ml of distilled water and 11.4 grams of barium hydroxide decahydrate (0.031 moles) were added. The mixture was refluxed for 3 hours and then cooled to room temperature followed by cooling to 0°C and the solution was saturated with CO₂ by bubbling the gas into the reaction vessel. The thus formed solid was isolated, washed twice with cold water and filtered off. The aqueous solution was evaporated in vacuum, dried and triturated in ether and dried. Yield: 4.274 grams, 70%. Melting point: 146°C.

Preparation of 4-aminopentanoic acid hydrochloride

4 ml of 6N HCl solution (0.024 moles) were added to 1.137 grams (0.0115 moles) of 5-methyl-2-pyrrolidone and the thus formed solution was heated to 110°C for 24 hours. The aqueous phase was evaporated to dryness to obtain 4-aminopentanoic acid hydrochloride, which was triturated in ether and dried. Yield: 1.507 grams, 85%. Melting point: 151°C.

Preparation of δ -aminocaproic acid

The synthesis of N-benzoyl-2-methyl-piperidine was carried out by dissolving 9.91 grams of 2-methyl-piperidine (0.1 moles) in 280 ml of 1.4 molar NaOH solution (0.39 moles) and the mixture was cooled to 0°C. 17 ml of benzoyl chloride were added drop-wise and mixing was carried out at the same temperature followed by mixing for two hours at room temperature. Then, 100 ml of water were added and the solution was warmed to dissolve the thus formed solid and 50 ml of diethyl ether were added and extraction was carried out. The organic phase was washed first with 50 ml of 1 molar NaOH solution followed by washing with 50 ml of 1N HCl solution and 50 ml of water. The phases were separated, the organic phase was dried over sodium sulfate and evaporated in vacuum to afford 18.72 grams of colorless oil (92% yield).

NMR spectrum:

δ (CDCl₃): 1.21 (d, 2H, J=7.0 Hz), 1.30-1.70 (m, 8H), 2.97 (t, 2H, J=12.4 Hz), 7.10-7.50 (m, 5H).

IR spectrum; amide 1620 cm⁻¹.

The synthesis of N-benzoyl- δ -aminocaproic acid was carried out by preparing a suspension of 5 grams of N-benzoyl-2-methyl-piperidine (0.025 moles) in 225 ml of water and the mixture was warmed to 90°C. A solution of 17 grams of potassium permanganate in 250 ml of warm water was prepared (0.17 molar) and allowed to cool to room temperature and then added drop-wise to the reaction mixture over 24 hours while mixing at room temperature. Then, 50 ml of diethyl ether were added and extraction was carried out. The aqueous phase was acidified, cooled in a water-ice bath to afford precipitation of a solid, which was filtered off and dried to afford 2 grams of the product (35% yield).

NMR spectrum:

δ (DMSO-d₆): 1.15 (d, 3H, J=7.0 Hz), 1.45 (m, 4H), 2.25 (t, 2H, J=6.4 Hz), 4.02 (m, 1H), 7.30-7.60 (m, 5H).

IR spectrum; amide 1580, 1650, 3420 cm⁻¹, acid 1710, 2800-3000 cm⁻¹, broad.

Melting point: 148°C.

The synthesis of δ -aminocaproic acid hydrochloride was carried out by dissolving 1.04 grams of N-benzoyl- δ -aminocaproic acid (0.00475 moles) in 50 ml of solution of 10% NaOH (0.125 moles) and the mixture was refluxed for one hour. The solution was allowed to cool down to room temperature and acidified with 1N HCl solution. The thus formed solid was filtered off and the solution was extracted twice with 50 ml each of diethyl ether, the phases were separated and the aqueous phase was evaporated in vacuum to afford 0.45 grams of δ -aminocaproic acid hydrochloride (56% yield). Melting point: 118°C.

The preparations of other unnatural amino acids that are mentioned in Table 2 were carried out in similar ways as described for N-methyl-4-aminobutanoic acid or for 4-aminopentanoic acid hydrochloride.

2. Preparation of amino esters

The advantage of preparing isopropyl esters of amino acids is due to the relatively slow spontaneous cyclization of the free isopropyl amino esters in organic solvents in comparison to the methyl, ethyl and n-propyl amino esters, namely conversion of the free amino ester to the corresponding lactam. Table 3 below demonstrates this advantage:

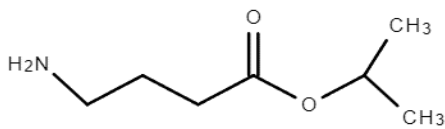
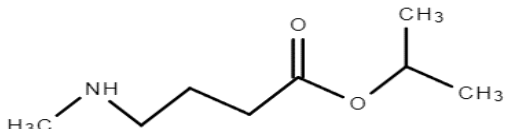
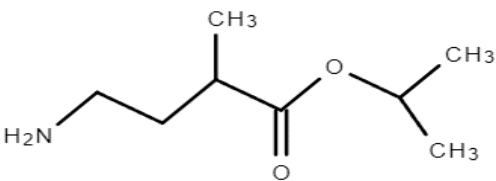
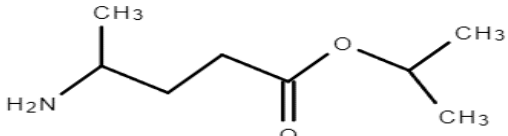
Table 3

Amino ester	Solvent	Reaction time	Conversion
γ -amino-methyl butanoate	Isooctane	12 hours	85%
γ -amino-methyl butanoate	Hexane	12 hours	70%
γ -amino-methyl butanoate	t-amyl alcohol	6 days	75%
γ -amino-ethyl butanoate	t-amyl alcohol	9 days	20%
γ -amino-ethyl butanoate	t-amyl alcohol	60 days	60%
γ -amino-isopropyl butanoate	t-amyl alcohol	6 days	2%
γ -amino-isopropyl butanoate	t-amyl alcohol	7 days	3%

The experiments were carried out by dissolving the free amino ester in 5 ml of the corresponding solvent and shaking the solution in a shaker at 200 RPM and 40°C for the time period mentioned in Table 3. The conversion was determined according to quantitative NMR analysis. γ -amino-methyl butanoate and γ -amino-ethyl butanoate were prepared as described for γ -amino-isopropyl butanoate using methanol and ethanol respectively instead of isopropyl alcohol.

Thus, several amino esters were prepared as detailed Table 4. The amino esters were obtained as the corresponding hydrochloride salts including γ -amino-isopropyl butanoate hydrochloride but are presented in Table 4 as the amino ester free bases.

Table 4

Entry	Compound's name	Compound's structure
1	γ -amino-isopropyl butanoate	
2	N-methyl- γ -amino-isopropyl butanoate	
3	4-amino-2-methyl-isopropyl butanoate	
4	4-amino isopropyl pentanoate	

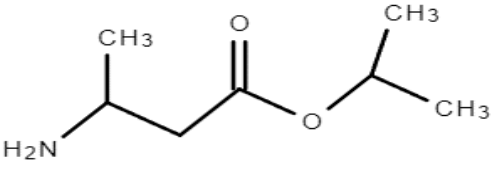
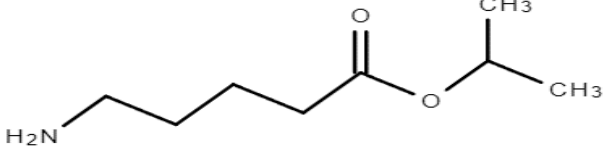
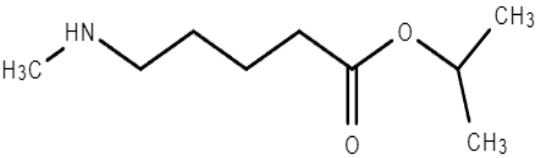
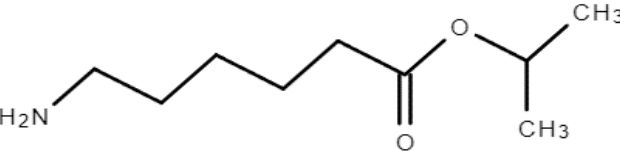
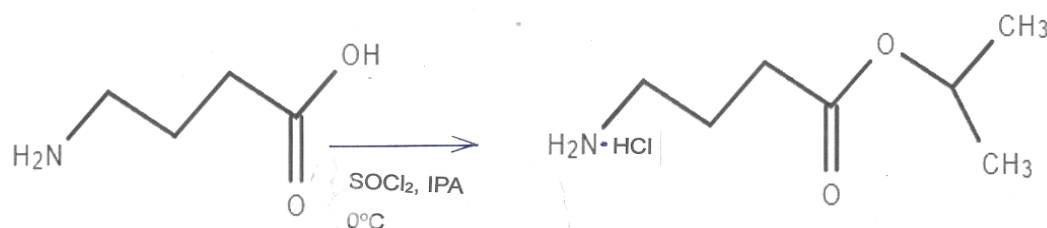
5	3-amino-isopropyl butanoate	
6	5-amino isopropyl pentanoate	
7	N-methyl-5-amino isopropyl pentanoate	
8	6-amino isopropyl hexanoate	

Figure 1 depicts the synthesis of γ -amino isopropyl butanoate. IPA refers to isopropyl alcohol and SOCl_2 refers to thionyl chloride:

Figure 1



The preparation of the compound γ -amino-isopropyl butanoate hydrochloride was carried out by suspending 1.03 g of 4-aminobutanoic acid, GABA, (0.01 moles) in 20 ml of dry isopropyl alcohol while cooling to 0°C. 1.2 ml (0.023 moles) of thionyl chloride were added drop-wise and the mixture was allowed to reach room temperature under mixing followed by refluxing the mixture for 1 hour. The solvent was evaporated in vacuum to afford a viscous oil, which was triturated in dry ether to afford 1.787 g of the product in 98.5% yield having melting point of 72-73°C. γ -amino-isopropyl butanoate free base was prepared by adding 300 mg (1.65 millimoles) of the hydrochloride salt into 3.3 ml of solution of gaseous ammonia dissolved in chloroform (2-fold molar excess). Mixing was carried out for few minutes to allow precipitation of ammonium chloride. The thus formed solid was filtered off, washed with chloroform and the solvent was evaporated to afford 178 milligrams of the free amino ester in 74% yield.

Other amino esters mentioned in Table 4 were synthesized in a similar way.

The NMR spectra and yield of the reactions for the preparation of the amino esters described in Table 4 are detailed in Table 5.

Table 5

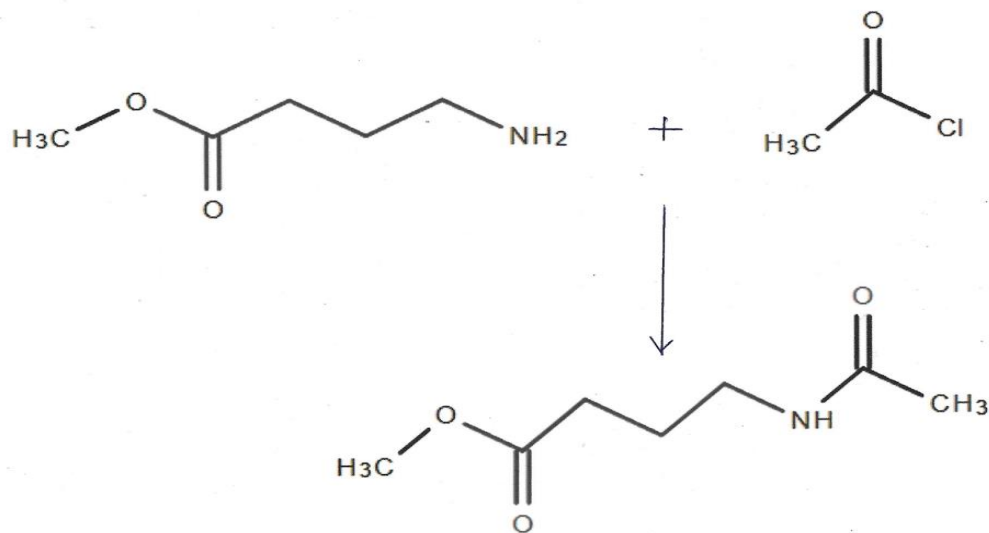
Entry	Yield %	NMR spectra of the products
1	98.5	<u>NMR spectrum of the hydrochloride salt $\delta(\text{CDCl}_3)$:</u> 1.20 (d, 6H, J=6.0 Hz), 2.05-2.20 (m, 2H), 2.42 (t, 2H, J=7.0 Hz), 3.05 (t, 2H, J=7.0 Hz), 4.95 (m, 1H), 8.10-8.40 (broad, 2H, NH ₂). <u>NMR spectrum of the free amine $\delta(\text{CDCl}_3)$:</u> 1.15 (d, 6H, J=6.5 Hz), 1.35 (s, 2H, NH ₂), 1.72 (m, 2H), 2.30 (t, 2H, J=6.0 Hz), 2.72 (t, 2H, J=6.0 Hz), 4.97 (m, 1H)
2	92	<u>NMR spectrum of the hydrochloride salt: $\delta(\text{CDCl}_3)$:</u> 1.22 (d, 6H, J=5.5 Hz), 1.60-2.10 (m, 2H), 2.15 (t, 2H, J=7.0 Hz), 2.75 (s, 3H), 3.05 (t, 2H, J=7.0 Hz)

3	51	<u>NMR spectrum of the hydrochloride salt: $\delta(\text{CDCl}_3)$:</u> 1.18 (d, 3H, J=7.2 Hz), 1.28 (d, 6H, J=7.0 Hz), 1.80-2.20 (m, 2H), 2.55 (m, 1H), 3.05 (t, 2H, J=7.0 Hz), 4.90-5.10 (m, 1H)
4	92	<u>NMR spectrum of the hydrochloride salt: $\delta(\text{CDCl}_3)$:</u> 1.21 (d, 6H, J=7.2 Hz), 1.42 (d, 3H, J=6.5 Hz), 2.46 (t, 2H, J=8 Hz), 3.35-3.55 (m, 1H), 4.97 (m, 1H)
5	96	<u>NMR spectrum of the hydrochloride salt: $\delta(\text{CDCl}_3)$:</u> 1.20 (d, 6H, J=6.5 Hz), 1.45 (d, 3H, J=6.5 Hz), 2.78 (m, 2H), 3.75 (m, 3H), 5.0 (m, 1H)
6	84	<u>NMR spectrum of the hydrochloride salt: $\delta(\text{CDCl}_3)$:</u> 1.18 (d, 6H, J=6.25 Hz), 1.75 (m, 4H), 2.30 (t, 2H, J=7.1 Hz), 3.05 (t, 2H, J=7.0 Hz), 5.0 (m, 1H)
7	87	<u>NMR spectrum of the hydrochloride salt: $\delta(\text{CDCl}_3)$:</u> 1.19 (d, 6H, J=6.5 Hz), 1.50-1.80 (m, 2H), 2.23 (t, 2H, J=6.7 Hz), 2.70 (s, 3H), 2.90 (t, 2H, J=7.3 Hz), 5.0 (m, 5H) (9.4-9.6 (broad, 1H, NH)
8	99	<u>NMR spectrum of the HCl salt: $\delta(\text{CDCl}_3)$:</u> 1.18 (d, 6H, J=6.2 Hz), 1.45 (m, 2H), 1.65 (m, 2H), 1.80 (m, 2H), 2.26 (t, 2H, J=7.1 Hz), 2.95 (t, 2H, J=7.0 Hz), 4.98 (m, 1H)

3. Preparation of the amide ester methyl-N-acetyl- γ -aminobutanoate

The synthesis of methyl-N-acetyl- γ -aminobutanoate was carried out by reacting methyl- γ -aminobutanoate with acetyl chloride as depicted in Figure 2 below.

Figure 2

methyl-N-acetyl- γ -aminobutanoate

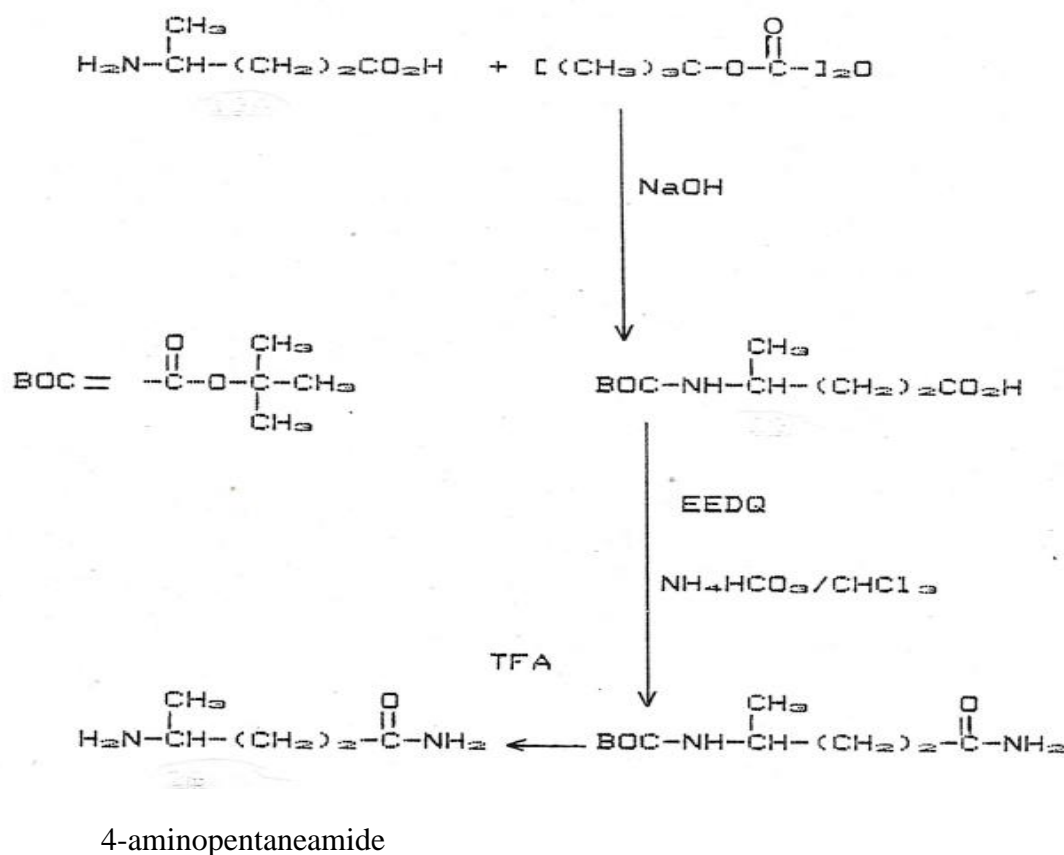
0.6 ml of acetyl chloride (8.4 millimoles) and 3 ml (11.6 millimoles) of 3.86 molar sodium carbonate solution were simultaneously added to a cold solution of 0.85 g (7.3 millimoles) of methyl- γ -aminobutanoate dissolved in 20 ml chloroform and the mixture was stirred for half an hour after which time another portion of 0.6 ml of acetyl chloride and 3 ml of sodium carbonate solution were added and the mixture was stirred for additional 1.5 hours. Then, another portion of 0.6 ml of acetyl chloride and 3 ml of sodium carbonate solution were added and the mixture was stirred for additional 2 hours. Finally, a fourth portion of 0.6 ml of acetyl chloride and 3 ml of sodium carbonate solution were added, the mixture was allowed to reach room temperature and stirred overnight. Then, 50 ml of chloroform were added and 30 ml of water and extraction was carried out. The layers were separated and the organic phase was washed with 30 ml of 0.5 molar HCl solution and 30 ml of water. The layers were separated and the organic phase was dried over sodium sulphate and the solvent was evaporated in vacuum. The residue was dissolved in ethyl acetate and subjected to liquid chromatography in a column packed with silica gel using an eluting solvent mixture of 70% hexane and 30% acetone to afford the product in 34% yield.

NMR spectrum: δ (CDCl₃): 1.81 (m, 2H), 1.95 (s, 3H), 2.37 (t, 2H, J=6.0 Hz), 3.27 (q, 2H, J=6.0 Hz), 3.70 (s, 3H), 5.60-5.80 (broad, s, NH). Infra-red spectrum: amide: 1510, 1670, 3430 cm⁻¹, acid: 1710 cm⁻¹, ester: 1730 cm⁻¹.

4. Preparation of the amino amide 4-aminopentaneamide

The preparation of 4-aminopentaneamide is depicted in Figure 3 below and includes reacting 4-aminopentanoic with di-tert-butyl-dicarbonate to afford N-BOC-4-aminopentanoic acid followed by reacting the product with N-ethoxycarbonyl-1,2-dihydroxy-quinoline (EEDQ) to obtain N-BOC-4-amino-pentanamide and reacting the product with trifluoroacetic acid (TFA) to afford 4-aminopentaneamide.

Figure 3



The preparation of N-BOC-4-aminopentanoic acid was carried out by dissolving 1.17 grams (10 millimoles) of 4-aminopentanoic acid in a solvent mixture of 20 ml dioxane, 10 ml of water and 10 ml of 1M NaOH solution. The solution was cooled to 0°C and 2.4 grams of di-tert-butyl-dicarbonate (11 millimoles) were added and the mixture was allowed to reach room temperature and mixed for half an hour. Then, the solution's volume was reduced to about half using vacuum distillation and the liquid was cooled to 0°C and 30 ml of ethyl acetate were added. A solution of 0.5 M KHSO₄ was added to pH 2 and extraction was carried out. The

phases were separated and the aqueous phase was washed with 30 ml of ethyl acetate, the organic phases were combined and washed with water, dried over sodium sulfate, filtered and the solvent was evaporated in vacuum to afford 2.016 grams of a white solid (93%), which was crystallized from ethyl acetate. Melting point: 84-85°C.

NMR spectrum: δ (DMSO_d₆): 1.17 (d, 3H, J=6.4 Hz), 1.40 (s, 9H), 1.72 (m, 2H), 2.40 (t, 2H, J=7.3 Hz), 3.55 (m, 1H), 4.30-4.60 (broad, s, 1H).

Infra-red spectrum: urethane: 1500 cm⁻¹, urethane/acid: 1710 cm⁻¹, acid: 2800-3000 broad.

The preparation of N-BOC-4-aminopentanamide was carried out by dissolving 1.37 grams (6.3 millimoles) of N-BOC-4-aminopentanoic acid and 1.714 grams (6.9 millimoles) of N-ethoxycarbonyl-1,2-dihydroxy-quinoline (EEDQ) in 15 ml of chloroform and the mixture was stirred at room temperature overnight. Then, water was added and extraction was carried out. The phases were separated and the organic phase was washed with water, dried over sodium sulfate, filtered and the solvent was evaporated to afford a solid, which was crystallized from ethyl acetate. Yield: 1.002 grams (74%). Melting point: 125°C.

NMR spectrum: δ (CDCl₃): 1.13 (d, 3H, J=6.4 Hz), 1.41 (s, 9H), 1.75 (m, 2H), 2.35 (t, 2H, J=7.0 Hz), 3.69 (m, 1H), 5.30-5.60 (broad, s, NH), 6.30-6.60 (broad, s, 1H).

Infra-red spectrum: urethane/amide: 1500, 1680 cm⁻¹, amide: 3430 cm⁻¹.

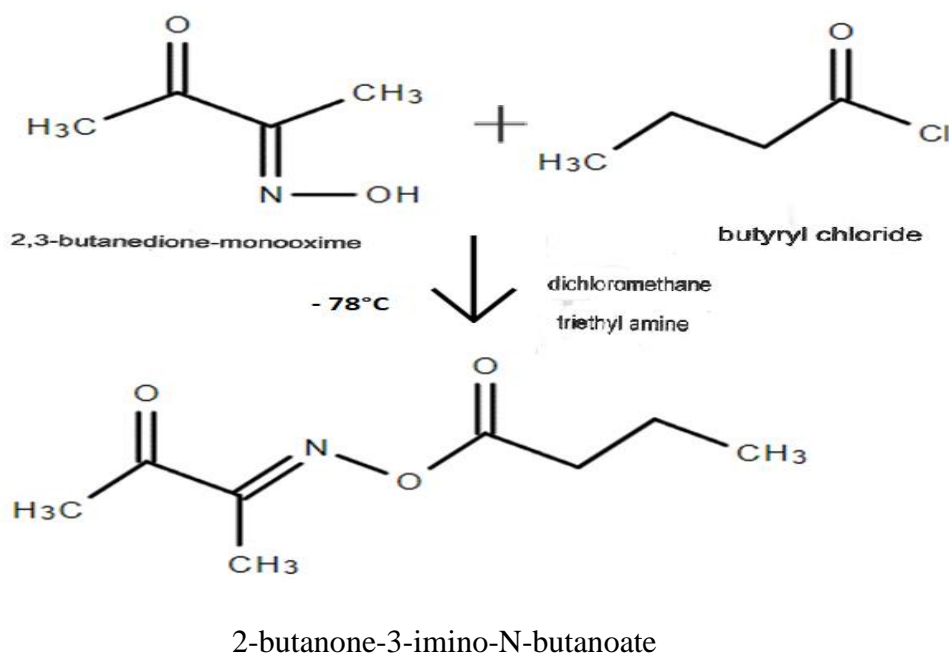
The preparation of 4-aminopentanamide was carried out by dissolving 0.246 grams of N-BOC-4-aminopentanamide (1.14 millimoles) in 10 ml of trifluoroacetic acid [TFA] (1.14 moles) and the mixture was stirred at room temperature for one hour followed by evaporation of the solvent to afford 0.132 grams of the product as an oil (100% yield).

NMR spectrum: δ (D₂O): 1.27 (d, 3H, J=7.0 Hz), 1.70-2.10 (m, 2H), 2.37 (t, 2H, J=7.5 Hz), 3.30-3.50 (m, 2H).

5. Preparation of the oxime ester 2-butanone-3-imino-N-butanoate

The synthesis of the oxime ester 2-butanone-3-imino-N-butanoate was carried out by reacting 2,3-butanedione-monooxime with butyryl chloride as depicted in Figure 4 below.

Figure 4



The preparation of 2-butanone-3-imino-N-butanoate was carried out by dissolving 3.033 g (30 millimoles) of 2,3-butanedione-monooxime in 50 ml of dichloromethane while mixing for 1 hour. Then, 4.2 ml of triethyl amine (30 millimoles) were added and the temperature of the mixture was lowered to -78°C using dry ice in acetone. 3.1 ml of butyryl chloride (30 millimoles) dissolved in 10 ml of dichloromethane were added drop-wise while mixing for half an hour at -78°C and the reaction mixture was allowed to reach room temperature while mixing was continued for an additional one hour. Then, 50 ml of water were added and extraction was carried out. The two layers were separated and a solution of saturated sodium bicarbonate was added to the organic phase and after extraction, the organic layer was once again washed with water, dried over sodium sulphate, filtered and the solvent was evaporated in vacuum to afford 3.615 g (90% yield) of 2-butanone-3-imino-N-butanoate.

NMR spectrum: $\delta(\text{CDCl}_3)$: 0.99 (t, 3H, $J=7.3$ Hz), 1.73 (m, 2H), 2.10 (s, 3H), 2.47 (s, 3H), 2.49 (t, 2H, $J=7.0$ Hz).

Infra-red spectrum: ketone 1700 cm^{-1} , oxime ester 1775 cm^{-1} .

Conclusion

The development of synthetic methods for the preparation of compounds such as derivatives of natural amino acids, unnatural amino acids, amino esters, oxime esters and amino amides is helpful in the organic synthesis of active pharmaceutical ingredients or drugs. The reported synthetic methods are not grouped according to the type of reactions (e.g., alkylation or esterification) but according to the synthesized compounds (e.g., amino esters, or amino amides) so the application of these methods can be useful for those skilled in the art for the synthesis of similar compounds as well.

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