Organic Process Research & Development **2000**, *4*, 450–459

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during April to July, 2000

Summary

This is the third and final review for this year of U.S. patents in the field of organic process development. During the period from 1 April to 31 July, 2000 there were 574 patents that fitted the original selection criteria, and of these, 26 are summarised which, hopefully, will be of interest to readers. There is no legal or commercial significance in the choice although some are in the same subject area as others that have been reviewed in the two previous reviews. The advantages given here are based on those claimed by the inventors of the patent unless this author has prior knowledge. It is worth bearing in mind that inventors or the patent authors are selective in their choice of references to earlier work when claiming advantages. Following a company's patent activity is a very good way to assess commercial plans by that company in the area of technology. On this point it may be significant that there are four patents in this selection from Merck on the subject of carbapenems. Also included in this review are patents on the production of ultrafine crystals by an atomisation technique and another on controlling particle size in the synthesis of photoresist chemicals used in the semiconductor business. There is also a patent that describes the use of unwanted ballistic missile propellant in the synthesis of nitroamines.

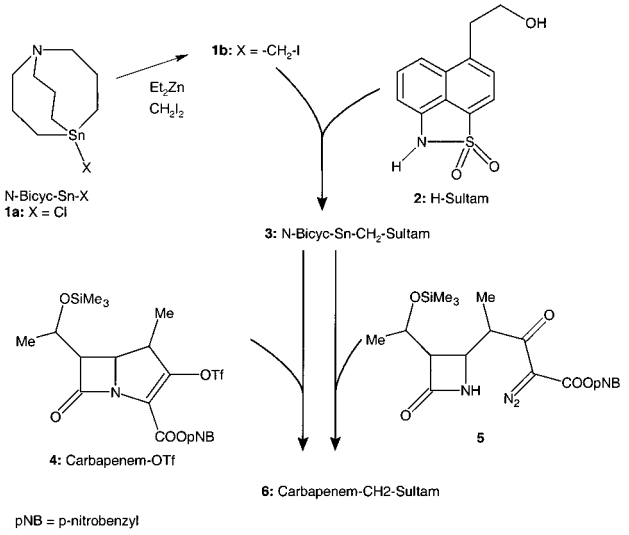
Patent Nos. U.S. 6,048,978, 6,060,607, 6,063,931, 6,080,854

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

Title or Subject: Synthesis of Carbapenem and Intermediates

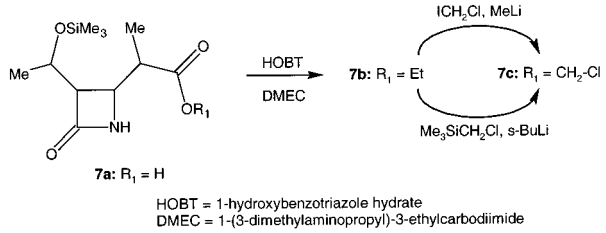
These four patents cover various aspects of synthesising carbapenems and intermediates used in the syntheses. Carbapenems are useful as antibacterial agents in human and veterinary medicine against methicillin resistant pathogens such as Staphylococci. The first patent U.S. 6,048,978 covers the synthesis of the stannatranes such as **1b** which is then used as a protective group to introduce the CH_2 group in the carbapenem sultam derivative **6** (Scheme 1). This is done by reaction of **3** with either the carbapenem **4** or diazoketone **5** which is a carbapenem precursor. The patent gives details for the synthesis of the sultam **2** and includes full NMR assignments for all intermediates.

Scheme 1



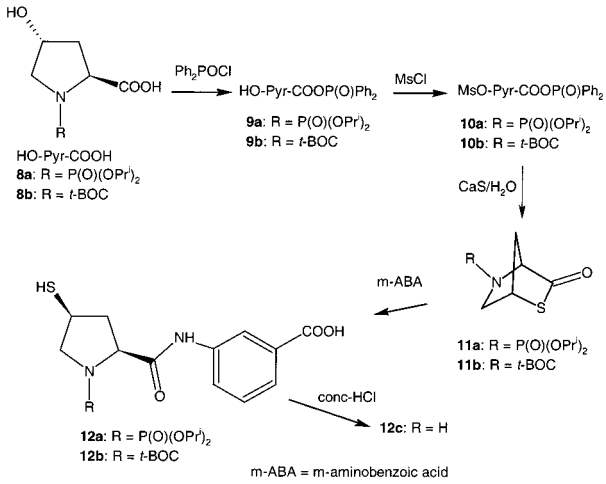
The patent U.S. 6,080,854 covers the synthesis of the intermediate **7c** (Scheme 2) which can form the non-β-lactam ring of the carbapenem and enable a β-methyl group to be introduced before cyclisation.

Scheme 2



The other two patents cover different aspects of the reactions shown in Scheme 3. A cursory glance at the two patents might lead one to think that they are identical. However, since the patent rules stipulate that one patent cannot cover more than a single invention, the work from Merck is split into two patents. Hence, U.S. 6,060,607 covers the synthesis of **12** from **11**, and U.S. 6,063,931 covers the synthesis of the bicyclo compounds **11**. Scheme 3 shows

Scheme 3



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the conversion of **11** using *m*-aminobenzoic acid (m-ABA), but there is a large selection of amines claimed in the patent for this step.

Advantages

Each patent claims various advantages, but the overall one appears to be the reduction in the number of steps using protecting groups that are normally employed for the synthesis of carbapenems.

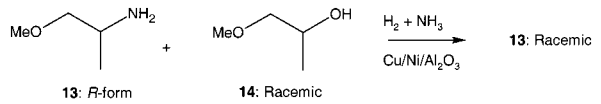
Patent No. U.S. 6,049,007

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Racemisation of Optically Active Amines

This patent describes a method to racemise amines in a vapour-phase process. This is done to recover the undesired form of an amine and increase yields. Scheme 4 shows that the amine **13** can be racemised by vaporising it together with its homologous racemic alcohol **14** in a stream of hydrogen and ammonia and passing over a over a Cu/Ni catalyst. The process is carried out in the presence of water by using wet alcohol at around 200 °C and at 15 bar pressure. The experimental details indicate that this was done on a substantial scale. It is also claimed that structurally analogous ketones can be used with or without the alcohol, but no example is given. Since the reaction is performed using a hydrogenation catalyst, this claim is not unreasonable.

Scheme 4



Advantages

Clearly, this method is only effective for vaporisable amines but is claimed to improve on previous vapour-phase methods because the process has a high space-time yield and uses readily available materials.

Patent No. U.S. 6,051,741

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Preparation of γ,δ-Unsaturated Ketones by the Carroll Reaction Using Novel Catalysts

The Carroll reaction is the synthesis of γ,δ-unsaturated ketones by chain extension of allyl or propargyl alcohols using ethyl acetoacetate (EAA) or diketene. The reaction is widely used to prepare terpenes, and a typical catalyst is crystalline aluminium acetylacetonate. Scheme 5 shows the synthesis of 6-methylheptenone **16** from the allylic alcohol **15**.

This patent uses liquid aluminium catalysts containing different ester groups **18**. These are produced from treatment of esters **17** with aluminium alkoxides, but the reaction is performed so that alcohols liberated in the transalcoholysis reaction are not removed from the system. The catalyst mixture therefore actually consists of several different aluminium alkoxy compounds, one of which is **18**. It is this

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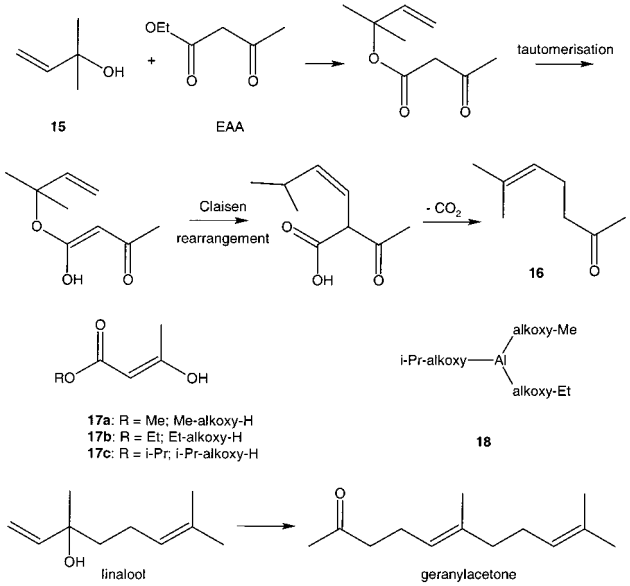
Scheme 5



liquid mixture that is used as the catalyst in this patent for the Carroll reaction. An example given is the synthesis of geranylacetone from linaolool using a catalyst system comprising (*s*-BuO)$_3$Al, MAA, MeOH, and *s*-BuOH.

Advantages

The handling of liquid catalysts is easier than solids on a commercial plant, and they are also very soluble in the reactants, whereas the solids are not particularly soluble. This increased solubility appears to give higher yields than the pure crystalline catalysts that are normally used.

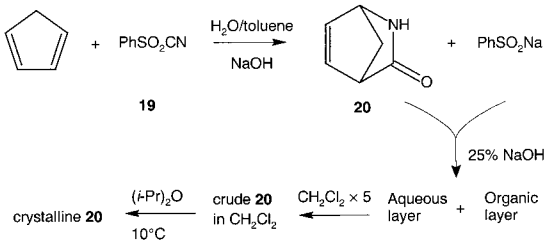
Patent No. U.S. 6,060,609

Assignee: Kuraray Co. Ltd, Kurashiki, Japan

Title or Subject: Process for Producing Crystalline 2-Azabicyclo[2.2.1]hept-5-en-3-one

The title compound **20** is an intermediate in the synthesis of carbocyclic nucleosides that are useful as anti-HIV agents. The synthesis of **20**, shown in Scheme 6, proceeds via addition of the cyanide **19** to cyclopentadiene in a solvent mixture of water and toluene with periodic addition of NaOH to maintain the pH in the range 4.4−4.7. After reaction the pH is increased to 7.5, and then the aqueous layer is separated, and **20** is obtained by crystallisation from isopropyl ether/methylene chloride.

Scheme 6



Advantages

Previous methods often employ large excess of cyclopentadiene in a multistep process that also results in waste

problems. In some procedures the product is obtained as an oil that is difficult to crystallise. The current method is a one-pot single-step process, and the work-up produces high yields of crystalline material.

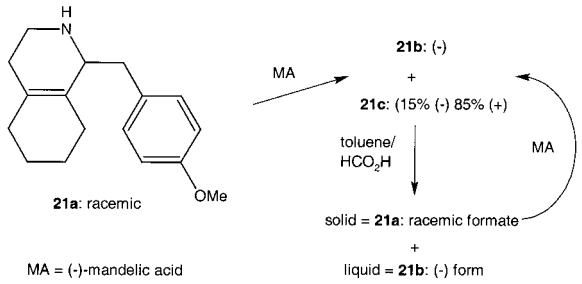
Patent No. U.S. 6,063,925

Assignee: B. I. Chemicals Inc., Virginia, U.S.A.

Title or Subject: Separating Octahydroquinoline Enantiomers

The (−) form of this compound **21b** is used to produce dextromethorphan, an antitussive agent. Normally, the racemic mixture **21a** is produced, and the (−) form is obtained using (−)-mandelic acid (MA). However, the remaining mixture still contains 15% (−) form; hence, recycling of the mixture is economically required, but racemisation is destructive. The process described here utilises the formation of a eutectic with formic acid that is close to the pure enantiomer. Scheme 7 shows the method employed. After resolution of **21a** with MA the remaining mother liquor is treated with formic acid in toluene, and the racemic formate is precipitated. This salt is then treated with MA to obtain the (−) form **21b**. The patent indicates that high concentrations of toluene and minimum amounts of formic acid are needed for optimum results. An unusual feature of this patent is its brevity. It is only one and a half pages long plus two figures and has only a single claim.

Scheme 7



Advantages

Other resolution methods result in the production of considerable amounts of impurities because of the destructive nature of the racemisation step, and hence lower yields than this process are obtained.

Patent No. U.S. 6,066,735

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

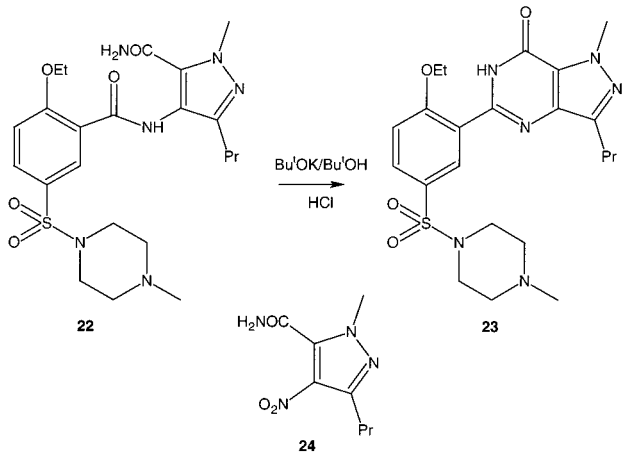
Title or Subject: Preparation of Sildenafil

Sildenafil **23** is the male anti-impotence drug commonly known as Viagra. A detailed account of Pfizer's work has appeared in this journal (*Org. Process Res. Dev.* **2000**, *4*, 17), and the subject of this patent is compound **22** which is the precursor to **23** in the final key cyclisation step of the whole synthesis. Experimental details are given for the synthesis of all of the intermediates in the route from 2-ethoxybenzoic acid to **23** (Scheme 8).

Advantages

An earlier preparation of **22** disclosed in a 1992 patent from Pfizer (EP0463756) gave only a 23% yield of **22** from **24**, whereas the current method can achieve a yield of 85%.

Scheme 8



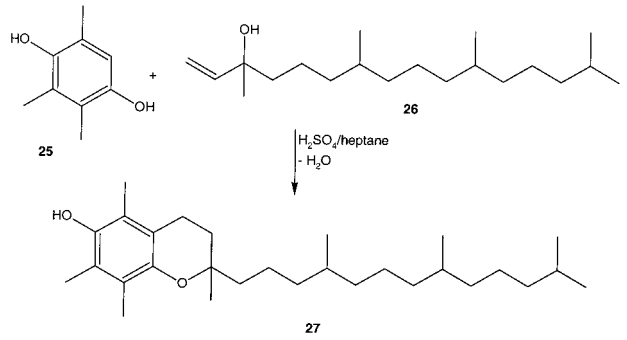
Patent No. U.S. 6,066,745

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

Title or Subject: Synthesis of Vitamin E

Vitamin E **27** is produced on a substantial scale by condensation of trimethylhydroquinone **25** with isophytol **26** using Lewis acids. This patent uses the same route but uses a sulphur-containing non-Lewis acid such as sulphuric acid (Scheme 9). The reaction can be carried out in a single-phase solvent consisting of ethylene carbonate (EC) or in a two-phase system of EC and heptane. The water that is eliminated is removed by azeotropic distillation with the heptane. The other preferred acid catalyst is *p*-toluenesulphonic acid (PTSA).

Scheme 9



Advantages

Processes that use Lewis acids often give rise to waste disposal problems and also cause corrosion of equipment. The waste from this method is easier to deal with, and corrosion is less of a problem. In addition, the recovery of the product is easier, and higher yields are obtained.

Patent No. U.S. 6,068,695

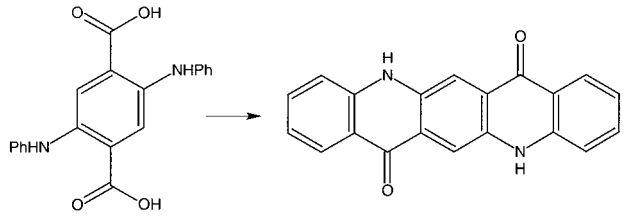
Assignee: Bayer Corporation, Pennsylvania, U.S.A.

Title or Subject: Continuous Preparation of Quinacridones in a Screw Extruder

In the last patent review (*Org. Process Res. Dev.* **2000**, *4*, 246) Bayer disclosed the use of microwaves in the preparation of quinacridone **29** from **28**. **29** is a violet pigment that is widely used in automotive paints. The current

method appears to use conventional heat sources but specifically claims that the process is continuously operated and is carried out by passing the anilinoacid **28** through a heated reactor in the presence of polyphosphoric acid as a dehydrating agent to effect the cyclisation. The key aspect of the invention is that a screw extruder is used as the reactor, and the various additives used to produce the final form of the pigment can be added during the reaction. Following the cyclisation step the reaction melt is poured into cold water or methanol containing alkali. This produces a slurry from which the pigment is easily recovered. Comparative examples of batch and continuous processing are given. Whether this process is combined with the microwave heating method remains to be seen (Scheme 10).

Scheme 10



28 **29**

Advantages

The ability to produce materials continuously can often give a more consistent product, which is the case here. The product is also of a higher quality than that produced in a batch process. The use of a screw extruder as a reactor and to simultaneously incorporate additives saves process time and costs.

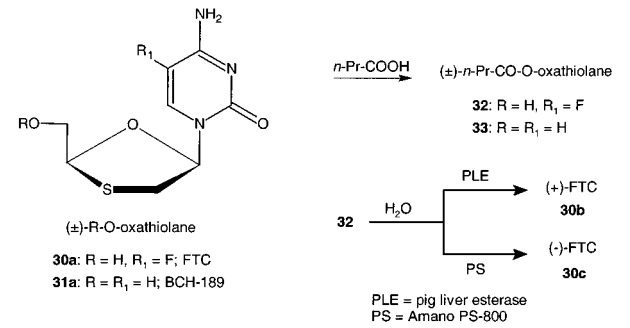
Patent No. U.S. 6,069,252

Assignee: Emory University, Georgia, U.S.A.

Title or Subject: Resolution and Antiviral Activity of 1,3-Oxathiolane Nucleosides

This patent covers the resolution of compounds such as **30b** and **30c** that are claimed in this patent to be effective against various viruses including HIV and hepatitis B. The resolution method employs an enzyme that will preferentially hydrolyze only one of the enantiomers of the butyrate esters **32** or **33** produced from the racemate **30a** or **31a** with butyric acid. Using pig liver esterase (PLE) the (+) enantiomer of **32** was hydrolyzed to give **30b** in >97% ee. When Amano PS-800 was used the (−) enantiomer of **32** was hydrolyzed and **30c** was produced. It was found that the rate of hydrolysis with the acetate ester was slower, and that of propionates, faster.

Scheme 11



The patent also gives details of testing for antiviral activity of various enantiomers of **30** and **31** (Scheme 11).

Advantages

This patent claims that **30b** and **30c** are new compounds with antiviral activity and by choosing different enzymes to hydrolyze the esters then high ee of the desired enantiomers can be obtained.

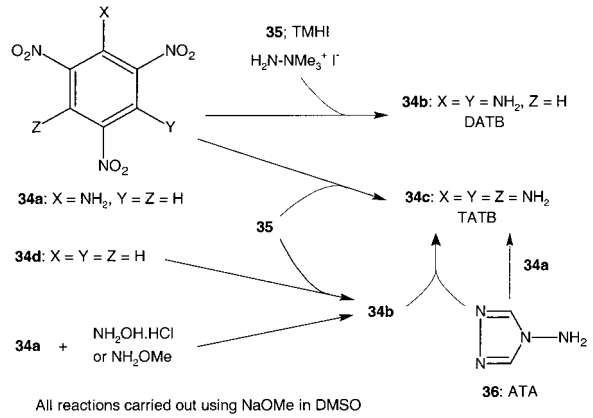
Patent No. U.S. 6,069,277

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

Title or Subject: Preparation of Diaminotrinitro Aryl Compounds by Vicarious Nucleophilic Substitution with Quaternary Hydrazinium Salts

The title compounds are insensitive high explosives, and it has been found that they can be made by direct amination of nitroaromatics using, for example, trimethylhydrazinium iodide (TMHI) **35**. Scheme 12 shows that picramide, **34a**, and TMHI with NaOMe as strong base in DMSO give the diamino derivative **34b** or the triamino compound **34c** by using a longer reaction time. It is also possible to produce **34b** or **34c** from TMHI and trinitrobenzene **34d**. The TMHI is made from dimethylhydrazine (DMH) and methyl iodide but it is also possible to carry out the aminations by preparing the TMHI in situ.

Scheme 12



The patent also covers aminations using other reagents such as hydroxylamine, *O*-methylhydroxylamine, *O*-benzylhydroxylamine, or 4-amino-1,2,4-triazole **36**. The direct monoamination of nitrobenzene using **36** was reported some time ago (Katritzky, A. R. et al. *J. Org. Chem.* **1986**, *51*, 5039), but this early work did not indicate that polyamination was possible. The current patent has shown that TATB can be made from **34a** or **34b** using **36** as amination reagent (Scheme 12). The monoamination of substituted nitrobenzenes using **35** is not as regioselective as **36** and tends to give mainly the 2-derivative. In contrast **36** exclusively gives monoamination in the 4-position. However, the very high reactivity of **35** means that diamination of *m*-dinitrobenzene is possible even under stoichiometric conditions.

The patent mentions that DMH was used as a propellant by the Russians for their intercontinental ballistic missiles. The changes in the world's political climate has meant that large quantities of DMH are available and require disposal. Apart from being used for high explosives DATB can be used to produce liquid crystals, and hence this patent provides a method for converting such fuel into useful chemicals.

Advantages

Production of high-explosive materials is clearly hazardous, and direct polyamination of nitroaromatics is advantageous over indirect methods involving nitration with nitric and sulphuric acids followed by reduction. This process claims to more environmentally friendly than such methods although the use of hydrazines clearly poses its own problems.

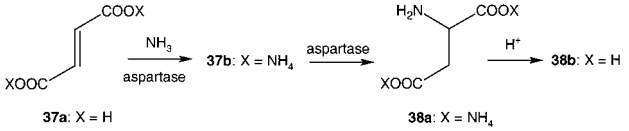
Patent No. U.S. 6,071,728

Assignee: Amylum Belgium N. V. Aaist, Belgium and A. E. Staley Manufacturing Co., Illinois, U.S.A.

Title or Subject: Process for the Production of Aspartic Acid

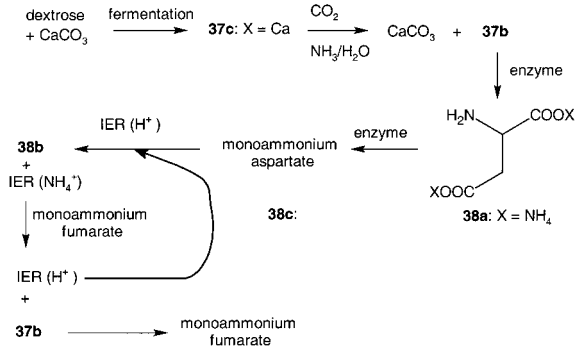
Aspartic acid **38b** is used in the manufacture of the sweetener aspartame and the biodegradable polymer polyaspartic acid. This is an environmentally attractive material, and a cheap method of producing **38b** is desirable. **38b** is usually produced from ammonium aspartate **38a** by treatment with mineral acid. **38a** is itself produced from ammonium fumarate **37b** by treatment of fumaric acid with ammonia in the presence of aspartase which then also converts **37b** to the asparate **38a** (Scheme 13). During this process the acidification of **38a** to produce **38b** also gives rise to ammonium salts that require disposal.

Scheme 13



The process described in this patent is shown in Scheme 14 and describes the use of ion-exchange resins (IER) to

Scheme 14



recycle the NH_4 group and eliminate losses. The process starts with a fermentation step to produce the calcium salt **37c** which is converted to the ammonium salt **37b** by NH_3 and CO_2. **37a** is then converted enzymatically to the diammonium salt **38a** and then further transformed to the monoammonium aspartate **38c**.

The key section of the process is the use of the acid form of the IER to produce the desired **38b** and the NH_4^+ form of the IER. Treating **38b** with monoammonium fumarate regenerates the acid form of the IER and also produces diammonium fumarate **37b**. The regenerated acid IER is reused, and **37b** is partially decomposed to provide the monoammonium fumarate salt for use in the regeneration step. The decomposition can be carried out using CO_2 under pressure, by using IER in the acid form, or thermally.

Advantages

The ability to reuse the IER significantly reduces the amount of wastes produced and also enables high purity **38b** to be obtained from a natural source via a fermentation route. Previous attempts to make **38b** via fermentation resulted in lower-grade material and high volumes of wastes.

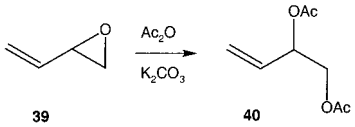
Patent No. U.S. 6,072,079

Assignee: Eastman Kodak Company, Tennessee, U.S.A.

Title or Subject: Continuous Process for 3,4-Diacetoxybut-1-ene

The title compound **40** is a useful chemical intermediate and is made from the epoxide **39** by various acetylation methods that involve amines, hydrochloric acid, or $(Bu)_4POAc$. Other routes to **40** involve catalytic acetoxylation of butadiene in a very corrosive system of acetic acid and oxygen. The current process simply involves the treatment of epoxide **40** with acetic anhydride in the presence of KOAc which is produced in situ from dry K_2CO_3 (Scheme 15). If the K_2CO_3 is wet, then acetic acid is formed, resulting in formation of a monoacetate. The use of pure KOAc is not as effective because it has a low solubility in Ac_2O, and this adds an induction time to the process. The induction period means that the use of KOAc is not suitable in batch processes but is acceptable in a continuous system where a steady state can be attained in the time needed for dissolution. The preferred process uses K_2CO_3 which is dissolved in Ac_2O and continuously fed to a reactor with the **39**.

Scheme 15



Advantages

This process uses less corrosive materials and produces higher yields with less byproducts than alternative routes, and the ability to use the cheaper potassium salts is a distinct advantage.

Patent No. U.S. 6,072,080

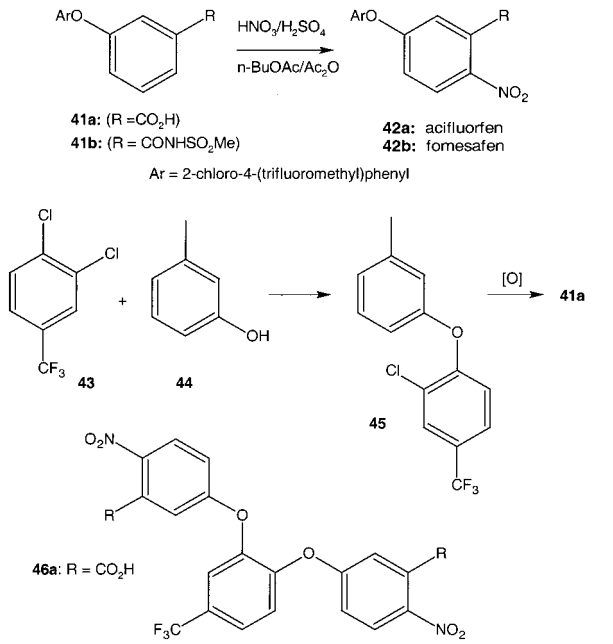
Assignee: Zeneca Limited, London, UK

Title or Subject: Process for the Purification of Nitrated Diphenyl Ethers

Ethers such as **42a** (acifluorfen) and **42b** (fomesafen) are used as herbicides and are produced by a nitration process

of the corresponding ethers (Scheme 16). This process was described in U.S. 5,952,531 and reviewed earlier this year (*Org. Process Res. Dev.* **2000**, *4*, 68). This new patent describes a detailed method for the purification of **42a** by crystallisation.

Scheme 16



As with many aromatic nitrations the key is to selectively produce the required isomer or to be able to separate it easily from the unwanted isomers. The purification process described here has some very specific requirements including the maximum concentration of the solution prior to recrystallisation, the number of washings, and the temperature. Apart from making **42a** the patent also describes the nitration of the Na salt of **41a** to give the Na salt of **42a**.

The purification scheme involves an initial washing of the crude solid reaction product in a water/acetic acid mixture. This step improves the quality of the final product. The partially purified solid is dissolved in *o*-xylene and then washed with acidified water at controlled pH up to five times to remove impurities. The aqueous washings can be back extracted with hot *o*-xylene to increase the yield, and this is claimed to be a novel aspect since the acid washings only dissolve the impurities and not **42a**. Crystalline **42a** is then obtained by cooling of the *o*-xylene solution. There is a large amount of experimental data provided from what was clearly a very detailed study.

The purification process is said to be particularly useful for producing **42a** from **41a** that has been made from *m*-cresol **44** and **43**. This reaction gives the ether **45** which is then oxidised to **41a** (Scheme 16). A by-product in this route to **41a** is the diether **46a** which previously was found to be difficult to remove, and hence other routes to **41a** generally start from 3-hydroxybenzoic acid (3-HBA). However, **44** is much cheaper than 3-HBA so that **41a** and hence **42a** can be made from **44** by using the purification method in this patent.

Advantages

The purification process appears to have been developed to allow the use of the *m*-cresol route to **41a**. Previous routes to **41a** from *m*-cresol gave impurities such as **46** that could not be removed, and they contaminated the herbicide **42a** and hence were unacceptable. The purification method developed here means that there is a cheaper route to the herbicide **42a** than has been previously used.

Patent No. U.S. 6,074,441

Assignee: Bayer AG, Leverkusen, Germany

Title or Subject: Production of Ultrafine Crystals

This patent describes a process to produce very small crystalline products (<1 μm) of organic chemicals with a narrow size distribution. These can be used in pharmaceutically active compounds where their small particle size increases the bioavailability because of their increased rate of dissolution. Previous methods of making such crystals are usually only applicable to inorganic materials. Such methods require the production of a microemulsion by using a high-energy homogeniser.

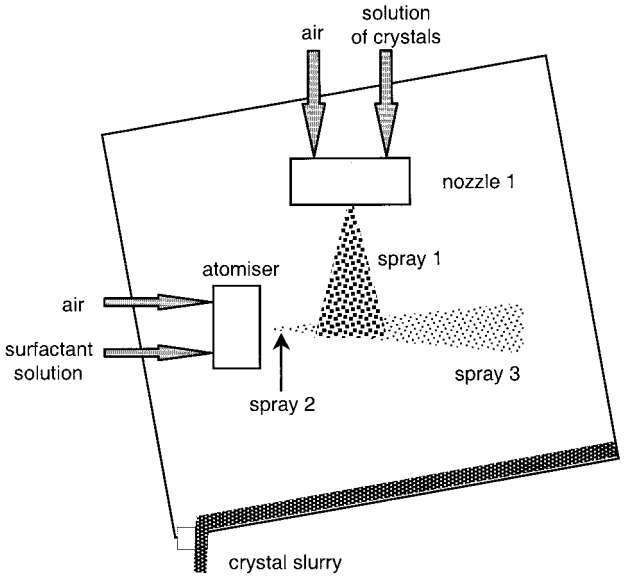


Figure 1. **Atomisation device for producing ultrafine crystals.**

The process shown in Figure 1 is carried out by directing two fine sprays at one another to cause atomisation of one by the other. Thus, an aerosol (spray 1) of the organic material in solution is produced by feeding air and a solution of the organic solute in a volatile solvent. This is then sprayed with an atomised aqueous solution (spray 2) of a surfactant to produce a cloud of very small droplets (spray 3). This process partially evaporates the solvent and produces a colloidal crystal suspension which falls to the base of the atomisation vessel where the crystals can be separated and collected. The equipment in Figure 1 is enclosed in a suitable vessel that will allow recycling of the solvent and can be operated under vacuum as well as moderate pressures. The only specific example given in the patent is to produce crystals of naphthalene from a solution in chloroform. The claims refer to producing crystals of water-insoluble materials because of the use of the aqueous solution of surfactant.

Advantages

Other methods for producing microcrystals are apparently only applicable to inorganic chemicals, whereas this technique is specifically applicable to organic chemicals. By directly producing the microcrystals there is no need for milling, and the potential for contamination is reduced.

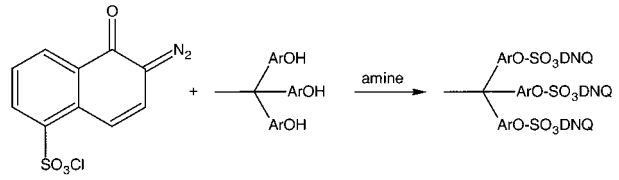
Patent No. U.S. 6,077,942

Assignee: Clariant Finance (BVI) Limited, British Virgin Islands

Title or Subject: Production of Controlled Particle Size Naphthoquinone Diazide Esters

The title compounds are used as photoresist compounds in the semiconductor industry, and the trend for smaller geometries has increased the need for smaller, more uniform, crystalline particles. The materials used are esters such as **49** formed from the diazo compound **47** with a polyol such as **48**. The reaction to produce **49** is carried out in a polar solvent mixture such as γ-butyrolactone and acetone and in the presence of an amine as catalyst and acid scavenger. This solution is then added slowly to aqueous methanol that is kept at between −10 °C and −20 °C. This causes precipitation of **49** and produces fine yellow crystals that are easily recovered, whereas if the drowning-out is carried out at room temperature the crystals that are formed are difficult to filter. The low-temperature precipitation produces small-sized crystals that are free from highly-coloured by-products that are common in other syntheses (Scheme 17).

Scheme 17



47: $DNQSO_3Cl$ **48**: ArOH = 4-hydroxyphenyl **49**

Advantages

Other methods cannot provide the high purity and consistently small particle size that are required for use in the semiconductor industry. This process is not sensitive to slight changes in operating conditions and hence would appear to be robust because major temperature changes are said to be necessary to affect product quality.

Patent No. U.S. 6,080,876

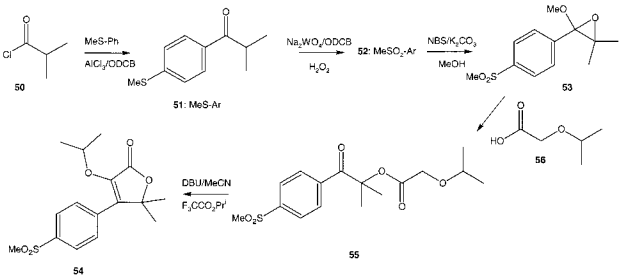
Assignee: Merck & Co Inc., New Jersey, U.S.A.

Title or Subject: Production of Phenyl Substituted Lactones as COX-2 Inhibitors

The enzyme cyclooxygenase (COX-2) is thought to be responsible for inflammation and pain and hence the interest in COX-2 inhibitors. Merck already has one drug on the market (Vioxx), and a patent claiming other candidates has previously been reviewed (*Org. Process Res. Dev.* **2000**, *4*, 246). This work describes the synthesis of **54** by a route shown in Scheme 18.

Thioanisole is reacted with isobutyryl chloride **50** to give the isobutyrophenone **51** that is then oxidised to the methylsulphonyl derivative **52** using H_2O_2. This oxidant gives high selectivity and is environmentally cleaner since water is the by-product. The enol ether epoxide **53** was obtained from **52** by conventional means using NBS/K_2CO_3, and unpurified **53** was treated with the alkoxy acid **56** to give the ester **55**. After recrystallisation of **55** it was converted to **54** by cyclisation using the strong base DBU and isopropyl trifluoroacetate as water scavenger. It is not possible to use either strong bases such as LHMDS or acid catalysts for the cyclisation because both cause cleavage of the ester.

Scheme 18



50 **51**: MeS-Ar **52**: $MeSO_2$-Ar **53** **54** **55** **56**

Advantages

The overall process is claimed to be an improvement on other routes to make **54** which involve the synthesis of bromosulphone intermediates which are difficult to handle.

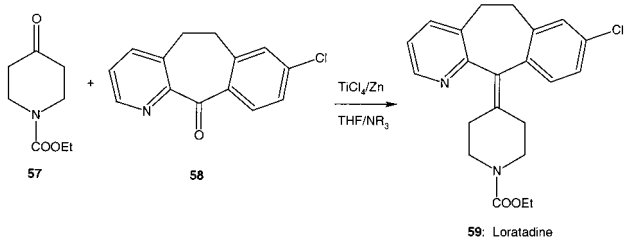
Patent No. U.S. 6,084,100

Assignee: Medichem S. A., Barcelona, Spain

Title or Subject: Process for Preparation of Loratadine

Loratidine **59** is an antihistaminic that can be made by a number of multistep routes. Some involve superacids or unstable reagents, and this can make industrial processing difficult. The route described here is based on a McMurry reaction which involves the reductive cross coupling of the keto-piperidine ester **57** and the pyridino-ketone **58**. The catalyst system of $TiCl_4$ and Zn dust produces the active catalyst $TiCl_3$ in situ before addition of the organic reagents. This process is an unusual example of the McMurry reaction which is normally observed to be intramolecular or a dimerisation reaction. When intermolecular reactions do occur between A and B there are three products that are possible and these are AA, BB, and AB. Thus the selectivity to any of these products may be low, and separation could be difficult. The key aspect of this process is that the use of the low-valent Ti catalyst selectively produces the desired AB product in acceptable yields (Scheme 19).

Scheme 19



57 **58** **59**: Loratadine

Advantages

This method allows the use of reagents that are readily synthesised and reduces the number of steps needed in

alternative routes.

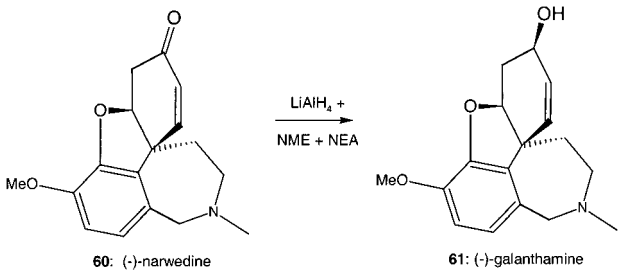
Patent No. U.S. 6,087,495

Assignee: Janssen Pharmaceutica N. V., Belgium

Title or Subject: Preparation of Enantiomerically Enriched Galanthamine

Galanthamine **61** and its salts are used in the treatment of Alzheimer's disease and may be obtained from snowdrops or daffodils as well as by the synthetic method in Scheme 20 which has been reviewed (*Org. Process Res. Dev.* **2000**, *4*, 246). The new patent describes a resolution method based on direct crystallisation that involves seeding a supersaturated solution of racemic **61** with an enantiomerically enriched form of a salt of **61**. The hydrobromide is the preferred salt, and the enantiomerically enriched form is prepared by the reaction shown in Scheme 20. The fact that this patent relies on the previous one does suggest some commercial significance.

Scheme 20



60: (-)-narwedine

61: (-)-galanthamine

NME = (-)-*N*-methylephedrine
NEA = *N*-ethyl-2-aminopyridine

Advantages

This is a simple and cost-effective process that relies on the previous patented reaction. Other resolution methods use resolving agents that are not inherent to the system.

Patent No. U.S. 6,087,497

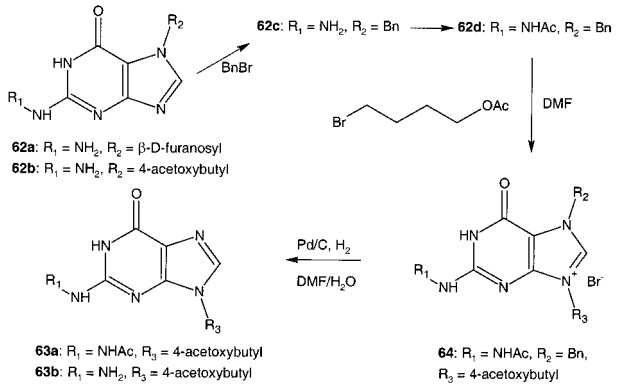
Assignee: Ajinomoto Co. Inc., Tokyo, Japan

Title or Subject: Production of 9-Substituted Purines

The title compounds are useful in synthesising drugs such as acyclovir, ganciclovir and famciclovir that are used against infectious viral diseases including as herpes, hepatitis, and AIDS. A difficulty with synthesising a compound such as **63b** is that the undesirable 7-isomer **62b** is thermodynamically favoured, and hence attempts to make **63b** also produce **62b**, often at up to 35% (Scheme 21). A recent patent (U.S. 6,043,364) from Lupin Laboratories in India (*Org. Process Res. Dev.* **2000**, *4*, 246) solved the problem by converting the 7- to the 9- isomer. The solution adopted here is to block the 7-position by introduction of a benzyl group before adding the substituent at the 9-position and subsequently removing the 7-benzyl group.

The process starts with a natural 7-substituted purine nucleosides such as guanosine **62a** which is converted to the benzyl compound **62c** using benzyl bromide. **62c** as its dihydrochloride may then be converted to the acetyl derivative **62d**, to protect the amino group, by treatment with Ac_2O in the presence of PTSA. The 9-substituent can then be added using 4-bromobutyl acetate to give **64**, and the benzyl group is removed by hydrogenation using Pd catalysts to give **63a** (Scheme 21). This route actually takes advantage of the fact that substitution at the 7-position in purines is favoured. As a result of this the benzyl compounds are formed readily and therefore block the 7-position so that further substitution by the desired group is only possible at the 9-position.

Scheme 21



Advantages

The route chosen here can very easily form the 7-benzyl isomer from purine nucleosides that are produced by fermentation. This reduces the total number of steps required to produce the desired 9-isomer, and this has advantages over other routes.

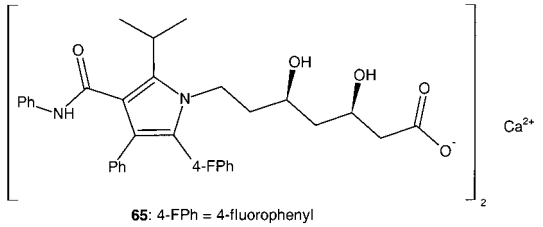
Patent No. U.S. 6,087,511

Assignee: Warner-Lambert Company, New Jersey, U.S.A.

Title or Subject: Production of Amorphous Atorvastatin

The amorphous form of atorvastatin **65** used as the Ca salt is an inhibitor of HMG-CoA-reductase and useful as a hypolipidemic and hypocholesterolemic agent. The Ca salt is preferred because it can be formulated into tablets, capsules, and so forth for oral administration. There are at least four crystalline forms of **65**, and it would seem that it is difficult to predict which form is obtained during synthesis of **65**. This is classic behaviour of polymorphs, and hence the crystalline forms are not desirable in the final formulations of **65**. Thus, the driving force behind this patent is the need to produce amorphous material that has consistent properties.

The solution disclosed is to dissolve the crystalline salt in a non-hydroxylic solvent and then remove the solvent. The preferred solvent is a mixture of THF and toluene. The patent describes the synthesis of over 70 kg of one polymorph of **65** which is then dissolved in THF, and toluene is then added. Removal of the solvent is carried out in vacuo initially at 35 °C to obtain a free-flowing powder which is further dried at 85 °C. The amorphous nature of the **65** that is obtained is shown by X-ray diffraction (XRD). The XRD patterns for both crystalline and amorphous forms are reproduced in the patent as is the solid-state ^{13}C NMR with full peak assignments.



65: 4-FPh = 4-fluorophenyl

Advantages

This method is simple and readily amenable to large-scale production as shown by the example to make a batch of 27 kg of amorphous **65**.

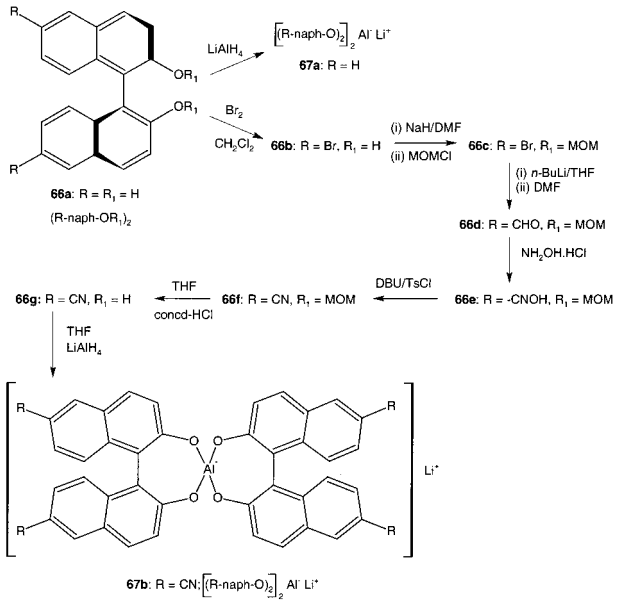
Patent No. U.S. 6,090,969

Assignee: Nagase and Co. Ltd., Osaka, Japan

Title or Subject: Production of a Chiral Binaphthol Compound Using a Non-Rare Earth Metal Complex

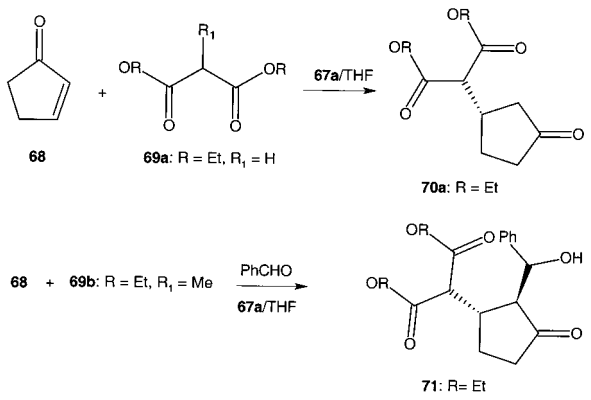
This patent describes *R*-binaphthol Li/Al complexes such as **67a** in high optical purity that are used as catalysts for both asymmetric Michael additions and hydrophosphorylation reactions. Previous work by this group on La binaphthol complexes is referred to (e.g., *Tetrahedron Lett.* **1994**, *35*, 227; *J. Am. Chem. Soc.* **1994**, *116*, 1571) and dismissed because of the difficulty of obtaining lanthanum. Hence, this patent claims that there is a need for the optically active non-rare earth *R*-binaphthol complexes such as **67a**.

Scheme 22



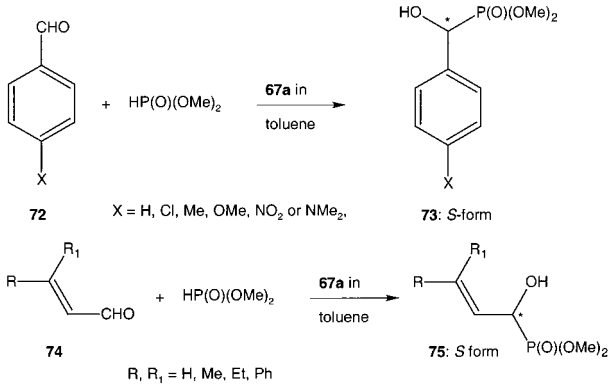
The complex **67a** is prepared by treatment of the *R*-binaphthol **66a** with $LiAlH_4$. Similarly the complex **67b** is made from the 6,6′-dicyano binaphthol **66g** which is prepared by a multistep route shown in Scheme 22. The patent also describes the preparation of analogous Na/Al and Ba/Al complexes and gives examples of the use of the *R*-form of **67a** or **67b** to catalyse asymmetric Michael reactions of cyclopentanone with malonate esters **69** (R = Me, Et, or Bn) to give the ketone **70** in 95% ee (Scheme 23). Also described is a three-component Michael reaction between **69**, benzaldehyde, and cyclopentanone to give the keto alcohol **71** in 93% ee. Examples of both types of reaction are also given using cyclohexanone.

Scheme 23



The final aspect of this comprehensive patent is the use of *R*-form of **67a** in a hydrophosphorylation reaction between various aldehydes and dimethyl phosphite (Scheme 24). Several benzaldehydes **72** are used to produce the *S*-form of the phosphonate **73**. The reaction is also effective when using unsaturated aldehydes **74** to give the unsaturated phosphonates **75**. In total the patent contains over 40 experimental examples most of which contain ^{1}H NMR data.

Scheme 24



Advantages

The key point made in this patent is that the binaphthol complexes do not contain rare earth metals and are therefore cheaper and more readily available. The catalysts are produced in high optical purity and give high optical yields in the various reactions.

Patent No. U.S. 6,093,823

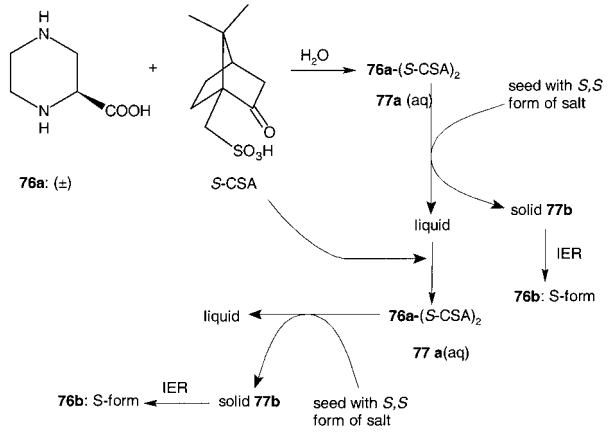
Assignee: Degussa AG, Frankfurt, Germany

Title or Subject: Continuous Production of Optically Active Piperazinecarboxylic Acid.

The title compound is an α-amino acid and the *S*-form **76b** is used in the synthesis of an HIV proteinase inhibitor. This patent provides a method of resolving the racemate **76a** and recovering the desired diastereomer. The method used is to react the racemate **76a** with *S*-camphorsulphonic acid (*S*-CSA) as a chiral auxiliary acid to obtain the diastereomeric salt pairs in solution **77**. The salt pairs have 2 mol of *S*-CSA per mole of **76**. This solution is seeded with the *S*,*S*-

diastereomer and allowed to crystallise. The crystals are the *S*,*S*-form and are removed and collected. The mother liquor is treated with more *S*-CSA, and this causes racemisation of the solution, and a second solution of the salt pairs **77** is produced. This is seeded as before, and then more *S*,*S* crystals are obtained. The cycle is repeated as often as needed, and finally the crystals of the salt can be converted to the *S*-form of **76** (>99% ee) by the use of a cationic IER. The key finding here is that the chiral acid used to resolve the racemate is also capable of racemising the mother liquor. This is claimed to be most unusual and is clearly of benefit in improving the economics of the process. The patent does claim that if racemisation of the amino acid is difficult then it is beneficial to add up to 0.1 equiv of benzaldehyde or salicaldehyde although no examples are given (Scheme 25).

Scheme 25



Advantages

The main advantage is the ability to use a single compound as both resolving and racemisation agent, namely the *S*-CSA. Thus, recycling of the *S*-CSA is much simpler, and extra components are not required so that the overall process yield is improved.

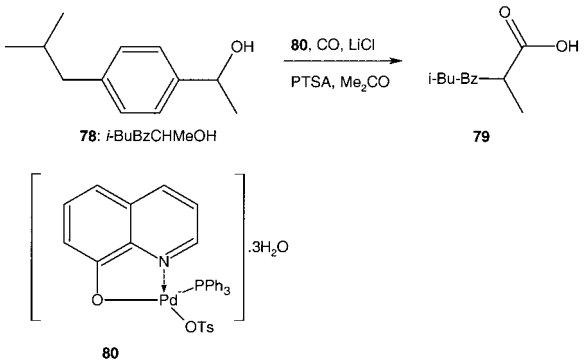
Patent No. U.S. 6,093,847

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

Title or Subject: Process for the Preparation of Ibuprofen

Ibuprofen **79** is a widely used antiinflammatory drug and made by several generic suppliers. The original multistep process has been changed radically and an environmentally friendly process was introduced a few years ago that involves the carbonylation of *p*-isobutylphenylethanol **78**, and this patent discloses a new Pd catalyst for this step. The process involves reacting **78** with CO in the presence of LiCl, PTSA, and the Pd catalyst **80** (Scheme 26). The reaction is carried out in a solvent such as acetone, THF, or MEK containing water and at a pressure of between 15 and 65 bar of CO. This reaction uses a homogeneous catalyst, and the major problem with such catalysts is the separation and recovery of them. This reaction can be run under biphasic conditions that certainly assist in the separation of the catalyst by keeping the product and catalyst separated. The patent claims that excess product does not lower reaction rate and there is a benefit of the biphasic process. The full details of the preparation of the catalyst are not given but are the subject of another U.S. patent application.

Scheme 26



Advantages

This process provides a highly selective carbonylation step that is claimed to be under relatively mild conditions by virtue of the novel active catalyst. However, some examples are carried out at 65 bar pressure, and if this is necessary, then increased equipment costs could outweigh other advantages. The process also avoids the use of excess ligands, thus improving the recovery and purification of the ibuprofen.

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