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Asymmetric synthesis of 3H- FURO [3,4-C] Isocoumarins

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Abstract
The chiral pool synthesis of (S)- isocoumarins, involves the synthesis of (S)- amino acid derivatives 95a-c and the conversion of 95a into their respective halides 96a-c followed by coupling of (S)- a chloroacid halides 96a-c with homophthalic acid to give (S)- isocoumarin derivatives 97a-c . Further derivatization of chloroacid halides by using $KBro_3$ with dropwise addition of sulphuric acid at 200^o C is done to get bromohomothalic acid which is then involved in coupling with (S)-a-chloroacid halides 96a-c to give (S)- isocoumarin deriatives 98a-c

KEY words
(S)- isocoumarins, chloroacid halides, Bromohomothalic acid

Introduction

Isocoumarins are secondary metabolites belong to wide variety of insect, microbial and plant sources. They are found in wide varieties of mold, lichens, bacteria, insects, fungi, and in numerous higher plants. Various isocoumarins are present in higher plant families e.g. myristicaceae, compositae, bigoniaceae, Liliaceae, leguminoseae and Saxifragaceae families. Most of isocoumarins have isolated from diverse fungal species of genere fusarium, Aspergillus, Ceratocystis, penicillum, Artemisia and streptomyces.

They were only few reports on biological activities of isocoumarins before review of R.D BARRY(1964). Later on literature survey showed comprehensive range of biological activities of isocoumarins. Some of these are fluorescent agents, laxatives, valuable sweeteners, and anticorrosive though others have anti-malarial actions anti- allergic, anti-inflammatory and are useful in treating Asthma.

The 6,8-dihydroxy-3,4,5-trimethylsochroman-1-one displays antifungal activity against S.fimicola.The 7-[(2-hydroxy-4-methoxy-6-methoxy carbonyl)phenyl carbonyl]-6.8-dihydroxy-3-methyl-1-oxo-1H-isochromene 4a; 2-hydroxy-5-methoxy-3-(methoxycarbonyl)phenyl-6,8-dihydroxy-3-methyl-1-oxo-1H-isochromene-7-carboxylate.

The 3-(3-chloroprop-1-yl) 1H-isocoumarin-1-one 6 (common name gymnoplaynes A) is chlro isocoumarin with an acetylenyl side chain. This compound was extracted from a species of basidiomycete of gymnopus genera originate from the rainy forests of Northern Thailand. Gymnoplaynes A exhibited moderate cytotoxic activities and antimicrobial.

Two isocoumarins xyridin A and b are present in a wild plant xyrisindica. Xyridine A 3-propyl-1H-6,7-dioxoloisochromen-1one 7a and xyridine B is 3-(1-oxopropyl)-1H6,7-dioxoloisochromen-1-one 7b. both xyridines inhibit growth of several Gram negative and Gram ositive bacteria. The xyridine B is slightly more effective than xyridine A

Many isocoumarins exhibit anticancer activity e.g. cytogenin 11 and 3- carboxymethyl-8-hydroxy-6-methoxy-1-oxo-1H- isochromene (NM-3) 12 posses antitumor activity. The NM-3 12 obstucts angiogenesis and enhance the antitumor effects of radiotherapy and cytotoxic drugs.

There are different inactive enzymes responsible for the blood coagulation, are activated in series of enzymatic reactions. Fibrin clot is produced in last step from fibrinogen by the action of the the enzyme protease thrombin. Other enzymes for example brovine thrombin, human factor Xa , factor IXa, human plasma factor xia and human plasma x11a are also used. Mostly the blood coagulating enzymes belong to serine proteases. The enzymes are more specific than trypsin and cause leavage of specific bond of their natural substrates.

In Angioenic activity new blood vessel are developed from pre existing vessels. The angiogenic inhibitors inhibit the development of blood vessels around tumour.

A synthetic isocoumarin NM-3 12 and cytogeny show antiangiogenic activity in the air sac assay system of mouse dorsa. The NM-3 12 and its analogue 16 with low toxicity were active antiangiogenic agent. Some isocoumarin for example 4-acetyl-6,8-dihydroxy isocoumarin 17a and 6,8-dihydroxy-4-(1-hydroxyethyl) isocoumarin 17b extracted from sesquicllium also inhibits angiogenesis.

Tumor is a growth of abnormal cells deprived of any function in the body. Tumor can be treated by deep x-ray or radiotherapy or both combined surgery and chemotherapy.

The reticulol (6,8-dihydroxy-7-methoxyisocoumarin) 18a is extracted from streptomyces mobaraensis and streptomyces rubrireticulate and 6-o-methylreticulol (8-hydroxy-6,7-dimethoxy-3-methyisocoumarin) 18b is extracted from fungus growing on the avicennia marine plant. Both of these are antitumor agents. The reticulol inactive topo 1 and block the replication of DNA or transcription involved in metastasis.

The 7-benzoylamino-3-(3-bromopropyloxy)-4-chloro-1-oxo-1H-isochromene 19 is an inhibitor of uPA. Urokinase-type plasminogen activater(uPA) is part of extracellular proteolytic actions related with angiogenesis, tumor cell migration and growth.

Human immunodeficiency virus(HIV) causes AIDS which is an immunosuppressive syndrome that gives in harsh malignancies and infections. The HIV initiates its effect by binding the CD4 receptors of the host cell. The HIV

needs a co-receptor to go into the cell. The genetic material of virus (RNA) is released when virus enters into the host cell and caused reverse transcription in DNA. The HIV can remain in dormant condition for years in genetic material of the host.

Recently different antiviriall drugs having isocoumarins been used for the treatment of AIDS. An isocoumarin coriandrin 20 extracted from Coriandrum sativum, has anti-HIV activities.

Allergy is the disorder of the immune system. Atopic syndrome is an allergic hypersensitivity. Several deriatives of 3-carboxyisocoumarins 21a-c are valuable for treatment of allergic reations.

Mutation is modification in coding sequence of the DNA in majority of organism and RNA in some viruses. A mutation in DNA sequence causes certain hereditary diseases. Two isocoumarin, papalentin dimer 23a and a paepalantine-9-a-glactopyranose 23b, which are isolated from paepalanthus bromelioides, express substantial mutagenric activity.

Experimental

Apparatus

The apparatus used in research include beakers (50, 100, 500 and 1000 ml), measuring cylinders (10 and 50 ml) single double and three necked round bottom flasks (250 and 500 ml) column, glass rods, separating funnel, thermometers, pipette sucker, test tubes, condenser, petri dishes, syringes, guard tube, stoppers, oil bath, bottles, glass jars, etc.

Chemicals

All chemicals were supplied by the companies: sigma-Aldrich, scharalau, Il USA MERCK, ACROS-organic and BDH biochemical.AL the solvents used were of commercial grade and were used after distillation. Dry solvents were used for absolute dry condition reactions. The reagnts used for desicatting purpose include: NaoH pellets(for ET_3N, pyridine etc.) CaH_2(for $CHCL_3$) and CaO(for CH_3OH).

Preparation of Reagents

Fuming HNO3

The H_2SO_4(31.8 ml, 58.5g, 0.6 mol, 1 eq) was added to the round bottom flask having KNO_3(60g, 0.6 mol, 1 eq). the reaction mixture was heated at 250c and produced fuming HNO_3 solution was collected in an ice-chilled Jar.

Ninhydrin dip:

Ninhydrin drip was prepared by dissolving ninhydrin (20 g) in EtOH (60 ml). It was used to identify unreated amino acids on TLC plates.

KMnO4 dip:

The KMnO4(1.5 g), K2CO3(10.0 g) and 10% NaoH (1.25 mL) were dissolved in H2O (200mL). it was useful for most of organic compounds which appeared as brown spots on background.

Iodine Chamber

Some crystals of I2 were adsorbed on flash silica gel (5.0 g) in an air tight wide moutherd jar. The iodine chamber was used for the organic compounds which appeared as shown spots on the TLC.

Techniques& Instruments

Different types of instruments and techniques were used for the separation and analysis of compound.

Rotary evaporator was used for concentration under reduced pressure, suction and drying purposes.

Electric oven was used for drying glass wares

Electric balance was for accurate weighing.

Hot plate/ Magnetic stirrer was used for heating and stirring.

Melting point apparatus was used for the deremination of melting point, which are reported uncorrected.

Heating Mantle was used for the distillation of solvents.

Optical Rotation: A polarimeter was used to measure optical rotation of chiral compounds at room temperature using a cell of 100 mm path length.

Chromatography: Chromatography is used to separate components of mixture. Thin layer chromatography(TLC) and column chromatography were used during research work.

Thin layer chromatography (TLC):

This Technique was used to monitor the progress of a reaction. For this purpose MERCK; pre-coated silica gel of 0.25 mm layer (70-230 mesh) on Al back with fluorescent 60 F 254 were used.

Column Chromatography: This technique was used for the purification of synthesized compounds. The column silica was used as solid support.

Single Crystal XRD: the XRD is one of the most latest and accurate tool of structure determination. The single crystal XRD of crystalline solids was recorded on bruker kappa APEXII CCD diffractometer. The XRD data recorded using fine- focus sealed tube monochromator graphite(Mo ka radiation, 0.71073) as radiation source.

Synthesis

General procedure for the synthsis of 2-chloroacids 95a-c

The (S)- amino acids 94a-c(1 eq, 10 mmol,) were separately dissolved in HCL (5N) (26 mL) at a temperature below -5 C in round bottom flask followed by dropwise addition of chilled aq $NaNo_2$ (2.0 eq 20mmol) to above solution by keeping the temperature below 0^oC. This solution was continuously stirred overnight without ice bath. TLC was taken to check the progress of reaction. Solution was exracted by solvent extraction using ethyl acetate in acidic media and washed with brine soluion. The extracted solution was concentrated and yellow oily products 95a-c were separated for further concentrated under high vacuum. The product was then concentrated by using vacuum rotary.

Procedure for the synthesis of 96a-c

A mixture of SoCl2 (1.1 mmol, 1.1 eq) and (2S)-2-alkyl-2- chlorocarboxylic acids 95a-c(1mmol, 1eq) was taken in round bottom flask and heated in oil bath at 600c for period of 1 hour in dry conditions to produce acid chlorides 96a-c. the SOCL2 present in excess was removed under vacuum. The synthesized acid halides were used without any purification.

Experinmental procedure for the coupling of 96a-c with homophthalic acid 38:

96a-c and homophthalic acid 38 were taken in round bottom flask. Mixture in round botto flask was heated for 6 h at 200oC in oil bath with constant stirring. After 6 hours oil bath was removed and reaction mixture was allowed to

cool and its distributed itself EtOAc and H_2O(20 ml) on solvent extraction. Anhydrous Na_2SO_4 was used to dry the organic content obtained from solvent extraction which was then filtered and its concentration is done under reduced pressure. The solid mass was adsorbed on silica gel and purified by column chromatography by using n-hexane in 2 % EtOAc as mobile phase to produce a crystalline product 97a-c.

Derivatization of homophthalic acid 38

Nitration of homophthalic acid 38

The homophthalic acid 38 95.0 g, 27.7mmol) was added to ice-chilled fuming HNO3(25ml) with continuous vigorous stirring. The mixture was stirred for 6 h at room temperature after the completion of addition. Then the reaction mixture was cooled to ambient, poured to ice and filtered. The solid mass obtained was washed using H2O and crystallized from Meoh to affor white crystals of 2.96g and 46.3% yield

Generral procedure for bromination of homophthalic acid 38

The mixture of KBro3 (3.43 g, 1.5 eq0 and homophtalic acid 38 (2.43 g, 1.0 eq) was taken in round bottom flask. Mixture was heated at 90 oc in oil bath with drop waise addition of dil. H2so4 by dropping funne fitted on round bottom flask. The reaction mixture was refluxed at 90oc for 30 min. the reaction mixture was continuously stirres for 2 two hours and then allowed to cool and the reaction mixture was filtered and product was crystallized.The product was then sent for X- crystallography. Isocounarins are natural products , synthesized by numerous plants, algal,fungal and bacterial species. Due to vast biological activity, scientist are working out on economical strategies to enhance the purity and yield of isocoumarins. Isocoumarines display variety of biological activities e.g. anticancer, antiangiogenic, antibacterial, antimalarial, antiallergic and anti-inflammatory. Asynthetic synthesis is used to synthesize enantiopure compounds. The practice to prepare enantiopure isocoumarins remain vital. Here chirol pool methodology is used to synthesize enantiopure isocoumarines. Enantiopure isocoumarins have different role at different positions.

Retrosynthesis

Following disconnection approach is found to be most appropriate for the synthesis of isocoumarins

Synthesis of bromo derivative of isocoumarins

The chiral pool synthesis of (S)- isocoumarins, involves the following steps.

1. Synthesis of (S)- aminoacid deriatives 95a-c and the conversion 95a-c into their respective halides 96 a-c.
2. Coupling of (S)-a- chloroacid halide 96a-c with homophthalic acid to give (S)- isocoumarin derivatives 97a-c
3. Derivatization of homophthalic acid.
4. Coupling of (S)-a- chloroacid halides 96a-c withbromo derivative of homophthalic acid to give (S)-isocoumarin derivative 98a-c.

Results and discussion

Isocumarins are natural products, synthesized by numerous plants, algal, fungal and bacterial species. Due to vast biological activity scientist are working out on economical strategies to enhance the purity and yield of isocounarins. Isocoumarins display variety of biological activities e.g. anticancer, antiangiogenic, antibacterial antimalarial, antiallergic and anti-inflammatory.

Asymmetric synthesis is used to synthesize enantiopure compound. The practice to prepare enantiopure isocoumarins remains vital. Here chiral pool methodology is used to synthesize enantiopure isocoumarins.

Enatiopure isocoumarins have different role at different positions. This chapter depates the results and characterization of enantiopure compounds prepared during our research work.

The synthetic plane presented was related with stereoselective synthesis of isocoumarins. Derivatives of different chiral aminoacid were synthesized and coupled with homophthalic acid.

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