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RESEARCH ARTICLE

SYNTHESIS AND CHARACTERIZATION OF NOVEL AMINO CARBOXYLIC ACIDS.

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Abstract

A series of substituted amino carboxylic acids were synthesized by simple addition and reduction reactions using easily available reagents. Nitroalkanes such as nitromethane and nitroethane were reacted with aromatic aldehydes to give nitroalkenes which were further converted to substituted nitro esters by Michael addition reaction under mild conditions using KF supported alumina as a basic catalyst. These nitro esters were reduced to give substituted amino carboxylic acids using nickel chloride hexahydrate and sodium borohydride.

Introduction:-

Importance of amino acid is well known because of its biological and chemical properties (Dwayer, 2008).Amino acids possesses diverse biological properties and so has a wide industrial application especially in food and pharmaceutical sector (Leuchlenberger et al. 2005). Apart from its main application as a nutritive supplement it is also used as a precursor for flavors in food industries (Izumi et al. 1978).

Amino acids widely exist in various forms of life. As both basic and acidic functional groups are present in amino acids they show amphoteric character i.e. they act as both acids and bases and thus form amide linkages between amino acids which are known as peptide bonds. A peptide chain with more than two amino acids is also called a polypeptide. Proteins are relatively large compounds also made of amino acids arranged in a linear chain joined by a peptide bond.

Purification and separation of amino acids plays a vital role in the synthesis of amino acids (Hurlbut et al. 1978). Amino acids are crystalline solids with relatively high melting points, so they decompose rather than melting when heated. Mostly amino acids are sparingly soluble in non-polar solvents and soluble in water. From the literature survey, it was found that during the synthesis of amino acids, reduction of nitro to amino group and introduction of carboxylic group in the moiety are the two main aspects to be taken care of. Expensive chiral catalysts such as BINOL (Dursma et al. 2003) and protecting group like N-Boc (Diaz-Coutino et al. 2009), were used for the conversion of nitro to amino group. Use of Strong oxidizing reagents such asHIO_5 and sensitive reactions like Diel Alders (Wang et al. 2005), were applied for the introduction of carboxylic acid group in the moiety (Masesane et al. 2004). In this present work we have synthesized amino acids using simple addition reactions such as Michael addition using KF/Basic alumina to get the carboxylic group, followed by reduction of nitro group using $NiCl_2.6H_2O$ and $NaBH_4$ under mild conditions.

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All reagents and solvents were purchased from Qualigens and S.D.Fine Chemicals, India. The progress of the reactions was monitored by TLC on pre-coated silica gel 60 F254, Merck. Melting points were noted on silicon oil bath using open capillary method with thermometer having least count of 1°C. Chromatographic purification was performed on silica gel having 60-120 mesh by Spectrochem India and using petroleum ether and ethyl acetate as solvents which distilled before using. Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as KBr pellets for solids and neat for liquids. ^{1}H NMR spectra were recorded on a Bruker Spectrospin spectrometer operating at 400 MHz using TMS as an internal standard.

General Procedure for Synthesis of β-nitrostyrenes (1b, 2b & 3b):-
(https://erowid.org/archive/rhodium/chemistry/345-meo-ns.html)
To a mixture of acetic acid 75 mL and nitromethane 20 mL **(Scheme-I)** and nitroethane **(Scheme-II)** there was added aldehyde **(A)** (103mmol) and cyclohexylamine 10 mL. The solution was heated to 95 °C and after 90 minutes of heating the orange solution was cooled to room temperature. With good stirring the solution was diluted slowly using 150 mL cold water, this caused the formation of a thick yellow crystalline mass. The formed crystalline mass was filtered and washed thoroughly with water (2 x 50 mL). The filtered crystals were dried under vacuum. The entire mass recrystallized with methanol-ethyl acetate.

General Procedure for Synthesis of Nitroalkanes (1c, 2c & 3c):-
In a cold water bath a solution of sodium borohydride (68mmol) in ethanol 40 mL and ethyl acetate70 mL was stirred and to this solution was added nitrostyrene **(B)** (17mmol) in small portions. The temperature was maintained below 25 °C during addition. After completion of addition the creamy white solution was stirred for 30 minutes more. To the solution was then added 50 mL water with stirring upon which the solution turned colorless. After five minutes of stirring acetic acid (50%) was slowly added to quench the excess borohydride. Acetic acid was added until gas evolution ceased. The mixture was saturated with solid sodium chloride and stirred for another five minutes which resulted in two layers. The organic phase was separated and the aqueous phase was extracted with (2x40 mL) ethyl acetate. The combined organic phase was dried over sodium sulphate. Solvent was distilled under vacuum to give nitroalkanes as white crystals.

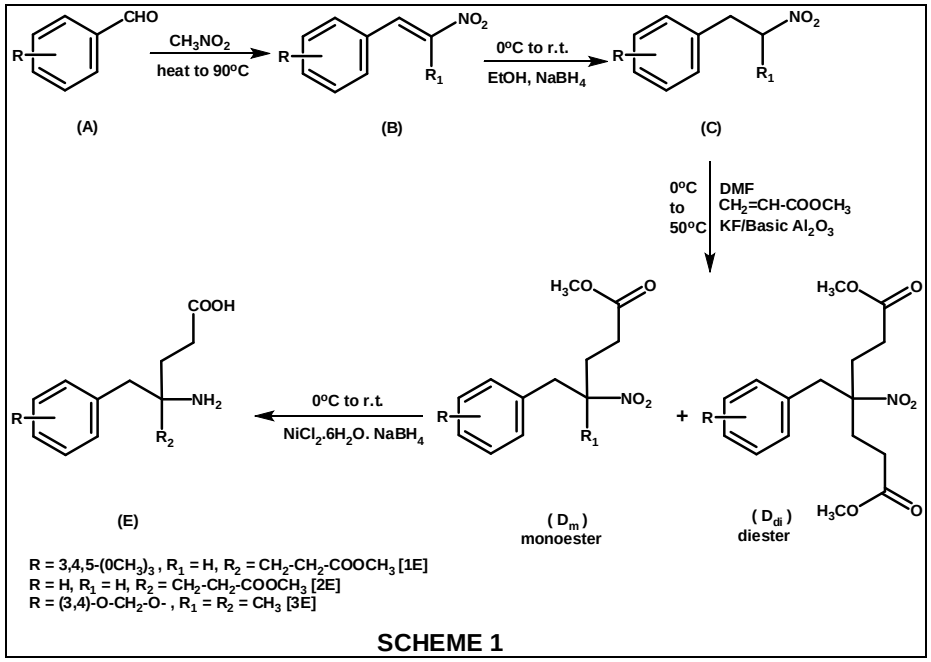
General procedure for Synthesis of Nitroesters (1d, 2d & 3d) (Scheme 1):-
To a stirred suspension of nitroalkane **(C) (**0.016mol) in dimethylformamide 25 mL at room temperature was added 1g KF/Al_2O_3 (Bergbraiter et al. 1987). The mixture was allowed to stir for 10 mins after which methyl acrylate (0.018mol) was added dropwise and the reaction mixture was stirred for 4 hours. Reaction was monitored by TLC and reaction mixture was warmed in some case for completion of the reaction. The reaction mixture was filtered to remove the catalyst. The filtrate was poured into ice cold water and stirred for 30 mins. The precipitated solid was filtered and dried. The nitro ester was purified by silica gel chromatography with petroleum ether-ethyl acetate (90:10) to give sufficiently pure compound. (1D obtained as mono:di 20:80, 2D and 3D were exclusively mono ester)

General procedure for Synthesis of Nitro esters (4f & 5f) (Scheme 2).
To a stirred suspension of nitroalkane **(C) (**0.016mol) in dimethylformamide 25 mL at room temperature was added 1g KF/Al_2O_3 (Bergbraiter et al. 1987). The mixture was allowed to stir for 10 mins after which diethyl malonate (0.018 mol) was added dropwise and the reaction was stirred for 4 hours. Reaction was monitored by TLC and reaction mixture was warmed in some case for completion of the reaction. The reaction mixture was filtered to remove the catalyst. The filtrate was poured into ice cold water and stirred for 30 mins. The precipitated solid was filtered and dried. The nitro ester was purified by silica gel chromatography with petroleum ether-ethyl acetate (90:10) to give sufficiently pure compound.

General Procedure for Synthesis of Amino Acids (1e, 2e, 3e, 4g & 5g).
(Scheme 1 & 2) (Nunez et al. 2013)
To a solution of nitro ester **(D)** (0.002 mol) in methanol 20 mL at 0°C was added $NiCl_2.6H_2O$ (0.6 g 0.004 mol) and stirred for 5 mins. To the above reaction mixture was added sodium borohydride (0.5g 0.01mol) slowly in small portions. Evolution of gas was observed during the addition. The resulting black mixture was stirred at 0 °C for 1 hour. The reaction was monitored by TLC**.** The reaction mixture was quenched with saturated ammonium chloride and extracted with dichloromethane (3 x 25 mL). The combined extracts were dried over sodium sulphate, filtered and concentrated. The resulting crude product was purified by column chromatography with methanol-ethyl acetate (20:80) to get the final amino acids.

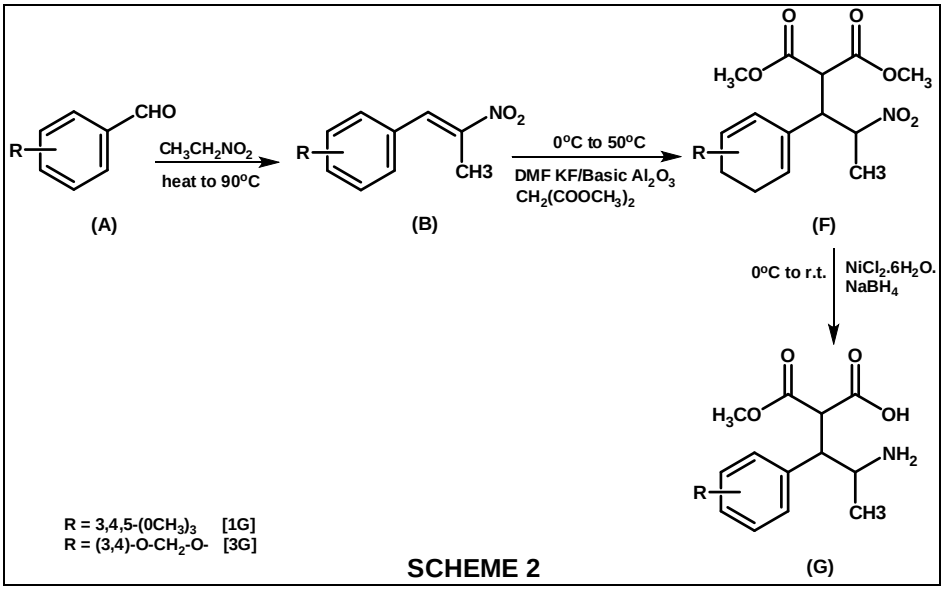
Results and Discussion:-

Different nitroalkenes were used as the precursors for the synthesis of amino carboxylic acids. In **Scheme I,** condensation of aldehydes with nitroalkane was carried out to get corresponding nitroalkenes. The nitroalkenes synthesized were converted to nitroalkanes by hydrogenation using sodium borohydride. Nitroalkanes were then subjected to Michael addition with methyl acrylate, under mild conditions in the presence of KF/Basic alumina as a catalyst. The nitroester obtained was then reduced to amino carboxylic acid using nickel chloride hexahydrate and sodium borohydride.



SCHEME 1

In **Scheme II** nitroalkenes were directly subjected to Michael addition under the same conditions and diethyl malonate as the reactant. The nitroester obtained from the above reaction was similarly reduced to amino carboxylic acid as mention in **Scheme I** above.



SCHEME 2

The reactions carried out were monitored by TLC. The products obtained were either recrystallized or separated by column chromatography.

Highly substituted amino acids were thus prepared using simple set of reactions. A new methodology was successfully developed to get these amino acids using readily available raw materials such as aldehydes and nitroalkanes. The schemes followed here also showed a new approach toward synthesis of highly substituted amino acids which can play a vital role in formulating new pharmaceutical intermediates in medicinal chemistry which otherwise shall be difficult to synthesize.

Spectroscopic and Analytical Data of Compounds:-

3,4,5-Trimethoxy-β-nitrostyrene (1B):-

Yellow solid; Yield:19.12 g (77%); mp:117-118 °C; IR (KBr, cm^{-1})1255 cm^{-1} and 1323 cm^{-1} Nitro, 1632 cm^{-1}-C=C-Stretching, 1583 cm^{-1} and 2939 cm^{-1} Aromatic; ^1H NMR ($CDCl_3$, δ) 3.9 [9H, s, -OCH_3], 6.75 [2H, s, Ar-H], 7.5 [1H, d, Ar-CH=CH-NO_2], 7.9 [1H, d, Ar-CH=CH-NO_2].

3,4,5-Trimethoxyphenyl-2-nitroethane (1C):-

White crystalline needles; Yield:3.76 g (92%); mp:82-83 °C; IR (KBr, cm^{-1}) 1319cm^{-1} and 1315cm^{-1} NO_2, 1592 cm^{-1} and 2931 cm^{-1} Aromatic; ^1H NMR ($CDCl_3$, δ) 3.3 [2H, t, Ar-CH_2-CH_2-NO_2], 3.9 [9H, s, -OCH_3], 4.6 [2H, t, Ar-CH_2-CH_2-NO_2], 6.4 [2H, s, ArH].

Dimethyl-4-nitro-4-(3,4,5-trimethoxyphenyl) octanedioate (1D di):-

Crystalline Solid; Yield:5g (73%); mp:105-108 °C; IR (KBr, cm^{-1}) 1315cm^{-1} NO_2, 1736 cm^{-1} Ester (broad),1596 cm^{-1} and 2950 cm^{-1} Aromatic; ^1H NMR ($CDCl_3$, δ) 2.1-2.4 [8H, 2m, (-CH_2-CH_2COOCH_3)$_2$], 3.2 [2H, s, Ar-CH_2], 3.7 [6H, s, (-$COOCH_3$)$_2$], 3.8 [9H, s, Ar-(OCH_3)$_3$], 6.3 [2H, s, ArH].

Methyl 4-nitro-5-(3,4,5-trimethoxyphenyl)pentanoate (1D mono):-

Yellowish Liquid; Yield:1.2 g (22%); bp:135 °C; IR (Neat, cm^{-1}) 1339 cm^{-1} NO_2, 1737 cm^{-1} Ester (sharp), 1593 cm^{-1} and 2947 cm^{-1} Aromatic; ^1H NMR ($CDCl_3$, δ) 2.1-2.4 [4H, m, -CH_2-CH_2-$COOCH_3$], 3.0 [1H, d, Ar-CH_{2a}-CH_2-NO_2], 3.2 [1H, d, Ar-CH_{2b}-CH_2-NO_2], 3.7 [3H, s, -$COOCH_3$], 3.8 [9H, s, Ar-(OCH_3)$_3$], 4.8 [1H, m, -CH-NO_2], 6.3 [2H, s, ArH]

4-Amino-7-methoxy-7-oxo-4-(3,4,5- trimethoxybenzyl) heptanoic acid (1E):-

White Solid**;** Yield:0.5 g (56%); mp**:** Above 225 °C; IR (KBr, cm^{-1}) 1676 cm^{-1} acid carbonyl, 1734 cm^{-1} Ester carbonyl, 2839 cm^{-1} Aromatic, 2941 cm^{-1} Amino, 3202 cm^{-1} Hydroxy; ^1H NMR ($CDCl_3$, δ) 1.8-2 [6H, 2m, -CH_2-C-CH_2-CH_2-COOH], 2 – 2.1 [1b, NH_2], 2.4 [2H, t, -OCH_3-C-CH_2-], 2.65–2.75 [2H, 2d, Ar-CH_2-CH-NH_2], 3.65 [3H, s, -$COOCH_3$], 3.8 [9H, s, Ar-(OCH_3)$_3$], 6.4 [2H, s, Ar-H], 6.7 [1H, b, -COOH].

2-nitro-1-phenylethene (2B):-

Yellow Crystalline Solid;Yield:10 g (68%); mp: 57 °C; IR (KBr, cm^{-1}) 1259 cm^{-1} and 1336 cm^{-1} NO_2, 1624 cm^{-1} -CH=CH- stretching, 1503 cm^{-1} and 2832 cm^{-1} Aromatic; ^1H NMR ($CDCl_3$, δ) 7.4-7.55 [5H, m, ArH], 7.6 [1H, d, Ar-CH=CH-NO_2], 8.0 [1H, d, Ar-CH=CH-NO_2].

1-(2-nitroethyl) benzene (2C):-

Light yellowish liquid; Yield:4 g (85%); bp: 88-90 °C (1-2mm); IR(Neat, cm^{-1}) 1249 cm^{-1} and 1298 cm^{-1} NO_2, 588 cm^{-1} and 2832 cm^{-1} Aromatic; ^1H NMR ($CDCl_3$, δ) 3.3 [2H, t, Ar-CH_2-CH_2-NO_2], 4.6 [2H, t, Ar-CH_2-CH_2-NO_2], 7.3-7.5 [5H, m, ArH].

Dimethyl-4-benzyl-4-nitroheptanedioate (2D):-

White Crystalline Solid; Yield:6 g (70.58%); mp: 85-90 °C; IR (KBr, cm^{-1}) 1318 cm^{-1} NO_2, 1590 cm^{-1} and 2849 cm^{-1} Aromatic, 1766 cm^{-1} Carbonyl stretching of ester; ^1H NMR ($CDCl_3$, δ), 2.05-2.35 [8H, 2m,(-CH_2-CH_2-$COOCH_3$)$_2$], 3.3 [2H, s, Ar-CH_2], 3.7 [6H, s, (-$COOCH_3$)$_2$], 7.3-7.5 [5H, m, ArH].

4-Amino-4-benzyl-7-methoxy-7-oxoheptanoic acid (2E):-

White Solid**;** Yield:0.86 g (50%); mp**:** Above 225 °C; IR (KBr, cm^{-1}) 1591 cm^{-1} and 2803 cm^{-1} Aromatic, 1672 cm^{-1} and1739 cm^{-1} Carbonyl ester, 3082 cm^{-1} Amino, 3307 cm^{-1} Hydroxyl; ^1H NMR ($CDCl_3$, δ) 1.75-2.0 [6H, m, -CH_2-C-CH_2-CH_2-$COOCH_3$], 2.1 [1b, NH_2], 2.4 [2H, t, CH_2-CH_2-COOH], 2.65 [1H, d, Ar-CH_a], 2.75 [1H, d, Ar-CH_b], 3.65 [3H, s, -$COOCH_3$], 7.4-7.6 [5H, m, ArH].

1-(3,4-methylenedioxyphenyl)-2-nitropropene (3B):-
Yellow sharp oval shaped crystals**;** Yield:14.5 g (76%); mp**:** 97-98 °C; IR (KBr, cm^{-1}) 1031 cm^{-1} Ether Linkage, 1264 cm^{-1} and 1320 cm^{-1} Nitro, 1641 cm^{-1} CH=CH Stretching, 1503 cm^{-1} and 2909 cm^{-1} Aromatic; ^{1}HNMR ($CDCl_3$, δ) 2.4 [3H, s, $-CH_3$-C-NO2], 6.0 [2H, s, $-O-CH_2-O-$], 6.8-7.0 [3H, m, 3Ar-H], 8.0 [1H, s, Ar-CH=C-].

5-(2-Nitropropyl)benzo[d][1,3]dioxole (3C):-
Light Yellow Liquid; Yield:2.5 g (70%); bp: 152 °C; IR (Neat, cm^{-1}) 1039 cm^{-1} Ether Linkage, 1198 cm^{-1} and 1249 cm^{-1} NO_2, 2897 cm^{-1} Aromatic; ^{1}HNMR ($CDCl_3$, δ) 1.5 [3H, d, $-CH_3$-CH-NO2], 2.9 [1H, dd, Ar-CH_{2a}], 3.2 [1H, dd, Ar-CH_{2b}], 4.7 [1H, m, $-CH_3-CH-NO_2$], 5.9 [2H, s, $-O-CH_2-O-$], 6.6-6.8 [3H, m, Ar-H].

Methyl- 5-(benzo[d][1,3]dioxol-5-yl)-4-methyl-4-nitropentanoate (3D):-
White solid powder; Yield:3.8 g (90%); mp: 79-80 °C; IR (KBr, cm^{-1}) 1037 cm^{-1} Ether Linkage, 1249 cm^{-1} and 1365 cm^{-1} NO_2, 1736 cm^{-1} Ester, 2903 cm^{-1} Aromatic; ^{1}HNMR ($CDCl_3$, δ) 1.45 [3H, s, $-CH_3$-C-NO2], 2-2.5 [4H, m, $-CH_2-CH_2-COOCH_3$], 2.9 [1H, d, Ar-CH_{2a}], 3.25 [1H, d, Ar-CH_{2b}], 3.7 [3H, s, $-COOCH_3$], 5.9 [2H, s, $-O-CH_2-O-$], 6.5-6.7 [3H, s, Ar-H].

4-amino-5-(benzo[d][1,3]dioxol-5-yl)-4-methylpentanoic acid (3E):-
White solid powder; Yield:0.85 g (58%); mp: Above 225 °C; IR (KBr, cm^{-1}) 1038 cm^{-1} Ether Linkage, 1679 cm^{-1} Carbonyl, 2897 cm^{-1} Aromatic, 3041 cm^{-1} Amino, 3372 cm^{-1} Hydroxyl; ^{1}HNMR ($CDCl_3$, δ) 0.9 [3H, s, $-CH_3$-C-NO_2], 1.7 [2H, m, $-CH_2-CH_2-COOCH_3$], 1.9 [1b, NH_2], 2.1 [2H, m, $-CH_2-CH_2-COOCH_3$], 2.6 [1H, d, Ar-CH_a], 2.8 [1H, d, Ar-CH_b], 5.9 [2H, s, $-O-CH_2-O-$], 6.5-6.7 [3H, m, 3Ar-H], 6.95 [1b, -OH].

Diethyl -2-[2-nitro-1-(3,4,5-trimethoxyphenyl)propyl]malonate (4F):-
White crystals**;** Yield**:**5.3 g (80%); mp**:** 72-75 °C; IR (KBr, cm^{-1}) 1262 cm^{-1} and 1362 cm^{-1} Nitro, 1736 cm^{-1} Ester (broad), 1588 cm^{-1} and 2979 cm^{-1} Aromatic; ^{1}HNMR ($CDCl_3$, δ) 0.95 [3H, t, $-COOCH_2-CH_3$], 1.3 [3H, t, $-COOCH_2-CH_3$], 1.45 [3H, d, $NO_2-CH-CH_3$], 3.7 [1H, d, $-CH-(COOC_2H_5)_2$, 3.8 [9H, s, Ar-$(OCH_3)_3$], 4.1 [1H, t., Ar-CH], 4.2 [2H. q, $-COO-CH_2-CH_3$], 4.3 [2H. q, $-COO-CH_2-CH_3$], 5.15 [1H, m, $-CH_3-CH-NO_2$], 6.3 [2H, s, Ar-H].

4-Amino-2-(ethoxycarbonyl)-3-(3,4,5-trimethoxyphenyl)pentanoic acid (4G):-
White solid; Yield:0.5 g (50%); mp: Above 225 °C; IR (KBr, cm^{-1}) 1707 cm^{-1} Ester, 1592 cm^{-1} and 2978 cm^{-1} Aromatic, 3218 cm^{-1} Amino, 3426 cm^{-1} Hydroxy; ^{1}HNMR ($CDCl_3$, δ) 0.85 [3H, s, $-CH_3-CH-NH_2$], 1.2 [3H, t, O-CH_2-CH_3], 2.1 [1b, $-NH_2$], 3.4-3.6 [1H, m, $-CH_3-CH-NH_2$], 3.75 [1H, d,-CO-CH-COOH], 3.8 [9H, s, Ar-OCH_3], 4.1 [1H, d, Ar-CH], 4.2 [2H, q, O-CH_2-CH_3], 6.4 [2H, s, Ar- H],7.1 [1b, OH]

Diethyl- 2-(1-(benzo[d] [1, 3] dioxol-5-yl)-2-nitropropyl) malonate (5F):-
Yellow crystals; Yield:5.3 g (80%); mp**:** 65-70 °C; IR (KBr, cm^{-1}) 1036 cm^{-1} Ether Linkage, 1181 cm^{-1} and 1249 cm^{-1} Nitro, 1729 cm^{-1} Ester, 2980 cm^{-1} Aromatic; ^{1}HNMR ($CDCl_3$, δ)1.0 [3H, t, CH_3-CH_2-OCO-], 1.3[3H, t, CH_3-CH_2-OCO-], 1.43 [3H, d, $CH_3-CH-NO_2$], 3.7 [1H, d, $H_5C_2OCO-CH-OCOC_2H_5$], 3.95 [2H, q, $CH_3-CH_2-O-C=O$], 4.15 [1H, d, Ar-CH], 4.25 [2H, q, $CH_3-CH_2-O-C=O$], 5.15 [1H, m, $CH_3-CH-NO_2$], 5.9 [2H, s, O-CH_2-O-], 6.5-6.75 [3H, m, Ar-H].

4-Amino-3-(benzo[d][1,3]dioxol-5-yl)-2-(ethoxycarbonyl)pentanoic acid (5G):-
White solid; Yield:0.6 g (50%); mp: Above 225 °C; IR (KBr, cm^{-1}) 1034 cm^{-1} Ether Linkage, 1695 cm^{-1} acid carbonyl stretching, 1759 cm^{-1} ester carbonyl stretching, 2903 cm^{-1} Aromatic, 2986 cm^{-1} Amino; ^{1}HNMR ($CDCl_3$, δ) 0.8 [3H, d, $-CH_3-CH-NH_2$], 1.2 [3H, t, $-CH_3-CH_2-O-$], 2.0 [1b, NH_2], 3.7 [1H, d, CH-NH_2], 3.9 [1H, d, $H_5C_2OCO-CH-COOH$], 4.1[1H, t, Ar-CH], 4.2 [2H, q, CH_3-CH_2 –O-], 5.9 [2H, s, $-O-CH_2-O-$], 6.6-6.8 [3H, m, Ar-H], 6.9 [1H, broad, -COOH]

Conclusion:-

An efficient and simple method has been developed for synthesis of substituted amino carboxylic acids. Nitro olefins were easily obtained by addition reaction of simple nitroalkanes viz.; nitromethane, nitroethane with substituted benzaldehydes. Michael addition on this substituted nitro olefins and corresponding nitroalkanes with methyl acrylate and diethyl malonate gave new highly substituted and branched nitro esters. A solid catalyst system i.e. KF/Basic alumina was successfully employed and reaction parameters optimized to get the best yields for corresponding nitro esters. Reduction of these nitroesters using $NiCl_2.6H_2O$ with $NaBH_4$ in protic solvent such as methanol gave highly substituted amino acids.

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