Organic Process Research & Development **2005**, *9,* 537–546

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during May and June 2005

Summary

The current review comprises 21 patents from an original list of 253 that fit the search criteria. The statin drugs continue to be of interest, and an improved method of producing the soluble amorphous form of atorvastatin is described. Drugs and chemicals obtained from plant extracts are always under investigation, and there are a number of examples in this selection. In one patent a method of making salts of the asiatic and madecassic acids is described. The salts have better wetting properties than the acids and are more useful in applications as skin dressings to treat wounds. Another patent describes the production of derivatives of illudin compounds that have potential in treating solid tumors. Most of the naturally occurring illudins are toxic to humans, whereas the derivatives are not. Two patents describe processes for the production of xylitol from sugars ribulose and xylose. Also on the subject of sugars is a patent covering the preparation of aspartame derivatives that are not as unstable as the parent. Protecting-group chemistry is widely used in many syntheses, and it has been found that some thiol-protecting groups are actually labile. The finding is used to selectively prepare disulphide bonds from cysteine residues in peptides. The formation of C−N bonds for producing *N*-arylamines using Pd−carbene complexes is reported. It is claimed to be a suitable method for preparing amines containing other functional groups. The problems of some COX-2 inhibitors are in the news in the nonscientific press, and there is a great deal of interest in developing compounds with minimal side effects. There are two patent is this review on the preparation of pyrazoles that are COX-2 inhibitors. An improved selective cis-hydrogenation step is described that is used in an improvement to the preparation of the antidepressant sertraline. In many applications the physical nature of a compound dictates the performance of the product. A method of preparing an isocyanurate cross-linking agent used in circuit boards is described that gives the crystal form that has the required low solubility and the desired size distribution. Synthetic fibres often require complex mixtures of dyes and additives to achieve the coloured materials that are so commonplace. A patent describes a one-pot multistep method of preparing Na sulphonate salts that are suitable as dye modifiers for polyester fibres. The production of cyclopropane carboxylate esters is described in which a range of Zr compounds is used as esterification catalysts. The normal acid catalysts gave ester products that were discoloured and not acceptable. There is no legal or commercial significance to the choice of patents although some are clearly at a more advanced stage than others. Several of the patents include experimental details that involve several kilos of materials, and one in fact describes treating 0.8 ton/h of a liquid stream. The advantages described are usually those claimed in the patent unless this reviewer has personal knowledge. However, it has to be remembered that the patent may only refer to previous work that shows the patent in a favourable light.

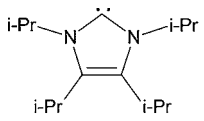
Patent No. U.S. 6,888,029

Assignee: Massachusetts Institute of Technology, U.S.A.

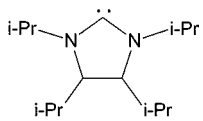
Title or Subject: Formation of Carbon−Nitrogen Bonds Catalysed by Transition Metal Carbene Compounds

This patent describes a process for preparing *N*-aryl-amines or -amides that primarily use Pd catalysts containing a carbene ligand such as L^1 or L^2. Pd-catalysed *N*-arylation

Carbenes



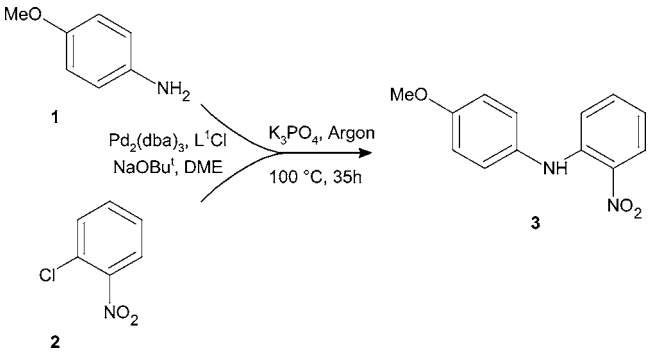
L^1



L^2

reactions are widely known and can be used for preparing *N*-aryl-amines or -amides. It is said that such reactions require strong bases and harsh conditions so that functionalised reagents cannot be used. This process uses weak bases thereby allowing a wider range of functionalised compounds to be prepared. The catalysts are prepared in situ from a dibenzylidineacetone complex of Pd such as $Pd_2(dba)_3$ and a carbene precursor such as L^1Cl in the presence of a base such as $NaOBu^t$. The production of **3** from **1** and **2** is carried out by adding the catalyst mixture to the reactants in a solvent such as DME (Scheme 1). The yield of **3** was 98% when using L^1Cl and 96% with L^2Cl. The patent gives several examples of preparing other amines but many of these give poor yields of <20%.

Scheme 1



10.1021/op050127e CCC: $30.25
Published on Web 08/13/2005

Advantages

The patent claims that the process can produce a wide range of amines containing functional groups. However, the examples do not support this, and many amines are formed in poor yields.

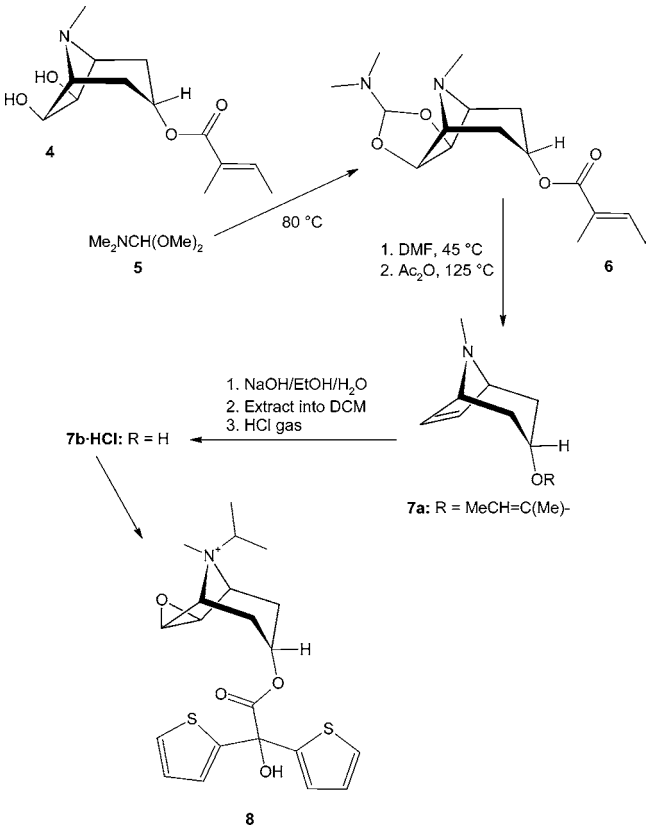
Patent No. U.S. 6,891,042

Assignee: Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany

Title or Subject: Industrial Process for Preparing Tropenol

Tropenol **7b** is used to prepare a variety of pharmacological materials such as tiotropium bromide **8**. The production of **7b** and its derivatives is said to be difficult because the removal of structurally similar impurities is a problem. This patent describes a method of preparing the HCl salt **7b**·HCl shown in Scheme 2, although the main claim of the patent actually relates to the acetal **6** rather than **7b**. The preparation of **7b**·HCl starts by reacting meteloidine **4** with **5** to form the cyclic acetal **6**. The acetal **6** is then decarboxylated to give the ester **7a** that is saponified and then treated with HCl to give the salt **7b**·HCl.

Scheme 2



The examples in the patent are carried out using >20 kg of **4**, thus indicating the advanced stage of development of the process.

Advantages

The procedure improves the preparation of **7b** by forming an acid salt that can be more easily purified than the free amine.

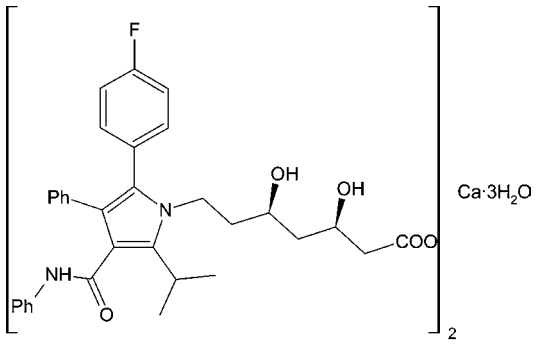
Patent No. U.S. 6,891,047

Assignee: LEK Pharmaceuticals d.d., Ljubljana, Slovenia

Title or Subject: Process for the Preparation of Amorphous Atorvastatin

The statin drugs are widely used to treat cardiovascular diseases and to lower cholesterol levels. Atorvastatin **9** is normally available as the Ca salt, and methods for its synthesis and purification have been reviewed (*Org. Process Res. Dev.* **2005**, *8*, 823). **9** exists in several crystalline forms and a more water-soluble amorphous form. This patent describes a reproducible method for the preparation of the amorphous form. The process involves formation of a solution of a crystalline form of **9** in a polar solvent followed by addition of an antisolvent such as an ether to precipitate the amorphous **9**. The product is then collected by filtration and dried on a rotary evaporator at 50 °C. The patent describes a number of examples for producing amorphous **9** from crystalline Form I in which the first solvent is MeOH, EtOH, or Me_2CO and the antisolvent is Et_2O.

Atorvastatin



9

Advantages

The process is straightforward and reproducible.

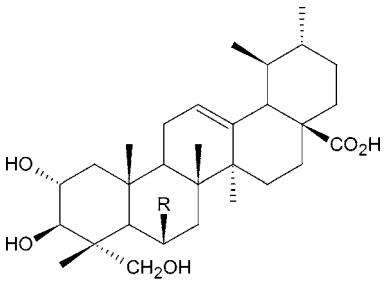
Patent No. U.S. 6,891,063

Assignee: Euphar Group S.r.l., Milan, Italy

Title or Subject: Preparation of Salts of Asiatic and Madecassic Acids for Use in Pharmaceutical Compositions

Asiatic acid **10a** and madecassic acid **10b** are found in the leaves of the plant *Centella asiatica* and have high bioactivity. The compounds are used to treat a variety of skin problems and to help to heal surgical and trauma wounds. However, the acids are themselves not very water soluble and have poor wetting properties; hence, a more appropriate form of these compounds is required that can be used to prepare suitable formulations. This patent discloses a method of preparing basic salts of **10a** and **10b** that are more useful for treatment.

The general procedure is to mix a solution of an organic base with a methanolic solution of the acid and then heat the mixture. The solvents are removed under vacuum, and the residue is washed and then crystallised from a range of solvents, depending upon the base and the acid used. For example the salt formed from **10a** and $H_2NCH_2CH_2NH_2$ contained 2 mol of **10a** and was crystallised from hot aqueous EtOH. Salts of **10a** and **10b** were also formed from $EtONH_2$, lysine, $PhCH_2Me_3NOH$, and Me_4NOH. The patent provides only elemental analysis, and no spectroscopic data are given. The patent does include an example of preparing a gel of the salt that is used in a test to indicate its bioactivity.



10a: R = H
10b: R = OH

Advantages

The process provides a means of preparing forms of these bioactive compounds that can be used in pharmaceutically useful forms.

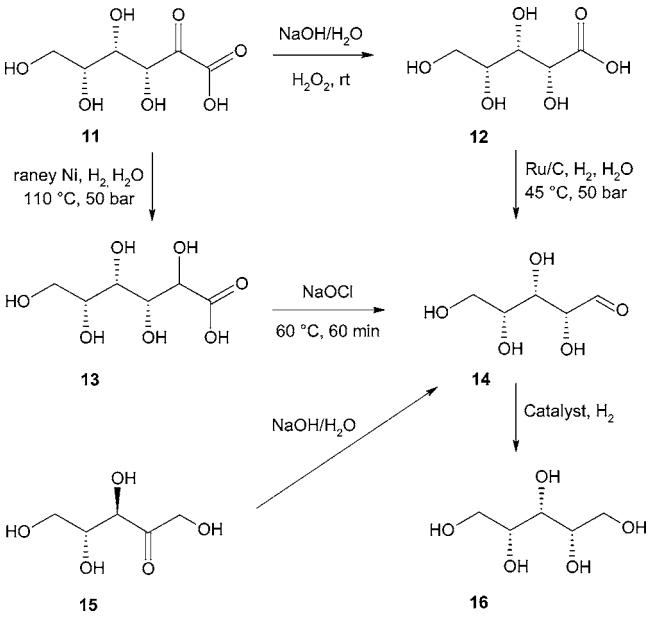
Patent No. U.S. 6,894,199

Assignee: Danisco Sweeteners Oy, Espoo, Finland

Title or Subject: Process for the Preparation of Xylitol from L-Xylose

This is the first of two patents covering xylitol **16** that is widely used in many foods and confectionary products. **16** occurs naturally in low concentrations in fruits but is normally produced by synthetic means from a variety of natural sources. This patent describes a method of preparing **16** from L-xylose **14** that is not a naturally occurring material since natural xylose exists in the D-form. The patent describes a number of methods of producing **14**, and Scheme 3 shows two of these that start from **11**. Two options are available, and the first converts **11** to **12** by a decarboxylation reaction using alkaline H_2O_2. Reduction of **12** using Ru/C forms **16** containing **14**. **16** can be obtained from the mixture by using an acidic ion-exchange resin (IER) to remove **14** and other impurities. The alternative route from **11** to **16** is via initial reduction using Raney Ni to give **13**. This is then decarboxylated with NaOCl to give **14** and reduction using Raney Ni gives **16**.

Scheme 3



The patent covers a substantial amount of work and gives details of the purification of **16** by crystallisation. There is also described a process for the production of L-xylulose **15** by a fermentation process, and **15** can be converted to **14** by alkaline isomerisation.

Advantages

The process allows the production of the important sweetener from synthetic reagents.

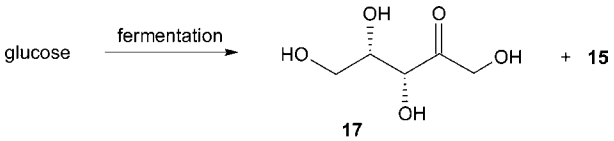
Patent No. U.S. 6,911,565

Assignee: Danisco Sweeteners Oy, Espoo, Finland

Title or Subject: Process for the Preparation of Xylitol from Ribulose

The second patent on **16** describes a method of preparing **16** from ribulose **17**. This is produced by fermentation of glucose giving a mixture of **15** and **17**. By treating the fermentation mixture with an enzyme such as tagatose epimerase, an epimerisation reaction takes place, and **17** is converted to **15**. The unconverted **17** is recycled, and the **15** can be used to produce **16** by the methods of the previous patent.

Scheme 4



As described in the previous patent an IER is used to purify the mixtures and fractions obtained from the various reactions.

Advantages

This patent allows the widely available raw material glucose to be used for the production of xylitol.

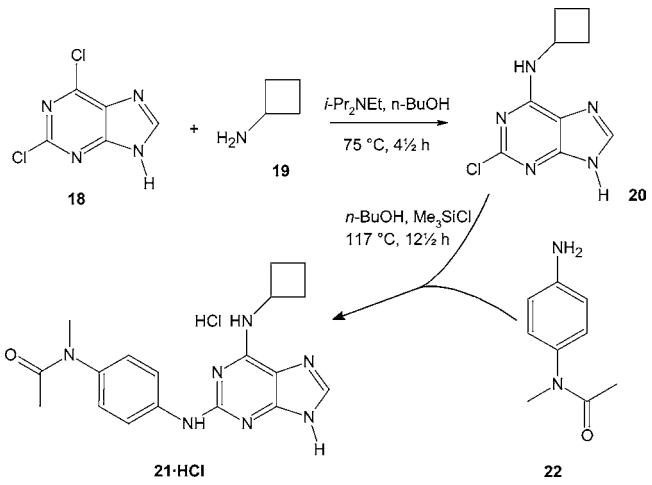
Patent No. U.S. 6,897,307

Assignee: Novartis AG, Basel, Switzerland

Title or Subject: Process for Preparing 2,6-Diaminopurine Derivatives

The purine derivatives described in this patent are used in the treatment of asthma and allergic rhinitis. The method used to prepare the compounds such as **21** is shown in Scheme 5 and proceeds via the aminopurine **20**. This is formed by the reaction of the amine **19** with the chloropurine **18** in the presence of a base such as *i*-Pr_2NEt. In the second stage of the synthesis **20** is reacted with the amide **22** in the presence of an acid catalyst. The catalyst used in the examples is Me_3SiCl, and this step forms the HCl salt **21**·HCl in 62% isolated yield. The patent also describes a one-pot synthesis of **21**·HCl that is carried out using the same catalysts but without isolation of **20**. The patent claims that a number of acid catalysts can be used, but only Me_3Si is used in the examples.

Scheme 5



A variety of other purine derivatives were prepared using the same synthetic route with varying degrees of success. The examples show that if a nonaromatic amine is used in the second acid-catalysed stage, then no reaction takes place. However, if nonaromatic amines are used in the first base-catalyzed step, then the reaction continues as shown. The reactivity of the 2-position on the purine ring is much less than that of the 6-position, and hence the displacement of the two Cl atoms proceeds via different rates. Previous work had shown that more forcing conditions were required to displace the 2-chloro substituent when using a basic catalyst.

Advantages

In this patent a change of catalyst allowed milder reaction conditions to be used to displace both 2- and 6-groups on the purine ring.

Patent No. U.S. 6,897,318

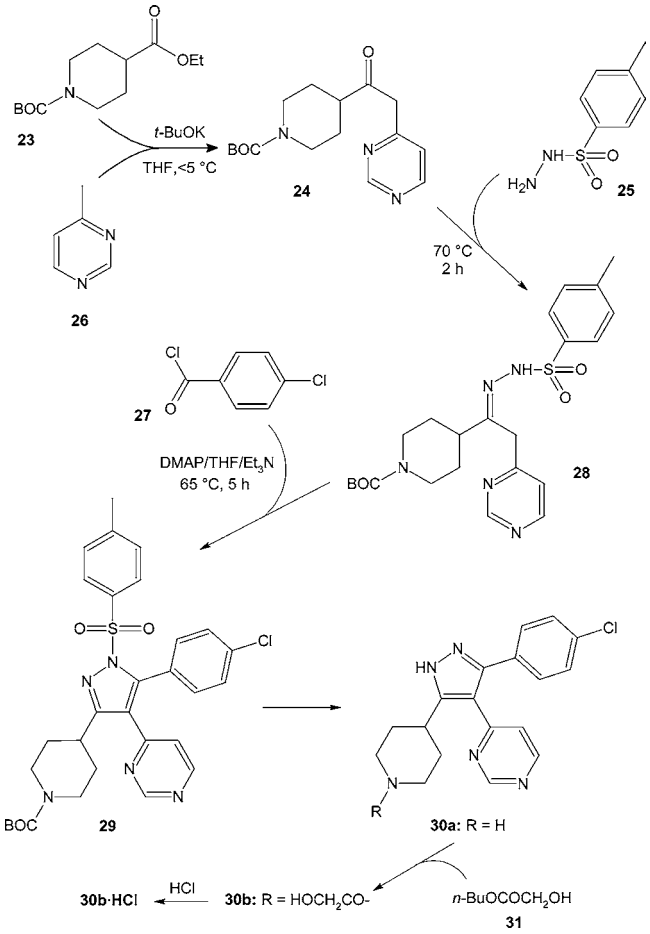
Assignee: Pharmacia Corporation, St. Louis, Missouri, U.S.A.

Title or Subject: Process for Making Substituted Pyrazoles

This is the first of two patents in this review on the subject of pyrazoles. This class of compounds has a variety of medicinal uses, and the first patent is a comprehensive document covering compounds such as **30b**. The patent gives an extensive list of conditions that can be treated by **30b**.

The route to **30b** has several steps that are described in detail in the patent. The reactions are summarised in Scheme 6, but since it is not feasible to include the details of each step, for clarity they are not shown. For some of the reactions shown there is more than one variation, and each of these is described in the patent. For example there are two routes from **29** to **30a** and three routes from **30a** to **30b**. Also described are a number of methods of treating the wet filter cake obtained in the formation of **30b**. This is done to reduce the level of impurities in the product.

Scheme 6



This patent contains an extensive amount of information and discusses in some detail the method of deprotection of **29** to give **30a**. It is mentioned that treatment of the solid filter cake with MeCN causes a polymorph transformation that gives a material that has more suitable physical characteristics in the downstream processing.

Advantages

The patent claims that the process provides an improved method of making pyrazoles that are important medicaments. The examples describe the production of several kilos of products, thus indicating the advanced stage of development of the process.

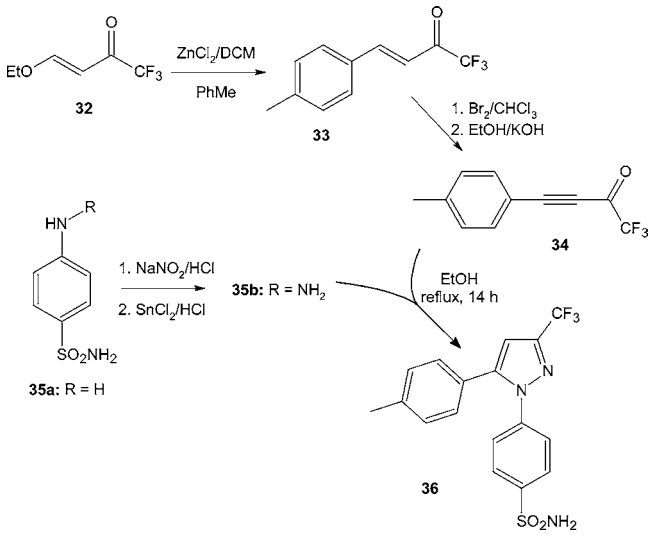
Patent No. U.S. 6,906,196

Assignee: Onconova Therapeutics Inc., Lawrenceville, New Jersey, U.S.A.

Title or Subject: Processes for the Preparation of 1,5-Diaryl-3-Substituted-Pyrazoles

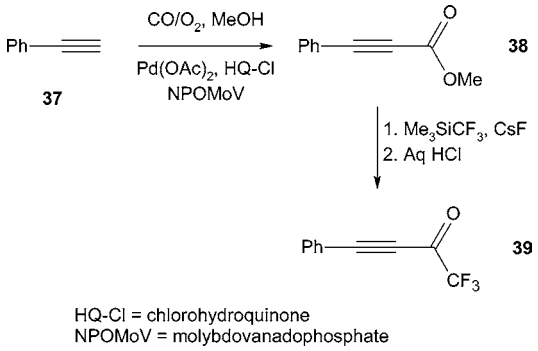
This is the second patent on pyrazoles and is aimed at those compounds such as **36** that act as COX-2 inhibitors and are used in treating various inflammatory diseases. The reaction used to prepare **36** is shown in Scheme 7 and involves the condensation of the hydrazine **35b** with the alkyne **34**. The scheme also shows the methods by which the reagents **34** and **35b** are produced.

Scheme 7



The patent also reports that compounds analogous to **34** can be made by the procedure shown in Scheme 8. Thus, **39** can be produced from phenylacetylene **37** via the production of the propargyl ester **38** that is formed in a Pd-catalysed carbonylation reaction. Treatment of the ester **38** with Me_3SiCF_3 in the presence of CsF then gives **39**.

Scheme 8



Advantages

The process uses inexpensive starting materials and gives high yields of products with simplified isolation and purification methods.

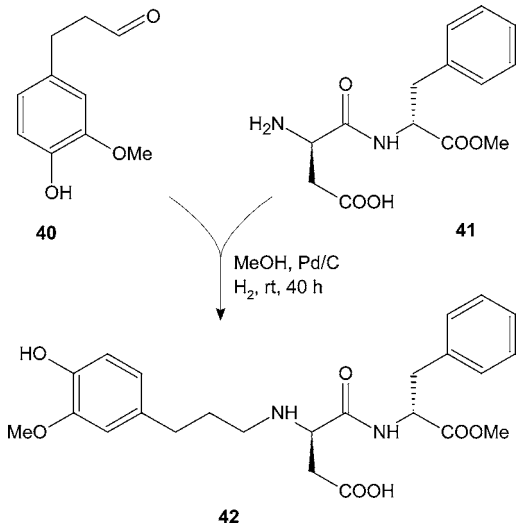
Patent No. U.S. 6,899,912

Assignee: Ajinomoto Co. Inc., Tokyo, Japan

Title or Subject: Method for Producing and Purifying a Crystalline Aspartame Derivative

Aspartame **41** and its derivatives are used as low-calorie sweeteners, and patents have previously been reviewed (*Org. Process Res. Dev.* **2005**, *9*, 9). The patent mentions that there have been reports that aspartame has stability problems. It is also reported elsewhere that aspartame can cause cancer, and hence alternatives are being sought. This patent discloses a method of producing pure crystals of the derivative **42** on an industrial scale. The reaction to produce **42** is shown in Scheme 9 and is by reductive alkylation of **41** with **40** in the presence of Pd/C.

Scheme 9



The main body of the patent is concerned with the recovery and purification of **42** by crystallisation. The reaction mixture contained <0.5% of **41**, and this was removed during the crystallisation procedure. One method is summarised as follows:

(i) concentrate solution under vacuum and dissolve the residue in EtOAc.

(ii) add MeOH to produce crystals of **42**.

(iii) collect crystals, wash in EtOAc, and dry.

(iv) redissolve crystals in MeOH, concentrate solution, and add water to form crystals.

(v) collect crystals, wash in MeOH and water, then dry under vacuum.

The product was obtained as 99% purity in 36% yield.

The key aspect of the purification method seems to be the use two crystallisation steps, the second of which uses water. There are a number of examples in the patent that use different catalysts and isomers of the aldehyde **40**. The patent includes comprehensive physical property data for **42** including ^1H NMR, IR, and X-ray data.

Advantages

The process provides a method of producing a low-calorie sweetener that may be more acceptable than its parent compound.

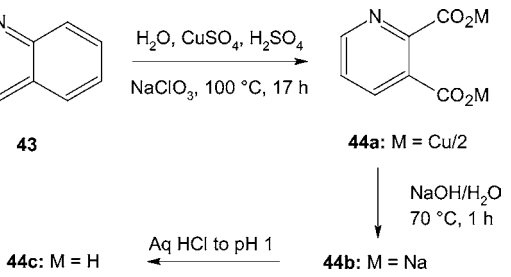
Patent No. U.S. 6,900,330

Assignee: Hebei Sinochem Fuheng Co. Ltd., Hebei, China

Title or Subject: Process for Producing 2,3-Pyridinecarboxylic Acid

The title compound **44c**, also known as quinolinic acid, is used as an intermediate for preparing agrochemicals, dyes, and pigments. Several methods are available for its synthesis, and commercially, it is produced by oxidation of quinoline **43** or 2,3-dimethylpyridine using ozone. An alternative method oxidises 8-hydroxyquinoline with NaOCl or HNO_3. All of these commercial methods have a waste problem, and the process described in this patent attempts to alleviate this problem and improve the overall process itself. The process developed is based on the observation that Cu(II) ions form an insoluble complex with **44c**. The complex is formed selectively over the byproducts that are present in the reaction mixture from oxidation of **43** and thus can be separated and purified. The route described in the patent is shown in Scheme 10 and is based on oxidation of **43** using $NaClO_3$. The reaction is carried out in the presence of Cu(II) so that the Cu complex **44a** is formed immediately and precipitates from the solution. The Cu complex is then converted to the Na salt **44b** that is acidified to precipitate **44c**. The product is obtained at a purity >98.5% and in yield of around 50%.

Scheme 10



The overall yield can be increased by about 8% by recirculating the mother liquor from the last stage to the first or second stages. In addition, it is possible to further recover **44c** by adding Cu(II) salts to the last-stage liquor and recirculating it to stage 1. It is stated that, surprisingly, this recirculation actually accelerates the rate of oxidation of **43** in the presence of $NaClO_3$. Hence, the process is specifically aimed at the use of chlorate oxidation of **43**.

Advantages

The process is a novel method of producing the acid that is commercially attractive.

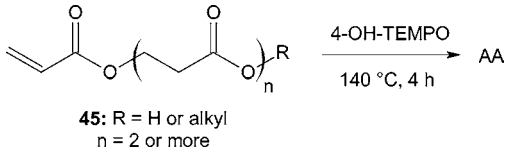
Patent No. U.S. 6,900,346

Assignee: Nippon Sokubai Co. Inc., Osaka, Japan

Title or Subject: Method for the Decomposition of Michael Type Adduct

The adduct **45** referred to in the title is a byproduct formed during the production of acrylic acid (AA) or acrylic esters (AE). **45** is thus a loss to the process of producing the AA and AE, and its presence can make purification of these products more difficult. It is common practice to concentrate the adduct as a high-boiling fraction in the distillation column and incinerate it. The adducts can be thermally decomposed to AA or AE, but this usually requires temperatures of 200 °C or more. Such conditions lead to very-high-boiling materials and low recovery rates of AA or AE. This patent describes a novel method of decomposing **45** and releasing AA or AE to improve the overall yield of the process. The adduct is decomposed by addition of an *N*-oxyl compound, and TEMPO and its 4-hydroxy derivative are effective. In a batch process the TEMPO is added to a mixture obtained from the AA or AE production process. This mixture contains AA, hydroquinone as a polymerisation inhibitor, and high-boiling impurities including the adduct **45**. It was possible to convert up to 75% of a mixture containing 60% **45** to AA and AE with a selectivity of 98% using about 3% of 4-H-TEMPO.

Scheme 11



The procedure is more effectively applied to continuous processes since AA and AE are more usually manufactured in this manner in large-scale plants. One example obviously describes such a plant in which 0.8 ton/h of liquid containing **45** is introduced into a column for decomposition.

Advantages

The process improves the overall process yield of manufacturing AA, and it is probably in commercial use.

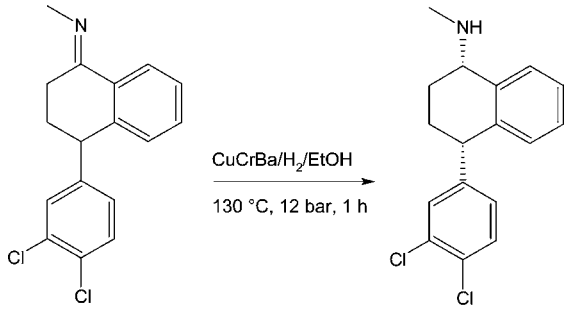
Patent No. U.S. 6,900,355

Assignee: Ciba Specialty Chemicals Corporation, Tarrytown, New York, U.S.A.

Title or Subject: Process for the Cis-Selective Catalytic Hydrogenation of Cyclohexylidenamines

This patent relates to the production of sertraline **47** which is a well-known antidepressant available as the HCl salt under the name Lustral or Zoloft. During the production of **47** the imine **46** is formed initially, and on hydrogenation of **46** to the amine there are two pairs of enantiomers, one cis and one trans. However, only one of the cis enantiomers is desired; hence, stereoselective hydrogenation catalysts are highly desirable. It has been found that the cis/trans ratio can be increased by the use of Cu catalysts in the presence of protic solvents. Examples are described in which a Ba-promoted copper chromite catalyst is used with EtOH as solvent and a cis/trans ratio of 98.8:1.2 was achieved. Scheme 12 shows the desired reaction to produce **47** although in practice the cis racemate is formed as the major product.

Scheme 12



46 47

Advantages

The process gives improved yields of the desired cis-racemic mixture, thereby improving the atom yield of the process.

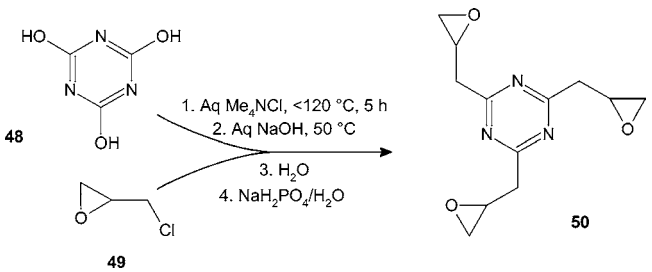
Patent No. U.S. 6,903,212

Assignee: Nissan Chemical Industries Ltd., Tokyo, Japan

Title or Subject: Method for Producing β-Form Tris-(2,3-epoxypropyl)isocyanurate Crystals with Reduced Solvent Content

The title compound **50** is used as a cross-linking agent in the production of epoxy resins that have applications in circuit board manufacture. The compound has three chiral centres and crystals of the enantiomeric pair (2*R*, 2′R, 2″*R*) and (2*S*, 2′*S*, 2″*S*) are known as the *β*-form. These crystals are more useful since they have higher melting point and lower solubility than the crystals containing the (2*R*, 2′*R*, 2″*S*) and (2*S*, 2′*S*, 2″*R*) pair that are termed the α-form. During the manufacture of **50** it is necessary to remove the α-form crystals by extraction, but this can leave large quantities of solvent in the *β*-crystals. A commonly used solvent is MeOH, but this does not give crystals of the desired size range. A further problem is the presence of residual **49** that is used in the production of **50**, and it is necessary to reduce the levels of **49** below 1000 ppm. Hence, this patent describes a method of reducing the level of both the α-crystals and of **49**. The reaction to produce **50** is shown in Scheme 13.

Scheme 13



48 49 50

After the crude **50** is formed the mixture is evaporated and MeCN is added to the residue. The mixture is heated to dissolve the residue, and when it is cooled, the *β*-crystals are obtained. After washing with MeOH and drying in N_2, the crystals were found to contain 150 ppm of MeCN and 20 ppm of **49**. The patent also gives examples of using PhMe, DMF, or dioxane in place of MeCN, and the product is also of high purity. The claims also mention the use of ultrasonic waves during the cooling stage of the crystallisation step.

Advantages

The process is simple and effective and gives high-purity product that has the desired crystal size.

Patent No. U.S. 6,906,171

Assignee: Amersham Health AS, Oslo, Norway

Title or Subject: Formation of Disulphide Bonds during Deprotection of Protected Thiols

The process described in this patent is used in the formation of disulphide bonds from thiols in the preparation peptides. The work is based on the unexpected finding that some thiol-protecting groups are labile to acids. The protecting groups are normally stable under acidic conditions, but it has been found that under oxidising conditions when the reaction temperature is increased certain groups are labile. The groups that are labile are acetamidomethyl, 4-MeBn, and Bu^t, and it has been found that when carrying out the deprotection step in the presence of an oxidising agent at raised temperatures the thiol groups form disulphide bonds. The reaction is especially useful when applied to thiols in cysteine residues using DMSO as oxidising agent. The examples describe the use of the reaction for the synthesis of a number of peptides such as α-conotoxin SI, oxytocin, and enterotoxin. In α-conotoxin the amino acid sequence is Ile-Cys-Cys-Asn-Pro-Ala-Cys-Gly-Pro-Lys-Tyr-Ser-Cys-NH_2 with disulphide bonds connecting Cys 2 with Cys 7 and Cys 3 with Cys 14. The peptide sequence was assembled using an automatic sequencer and the thiol groups on Cys 2 and Cys 7 were protected with the trityl group, whereas the Cys 3 and Cys 13 thiols were protected with acetamidomethyl groups. When the protected peptide was removed from the sequencer, it was treated with TFA and DMSO. The recovered product was found to be α-conotoxin.

Advantages

This procedure enables the selective formation of disulphide bonds at specific positions in the peptide. It is especially useful in the preparation of cyclic peptides.

Patent No. U.S. 6,906,201

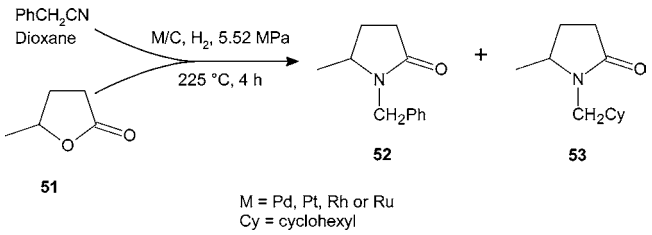
Assignee: E.I. Du Pont De Nemours and Company, Wilmington, Delaware, U.S.A.

Title or Subject: Production of N-Methylaryl-2-Lactam, N-Methylcycloalkyl-2-Lactam and N-Alkyl-2-Lactam by Reductive Amination of Lactones Using Cyano Compounds

This patent is similar to an earlier one from the same company that used arylnitro or arylamines to prepare lactams, and this has been reviewed (*Org. Process Res. Dev.* **2005**, *9*, 235). The 2-lactam compounds are used in a variety of

applications, and the patent includes examples that cover the formulation of a number of end products containing the lactams that range from cleaning compositions to antifungal creams. The reaction is shown in Scheme 14 and uses a range of supported catalysts to convert the lactone **51** to the lactams **52** and **53**. The most selective catalyst for the formation of aryl lactam **52** was Pt/C that gave no **53**.

Scheme 14



Advantages

The reaction is novel, but I am skeptical that it is commercially attractive because the conditions for the reaction are rather extreme.

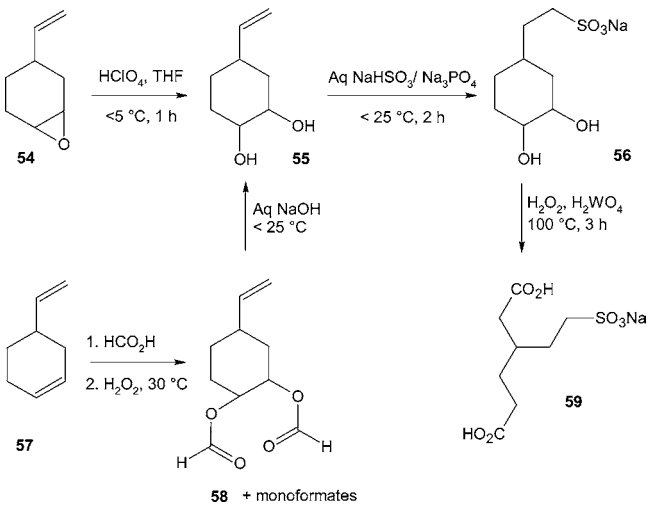
Patent No. U.S. 6,906,220

Assignee: Invista North America S.Ar.l., Wilmington, Delaware, U.S.A.

Title or Subject: Process to Produce 4-(2-Sulfoethyl)cyclohexane, 1,2-Diol Sodium Salt from 4-Vinylcyclohexane-1,2-diol

The Na salt **56** is used as a precursor to **59** that is a modifier used in the dyeing of polyester fibres. The fibres are resistant to staining with some dyes, and hence such modifiers are necessary. Processes for producing **56** can give rise to poly-substituted products, and hence the patent provides a route to the desired monosubstituted compound. The various routes used are shown in Scheme 15. The production of **56** can start from the epoxide **54** that is hydrolysed to give the diol **55**. This hydrolysis can be carried out with $HClO_4$ as shown or by using an acidic IER. An alternative route to **56** is to start from the **57** and produce a mixture of the diformate **58** and the two monoformates. This is done by reaction of **57** with HCO_2H and H_2O_2. The mixture of crude formates is then hydrolysed using aqueous NaOH to give the diol **55**. Again the crude reaction mixture can be used for the last stage to make **56** in which $NaHSO_3$ is used to sulphonate the diol **55**. The reaction is carried out in the presence of Na_3PO_4 as a buffer so that the pH is maintained in the range 6−6.8. The final step in producing **59** is the oxidation of **56** carried out by using H_2O_2 in the presence of tungstic acid. This reaction is carried out using the crude reaction mixture from the previous step. The use of Na_3PO_4 as a buffer in the sulphonation step means that during oxidation Na_2HPO_4 is formed. This is very soluble in water and does not precipitate during oxidation of **56**. If either NaOH or $NaHSO_3$ were used to adjust pH, then Na_2SO_4 would be precipitated, thereby requiring a filtration step. This is a simple method of avoiding this happening, and it improves the product purity.

Scheme 15



Advantages

The process can be carried out without purification of the intermediates, thus simplifying the process and increasing overall yield. Some of the examples describe experiments in 30-gallon reactors, thus indicating the advanced stage of development.

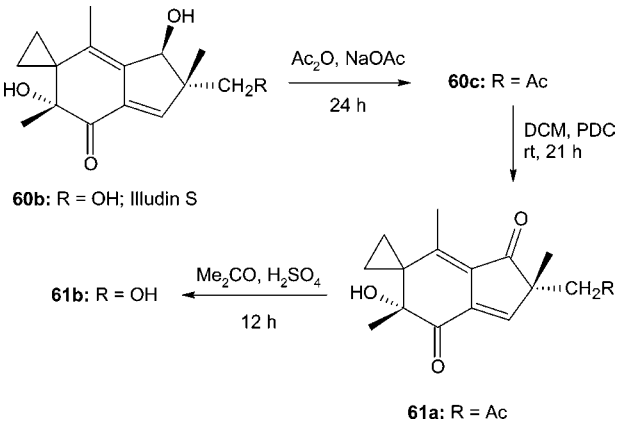
Patent No. U.S. 6,908,918

Assignee: Regents of the University of California, Oakland, California, U.S.A.

Title or Subject: Preparation of Illudin Compounds and Their Use as Antitumour Agents

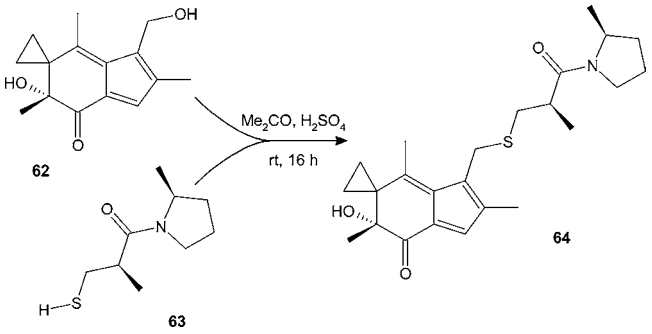
The compounds **60a** (R = H; illudin M) and **60b** (R = OH; illudin S) are extremely toxic sesquiterpenes that can be isolated from certain types of mushroom. These and other illudin compounds have been found to be active in treating leukaemia in small mammals but are not effective against solid tumours. Their toxicity prevents their use in treating cancer in humans, but nontoxic synthetic analogues have been produced and are under investigation as antitumour agents in humans. This patent describes a method of converting natural illudins into compounds that are nontoxic and have potential for treating solid tumours. The first compound is **61b** and is produced from **60b** by treatment with Ac_2O and NaOAc to form the monoacetate **60c**. Oxidation with PDC in dichloromethane (DCM) gives **61a** that upon hydrolysis produces **61b**.

Scheme 16



The patent also describes methods for the synthesis of a range of compounds such as **64** that may also have similar uses. **64** is prepared from **62** and **63** by acid-catalyzed coupling in Me_2CO as shown in Scheme 17. The same type of reaction was used to prepare over 30 compounds similar to **64** in which various amino acids were used to couple with compounds such as **62**.

Scheme 17



Advantages

This patent provides a synthetic route to a wide range of novel compounds that have potential use in the treatment of tumours.

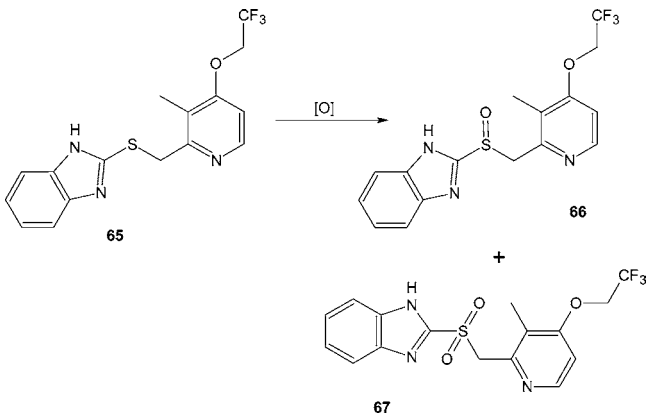
Patent No. U.S. 6,909,004

Assignee: Teva Pharmaceutical Industries Ltd, Petah Tiqva, Israel

Title or Subject: Method for the Purification of Lansoprazole

The compound **66** is one of a group of benzimidazole derivatives that are gastric pump inhibitors and therefore used to prevent ulcers. Several methods are known to prepare **66**, and the majority involve oxidation of the thioether group in **65** as the last step to make as shown in Scheme 18. Many reagents are used in this step, but it is claimed that none of the methods used is highly selective, and thus byproducts are formed. A major byproduct is the sulphone **67**, and it is the objective of this patent to provide a method of producing **66** that is free of both **65** and **67**. The process that is described is a crystallisation method that also allows the water content to be maintained below 0.1% as required by the USP forum. The oxidation of **65** to **66** is carried out in this patent by using $V(acac)_3$ and Bu^tOOH in EtOH containing Na_2CO_3.

Scheme 18



The crude **66** containing up to 0.3% **67** and 0.3% **65** was purified as follows:

(i) dissolve in a mixture of $EtOH/NH_4OH$ and H_2O

(ii) add activated C and heat to 52 °C

(iii) filter and wash cake with EtOH and H_2O

(iv) cool the solution and add HOAc to precipitate crystals of **66**

(v) collect crystals and dry

The product obtained had <0.05% **67**, and **65** was not detectable. The method was also carried out using other lower alcohols and Et_3N as the base. To reduce the water content, <0.1% the crystals of **66** are recrystallised from Me_2CO.

Advantages

The process improves the purity of the final product by reducing the level of byproducts formed.

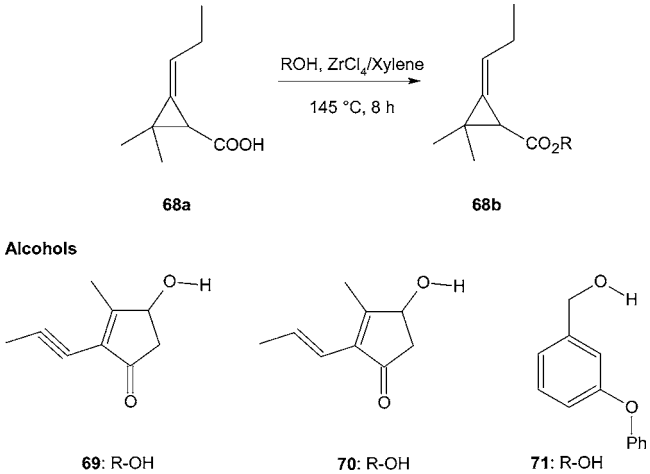
Patent No. U.S. 6,909,013

Assignee: Sumitomo Chemical Corporation Company Limited, Osaka, Japan

Title or Subject: Process for Producing Cyclopropanecarboxylates

This patent discloses an esterification process for producing the esters **68b** from the acid **68a**. The main alcohols claimed are **69**, **70**, or **71** as shown in Scheme 19, but others are also mentioned. The group of esters is known as pyrethrin insecticides. The catalysts used in the process are Zr compounds, and these are employed so as to prevent discolouration of the esters that occurs if conventional catalysts such as H_2SO_4 or PTSA are used. There are examples in the patent that use $ZrCl_4$, $Zr(OBut)_4$, $ZrCp_2Cl_2$, and other similar materials as catalysts. The reaction maintained the *E/Z* ratio that was in the starting alcohol, and these generally contained at least 80% *Z*.

Scheme 19



Advantages

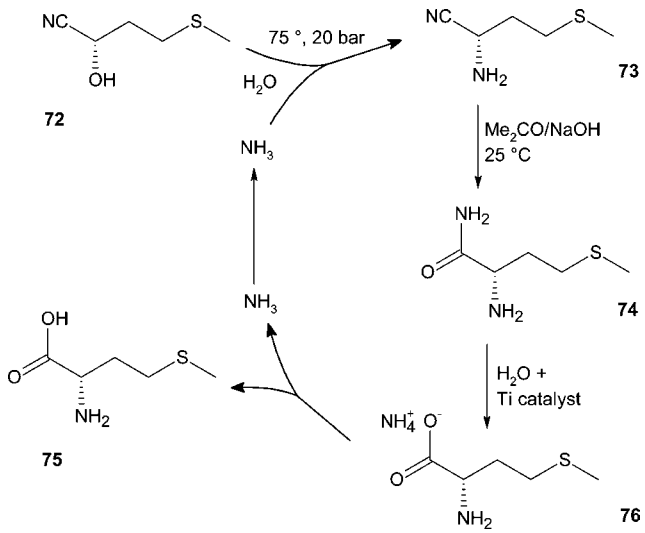
The process gives products that are not discoloured and hence more suitable for subsequent use.

Patent No. U.S. 6,911,557

Assignee: Process for the Production of Methionine
Title or Subject: Adisseo France S.A.S., Antony, France

Methionine **75** is an essential amino acid and is produced on a substantial scale by hydrolysis of the amide **74** using strong bases. However, it is said that the subsequent neutralisation step in these processes uses strong acids, and this produces substantial quantities of aqueous waste streams. The purification of **75** is also difficult because of the need to remove the salts formed in the neutralisation step. There have been reports of the use of titanium catalysts for the amide hydrolysis, but whether these have been commercialised is not mentioned. The process described in this patent uses solid catalysts that are prepared from TiO_2. The catalysts are in the form of granules, pellets, or extrudates, and a selection of these is described and compared to commercial products from catalyst manufacturers. The patent describes an industrial process for making **75** using a catalyst prepared by mixing wet TiO_2 with HNO_3, followed by extruding and thermal treatment. The commercial route to **75** from the nitrile **72** is shown in Scheme 20. The hydrolysis of the amide **74** is catalysed by the Ti catalyst, and this produces the NH_4 salt **76**. The salt is decomposed to give **75** by stripping off the NH_3 that is recycled to the first step where it is used to produce the aminonitrile **73**.

Scheme 20



The patent provides several tabulations of analytical data showing the composition of the various streams from a continuously operating process. There are also graphs indicating the rates of conversion of the amide and the yield of **75** for different catalysts. An additional aspect of the patent is the use of an acidic IER to remove salts from the solution after **75** is produced from **76**.

Advantages

The process simplifies the purification of the methionine and reduces the amount of waste products.

Keith Turner

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