Organic Process Research & Development **2000**, *4,* 68–76

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during September to November, 1999

This review covers 20 U.S. patents published during the period from September first to mid-November 1999. Around 700 patents were published that were in the field of organic chemistry and mentioned the word "process" in their title or abstract. The titles of these were examined, and from this list the final 20 are reviewed here as having possible interest to readers of this journal. No legal or commercial significance should be attached to the patents included. The novelty, usefulness, or legal validity of these patents has not been assessed, and any claims to the advantages are based on those discussed in the patent itself unless this reviewer has prior knowledge of the topic. A very wide variety of chemistry and processes is covered, ranging from the synthesis of novel cryptophycins to the use of membranes in removing sodium ions from diazonium salts. For those patents describing novel compounds spectroscopic data are often provided. A number of the patents reviewed give experimental details of a pilot or semi-works scale plant since kilo quantities are mentioned, and this can give clues as to the commercial status of the work. When reading patents it should be remembered that trivial or non-systematic chemical names are often used. No attempt has been made here to rename compounds described in the patents, and generally the name used in the patent is the one used here. For those chemists brought up on IUPAC names this can be confusing and can make reading and searching patents more difficult but still worthwhile.

Patent No. U.S. 5,952,498

Assignee: Bayer AG, Leverkusen, Germany

Title or Subject: Process for the Preparation of Enantiomerically Pure Cycloalkanoindole-, Azaindole-, and Pyrimido-1,2a,indole-carboxylic Acids and Their Activated Derivatives

The amide **4** (R = L-menthyl or *t*-Bu) is a useful drug intermediate that was prepared from the *p*-tolyl ester **1** in a multi-step process shown in Scheme 1. The key step is the first which is a diastereoselective alkylation at the α carbon with cyclopentyl bromide (c-PnBr) giving crystalline products that are easily recovered. The subsequent bromination with NBS gives **3a**, and then **3b** is produced by reaction of **3a** with the pyrimidoindole **5** (AH). These steps also occur without racemisation, thereby giving high overall ee. After hydrolysis of **3b** the desired amide **4** is then produced using either D- or L-phenylglycinol **6**. Kilo scale examples are provided.

Advantages

The process starts from cheap starting materials such as **1** and gives a higher atom yield than alternative routes by allowing the base-catalysed epimerisation of the unwanted diastereomer from step 1. The overall high ee is possible because racemisation at step 1 does not occur in the alkylation or in subsequent steps.

Patent No. U.S. 5,952,531

Assignee: Zeneca Limited, Huddersfield, UK

Title or Subject: Nitration Process for Substituted Diphenyl Ethers

The nitrated ethers **8a** and **8b** are used as herbicides and were synthesised by nitration of the corresponding ether **7**, using nitric and sulphuric acids in the presence of acetic anhydride and in a solution containing at least 75% *n*-butyl acetate (Scheme 2). The presence of this quantity of solvent improved reaction rate and efficiency.

Advantages

The use of non-halogenated solvents is environmentally desirable and eliminates problems associated with the use of a solvent such as dichloroethane that is normally employed for this type of reaction. The use of the ester solvent dissolves the reactants and leads to an efficient conversion with low levels of dinitro- or other mononitro- isomers. An additional advantage is that separation and purification of the required products is greatly simplified.

Patent No. U.S. 5,952,537

Assignee: Wiley Organics Inc, OH, U.S.A.

Title or Subject: Preparation of Cycloalkylacetylene Compounds Using Dialkylaminomagnesium Halides or Bis(dialkylamino)magnesium

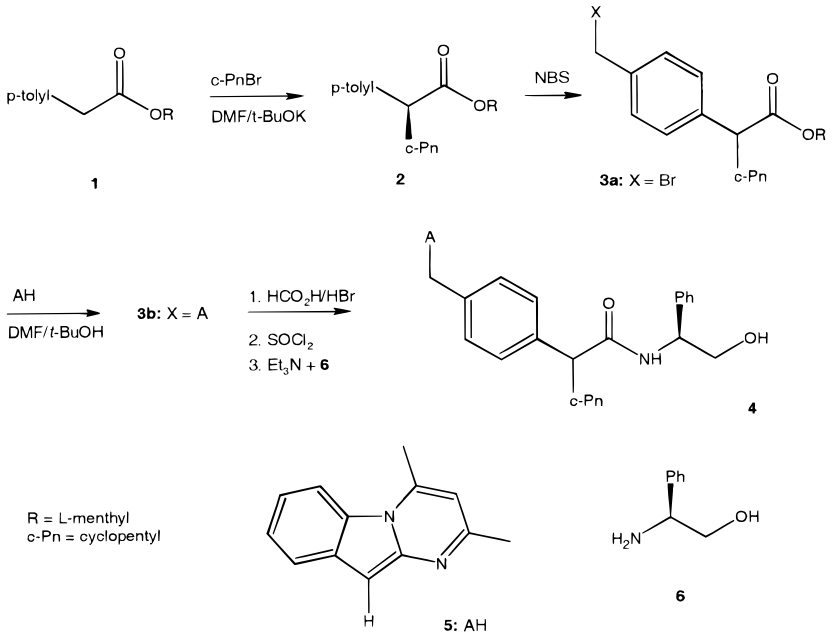
This is the first of two patents describing the synthesis of cyclopropylacetylene **11**. This is used in the manufacture of Du Pont's anti-AIDS drug efavirenz. **11** is often prepared from 5-chloropentyne **9** using either *n*-BuLi or lithium dialkylamides (LiDAA) to effect the cyclisation. The process here uses Grignard reagents for cyclisation at moderate temperatures giving yields of **11** >90% (by GC). The synthesis of **11** from the reaction of **9** with the monoamino-Grignard **10a** is shown in Scheme 3. Alternatively the bis-amino Grignard **10b** was used successfully.

Advantages

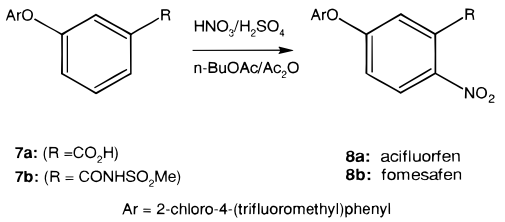
The use of the Mg compounds in place of *n*-BuLi or LiDAA removes the need to run this reaction at low temperatures that are costly to achieve and to operate on a commercial scale. This process runs at temperatures above

 10.1021/op0000024 CCC: $19.00
Published on Web 02/01/2000

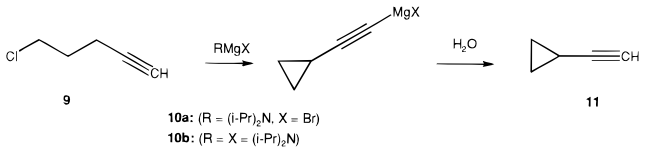
Scheme 1



Scheme 2



Scheme 3



−5 °C, and therefore no special equipment is needed, and the process is less hazardous than using the Li compounds.

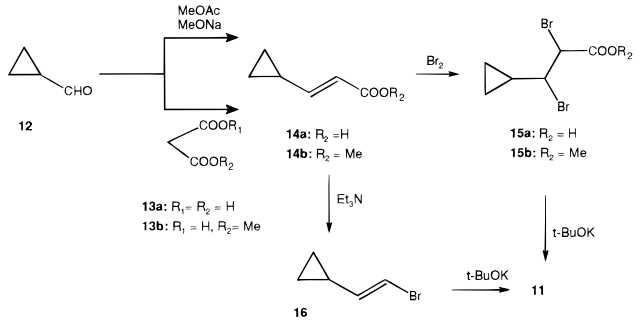
Patent No. U.S. 5,955,627

Assignee: Kuraray Co. Ltd, Kurashiki, Japan

Title or Subject: Process for the Preparation of Cyclopropylacetylene Derivatives

This patent provides quite different routes to **11** from the method described in the previous patent, and these are shown in Scheme 4. Here **11** was obtained by treatment of the aldehyde **12** with the appropriate malonic derivative **13a** or **13b** via cyclopropylacrylic acid **14a** or its ester **14b**. An alternative route to ester **14b** is by condensation of the aldehyde **12** with methyl acetate. The conversion of the acrylic compounds **14a** and **14b** to **11** is either a one-, two-, or three-step process. The two- and three-step routes from **12** to **11** allow the isolation of the intermediates **15a**, **15b,** or **16.** The intermediate **16** can be isolated if a weak base is added to **14**, whereas if a strong base is used, **11** is obtained directly. The single-step route from **12** to **11** is a one-pot process involving bromine addition followed by treatment with base.

Scheme 4



Advantages

Alternative routes are claimed to give low yields, use expensive reagents such as *n*-BuLi or LiDAA, or produce large quantities of by-products that are difficult to separate. For example, Wittig reagents produce triphenylphosphine oxide which can be difficult to remove. This route claims to produce good yields under moderate conditions, and some of the examples give kilo scale reactions.

This and the previous patent demonstrate the selective use of references to earlier work that is found in the discussion section of a patent. This patent more fully describes alternative routes, whereas the previous one focuses on Li reagents and does not mention Wittig reagents.

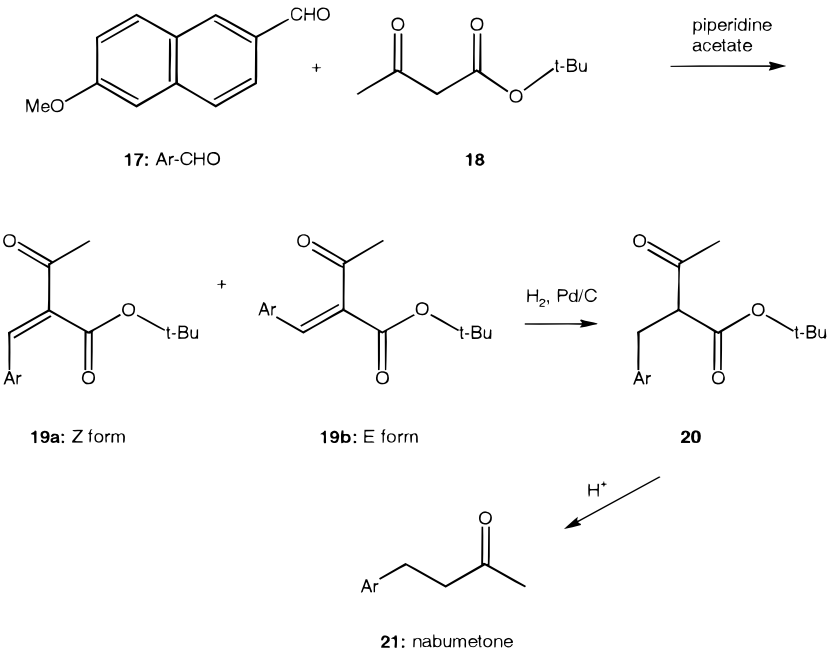
Patent No. U.S. 5,955,635

Assignee: Secifarma S.p.A., Baranzate di Bollate, Italy

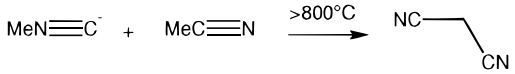
Title or Subject: Process for the Preparation of 4-(6′-Methoxy-2′-naphthyl)butan-2-one (Nabumetone)

This patent provides a new three-step route to Nabumetone **21** which is an antiinflammatory drug used to treat rheumatic or arthritic diseases. The key point of the patent is the use of *tert*-butyl acetoacetate **18** in the condensation step in place of benzyl or ethyl acetoacetate (EAA) often used in industrial processes. The initial condensation is

Scheme 5



Scheme 6



carried out under reflux, using a secondary amine salt catalyst such as piperidine acetate. The *E*/*Z* mixture **19a** and **19b** is hydrogenated to the *tert*-butyl ester **20** which on acid hydrolysis produces Nabumetone **21** (Scheme 5).

Advantages

The advantage claimed is that **18** is an inexpensive starting material, yet it must be less readily available than the more common EAA. The use of **18** in place of EAA is claimed to need less Pd catalyst in step 2 which may compensate for the increased cost of **18** over EAA. A further advantage is that the intermediate *tert*-butyl esters **19a** and **19b** are stable to acids and may be more crystalline than their ethyl analogues.

Patent No. U.S. 5,959,136

Assignee: Lonza Ltd, Gampel/Valais, Switzerland

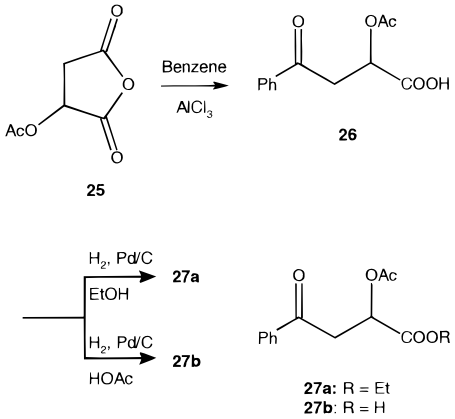
Title or Subject: Process for the Preparation of Malononitrile

Malononitrile **24** is a useful chemical intermediate, and this process describes its synthesis by thermolysis of methyl isocyanide **22** with acetonitrile **23** in a tubular reactor at temperatures above 800 °C. This is shown in Scheme 6, and as with any high-temperature reaction many side reactions occur and succinonitrile, maleonitrile, and fumaronitrile are all produced. It is suggested in the patent that the reaction may proceed by isomerisation of **22** to **23**. If this is the case, then perhaps direct thermolysis of **23** alone should give **24**, and thus **22** is superfluous.

Advantages

Although the conditions described are severe, it is claimed that this route is better than the current method which uses the hazardous chemical cyanogen chloride at temperatures over 700 °C.

Scheme 7



Patent No. U.S. 5,959,139

Assignee: Ajinomoto Co. Inc, Tokyo, Japan

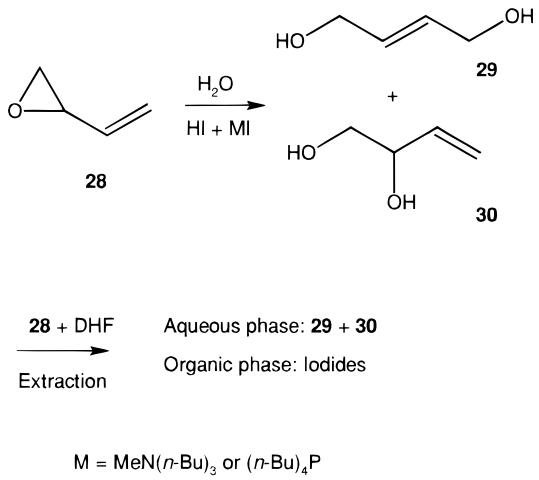
Title or Subject: Process for Producing Optically Active 2-Hydroxy-4-arylbutyric Acid or Its Ester

The title compounds **27a** and **27b** are intermediates for the synthesis of the antihypertensive drugs enalapril or cilazapril. The process converts the *R*-anhydride **25** to *R*-acetoxy compound **26** via a Lewis acid-catalysed addition of **25** to benzene. **26** is then converted to the hydroxy ester **27a** by a combined hydrogenation and esterification with Pd/C in ethanol. The hydroxy acid **27b** was obtained by hydrogenation of **26** in acetic acid followed by acid hydrolysis (Scheme 7).

Advantages

The optically active succinic anhydrides used in this route can be prepared from malic acid which is an optically active

Scheme 8



cheap starting material. Other routes that produce racemic mixtures of the product require a resolution step; thus, overall atom yields are <50%. Asymmetric synthetic routes give low yields, and intricate procedures are involved, whereas this route proceeds with retention of activity and is highly efficient.

Patent No. U.S. 5,959,162

Assignee: Eastman Chemical Company, TN, U.S.A.

Title or Subject: Process for the Preparation of 2-Alkene-1,4-diols and 3-Alkene-1,2-diols from Epoxyalkenes

1,4 butenediol **29** is an intermediate for the production of 1,4 butanediol which is used in the manufacture of THF, polyesters, and polyurethanes. This patent describes the hydration of 3,4 epoxybut-1-ene **28** to give **29** which is catalysed by a mixture of HI and organic iodide salts such as methyltri-*n*-butylammonium iodide or tetra-*n*-butylphosphonium iodide. By controlling the pH it is possible to direct the allylic rearrangement reaction and increase the selectivity to give the desired high ratio of **29** to **30** (Scheme 8).

The recovery of the product diols is a key aspect of the process and is carried out using liquid/liquid extraction in a countercurrent column. The extracting solvent is a mixture of **28** and 2,5-dihydrofuran (DHF) which extracts the catalyst from the reaction mixture. This leaves the diol mixture in the aqueous phase from which the 1,4 isomer is subsequently recovered.

Advantages

Alternative processes to **29** involving hydration of epoxybutene are claimed to have problems in separating the mixture of diols and give a low ratio of **29** to **30**. This process is claimed to be safe to operate, produces high ratio of **29** to **30**, and includes an effective separation method. Since **29** is really only used for making 1,4-butanediol, this patent competes with the many other routes to 1,4-butanediol. These include catalytic acetoxylation of butadiene and use pure oxygen and acetic acid at high temperatures. Such processes are hazardous to operate and require expensive alloys to prevent corrosion. Other processes to 1,4-butanediol start from maleic anhydride (MA) and either involve hydrogenation of MA at high pressure or low-pressure hydrogenolysis of the maleate ester and require an extra processing step.

Patent No. U.S. 5,962,693

Assignee: DuPont Pharmaceuticals Company, Delaware, U.S.A.

Title or Subject: Efficient Method for the Conversion of Nitriles to Amidines

The nitrile compound **31** can be converted to amidine **35** which is used in preparing drugs to treat thromboembolic disorders. The patent covers methods for all of the transformations shown in Scheme 9 and the Experimental Section of the patent describes processes to make kilo batches. In step 1 to produce the hydroxyimino compound **32** the reaction was complete in about 3 h at 60 °C and produced crystalline product directly. The acylhydroxyamidine **33** when hydrogenated in the presence of acid gave a solution of **35** that could be recovered by precipitation. Alternatively, **35** was produced by hydrogenation of the intermediate oxadiazole **34** that is formed by heating **33**.

Advantages

This process allows the conversion of the nitrile group in **31** to the amidine **35** via a novel catalytic hydrogenation reaction of a 1,2,4-oxadiazole moiety **34**. Previous methods of producing amidine compounds such as **35** from nitriles have involved the Pinner reaction using HCl gas which is difficult to handle on a commercial scale and produces salts making product purification difficult.

Patent No. U.S. 5,962,741

Assignee: Novartis AG, Basel, Switzerland

Title or Subject: Process for the Production of Aromatic Halogen−Amino Compounds

This is a process for the catalytic hydrogenation of aryl halonitro compounds such as the fluorodinitrobenzene **36a** to give the corresponding fluorodiamine **36b.** The catalyst was a mixture of Pt/C and vanadyl acetylacetonate in the presence of hypophosphorous acid and a 95% yield of **36b** was obtained (Scheme 10). The method was also applied to producing pyridine derivatives such as **37**.

Advantages

The use of the multi-component catalyst prevents the production and accumulation of undesirable by-products such as arylhydroxylamines which are intermediates and which can explode because of their thermal instability.

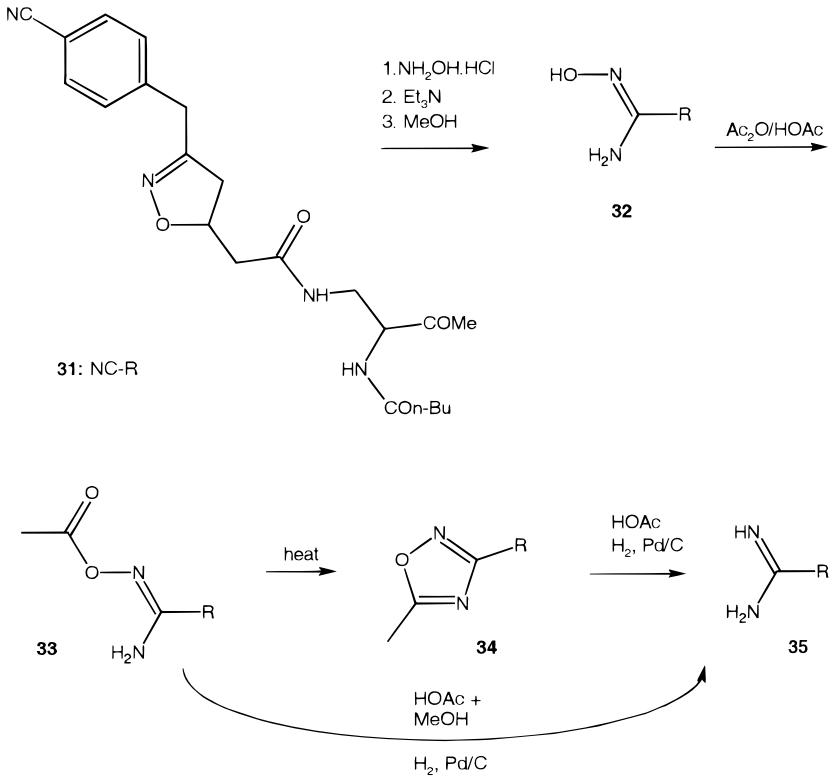
Patent No. U.S. 5,962,744

Assignee: The Research Foundation of State University of New York, U.S.A., and Mitsubishi Chemical Corp. Tokyo, Japan

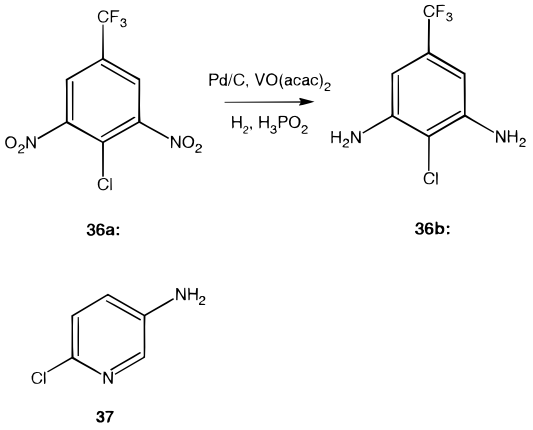
Title or Subject: Process for Hydrocarbonylations in Supercritical Carbon Dioxide

The use of supercritical fluids in chemical processing has been increasing over the recent years. The solvent power of supercritical carbon dioxide ($scCO_2$) makes it very attractive as a solvent for many reactions. This patent describes a

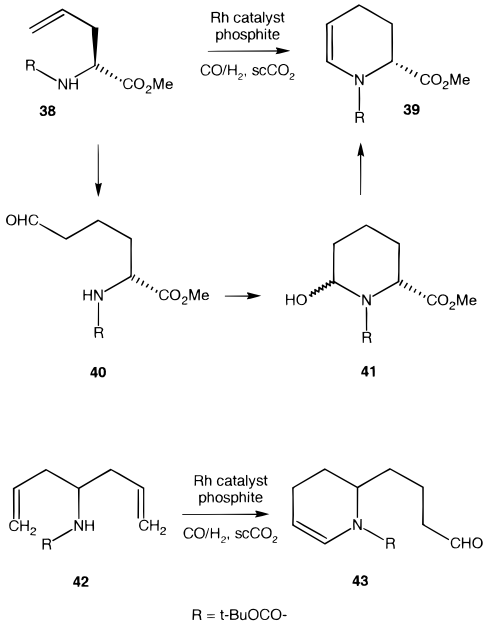
Scheme 9



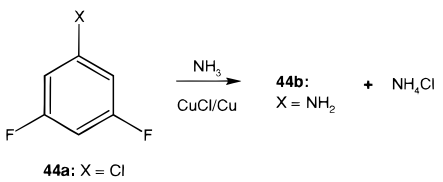
Scheme 10



Scheme 11



Scheme 12



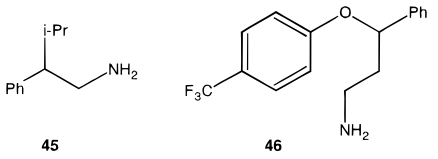
hydroformylation process to convert the allyl glycinate **38** to the tetrahydropyridine **39** via aldehyde **40** by using a rhodium/phosphite catalyst in $scCO_2$. It is postulated that the reaction proceeds via the linear aldehyde **40** that cyclises to give **41**, and this is dehydrated giving **39**. The high selectivity of Rh hydroformylation catalysts to give linear aldehydes supports this proposal (Scheme 11). Another example of the process is given by reaction of the diene **42** that produces tetrahydropyridine **43**. The hydroformylation of other substituted alkenes and acetylenes, dienes, and allyl esters was also described, and since reaction of substituted alkenes is quite difficult, this method may have potential. Note that the yields given in the examples are all calculated from chromatographic analysis and may not represent actual yields once the catalyst recovery has been carried out.

A large proportion of the patent is devoted to structures of probably over 100 different phosphite ligands.

Advantages

Using a non-toxic non-flammable solvent is a major attraction when producing chemicals on a commercial scale.

Scheme 13



45 **46**

Water is not a suitable solvent for many transition metal-catalysed processes, and hence alternative safe solvents are sought. The use of $scCO_2$ gives a highly selective reaction, and although this requires high pressures, for high value materials the increased cost of the equipment may be offset by the reaction selectivity and easier product recovery.

Patent No. U.S. 5,965,775

Assignee: Clariant GmbH, Frankfurt, Germany

Title or Subject: Process for the Preparation of 3,5-Difluoroaniline

3,5-Fluoroaniline **44b** is an industrial intermediate and was produced by the catalytic amination of the chlorofluoroaniline **44a** using aqueous ammonia (Scheme 12). The catalyst was a combination of copper metal and a copper halide since using either the metal or the halide alone reduced the yield of the product.

The patent also describes the preparation of **44a** from 1,3,5-trichlorobenzene **44c** which is a readily available commercial starting material. This conversion was carried out using KF and tetrakis(diethylamino)phosphonium bromide.

Advantages

Previous routes to **44b** start with more expensive reagents than **44a** and involve more processing steps, thus increasing the costs and complexity.

Patent No. U.S. 5,969,186

Assignee: Nagase & Company Ltd, Osaka, Japan

Title or Subject: Process for Racemising Optically Active Amines

This describes a process to racemise an optically active form of the **45** or **46**. **45** is a resolving agent that is used to obtain single enantiomers from racemic ibuprofen or ketoprofen (Scheme 13). The racemisation process is carried out by treatment of the amine with a sodium naphthalene complex. The rationale behind the patent is that if racemisation is coupled with a resolution step, then it is possible to increase the yield of the desired optically active compound.

Advantages

This process is claimed to be the only effective one for racemising amines that contain an asymmetric centre at the β position or beyond from the amino group.

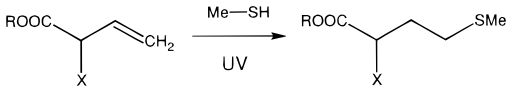
Patent No. U.S. 5,973,200

Assignee: Novus International Inc, St. Louis, MO, U.S.A.

Title or Subject: Process for the Preparation of 2-Hydroxy-4-(methylthio)butanoic Acid or Methionine by Mercaptan Addition

This describes a process for the free radical addition of a thiol to a non-conjugated olefin where the addition occurs

Scheme 14



47a: R = H, X = OH
47b: R = Me, X = OH
47c: R = H, X = NH_2

48a: R = H, X = OH
48b: R = Me, X = OH
48c: R = H, X = NH_2

at the terminal carbon−carbon double bond. **48a** is the hydroxy analogue of methionine **48c** and may be prepared from methanethiol and 2-hydroxy-3-butenoic acid **47a** (Scheme 14).

The free radical nature of the reaction results in anti-Markovnikov addition and the production of the desired products. The reaction was initiated by using UV light or by adding a free radical initiator such as AIBN. It is claimed that methionine **48c** can be prepared from methanethiol and 2-amino-3-butenoic acid **47c**, but no details are given.

Advantages

The preparation of the thio derivatives **48** from readily available starting materials is seen as the main advantage of this process.

Patent No. U.S. 5,977,368

Assignee: Rohm & Haas, Philadelphia, PA, USA

Title or Subject: Process to Prepare Chloroketones Using Oxazolines

The dichloroketone **52** is used as fungicide and was prepared from the oxazoline **51**. One route to **51** was cyclisation of alkynyl amide **49** to the methyleneoxazoline **50** using anhydrous methanesulphonic acid in butyl acetate. A second method of cyclisation of **49** is by using aqueous NaOH but the former method using acid was preferred. The methyleneoxazoline **50** was converted to **51** using trichloroisocyanuric acid (TCIA) as a novel chlorinating agent in ethyl acetate. Finally acid hydrolysis of **51** gave the dichloroketone **52** (Scheme 15).

Advantages

The key aspect is certainly the use of TCIA as a chlorinating agent as opposed to using conventional agents such as chlorine or NCS. TCIA gives high selectivity as long as the amount used is strictly controlled between quite narrow limits.

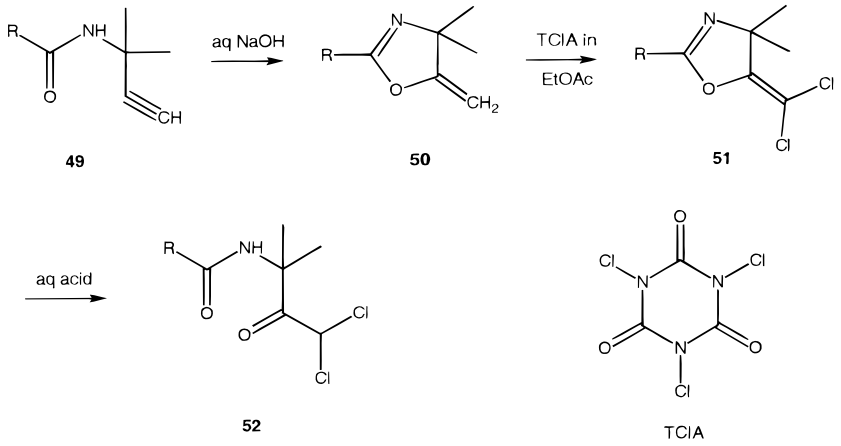
Patent No. U.S. 5,977,387

Assignee: Eli Lilly and Company, Indianapolis, IN, U.S.A., Wayne State University Detroit, MI, U.S.A., and University of Hawaii, Honolulu, HI, U.S.A.

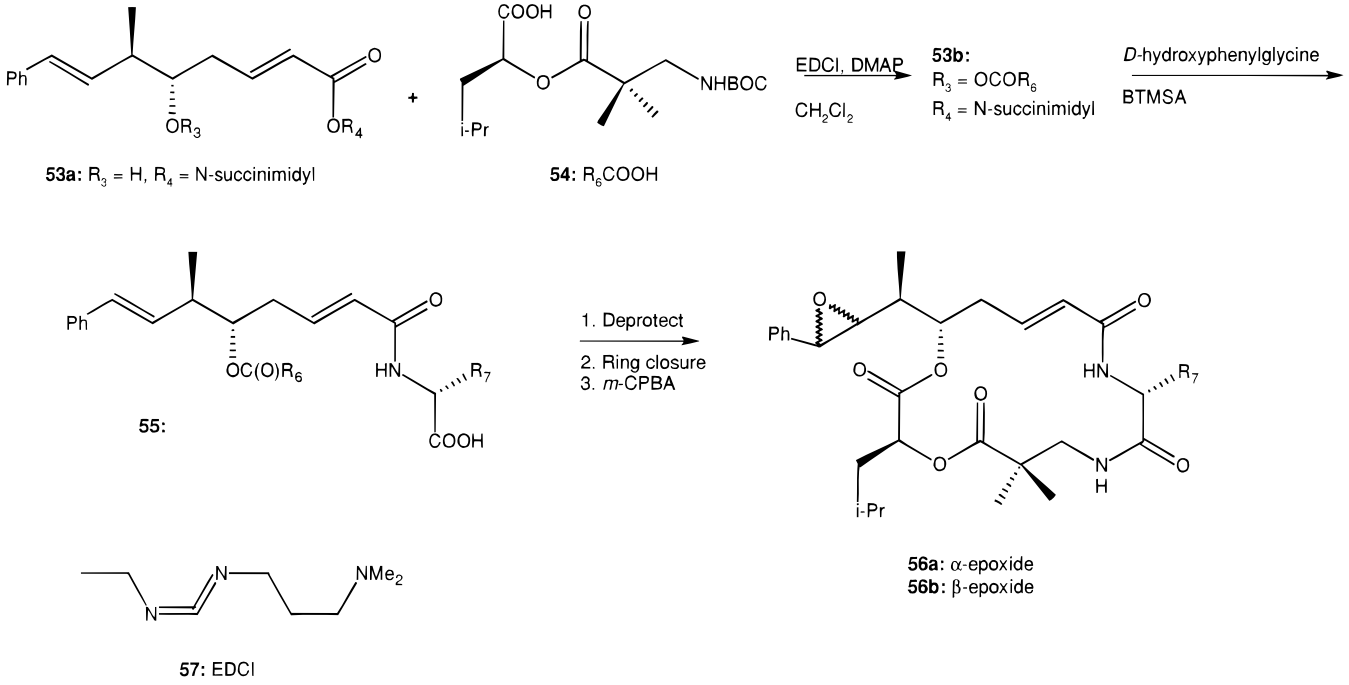
Title or Subject: Process for Preparing Pharmaceutical Compounds (Cryptophycins)

The title compounds such as **56** are potentially useful in cancer treatment, and they were prepared from the styrene compound **53a** by a multi-step route from commercially available materials (Scheme 16). IR and NMR spectroscopic details are provided for many novel compounds that are synthesised in the examples given.

Scheme 15



Scheme 16



The basic route in Scheme 16 can be summarised as involving the following steps:

(a) Contacting **53b** with an amino acid such as D-hydroxyphenylglycine in the presence of a silylating agent,

(b) Removing the protective *tert*-butoxycarbonyl group (BOC) from **55**,

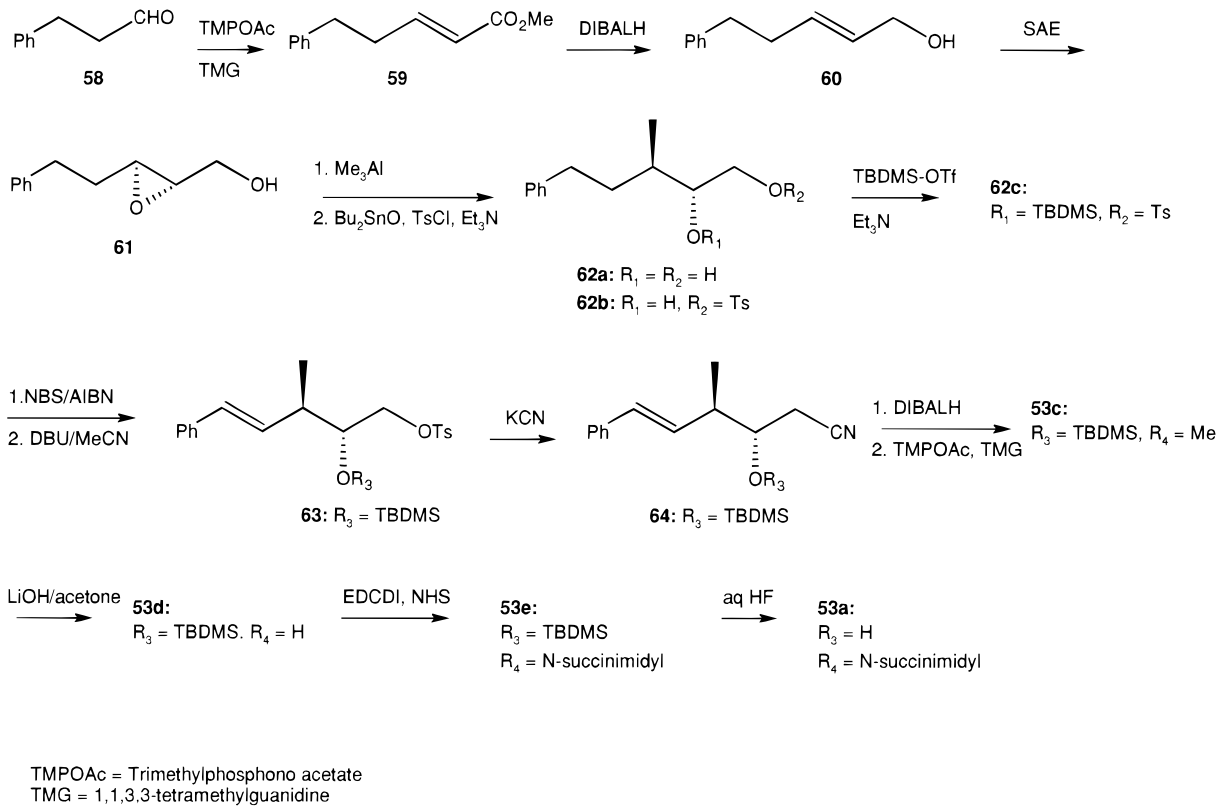
(c) Cyclising the product of step b,

(d) Forming the epoxide of the ring-closed product in step c, using *m*-CPBA to give **56**.

(e) The α and β form of the epoxides **56a** and **56b** may be separated if desired.

The synthesis of the precursor **53a** is described in some detail and shown in Scheme 17. This involves treating the aldehyde **58** in a Homer−Emmons−Wadsworth (HEW) reaction with trimethylphosphonoacetate (TMPOAc) to give the allylic ester **59**. This was then reduced to the alcohol **60** and then converted by a Sharpless asymmetric epoxidation (SAE) reaction to **61**. Treatment with Me_3Al gave the diol **62a** which was then converted to the monotosylate **62b**. The second hydroxy group was then protected by silylation, giving **62c** and bromination with NBS followed by standard treatment with DBU produced the styrene derivative **63**. Cyanide treatment of **63** followed by another HEW reaction gave the methyl ester **53c** that on hydrolysis gave the acid **53d**. This was converted to **53e** in a step in which the *N*-succinimidyl leaving group is attached by treatment of **53d** with the carbodiimide **57** and *N*-hydroxysuccinimide (NHS). Treatment of **53e** with aqueous HF resulted in desilylation to give the desired **53a**.

Scheme 17



TMPOAc = Trimethylphosphono acetate
TMG = 1,1,3,3-tetramethylguanidine

Advantages

Despite the very large number of steps involved, it is claimed that the process is shorter and more efficient than previous methods and uses commercially available amino acids as starting materials.

Patent No. U.S. 5,977,406

Assignee: DSM BV, Heerlen, The Netherlands

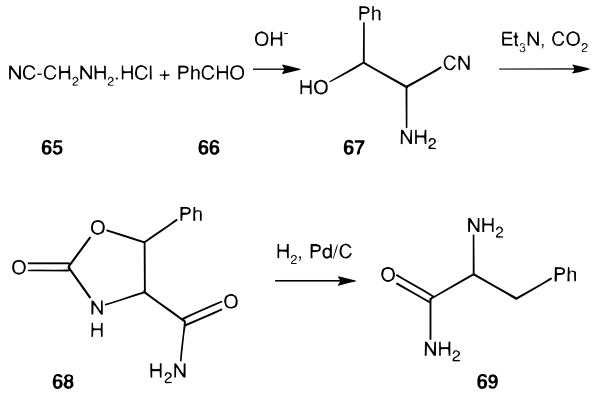
Title or Subject: Process for Preparing α-Amino Acids and Their Amides and Other Derivatives

The patent focuses on the preparation of phenylalanine and its amide **69** which can be used to make the artificial sweetener aspartame. The process involves the preparation of a substituted 2-oxazolidinone **68** which is a novel intermediate and was prepared from the *N*-benzylidene acetonitrile **67**. This was formed by base condensation of the aminoacetonitrile salt **65** with benzaldehyde **66**. Carboxylation of **67** with CO_2 gave **68**, and then hydrogenation using Pd/C catalyst gave **69** in 100% conversion and 89% selectivity (Scheme 18).

Advantages

The normal methods for the preparation of amino acids are the Strecker synthesis or are based on hydantoin. In each case the raw materials are expensive, and high levels of by-product salts are formed. This process claims to use cheaper starting materials and also produces lower amounts of salts.

Scheme 18



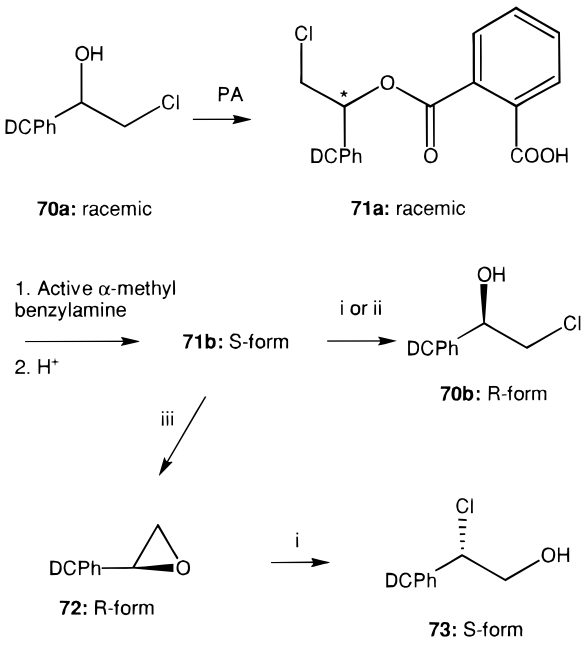
Patent No. U.S. 5,981,807

Assignee: Nihon Nohyaku Co. Ltd, Tokyo, Japan

Title or Subject: Production of Optically Active 2-Chloro-1-(2,4-dichlorophenyl)ethanol and 1-(2,4-Dichlorophenyl)-1,2-ethylene oxide

The 2-chloro-(aryl)ethanol **70b** is used as an intermediate in the synthesis of drugs and agrochemicals. This patent describes a method of resolving a racemic mixture of **70a** via conversion to the phthalate half ester **71a** with phthalic anhydride (PA) (Scheme 19). The racemic mixture **71a** was then treated with (+)-α-methylbenzylamine to give the amine salt and this was resolved by fractional crystallisation. Acid hydrolysis of the salt gave the *S*-form of the ester **71b**. This ester was converted to **70b** in high optical purity by hydrolysis, using either HCl or a weak base such as Et_3N. If the phthalate half ester **71b** is hydrolysed by a strong base such as KOH, then the styrene oxide **72** is produced.

Scheme 19



i. HCl in dioxane; ii. Et_3N in propanol; iii. aqueous KOH

DCPh = 2,4-dichlorophenyl

Treatment of **72** with HCl gave derivative **73** with inverted configuration.

Advantages

Although the conversion to phthalates is a known method when resolving alcohols, it is claimed that there are no specific suitable resolving agents for substituted 2-chloro-(aryl)ethanols. The use of α-methylbenzylamine as a resolving agent is claimed to be novel.

Patent No. U.S. 5,986,075

Assignee: Bayer Corp., Pittsburgh, PA, U.S.A., and Bayer AG, Leverkusen, Germany

Title or Subject: Process for Production of Diazonium Compounds with Low Sodium Ion Content

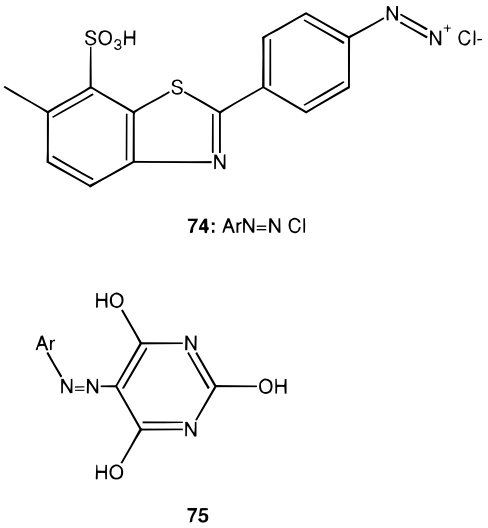
This is a method of desalting aqueous mixtures of diazonium salts by using tubular membranes. The process involves cross-flow ultrafiltration to remove the Na ions as an aqueous solution permeates through inorganic or organic polymeric membranes and the purified diazonium salts are retained within the membrane. The process is applied to preparing azo dyes such as **75** which are used in producing inks for ink jet printers and which require low Na ion content to enhance their solubility (Scheme 20).

One example describes how 72 kg of a suspension of the diazonium salt **74** was purified and then used to produce the dye **75**.

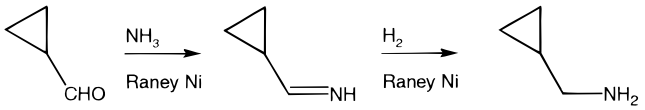
Advantages

Conventional drying and water washing of the diazonium salts can lead to explosive decomposition of the dried materials. This method allows safe removal of the Na in aqueous suspension without drying the salt.

Scheme 20



Scheme 21



Patent No. U.S. 5,986,141

Assignee: Eastman Chemical Co., Kingsport, TN, U.S.A.

Title or Subject: Process for the Production of Cyclopropanemethylamine

This is a two-step process that is carried out in one pot and involves hydrogenation of the imine **77** that was produced from the aldehyde **76** and ammonia (Scheme 21). The whole process takes place in the presence of Raney nickel catalyst. The aldehyde **76** can be made from 2,3-dihydrofuran and can contain up to 15% of crotonaldehyde, but this does not create problems since it is removed by forming high boiling materials by reaction with ammonia.

Advantages

Alternative methods to make **78** use hazardous reagents such as diazomethane or expensive reagents such as cyanocyclopropane. Another method that goes via an imine and involves reductive alkylation is apparently difficult to control. The current process is claimed to be economical, requiring no expensive or hazardous chemicals, and since it is not necessary to use high purity aldehyde **76**, this is advantageous.

Received for review January 6, 2000.

Keith Turner
Kappa Tau Consulting, Stockton-on-Tees, UK

OP0000024