Organic Process Research & Development **2001**, *5*, 350−360

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published between December, 2000, and March, 2001

Summary

The current selection of U.S. Patents produced 23 from a list of 714 that fitted the original criteria. There are several that deal with methods of recovery and purification with some interesting techniques being described. There are good examples of lateral thinking and innovation in development where techniques developed for one industrial sector are applied in another. One of these uses a mixing device that was originally developed in the nuclear industry to extract antibiotic materials. The development of supported homogeneous catalysts has been of interest for many years, and a new approach is described which produces supported catalysts which are soluble polymers and are recovered by using membranes. An alternative synthesis of sildenafil is disclosed which includes some elegant synthetic steps and may provide a real alternative route to that from Pfizer. Supercritical fluids are receiving increased attention, and a hydrogenation in liquid CO_2 is described. As is usually the case there appear to be deliberately misleading chemical names and spelling errors in the patents. The title of a patent is not always very useful, but it usually does say something of the subject matter. One patent that was on the original list was entitled Chemical Process, which all of these patents could claim to be, and another was simply called Process. Both patents were from Zeneca in the UK, and it is surprising that the U.S. Patent Office allowed these titles to stand. In one patent reviewed here the title relates to synthesising pyrrole compounds, but the single claim in the patent is related only to a novel dioxole. This is used in the synthesis of pyrroles, but no mention is made in the claims. This is a good example of why patents are extremely important sources of information that can easily be missed. Scanning titles is useful but much can be missed. As usual the advantages described are those claimed in the patent unless this author has specific knowledge of the subject. No commercial significance should be attached to the selection here, but there are some patents where 100-kilogram-scale experiments are described, so the commercial status of these can be inferred to be advanced.

Patent No. U.S. 6,156,933

Assignee: Degussa-Huls AG, Frankfurt am Main, Germany and Thomas Swan & Co. Ltd., Durham, UK

Title or Subject: Hydrogenation of Organic Compounds under Supercritical Conditions

The use of supercritical fluids as solvents has grown in importance in recent years, and Thomas Swan & Co. in the UK is certainly one of the companies active in the field. This patent describes a continuous method for the hydrogenation of a long list of organic compounds using a fixed bed catalyst. Experimental data are given for cyclohexene, aniline, benzaldehyde, acetophenone, and phenylacetonitrile. These substrates give benzene, nitrobenzene, 1-phenylethanol, and tris-2-phenylethylamine, respectively. The work has been reported in this journal (*Org. Process Res. Dev.* **1998**, *2*, 137). The preferred solvent is CO_2 or propane and the catalysts used were Pd on Deloxan from Degussa with supported Ru also mentioned. The work was carried out at substrate flow rates of up to 60 mL/h in and at a total pressure of 80−240 bar with low H_2/substrate ratios of less than 10:1 with most tests run at 3:1.

The claims also specifically cover the reductive amination of carbonyl compounds and phenols, but no actual examples are provided. The patent mentions that the process can be carried out in two consecutive reactors at different temperatures or using different catalysts. This aspect seems to be specifically directed at reductive amination of carbonyls.

The reluctance to using supercritical fluids often relates to the high pressures that are necessary. However, compared to the widespread use of hydrogenations at up to 250 bar these concerns actually are not comparable. Although continuous operation is not always feasible, this work should urge others to consider supercritical fluids as solvents in future.

Advantages

The continuous-flow process reduces inventory and generally provides higher purity products. The use of low H_2/substrate ratios is advantageous from a safety point of view and may even be outside of the explosive limits when CO_2 is the solvent. This process claims that higher productivity and yields are more possible than in alternative technology.

Patent No. U.S. 6,166,217

Assignee: AlliedSignal Inc., New Jersey, U.S.A.

Title or Subject: Production of N-Carboxyanhydrides That Are Useful Intermediates in the Synthesis of Lisinopril

The drug lisinopril is used to treat hypertension and can be made via intermediates such as the alkoxycarbonyldipeptide **3**. This patent describes a method of producing **3** via the anhydride **2**, and it is compound **2** which is claimed in the patent. The process begins with protection of the amino groups in L-lysine **1a** using benzylchloroformate to give the phenoxycarbonyl **1b** which is then converted to the anhydride **2** with DMF/$SOCl_2$. Treatment of **2** with L-proline in alkaline

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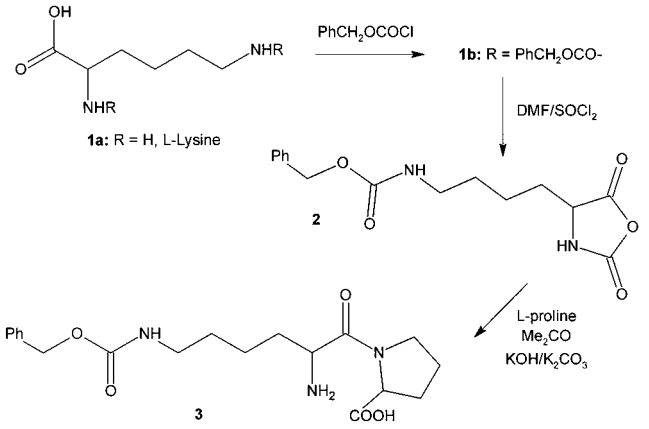
Scheme 1



acetone gave the desired intermediate **3** which was obtained as a solution in butanol in 90% yield (Scheme 1).

Advantages

Other methods of producing analogues of **3,** such as the *tert*-butoxycarbonyl derivative (**1c:** R = *t*-BuOCO−), are claimed to involve complex steps using expensive reagents. This process uses readily accessible and hence cheaper materials.

Patent No. U.S. 6,166,273

Assignee: E. I. du Pont de Nemours and Co., Delaware, U.S.A.

Title or Subject: Fluorination of Aromatic Ring Compounds

Fluoroaromatic compounds are widely used in agrochemicals, and producing them can be quite difficult and expensive. The general subject of this patent is aromatic fluorination, but the only example is the preparation of fluorobenzene from benzene. This is carried out by passing benzene over CuF_2 above 250 °C. During the process the CuF_2 is reduced to Cu metal, and this is reconverted to CuF_2 by passing a mixture of HF and O_2 over the Cu at 400 °C. The regenerated fluoride can then be used for further fluorination. The patent also claims the method is suitable for substituted aromatics including pyridines, but no examples are given.

Advantages

Despite the use of HF and O_2 at 400 °C it is claimed that this process is preferable to the liquid-phase fluorination of diazonium salts with HF. The normal methods of fluorination involve several stages and produce large quantities of aqueous effluent.

Patent No. U.S. 6,171,501

Assignee: Yissum Research Development Company of the University of Jerusalem, Jerusalem, Israel

Title or Subject: Separation of Amino Acids and Their Salts From Aqueous Solutions Using a Solvent Extraction Process

Amino acids are invariably produced in fermentation processes as a dilute aqueous solution. Their separation and purification therefore involve several stages, and these may be up to 20% of the total production costs. This patent describes how technology that has been used for decades for the extraction of metals can be applied to the recovery of amino acids. This involves the use of acid and basic extractants, and the method relies on the zwitterionic nature of amino acids and their ability to act as cations or anions as the pH changes.

The procedure involves the use of a solution of long-chain tertiary amines and an acid dissolved in a mixture of octanol and low-aromatics kerosene. An amine such as tri-octylamine (Henkel's Alamine 336) is used, and the acid is di-2-ethylhexyl phosphoric acid (DEHPA) or lauric acid. This organic solution is mixed counter-currently with the aqueous amino acid solution at a ratio of around 5:1 organic to aqueous. The amino acids and salts are extracted into the organic phase and the impurities are left behind. The organic phase is immiscible with the aqueous phase and is allowed to separate, then it is backwashed with neutral water, and the purified amino acids are recovered from the aqueous solution.

Examples given in the patent cover valine, proline, lysine hydrochloride, betain, and monosodium glutamate.

Advantages

Other methods for extracting amino acids from aqueous solutions can involve several steps and hence are expensive. This method is much more straightforward, and the use of a counter-current extraction method is very efficient and hence economically attractive.

Patent No. U.S. 6,172,221

Assignee: SmithKline Beecham plc, Brentford, UK

Title or Subject: Extraction of β-Lactam Antibiotics Using Vortex Mixers

Like the previous patent this is also concerned with the application of solvent extraction technology that was developed in a totally unrelated area. In this case use is made of vortex mixing devices, which have no moving parts, and were developed for use in the nuclear industry. The patent is concerned with extracting antibiotics such as clavulanic acid (CA) that is produced in dilute aqueous solution.

The process consists of producing a salt of the antibiotic by addition of an amine such as *tert*-butylamine. The aqueous solution of the antibiotic salt is then mixed with a water immiscible solvent such as methyl isobutylketone (MIBK) in a vortex mixer (Figure 1). This type of mixer is very

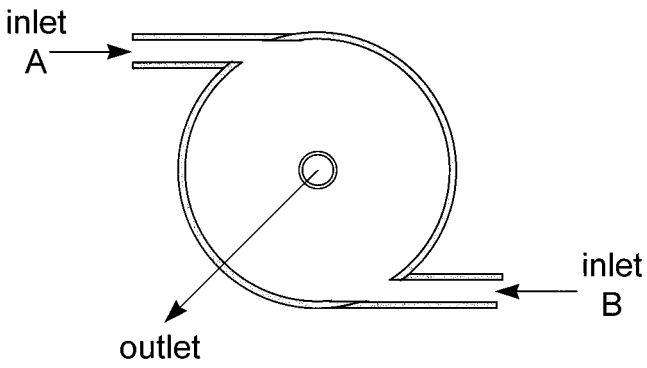


Figure 1. **Vortex mixer used in solvent extraction of antibiotics.**

compact and gives extremely rapid mixing with a high rate of mass transfer. An emulsion is often produced, and hence the two-phase mixture is separated in a centrifugal separator. After recovery of the aqueous solution the antibiotic is obtained from the salt by an appropriate method.

The mixer in Figure 1 works by admitting the solutions tangentially. As they flow towards the centre, they increase in velocity, and intimate contact occurs resulting in rapid mixing. The mixture leaves the centre of the mixer axially. These mixers have no moving parts and hence require no maintenance having been originally developed for use in the nuclear industry at the UK Atomic Energy Authority. The absence of moving parts is also clearly attractive in the food and pharmaceutical industries where cleanliness and sterility are vital. Further applications of these efficient devices are encouraged.

Advantages

The antibiotics are normally produced in dilute aqueous solution and their recovery can involve considerable amounts of large-scale equipment. The vortex mixer allows short residence times and efficient mixing; being of a compact size, they are economical to use.

Patent No. U.S. 6,180,837

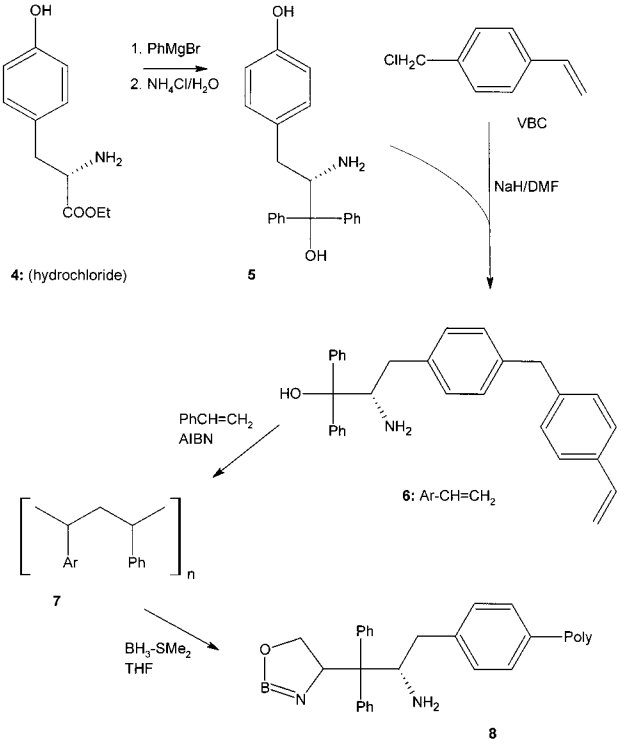
Assignee: Degussa-Huls AG and Forschungzentrum Julich GmbH, Germany

Title or Subject: Enantioselective Reduction of Ketones to Alcohols Using a Homogeneous Catalyst in a Membrane Reactor

Although homogeneous catalysts can be very selective, they suffer from the problem of separating the products and reactants from the catalysts. Since such catalysts are usually expensive, particularly the chiral types, and since they are used in very small amounts, their loss cannot be tolerated. This patent describes an elegant and interesting method of solving the problem. The reduction is carried out using homogeneous chiral oxazaborolidine catalysts such as **8**. These catalysts are soluble in the reaction medium even though they contain ligands with a high molecular weight (>13,500). This high molecular weight means that the catalyst molecule is too large to pass through a membrane that is used to separate it from the products.

The synthesis of the active catalyst is shown in Scheme 2. The monomeric catalyst precursor **6** is produced from the tyrosine ester **4** via the diphenyl tyrosinol **5**. This is carried out by reaction of NaH with **5** to give the sodium phenylate salt followed by treatment with vinyl benzyl chloride (VBC). The vinyl compound **6** is then copolymerised with styrene using AIBN to give the tyrosinol polymer **7**. The polymer **7** was then dissolved in THF and transferred to a reactor cell containing a polypropylene membrane. Treatment of the polymer solution with BH_3-SMe_2 gave the oxazaborolidine catalyst polymer **8**. This was then used in a continuous process to reduce acetophenone to 1-phenylethanol in >90% ee. The patent also claims that **5** may be replaced by diphenyl hydroxyproline and that the polymer **7** may be replaced by a polysiloxane, but no examples are given for either claim.

Scheme 2



Advantages

The use of BH_3-SMe_2 to reduce ketones provides good yields and high ee, but catalyst removal can be problematic. By attaching the catalyst to a polymer and maintaining its solubility gives an efficient separation of catalysts from products while at the same time providing an active catalyst.

Patent No. U.S. 6,180,839

Assignee: BASF AG, Ludwigshafen, Germany

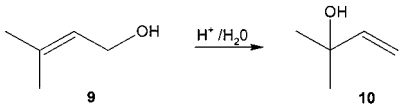
Title or Subject: Continuous Preparation of Dimethylvinylcarbinol by Isomerisation of Prenol

The title compound **10** is used in the manufacture of fragrances and as an additive in soaps and detergents. It is stated that tertiary allylic alcohols such as **10** were previously obtained from the condensation of acetylene ketones. However, the decline in the use of acetylene as a major raw material has meant alternative routes to these compounds are required. Since **9** can be produced from olefin feedstocks, this patent describes a method of preparing **10** by allylic rearrangement of **9** using protic acid catalysts. Allylic rearrangements can produce unwanted side reactions and by-products, and hence this process attempts to overcome these problems.

The process is carried out in a distillation column containing phosphoric acid in a large amount of water. **9** is added to the base of the column where the reaction goes to completion, and **10** is distilled off overhead as an azeotrope with water. The azeotrope is condensed and mixed with cyclohexane where **10** is extracted into the cyclohexane. This solution is then distilled to obtain pure **10** and cyclohexane for recycle to the extraction step. Overall, the conversion of **9** is 100% and over 99% purity, and there is data from 30

examples with flow rates from 120 to 250 mL/h (Scheme 3).

Scheme 3



Advantages

The rearrangement is an equilibrium reaction and hence, on a batch system, will not achieve high conversion without removal of the product. Side reactions are a problem in this reaction, and running continuously has reduced this significantly.

Patent No. U.S. 6,184,004

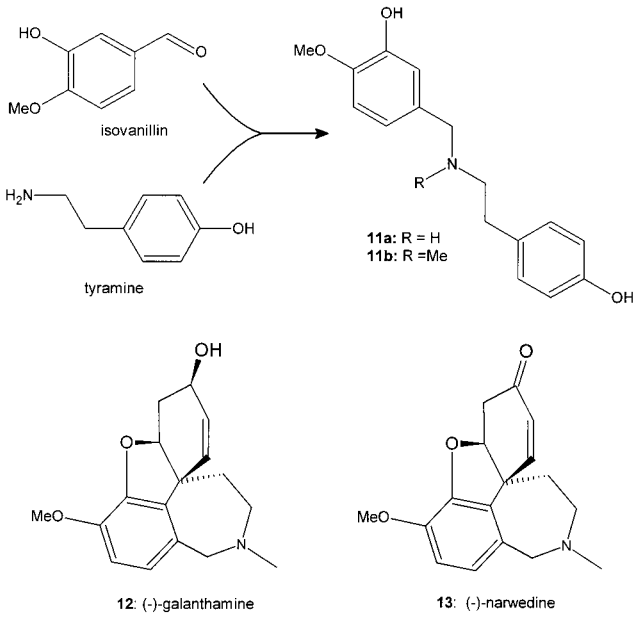
Assignee: Janssen Pharmaceutica N. V., Belgium

Title or Subject: Process for Preparation of Galanthamine and Its Derivatives

There is great interest in galanthamine **12**, narwedine **13**, and their derivatives for the treatment of Alzheimer's disease. Two earlier patents on this subject from Janssen have already been reviewed over the past year (*Org. Process Res Dev.* **2000**, *4*, 246 and 450). **12** can be extracted from the bulbs of snowdrops or daffodils, and there are also synthetic routes. This patent presents a route to **12** and with a modification of an extraction method that improves the yield of product.

It is believed that the biosynthesis of **12** and **13** proceeds via an oxidative cyclisation of the secondary amine **11b** (R = Me). When R = H (**11a**), this step is not favoured, and other products result. It has been found that by adding **11a** to the crushed plant bulbs, before further extraction, 3 times the amount of **12** was recovered when compared to using no **11a**. In view of the biosynthesis information this is claimed to be a surprising result. The patent claims that **11a** is made from isovanillin and tyramine via a reductive alkylation, but no details are provided (Scheme 4).

Scheme 4



Advantages

This process dramatically increases the yield of **12** extracted from plant bulbs and does not require a complex synthetic route.

Patent No. U.S. 6,184,404

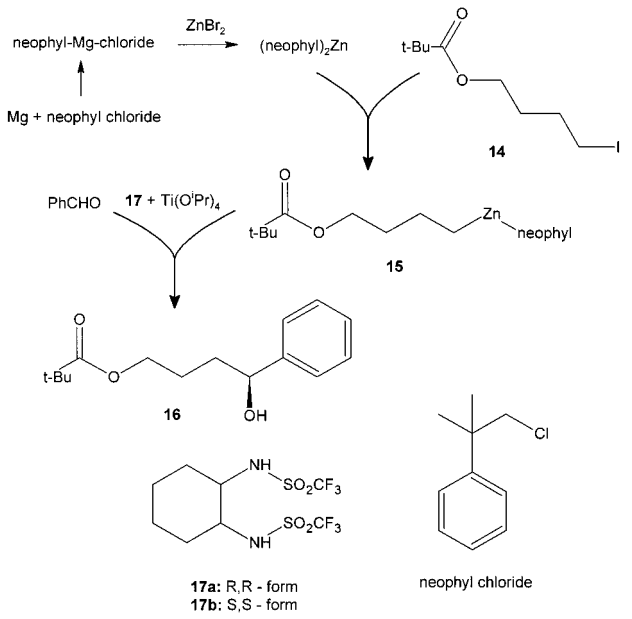
Assignee: Metallgesellschaft AG, Frankfurt am Main, Germany

Title or Subject: Process for the Selective Alkylation of Aldehydes Using Organozinc Compounds

Organozinc compounds are useful for the enantioselective transfer of functional groups from zinc compounds to aldehydes, giving functionalised secondary alcohols. It is possible to transfer only one alkyl group from the Zn if the second group is sterically demanding. This group is termed the dummy group since it takes no part in the reaction, and work elsewhere had suggested that it must contain an Si atom β to the Zn atom such as the trimethylsilylmethyl group. This patent shows that this restriction is not necessary, and much less expensive ligands such as neopentyl or neophyl (2-methyl-2-phenylpropyl) groups are in fact suitable.

Scheme 5 shows the route used to make the organozinc compound **15** which is used to convert benzaldehyde to the

Scheme 5



pivalate **16**. Treatment of neophyl-Mg chloride with $ZnBr_2$ gives dineophyl zinc which on reaction with the iodopivalate **14** produces **15**.

The alkylation of benzaldehyde to give **16** in 82% yield and 89% ee is carried out using a catalyst system consisting of **15**, the chiral ligand **17a or 17b,** and an alkoxy titanium salt. A range of other chiral ligands is also claimed, including 2-naphthol derivatives, but no examples are given. The synthesis of (*S*)-1-phenylethanol in 93% ee from methyl-(neopentyl)zinc is described, indicating that the process can be applied to alkylation of simple as well as functionalised groups. The organozinc compounds described in the patent are all novel compounds and are perhaps the subject of a separate patent.

Advantages

The use of more readily available alkyl groups than substituted silyl groups is an improvement on the previous work. It is claimed that the new process does not require such an excess of the zinc compounds as did earlier methods.

Patent No. U.S. 6,187,932

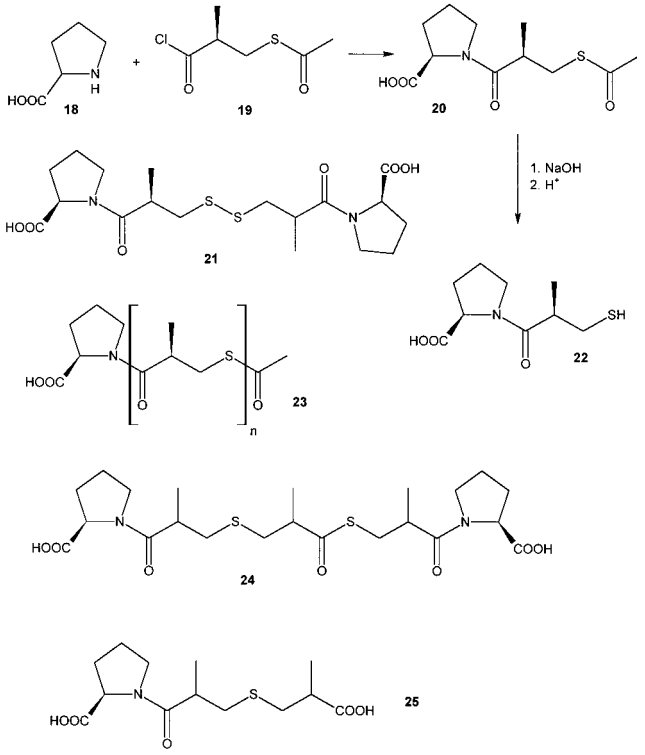
Assignee: Kaneka Corporation, Osaka, Japan

Title or Subject: Simple Process for Producing High Quality Captopril

Captopril **22** is used as an antihypertensive compound and can be made from the proline **20** by treatment with 3 mol of NaOH. However, a problem with this reaction is that the disulphide **21** is produced, and its removal can be very difficult. It is known that **21** is produced by an oxidation reaction, and an inert atmosphere is necessary to suppress this. The complete exclusion of oxygen is needed because 1 mol of O_2 can remove 4 mol of **22** by several different reactions. Hence, this patent describes a method of producing **22** by a process that is not so sensitive to the presence of oxygen.

The patent specifically claims that the conversion of **20** to **22** uses **20** that contains small amounts of either or both impurities **23** and **24**. These are formed during the synthesis of **20** by the Schotten−Baumann reaction of **18** and **19** under basic conditions. The presence of **23** and **24** during this reaction can result in the formation of the proline **25** which cannot be easily removed from **22**. The reason for using impure **20** is not at all clear (Scheme 6).

Scheme 6



Advantages

The advantages claimed are that the process produces better quality products by a simple procedure, but the deliberate use of impure starting materials is unusual. This may be to avoid a problem with other patents, but this is not discussed.

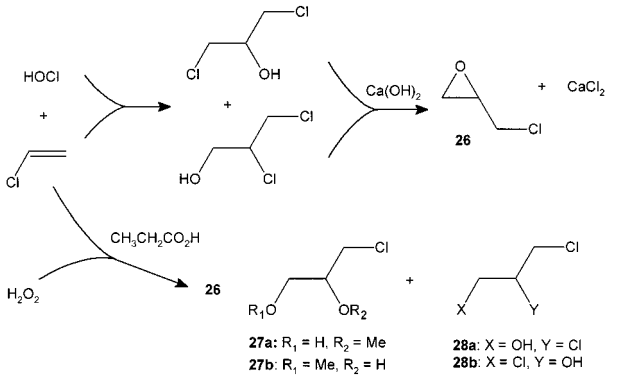
Patent No. U.S. 6,187,935

Assignee: Solvay SA, Brussels, Belgium

Title or Subject: Removal of Water-Soluble By-Products Formed in the Synthesis of Epoxypropanes

The conventional method for the production of the epichlorohydrin **26** from allyl chloride uses a two-stage hydrolysis and produces stoichiometric amounts of $CaCl_2$. Scheme 7 shows the original and new route that uses

Scheme 7



hydrogen peroxide which significantly simplifies the synthesis and produces various water-soluble by-products such as chloromethoxypropanols **27** and dichloropropanols **28**. The presence of these materials in the plant effluent is not acceptable, and this patent describes a method of extracting these materials using xylene or other aromatics.

The epoxidation reaction is carried out in aqueous solution and produces an aqueous portion which is mixed with xylene. The mixture is distilled under vacuum and the overhead product allowed to separate into two phases. The aqueous phase was analysed for the presence of **27** and **28**, and it was found that when the distillation was carried out without addition of xylene the aqueous phase contained around 50 times more of **27** and **28**. This is an example of the use of azeotropic distillation to improve a separation which, in a suitable case such as this one, can be very effective.

Advantages

The improved process of producing epichlorohydrin using H_2O_2 is further improved by this method of removing the by-products **27** and **28** from the plant effluent.

Patent No. U.S. 6,191,148

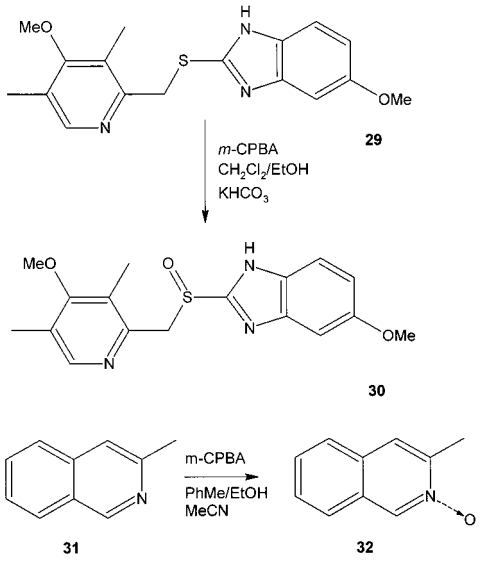
Assignee: Merck & Co., New Jersey, U.S.A.

Title or Subject: Process for the Preparation of Omeprazole

The anti-ulcer agent omeprazole **30** is available as the drugs Losec or Prilosec, and this patent describes a process for its preparation and purification. The last stage in the preparation of **30** is the oxidative conversion of pyrmetazole **29**, and it is improving this step that is covered by the current

patent. The normal process for this step uses *m*-CPBA or other peroxy acids in a mixed-solvent system such as toluene or CH_2Cl_2 and ethanol (Scheme 8).

Scheme 8



Problems claimed for this procedure are the removal of residual solvents and the control of the degree of oxidation. Over and under oxidation are possible, and each gives rise to undesirable impurities. It is claimed that the control of the oxidation is complicated because the method of addition of the *m*-CPBA is important and the *m*-CPBA is not available with an accurately known purity. This means it is difficult to control accurately the amount used.

To overcome one of these problems an accurate method of analysing the purity of *m*-CPBA has been developed. This is based on the formation of an isoquinoline *N*-oxide from **31** in a reaction shown in Scheme 8 that proceeds rapidly and quantitatively. A known excess amount of **31** is reacted with *m*-CPBA, and the remaining **31** is determined by reverse phase HPLC. The accurate assay of *m*-CPBA is then calculated. The method of addition of *m*-CPBA to **29** has been optimised with the *m*-CPBA solution being kept at 0−5 °C and then added subsurface which limits localised over-oxidation. The reaction solution during addition is kept at a temperature of −5 to + 5 °C, and this limits by-product production.

A further improvement in the overall process is in the recovery by employing a reactive crystallisation step. The procedure is to concentrate the solution of crude **30** and add methyl formate or a solution of formic acid, methanol, and water below the surface. The patent suggests that this promotes crystal growth rather than nucleation, and the result is improvement in yield and purity.

Advantages

There are a number of process improvements based on the current process, and if they are effective, they could prove significant in the production of this extremely successful drug.

Patent No. U.S. 6,191,318

Assignee: Korea Research Institute of Chemical Technology

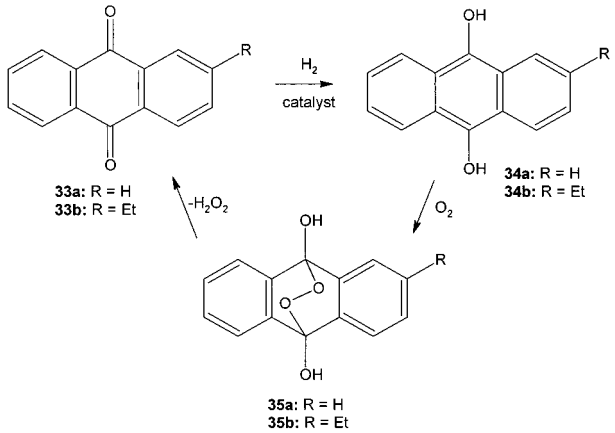
Title or Subject: Process for Preparing Hydroxylated Aromatics Using Hydrogen Peroxide Prepared in Situ from Hydrogen and Oxygen

gen

This patent describes a catalytic process for the production of hydrogen peroxide which can be used in situ to hydroxylate aromatic hydrocarbons. Hydrogen peroxide can be used to convert benzene to phenol, but the cost of H_2O_2 makes the process too expensive, and the direct production of phenol from benzene and oxygen at a commercially attractive rate is a major goal in the chemical industry. Whether this patent provides an acceptable solution remains to be seen.

This process is based on the use of alkylanthraquinones as hydrogen-transfer compounds and as a source of hydrogen peroxide. The process is similar to the commercial manufacture of H_2O_2 in using anthraquinone **33a** in a two-step process shown in Scheme 9. The commercial process in

Scheme 9



Scheme 9 proceeds by catalytic hydrogenation of **33a** to give **34a** which is then undergoes extremely rapid autoxidation to the endoperoxide which decomposes to give **33a** and releases H_2O_2. The current patent follows the same route as Scheme 9 with the ethyl compound **33b** and uses the H_2O_2 to hydroxylate benzene to give phenol.

The process here is a single-step approach with a two-component heterogeneous catalyst system. One catalyst is a Y-zeolite containing 2-ethylanthraquinone and Pd which catalyses the hydrogenation step. The second catalyst is ZSM-5 zeolite containing Ti, and this catalyses the oxidation step. When a mixture of H_2 and O_2 gases is passed through a solution of benzene and acetic acid at 60 °C at atmospheric pressure, phenol was produced in >97% selectivity but with low turnover.

Advantages

If this process can be developed and the turnover number raised, then there is clearly an advantage over current technology.

Patent No. U.S. 6,191,325

Assignee: Rhodia Chimie, Courbevoie Cedex, France

Title or Subject: Recovery of Nitric Acid from Dinitration Process Streams

Nitration of aromatics is an extremely important industrial process, and this patent addresses the problems of the recovery of nitric acid in dinitration processes. These processes usually have two stages, and after the second nitration step, the acid and organic phases are separated. The organic stream usually contains nitric and sulphuric acids as well as the dinitrated aromatics and typically contains <5% nitric acid. The treatment of this stream is the subject of the process described in this patent.

It has been found that distillation or stripping of this stream can be done safely. Conventional wisdom would suggest that such a course is dangerous, but it has been found that this can be done in an evaporator under vacuum or with a carrier gas such as nitrogen and the nitric acid can be distilled overhead or stripped off and recycled. The organic phase is then washed with water containing a base to remove the last traces of acids. Final purification of the nitroaromatics can then be carried out. The resulting wastewater stream can be dealt with more easily and the overall usage of nitric acid is reduced.

Advantages

This procedure significantly reduces the duty of the effluent treatment plant and at the same time recovers nitric acid for reuse in the nitration step.

Patent No. U.S. 6,194,623

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Hydrogenation of Organic Compounds Using the NEMCA Effect

The NEMCA effect is "non-Faraday electrochemical modification of catalytic activity" and is the application of an electrical voltage to a catalyst to alter its activity and selectivity. Electrochemical reduction, theoretically, can be highly selective since the required voltage for a reaction can be precisely chosen. In a mixture of different compounds or a multifunctional compound it should be possible to dial up the voltage for only one compound or group. However, there are still relatively few large-scale commercial applications of electrochemistry.

This patent describes a method of selectively hydrogenating acetylenes to olefins in the presence of olefins using supported Pd catalysts in an electrochemical cell. Although the patent mentions the hydrogenation of dehydrolinalool to linalool as a desirable reaction, the examples are all focused on hydrogenation of acetylene to ethylene

Advantages

Although not of direct interest to readers of this journal there is actually a very large-scale requirement for this. All ethylene crackers around the world do have plants that perform this reaction, and whether this process is commercially viable remains to be seen.

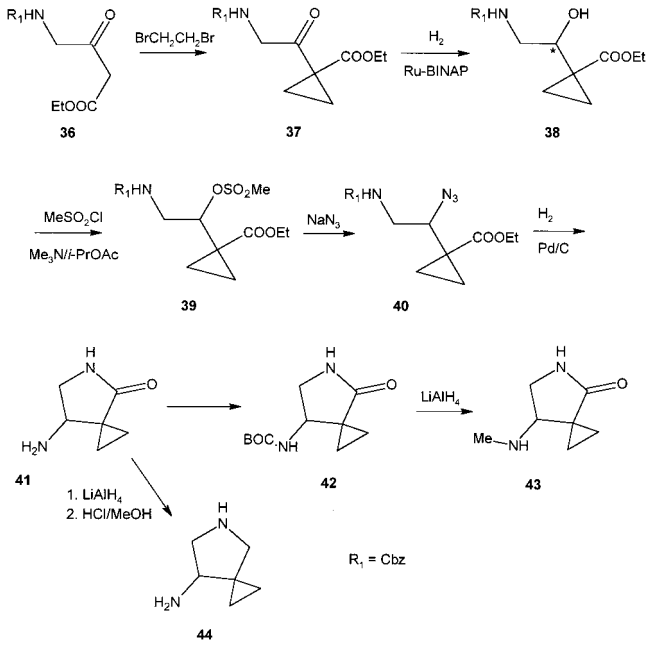
Patent No. U.S. 6,197,974

Assignee: Abbott Laboratories, Illinois, U.S.A.

Title or Subject: Enantioselective Synthesis of 3-Aminopyrrolidines

This patent describes a route for preparing the compounds **43** and **44** which are used as an intermediate for preparing pyrimidine and quinolone antibacterial agents. The route contains what is claimed to be the first enantioselective reduction of a β-hydroxyester **37** to give the chiral alcohol **38** (Scheme 10).

Scheme 10



The patent provides experimental details for all steps in Scheme 10 and starts with the β-ketoester **36** which is obtained from a published method although no experimental details are given in the patent. The conversion of the spirocyclopropane compound **37** to **38** is the key step in the patent, namely the enantioselective reduction using Ru−BINAP in 82% yield with 98% ee. The chiral alcohol **38** is then converted to the azide **40** via **39** by activating the OH group through reaction with mesyl chloride in the presence of Me_3N. When **40** is reduced, the amino-protecting group is removed, and cyclisation also occurs giving **41**. Reduction of **41** with $LiAlH_4$ affords **44** which is isolated as its hydrochloride salt. Alternatively **41** can be converted to the BOC derivative **42** and then similarly reduced to produce the methylamino analogue **43**.

Advantages

Other methods for preparing the title compounds involve production of an optically active tartrate ester which is apparently a less attractive route. The key step here is the enantioselective reduction of **37** to **38** which produces the chiral centre in high yield.

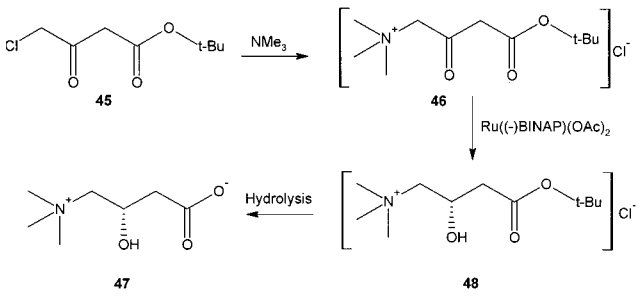
Patent No. U.S. 6,197,996

Assignee: Takasago International Corporation, Tokyo, Japan

Title or Subject: Process for Preparing Optically Active Carnitine Ester

R-Carnitine **47** is present in living tissue and is used as a vitamin supplement in both animal and human use. The *S*-form is reported to be toxic, or at the very least, it can cause depletion of *R*-carnitine in cardiac tissues. Any method of production therefore must eliminate the undesired enantiomer. Other methods employ resolution and Lonza have a process that involves a biological hydroxylation of $Me_3N^+CH_2$-$CH_2CH_2CO_2^-$. The process described here is the catalytic asymmetric hydrogenation of the trimethylammonium salt **46** to produce the *R*-carnitine ester salt **48** (Scheme 11). The

Scheme 11



catalysts used are chiral Ru phosphine catalysts and by using the *S*(−)BINAP ligand the *R*-carnitine is obtained. Examples are also given for producing the *S*-form. The claims of the patent cover a wide range of such Ru catalysts with various chiral phosphine ligands. The ester salt **46** is produced by quaternisation of the chloroacetoacetic ester **45** using Me_3N, but no details are given for this step.

Advantages

This patent claims its advantages are that resolving agents are not used and biological routes involve long complex recovery procedures. This is not necessary because this process starts with the ester **46** which is fairly readily available.

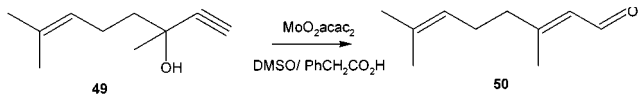
Patent No. U.S. 6,198,006

Assignee: Roche Vitamins Inc., New Jersey, U.S.A.

Title or Subject: Process for the Manufacture of Citral

Citral **50** is used as an intermediate in the manufacture of odorants and vitamins and is usually made by acid-catalyzed rearrangement of α-alkynols such as dehydrolinalool **49** (Scheme 12). This patent describes a process

Scheme 12



whereby **49** is converted to **50** using MoO_2acac_2. Work elsewhere had been unable to carry out this transformation in an acceptable yield using molydenum oxide catalysts; hence, this route seemed unattractive.

Reference to several other catalysts for this reaction are given, including Ti or V compounds, Cu or Ag ions. All are said to suffer from low selectivities or low yields. The process here is carried out using MoO_2acac_2 in toluene containing DMSO and an organic acid. It is claimed that the acid should have a p*K* between 4.0 and 6.5, and phenylacetic acid with a p*K* of 4.25 is preferred although others are also given in the examples.

Advantages

The process claims to achieve high conversions and high yields making recovery of **50** easier than that in previous methods.

Patent No. U.S. 6,200,786

Assignee: Givaudan S. A., Vernier, Switzerland

Title or Subject: Process for the Preparation of Nootkatone by Laccase Catalysis

Nootkatone **53** is a constituent of grapefruit and is used as a natural flavouring in soft drinks and beverages and also has uses in perfumery. It is usually made by chemical oxidation of valencene **51**, and in the trend towards the use of natural flavours this route is not attractive. The high cost of **51** also detracts from using it as a starting material for **53**. Biotransformation of **51** has been attempted but only low yields resulted; hence, the patent claims that a commercially viable process for producing **53** is required.

The conversion of **51** to **53** is carried out using the enzyme laccase that is a naturally occurring lignolytic enzyme found in woody plants that synthesise lignin and in fugal species that degrade lignin. The enzyme can be obtained commercially or generated using recombinant techniques.

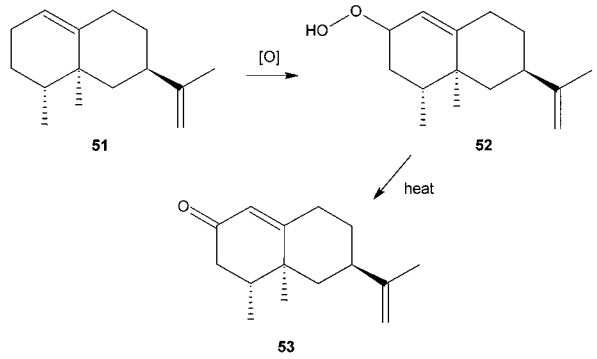
The process involves the formation of the hydroperoxide **52** from **51** this is catalysed by laccase with a mediator such as hydroxybenzotriazole (BHT). In the absence of mediators the rate of conversion was significantly reduced. The laccase was used either in the soluble form or in immobilised form, and in this case the reactions were carried out with up to 86% of **51** in the solution. The hydroperoxide **52** is decomposed to **53** when heated during work up. Recovery of **53** was carried out by extraction using CH_2Cl_2, and then it was purified by vacuum distillation.

The patent contains copies of ^1H and ^{13}C NMR spectra for **52** with full peak assignments as well as the chromatograms (HPLC and GC) from the enzymatic reaction. The patent also claims the method can be applied to essential oils such as orange, lemon, and others (Scheme 13).

Advantages

The use of naturally occurring oxidants allows the marketing of **53** to be carried out under the natural banner. The fact that the reaction can be performed with very high concentrations of substrate is attractive from a commercial point of view.

Scheme 13



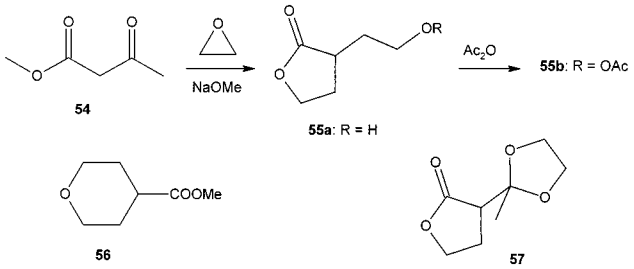
Patent No. U.S. 6,201,135

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Purification of 3-(2′-Acetoxyethyl)-dihydro-2(3H)-furanone

The tile compound **55b** is used in the manufacture of the pyran **56**, an intermediate in production of crop-protection agents. The synthesis of **55b** also produces by-products and in particular the furanone **57**. The presence of **57** deactivates the catalyst used in the preparation of **56** as well as severely reducing the yield. Separating **55b** from **57** is difficult, and the close and high boiling points of the compounds mean distillation is costly (Scheme 14).

Scheme 14



The synthesis of purified **55b** is achieved in this process by first forming the hydroxyethyl compound **55a** from reaction of ethylene oxide with **54**. Treatment of **55a** with acetic anhydride gives **55b**, and addition of sulphuric acid to the reaction mixture decomposes the **57** which after neutralisation allows **55b** to be recovered via extraction and purified by vacuum distillation. Examples are given for preparation of >350 kg of **55b** indicating the advanced commercial status of the process. This simple method gives **55b** in purity > 99% and in high yield.

Advantages

The treatment of crude **55b** with hot sulphuric acid does not cause degradation which is surprising, and it is a simple method of obtaining pure product. Although the same synthetic route is used, such a simple method of purification has presumably not been attempted.

Patent No. U.S. 6,201,159

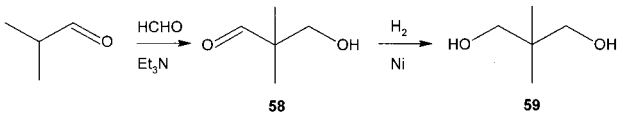
Assignee: LG Chemical Limited, Seoul, Korea

Title or Subject: Continuous Production of Neopentyl Glycol

Branched chain polyols are often produced via an aldol condensation reaction of aldehydes, and such reactions are notoriously messy and produce several hydroxy and carbonyl by-products. Neopentyl glycol **59** is used to manufacture a range of saturated and unsaturated polyesters, and the presence of such by-products creates problems in the preparation and affects the performance of the polyesters. Hence, there is the need for a clean synthesis of **59** or a suitable purification method.

This process involves the condensation of formaldehyde with isobutyraldehyde catalysed by triethylamine to give hydroxypivaldehyde **58**. The crude reaction mixture is extracted with octanol and the organic phase distilled to remove the volatile materials. The bottoms product containing mainly **58** and octanol was then hydrogenated using a Ni catalyst. The hydrogenation product mixture containing crude **59** was contacted with water in a multistage extractor, and an aqueous solution of **59** was obtained. This solution was then distilled to obtain **59** at 99.5% purity as a bottoms product. The overhead product is the azeotrope of **59** and water which was recycled to the extractor section. All steps were run continuously, and one example produced **59** at rates of up to 14 g/min (Scheme 15).

Scheme 15



Advantages

Hydrogenation of the crude mixture enables a relatively straightforward purification method to be developed. Other methods tend to attempt purification prior to hydrogenation and are claimed to be less efficient.

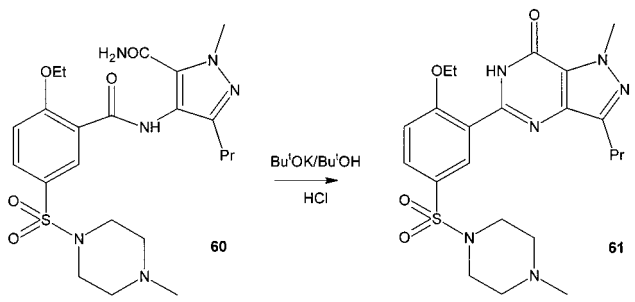
Patent No. U.S. 6,204,383

Assignee: Torcan Chemical Ltd, Ontario, Canada

Title or Subject: Process for Preparing Sildenafil

The interest in methods of synthesising sildenafil **61**, the male anti-impotence drug, is increasing, and some have been covered in previous patent reviews. The method used by Pfizer, the producers of Viagra, has a key last step in its route which is the ring closure to go from **60** to **61**, and which was was reviewed in this journal last year (*Org. Process Res. Dev.* **2000**, *4*, 17) (Scheme 16).

Scheme 16

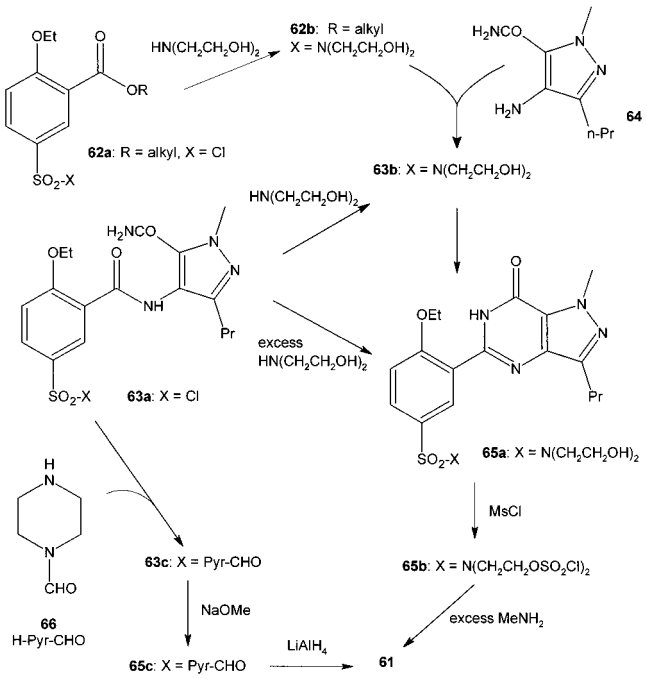


The approach taken in the current patent is to go by a quite different synthetic route and is based on an elegant

strategy of producing a final intermediate that is significantly less basic than **61**. This means that extraction of **61** into an acidified aqueous phase is preferred, and the by-products and contaminants are left behind after this reaction step. As a result of taking this approach, the by-products are extracted into the organic phase and **61** can be obtained from the aqueous phase.

There are actually two alternative routes in this patent to **61**, and for one of these there are variations to the synthesis of key intermediates. In each of these routes the final intermediates **65b** and **65c** are both less basic than **61**, and the selective extraction strategy is used. The new route to **61** includes several novel compounds such as **63a**, and these are part of the claims of the patent (Scheme 17).

Scheme 17



The first route starts from the chlorosulphonyl compound **62a** going via the bis-hydroxyethylamino derivative **62b**. This forms the intermediate **63b** by reaction with the pyrazoleamido compound **64**. **63b** can also be produced from **63a** by reaction with a stoichiometric amount of diethanolamine (DEA). The method for the ring closure of **63b** to give **65a** is not provided, but it is stated that standard organic procedures are involved. Compound **65a** can also be formed from the chloro compound **63a** by reaction with excess DEA which acts as both reagent and catalyst for this step. Treatment of **65a** with MsCl gives the mesylsulphonyloxy compound **65b** which with excess $MeNH_2$ gives **61**. An alternative route from **63a** to **61** forms the piperazine group by addition of formyl compound **66** to give **63c**. The formation of the pyrimidine ring is effected by NaOMe, and then the formyl group is reduced using $LiAlH_4$ to give **61**.

Advantages

This route to **61** is quite different from that used by Pfizer and claims to have a rugged procedure including a simplified purification method that may provide an alternative route to this important drug.

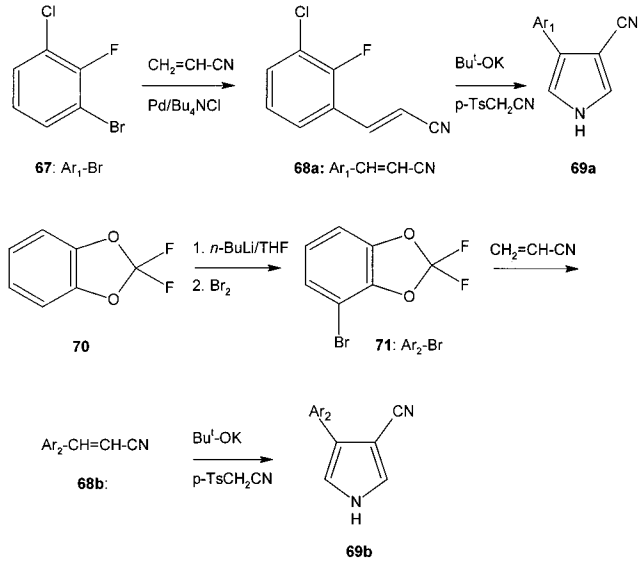
Patent No. U.S. 6,204,397

Assignee: Bayer AG, Leverkusen, Germany

Title or Subject: Process for the Preparation of 3-Aryl-Substituted Cyano-Pyrroles

Despite the title of this patent the only claim is for the novel dioxole compound **71**. The title compounds are used to produce pesticides, and **71** is used in the synthesis of the cinnamonitrile compound **68b** that is used to prepare the pyrrole **69b** (Scheme 18). The patent thus describes a novel method of making **71** and other halo-aromatics.

Scheme 18



There are other methods of preparing the cinnamonitrile such as **68a** from benzaldehydes, but these are said to be extremely difficult and not commercially viable. The route to the pyrrole **69b** via **68b** is therefore also not feasible. It is possible to prepare some cinnamonitriles from bromo- or iodo-aromatics by reaction with acrylonitrile using Pd/Ph_3P catalysts, but these reactions fail when 2,3-disubstituted aromatics are used. When this conversion of **67** to **68a** was attempted by a method described in the literature using Ph_3P and NEt_3 with acrylonitrile, there was no production of **68a**. Hence, this patent has developed the route to pyrroles with an improved method of preparing the cinnamonitriles. However, many of the bromoaryl compounds such as **67** that could be used to make a variety of the pyrroles are unavailable or not even known, and hence the patent also provides a method of preparing some of them.

For example, **71** is prepared from **70** by low-temperature lithiation followed by treatment with Br_2. Other bromoaryl compounds such as **67** are said to be produced from the amines via the diazo compounds which are treated with HBr. No details are given here, and presumably they are the subject of other patents.

The pyrrole compound **69a** is obtained in two stages. In the first step **68a** is obtained by treatment of **67** with acrylonitrile in the presence of $Pd(OAc)_2$ and NBu_4Cl.

Reaction of **68a** with *p*-tosylsulphonyl methylisocyanide in the presence of strong base caused formation of the pyrrole ring and formation of **69a**.

Advantages

The route to the pyrroles via the cinnamonitriles has been improved by providing a better method of preparing the bromo precursors **67**.

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