Organic Process Research & Development **2005**, *9*, 235–243

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during November and December 2004

Summary

The selection of 20 patents summarised in this review is from an original list of 223 that fitted the original criteria, and it is hoped that there is something to stimulate readers. The control of exothermic reactions is critical in improving the selectivity in many reactions. The rate of removal of heat is the key factor yet is often a limitation on a plant scale and can be forgotten by chemists in the laboratory. This can be done by a number of methods, and there are two patents in this selection that address this issue. One uses a solvent as a heat sink in the synthesis of an intermediate for salmeterol. The second solves the problem by changing the order of addition of the reactants in the preparation of a neurokinin-1 receptor antagonist. An improved process for the stereoselective formation of 1,3-diols by catalytic hydrogenation of ketones is described that simply involves the addition of magnesium salts to the catalyst. This improves conversion and the ratio of *syn* and *anti* isomers. A novel range of seleno compounds that are prepared from nitrones is described that could be useful in treating brain cell decay. Fluorinated derivatives are important intermediates in many areas, and a number of patents cover such compounds. A novel process for preparing an intermediate for liquid crystals that contains a CF_3 group is described. Previous commercial routes did not use fluorinated starting materials, but the new method uses a readily available compound already containing the CF_3 group. One patent claims a method for making fluorinated ketones using TFA, but it is carried at >280 °C and hence is limited to relatively low-molecular-weight, thermally stable compounds. A method of preparing fluoroisocyanates from the chloro derivatives using HF is described although the actual fluorination appears to proceed via carbamoyl fluorides. These are formed as intermediates in the reaction. The production of flavours and fragrances is an important industry, and one patent reports on an improved method for making carvone and carveol by selective rearrangement of limonene oxide using metal oxides and phenolic activators. As older male readers will be aware, the incidence of prostate problems increases with age. Hence, these readers may be interested in an improved method for the production of tamulosin, a drug used in treating enlarged prostate. Some of the patents describe improvements or new methods for making established drugs often because the original patents have expired. However, the inclusion of a patent in this review does not imply any legal or commercial significance. It is worth reiterating that patents do contain physical property and spectroscopic data that may not be published elsewhere. Some patents describe experiments involving the production of tens if not hundreds of kilograms, and it can be surmised that such processes are in advanced stages of development. The advantages listed for any patent are those claimed by the assignees unless this reviewer has prior knowledge.

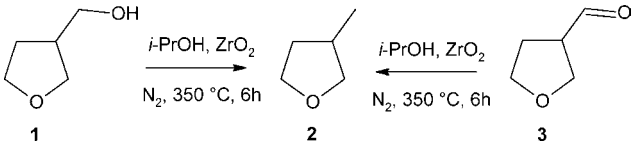
Patent No. U.S. 6,812,354

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

Title or Subject: Process for Preparing 3-Methyltetrahydrofuran

3-Methyltetrahydrofuran, **2**, is a solvent with properties similar to those of THF but is less volatile and boils at 86 °C. **2** is also used in the production of elastomers, and there is a range of processes for its production, some of which have previously been reviewed (*Org. Process Res. Dev.* **2004**, *8*, 311). The current patent describes a process involving a hydrogen transfer reaction. The method starts from **1** or **3** and a *sec*-alcohol in the presence of a hydrous zirconia catalyst in an inert atmosphere. The route, shown in Scheme 1, uses *i*-PrOH; although cyclohexanol is also said to be suitable, there are no examples in the patent. Both batch and continuous flow experiments are described with the best conversion being 62.5% at a selectivity of 74.7% to **2**. The patent describes how to prepare the catalysts, although all of the examples use commercially available materials.

Scheme 1



1 **2** **3**

Advantages

The process uses commercially available starting materials and uses a single step compared to alternative methods that use multistep routes.

Patent No. U.S. 6,812,368

Assignee: Solvias AG, Basel, Switzerland

Title or Subject: Diastereoselective Hydrogenation of 1,3-Hydroxyketones

The production of 1,3-diols stereoselectively from 1,3-hydroxyketones is a synthetically useful reaction. There are enzymatic routes; however, industrially these are not usually suitable, and most methods use standard platinum group metal hydrogenation catalysts. When using homogeneous catalysts there can be difficulties with product recovery and

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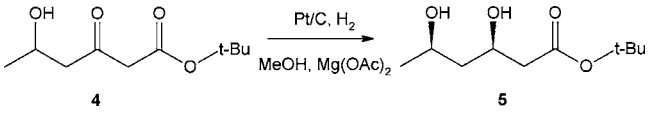
separation from the catalysts. This patent provides a method using heterogeneous catalysts that are easily removed from the reaction mixture and that are active at room temperature. The key finding is that the diastereoselectivity of the hydrogenation of 1,3-hydroxyketones using conventional Pt catalysts can be significantly improved by the use of additives. The first improvement is made by the addition of Mg salts to the catalyst system. The patent also claims that further improvements in the selectivity are seen when catalytic amounts of oxidants such as H_2O_2 are also added. The overall process improvement is said to be particularly effective in the reaction of acyl derivatives such as **4**. The patent describes how 83% of **4** can be converted to the diol **5** that contains a *syn:anti* ratio of 6.5:1 as shown in Scheme 2. When the reaction is carried out without the Mg salt, the ratio of *syn:anti* fell to 1:6, and conversion of **4** to **5** was only 18%. Examples are also given in which H_2O_2 was added to the reaction with the Mg salt to improve the conversion of **4** to about 95% and the *syn:anti* ratio of **5** to 7.2:1.

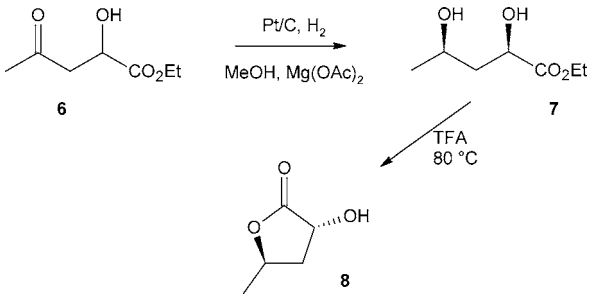
Scheme 2



4 5

In a similar manner, the mixture of diols **7** (*syn:anti* ratio of 70:30) is formed from **6**, and then treatment of **7** with TFA gives the hydroxylactone **8** containing a mixture of *syn:anti* in the ratio 30:70 (Scheme 3). The patent provides extensive ^1H and ^{13}C NMR data for the wide range of compounds that are prepared.

Scheme 3



6 7 8

Advantages

The procedure gives a simple improvement on a known method of preparing 1,3-diols.

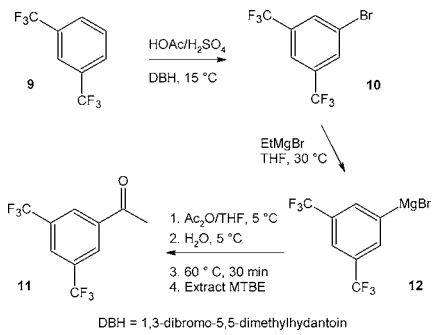
Patent No. U.S. 6,814,895

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

Title or Subject: Process for the Synthesis of 1-(3,5-Bis(trifluoromethyl)phenyl)ethan-1-one

The ketone **11** is an intermediate in the preparation of neurokinin-1 receptor antagonists that are used to treat inflammatory diseases, psychiatric disorders and emesis. Alternative processes for preparing **11** are said to be exothermic and give low and inconsistent yields of product. The process disclosed in this patent is shown in Scheme 4 and begins by bromination of **9** followed by formation of the Grignard **10**. The next step is coupling of **10** with Ac_2O to give **12** by adding **10** to Ac_2O. It is stated that it is surprising that there is little by-product formed when the addition is carried out in this way and yields of **12** are 85−90% are obtained. The key feature is to maintain an excess of Ac_2O over the Grignard reagent, and this is achieved by adding **12** to the solution of Ac_2O in THF. Close control over the temperature is important in this step. In the final step **11** is obtained by hydrolysing **12**, extracting with MTBE followed by vacuum distillation. The examples in the patent describe the preparation of **11** in a 1500-L reactor thus indicating the advanced stage of the process development.

Scheme 4



9 10 11 12

DBH = 1,3-dibromo-5,5-dimethylhydantoin

Advantages

The new process is claimed to be safer and gives higher yields than alternative procedures.

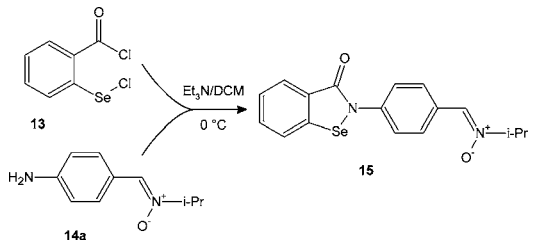
Patent No. U.S. 6,815,459

Assignee: Sam-Sung Electronics Co., Ltd., Suwon, Korea

Title or Subject: The Preparation of Seleno Compounds Containing Nitrone Moiety and Their Therapeutic Uses

Antioxidants are said to have several health benefits. This patent describes a range of novel compounds such as **15** that can trap free radicals and may be candidates for treating a range of diseases that cause the death of brain cells. Scheme 5 shows the basic reaction used to prepare **15** by reaction of the nitrone **13** with the selenenyl chloride **14a**.

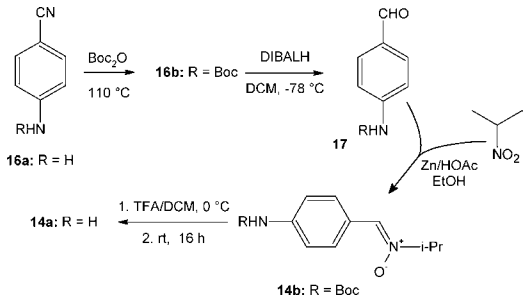
Scheme 5



13 14a 15

The patent also describes a route used to prepare **13** from the protected aminoaldehyde **17**, and this is shown in Scheme 6. The first step is protection of the amino group in **16a** to give **16b**, and this is reacted with nitropropane in Zn/HOAc to give the Boc-protected nitrone **14b**. Removal of the Boc group by using TFA gives **14a**.

Scheme 6



The patent also describes the synthesis of a wide range of similar nitrones and provides much data for them. For example, water solubility and ^{1}H and ^{13}C NMR data are given for all intermediates shown in the two schemes and for related compounds. Also included are activity data of the compounds in the inhibition of lipid peroxidation and cell protection information. Toxicity studies are included, and these show that some of the compounds are less toxic than reference compounds including ebselen that is currently undergoing phase III clinical trials.

Advantages

The novel compounds are said to be more effective and less toxic than other selenium antioxidants that are in advance clinical trials.

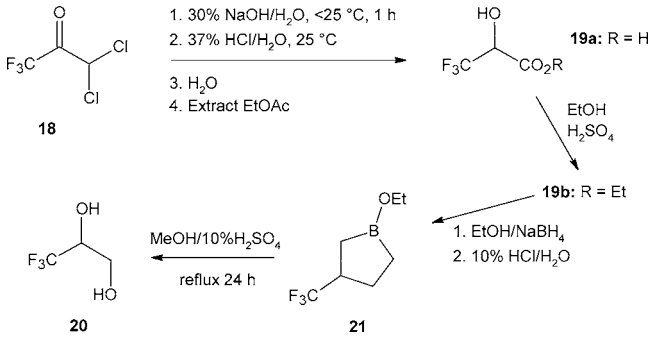
Patent No. U.S. 6,815,559

Assignee: Central Glass Company, Limited, Yamaguchi, Japan

Title or Subject: Process for Producing 3,3,3-Trifluoro-2-hydroxypropionic Acid and Its Derivatives

The subject of this patent, **19a**, is an intermediate in the production of liquid crystals and medicines. Previously known processes starting from compounds containing a CF_3 group are said to be commercially unavailable. Hence, the patent describes a method for producing **19a** from **18** that is industrially available at low cost and is shown in Scheme 7. The reaction is carried out using the trihydrate of **18** that is reacted with a strong base at a pH >12. Below this pH the conversion of **18** and selectivity to **19a** both fall.

Scheme 7



Scheme 7 also shows how **19a** can be converted to the ethyl ester **19b** by conventional esterification and then to the diol **20** via the cycloborane **21**. In the latter step the ester **19b** is reduced with $NaBH_4$/EtOH to give initially **21**, and this is easily hydrolysed by using an inorganic acid to give **20** that is purified by vacuum distillation.

Advantages

The process uses cheaper raw materials than alternative methods to make **19a** and allows the production of the diol **20** without the need to protect the OH group in **19a**.

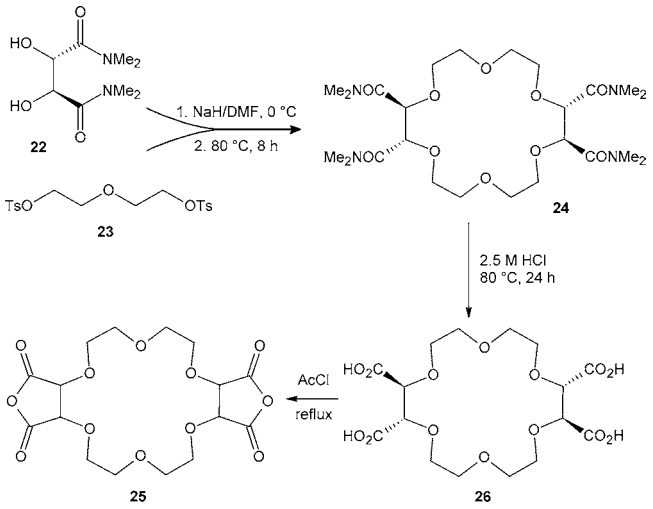
Patent No. U.S. 6,818,778

Assignee: Rstech Co. Ltd., Daejon, Korea

Title or Subject: Process for Preparing an 18-Crown-tetracarboxylic Acid and Its Use in the Resolution of Racemic Compounds

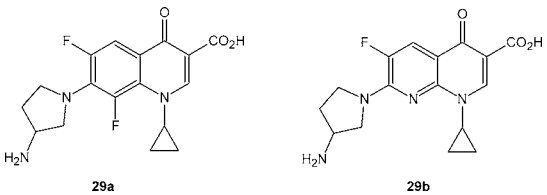
The patent describes a process for preparing the crown compound **26** and its use in preparing a chiral stationary phase for the resolution of enantiomers of compounds such as **29a** and **29b**. The (+)-isomer of **26** has previously been reported and used in resolutions, but this is the first report of the preparation and use of the (−)-isomer. Scheme 8 shows the route to **26** via the formation of the tetracarboxamide **24**; also shown is the formation of the dianhydride **25** that is used to prepare the chiral stationary phases. **24** is formed by condensation of the D-tartaramide **23** with the glycol ether ditosylate **24** in DMF in the presence of NaH. Hydrolysis of **24** with concentrated HCl gives **26**, and this can be acetylated to give the dianhydride **25**.

Scheme 8



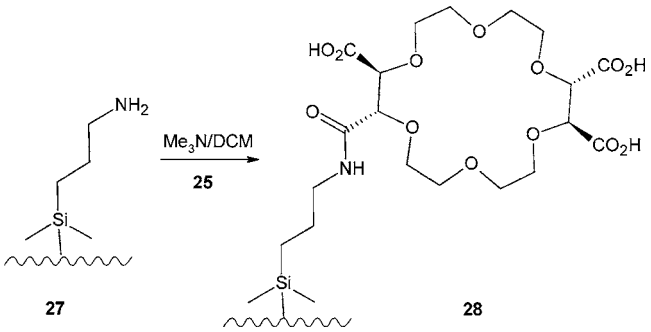
The chiral stationary phase **28** is used in the resolution of a range of racemic mixtures including the quinolones **29a** and **29b**.

Quinolones



28 is made by reaction of the dianhydride **25** with the aminated silica gel **27** in DCM containing Me_3N (Scheme 9).

Scheme 9



Advantages

The crown ethers are novel compounds and are useful for obtaining (−) isomers from racemic mixtures that may be unobtainable by other means.

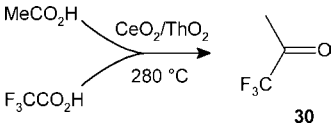
Patent No. U.S. 6,818,796

Assignee: Rhodia Chimie, Cedex, France

Title or Subject: Method for Preparing Fluorinated Ketones

Fluorinated compounds are useful chemical intermediates, and there are many methods of preparing them. The main subject of this patent is the preparation of **30**. One method used to prepare fluorinated ketones involves the use of TFA or its esters in a multistep process that is said to have a number of disadvantages and is difficult to transfer to an industrial scale. An example of the process disclosed in this patent to give **30** is carried out in the gas phase at around 280 °C by passing TFA and HOAc over a catalyst containing a rare earth metal oxide (Scheme 10). There are a number of examples given, and the yield of **30** can be as high as 70% even with recycled catalyst. When an alumina catalyst is used, the yield drops to 5% and instead of HOAc it is possible to use Ac_2O.

Scheme 10



The patent mentions that the process proceeds via a ketonisation reaction. This probably goes via the mixed anhydride of TFA and HOAc and thus will generate CO_2. Since the process is carried out in the gas phase with a carrier gas, this is unlikely to lead to the same type of process problems that gas production from a liquid phase would cause.

Advantages

Although the reaction is a single-stage process and has good selectivity, it probably has limited application for low-molecular-weight trifluoroketones because of the conditions used.

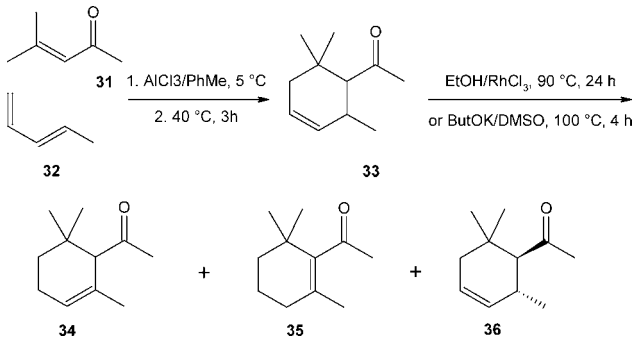
Patent No. U.S. 6,822,121

Assignee: Takasago International Corporation, Tokyo, Japan

Title or Subject: Production Process of Cyclohexenyl Ketones

The compounds of interest in this patent, **34**, **35**, or **36** are used as intermediates in the preparation of damascones that are perfumery products. The three ketones are prepared by isomerisation of **33** that is synthesised by Diels−Alder reaction of **31** and **32** (Scheme 11). The isomerisation reaction of **33** to give the ketones is claimed to be a novel reaction that has not previously been reported. The main product, **34**, is obtained as 65% or more of the reaction mixture. Alternative routes to **34** start from more expensive materials. The patent describes experiments using a range of catalysts for the isomerisation reaction. Examples include strong bases such as $KOBu^t$, acids such as PTSA, or transition metal compounds such as $RhCl_3$. However, the claims focus on the use of basic catalysts. The patent provides ^1H NMR and MS data for the ketones.

Scheme 11



Advantages

The patent provides a novel route to useful intermediates that may be cheaper than alternative processes.

Patent No. U.S. 6,825,218

Assignee: Aventis Pharma S.A., Antony Cedex, France

Title or Subject: Preparation and Use of Spherical Agglomerates of Telithromycin

The title compound is an antibiotic used to treat bronchitis, pneumonia, and sinus infections. Telithromycin is a ketolide antibiotic that is usually administered by oral means, but it has an unpleasant taste. Micro-encapsulation is a method used to prepare forms of the drug that are coated with a material that masks the taste without hindering the bioavailability. Such forms require spherical particles to be used and it is the production of such particles that is the subject of this patent. The process by which the desired spherical particles are formed is the crystallisation of an acetone solution of telithromycin. The procedure involves addition of a suspension of telithromycin in isopropyl ether and the use of sonication to suspend the seeds while initiating the crystallisation. The particles so obtained are then used to prepare microcapsules by direct spraying with a suitable polymer.

Advantages

The process allows the controlled production of spherical particles that can be formulated into pharmaceutically acceptable forms.

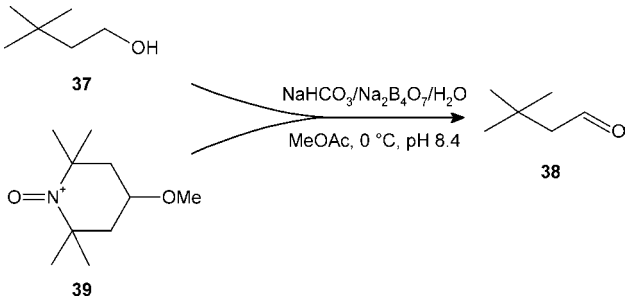
Patent No. U.S. 6,825,384

Assignee: The Nutrasweet Company, Chicago. Illinois, U.S.A.

Title or Subject: Bromine-Free TEMPO Catalyst System for Oxidation of Primary and Secondary Alcohols Using NaOCl as an Oxidant

Oxidation reactions with TEMPO derivatives such as **39** are widely used and are carried out using bromide cocatalysts. However, there are environmental concerns over the disposal of the bromine-containing wastes. This patent describes a procedure for oxidising alcohols to aldehydes that does not use such cocatalysts and instead uses $Na_2B_4O_7$ with NaOCl as oxidant. The main focus of the patent shown in Scheme 12 is the production of **38**, but there are examples of the preparation of other aldehydes by the same procedure. The reaction can proceed without the use of solvent, but if the alcohol is a solid, then solvents such as heptane, PhMe, or EtOAc will be required.

Scheme 12



Examples are described in which the yield of **38** is in excess of 90% over 60 min, and this can be increased to 99% after 90 min. The patent also describes the use of other oxidants including $ZrOAc_2$ that also gives high yields of **38**.

Advantages

The novel process gives high selectivity to the desired product while avoiding the use of bromine salts that can cause disposal problems.

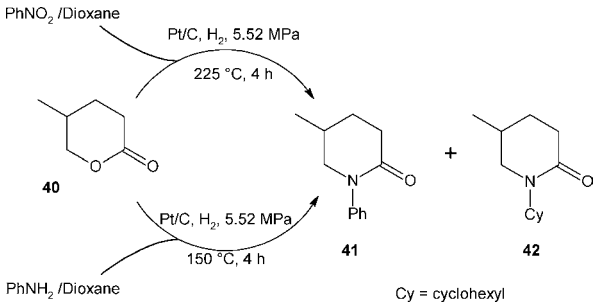
Patents No. U.S. 6,828,277 and No. U.S. 6,828,278

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

Title or Subject: Production of N-Aryl-2-lactam, N-Cycloalkyl-2-lactam, and N-Alkyl-2-lactam by Reductive Amination of Lactones

These two patents describe the production of a range of 2-lactam compounds that are versatile compounds used in a variety of applications. The patent includes examples that cover the formulation of a number of end products, containing the lactams, that range from cleaning compositions to antifungal creams. The first patent focuses on aryl- and alkyl-substituted lactam compounds that are made from lactones and nitro-compounds. The second patent covers aryl and cycloalkyl compounds that are made from lactones and arylamines. Scheme 13 shows the formation of **41** and **42** from both routes: the reductive amination of **40** using either $PhNO_2$ or $PhNH_2$ over a Pt/C catalyst. The reaction conditions are quite severe, and unless there is a misprint in both patents, the procedure requires 50 g of catalyst with 1 g of the reaction solution. However, since the reactor volume is stated as only 5 mL, one would hope that the quantity of catalyst used is incorrect. Under the reactions conditions the nitro compound will be converted to the amine, and the aryl group is also hydrogenated to the cyclohexyl group so that **42** is formed.

Scheme 13



The patent also describes the formation of other compounds using a variety of supported precious metal catalysts. For example, $PrNO_2$ is used to prepare propyl derivatives, and other catalysts used include Rh/C, Ru/C, and Ir/C.

Advantages

The process is claimed to be efficient and low in cost since it can start from the nitro compound. However, if the use of such large quantities of catalyst is correct, then it cannot be said to be particularly cheap or efficient.

Patent No. U.S. 6,828,461

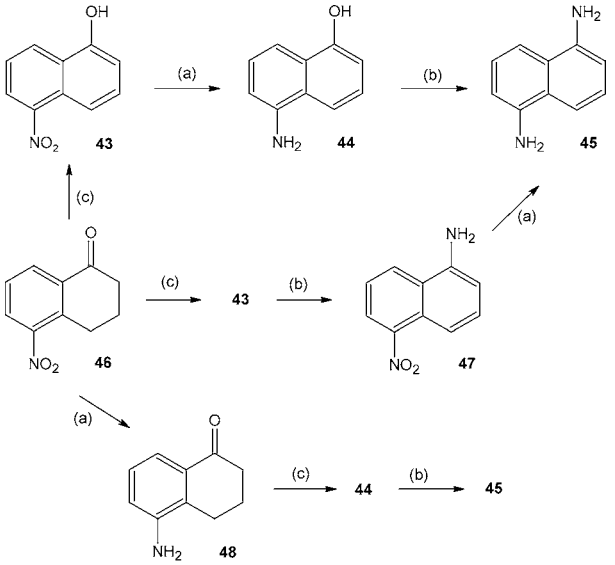
Assignee: Mitsui Chemicals Inc., Tokyo, Japan

Title or Subject: Process for Producing 1,5-Diaminonaphthalene

The title compound **45** is used to produce a range of resins and polyurethanes, and there are various processes for its preparation. An objective of this patent is to avoid production of nitro-imines or -enamines that are relatively unstable and said to be difficult to handle on an industrial scale. Some methods involve substitution of naphthalene, and these invariably form a range of isomers that are difficult to separate. Other processes begin with a substituted benzene that undergoes a ring-closure reaction, and an example was reviewed previously (*Org. Process Res. Dev.* **2004**, *8*, 553). The current patent starts from the tetralone **46**, and the patent describes three methods for the conversion of **46** to **45** as shown in Scheme 14.

One method proceeds via the dehydrogenation of **46** to give **43** that is reduced to the amine **44** and then converted to **45** by amination. The second route also converts **46** to **43** that is aminated to give **47** followed by hydrogenation to give **46**. The third method begins by reducing **46** to the aminotetralone **48**, and this is converted to **45** via **44**.

Scheme 14



In practice there are only three basic reactions indicated in the scheme, and mixtures of products are obtained. For example the dehydrogenation of **46** gives **43**, **44**, and **48**; the relative amounts of each depends on the catalyst and conditions that are used. All catalysts are supported platinum group metals, and the dehydrogenation reaction is usually carried out at about 130 °C in solvents such as DMF, *i*-PrOH, PhMe, MIBK, or diglyme. The aminations are carried out using aqueous $(NH_4)_2SO_4$ solution containing NH_3, and the reductions are catalysed by Pd/C in *i*-PrOH/H_2O.

Advantages

The process allows the formation of the desired product without the formation of positional isomers that are difficult to separate. It also avoids the formation of unstable imines or enamines that can give rise to safety handling issues.

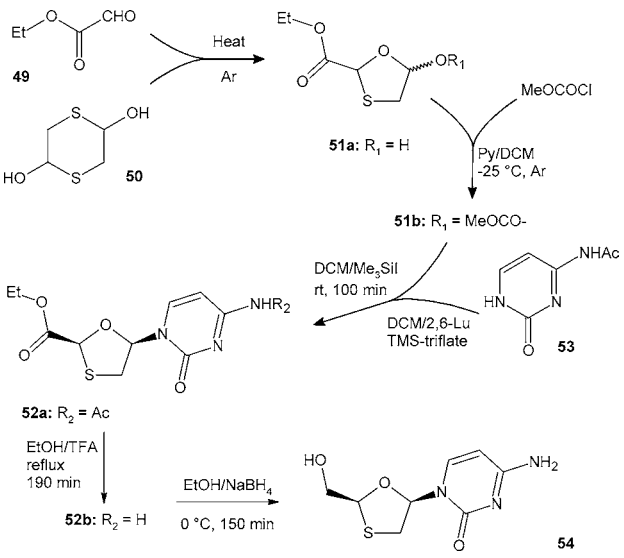
Patent No. U.S. 6,831,174

Assignee: Shire BioChem Inc., Quebec, Canada

Title or Subject: Processes for Preparing Substituted 1,3-Oxathiolanes with Antiviral Properties

This comprehensive patent covers the production of a range of compounds such as **54** that have antiviral properties without being toxic. Scheme 15 shows a route to **54** from **51a** that is made by simply heating **49** and **50** together and then subjecting the crude mixture to flash chromatography. This gives a mixture of the C-5 epimers of **51a** that are converted to methoxycarbonyl derivative **51b** by reaction with MeOCOCl at −25 °C in pyridine (Py) and CH_2Cl_2 (DCM). Reaction of **51b** with *N*-acetylcytosine **53** gives **52a**, and this is converted to the amino compound **52b** by reaction with TFA. In the final step the hydroxyl group is formed by reduction with $NaBH_4$.

Scheme 15



The patent describes the preparation of several compounds analogous to **54** in which **53** is replaced by other purine or pyrimidine bases. There are also variations on the route shown in Scheme 15 that use alternative protecting group strategies in the synthesis. A key feature of the method shown above is that it gives a higher *cis:trans* ratio (10:1 or more) in the formation of **52a**.

Advantages

The process is a novel route to a range of intermediates that are formed with a high selectivity to the desired *cis*-isomers.

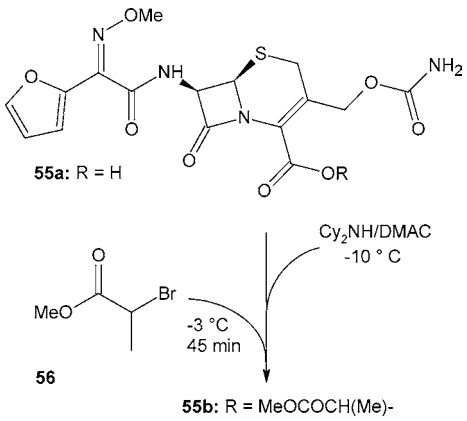
Patent No. U.S. 6,833,452

Assignee: Ranbaxy Laboratories Limited, New Delhi, India

Title or Subject: Process for the Preparation of Highly Pure Crystalline (R,S)-Cefuroxime Axetil

The subject of this patent **55b** is a cephalosporin antibiotic with broad spectrum of activity against Gram-positive and -negative microorganisms. The patent describes a single-step method for converting the acid form (cefuroxime) **55a** to the acetoxyethyl ester compound **55b** that is the active form of the drug. The method involves the preparation an amine salt of the acid **55a** by reaction with dicyclohexylamine followed by esterification with **56** to give **55b** (Scheme 16). The process uses racemic **56**, and the product is the racemic mixture that is obtained by recrystallisation. The mixture is approximately 1:1 *R,S* isomers and is generally >96% pure. No attempt at resolving the mixture is described, although references to earlier methods are given. The patent states that the amorphous form of **55b** is more active than the crystalline form, and the product made by this route is of a high purity that is suitable for producing the amorphous material.

Scheme 16



Advantages

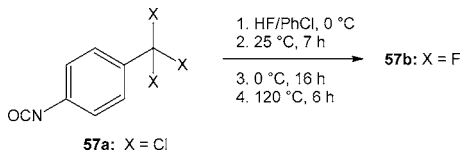
This is a new commercially suitable process for producing an established drug in high purity.

Patent No. U.S. 6,833,476

Assignee: Rhodia Chimie, Boulogne Billancourt, France
Title or Subject: Method for Using a Carbamoyl Fluoride as a Fluorinating Agent

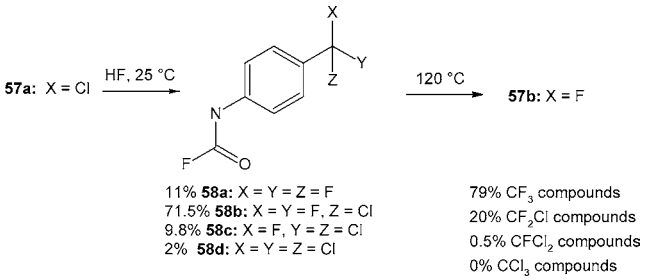
Fluorinated derivatives are particularly useful in the synthesis of agrochemical and pharmaceutical products. This patent is particularly aimed at the preparation of the isocyanate **57b** from the corresponding trichloro derivative **57a**. The isocyanate used can be prepared from the corresponding amine, and the patent does suggest that the isocyanate is used as an amine protective group so that the desired end product may be a perfluoroalkylaniline. The reaction is carried out by treating the substrate **57a** with HF in PhCl initially at 25 °C and then at 120 °C as shown in Scheme 17.

Scheme 17



The reaction proceeds in two stages, and during the first stage, that takes place at or below 25 °C, the carbamoyl compounds **58a**−**d** are formed. It is suggested that these compounds are the fluorinating agents in the reaction and are in equilibrium with HF and the isocyanate. Scheme 18 shows the relative amounts of the four compounds as analysed by GC. The relative proportion of the carbamoyl fluorides to isocyanates at this stage is 24:1. After reaction at 120 °C the relative proportion of carbamoyl fluorides to isocyanates is 77:21 with the relative amounts of the products shown in Scheme 18.

Scheme 18



There are reports of other methods that proceed via the carbamoyl fluorides, but these require large excess of HF and can produce fluorophosgene which is even more dangerous than phosgene. The patent also reports that Lewis acids such as $SnCl_5$, $TiCl_4$, or $SnCl_4$ can be used to increase the conversion in the second stage of the reaction.

Advantages

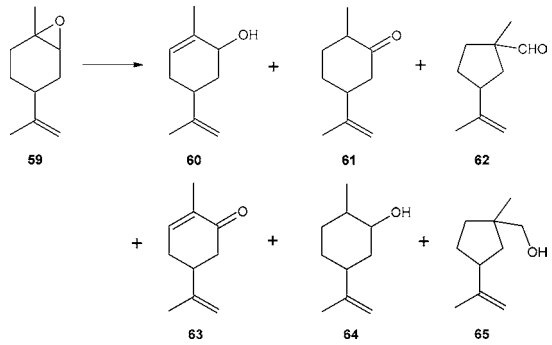
The process does not require the use of excessive amounts of HF, and it produces perfluorinated products more efficiently than alternative procedures.

Patent No. U.S. 6,835,686

Assignee: Millennium Specialty Chemicals, Jacksonville, Florida, U.S.A.
Title or Subject: Catalytic Process for the Rearrangement of Epoxides to Allylic Alcohols

The examples in this patent are mainly aimed at the conversion of limonene oxide **59** to carveol **60** or carvone **63** that is used in flavours and fragrances. The actual claims in the patent all cover a catalyst system for the conversion. This conversion can be carried out by a number of methods including the use of strong bases, heterogeneous metal oxides, or homogeneous metal alkoxides. All of these methods are said to give relatively low selectivity to **60** or **63**, and the main products are shown in Scheme 19. Some of these compounds result from Oppenauer oxidation reactions that occur under the conditions of the rearrangement of **59**. The catalyst system employed is a metal oxide combined with a phenolic compound as an activator. One catalyst system is CaO and isopropyl salicylate that gave a selectivity of 83% to **60**.

Scheme 19



The patent also describes how to selectively produce **63** in a one-pot process that involves rearrangement of **59** and

Oppenauer oxidation of **60**. This reaction can be carried out at 95% conversion by heating **59** with $ZnCO_3$ and 2-nitrophenol. The product was obtained in 99.6% purity by distillation. The patent contains over 60 examples that are primarily concerned with the rearrangement of **59**. The reactions are stereoselective with *R*-**59** giving *R*-**60** and *R*-**63**.

Advantages

The process provides a facile one-pot method of selectively preparing either the allylic alcohol or the unsaturated ketone.

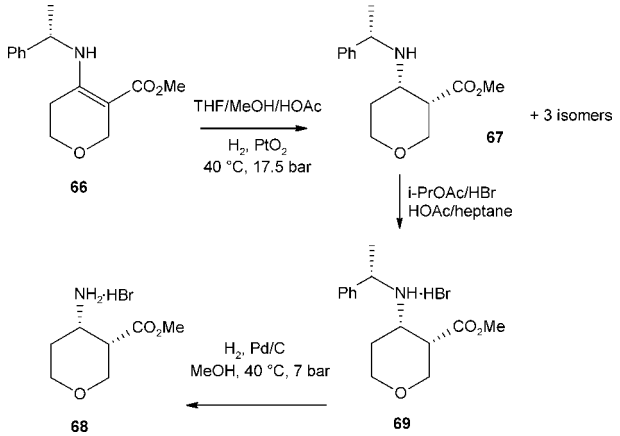
Patent No. U.S. 6,835,841

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

Title or Subject: Asymmetric Catalytic Hydrogenation Process for Preparing Chiral Cyclic β-Aminoesters

The title compounds such as **68** are used as intermediates for the synthesis of inhibitors of matrix metalloproteinase and TNF-α converting enzymes that give rise to inflammatory diseases such as arthritis. Alternative routes to these compounds are said to give low yields of the desired stereoisomer. The particular focus of this patent is the reduction of the C═C bond as shown in Scheme 20. This is often carried out using borohydrides and gives low yields. The novel procedure described here uses a catalytic method using PtO_2 catalyst in the presence of HOAc. This gives an improved production rate and facilitates the recovery procedure by removing the need for aqueous work-up methods. The reduction of **66** gives **67** plus three diastereoisomers of **67**; the diastereomeric ratio (dr) for this step is claimed to be at least 85%. The next step is formation of a hydrobromide salt **69** that is obtained in 98.9% dr as a crystalline solid. The final stage is hydrogenolysis of **69** to give the salt **68** using Pd/C catalyst in MeOH. This reaction gives two diastereoisomers of **68**, and the dr is said to be >85% although there is no explanatory detail as to how this is achieved. The enantiomeric ratio of this step is also claimed to be >85%. The patent gives detailed ^1H and ^{13}C NMR and IR data for all compounds and includes examples for the preparation of a number of compounds similar to **68**.

Scheme 20



Advantages

The patent has an improved method for a key reduction step in the synthesis that improves productivity and gives a cleaner work-up procedure.

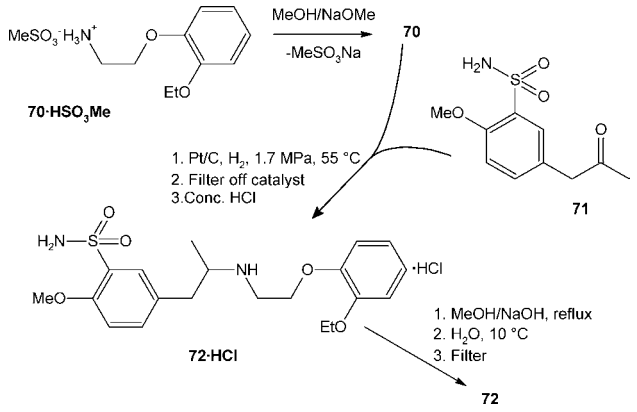
Patent No. U.S. 6,835,853

Assignee: Synthon BV, Nijmegen, Netherlands

Title or Subject: Process for the Resolution of Tamulosin and Associated Compounds, Compositions, and Processes

Tamulosin **72** is in a class of drugs called α-adrenergic blockers that cause the blood vessels to relax and expand so that blood passes through them more easily. The (*R*)-enantiomer is available as flomax and is used to treat benign prostatic hyperplasia or enlarged prostate, a problem found increasingly in middle-aged men. One route that has been used to make **72** is from **70** and **71** and is shown in Scheme 21. However, it is said that the original patents did not indicate how to prepare either of the reactants, and the product was the racemate of the HCl salt of **72** that was not resolved. This patent provides a route to **72** including its resolution; also disclosed is a method of preparing **70** and **71**. The preparation of racemic **72** proceeds via the HCl salt, and this is made by reductive amination of **70** with **71** in the presence of Pd/C under a pressure of hydrogen. The HCl salt is converted to the free base by refluxing with MeOH/NaOH.

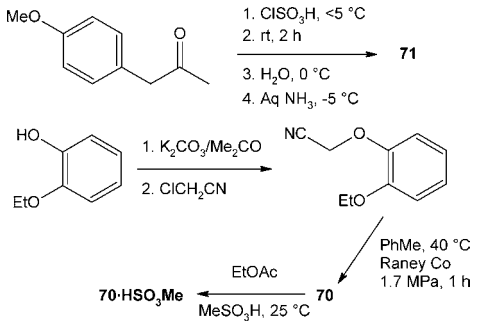
Scheme 21



The crude free base **72** was then recrystallised by two different methods to give two racemic polymorphs designated Form 1 and Form 2. Form 1 was obtained by dissolving crude **72** in refluxing EtOAc/MeOH and then cooling to 15−20 °C to obtain crystals. Form 2 was obtained by refluxing a solution of crude **72** in MeOH/H_2O, followed by addition of concentrated HCl and then treatment with NaOH. The DSC and XRD spectra of both forms are given plus ^1H and ^{13}C NMR spectra. The racemic mixture of **72** was resolved and the (*R*)-enantiomer obtained by conversion to the (−)-camphor-10-sulphonic acid salt.

The patent describes how to prepare both **70** and **71**, and the basic methods are shown in Scheme 22.

Scheme 22



The reason for making the methanesulphonate salt of **70** and then decomposing it is not mentioned in the patent, but it may be unstable in the free amine form.

Advantages

The process allows the production of new polymorphs of the drug and an improved synthetic route that gives pure enantiomers after resolution. The patent also provides syntheses of the two starting materials.

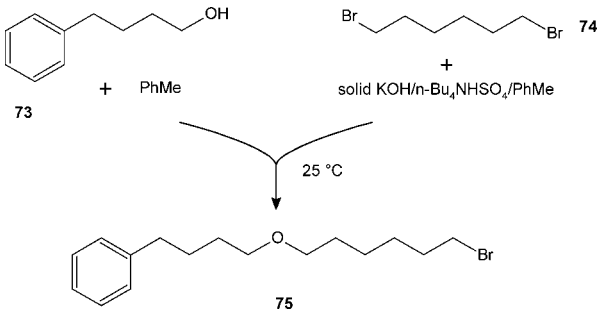
Patent No. U.S. 6,835,857

Assignee: Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany

Title or Subject: Process for the Manufacture of 4-(6-Bromohexyloxy)butylbenzene

The title compound **75** is an intermediate in the production of salmeterol, a bronchodilator used to treat asthma and chronic bronchitis. The route generally used to prepare **75** is from **73** and **74**, but it is claimed that alternative procedures involve dangerous materials or procedures. For example, one method uses NaH dispersions that are said to be unsafe in large-scale operations. Another carries out the reaction without solvents, and the exothermic temperature rise cannot be controlled. The improvement disclosed in this patent is to use toluene as a diluent and to add **73** to a mixture of **74** in the same diluent containing powdered KOH plus the phase transfer catalyst. After the addition step, water is added to the mixture, and the product is obtained from the organic phase and purified by vacuum distillation.

Scheme 23



In a comparative example that did not use a diluent, the temperature of the reaction mixture could not be controlled, and it became too lumpy to stir. It is good practice to use a solvent to control exothermic reactions, and it is surprising to this author that such a procedure has not been examined before now.

Advantages

The process gives better control over the exothermic nature of the reaction and enables higher yields of products to be obtained.

Keith Turner

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

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