Organic Process Research & Development **2007**, *11*, 663–673

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published Between January and March 2007

Summary

The current review covers 22 patents from an initial selection of 439 that fit the search criteria. There are six patents covering three different statins, and these provide new processes for the manufacture of the drugs and various intermediates plus novel amorphous and crystalline forms. Two of the patents on the synthesis of rosuvastatin could very well result in some heated debate between the applicants and their legal advisors. The use of metal-containing reagents can create problems in purification of any compound. An interesting method of removing residual Cu residues from quinolinic acid has been described. It involves formation of insoluble sulphides using H_2S and brings back memories of using Kipps apparatus from many years ago. Another unpleasant but seemingly indispensable material in the development chemist's arsenal is dichloromethane. A patent describes how to recover the solvent from aqueous streams; something that development chemists will have to consider if they insist on using the solvent in commercial processes. It is interesting to find how many drugs that are developed to treat one problem end up being used for apparently unrelated problems. The drug finasteride was developed to treat prostrate enlargement and is now under investigation for treating male-pattern baldness, and a patent describes a new method for its preparation. These two conditions that frequently arise at the same stage of life are related to high levels of testosterone. Ritalin is used to treat hyperactive children and is usually used as a mixture of enantiomers. A method for isolating the more active isomer is disclosed that recovers and racemises the less active material. Cyclopropyl compounds are of interest in preparing a number of chemicals, and a new method of preparing cyclopropylethanol and -acetonitrile derivatives is reviewed that is claimed to avoid using toxic or hazardous reagents such as diazomethane or ethylene oxide. The antidepressant citalopram is of interest now that the original patents have expired. A new synthesis is described that uses a reagent made by a process described in 1931; hence, a visit to the dusty bookshelves in the library would seem to be necessary for experimental details. Molecular sieves are very widely used to dry solvents and are also used in reactions such as Sharpless oxidations. One patent describes their use as co-reagents for the preparation of epoxy acids using La isopropoxides. These reagents are extremely susceptible to hydrolysis; thus, molecular sieves are added to the reaction mixture to protect them. The same patent also reports the use of an enzyme in an asymmetric ester hydrolysis to give the desired enantiomers of the acid. The manner of carrying out a reaction can be more important than the reagents that one chooses. An example is given in the oxidation of alkyne alcohols to acids. In the process it was found that simultaneous addition of reagents gave product yields of 75−92% compared to yields <20% by sequential addition. As this review is being written, the hay-fever season has begun, and a patent on the synthesis of the drug fexofenadine is therefore topical. An interesting finding in the work is that Pd residues from an earlier reaction accelerate a Cu-catalysed hydration reaction. The finding is very fortuitous since removing the Pd residues is apparently difficult. A new process for a drug used in treating osteoarthritis is described that has some kilogram-scale experiments, thus indicating that the process is at an advanced stage of development. The imidazole molecule is found in many useful compounds, and the synthesis of some difficult derivatives is described using silylated isocyanides. However, the same patent also reports some experiments that are seriously misleading or totally wrong. The increasing use of highly conductive polymeric materials has given rise to a new method for the synthesis of thiophenes that are used in preparing the polymers. The extraction of salts of 2-hydroxypyridines is used as a means of their purification prior to use in a Williamson etherification reaction. The method removes two steps from the route for making agrochemicals. An improved method of synthesising a key intermediate for the drug Inspra is described that does not require the use of toxic reagents such as diazomethane.

Patent No. U.S. 7,157,583

Assignee: Sumikin Air-Water Chemical Inc., Tokyo, Japan and Hebel Sinochem Fuheng Co. Ltd, Hebei, China

Title or Subject: Process for Producing High Purity 2,3-Pyridinedicarboxylic Acid

The title compound **2c**, also known as quinolinic acid, is used as an intermediate in the preparation of agrochemicals, dyes, and pigments. This patent is related to an earlier patent from one of the assignees that has been reviewed previously (*Org. Process Res. Dev.* **2005**, *9*, 537). The process used to make **2c** involves the oxidation of quinoline using Cu catalysts (Scheme 1). This produces a solution of **2c** that can contain 100−300 ppm of Cu, and this exceeds the allowable limits for Cu in the applications of **2c**. The patent points out that Fe and other heavy metals may be leached from steel equipment used to manufacture **2c** and hence alternative processes used to prepare **2c** had to be carried

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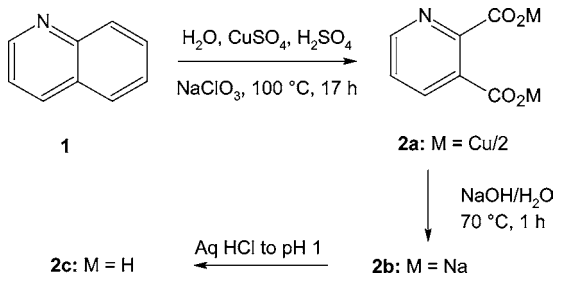
out in nonmetallic equipment to avoid contamination of the product with heavy metals. The patent describes a method for removing Cu by forming the insoluble sulphide that is then filtered off. The procedure also reduces the content of Fe and other heavy metals from the solution and so allows steel equipment to be used. Methods of forming insoluble metal sulphides using H_2S are well-known, and readers may recall the Kipps apparatus used in inorganic analysis. However the use of H_2S is certainly not desirable on an industrial scale.

Scheme 1



The experimental details describe that the sulphides are formed by addition of a solution of Na_2S to the salt **2b**. This precipitates the metal sulphides that can be removed by filtration, and the solution is acidified to form **2c**. The patent claims that hydrosulphides, polysulphides, and sulphur may be used, although no examples are given. In one example Cu is reduced from 211 to 5 ppm and Fe from 31 to <1 ppm, while unspecified heavy metals fall from 120 to <10 ppm.

A concern about this process is the possible formation of H_2S from excess Na_2S upon acidification of the solution after removal of the precipitated sulphides.

Advantages

The process enables the improved oxidation method to be carried out in steel equipment as well as removing excess Cu catalyst.

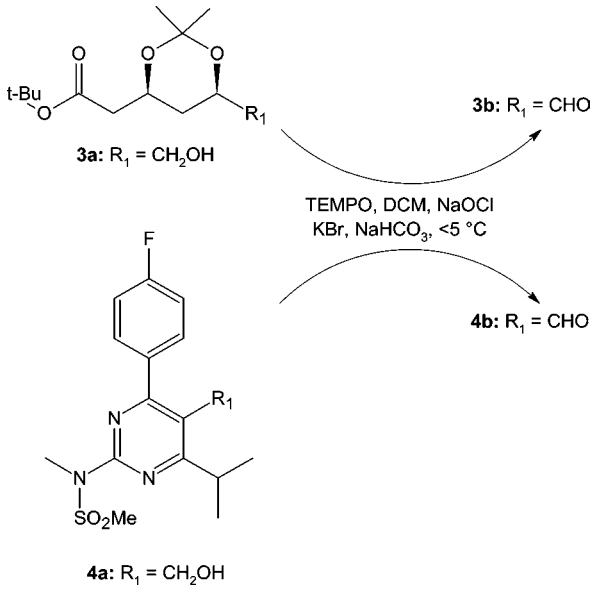
Patent No. U.S. 7,161,004

Assignee: Dr. Reddy's Laboratories, Hyderabad, India, and Bridgewater, New Jersey, U.S.A.

Title or Subject: Process to Produce Intermediates for Rosuvastatin

The various statins are important drugs that are used to treat cardiovascular diseases and to lower cholesterol levels. This is the first of six patents on statins, and one of the two that cover rosuvastatin **7c** that is available as the Ca salt and known as Crestor. This patent describes preparing the compounds **3b** and **4b** that are intermediates in preparing **7c**. Scheme 2 summarises the reactions used to prepare **3b** and **4b** by oxidation of their respective alcohols **3a** and **4a**.

Scheme 2



The oxidation is carried out at <5 °C using TEMPO and NaOCl in dichloromethane (DCM) containing KBr and $NaHCO_3$. The two intermediates have been prepared previously by identical reactions using alternative oxidants such as the expensive per-ruthenates or the hazardous $(COCl)_2$. However, these materials are said to be unsuitable for large-scale use, and hence there is the need to use reagents more suitable for use on commercial-scale production. The actual synthesis of **7c** from the intermediates is not covered in this patent.

Advantages

The process uses more useful, cheaper, and less hazardous oxidants than alternative procedures.

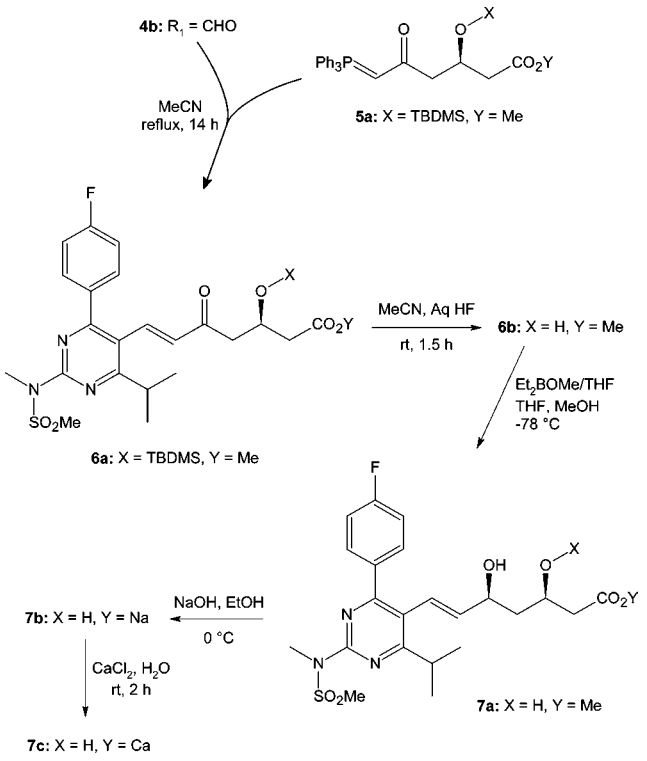
Patent No. U.S. 7,179,916

Assignee: Teva Pharmaceutical Industries, Ltd., Petah Tiqva, Israel

Title or Subject: Process for the Preparation of Rosuvastatin

This is the second patent on the drug rosuvastatin **7c**, and it also describes a method of preparing the intermediate **4b** by oxidation of **4a**. This patent uses the same synthetic route shown in Scheme 2, but the solvents used in the examples are EtOAc, MeCN, MTBE, and PhMe rather than DCM although this solvent is referred to in the claims. It is not the purpose of this review to comment on the legal status or validity of this patent versus the previous one. However, there are striking similarities in the two processes described, and the legal status of these patents will undoubtedly be strongly debated by both parties. This patent describes the use of **4b** in the synthesis of **7c** as shown in Scheme 3. The route shown is straightforward starting from the ylid **5a**, and this compound is prepared by a method from a 1990 Japanese patent.

Scheme 3



Advantages

The intermediates are prepared using oxidising agents that are suitable for large-scale use, but the question of the status of this and the previous patent will obviously need to be addressed.

Patent No. U.S. 7,161,012 and 7,189,861

Assignee: Teva Pharmaceutical Industries, Ltd., Petah Tiqva, Israel

Title or Subject: Processes for Preparing Amorphous Atorvastatin Hemi-Calcium

Atorvastatin is the Ca salt **11** and is available as the drug Lipitor. These two patents describe the preparation of six novel forms of **11** plus novel processes for preparing three known forms and an amorphous form. The various polymorphs are obtained by crystallisation from different solvents or solvent mixtures at differing temperatures. The amorphous form is obtained by either sonication of Forms 1 or VII (covered by the first patent) or by ball milling any form. This is covered in the second patent. Both patents provide detailed methods and XRD data.

Advantages

Additional polymorphic forms of these drugs can improve the commercial value by allowing better formulations to be prepared.

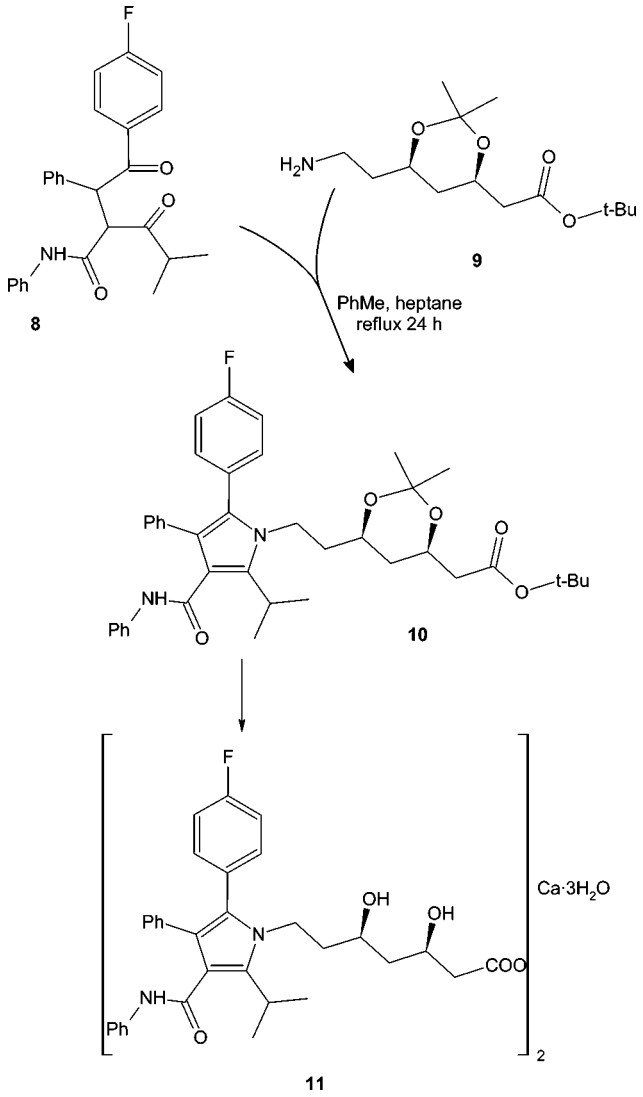
Patent No. U.S. 7,186,848

Assignee: EGIS Gyogyszergyar Rt., Budapest, Hungary

Title or Subject: Polymorphs of a 1-Pyrrole Derivative, An Intermediate for the Preparation of Atorvastatin

This patent describes two new polymorphic forms of **8**, an intermediate used to prepare **11**. The method for preparing an amorphous form of **8** is shown in Scheme 4, but no experimental details are given. The production of the new polymorph is carried out by crystallising the existing amorphous form. The new form is said to be more easily filtered than the amorphous form and can be obtained in higher purity.

Scheme 4



Advantages

The new form is available in higher purity and can be more easily handled, thereby making it more useful in commercial use.

Patent No. U.S. 7,193,090

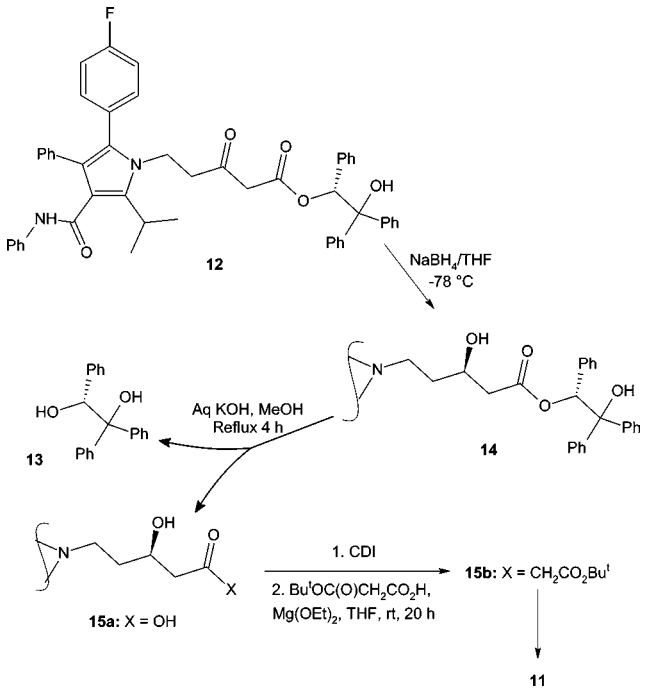
Assignee: Apotex Pharmachem Inc., Brantford, Canada

Title or Subject: Preparation of Atorvastatin

This is the final patent on the subject of statins, and it discloses a method of preparing **11** that allows the recovery and reuse of the key reagent **13**. Scheme 5 shows the route used to prepare **11** via the intermediate **12**. Reduction of **12**

followed by hydrolysis gives the acid **15a** and release of **13**. Under the conditions of the reaction **13** is precipitated and can be filtered off and reused. **15a** is then recovered from the solution and converted to **11** via **15b**.

Scheme 5



Advantages

The process allows recovery and reuse of a key chiral intermediate, thereby improving the process efficiency and reducing the production costs.

Patent No. U.S. 7,163,606

Assignee: Xerox Corporation, Stamford, Connecticut, U.S.A.

Title or Subject: Process for Recovery of Methylene Dichloride

It does not seem possible to persuade chemists to stop using the useful but environmentally unacceptable solvent DCM. Hence, it would seem to be desirable to have a method of recovering the solvent and preventing its escape into the environment. This patent describes a method for recovering DCM from aqueous streams by distillation. The key to the method is the installation of an arrangement of a control system and control valves employed in the distillation unit. Details are of direct interest to control engineers, but if chemists insist on using DCM then they should understand how to control emissions and recover the solvent.

Advantages

The process employs good engineering practice to reduce levels of DCM.

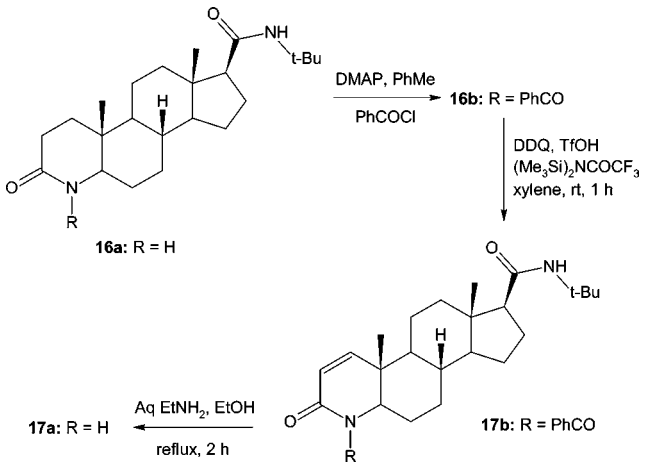
Patent No. U.S. 7,164,022

Assignee: Aurobindo Pharma, Ltd., Hyderabad, India

Title or Subject: Process for the Preparation of Finasteride

Finasteride **17a** was initially developed to treat prostate enlargement but has also been studied as a cure for male-pattern baldness. A number of methods are known for the preparation of **17a** and these are said to suffer from a variety of problems that make it difficult to use them on a commercial scale. The process used in this patent involves the formation of the protected amide **16b** that is oxidised to **17b** with improved selectivity. Scheme 6 summarises the method. The yield and purity of the product are not given although they are claimed to be very high.

Scheme 6



Advantages

The process is claimed to give high-purity product at lower cost than alternative processes.

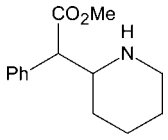
Patent No. U.S. 7,164,025

Assignee: Celltech Pharma Europe Limited, Cambridge, United Kingdom

Title or Subject: Manufacture of Single Isomer Methylphenidate

Methylphenidate **18** is available as the hydrochloride salt under the name ritalin and is used to treat hyperactive children. The commercial drug comprises the threo pair of *d*- and *l*-enantiomers and is used as a racemic mixture. It is now considered that the *d*-threo enantiomer has the better activity. Resolution is therefore necessary to recover this isomer, and a method of recovery and reuse of the less desirable isomer would improve the overall economics of the process. This patent describes a method of resolving a *dl*-mixture of **18** by formation of the ditoluoyl D-tartrate salt. The racemisation of the *l*-threo isomer is carried out by heating in PhMe containing $MeCH_2CO_2H$. It is suggested in the patent that the racemisation takes place by activation of the piperidine N atom, causing fragmentation of the ring by an unknown mechanism. The intermediate thus formed has no chiral centre and recloses to give a racemic mixture.

Methylphenidate



18

Advantages

The process improves the overall selectivity of preparing the product by recycling the less desirable isomer.

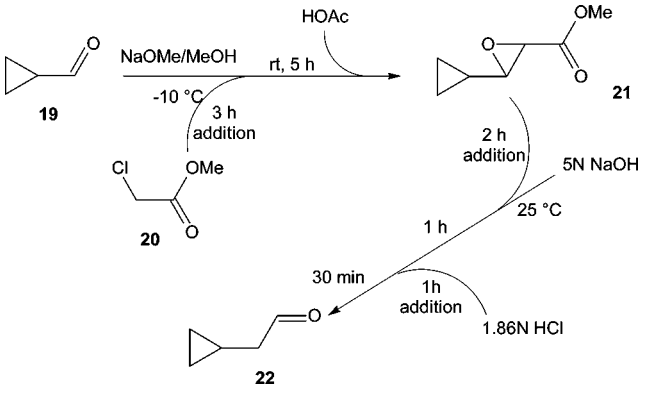
Patent No. U.S. 7,164,047

Assignee: Kuraray Co., Ltd., Kurashiki, Japan

Title or Subject: Process for Preparation of Cyclopropylethanol and Cyclopropylacetonitrile and Their Intermediates

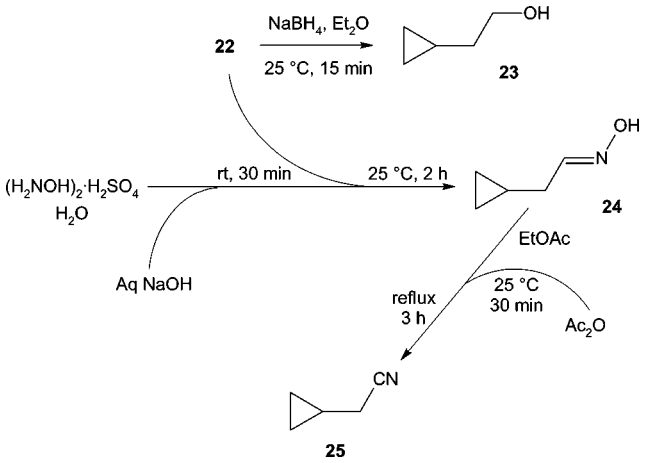
The title compounds are used in the production of pharmaceuticals and agrochemicals. The previously known methods for preparing these compounds are claimed to suffer from several problems that preclude their use on an industrial scale. Some problems mentioned are the use of toxic and explosive reagents, such as diazomethane or ethylene oxide, and carcinogenic compounds, such as bromoform. The routes used to make the two compounds are based on the initial synthesis of the aldehyde **22** from an ester such as **21**. This ester is prepared in 70% yield by treating **19** with **20** in the presence a strong base (Scheme 7). **21** is then converted to the key compound **22** in 80.5% yield by the base hydrolysis.

Scheme 7



The conversion of **22** to the two products of interest is shown in Scheme 8. Reduction of **22** by a variety of reagents results in the production of **23**. The two patent examples only describe using $NaBH_4$ although the claims cover the use of a metal hydride complex, hydrogenation catalysts, or Al alkoxides with *sec*-alcohols. The aldehyde can be converted to the oxime **24** by reaction with the neutralised hydroxylamine sulphate. **24** is purified by column chromatography and obtained in 95% yield. The formation of the nitrile **25** is carried out by treatment of **24** with Ac_2O in EtOAc, and the final product is purified by vacuum distillation and obtained in 76.7% yield.

Scheme 8



There are experiments described in which the intermediate **21** is converted to **23** without isolation of **22.** Similarly the oxime **24** was obtained from **21** without isolating **22**. However, in both cases the yield of the final product was lower. ^{1}H NMR data are given for all intermediates described.

Advantages

The process does not require the use of toxic or hazardous reagents and hence has the potential for improved commercial production.

Patent No. U.S. 7,166,729

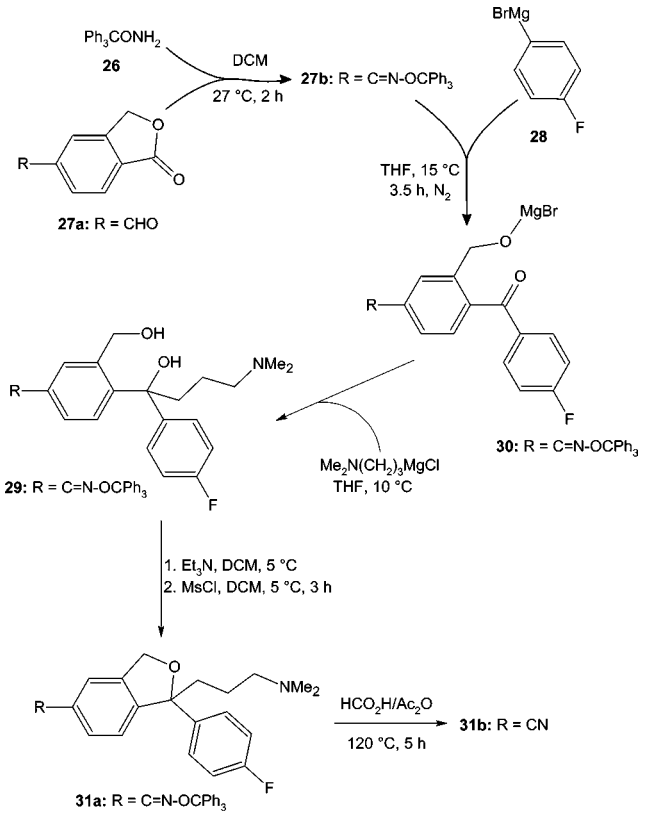
Assignee: Infosint SA, Cantoni Dei Grigioni, Switzerland

Title or Subject: Process for the Preparation of 5-Substituted Isobenzofurans

This patent is concerned with the synthesis of citalopram **31b** from **27a**. **31b** is a drug that is used to treat depression as a racemate in the HBr or oxalate salt form. There are several processes known for the synthesis of **31b**, and since the original patent has now expired, there is increased interest in new synthetic methods that have been previously reviewed (*Org. Process Res. Dev.* **2006**, *10*, 184).

The route used to make **31b** is shown in Scheme 9 and begins with the formation of the oxime **27b** in 90% yield from **27a** using Ph_3CONH_2. Treatment of **27b** with the Grignard reagent **28** produces the intermediate **30** that is not isolated and reacts with another Grignard to give, after hydrolysis, the diol **29** in 75% yield. Cyclisation of **29** is carried out by formation of a mesyl monoester that after hydrolysis gives **31a**. In the final step to give **31b** the oxime protective group is removed from **31a** using the mixed anhydride formed from HCO_2H/Ac_2O.

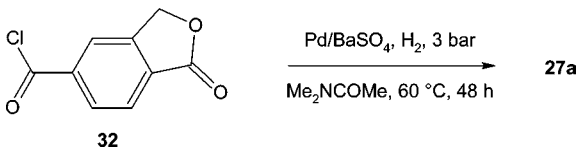
Scheme 9



The free base **31b** is obtained in a yield of 73% and purity (HPLC) of 98.2%. This step is said to be particularly convenient in giving a product that can be isolated in high purity. This is attributed to the formation of HCO_2H and $MeCO_2CPh_3$ that prevent the formation of undesired by-products such as the aldehyde of free oxime. The base may be converted to the HBr salt in which form it is usually used.

Experiments are described in which benzaldoximes are produced in place of the triphenylmethoxy oxime. The patent also gives a method for the preparation of the phthalide **27a** by hydrogenation of **32** (Scheme 10). The preparation of **32** is by a method published in 1931, but details are not given in the patent.

Scheme 10



Advantages

This is a novel process for producing this well-established drug using a precursor different from those of the alternative methods.

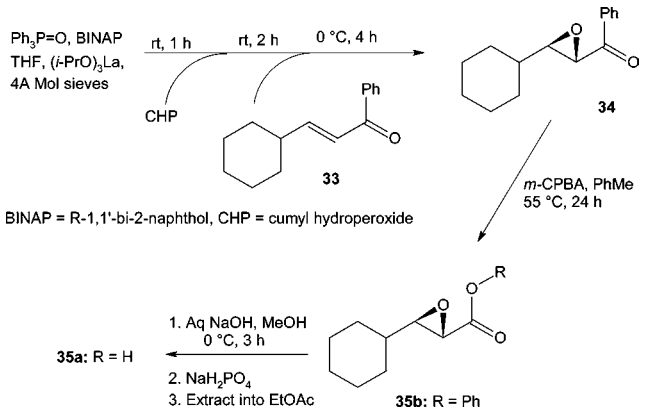
Patent No. U.S. 7,169,944

Assignee: Tosoh Corporation, Yamaguchi-Ken, Japan

Title or Subject: Optically Active Epoxy-Compounds and Process for Their Production

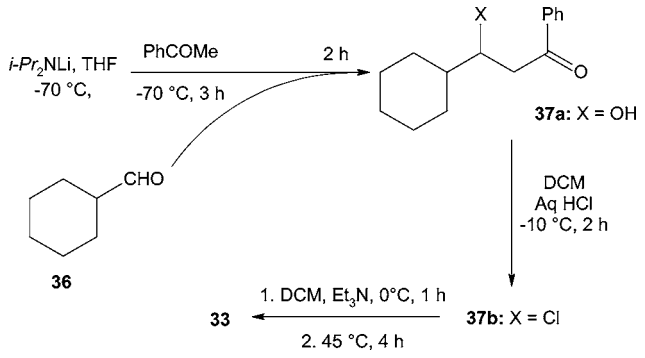
This patent's claims are primarily directed at the production of the acid **35a** and ester **35b**, intermediates for preparing agrochemicals and pharmaceuticals. The patent states that there are processes for preparing these compounds, but they are not amenable to industrial operation. Another aspect of the process is the use of an enzyme in an asymmetric ester hydrolysis to produce the desired enantiomer of the acid. One method for the production of the acid is shown in Scheme 11. The epoxy compound **34** is prepared from **33** using cumyl hydroperoxide (CHP) in the presence of $Ph_3P{=}O$, $(i\text{-}PrO)_3La$, and the chiral ligand BINAP. The reaction is carried out with molecular sieves present to ensure an anhydrous medium since it is well-known that metal isopropoxides are very sensitive to water. In the next step the ester **35b** is formed by oxidation of **34** using *m*-CPBA. This reaction takes 24 h with half of the *m*-CPBA being added initially and the remainder 12 h later.

Scheme 11



The patent also describes the preparation of the halogenoketone **37b** that is used to prepare **33** by the method shown in Scheme 12. The route starts from the PhCOMe that after treating with $i\text{-}Pr_2NLi$ reacts with the aldehyde **36** to give the **37a** that upon reaction with HCl gives **37b**. The HCl may also be used in the gaseous form, and alternative lithiated amines are suitable.

Scheme 12



The other aspect of the patent is the asymmetric hydrolysis of the racemic form of the methyl equivalent of ester **35b** using enzymes to give the acid **35a** in 99.1% ee yield. The patent describes the use of an esterase from *Candida rugosa* and claims that other esterases are also suitable.

Advantages

The new process gives high ee yields, is claimed to be more suitable for large-scale operation than alternatives, and in particular, is inherently safer.

Patent No. U.S. 7,173,149

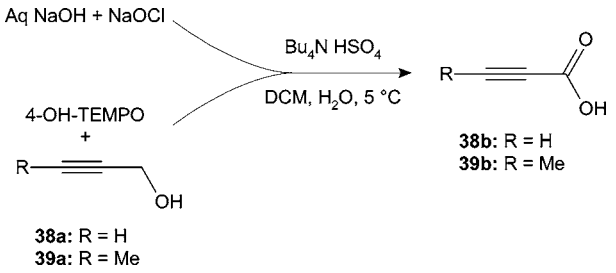
Assignee: Consortium für Elektrochemische Industrie GmbH, Munich, Germany

Title or Subject: Process for Preparing Alkynecarboxylic Acids by Oxidation of Alkyne Alcohols

This patent describes taking a known reaction and improving the method by carrying out the procedure in a different manner. The oxidation of alcohols to acids is possible with the use of a variety of reagents and methods. An example is the use of TEMPO catalyst with NaOCl as oxidant that generally involves biphasic mixtures with phase transfer catalysts (PTCs). The patent states that in using this method the oxidant is dissolved in the aqueous phase at pH 8.5−9, and this is added to a batch of the alcohol containing TEMPO and a PTC. This process is said to be unsuitable when applied to unsaturated alcohols, and yields of the acid are only between 5 and 20%. One reason given for the poor yield is the sensitivity of the terminal CH group of an alkyne to chlorination by the NaOCl.

The problem in using the above method has been overcome by separately feeding the alcohol and NaOCl to the reaction vessel rather than adding everything at once. Scheme 13 summarises the reaction for two alkyne alcohols that are described in the patent. The alcohol is mixed with 4-OH-TEMPO, and this mixture is fed simultaneously with a solution of basic NaOCl to the flask containing PTC dissolved in a biphasic mixture. The products are obtained in yields in excess of 75%.

Scheme 13



One experiment is described that uses continuous addition of reactants and simultaneous removal of reaction mixture. The reactants **38a** and 4-OH-TEMPO comprise a mixture that is fed into EtOAc at the rate of 7.2 g/min over a 2-h period, and a solution of NaOCl is fed at the rate of 91 g/min over a 2-h period. The overall yield of **38b** is 92 mol %.

Advantages

The process employed is straightforward and does not involve any extra reagents or new materials while providing improved yields of product.

Patent No. U.S. 7,176,318

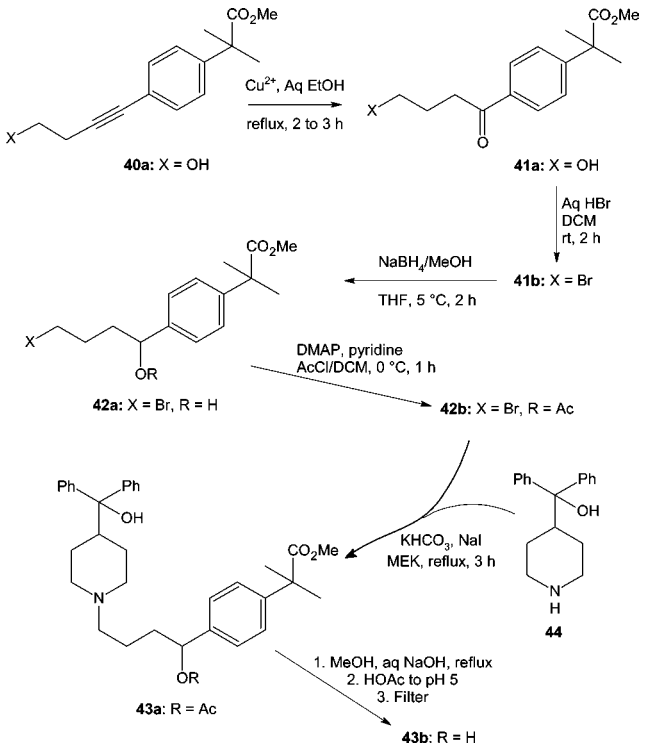
Assignee: Texcontor Establissement, Vaduz, Liechtenstein

Title or Subject: Processes for the Production of Fexofenadine

Fexofenadine **43b** is a nonsedating antihistamine drug that in the U.S.A. is sold under the name of Allegra. A patent on its synthesis has been reviewed previously (*Org. Process Res. Dev.* **2004**, *8*, 697). It is believed that **43b** lacks the side effects of a similar drug known as terfenadine that has been linked with causing fatal abnormal heart rhythms when taken with other medications. It has been suggested that terfinadine is a pro-drug and **43b** is in fact the active ingredient. One of the routes used to prepare **43b** involves the use of a hydration step using mercury compounds. These obviously have the potential for significant waste-disposal problems. Hence, this patent attempts to provide a route that avoids such problems.

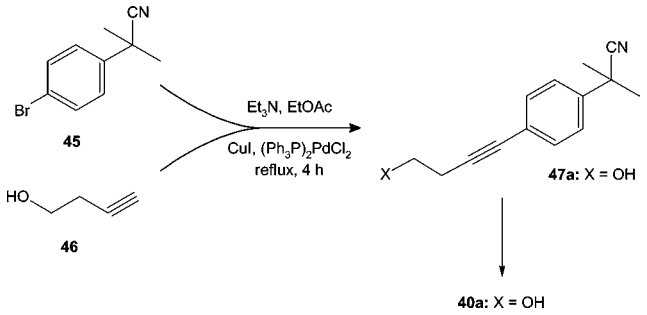
This patent discloses a process to prepare **43b** by the route outlined in Scheme 14. This begins with the alkyne alcohol **40a** that is hydrated to give **41a** using Cu catalysts such as $CuCl_2$, $Cu(BF_4)_2$.

Scheme 14



A surprising finding in this step is that the presence of Pd actually accelerates the formation of **41a**. Without Pd the reaction can take 36 h for completion, but with Pd it takes only 2−3 h. This finding seems to have been observed because **40a** is made by a Pd-catalysed coupling reaction shown in Scheme 15. The patent claims that isolation and purification of **40a** is difficult, and this finding makes the laborious isolation process unnecessary.

Scheme 15



Following production of **41a** the product is then brominated to give **41b,** and the ketone group is reduced using $NaBH_4$ to give **42a** that is acetylated to form **42b**. In the next step **42b** is reacted with **44** in basic NaI to give **43a**. The patent states that it is preferable to convert **41b** to **42b** before reacting with **44**, because if **44** is reacted directly with **41b**, then cyclopropyl derivatives are formed, and the yield of **43a** is much reduced. The patent states that this is a surprising finding, but this reviewer is not too surprised since it is well-known that ketones are more susceptible to condensation-type reactions in the presence of bases such as **44**. In the final stage of the process basic hydrolysis of **43a** gives the desired product **43b**.

As mentioned above, **40a** is made by a process involving a Pd-catalysed coupling reaction by the sequence shown in Scheme 15. The patent only provides details for the preparation of **47a** from **45** and **46**.

It is interesting to speculate how the benefit of Pd residues came about. Perhaps good experimental technique is not always beneficial.

Advantages

The process provides an improved method that does not require the use of hazardous reagents and can use crude intermediates.

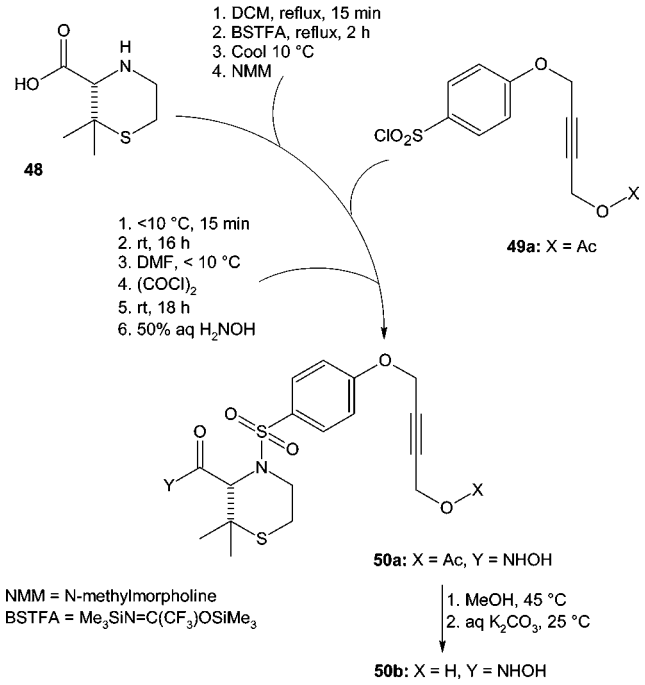
Patent No. U.S. 7,179,911

Assignee: Wyeth, Madison, New Jersey, U.S.A.

Title or Subject: Method for Preparing Hydroxamic Acids

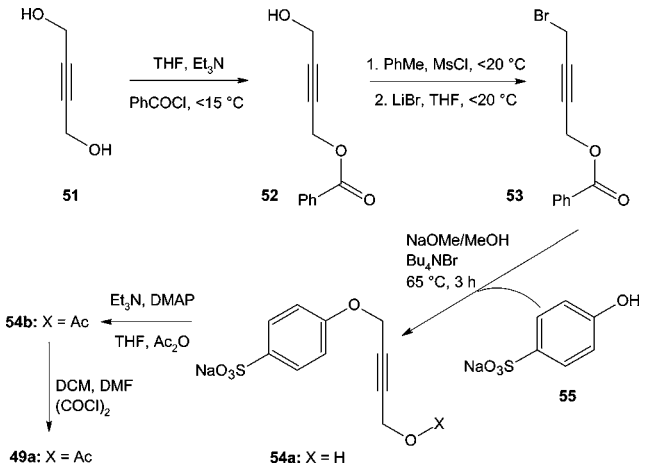
The thiomorpholine compound **50b** is of interest in treating rheumatoid arthritis and osteoarthritis. The initial steps in the synthesis produce **50a** from the acid **48** and the sulphonyl chloride **49** as shown in Scheme 16. There are several steps in the process that are all carried out sequentially in the same reaction vessel. The final yield of **50a** from this method is 60% and this is then hydrolysed using K_2CO_3 to give **50b** in 85% yield.

Scheme 16



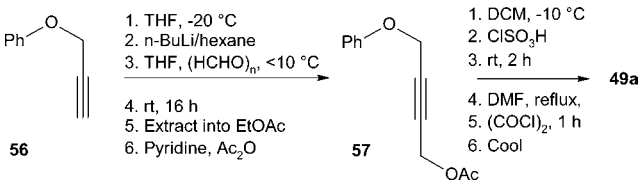
The patent also describes the preparation of the compound **49a** by the route shown in Scheme 17. The first stage is the conversion of the diol **51** in two steps to **53** that is treated with the Na salt **55** to give the salt **54a**. Acetylation of **54a** then forms **54b**, and on treatment with $(COCl)_2$ the sulphonyl chloride **49a** is obtained. ^1H and ^{13}C NMR data are given for all the intermediates and products.

Scheme 17



An alternative preparation of **49a** shown in Scheme 18 is also described. This starts from the propargyl ether **56** that is lithiated, reacted with paraformaldehyde and finally acetylated to give **57** in 87% yield. **57** is then converted to **49a** by treatment with $ClSO_3H$, and the product is obtained after crystallisation in a yield of 55%.

Scheme 18



Advantages

This patent provides a number of options in the preparation of intermediates and gives good yields of the final product. Some of the experiments are carried out on kilogram scale, suggesting the process is at an advanced stage of development.

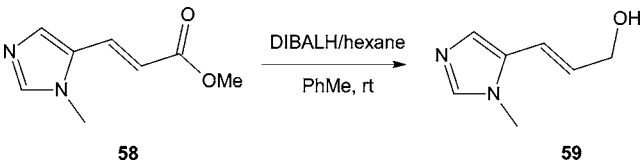
Patent No. U.S. 7,179,925

Assignee: Merck Patent GmbH, Darmstadt, Germany

Title or Subject: Method for Reducing Organic Compounds in a Microreactor by Means of Hydrides and/or Derivatives Thereof

This patent is somewhat similar to one from the same company that has been reviewed that uses microreactors for dehydration reactions (*Org. Process Res. Dev.* **2005**, *11*, 178). A microreactor is defined in the patent as having a volume preferably <50 μL. Hence, the process is not applicable to commercial production but rather the use of multivessel reaction stations. The system described in the patent is for a continuous-flow static micromixer. The objective of developing the process as stated in the patent is to reduce the hazards associated with reduction reactions when large quantities of reagents are used. By working on such a small scale this has clearly been achieved. The patent claims cover a large number of reduction reactions using several different types of hydrides. However, the only experimental details provided relate to the use of DIBALH for the conversion of the acrylate **58** to **59**.

Scheme 19



Advantages

The patent claims that the process reduces the hazards of carrying out reduction reactions on a small scale. This is certainly true, but the utility of this patent is not obvious since it seems to be limited to reactions on too small a scale for commercial production.

Patent No. U.S. 7,183,305

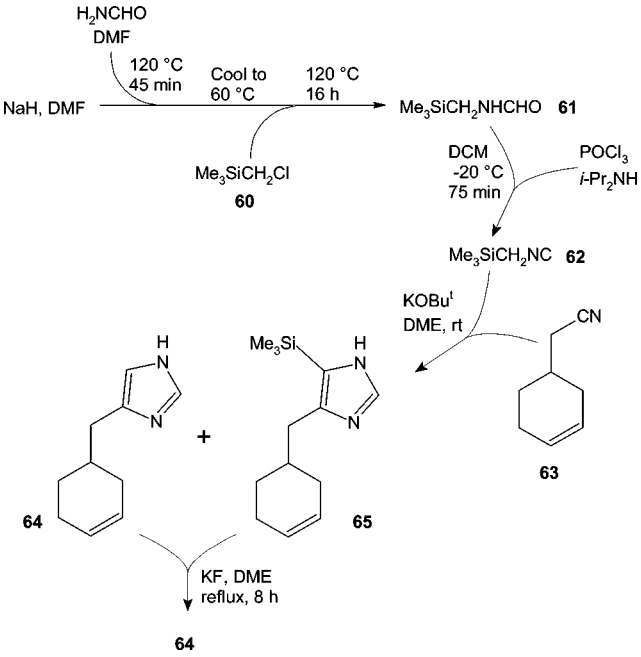
Assignee: Allegan Inc., Irvine, California, U.S.A.

Title or Subject: Process for the Synthesis of Imidazoles

Many pharmacological compounds contain imidazole molecules, and hence the synthesis of them is important. The patent describes the preparation of functionalised imidazoles such as **64** by the reaction of the silylated-isocyanide **62** with a cyanide R-CN such as **63**. The patent claims the reaction takes place with a large number of cyanides, and experimental details are given. The group R ranges from *i*-Bu and Ph to thiophene or **63**. However, it is also stated that the R-group in the cyanide should not be bonded to the CN group via a S, O, or N atom. In addition R does not contain an allylic or benzylic H-atom to the CN group. Whether this is because the reaction does not work or because such a claim would infringe other patents, is not known.

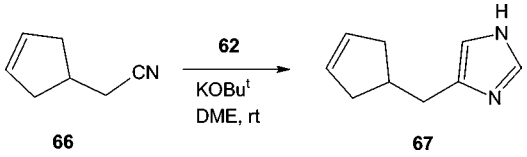
Scheme 20 shows the procedure used to prepare **62** and then its use in the synthesis of **64**. In the first stage **61** is prepared by adding Me_3SiCH_2Cl to a solution containing formamide that has been metalated using NaH in DMF. Addition of $POCl_3$ and *i*-Pr_2NH in DCM at −20 °C to the solution of **61** produces the key compound **62** in 55% yield after purification by vacuum distillation. Reaction of **62** with cyanide **63** in the presence of a strong base forms a mixture of **64** and **65**. When this mixture is refluxed with KF, hydrolysis of **65** takes place and the product **64** was obtained in 52% yield after purification by flash column chromatography.

Scheme 20



The patent also purports to give details of the preparation of the compound **67** from **66** and of the preparation of **66**.

Scheme 21



However, the examples described for the preparations of **67** omit the need to add any **66**, and furthermore, the preparation of **66** is carried out by heating a mixture of NaCN and **62** in

DMSO. How this produces a cyclopentyl group in **66** is a complete mystery. Such serious errors in a legal document are not acceptable and can originate if proof reading is not carried out by chemists.

Advantages

The process is claimed to be suitable for difficult-to-prepare imidazoles.

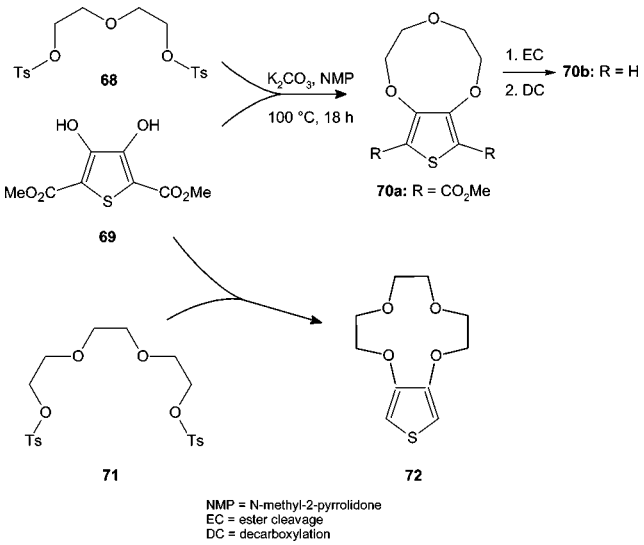
Patent No. U.S. 7,183,419

Assignee: H.C. Starck GmbH & Co. KG, Goslar, Denmark

Title or Subject: 3,4-Dioxythiophene Derivatives

The compounds of interest in this patent are thiophenes such as **70b** and **72** that are used as building blocks for π-conjugated polymers. These are highly conductive materials and hence of interest in various electrical and electronic applications. The thiophenes are also potentially useful intermediates for synthesising a range of chemical products. Alternative processes to prepare the desired compounds can involve the use of PTCs that create difficulties in purification. Waste disposal problems are also said to arise when using PTCs. This patent does not use PTCs, and the method used to prepare **70b** is to react diol **69** with tosylate **68** followed by ester cleavage and decarboxylation (Scheme 22). After recrystallisation, the yield of **70a** was only 26%, and the experimental details of the conversion of **70a** to **70b** are not given. Compound **72** was prepared similarly from **69** and **71**.

Scheme 22



Advantages

By not using PTCs the process claims to have improved upon alternative methods. However, the final yield of product does appear to be quite low.

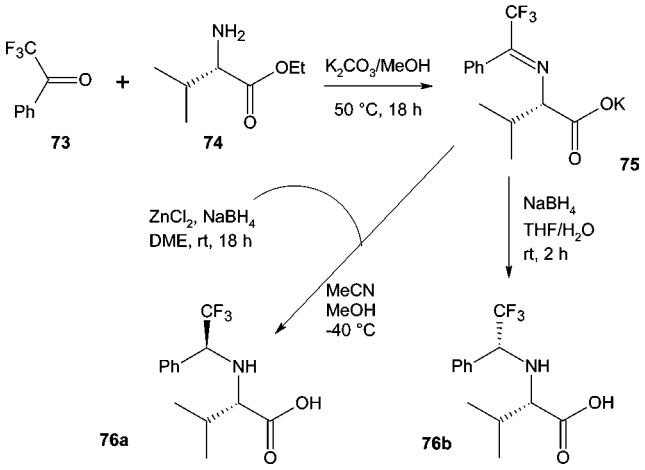
Patent No. U.S. 7,183,425

Assignee: Merck Frosst Canada, Ltd., Quebec, Canada

Title or Subject: Diastereoselective Reductive Amination Process

This patent discloses a method of obtaining either of the two diastereomers of amino acids by reduction of imine metal carboxylates such as **75**. Scheme 23 summarises the process where the carboxylate **75** is formed from the ketone **73** and aminoester **74** under basic conditions.

Scheme 23



The patent aims at addressing two problems that are said to be associated with preparing α-fluoro-aminoacids and esters. The first problem is the formation of imines from ketones with α-fluoro groups, and the second is the ability to obtain either diastereoisomer of the amino acid. The patent states that the formation of **75** is difficult because the intermediate hemiaminal is not easily dehydrated to give **75**. Alternative methods had used strongly acidic conditions that decomposed the starting material and gave low yields. The use of basic conditions overcomes this problem. The second problem is addressed by carrying out the reduction of **75** under different conditions that give the separate diastereoisomers (Scheme 23). To obtain **76a** the reduction is carried out using $Zn(BH_4)_2$ at −40 °C, and ^{19}F NMR showed a diastereoisomeric ratio of 33:1. When the reduction is carried out using $NaBH_4$ at 20 °C, **76b** is obtained with a diastereoisomeric ratio of 65:1. The yields of the reactions are not reported. The reduction can be carried out without isolation of the K salt. The patent also provides details using alternative aminoesters to **74**. The claims of the patent cover borohydrides other than Zn, but no experimental details are provided.

Advantages

The process provides a highly selective route for obtaining the intermediate and subsequently converting it to either diastereoisomer.

Patent No. U.S. 7,186,839

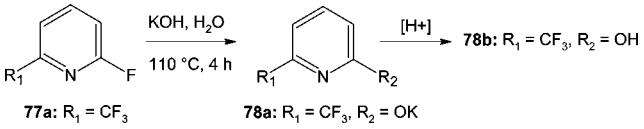
Assignee: Syngenta Limited, Guildford, United Kingdom

Title or Subject: Chemical Process for the Extraction of 2-Hydroxypyridine Derivatives, 2-Hydroxyquinoline and 2-Hydroxybenzothiazole

This patent describes a method of extracting the salts such as **78a** from an aqueous solution. These materials are used in a Williamson's ether synthesis in the preparation of agrochemicals. In these processes it is usually necessary to convert the salt **78a** to the hydroxy compound **78b** that is

then isolated, converted back to the salt **78a**, and then reacted with a halo compound to give the ethers. Clearly, this procedure is prone to losses, and hence, the patent describes a method of removing both the need to isolate the hydroxyl compounds and its subsequent conversion to a salt. The patent describes a procedure for extracting the salt **78a** from an aqueous solution and then using the extracted solution directly in the etherification reaction. Therefore, this has the potential to increase yields. The salt **78a** and hydroxy compounds **78b** are prepared by basic hydrolysis of the fluoro compounds **77** followed by acidification (Scheme 24). In the process, upon completion of the reaction of **77** with KOH, the aqueous solution is mixed with cyclohexanone at 80 °C. The salt **78a** is extracted into the organic phase in yields >90%, and the organic phase can be used directly in subsequent synthetic stages. This reduces losses and eliminates extra processing steps. The patent suggests that the electron-withdrawing nature of the 6-substituent encourages salt formation at the O-atom rather than the N-atom and this increases the solubility of the salts in the cyclohexanone.

Scheme 24



The patent primarily focuses on the pyridines **77a** ($R_1 = CF_3$), **77b** ($R_1 = CF_2H$), and **77c** ($R_1 = Cl$) and also covers 2-hydroxyquinoline and 2-hydroxybenzothiazole. There are also examples provided in which solvents other than cyclohexanone are used, but these are not included in the claims.

Advantages

The process reduces the number of steps needed in an etherification process and therefore improves the final yield of the desired ether product.

Patent No. U.S. 7,196,208

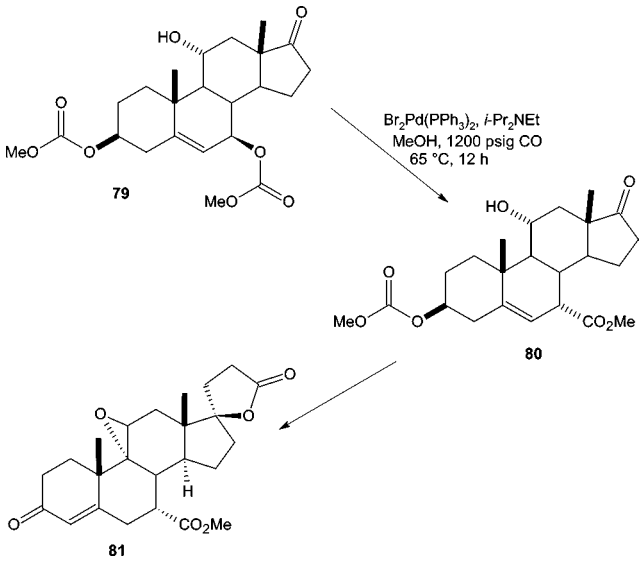
Assignee: Peter G. M. Wuts, N. Mattawan, Michigan, U.S.A.

Title or Subject: Processes for Preparing 7-Carboxy-Substituted Steroids

Unusually this patent is assigned to an individual and not a company, and the subject matter is the production of eplerenone **81**. This compound is marketed as the drug Inspra and is used to treat heart disease and works by blocking the action of aldosterone, a natural substance in the body that raises blood pressure. It is stated that a major obstacle in the synthesis of **81** is the introduction of a carboxy group at C-7, and the patent states that currently known methods use toxic cyanide reagents to effect this. This patent avoids the problems associated with such reagents, and the critical step is performed by a carbonylation reaction of **79** to give **80** catalysed by Pd complexes.

Scheme 25 shows the conversion of **79** to **80**, and the highest reported yield is by using the reagents shown although other Pd complexes are also tested.

Scheme 25



The patent includes experimental details for the many steps needed in the preparation of **79** and also for the conversion of **80** to **81**. ^{13}C NMR data are given for the various intermediate compounds formed.

Advantages

The new process does avoid the use of toxic cyanide reagents although their replacement by the use of CO at high pressures may not be any safer.

Keith Turner

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