Organic Process Research & Development **2006**, *10,* 19–27

Highlights from the Patents

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

Summary

The current selection of 20 patents was from an original list of 191. This is about 70 less than usual, so it is tempting to wonder whether the rate of innovative process patents is reducing. Despite the reduced number, it is hoped that there is still something of interest. Metathesis reactions can be very useful, but many catalysts are extremely reactive and difficult to handle. An air-stable, recyclable chiral Ru carbene catalyst has been developed that catalyses functionalised olefins metathesis reactions. The purifications of products can present as many challenges as do their syntheses whether the compound is a drug or a monomer. Lactic acid is used to prepare biodegradable plastics, and as is common in plastics, clarity, and colour of the monomers are important. The presence of pyruvic acid impairs the quality of the final material, and a process for its removal from lactic acid uses ion-exchange resins. A range of novel triazoles has been described that are useful in preparing antifungal compounds. The process is highly stereoselective to one pair of enantiomers, thus making separation and purification easier. Supercritical fluids are becoming of more interest for reactions and extraction of products. A patent describes an extremely selective hydrogenation process for preparing levulinic acid in supercritical fluids, but unfortunately it requires a pressure of 250 bar of H_2 which will limit its commercialisation. A new process for preparing the versatile reagent DMAP is described that gives high-purity product but at the expense of using benzene as an extraction solvent. A highly selective and mild reductive amination process has been described for the production of several benzodiazepines that are used in treating various cancers. Two patents describe improved methods of making acetylenic alcohols by reaction of acetylene with carbonyl compounds. In one an ion-exchange resin is used as the catalyst, and the other uses strong alkoxides. A method for the large-scale synthesis of oxadiazoles is described, but the patent does not give any examples of the large-scale process. Catalytic hydrogenation of nitriles is a common procedure for making amines. Unfortunately, the reactions tend to be nonselective with mono-, di-, and triamines all being produced. An improved process for producing dimethylaminopropylamine is described in which NaOH is added to the hydrogenation catalyst to improve the reaction selectivity. The use of ozone on a large scale is not an attractive proposition, but a patent describes its use as an oxidant for producing a β-aminoaldehyde that is used in making the antibiotic vancomycin. Donepezil is used in treating senile dementia, and a new method for producing the drug is described. There is certainly a trend towards claiming that new processes are ecofriendly or environmentally benign. A number of patents claim to have these qualities, but they are not always obvious. A process for making bromobenzene has such claims and uses in situ generated HOBr as the brominating agent. On the same theme an improved method of dealing with by-product streams in the production of dinitrotoluene in a nitration reaction is described. The new process recovers the desired product and oxidises several by-product nitrophenols, thus reducing the load on the waste treatment facilities. A process for making 1,2,4-butanetriol also has an environmental aspect. It avoids using THF in a reduction reaction since it claims that THF forms peroxides and is difficult to remove from waste streams. Alcohol or glycol ether solvents are preferred. A number of the patents report experimental details involving the production of multikilogram quantities of products. These processes may therefore be assumed to be in an advanced stage of development if not in commercial production. Apart from this there is no legal or commercial significance for the selection. The advantages mentioned are those claimed in the patent unless this reviewer has prior knowledge.

Patent No. U.S. 6,939,972

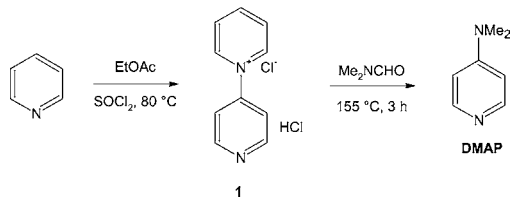
Assignee: M/s Jubilant Organosys Limited, Noida, India

Title or Subject: Process for Producing DMAP

DMAP is very widely used as a catalyst for acylation reactions, and there are a number of processes for its preparation. It is claimed that these are not technically or economically viable but since the material is commercially available this is clearly not the case. However, some processes for making DMAP do produce HCN and NaCN; hence, there are known safety problems. The patent describes a process for producing DMAP that is summarised in Scheme 1. The process begins with the preparation of the HCl salt **1** by a quaternisation reaction of pyridine using $SOCl_2$ in EtOAc. There are examples describing this step using both virgin and recovered raw materials. In the second step the salt **1** is treated with DMF as the aminating agent. Following this reaction there is a neutralisation stage using NaOH, and the product is extracted with benzene. As an alternative the neutralisation can be carried out after the reaction mixture has been extracted with $CHCl_3$. Examples of both methods are given with the preferred method being the use of benzene which gives DMAP of purity >99.8% and a molar yield of 65%. A problem with the use of $CHCl_3$ is a greater loss of solvent and a slightly lower yield of DMAP (63.8%).

10.1021/op050238d CCC: $33.50
Published on Web 12/23/2005

Scheme 1



Advantages

The process gives high-purity product but uses benzene for extraction, and this is not a favoured solvent.

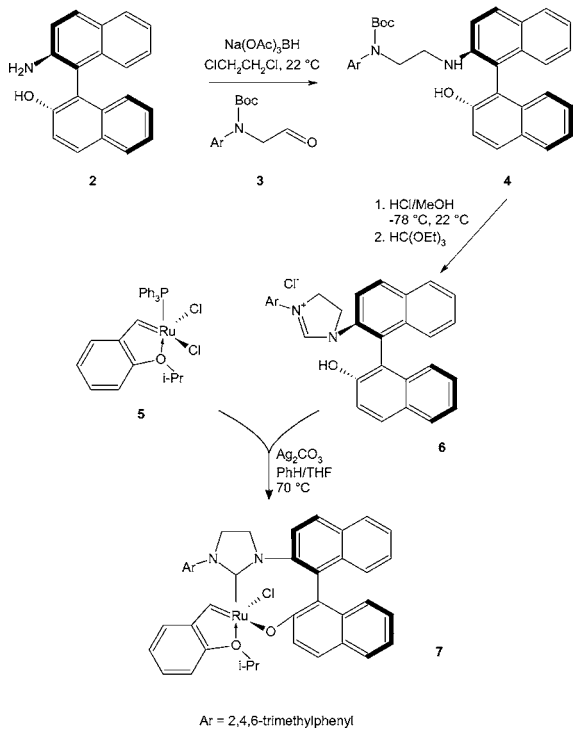
Patent No. U.S. 6,939,982

Assignee: the Trustees of Boston College, Chestnut Hill, Massachusetts, U.S.A.

Title or Subject: Recyclable Chiral Metathesis Catalysts

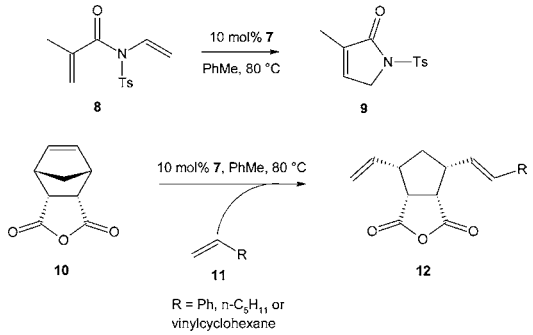
Metathesis reactions are finding greater use since the development of chiral catalysts that can metathesise functionalised olefins. Both ring-opening and ring-closing asymmetric reactions are known in which chiral catalysts are used. One drawback is that the catalysts are extremely air sensitive and hence require special handling techniques. It is also not always appreciated that the high sensitivity and reactivity of the catalysts means that high-purity starting materials are required. This patent discloses catalysts that are relatively stable and that can be recycled and reused. The main subject of the patent is the ruthenium complex **7** that is prepared by the route shown in Scheme 2. The amino alcohol is prepared in 98% yield by reductive amination involving pure **2** and aldehyde **3** in the presence of $Na(OAc)_3BH$. The optically pure salt **6** is prepared in a two-step procedure and is obtained in 83% yield. Reaction of **6** with the Ru carbene complex **5** gives **7** that is purified by silica gel chromatography and isolated in 52% yield.

Scheme 2



Compound **7** is shown to be an active and stable metathesis catalyst. Scheme 3 shows some of the reactions that it is used in, and the patent contains examples of several other olefins. The *ee* of product **12** is >98% showing that they are highly enantioselective. Some of these reactions can take place in air, and this is an unusual feature with metathesis reactions. The catalysts can also be recovered by chromatography and reused. The patent includes X-ray crystallographic data for **7**.

Scheme 3



Advantages

The main advantage of these catalysts appears to be that they are stable and can be recovered and reused.

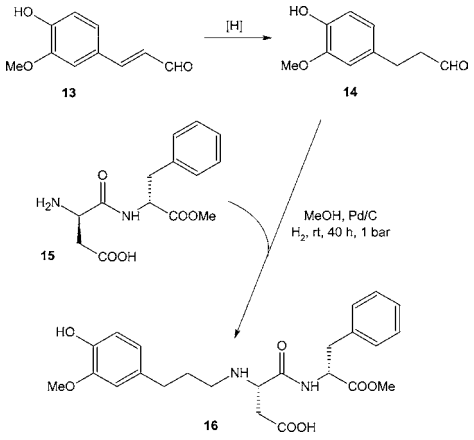
Patent No. U.S. 6,939,987

Assignee: Ajinomoto Co., Inc., Tokyo, Japan

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

Aspartame **15** is a sweetener that is suspected of having adverse health effects but its derivatives do not have these problems. Patents on this topic have been reviewed (*Org. Process Res. Dev.* **2005**, *9*, 244 and 719), and a great deal of work is underway to develop commercially viable methods for the production of aspartame derivatives. This patent describes the preparation of compound **16** from **15** and the aldehyde **14** and also describes how **16** can be purified by crystallisation. The preparative route to **16** is carried out in the presence of a reducing catalyst under hydrogen. The patent mentions that the reduction of unsaturated aldehydes such as **13** to give **14** uses the same types of catalyst as for the production of **16**. It would seem that **13** cannot be used directly to prepare **16** and its acetals or hydroxy-protected derivatives are preferred.

Scheme 4



The purification of **16** is carried out by initial crystallisation from solvents such as EtOAc/MeOH followed by extracting with water to remove impurities and recrystallising from MeOH/water. The final product purity was >99%.

Advantages

The novel compound **16** is a possible replacement as a sweetener for a product that is not considered totally safe.

Patent No. U.S. 6,942,803

Assignee: A. E. Staley Manufacturing Co., Decatur, Illinois, U.S.A.

Title or Subject: Process for Purifying a Organic Acid

The patent is aimed at the purification of lactic acid (LA) produced by fermentation. LA is used to produce polylactic acid (PLA) that is a biodegradable plastic with a wide variety of uses. As with many plastics, clarity and colour are important, and the presence of impurities impairs the quality of the final material. When LA is produced by fermentation it contains other organic acids such as pyruvic acid (PA) that give rise to colour problems in PLA. The patent discloses a process for removing acids such as PA by a multistep procedure. This process removes PA and other acids using a basic extractant that is immiscible with the fermentation mixture. The patent describes examples in which weakly basic ion-exchange resins (IER) are used or primary amines with >8 C atoms. The amine or IER is chosen so that it preferentially complexes with the PA. The choice is based on pK_a values, and the separation of the complexed acid from the solution of LA is simple because it is insoluble. Acidification of the complex releases the PA, and the amine or IER can be regenerated and reused. The LA can then be further purified by being removed itself by complexation using a different amine or IER. The LA is then released by treating the complex with an acid, and the released aqueous LA is concentrated prior to crystallisation.

Advantages

The process is capable of purifying large volumes of aqueous solutions that are commonly produced in fermentation.

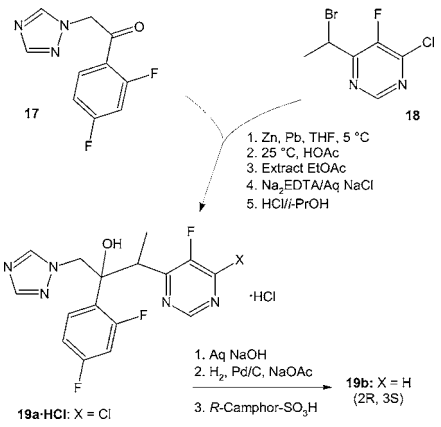
Patent No. U.S. 6, 946,555

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

Title or Subject: Preparation of Triazoles by Organometallic Addition to Ketones

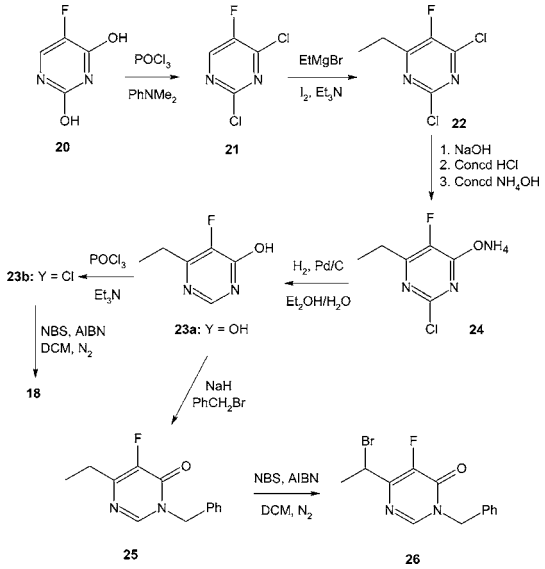
The two claims of this patent cover the compounds **18** and **26** that are both novel, and hence the patent is what is known as a composition of matter patent. However, the subject matter covers the preparation of triazoles such as **19** that are useful in preparing compounds having antifungal activity. Scheme 5 shows the preparation of the HCl salt of **19a** from **17** and **18**. This reaction produces a mixture of the enantiomers with the *2R,3S/2S,3R* pair being desired over the *2R,3R/2S,3S* pair. It has been found that the reaction gives a stereoselectivity >90% to the desired pair of enantiomers. The desired stereoisomer was obtained from this mixture by first converting the salt **19a**·HCl to the mixture of free bases **19b**, and this was then resolved by forming the *R*-camphorsulphonate salt.

Scheme 5



The patent also provides a method of preparing compound **18** shown in Scheme 6. The method starts from **22** that is made from **20** by chlorination using $POCl_3$ followed by alkylation in a Grignard reaction. **22** is converted to **23b**; when this is treated with NBS/AIBN, **18** is obtained. The examples describe the preparation of over 60 kg using this procedure so that it is clearly a viable large-scale method. Scheme 6 also shows how **23a** can be converted to **26** that can be used in place of **18** to produce an analogous triazole to **19a** and **19b**. Basic ^{1}H NMR data are provided for the novel compounds.

Scheme 6



Advantages

The patent provides some novel multifunctional compounds that have uses in producing pharmaceutical materials.

Patent No. U.S. 6,946,563

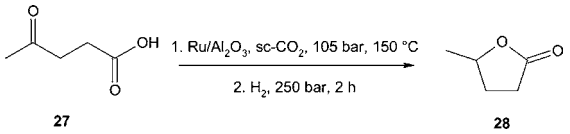
Assignee: E.I. Du Pont De Nemours and Company, Wilmington, Delaware, U.S.A.

Title or Subject: Production of 5-Methyldihydrofuran-2-one from Levulinic Acid in Supercritical Media

Levulinic acid **27** is easily obtained from various cellulose feedstocks and has been the subject of previous patent reviews (*Org. Process Res. Dev.* **2005**, *9*, 244). **28** is a useful

synthetic intermediate and can also be used to prepare polyesters. The process described here exploits advantages of using supercritical fluids (SCFs) as reaction solvents. The use of SCF-mediated reactions and SCF extraction has seen a significant increase in interest the past few years, and in fact commercial processes are widely used. SCFs are used in this process in the hydrogenation of **27** to **28** as shown in Scheme 7. The catalyst used is a commercially supported Ru that is reduced prior to use. The process is extremely efficient for producing **28** with a 99.5% conversion of **27** and a selectivity of 99.7%, and the patent gives examples of both batch reactions and of a continuous flow method

Scheme 7



27 **28**

Advantages

The process in this patent provides a very efficient method for producing **28**, but unfortunately it involves the use of hydrogen at 250 bar pressure.

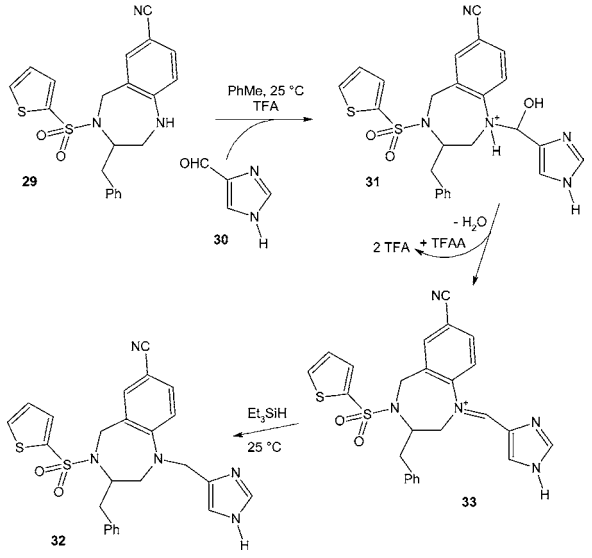
Patent No. U.S. 6,949,642

Assignee: Bristol-Myers Squibb Co., Princeton, New Jersey, U.S.A.

Title or Subject: Production of Tertiary Amines by Reductive Amination

The particular amines of interest in this patent are benzodiazepines such as **32** that are inhibitors of farnesyl protein transferase and have potential in treating a variety of cancers. Alternative routes to these compounds are known but are not very selective. The route used is shown in Scheme 8 and begins with the formation of the aminal **31** from **29** and **30**. **31** is not isolated and decomposes by loss of water to give the iminium salt **33** that again is not isolated but reduced to **32** by using Et_3SiH. All reactions take place at about room temperature, giving a 100% yield of crude **32**. The mesylate salt of **32** can be prepared directly in yields of up to 97%.

Scheme 8



Water is formed In production of the iminium salt **33**, and the patent stresses that the water is removed by a using TFAA as water scavenger. The use of TFAA dramatically increases the rate of the reaction; hence, the time is reduced, making production less costly. An additional benefit of using TFAA is that a near quantitative yield of **33** is obtained, and this eliminates costly competitive side reactions and losses of the expensive Et_3SiH in the reducing step.

Advantages

The process clearly gives extremely high yields of desired product using very mild reaction conditions.

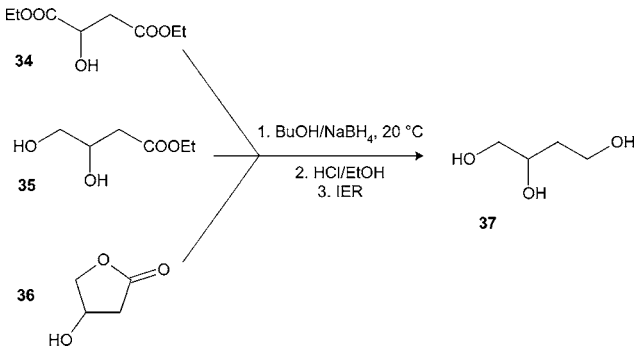
Patent No. U.S. 6,949,684

Assignee: Daiso Co., Ltd., Osaka, Japan

Title or Subject: Process for Preparing 1,2,4-Butanetriol

Chiral **37** is a useful intermediate for the production of pharmaceutical and agricultural chemicals. **37** can be prepared by hydrogenolysis of diethyl malate **34**, but maintaining the stereochemistry is difficult because nonspecific reagents such as $LiAlH_4$ or BH_3/Me_2S are used. In addition the patent states that when using THF as a solvent this may form peroxides and produces waste-disposal problems. The patent describes a stereospecific process for the production of **37** from malate esters or other precursors such as **35** or **36** that avoids the use of THF. The various reactions are shown in Scheme 9. The patent claims that the reduction step should be carried out using an alcohol with at least four C atoms. Examples using the various butanols are given. However, there are many examples of alternative solvents such as EtOH or even glyme, diglyme, or EtOH/PhMe, and they seem to be as selective as the butanols. After the reduction step a second alcohol is added to the mixture, and then it is acidified. In this step the patent claims that a different alcohol is needed, and EtOH seems to be preferred. The acidified solution is then passed over an anionic IER to remove residual boron, and the product is purified by distillation. In the examples racemic precursors as well as chiral precursors are used, and either *R*- or *S*-enantiomers produce a product **37** that has high ee, and this is often 99%.

Scheme 9



Advantages

The process maintains the stereochemistry of the starting material, and it does not produce waste streams that are difficult to handle.

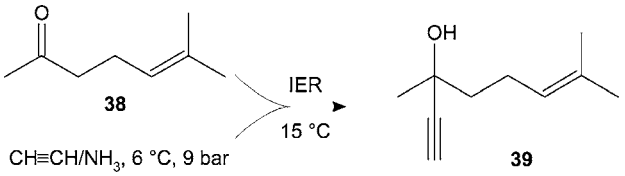
Patent No. U.S. 6,949,685

Inventors: W. Bonrath, B. Englert, R. Karge and M. Schneider, Germany and Switzerland

Title or Subject: Ethynylation Process

Acetylene-based chemistry was the backbone of the chemical industry for many years before ethylene and is still of importance where acetylene is readily available. This is the first of two patents for producing acetylenic alcohols from carbonyl compounds and acetylene. This patent using strongly basic IER catalysts as opposed to strong bases for the reaction, and the single example in the patent details the production of **39** from the ketone **38** (Scheme 10). The reaction is carried out by passing a solution of acetylene in liquid NH_3 and **38** over an IER in a tubular reactor. The product is recovered in a separator and the acetylene solution recycled. The GC showed that the alcohol contained about 0.34% by area of a diol by-product. The identity of this diol is not revealed, nor is there any proposal as to how it is formed. The catalyst was operated for 1000 h and can be regenerated by washing with MeOH containing 5% KOH.

Scheme 10



The reaction is not new, and IERs catalysts have been used in other work. However, the present process uses macroporous IERs unlike the gel-type IERs that have been used previously without success. It is well-known that gel-type resins are less physically strong than the macroporous types, and this seems to be the reason for the improved reaction activity and life. Although there are no other examples, the patent does claim that a wide range of carbonyl compounds can be used in the reaction.

Advantages

The reaction uses more active and robust IERs to improve the process.

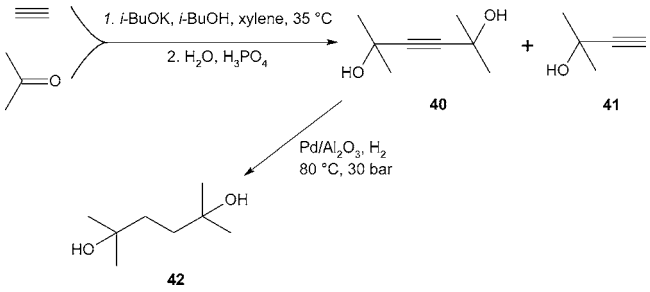
Patent No. U.S. 6,956,141

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Method for Preparing Acetylene Alcohols and Their Secondary Products

This is the second patent on acetylenic alcohols, and its stated aims are to provide an economic and ecologically efficient method of producing unsaturated and saturated alcohols from acetylene and carbonyl compounds. This patent focuses on the preparation of **40** that can be hydrogenated to give **42** as shown in Scheme 11. The production of **40** is carried out on a continuous basis by the condensation of acetylene and acetone in the presence of *i*-BuOK followed by hydrolysis and neutralisation using aqueous H_3PO_4. The conversion is 98% with a 90% yield of **40**. The reaction also produces 2.3% of **41.** The process can be altered to give **41** as the major product. This can be done by adjusting the ratio of starting materials and the residence time in the reactor. An alternative method that can increase the quantity of **41** is to use catalytic quantities of base. Using the former method the yield of **40** in **42** was 14% but using the latter method it was reduced to 3%. Whatever the desired product, the purification is by distillation.

Scheme 11



Advantages

The process gives high yields of product, but this is probably only feasible if the reaction is run on a continuous basis.

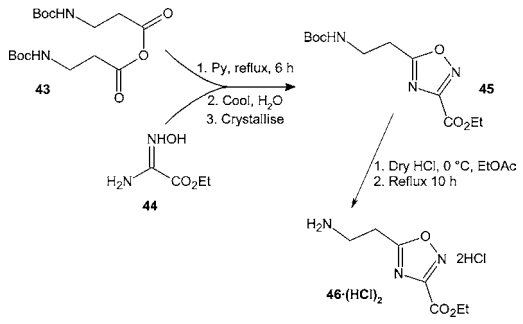
Patent No. U.S. 6,951,946

Assignee: Lexicon Pharmaceuticals Inc., New Brunswick, New Jersey, U.S.A.

Title or Subject: Large-Scale Synthesis of 1,2,4- and 1,3,4-Oxadiazole Carboxylates

The title compounds are said to be useful as antiviral agents, antiinflammatory agents, and neuroprotectants. Methods for the preparation of both types of compounds are said to be inefficient, involve hazardous procedures or compounds, and are not suitable for scale-up. The preparation of the 1,2,4 oxadiazole compound **46** is by reaction of the Boc protected anhydride **43** with the amidoxime **44**. This gives compound **45**, and when the Boc protection is removed, the dihydrochloride salt of **46** is obtained (Scheme 12).

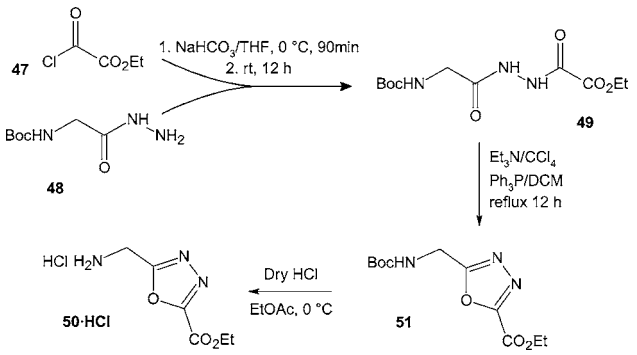
Scheme 12



The patent also provides details of a range of analogues of **46** in which the 2-aminoethyl group is replaced by 1-aminoethyl or aminomethyl.

The second part of the patent covers the preparation of 1,3,4 oxadiazole compounds such as the HCl salt of **50**. Scheme 13 summarises the reactions to give **50** via **51** that is prepared by cyclisation of the diacylhydrazide **49**.

Scheme 13



The patent provides NMR data for all of the compounds prepared, and details of the preparation of intermediates **43, 44**, and **49** are also given.

Advantages

The processes are claimed to be capable of being scaled-up but no examples are given to support this.

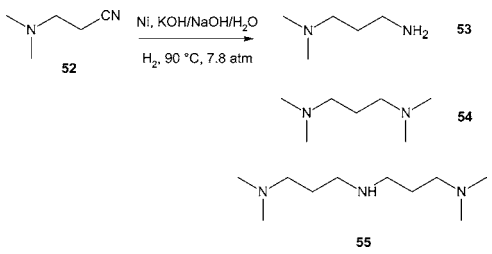
Patent No. U.S. 6,951,959

Assignee: Solutia Inc., St. Louis, Missouri, U.S.A.

Title or Subject: Low Pressure Process for the Manufacture of 3-Dimethylaminopropylamine(DMAPA)

DMAPA **53** is used to manufacture a variety of industrial products, and it also has uses as a synthetic intermediate. A common method of producing amines is by catalytic hydrogenation of nitriles. Ni catalysts are usually used although other platinum group metals are also suitable. The reaction is usually carried out in the presence of NH_3, and this inhibits formation of secondary amines and other by-products. The normal route used to produce **53** is from **52**, and this gives by-products such as **54** and **55** as shown in Scheme 14. The removal of **54** is especially difficult by distillation, and new uses for **53** require levels of **54** <300 ppm so that improved methods for the synthesis or purification of **50** are needed. The patent discloses that the amount of by-products can be reduced by modifying the Raney Ni hydrogenation catalyst using alkali hydroxides. The reaction takes place under very moderate conditions and gives a very high selectivity to **53** with the total level of by-product amines <300 ppm and that of **54** <45 ppm.

Scheme 14



Advantages

The reaction is more selective than previous processes and takes place under much milder conditions than some alternative procedures.

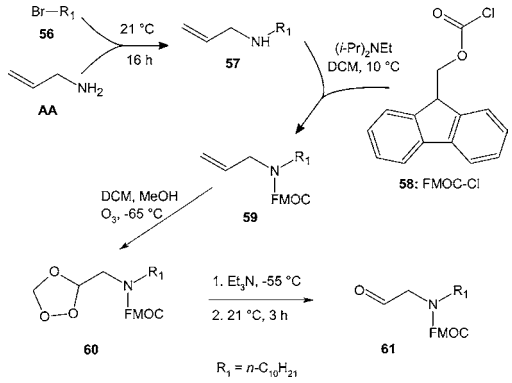
Patent No. U.S. 6,951,963

Assignee: Theravance Inc., South San Francisco, California, U.S.A.

Title or Subject: Process for Preparing N-Protected β-Amino Aldehyde Compounds

This patent describes a method of producing intermediates such as **61** that are useful in the synthesis of glycopeptide antibiotics. The alternative methods for preparing **61** involve an oxidation reaction using SO_3, $(COCl)_2$, or DMSO. It is stated that these reagents give rise to an unpleasant odour in the final product and hence claim that an improved oxidation procedure is required. The oxidant used in this procedure is ozone, and the route to **61** is shown in Scheme 15. The amine **57** is easily prepared from allylamine (AA) and **56**; its amine group is then protected by conversion to **59** using **58**. The ozonolysis of **59** gives **60** that is not isolated but is converted to **61** using Et_3N. The by-product amine oxide is water soluble and is easily removed from **61** that is obtained in at least 61% yield.

Scheme 15



The product **61** was used to prepare vancomycin hydrochloride, a commercially available antibiotic.

Advantages

The process removes the odour problems from alternative oxidants but does involve hazards by using ozone.

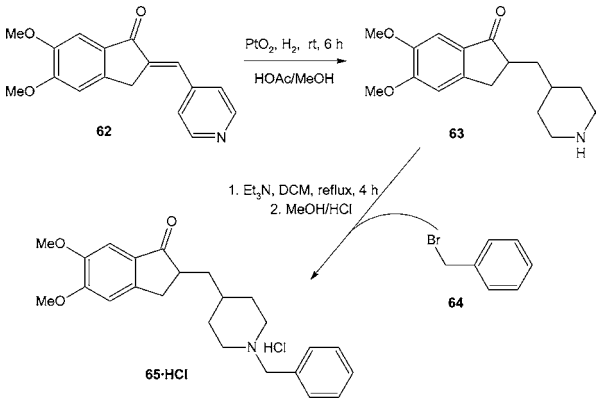
Patent No. U.S. 6,953,856

Assignee: USV Limited, Mumbai, India

Title or Subject: Process for the Preparation of Donepezil Hydrochloride

Donepezil **65** is used as its hydrochloride salt **65**·HCl in the treatment of senile dementia. This patent describes a new method for the preparation of **62**, and new polymorphs of this compound have been reviewed previously (*Org. Process Res. Dev.* **2001**, *5*, 557). There are several alternative syntheses of **65** that are said to have a numerous shortcomings such as having a large number of steps or using expensive and hazardous reagents. The route used in this patent is shown in Scheme 16 and begins with **62** that is hydrogenated to **63** using PtO_2 in HOAc as solvent containing MeOH. In what must be a gross oversight the patent does not mention using H_2 in the hydrogenation reaction. In the next step **63** is alkylated with **64** in the presence of Et_3N to give **65**. The free base is not isolated but is converted to the HCl salt that is obtained in an overall yield of 95.5%.

Scheme 16



Advantages

The process described is straightforward and is claimed to use cheap nonhazardous raw materials and that the key starting material, the indanone **62**, is readily prepared.

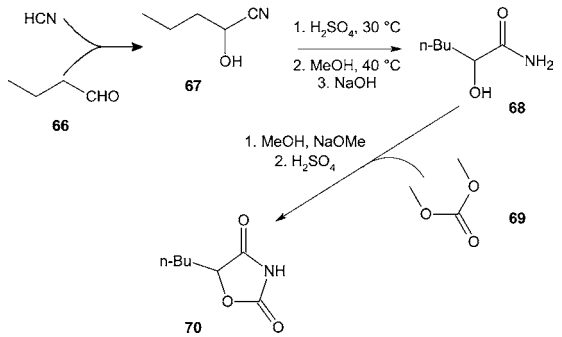
Patent No. U.S. 6,953,859

Assignee: Showa Denko K. K., Tokyo, Japan

Title or Subject: Process for the Production of 5-Alkyloxazolidin-2,4-dione

The subject of this patent **70** is used in the production of agrochemicals and photographic chemicals. There are industrial processes for unsubstituted analogues of **70**, but it is said that only one patent covers a method for **70** itself. The method is described as prolonged because it produces waste streams resulting from the use of 2-halocarboxylic acids. The process described in this patent is shown in Scheme 17. The starting point is the cyanohydrin **67**, formed from HCN and **66**, that is hydrolysed to the hydroxyamide **68**. This is condensed with dimethyl carbonate **69** using NaOMe to give **70**. The reaction is carried out by feeding a solution of NaOMe and **69** to **68** in MeOH over 2 h at 60−70 °C. The reaction initially gives the Na salt, and upon acidification with H_2SO_4 **70** is obtained in 99.5% purity. The patent claims cover other alkyl substituents of **70** although there are experimental details for only the butyl compound.

Scheme 17



Advantages

The process is very straightforward, with the handling of HCN the only obvious difficulty.

Patent No. U.S. 6,953,869

Assignee: Bayer MaterialScience AG, Leverkusen, Germany

Title or Subject: Process for Working Up Secondary Components in the Preparation of Dinitrotoluene

The production of nitroaromatics can often give rise to waste disposal problems. In the production of dinitrotoluene (DNT) nitrophenols are the major cause for concern, and the patent provides a method for dealing with them. The offending compounds are present in the acidic and alkaline wastewater streams from the washing of DNT. They are also present in aqueous distillate obtained from the concentration of H_2SO_4. The process combines these streams in a static mixer at 70 °C and adjusts the pH to be <5. It is also mentioned that $PhNO_2$ can be added to the combined waste streams to give a concentration of up to 4 wt %. This is said to assist in phase separation, and it also lowers the melting point of the mixed stream, thus allowing it to be easily pumped. The combined stream is allowed to separate, and the organic phase that contains DNT and $PhNO_2$ can be recycled to the nitration process. The patent states that the by-products are oxidised by nitric acid during the mixing step, and evidence for this degradation is provided by the presence of oxalic acid. No analytical data are provided, but clearly the oxalic acid would be present in the aqueous phase and can be dealt with in a waste treatment plant.

Advantages

The process improves efficiency by recycling $PhNO_2$ and recovering product that would be lost in the waste streams. In addition the removal of aromatic compounds from the aqueous waste obviously reduces the load on the waste treatment facilities.

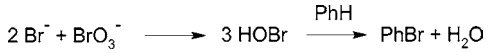
Patent No. U.S. 6,956,142

Assignee: Central Salt and Marine Chemicals Research Institute, Bhavnagar, India

Title or Subject: Process for Eco-Friendly Synthesis of Bromobenzene

Any process that uses or produces halogenated compounds will invariably have a negative environmental aspect. Several methods are known and used to prepare PhBr, and they all have hazards or waste problems associated with them. This process attempts to overcome many of these difficulties by generating in situ HOBr and using this as a highly reactive brominating agent. This is done by treating a mixture of NaBr and $NaBrO_3$ with a strong acid such as H_2SO_4, HCl, or $HClO_4$. The reaction is carried out by refluxing the bromine mixture with benzene in the presence of a surfactant compound as a phase transfer catalyst (PTC). Sodium lauryl sulphate is used as PTC. The reaction is proposed to proceed via the steps shown in Scheme 18. The product is recovered by extraction into Et_2O and purified by distillation. Yields of up to almost 90% of PhBr are obtained. The process is specifically used to prepare PhBr, and there no mention of its being applicable to other bromoaromatics.

Scheme 18



Advantages

The bromine compounds used in the process are described as nonhazardous so that handling problems are minimised.

Since the process produces only ionic bromides as wastes, the environmental effect is reduced.

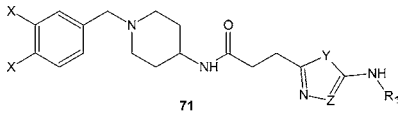
Patent No. U.S. 6,958,350

Assignee: AstraZeneca AB, Södertälje, Sweden

Title or Subject: Piperidine Compounds and Their Use in Treating Chemokine Receptor Diseases

The actual title of this patent is "Chemical Compounds" and this is clearly not meant to be very informative. It was only examined out of curiosity, and it relates to piperidine compounds that are useful in the treatment of chemokine receptor diseases such as asthma and other allergic disorders. It is also claimed that such compounds can be used in treating AIDS and as antirejection drugs in organ transplants. The patent covers a substantial amount of work and includes many novel compounds, most having the general formula of that of **71**.

Piperidines

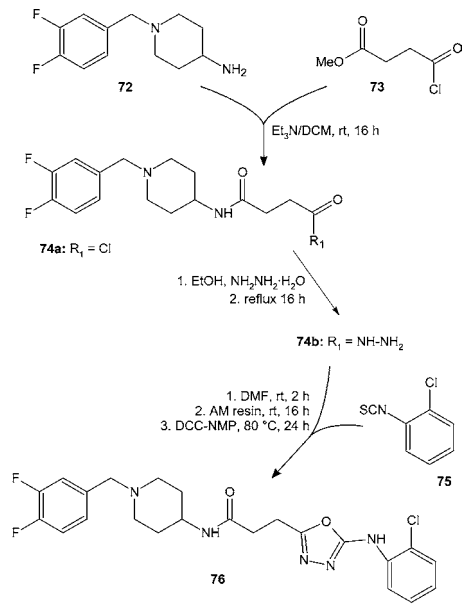


71

X = F or Cl
Y = N, O or S
R_1 = aryl, aklyl or hetero

This review covers only one of these, **76**, and its synthesis is summarised in Scheme 19. The initial reaction is between **72** and **73** to give the intermediate chlorocarbonyl propionamide **74a** that is not isolated but on reaction with hydrazine gives **74b**. This compound then undergoes a condensation reaction with **75** and eventually gives **76.** This multistep reaction sequence is again carried out without isolation of any of the intermediates. The ring-closing reaction is promoted by the polystyrene-supported DCC.

Scheme 19



DCC-NMP = dicyclohexylcarbodiimide N-methylpolystyrene HL

The patent covers over 70 compounds and includes a substantial amount of ^{1}H NMR data for many of these. There are also details of the pharmacological analysis in tests in which the compounds were used.

Advantages

The patent describes several novel compounds and processes for their preparation, and these have potential as pharmaceutical ingredients for a range of treatments.

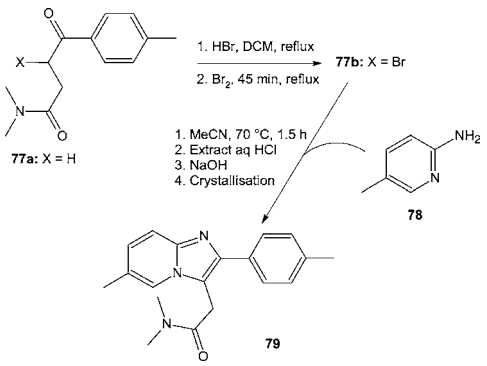
Patent No. U.S. 6,958,417

Assignee: Boehringer Ingelheim Pharma KG., Ingelheim, Germany

Title or Subject: Process for Preparing Zolpidem

Zolpidem **79** is a sedative that can be made by a process involving six steps, and the patent claims that the process is laborious. The claims and subject of this patent, in fact, cover the preparation of **77b** by bromination of **77a** using HBr and Br_2 in DCM (Scheme 20). An alternative method is also described in which **77a** is reacted with Br_2 in HOAc. By using the preferred procedure **77b** is not isolated and is converted to **79** by reaction with **78**. This condensation and ring-closure reaction takes place in MeCN. The product is recovered by extraction into HCl, and after neutralisation and washing, **79** is obtained as a crystalline material in 30% yield.

Scheme 20



Advantages

The process involves fewer steps than the alternative but only gives a yield of 30%.

Patent No. U.S. 6,958,418

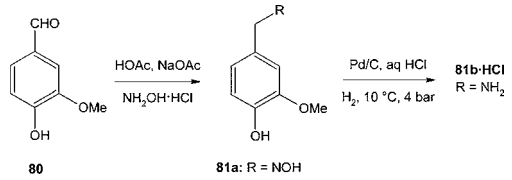
Assignee: Boehringer Ingelheim Pharma KG., Ingelheim, Germany

Title or Subject: Process for Preparing Vanillylamine Hydrochloride

The HCl salt of vanillylamine **81b** is used in the preparation of compounds used in plasters to help increase the blood flow in the protected tissue. **81b** is prepared from the oxime **81a** by hydrogenation, but there are said to be difficulties with the method on an industrial scale. Hence, this patent discloses an improved process for the preparation of **81a** and thus **81b**. The method used is shown in Scheme 21 and begins with the preparation of the oxime **81a**. The key to this step is the use of NaOAc in glacial HOAc. The

product is not isolated, and the process is continued in the same vessel with the hydrogenation using Pd/C, giving a yield of **81b** of 82%.

Scheme 21



80 **81a**: R = NOH

Advantages

The process is claimed to be much simpler and can be cheaper than the alternative when used on an industrial scale.

Keith Turner

Kappa Tau Consulting, 12 The Avenue, Fairfield, Stockton-on-Tees TS19 7EY, United Kingdom, Telephone/fax: +44 (0)1642 653484. E-mail: keith@kappa-tau.co.uk

OP050238D