Organic Process Research & Development **2005**, *9*, 244–252

Highlights from the Patents

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

Summary

The review this time contains 21 patents from an initial collection of 241 that fit the search criteria. It is hoped that there are some patents of interest to readers, but there is no legal significance in the choices. There are three patents that make use of the well-known Sharpless asymmetric dihydroxylation of olefins. One is for producing intermediates for anti-depressant drugs and another is from Sharpless' group itself. They disclose an improved ligand for improving the second-cycle asymmetric dihydroxylation of cinnamate esters. The third patent involving this reaction describes a range of novel substituted pyridines that are used in treating obesity in diabetic patients. New polymorphs of known drugs are always of interest, and four new forms of the muscle relaxant zalepon are disclosed. Another patent describes new forms of zonisamide plus a novel sulphonation process for use in its production. Several patents claim process improvements that enhance the environmental aspects of the process. However, it has to be said that some of these are stretching the point when the improvement involves the use of chlorinated solvents. One patent claims to improve the ability to treat a very large number of waste streams containing organic chemicals. This is done by using phase transfer catalysts to enable reactions of the low-level contaminants in the waste streams with chemicals that remove the offending materials. The difficulty with this patent is that it may be very difficult to enforce and it may already be in use. Alkyl nitrites can be used to prepare dialkyl oxalates and carbonates, and a catalytic method of making some is described. It has been said that drinking red wine is beneficial, and a patent describes an improved method of making resveratrol that is believed to be the active ingredient providing such benefits. The control of particle size is often required, and one patent describes how this can be done to make HNS that is a compound used as an explosive. The calcium channel blocker amlodipine is the subject of two patents from different companies. One patent describes how to resolve a mixture and obtain either enantiomer by forming chiral tartrates. The second patent discloses a new route to the drug from a novel starting material. A very large range of pyrazoles that are used as insecticides is described in one patent, and they are said to be nontoxic to aquatic life. The use of naturally available compounds for chemical production is an active area of research, and two patents cover this area. One is for the production of anhydrosugars and the other for furans and tetrahydrofurans. An improved method for the production of phenyl hydrazines from diazonium salts is described that avoids the use of metal-reducing agents. The process proceeds via the formation of *N*,*N*-disulphonates that are easily decomposed to the hydrazine. The details provided in patents vary enormously, and some contain extensive physical property data, and others have little. The experimental details vary widely, and one patent does not have any quantities of reagents mentioned although the description seems comprehensive. The advantages given are those claimed in the patent unless this reviewer has personal knowledge of the subject.

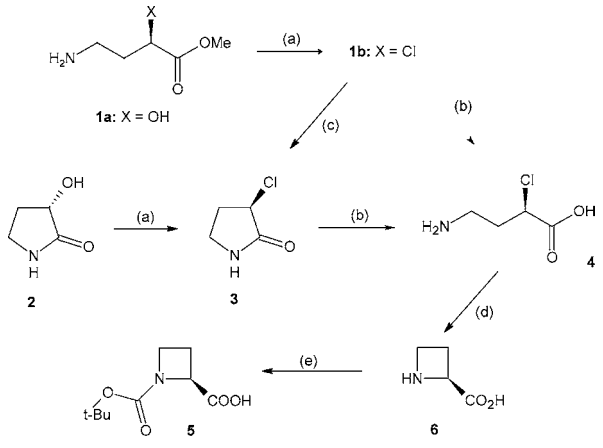
Patent No. U.S. 6,838,567

Assignee: Kaneka Corporation, Osaka, Japan

Title or Subject: Process for Producing Azetidine-2-Carboxylic Acids

The title compounds such as **5** are intermediates in the production of antithrombotic agents, and methods for their resolution and synthesis have been reviewed previously (*Org. Process Res. Dev.* **2003**, *7*, 784). This patent summarises a number of methods available for the synthesis of compounds such as **5** but claims that they are not industrially viable since they are multistep and require the use of expensive resolving agents. The variations on the process described in this patent are shown in Scheme 1. One route to **5** involves the initial formation of the chloro-amino ester **1b** by chlorination of **1a** using $SOCl_2$. **1b** can then be converted to the chloro-amino acid **4** directly or via the pyrrolidinone **3**. Dehydrochlorination and cyclisation of **4** gives **6** which on treatment with $(BOC)_2O$ gives the amino-protected product **5**. These steps all proceed with retention of configuration, but an alternative approach to **4** is from **3** that is prepared from **2** by chlorination with inversion of configuration in the preparation of **3** from **2**. The patent also describes a number of methods for the recrystallisation of **5** from a range of solvents, and the ee for the purified product exceeded 99.9%. ^1H and ^{13}C NMR data are given for all compounds indicated in Scheme 1.

Scheme 1



(a) 1. $SOCl_2$/dioxane, rt; 2. Pyridine, 50 °C
(b) 1. H_2SO_4/H_2O, 80 - 90 °C; 2. IER (H^+); 3. Aq NH_3,
(c) 1. $CHCl_3$/aq $NaHCO_3$; 2. extract with $CHCl_3$; 3. distil off solvent
(d) 1. 30% NaOH, 2. $Ba(OH)_2$, 3. 6M HCl, 4. IER (H^+), 5. Aq NH_3
(e) $Na_2CO_3/(BOC)_2O$

Published on Web 04/22/2005
10.1021/op050055r CCC: $30.25

Advantages

The process is said to be more suitable for large-scale production than alternatives.

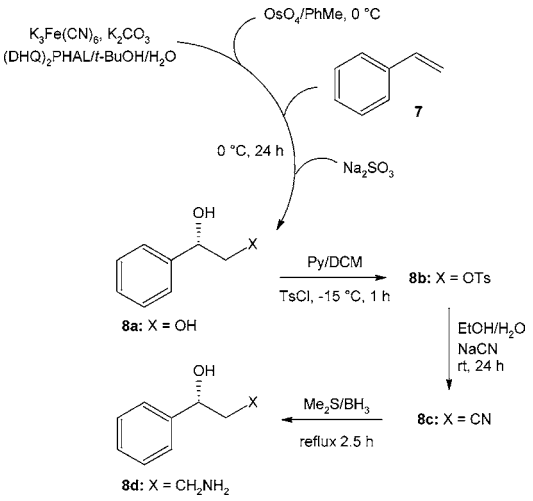
Patent No. 6,838,581

Assignee: Council of Scientific and Industrial Research, New Delhi, India

Title or Subject: Process for the Preparation of Enantiomerically Pure 3-Phenyl-3-Hydroxypropylamine

The title compound **8d** is used to prepare a variety of anti-depressant drugs such as fluoxetine, tomoxetine, or nisoxetine. Alternative methods for the synthesis of **8d** are described in the patent but are said to suffer from many drawbacks such as multistep synthesis, the use of expensive reagents, and the need for complex procedures. The method used in this patent employs a variation of the Sharpless asymmetric dihydroxylation procedure and starts from styrene **7** that is readily available (Scheme 2). The ee of the initial dihydroxy compound **8a** is >97%. The subsequent monotosylation to give **8b** is said to be selective although none of the examples quote yields. Also omitted from the examples are the actual quantities of reagents used. The patent also describes the steps used for the purification of the intermediates by extraction or column chromatographic methods. There are a number of examples that describe the use of different chiral reagents in the Sharpless procedure. In addition the process is used to make to the *S*-enantiomers of **8a**−**d**.

Scheme 2



Advantages

On the face of it the process provides an improved route to **8d** using a very cheap starting material. However, it cannot be said to be very attractive from an environmental viewpoint since it uses a number of reagents, such as DCM and $Me_2S{\cdot}BH_3$, that are not usually considered if cleaner processes are desired.

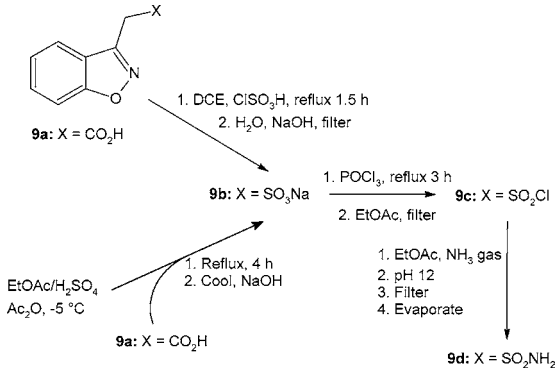
Patent No. U.S. 6,841,683

Assignee: Teva Pharmaceutical Industries Ltd, Petah Tiqva, Israel

Title or Subject: Novel Sulphonation Method of a Zonisamide Intermediate and Its Novel Crystal Forms

Zonisamide **9d** is used as an anti-epileptic agent that has anti-convulsant and anti-neurotoxic effects. Of the three commonly used methods for preparing **9d**, two use $ClSO_3H$ to introduce the sulphonic group. However, it is claimed that the procedures involved are neither convenient nor environmentally safe. This patent discloses a novel improved sulphonation procedure, and it also describes new polymorphic forms of intermediates in the preparation of **9d**. There are two sulphonation methods described, and Scheme 3 shows that these begin with the preparation of the Na salt **9b**. Both routes start from **9a** and in one this is converted to **9b** using Ac_2O and concentrated H_2SO_4. The second method uses $ClSO_3H$ in dichloroethane (DCE); using this solvent makes it difficult to justify the claim that the procedure is environmentally safe. The next stage of the synthesis is the formation of **9c** using $POCl_3$. The final step is treatment of **9c** with NH_3 gas in EtOAc to precipitate **9d**. The patent also describes four novel polymorphs of **9b**, and these are designated Forms I, II, III, and V with no mention being made of Form IV. The patent also describes Ca, Ba salts of some of these polymorphs, and extensive physical data are given for all the polymorphs. It is pointed out that the free acid form **9a** is hygroscopic and hence that the conversion to the Na salt is easier to isolate.

Scheme 3



Advantages

The process is claimed to be more convenient and safer than alternatives and can produce a range of polymorphic intermediates.

Patent No. U.S. 6,841,697

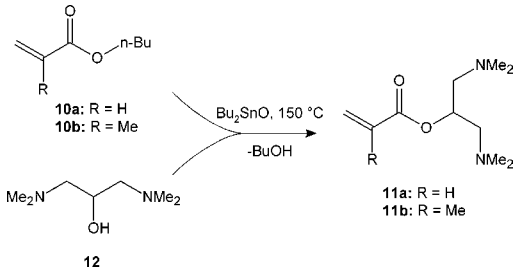
Assignee: Atofina, Puteaux, France

Title or Subject: Process for Preparing 2-(Dimethylamino)-1-(Dimethylaminomethyl)ethyl Acrylate or Methacrylate

This patent describes a transesterification method for preparing **11a** and **11b** using Bu_2SnO catalyst. An alternative

process uses anhydrides of acrylic or methacrylic acids with **12** in the presence of Et_3N, but the reactions produce large quantities of wastes in the form of amine salts. The acrylate **11a** and methacrylate **11b** can be quaternised on one or both N atoms to prepare polymers intended for used as cationic flocculants in water treatment. The transesterification reaction is carried out in the presence of polymerisation inhibitors and is outlined in Scheme 4. The alcohol **12** contains water that is first removed as an azeotrope of **11a** and water. After this step the BuOH formed in the reaction is removed as an azeotrope with **11a**, and the products **11a** or **11b** are obtained in 99% purity by vacuum distillation. Instead of using Bu_2SnO the patent also describes the use of $(BuO)_4Ti$ or $Zr(acac)_2$ which both gave **11a** of a slightly lower purity of 98%.

Scheme 4



Advantages

The process gives improved yields and purity of the products with less waste than alternative methods.

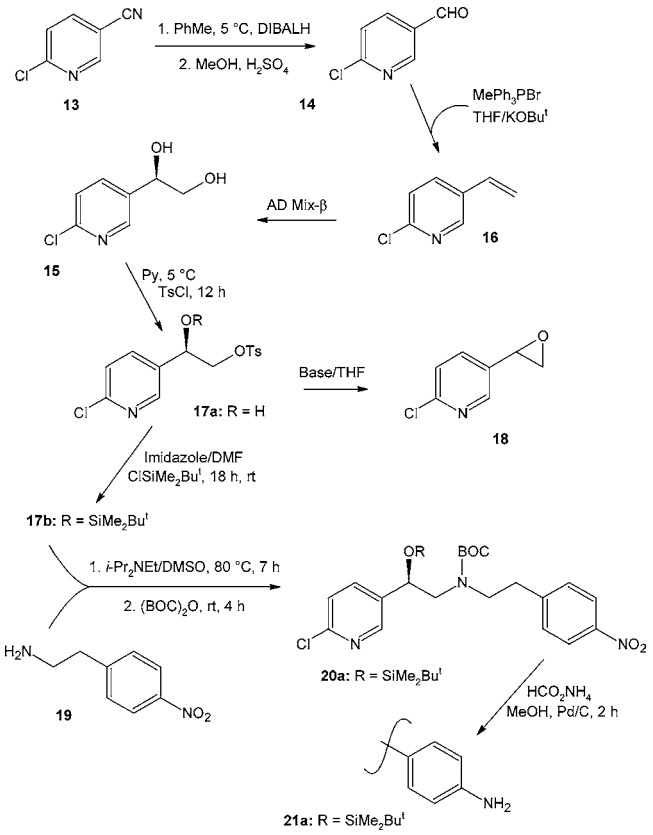
Patent No. U.S. 6,844,441

Assignee: Pfizer Inc., New York, New York, U.S.A.

Title or Subject: Process for Preparing Substituted Pyridines

This patent covers an extensive range of compounds such as **21a** that is an intermediate in the synthesis of hypoglycemic and anti-obesity drugs that are useful in treating patients with diabetes. The patent describes experimental details for a multistep route to prepare **21a**, and this is shown in Scheme 5. There is also reference to related compounds such as the free amine formed from **21a** and the hydroxyl compound **20b** (R = H). However, no experimental details related to these compounds are given, and they may be the subject matter of other patents. There is also mentioned, almost in passing, the interesting looking compound **18** that is said to be prepared from **17a** by treatment with a non-nucleophilic base. The stereochemistry of the products is ensured by the use of the asymmetric dihydroxylation reaction to convert **16** to **15** using the Sharpless reaction. However, the actual yield and optical purity obtained in this step are not disclosed.

Scheme 5



The patent covers a great number of alternative intermediates in the overall route, and this summary has only scratched the surface. Brief NMR data are given for most of the compounds mentioned in Scheme 5.

Advantages

The compounds disclosed in the patent are novel and are claimed to have pharmaceutical applications.

Patent No. U.S. 6,844,464

Assignee: Ube Industries, Ube, Japan

Title or Subject: Process for Producing Alkyl Nitrite

The patent describes a method of making alkyl nitrites that can be used as part of a catalyst system in the production of dialkyl oxalates or carbonates. The process to prepare oxalates is outlined in eq 1 and was first described and commercialised by Ube over 25 years ago. The nitrites are used in a redox cycle to regenerate the catalysts.

Equation 1

$$2MeOH + 2CO + 0.5O_2 \xrightarrow{Pd/HNO_3} (MeCO_2)_2 + H_2O$$

The examples in the patent use MeOH with NO gas in aqueous HNO_3 in the presence of metal nitrate catalysts. The catalysts are group VIII metals, excluding platinum group metals, plus a group IB metal such as $Cu(NO_3)_2$. Examples of group VIII catalysts are nitrates of Ni, Co, and Fe. The exclusion of platinum group metals is to avoid interference with earlier patents in this area that use Pd catalysts.

The production of alkyl nitrites by the reaction of NO with alcohols is not new, but it is claimed that alternative processes use gaseous mixtures containing O_2. Hence, the NO is oxidised to give NO_2, and the overall yield of nitrite is reduced.

The new process is carried out in a column reactor in which the solution of alcohol, HNO_3, and catalysts flows downwards to meet NO gas flowing upwards. Recycling of the liquid and gas flows is used to ensure a high conversion process. To achieve efficient mass transfer in the system the column contains packing such as Raschig rings. Although the process is primarily aimed at large-scale continuous production, the chemistry may be applicable to other dialkyl nitrites.

Advantages

The process is useful for treating streams containing low concentrations of nitric acid so that by-product streams can be used.

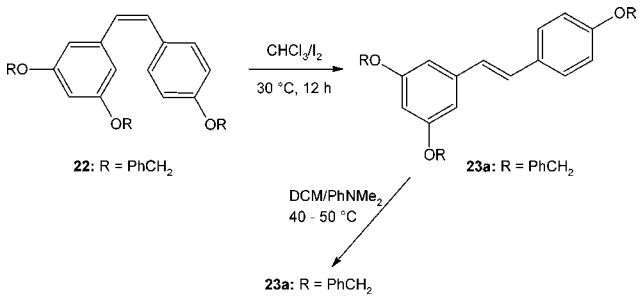
Patent No. U.S. 6,844,471

Assignee: Orchid Chemicals and Pharmaceuticals Limited, Tamilnadu, India

Title or Subject: Method for the Conversion of a Z-Isomer of Phenylethylenes into the E-Isomer

The E-isomer **23a** is used to prepare *E*-resveratrol **23b** (R = H) that is an anti-oxidant and has been used to treat and prevent various cancers. The beneficial effects of drinking red wine are ascribed to the fact that *E*-resveratrol is found in grape skins. Commercial processes for making **23b** are said to give both isomers; hence, a separation step is needed to improve the atom efficiency and reduce process costs. Scheme 6 shows the new route used to convert **22** to **23a** in 90% yield. In the second step **23b** is obtained by stirring a mixture of **23a** and I_2 in $CHCl_3$ at about 30 °C for 12 h. After quenching with $Na_2S_2O_7$ the product is obtained containing no *Z*-isomer. One of the alternative processes for the conversion uses photochemical irradiation in the presence of diaryl sulphides. These are said to produce bad smells and are not environmentally acceptable. However, the use of chlorinated solvents can hardly be said to be a good example of green chemistry.

Scheme 6



Advantages

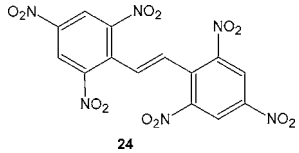
The process is claimed to give higher yields of product without the need to use expensive reagents or photochemical methods.

Patent No. U.S. 6,844,473

Assignee: BWXT Pantex, L. L. C., Amarillo, Texas, U.S.A.

Title or Subject: Continuous Aspiration Process for Manufacture of Ultra-Fine Particle HNS

HNS **24** is a heat-resistant explosive commonly used in deep-well charges in oil fields. The particle size of the material is very important, and for some unspecified reason uses a surface area >10 m^2/g as well as a low residual solvent content. The patent describes four attempts to prepare the appropriate material, and these are described as concepts. In three of these **24** is dissolved in boiling MeCN, and the solution is either drawn by vacuum or pushed by air through a vessel containing cold water. The crystals are formed as the slurry mixes with the water. Suitably sized crystals may be formed this way, but an improved process involves the use of *N*-methylpyrrolidone solvent. By this method the crystalline product obtained had a surface area >38−43 m^2/g and had a purity of >98% with < 0.1% solvent. This process is somewhat similar to one reviewed previously in which atomisation of impinging jets was used to obtain small particles (*Org. Process Res. Dev.* **2000**, *4*, 450).



24

Advantages

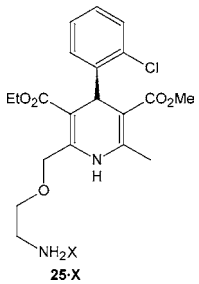
The process easily allows the production of high-purity product with the desired crystal size.

Patent No. U.S. 6,846,932

Assignee: Council of Scientific and Industrial Research, New Delhi, India

Title or Subject: Process for Preparation of Chiral Amlodipine Salts

This is the first of two patents covering the preparation of **25** that is a calcium channel blocker used to treat hypertension and angina. This patent describes a method of resolving a mixture of the two enantiomers of **25** and allows the production of each form separately. Alternative resolution processes are said to require expensive resolving reagents and require the isolation of the free base. The new method relies on the formation of tartrate salts by using either L- or D-tartaric acid (TTA). The procedure involves adding the TTA to a solution of the racemic mixture of **25** in DMSO. The tartrate salt is then filtered off and treated with $PhCH_2SO_3H$ to give the pure benzyl sulphonate salt of **25**.



25·X

Advantages

The process provides a means of obtaining the pure enantiomer salts without the need to isolate the free base.

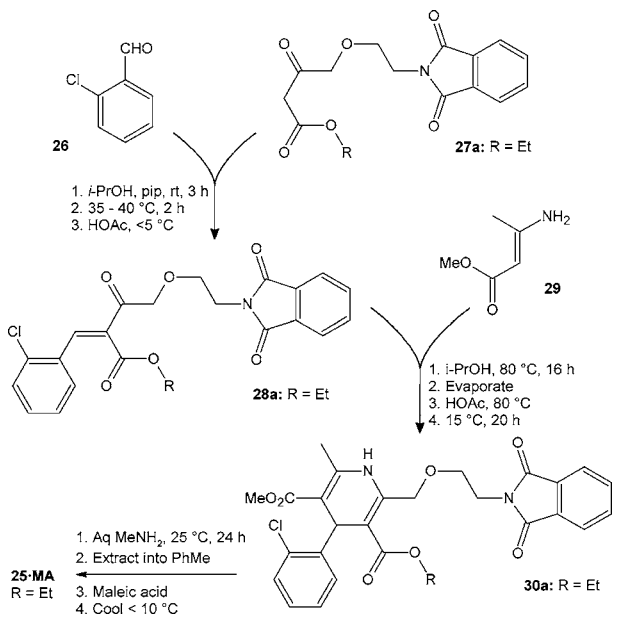
Patent No. U.S. 6,858,738

Assignee: Synthon BV, Nijmegen, Netherlands

Title or Subject: Process for Making Precursors for and Derivatives of Amlodipine

The second patent covering **25** provides a new synthetic route to **25** and also describes the preparation of precursors to **25** plus some of its derivatives. Some of the routes to **25** summarised in the patent are said to give low yield and low product purity; hence, this process is aimed at improving these deficiencies. The first aspect of the patent is the preparation of **28a** by condensation of **26** with **27a** in the presence of piperidine (pip). The phthalimide moiety in **27a** is used as a means of protecting the amine group throughout the whole sequence. The reaction to form **28a** produces a mixture of *Z*- and *E*-isomers in the ratio of 6:4, and in the next step **28a** is reacted with the aminocrotonate **29**. This reaction results in a cyclisation producing the dihydropyridine derivative **30a** that is referred to as phthalimidoamlodipine in the patent. This reaction is an important aspect of the patent and is claimed to reduce side products in forming **30a** when compared to alternative methods, and a single recrystallisation gives **30a** in >98% purity. Deprotection of the amino group in **30a** is then carried out followed by treatment with maleic acid to give the maleate salt **25**·MA.

Scheme 7



The patent also describes a number of other derivatives and intermediates in which R in **27**, **28**, and **30** is Me or *i*-Pr. It is pointed out that where the alkyl group R is different from the alcohol reaction solvent then there is the possibility of transesterification reactions taking place.

Advantages

The process discloses a novel starting material for producing the desired product, and this gives a higher yield and purity than alternative processes.

Patent No. U.S. 6,846,946

Assignee: Value Recovery Inc., Bridgeport, New Jersey, U.S.A.

Title or Subject: Process for Improving the Quality of Non-Product Streams in Organic Synthesis Using Phase Transfer Catalysis

This wide-ranging patent is aimed at preparing organic products from waste or by-product liquid streams. It is a classic end-of-pipe solution to waste treatment and is of potential interest to many chemicals producers. The process is carried out by using phase transfer catalysts (PTCs) to transfer low concentrations of species from the aqueous phase to organic phase or to the interface where reaction can occur. The overall process consists of a number of distinct steps, and the detail of each will vary with the type of reaction being carried out. A key feature is a reactor where good contact is provided for the aqueous stream, the organic phase, and the PTC. The next stage is phase separation from which the cleaned aqueous raffinate is discarded and the organic phase collected. Solvent is recovered from the organic phase and the desired product obtained while the PTC is recycled for further use.

There are a large number of examples included in the patent that use a variety of commercially available PTCs, and the following are a small selection:

1. $PhCH_2CN$ from $PhCH_2Cl$ and an aqueous stream containing NaCN, NaI, and NaOH

2. $PhCO_2CH_2Ph$ from $PhCO_2H$ and a stream containing NaOH and Na 4-hydroxybenzoate

3. PhO-allyl from allyl bromide and a stream containing PhOH and NaOH

4. *n*-$PrNO_2$ from *n*-*P*rBr and a stream containing $NaNO_2$ and K_2CO_3

The above reactions were carried out using synthetically prepared streams, but there is one that uses authentic waste stream from a resorcinol production plant. This contained various phenols and was used to prepare PhO-allyl from allyl bromide.

Advantages

This procedure is undoubtedly good environmental practice and could have wide potential applications. How such a patent is policed is another question.

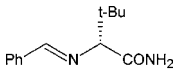
Patent No. U.S. 6,846,955

Assignee: DSM N. V., Heerlen, Netherlands

Title or Subject: Process for Racemising an Enantiomeric-Enriched Schiff Base of an Amino Acid Amide

This patent describes a method of racemising compounds that are often obtained as by-products in cleavage reactions in which the other enantiomer is required. The process uses a strong base that is chemically reactive towards water, and the reaction is actually carried out in an organic solvent to avoid decomposition of the base. It is claimed that processes that use bases such as KOH or quaternary ammonium salts

that are water soluble are ineffective or that the reactions are very slow. The specific Schiff base that is the subject of the patent is exemplified by **31**. The procedure involves mixing the enantiomerically pure **31** and $KOBu^t$ in a solvent and refluxing the suspension. Using THF the ee of the mixture fell from 95.6% to 37.2% after 4 h, with PhMe it fell to 1.8% after 3 h, and in anisole it fell to 10.0% after 3 h. Experiments were also carried out using NaOEt in EtOH (ee = 4.6%, 3 h) and NaOMe in PhMe (ee = 3.5% 7.3 h). By comparison when KOH in anisole was used, there was little racemisation, and the ee was still 92.6% after 3 h. The process can be applied to racemisation of primary amino acid amides by first converting to the Schiff base using benzaldehyde.



31

Advantages

The process provides a relatively fast racemisation method using strong bases without problems of decomposition of the base.

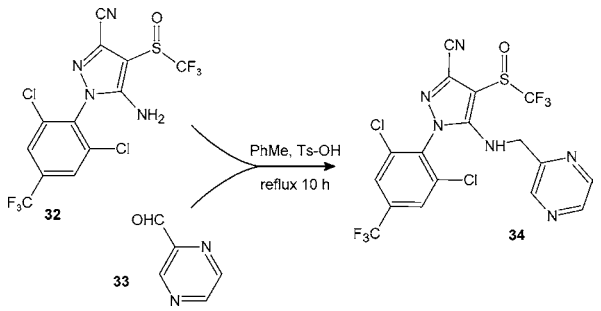
Patent No. U.S. 6,849,633

Assignee: Nihon Nohyaku Co. Ltd., Tokyo, Japan

Title or Subject: Process for the Production of Pyrazole Derivatives Used as the Active Ingredient in Pest Control Agents

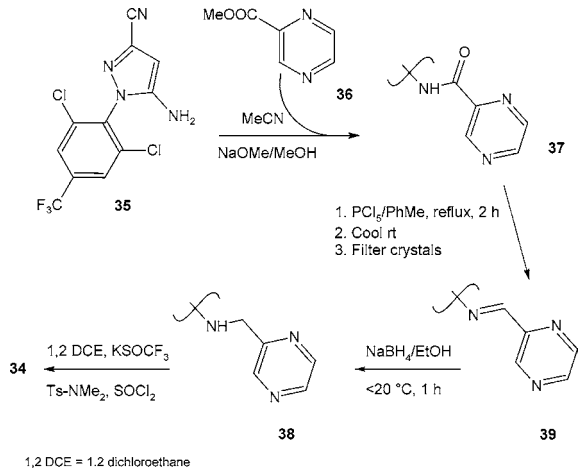
This patent covers a vast range of novel pyrazole derivatives such as **34** that have high insecticidal activity and yet show low toxicity to fishes. Other pyrazole compounds that have insecticidal activity have been reported, and methods for their synthesis are reviewed. The toxicity of some of the alternatives is too high, and it is said that this is one reason for preparing new types with lower toxicity. The key to the high activity and low toxicity is said to be the presence of an amino group containing a pyrazine derivative at the 5-position of the pyrazole ring. Scheme 8 shows one method for making **34** by condensation of the pyrazine **33** with **32** in the presence of Ts-OH.

Scheme 8



An alternative method of making **34** is shown in Scheme 9, and this starts by reacting **35** with the pyrazine ester **36** in the presence of NaOMe to give the carboxamide **37**. Treatment of **37** with PCl_5 produces the imine **39**, and this is reduced to the amine **38** using $NaBH_4$. Finally reaction of **38** with $KSOCF_3$ produces **34**. By using CF_3SCl in this last step the sulphide group CF_3S- can be introduced into the pyrazole ring in place of the $CF_3S(O)$- group. The patent also contains examples of introducing other S-containing substituents at the 4-position on the pyrazole ring.

Scheme 9



As well as describing methods for the synthesis of the various compounds the patent also provides details of testing for insecticidal activity against a variety of pests.

Advantages

Several of the compounds disclosed in this patent are novel materials and are useful pest control agents that have reduced toxicity compared to alternatives.

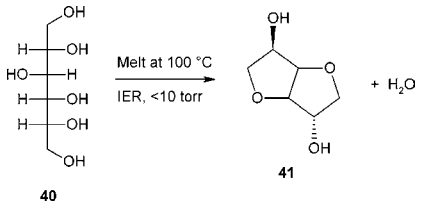
Patent No. U.S. 6,849,748

Assignee: Archer-Daniels-Midland Company, Decatur, Illinois, U.S.A.

Title or Subject: Process for the Production of Anhydrosugar Alcohols

The use of natural materials that are regenerable or renewable to produce industrial products is of great interest. This patent describes a process to obtain **41** from sugar alcohols without the use of organic solvents. **41** can be used to prepare plastic and polymer products as well as pharmaceutical compounds. There are processes available for the production of **41** from sugar alcohols, but they are said to involve the use of concentrated acids and extraction with organic solvents. The method disclosed in this patent involves melting the sugar alcohol and then using an ion-exchange resin (IER) as a dehydrating agent. The final product is then purified by conventional techniques. The starting material for the process is preferably sorbitol **40** although other sugar alcohols are also mentioned. The procedure is to melt the sugar under a high vacuum, add the IER, and remove the water. After the removal of water the product is vacuum distilled, further purified by melt crystallisation at 65 °C, and finally centrifuged at 35 °C to obtain **41** in 48% yield at 99.3% purity. The IERs used are strong acid types that are commercially available.

Scheme 10



Advantages

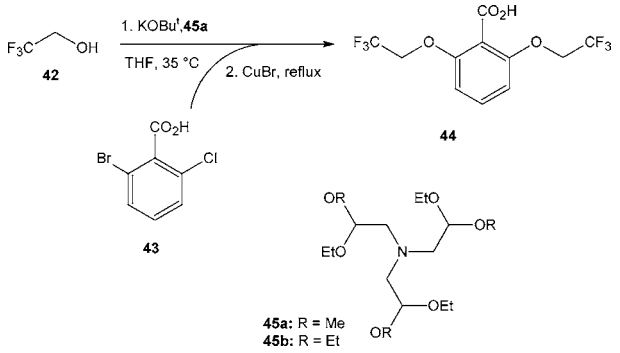
The process achieves a high purity product without the use of organic solvents.

Patent No. U.S. 6,849,762

Assignee: Merck Patent GmbH, Darmstadt, Germany
Title or Subject: Process for Preparing a Trifluoroethoxy-Substituted Benzoic Acid

The title compounds such as **44** are useful in preparing medicaments, and **44** is an intermediate in the preparation of flecainide acetate, an anti-arrhythmic. There are a number of processes known for preparing **44** that are summarised and said to be expensive because of the raw materials needed or because they require several stages. It has been found that halogenated benzoic acids such as **43** can be efficiently converted to **44** by reaction directly with **42** in the presence of a strong base and a copper salt (Scheme 11). The strong base used is KOBu^t with or without a PTC. The PTC used in the example is **45a**, and its use gives a better yield than KOBu^t on its own although the patent does claim that **45b** is preferable. The use of THF as solvent is said to simplify the work-up since the product is soluble in the solvent, whereas the copper salt and by-products are not. After the reaction the mixture is washed in dilute HCl and extracted. The crude **44** is purified by crystallisation and is obtained in 68% yield when a PTC is used compared with 45% yield without any PTC. In both cases the purity of **44** is above 98%.

Scheme 11



Advantages

The use of PTC and THF improves product recovery and purification, while the low reaction temperature reduces by-product formation when compared with alternative processes.

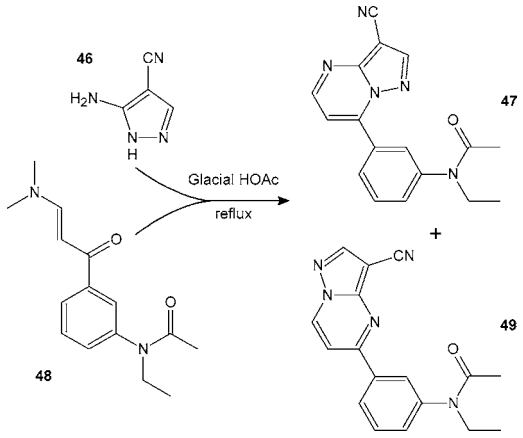
Patent No. U.S. 6,852,858

Assignee: Biogal Gyogyszergyar Rt., Debrecen, Hungary
Title or Subject: Process for Purifying Zalepon and for the Preparation of Novel Crystalline Polymorphs

Zalepon **47** is a sedative, hypnotic and muscle relaxant for use in the short-term treatment of insomnia. This patent describes four new polymorphs of **47** and a method for the purification of all five forms.

The standard preparation of **47** is by reaction of **46** and **48** in refluxing HOAc (Scheme 12). This also produces a regioisomer **49** although it is stated that the original patent disclosing **47** did not mention formation of **49**. The current patent states that **49** is an impurity that can be used as a reference standard in the analysis of **47**. However, the presence of **49** is undesirable and yet can be found at levels of up to 0.5% in **47**. This patent describes a process that can reduce the amount of **49** in **47** by precipitation of **47** from the reaction mixture while leaving impurities in the solution.

Scheme 12



In the improved process the reaction is carried out in a mixture of aqueous H_3PO_4 and EtOH, and after refluxing for 8 h the mixture is cooled to obtain crude **47** mixed with **49**. The crude solids are dissolved in a refluxing solvent and then cooled to 6 °C for 1 day. A wide range of solvents was used with data for MeOH, MeCN, Me2CO, THF, EtOAc, and PhMe. After collection and drying the purity of the crystals of **47** by HPLC were >99.5%, and the amount of **49** was <0.15%. The crystals were also obtained by addition of an anti-solvent with hexane or water being given as examples. The patent also describes methods for the preparation and interconversion of the four new forms of **47** by refluxing in solvents and crystallisation methods. There are detailed ^{1}H and ^{13}C NMR data for **49** and the polymorphs of **47** as well as X-ray diffraction data. A method for preparing **49** is provided that involves refluxing **46** and **48** in concentrated HCl.

Advantages

This process gives a higher-purity product than the alternative procedure and also provides a novel method of preparing pure forms of the regioisomer **49**.

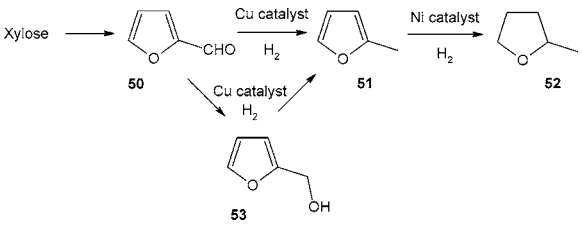
Patent No. U.S. 6,852,868

Assignee: Pure Energy Corporation, Paramus, New Jersey, U.S.A.

Title or Subject: Processes for the Preparation of 2-Methylfuran and 2-Methyltetrahydrofuran

The two compounds **51** and **52** are useful solvents and synthetic intermediates; in addition it is said that **52** is useful as a fuel additive for clean-burning fuels. Both compounds may be made by hydrogenation of furfural **50** that itself can be obtained from various natural sources such as xylose sugars. The hydrogenation of **50** can be carried out in either the vapour or liquid phases, and each method has advantages and disadvantages. The process described in this patent is a vapour-phase process using commercially available catalysts in a two-stage process at atmospheric pressure. The first stage uses a reduced Cu-based catalyst at about 175 °C, and the second stage uses a reduced Ni-based catalyst at about 125 to 155 °C, depending on the product needed. Scheme 13 shows the route from the xylose to **51** and **52** plus **53**.

Scheme 13



By adjusting the temperatures and reactor throughput, the amounts of each compound can be varied. There are also by-products that can form such as straight-chain C5 compounds, and these are controlled by carefully monitoring the reaction conditions. The products are generally separated and purified by fractional distillation. From my own experience an important feature of this process is likely to be the careful reduction of the catalysts before use. One aspect not addressed in the patent is deactivation or poisoning of the catalyst. It is stated that the Cu-based catalyst is not particularly susceptible to traces of S and Cl residues, but if this is the case then it is very unusual and contrary to my experience.

Advantages

The process gives good yields of products and can be controlled to achieve the desired product mix. Being operated at atmospheric pressure, it is less expensive than other vapour-phase processes.

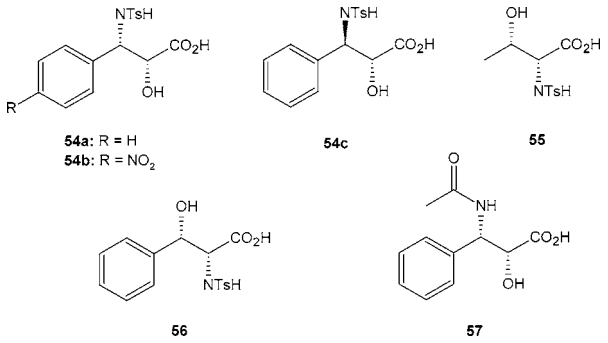
Patent No. U.S. 6,852,874

Assignee: The Scripps Institute, La Jolla, California, U.S.A.

Title or Subject: Second Cycle Asymmetric Dihydroxylation Reaction

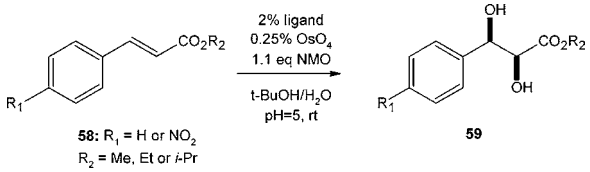
This patent is from the Sharpless group that developed this important method for producing diols from olefinic compounds. It is generally accepted that the asymmetric dihydroxylation (AD) process has two catalytic cycles, and either can dominate, depending on the reaction conditions. The second cycle normally results in lower enantioselectivity, and conditions are chosen so that this is normally avoided. However, the patent states that it does open new opportunities for developing new catalytic processes via the second cycle route. To do this the ligands need to have the specific properties. The patent describes chiral bidentate ligands such as **54**−**57** that favour second-cycle AD reactions.

AD Ligands



These ligands were used in the AD reaction of cinnamate esters such as **58** to give the diol **59** as shown in Scheme 14. The most effective ligand described was **55**, and this gave an ee of only 70% of the *2R,3S* diol from **58** (R_1 = NO_2, R_2 = Me). Although this may ee appear low, it is considerably higher than that normally found in second-cycle AD reactions.

Scheme 14



It is revealed that free carboxylate groups in the ligand are essential, and only racemic diols were obtained if the methyl ester of ligand **54a** was used. It is also disclosed that the position of the OH and TsNH group is important. Thus, the ligand **54a** gave a higher ee than **56**. Other substituents such as RSO_2NH had only a minor effect on the stereochemical outcome. The presence of an *N*-sulphonyl moiety is preferable since replacement by an amide as in **57** or a carbamate gave little or no enantioselectivety.

Advantages

This patent discloses a novel improvement to the well-known reaction that has potential significant applications.

Patent No. U.S. 6,852,890

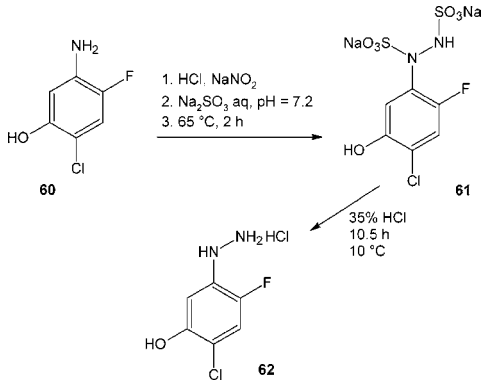
Assignee: Sumitomo Chemical Company Limited

Title or Subject: Process for the Preparation of Phenylhydrazines

The compounds such as **62** are useful in the synthesis of a range of pyridazine-3-one compounds that are used as herbicides. One method of producing phenylhydrazines is the diazotisation of anilines followed by reduction with $SnCl_2$. However, it is claimed that this process has problems due to low filtration rates resulting from the presence of insoluble Sn salts. An objective of the patent is to devise a method of making **62** that does not involve using metal-reducing agents. The new route is shown in Scheme 15 and

involves the production of a disulphonate compound that is decomposed to give the hydrazine. The diazonium salt is formed as normal, and then this treated with Na_2SO_3 to form the disodium salt **61**. Acidification of this gives the HCl salt of **62** in yields >85%. This can be recovered by filtration.

Scheme 15



Alternative sulphonation reagents are used such as HSO_3 salts of Na, NH_4, or K.

Advantages

This process does not require the use of Sn compounds and gives a more efficient method of making the hydrazines.

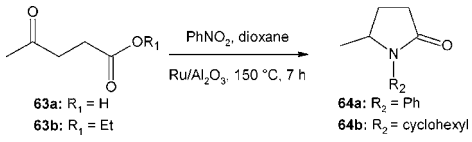
Patent No. U.S. 6,855,731

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

Title or Subject: Production of 5-Methyl-N-Substituted-Pyrrolidones by Reductive Amination of Levulinic Acid Esters with Nitro Compounds

Levulinic acid **63a** is produced by hydrolysis of hexose acid and can be obtained from cellulose feedstocks that are a readily available natural resource. **63** is a starting material for a range of five-carbon compounds, and this patent describes a process for preparing a range of substituted pyrrolidones **64a** and **64b** from **63a** or its esters such as **63b**. The pyrrolidones have a very wide range of uses, and the patent contains some of these such as in cleaning compositions, disinfectants, and automotive paint finishes. The process to make **64a** and **64b** is shown in Scheme 16 and is carried out by heating a mixture of **63b** with a nitrocompound such as $PhNO_2$ in dioxane in the presence of a catalyst. A variety of group VIII metals catalysts is used that are supported on alumina, silica, or C. When using an aryl nitrocompound, there is hydrogenation of the aryl ring so that cyclohexyl derivatives such as **64b** are formed. The reaction can also be applied to producing alkyl derivatives if an nitroalkane is used, and $PrNO_2$ is an example.

Scheme 16



The relative amounts of **64a** and **64b** vary with the catalysts and the reaction conditions. The two compounds are probably easily separable by distillation, but this is not discussed. This process is similar to a very early method (1907) for converting a mixture of **63a** and $PhNO_2$ to **64a** using electrolytic reduction. Other methods of making **64a** and **64b** involve reactions of **63a** with volatile primary amines, and these methods are said to be inefficient and costly on a commercial scale.

Advantages

The process provides an efficient low-cost method using naturally available raw materials.

Patent No. U.S. 6,858,414

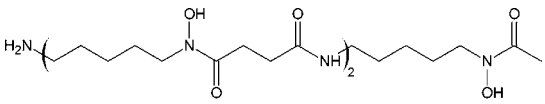
Assignee: Biogal Gyogyszergyar Rt., Debrecen, Hungary

Title or Subject: Multistage Process for Preparing Highly Pure Deferoxamine B Mesylate Salt

The subject of this patent **65** is a polyhydroxamate iron chelator that is used for reducing the Fe concentration in human blood. This patent describes a method of purifying the crude material that has been synthesised by fermentation processes. The main difficulties with such processes are associated with the large volumes. A problem with **65** is that it is often obtained as a HCl salt, and this involves HCl so that there may be residual Cl ions in the product. Since this is undesirable, the objective of this patent is to remove the need to use HCl. There are three stages to the purification, and these are summarised as follows

1. removal of chemically unrelated impurities by chromatographic adsorption
2. precipitation of **65** as free base to separate it from chloride ions and other polyhydroxamates
3. formation of mesylate salt of **65**

The first stage uses commercial resins, with Amberlite XAD 1180 or Dianion SP207 being preferred. This step is carried out by passing an aqueous solution of **65** through a column of the resin. In the second stage the eluent from stage one is concentrated by evaporation, and then an equal volume of MeCN is added followed by aqueous NH_3 to a pH of 9.8. Further addition of MeCN causes precipitation of **65**, and this is collected by filtration. Treatment of the free-base **65** with $MeSO_3H$ in $EtOH/H_2O$ forms the mesylate salt in 98% purity.



65

Advantages

This process does not require HCl, and hence there is no residual Cl remaining in the final product.

Keith Turner

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E-mail: keith@kappa-tau.co.uk

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