Organic Process Research & Development **2007**, *11*, 318–327

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during October to December 2006

Summary

In the current review there are 22 patents from an original list of 415 that fitted the search criteria. The existence of polymorphs is a problem in drug preparation, and one patent reports on 26 new forms of nateglinide, a drug used to treat diabetes. Such numbers are mind-numbing and make experimental work extremely challenging. New polymorphs of the stimulant modafinil are reported when there was only one known previously. However difficult the existence of new polymorphs makes the experimental work, they can extend the patent life and hence the commercial value of a drug. An improved process for preparing the essential amino acid methionine is disclosed that allows for reprocessing of dipeptide by products. Since the product is made on a large scale the process is operated continuously. The removal of impurities to very low levels is vital in drug production as well as in other materials, and several patents cover this subject. A method of preparing a compound used in treating asthma gives low levels of byproducts while using intermediates that do not require purification. The impurities in an *N*-oxide, used in treating HIV-1 infections, are found to be very much less when using oxone as an oxidising agent. Another patent focuses on byproducts in the production of the painkiller oxycodone and reports on the reduction of a key byproduct from >100 ppm to <5 ppm. The purification of the widely used statin drugs is the subject of one patent. The method used is a modification of conventional column chromatography. The technique is applied to several statins, and very low levels of impurities are attainable. Byproducts in dyes can seriously affect their colour fastness. One patent describes an improvement in making an aminoquinolone that reduces a key byproduct from 14% down to <5%, and as a result dye is much more stable. The use of fluorinated molecules in drugs is very important. A new method of preparing the veterinary antibiotic florfenicol is described using the conventional Ichikawa reagent. There is an improved method for making an intermediate used for preparing the weed killer glyphosate. This involves a catalytic dehydrogenation of an iminoalcohol to give a carboxylic acid salt. An improved method of making an intermediate used in the preparation of vitamin E is reported. This uses fluorinated amines or methanes as acid catalysts in place of more corrosive inorganic acids. The antimalarial drug tafenoquine can be given in low doses because of its long half-life, and a new process for its preparation is described. This is based on a 1997 process and is claimed to have much fewer stages than the original route. The patent does include serious errors making one wonder if anyone proofreads these legal documents. Two patents describe phosphorous oxynitride catalysts for preparing methylene lactones. One uses supercritical fluids as solvent, but both suffer from the need to use such high pressures that commercialisation is unlikely. The improved preparation of iodo compounds used in photocopying is described. The method uses an Ullmann condensation and minimises the formation of diiodo products that are difficult to remove. An aqueous based process for preparing aryl hydrazines and hydrazones is disclosed that has a lower environmental impact than previous methods. Another patent addressing waste problems is for the production of the isolongifolene that is used in flavours and fragrances. The use of solid acid catalysts based on sulfated zirconia gives improved selectivity and conversion. The use of phase transfer catalysts seems to be increasing, but a patent for producing the epilepsy drug levetiracetam (keppra) specifically excludes their use. This improves the recovery method and presumably avoids infringing other patents. An improved oxidation step in the synthesis of benzimidazoles is reported and applied to the synthesis of a range of proton pump inhibitor drugs. The method uses *tert*-butyl hydroperoxide and $VO(acac)_2$. The advantages referred to in this review are those claimed in the patent unless this reviewer has personal knowledge of the subject. There is no legal or commercial significance in the choice of patents reviewed, although some of the patents do describe large-scale experiments. This could be an indication of the process being in commercial operation.

Patent No. U.S. 7,119,199

Assignee: Scios Inc., Fremont, California, U.S.A.

Title or Subject: Process for the Preparation of Pyridopyrimidones

The basic molecular structure of the title compounds is found in several biologically active molecules. Methods for the preparation of these compounds are said to suffer disadvantages such as requiring multiple steps or having side reactions. The patent claims to offer a facile synthesis for compounds such as **5**. The synthetic pathway to produce **5** depends on whether the starting reagents are compounds **1a**, **1b**, or **1c**. If **1a** is reacted with **2** the patent states that intermediate **4a** is formed and **1b** produces **3b**. By analogy reagent **1c** would give **4c** (X = F). The route via **4a** or **4c** gives a higher yield than the route via **3b**. The yields for the

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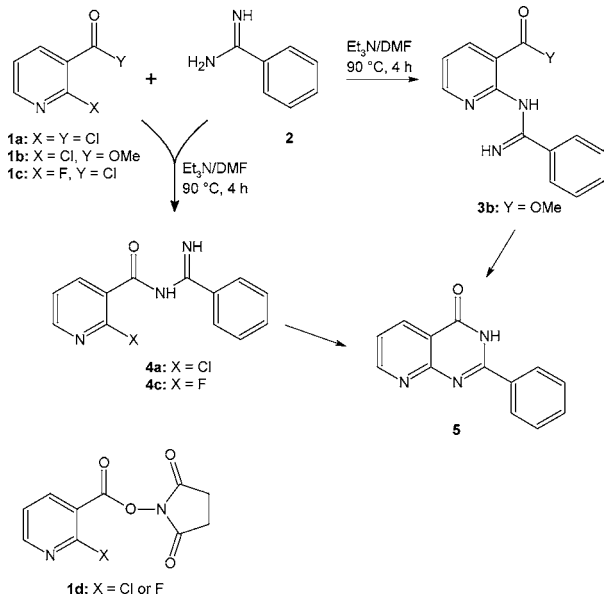
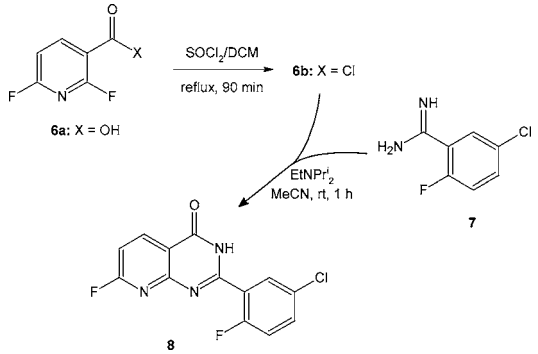
three reagents were 87% using **1c**, 56% from **1a**, and 34% from **1b**. It is suggested that the intramolecular cyclisation is optimised by activation of the associated halogen bond so that reagents **1a** or **1c** are preferred to **1b**. It was shown that the acylation of both **1a** and **1c** was very rapid but that the cyclisation to give **5** was much faster for **4c** than for **4a**. Hence **1c** is the preferred reagent for producing **5**.

Scheme 1



The patent also gives experimental details for the preparation of the fluoro compound **8** that is prepared from the acid **6** and **7** as shown in Scheme 2.

Scheme 2



One of the claims of the patent specifically mentions the use of a reagent **1d** that is described as an activated ester. There are no experimental details on the use of this compound, and since the patent does state that **1a** or **1c** are the preferred reagents the reason for the inclusion of **1d** is unclear.

Advantages

The patent provides a facile route to give these useful compounds especially if the required reagents are readily available.

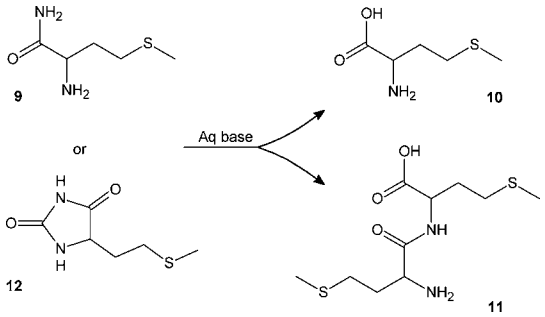
Patent No. U.S. 7,119,228

Assignee: Degussa AG, Dusseldorf, Germany

Title or Subject: Process for Producing Methionine

Methionine **10** is an essential amino acid and is produced on a substantial scale by hydrolysis of the materials such as **9** or **12** (Scheme 3). Improvements in processes for producing **10** have been reviewed previously (*Org. Process Res. Dev.* **2005**, *9*, 537). The process of hydrolysis can give rise to byproducts such as the dipeptide methionyl methionine **11**, and this is not easily removed or converted to **10**. The patent discloses a process for a hydrolysis process that converts **11** to **10** and thus improves the overall product yield. The process involves initial hydrolysis of **12** using KOH and $KHCO_3$ followed by saturation of the solution with gaseous CO_2. This precipitates **10** and leaves a filtrate that is heated to between 220 and 260 °C and then further saturated with CO_2. This also results in the precipitation of more **10** and $KHCO_3$. The initial heating is carried out for about 3 min, and the process is carried out continuously.

Scheme 3



Advantages

The process is said to have a high space−time yield and improved efficiency thereby being more economically attractive.

Patent No. U.S. 7,119,199

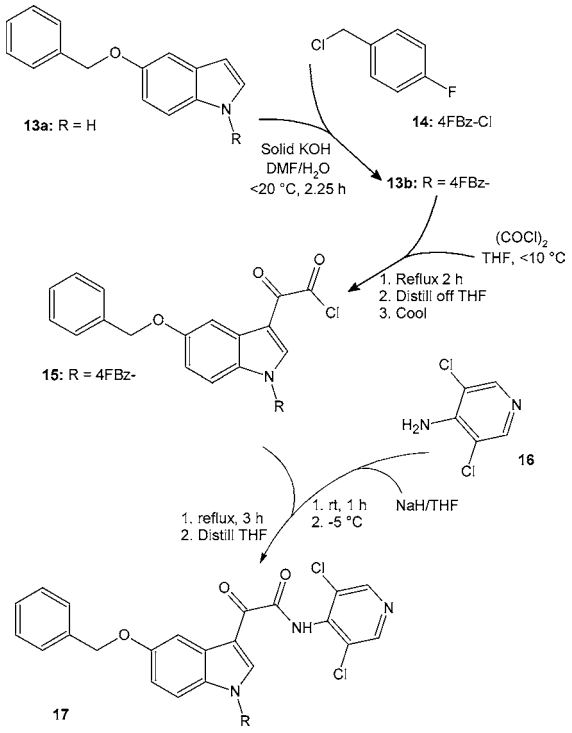
Assignee: Elbion AG., Radebeul, Germany

Title or Subject: Process for Preparing High-Purity Hydroxyindolylglyoxylamides

The compounds of interest in this patent such as **18** are phosphodiesterase IV inhibitors and are useful in treating asthma and allergic rhinitis. Other methods used to prepare compounds similar to **18** are said to use reactions that are not amenable to commercial operation. This is attributed to the difficulty in removing byproduct impurities. The first part of the process reported in this patent is shown in Scheme 4 and takes place in three stages. In the first of these, the indole **13a** is converted to **13b** in 95% yield by base-catalysed condensation with the benzyl chloride **14**. The product is said to be of very high purity and is used directly in the reaction with oxalyl chloride to produce **15**. Again the

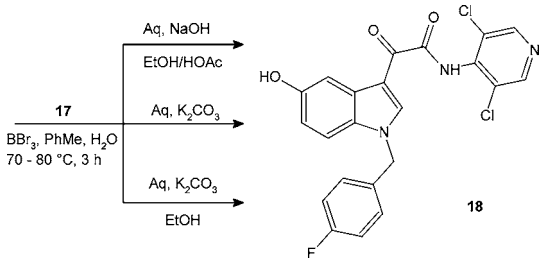
product is used without working up to give **17** by reaction with a THF solution of **16** that has been treated with NaH.

Scheme 4



The final step in the overall process is the removal of the protective benzyl group to give **18** (Scheme 5). The initial procedure is to treat **17** with BBr_3 in hot PhMe/H_2O followed by base hydrolysis. There are three different hydrolysis methods used that differ in the base that is used. Of the three procedures reported, the third one using EtOH/K_2CO_3 is carried out using multi-kilo quantities and gives the highest yield of 95%. The other two methods are carried out on a gram scale and give yields of 85−90%. Whether this is the preferred method is not clear, since one of the patent claims specifically mentions using EtOH and NaOH for this step.

Scheme 5



The patent claims specifically mention that the residual amount of the intermediate **17** in the final product is no more than 0.2% and total impurities are <0.5%.

Advantages

The process gives high yields of the desired product in high purity without extensive purification and can use intermediates that have not been purified.

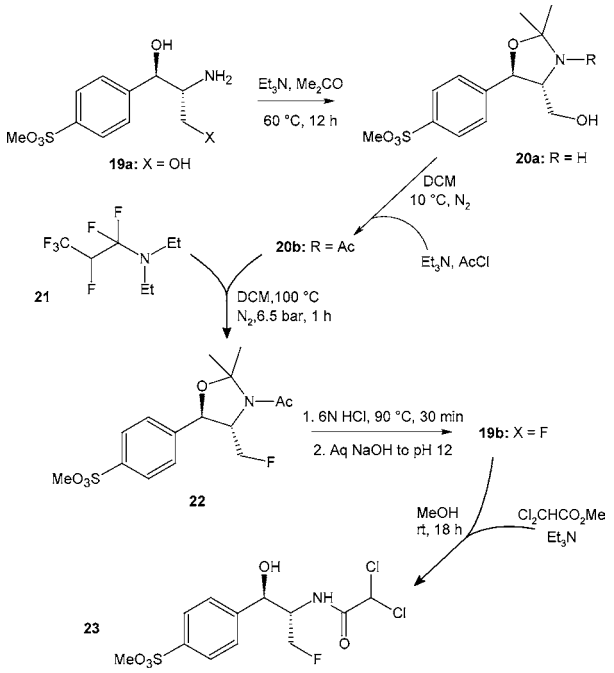
Patent No. U.S. 7,126,005

Assignee: Aurobindo Pharma Ltd., Ameerpet, Hyderbad, India

Title or Subject: Process for Preparing Florfenicol

Florfenicol **23** is a broad-spectrum antibiotic used in veterinary medicine. The most difficult aspect of alternative syntheses is the introduction of the F atom. The process described here is shown in Scheme 6 and uses the Ichikawa reagent **21** to introduce the F atom. The synthesis starts by protection of OH and NH_2 groups in **19** by formation of the oxazolidine **20a** by base-catalysed reaction of **19a** with Me_2CO. The acetyl derivative **20b** is then formed, and this is fluorinated with **21** to give **22**. Acid hydrolysis of **22** forms the fluoroamine **19b** that is treated with Cl_2CHCO_2Me to give **23**.

Scheme 6



Several of the intermediate compounds such as **20a** and **20b** are novel, and ^1H NMR data are given for these and other related oxazolidine compounds.

Advantages

The process provides an improved method of making this compound using a well-established fluorination technique.

Patent No. U.S. 7,126,024

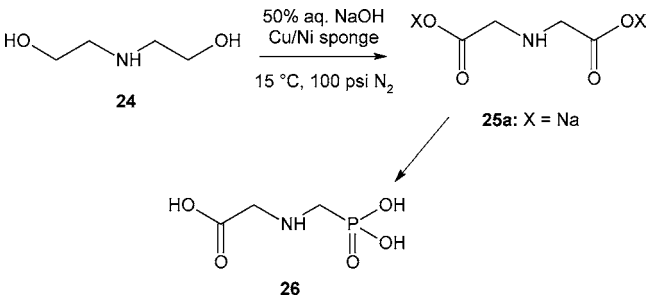
Assignee: Monsanto Technology LLC., St. Louis, Missouri, U.S.A.

Title or Subject: Process for Dehydrogenating Primary Alcohols to make Carboxylic Acid Salts

The main subject of the patent is the Na salt **25a** that is used in the production of the well-known weed killer glyphosate **26**. Much of the patent focuses on the composition and preparation of the catalysts used in the process. This is

a Cu doped Ni sponge catalyst that is used in alkaline conditions to dehydrogenate **24**. The catalyst may also contain Zn or Fe promoters. Cu catalysts are well-known as dehydrogenation catalysts, but they can be easily deactivated and this patent addresses this problem. Scheme 7 shows the basic route used to prepare **25a** in yields of up to 95%. The Na salt is phosphorylated to give **26**, but no experimental details are provided for this step.

Scheme 7



Advantages

The patent describes a catalyst for this important conversion that is claimed to have high activity and better stability than alternatives.

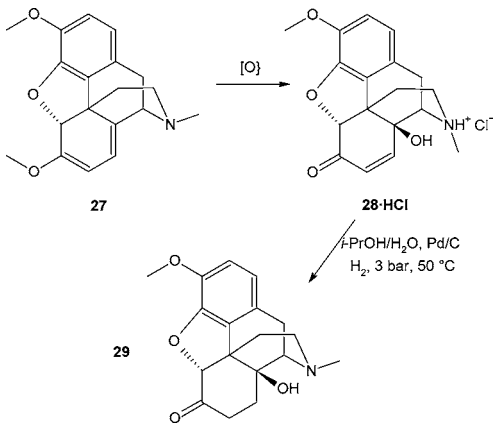
Patent No. U.S. 7,129,248

Assignee: Euro-Celtlque S.A., Luxembourg, Luxembourg

Title or Subject: Process for Preparing Oxycodone Hydrochloride having <25 ppm of 14-Hydroxycodeinone

Oxycodone **29** is a well-known narcotic used in pain management and is made by oxidation of thebaine **27** to form 14-hydroxycodeinone **28** followed by reduction (Scheme 8). An improved synthesis of compound **29** was discussed in the last review (*Org. Process Res. Dev.* **2007**, *11*, 178). This patent claims that processes for converting **28** to **29** can have upwards of 100 ppm of **28** in the final product, and it aims to significantly reduce that level. This is achieved by reducing the HCl salt of **28** in a solvent mixture of *i*-PrOH and H_2O using a Pd/C catalyst. Some examples are provided in which the level of **28** is below 5 ppm.

Scheme 8



Advantages

The process gives a product with very much lower levels of the starting material than was previously attainable.

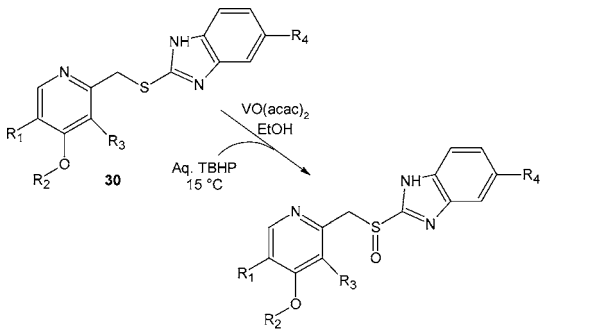
Patent No. U.S. 7,129,358

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

Title or Subject: Processes for the Production of Substituted 2-(2-Pyridylmethyl)Sulfinyl-1H-Benzimidazoles

There are a number of benzimidazoles that are gastric proton pump inhibitors and are used to treat ulcers. Some common examples are the drugs omeprazole **30a**, pantoprazole **30b**, lansopazole **30c**, and rabeprazole **30d**. A key step in the preparation of these compounds involves the oxidation of a thioether to a sulfinyl compound. Several oxidising methods have been used, and a recently reviewed patent uses an oxidant found in household cleaning products (*Org. Process Res. Dev.* **2007**, *11*, 178). The claims of the current patent cover the use of *tert*-butyl hydroperoxide (TBHP) with $VO(acac)_2$ for the oxidation step. Scheme 9 shows the reaction used for preparing the four compounds **31a**−**31d** from the respective thioethers **30**. In place of EtOH, PhMe can be used as a reaction solvent. The yields for all cases are about 80%. The patent also provides details of experiments in which the persulfate salt Oxone is used as the oxidising reagent for preparing the four compounds. The yield of these reactions is not reported, but the purity of the all products is 98%.

Scheme 9



Advantages

The process provides an efficient method for the synthesis of these important drugs.

Patent No. U.S. 7,132,544

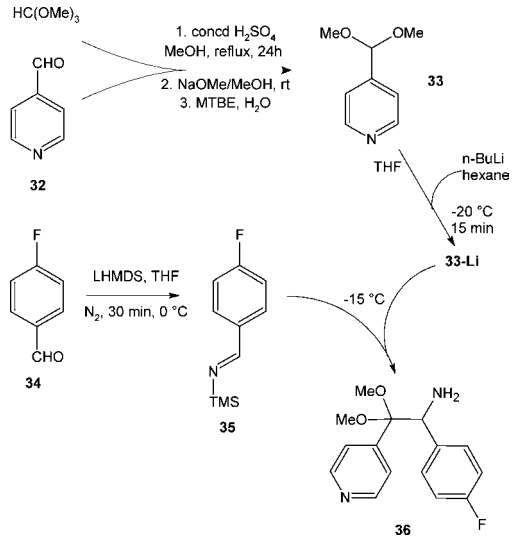
Assignee: Ortho-McNeil Pharmaceutical Inc., Raritan, New Jersey, U.S.A.

Title or Subject: Process for Preparation of Tetrasubstituted Imidazole Derivatives and Novel Crystalline Structures Thereof

The single claim in this patent relates to a process for preparing compound **42b** that is an active inhibitor of p38 kinase and hence has potential as an anti-inflammatory agent. The patent reports that two forms of **42b** can be prepared from **36** and **39** by the route shown in Scheme 11. The

intermediate **36** used in the synthesis is prepared by the process outlined in Scheme 10. This involves the reaction of the Li derivative **33-Li** with the imine **35** at −15 °C and gives **36** in 79% yield. The methods of preparation for both **33-Li** and **35** are described in the patent, and Scheme 10 outlines these. **33** is prepared in 62% yield from aldehyde **32** by condensation with $HC(OMe)_3$ in the presence of concd H_2SO_4 followed by treatment with NaOMe. The lithiation of **33** with *n*-BuLi gives **33-Li**. **35** is formed from **34** with LHMDS.

Scheme 10



The production of **42b** which is shown in Scheme 11 initially involves the preparation of **39** from **37** and **38**. This reaction takes place at room temperature. Reaction of **36** with **39** in refluxing PhMe gives the urea **41** in 47% yield. Treatment of **41** with HCO_2H causes cyclisation to give the imidazolone **40** that is converted to the bromo compound **42a** using $POBr_3$. The reaction of **42a** with the alkynol **43** using a Pd catalyst, PPh_3, Fe powder, and a base gives **42b**. If this is recrystallised from MeCN, Form A is obtained, whereas using THF/PhMe produces Form B.

Advantages

The patent provides an efficient method of preparing this potentially useful drug agent.

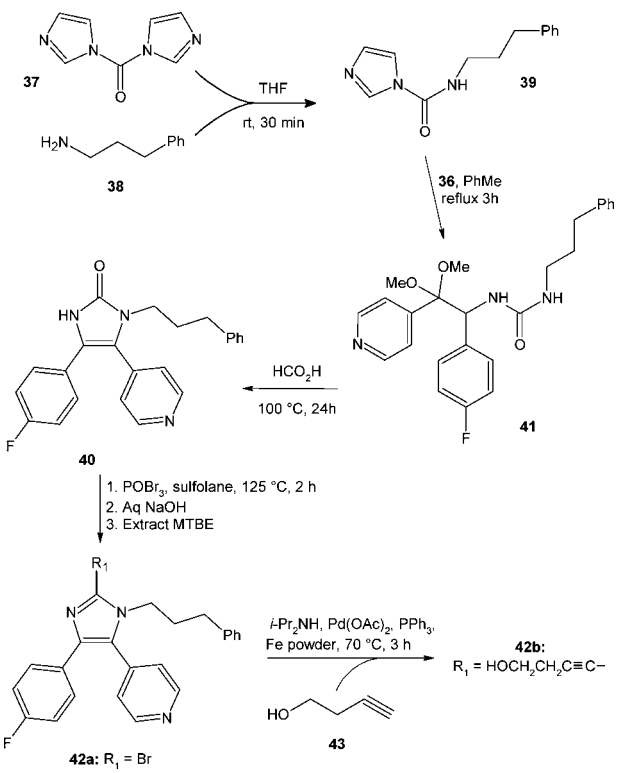
Patent No. U.S. 7,132,552

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

Title or Subject: Process for Producing Levetiracetam

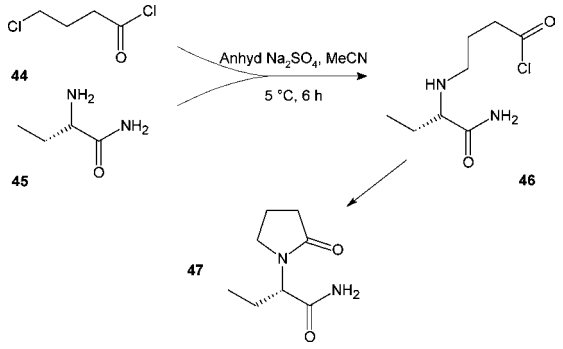
The title compound **47** is available under the name keppra and is used in treating epilepsy. This patent describes a method of producing **47** that specifically excludes the use of Bu_4NBr. This compound is used in alternative syntheses of **47** and acts as a phase transfer catalyst (PTC). The method is quite simple and involves the reaction of **44** with **45** in MTBE or MeCN. The reaction presumably proceeds via **46** since one of the patent's claims mentions the cyclisation of

Scheme 11



46 to **47**. The product is preferably recrystallised from EtOAc and contains <0.2% of the *R*-isomer. Key features of the process are the requirement to maintain anhydrous conditions, and this is possible using molecular sieves, Na_2SO_4 or K_2CO_3.

Scheme 12



Advantages

The process gives the product with low levels of impurity in a one-step reaction that does not require PTCs that could be difficult to remove.

Patent No. U.S. 7,132,570

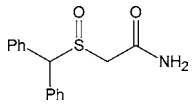
Assignee: Cephalon France, Maisons-Alfort Cedex, France

Title or Subject: Production of Crystalline Forms of Enantiomers of Modafinil

Modafinil **48** has been known for some time and is used as a stimulant to overcome the effects of narcolepsy. Original reports of **48** mentioned a single form of the drug, and the current patent describes four additional polymorphs of each

enantiomer. The original form designated Form I is thermodynamically the most stable form. The new forms can be obtained by recrystallisation from a range of solvents except EtOH or by various thermal treatments. The use of EtOH or solvents containing EtOH appear to give Form I. The patent describes in some detail some of the methods used to obtain the alternative forms. Phase diagrams are provided in the patent, and some of the procedures appear quite complicated. Readers are encouraged to consult the patent for full details.

Modafinil



48

Advantages

The patent provides novel polymorphs of this widely used drug.

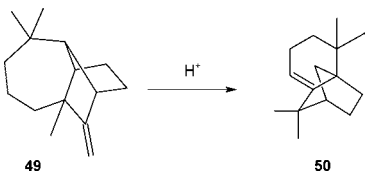
Patent No. U.S. 7,132,582

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

Title or Subject: Catalytic Process for the Preparation of Isolongifolene

Isolongifolene **50** is obtained by the isomerisation of longofolene **49** that is obtained from Indian turpentine oil and is widely used in flavours and fragrances. The conversion of **49** to **50** is shown in Scheme 13 and uses strong mineral acids. It is stated that the reaction usually requires several steps and produces a large quantity of waste products. The process described in this patent uses solid acid catalysts that are based on sulfated zirconia. Much of the patent is directed towards the preparation of the catalyst, and this involves hydrolysis of a Zr alkoxide followed by treatment with H_2SO_4 and calcination. The production of **50** is carried out by heating **49** and the catalyst at 180−200 °C for 2 to 6 h. The conversion of **49** measured by HPLC is 90% with a selectivity to **50** of up to 100%. There are no details of yields for recovered products or of the methods used for recovery.

Scheme 13



49 50

Advantages

The process uses solid catalysts, and hence waste products are eliminated.

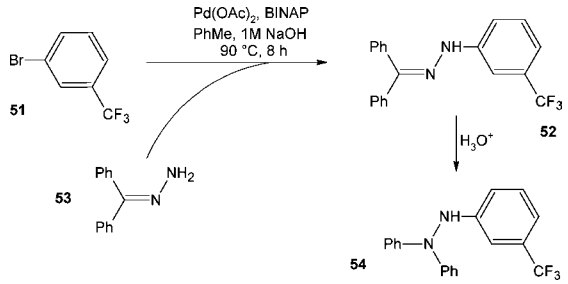
Patent No. U.S. 7,138,548

Assignee: Avecia Limited, Manchester, United Kingdom

Title or Subject: Process for Preparing Aryl Hydrazones and Aryl Hydrazines

Aryl hydrazones and hydrazines are useful intermediates in the synthesis of heterocyclic compounds. There are processes known for the preparation that are carried out in nonaqueous systems, but these are said to be expensive and impose a high chemical oxygen demand (COD) on effluent treatment systems. Scheme 14 shows the preparation of the hydrazone **52** by reaction of **51** and **53**. This is carried out in the presence of a $Pd(OAc)_2$ and BINAP in PhMe containing aqueous NaOH. The acid hydrolysis of **52** then produces the hydrazine **54**, but no experimental details of this reaction are provided.

Scheme 14



Advantages

This process takes place in aqueous solution and compared to alternative methods has a reduced effluent disposal problem.

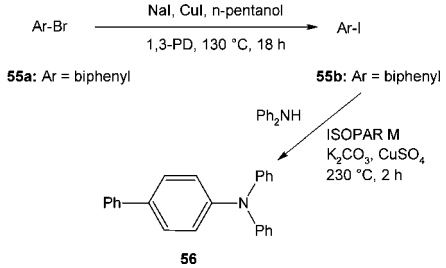
Patent No. U.S. 7,138,555

Assignee: Xerox Corporation

Title or Subject: Process for Preparing Iodoaromatic Compounds and Using the Same

The compounds of interest in this patent are used to prepare triarylamines such as **56** that act as charge-transporting materials and are used in photocopying equipment. Alternative methods for preparing the desired iodo compounds are said to be expensive and can yield diiodo compounds that are difficult to remove. Scheme 15 shows the route used to prepare **56** by an Ullmann condensation reaction of **55b** with Ph_2NH. The reaction takes place above 200 °C and requires an inert hydrocarbon solvent with a base and hydrated $CuSO_4$. A yield of 86% of **55b** with a purity of almost 99% is reported. The preparation of **55b** is from the bromide **55a** and uses 2 mol equiv of NaI, 5 mol % of CuI as catalyst, and 10 mol % of 1,3-propanediamine (1,3PD) as a coordinating ligand. The reaction time depends on the temperature, and this is dictated by the choice of solvent. For example using *n*-pentanol requires 18 h, but *n*-hexanol requires only 4 h. The product **55b** is purified by recrystallisation from *n*-pentanol and obtained in 92% yield.

Scheme 15



56

Advantages

The process is claimed to be low cost and gives high purity products.

Patent No. U.S. 7,141,602

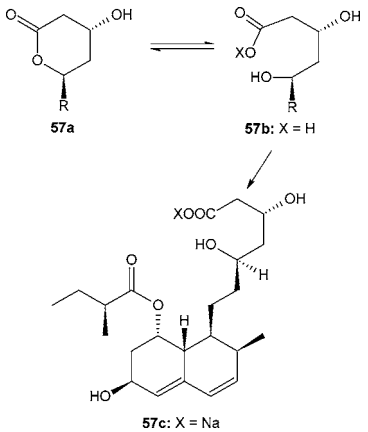
Assignee: LEK Pharmaceuticals d.d., Ljubljana, Solvenia

Title or Subject: Process for Obtaining High purity HMG-COA Reductase Inhibitors

The claims of this patent cover a process for the isolation and purification of the Na salt of pravastatin **57c**. However, the patent also describes the purification of other statin compounds. This range of compounds is of great importance in reducing cholesterol levels in blood and hence in preventing cardiovascular disease. The purification method used is displacement chromatography (DC) that is a technique that has been known since 1943. The patent gives a very brief review of the method and references that readers, who are unfamiliar with the method, are urged to consult.

As with isolating any chemical there are several possible methods for purifying statins, and combinations of crystallisation, extraction, chromatography, and other techniques have all been used. A major problem with the isolation and purification of statins is that the molecule exists as a lactone **57a** or a hydroxy-acid **57b**, and during isolation these forms can readily interchange (Scheme 16). Salts such as **57c** are often prepared to ease this problem. Statins are obtained by fermentation methods, and hence large volumes of solutions are handled. The patent states that conventional methods used for isolation require large volumes of materials and are therefore difficult and expensive. The focus of this patent is on limiting the total level of 12 specific impurities in **57c** to below 0.3%. For a number of individual impurities, there are also specified maximum levels.

Scheme 16



The process used in this patent is applied to the salt **57c** as well as the lactone **57a**. A range of stationary phases is used in the examples such as Grom-Sil 120-OPDS, Hypersil ODS, or Kromasil 100-C18. These are cross-linked styrene and divinylbenzene polymers. The purification process is summarised as follows:

(a) Condition the column with a mobile phase A.

(b) Feed a solution of the crude product dissolved in mobile phase A.

(c) Displace the product from the column using mobile phase B.

(d) Collect fractions of displaced solution.

(e) Recover product from collected fractions.

(f) Regenerate column using an aqueous solution of MeOH.

The patent does not mention how to recover the product from the final step, and the purity and yields are all measured by HPLC on the solutions. Mobile phase A is water, MeCN/water, or MeOH/water adjusted to pH 7 with NH_4HCO_3. The displacing medium, mobile phase B, is an amphiphilic material such as a surfactant, and a number of polyglycol ethers are used in the examples.

The process is applied to **57a**, **57c** and also to the lactone forms of simvastatin, lovastatin, and mevastatin.

Advantages

The process is claimed to provide high purity products and offer economic advantages over other techniques. However, it does seem to require the use of significant volumes of different solvents, and hence it is difficult to see how the claim can be justified.

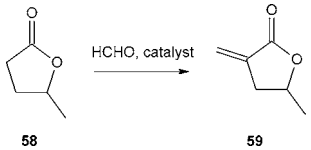
Patent No. U.S. 7,141,682 and 7,153,981

Assignee: E.I. DuPont de Nemours and Company, Wilmington, Delaware, U.S.A.

Title or Subject: Synthesis of Methylene Lactones Using Phosphorous Oxynitride Catalysts

These two patents cover the reaction of HCHO with lactones such as **58** to give the methylene derivative **59** using catalysts described as aluminium phosphorous oxynitrides (Scheme 17). The two patents differ in that the second uses supercritical fluids (SCFs) whereas the first does not. The product **59** is said to be useful in preparing polymers or is a structural feature of many sesquiterpenes. Alternative methods of carrying out this reaction to prepare **59** are said to use catalysts that deteriorate at the temperatures needed for the reaction. In the second patent that uses conventional solvents such as PhMe, the HCHO precursor is paraformaldehyde, and the reaction takes place at 200 °C at a pressure of around 55 bar. The SCF used in the second patent is CO_2 at a pressure of 235 bar and at 300 °C. In this case the HCHO precursor is the hemiacetal $CH_2(OH)OEt$. The selectivity of the reaction in both patents is not very high being $<16\%$ in the first case and $<57\%$ in the second.

Scheme 17



The patent describes the preparation of the catalysts, and these may be doped with alkali or alkaline earth metals. The process is also applicable to butyrolactone as well as to **58**.

Advantages

The severe conditions required for this process do not seem to give a significant advantage that would justify using the process commercially.

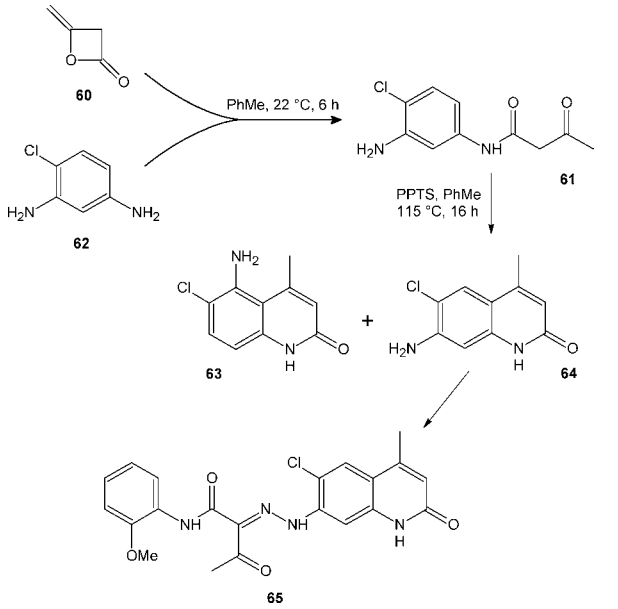
Patent No. U.S. 7,144,993

Assignee: Ciba Specialty Chemicals Corp., Tarrytown, New York, U.S.A.

Title or Subject: Process for the Preparation of 4-Methyl-7-Aminoquinolones

The title compounds such as **61** are used to prepare azo pigments such as **65** that are used to improve colour fastness to weathering. The effectiveness of **65** is reduced by the presence of **63** that is a byproduct in the preparation of **64**. Hence the objective of the patent is to minimise the formation of **63** during the synthesis of **64**, and some alternative processes give rise to up to 14% of **63**. This byproduct is usually removed by recrystallisation. The patent describes a two-step process to prepare **64** that gives low yields of **63** and is outlined in Scheme 18. The first stage gives a 98% yield of **61** and takes place in an aprotic solvent at room temperature. The product **61** is then heated in the presence of strong acid to cause cyclisation and giving **64** with some byproduct **63**. There are several examples in the patent using a variety of solvents and catalysts. For example using PPTS in PhMe gives a 90.5% yield of **64** with only 3.1% of **63**, and when TsOH is used in Bu_2O this gives a 93.5% yield of **64** containing 4.5% of **63**. The reaction can be carried out in a single step without isolation of the intermediate **61**. In fact one of the claims in the patent states that the process of producing **64** is carried out in a one-pot reaction.

Scheme 18



Advantages

The process gives a greatly reduced yield of byproduct and can be carried out in a single step.

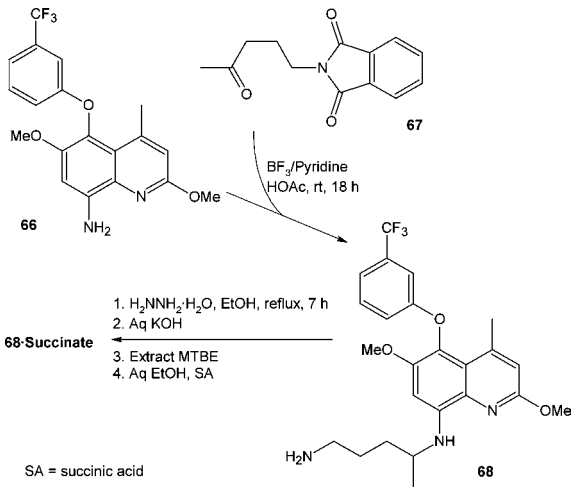
Patent No. U.S. 7,145,014

Assignee: SmithKline Beecham Plc, Brentford, United Kingdom

Title or Subject: Process for the Preparation of Quinoline Derivatives

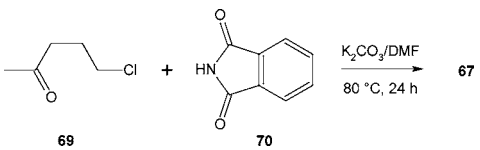
The single claim in this patent is a process to prepare tafenoquine **68·succinate**, a compound under trial as a promising antimalarial agent. The main advantage of tafenoquine is that it has a long half-life and therefore does not need to be taken as frequently as other drugs. The synthesis of **68** is by reductive alkylation reaction of **66** with the phthalimido compound **67** using the BF_3/pyridine complex (Scheme 19). The current process gives a 94% yield of **68**, and the succinate salt is recovered in 74% yield. It is claimed that there is no need to purify **68** before conversion to the salt, and hence this improves the overall process. The synthesis of the basic quinoline structure in **68** was disclosed in 1986 and is said to be an inefficient 12-stage procedure with many problems on a large scale. An improved eight-step procedure was published in 1997.

Scheme 19



The new process is claimed to be a further improvement on the 1997 process by using **67** containing a phthalimide protecting group. The 1997 patent used an iodo-amine and gave rise to iodinated waste compounds. The preparation of **67** in 88% yield is shown in Scheme 20.

Scheme 20



The patent describes the single-step reaction to prepare **68**, and there is no indication as to how the important reagent **66** is prepared. In order to compare the efficiency of the current process with the earlier methods it would be necessary to have knowledge of this route.

There are a number of errors in this patent with the most serious being in the single claim. The structure of **66** shown in the patent actually has the methyl group in the 3-position,

and hence one could read this as meaning that the patent really is novel in converting a 3-methyl group in **66** to a 4-methyl in **68**.

Advantages

The patent claims to be an improvement over earlier procedures and does not produce toxic wastes.

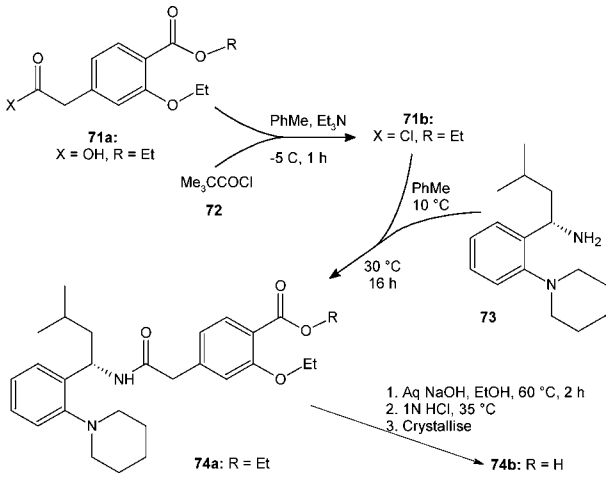
Patent No. U.S. 7,148,355

Assignee: Ranbaxy Laboratories Ltd., Gurgaon, India

Title or Subject: Process for the Preparation of Repaglinide

This and the next patent are both concerned with the production of drugs that are used to treat diabetes. The current patent focuses on repaglinide **74b** that is used for noninsulin dependent diabetes. There are several processes known for the preparation of **74b**, and these involve the reaction shown in Scheme 21 in which the amine **73** reacts with compounds similar to **71a**. A variety of catalytic reagents is used such as DCC and Ph_3P. These are said to have drawbacks such as requiring the use of expensive reagents or have several steps limiting their use in commercial production. The improvement reported in this patent is to carry out the reaction of **73** with **71a** in the presence of a slight excess of **72** and a base. Presumably the initial stage is the formation of acyl chloride **71b**, and the overall reaction to produce the ester **74a** in 74% yield is actually carried out in one vessel without isolation of **71b**. The final hydrolysis of **74a** to give **74b** in 94% yield is carried out after purification of **74a**.

Scheme 21



Advantages

The process is economical and avoids the use of purification methods such as chromatography or extensive recrystallisation techniques.

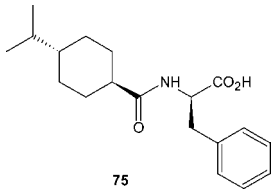
Patent No. U.S. 7,148,376

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

Title or Subject: Polymorphic Forms of Nateglinide

This patent describes another drug to treat diabetes. The drug of interest in this patent is nateglinide **75** that is used to treat type II diabetes. **75** is known to exist in several crystalline forms, and the patent summarises the literature relating to these. This patent describes the discovery of 26 new crystalline forms of **75**. The number of polymorphs is so large that they are designated by the use of letters from both the Latin and Greek alphabets. As is usually the case, the various polymorphs are formed by heating and by using different solvents for crystallisation. For full details the reader is referred to the patent that contains X-ray diffraction, FTIR, and calorimetric data for the polymorphs.

Nateglinide



75

Advantages

The patent describes a large number of new polymorphs of this drug that may have application in novel formulations.

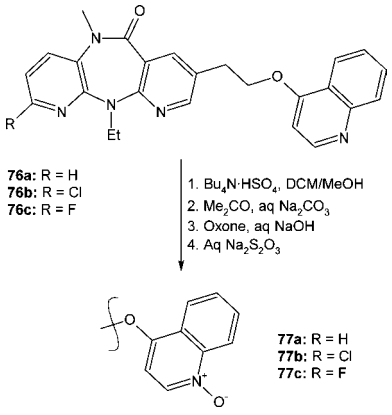
Patent No. U.S. 7,151,174

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

Title or Subject: Process for Making a Non-Nucleoside HIV-1 Reverse Transcriptase Inhibitor

N-Oxides such as **77** have HIV-1 inhibitory activity and hence are useful in treating AIDS and related disorders associated with HIV-1 infection. Alternative methods for preparing structurally similar compounds involve oxidation steps that can lead to unwanted byproducts. The patent describes an oxidation method for making **77** that uses Oxone in a ketone and in the presence of a PTC. It is suggested that the ketone forms a dioxirane, and this transfers an O atom to form the *N*-oxide. Control of the pH is important, and inorganic bases are used to maintain the required pH. It is noted that the reaction is carried out in dim light or in darkness. The starting materials **76** are prepared by patented procedures described although details are not given.

Scheme 22



Advantages

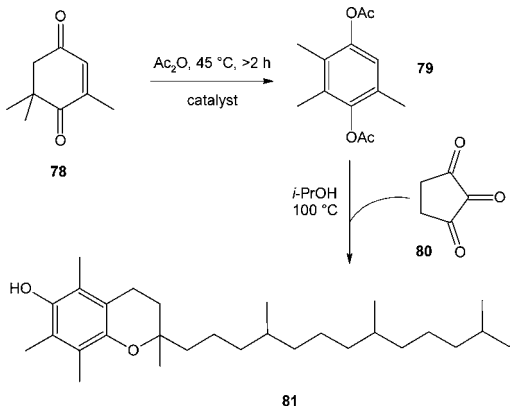
The process uses selective oxidising agents that do not give rise to high levels of byproducts.

Patent No. U.S. 7,153,994

Assignee: DSM IP Assets B.V., TE Heerlen, Netherlands
Title or Subject: Manufacture of Trimethylhydroquinone Diacylate

The product of this process **79** is used in the synthesis of intermediates that can be used to prepare vitamin E derivatives such as **81**. The production of **79** involves an acylation of ketoisophorone **78** followed by a rearrangement reaction by using an acylating agent in the presence of strongly acidic catalysts. Alternative processes use inorganic acids or Lewis acids, and these can give rise to corrosion problems. The catalysts used in this process are those containing NH or CH groups such as $(CF_3SO_2)_2NH$ or $(CF_3SO_2)_3CH$. The reaction is carried out in Ac_2O that is both the solvent and acylation agent. After removal of solvent the product is obtained in yields above 82%. The conversion of **79** to α-tocopherol **81** is carried out by heating in **80** at 100 °C followed by a transesterification reaction with *i*-PrOH.

Scheme 23



Advantages

The process avoids the use of corrosive materials and does not give rise to waste problems. At the same time the product is obtained in high selectivity and with high purity.

Keith Turner

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