Organic Process Research & Development **2008,** *12,* 556–565

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published During February and March 2008

Summary

The current review summarises 25 patents out of a total of 217 that fitted the search criteria. Some of these are continuations of previously published patents from the same company and hence do not always include novel procedures or chemistry but merely extend the legal coverage of the work. An example of such a patent is one covering the preparation of high-purity perindopril, a drug used to treat cardiovascular problems. A second covers the purification of polymorphs of zaleplon, a drug used to treat insomnia; and a third describes novel polymorphs of losartan, a drug used to treat high blood pressure. Another patent on losartan from a different company describes a novel method of making the drug that reduces material handling problems for operators by avoiding the use of KOBu^t powder. A patent disclosing a process for the preparation of the antibiotic imipenem shows that work described in an earlier patent from the same company was wrong and the result of poor experimental technique and analysis. Improved processes are described for a number of established drugs, and there are patents covering olanzapine for bipolar disorders, clopidogrel and isradipine for the treatment of atherosclerosis and coronary diseases, tamulosin for prostate problems and zolmitriptan for migraines. In this latter patent the improvements relate to the avoidance of toxic tin compounds, but this is offset by the use of dichloromethane in many processing steps. Avoiding the use of heavy metals is the subject of a patent for the preparation of intermediates used in perfumes and flavours. The new process uses a commercially available sodium salt for the dimerisation of glyoxals. Genistein is an isoflavone used to treat hormonal cancers, and a process for its production is described that includes an improved formylation step avoiding the use of mixed formic−acetic anhydride that can be unstable. Chiral heptynes are used to prepare epothilones that have cytotoxic properties, and a process claimed to be unlike any other related to epothilones is described. Cross-coupling reactions are very important tools, and a patent describes using indoles in such reactions to produce multikilo quantities of compounds used to treat hepatitis C viral infections. Another patent on drugs to treat the same problem describes branched ribonucleosides that are made from 1,2-anhydroribofuranoses and again describes producing multikilo quantities. Carotenoids are natural pigments that are used as dietary supplements, and one patent describes a process using supercritical fluids to extract them from microalgae. A second patent on carotenoids discloses a method of making a trienedial that is an intermediate in making carotenoids. Another important dietary supplement is vitamin E, and a method of producing a succinate derivative is disclosed that is claimed to produce higher density solids that are useful in preparing formulations. Again on the subject of vitamins, a new process to prepare tetrahydrogeranylacetone is described, and this is used to produce isophytol, a reactant in the synthesis of vitamins E and K. Tuberculosis is still a problem in the developing world, and a process is described to prepare amide intermediates that are converted to isoniazid, a drug for treating the disease. The process involves specially prepared MnO_2 for an oxidation step. Electrophotographic imaging systems are very widely used, and triarylamines are important intermediates in the manufacture of layer components. A new process for preparing triarylamines is described using aryl chlorides in place of iodides and a catalyst containing Pd and a phospha-adamantane ligand. Hydroxyaromatic acids are intermediates in the production of a range of commercial products. The Cu-catalysed hydrolysis of halogenated aromatic acids is described that gives products in >99% yields. The process requires a diamine ligand to achieve such yields. Nitration reactions are notoriously dangerous and unselective, and a patent discloses a process to prepare mononitro diols using nitric acid that contains <10 ppm of nitrogen oxides. This is obtained by treating the normal acid with urea, and its use significantly improves the safety aspects and selectivity of the nitration reaction. There is an improved process and catalyst for the production of the widely used weed killer, glyphosate. The catalyst consists of Cu on a Ni sponge. Several of the patents include examples for the preparation of kilo and multikilo quantities of materials, thus indicating the advanced commercial status of the process. However, there is no legal or commercial significance in the choice of any of these patents, and the advantages claimed are those stated in the patent unless this reviewer has personal knowledge of the subject.

Patent No. U.S. 7,326,794

Assignee: Les Laboratoires Servier, Courbevoie Cedex, France Title or Subject: Process for the Preparation of High Purity Perindopril and Intermediates Used in its Synthesis

Perindopril **3** is used in treating cardiovascular problems, and other related patents from this company on this compound were reviewed recently (*Org. Process Res. Dev.* **2008**, *12*, 146). This patent extends the work covered in the earlier patents and involves the same route that is shown in Reaction 1.

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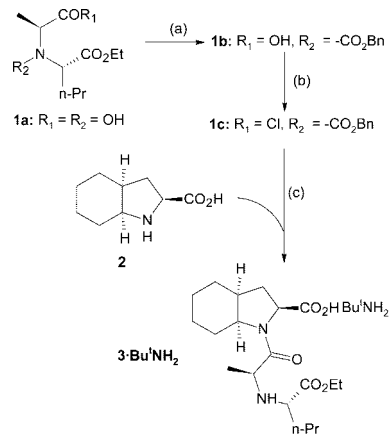
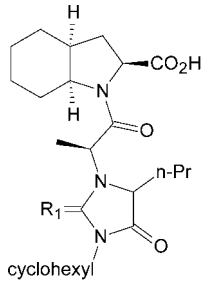
Reaction 1



(a) (1) K_2CO_3, Me_2CO/H_2O (2) $ClCO_2Bn$, <5 °C (3) rt, 2 h, Evaporate
(4) Aq NaOH (5) Extract in EtOAc (6) Aq HCl
(b) (1) DCM, $SOCl_2$, <5 °C (2) rt, 3 h (3) Evaporate
(c) (1) THF, reflux, 4.5 h (2) Evaporate (3) EtOAc, Bu^tNH_2
(4) Heat to dissolve (5) Cool, filter

The process involves acylation of **1a** to give **1b** that is activated using $SOCl_2$ to form **1c**, and this is coupled with **2** to form **3** that is isolated by formation of the *tert*-butyl salt in 45% yield. The main claim of this patent specifically mentions the synthesis of **3** or the salt that is free from contamination by the benzyl esters **4a** and **4b**. These compounds are present when DCC is used as a coupling reagent in the alternative synthesis from **1c** and the Ts salt of the benzyl ester of **2** Benzyl Esters. The patent also describes the synthesis of the methyl and ethyl



4a: R_1= O
4**b:** R_1 = Cyclohexyl-N

analogues of **1b** and **1c** (R_1 = OMe or OEt) from the corresponding chloroformates and Et_3N is used in place of K_2CO_3 in step (a). The Bu^t analogue is formed by using $(BOC)_2O$ in place of the chloroformates and K_2CO_3. All of these compounds are novel, and basic ^1H NMR data are given for them.

Advantages

The new process prevents the formation of byproducts that are difficult to remove and produces a high purity product.

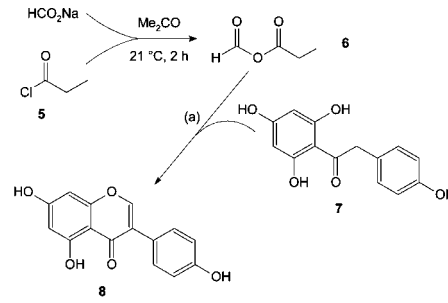
Patent No. U.S. 7,326,797

Assignee: DSM IP Assets B.V., Heerlen, Netherlands

Title or Subject: Manufacture of Isoflavones

Isoflavones have a range of biochemical effects, and the particular compound of interest in this patent is genistein **8** that is found in soybeans. **8** has potential for use in treating hormone-related cancers such as prostate and breast cancers. There are several methods available to prepare isoflavones, and these are summarised. One method involves a formylation step that uses the mixed formic−acetic anhydride, but it is said that this reagent is too unstable to be useful for a commercial-scale process. The key finding in this patent is that anhydrides of HCO_2H and acids other than HOAc are suitable formylating reagents, and the preparation of **8** by formylation of **7** is shown in Reaction 2. The anhydride **6** is initially prepared from the acyl chloride **5** and HCO_2Na. **6** is not isolated and treated with **7** in the presence of Et_3N followed by acid hydrolysis and workup produces **8**. Several examples are described in which the yield of **8** is in excess of 90%. There is also an example using the formyl-isobutyryl anhydride that produces **8** in very high yield. The starting material **7** can be prepared by known methods, and references to these are provided.

Reaction 2



(a) (1) Et_3N, Me_2CO, 25 °C, 2 h (2) EtOH, rt, 16 h (4) 50% H_2SO_4, EtOH
(5) Distil solvents (6) H_2O, 10 °C, filter, dry (7) EtOH, reflux, cool, filter, dry

Advantages

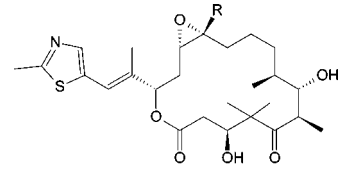
The process provides very good yields of genistein and is claimed to be applicable to other isoflavones.

Patent No. U.S. 7,326,798

Assignee: Schering AG, Berlin, Germany

Title or Subject: Processes for the Preparation of Chiral Heptyne Derivatives and Epothilones

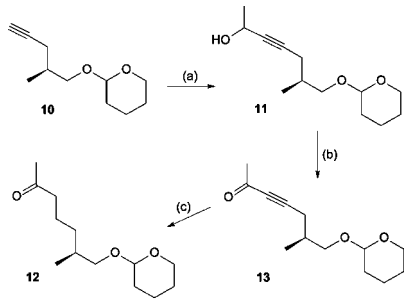
Epothilones such as **9a** and **9b** are relatively new 16-membered macrolides that have cytotoxic properties and potential in treating cancers. There are several steps involved



9a: Epothilone A (R = H)
9b: Epothilone B (R = Me)

in synthesising these compounds, and these are briefly reviewed. This patent focuses on the synthesis of **12** that is described as a key structural intermediate in the overall synthesis of **9a** or **9b**. Reaction 3 shows the route used to prepare **12** from **10** via **11** and **13**. The THP group is used to protect an OH during these transformations. The sequence of reactions begins with the deprotonation of the alkyne **10** using Bu^nLi, then treatment with MeCHO to give **11** that is isolated in almost quantitative yield. The next step is oxidation using MnO_2 giving **13** in 94% yield.

Reaction 3



(a) (1) Bu^nLi, hexane, -10 °C; (2) MeCHO/THF, -10 °C, 30 min;
(3) MTBE, aq NH_4Cl; (b) (1) MnO_2, THF, rt, 48 h
(c) (1) Pd/C, THF, H_2, 8 bar, rt, 1 h

The alkyne group in **13** can then be hydrogenated using Pd/C to give **12** in quantitative yield. Compounds **11** and **12** are novel and the synthetic route described in this patent is claimed to be unrelated to any synthesis that is reported in the literature related to epothilone.

An alternative method of preparing **12** is described in which Me_2NCOMe is used in place of MeCHO after deprotonation of **10**. This gives an excellent yield of **13** (95%).

Advantages

This process gives excellent yields of some novel compounds and a key intermediate in the synthesis of a potentially important compound.

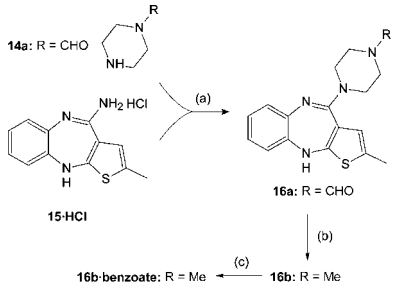
Patent No. U.S. 7,329,747

Assignee: Synthon IP Inc., Gainesville, Virginia, U.S.A.

Title or Subject: Synthesis of Olanzapine and Intermediates Thereof

Olanzapine **16b** is a drug used for treating patients with schizophrenia and manic episodes associated with bipolar disorder. The shortcomings of alternative routes to make **16b** are primarily associated with the difficulty of removing byproduct from the final product. The patent describes a method of preparing the formyl derivative **16a** that can be readily converted to **16b** without high levels of byproduct being formed. Reaction 4 outlines the preparation of **16a** from **14a** and the HCl salt of **15** and its isolation in 96.7% yield after purification by crystallisation. The purified **16a** is then reduced to give **16b** using the commercially available reagent $NaAlH_2(OCH_2CH_2OMe)_2$. The final step is formation of the benzoate salt in 94.8% yield by treating **16b** with $PhCO_2H$.

Reaction 4



(a) (1) DMSO/PhMe, reflux, 16 h; (2) Cool 40 °C, H_2O;
(3) Cool to 0 °C, filter, dry; (4) Crystallise from MeOH
(b) (1) $NaAlH_2(OCH_2CH_2OMe)_2$, PhMe, rt, 5 h; (2) Extract into EtOAc
(c) $PhCO_2H$, 4 °C, 4 h, filter, wash in EtOAc and Et_2O, dry

Advantages

The process gives a very high yield of the desired compound without the purification problems of alternative routes.

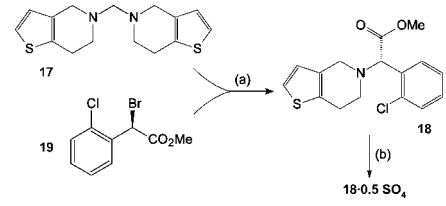
Patent No. U.S. 7,329,751

Assignee: Dipharma S.p.A., Mereto Di Tompa, Italy

Title or Subject: Process for the Preparation of Clopidogrel

Clopidogrel **18**, available as Plavix, is used to treat atherosclerosis and can prevent strokes and heart attacks in susceptible patients. Patents on this drug have been reviewed previously (*Org. Process Res. Dev.* **2005**, *9*, 9), and several methods of the synthesis of **18** are described in this patent. Many processes require a resolution step and have overall low yields. This patent claims a new stereoselective synthetic route to **18** plus a novel compound **17** that is the starting material used in the synthesis. Reaction 5 shows the condensation of **17** and the chiral ester **19** to prepare **18** that is isolated as the hemisulphate. Examples are described using MeOH, Me_2CO or MeCN as solvents, and the final yields range from 45 to 84%. The highest yield is obtained in an example using Me_2CO.

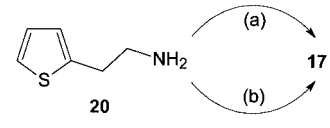
Reaction 5



(a) (1) Me_2CO, reflux, 2 h; (2) Cool,filter;
(b) (1) Me_2CO, H_2SO_4, 20 °C, 12 h, filter

The key to the process is the use of **17**, and the patent also describes how this is produced. Reaction 6 shows how **17** is prepared by treatment of **20** with HCHO in the form of paraformaldehyde or in aqueous solution. The reaction is carried out in acidic solution, and HCO_2H is used in an anhydrous reaction or HCl in an aqueous system. A yield of 45.5% is obtained in the aqueous system compared to 81% in the anhydrous although the anhydrous process takes longer and is carried out at ambient temperature.

Reaction 6



(a) (1) HCO_2H, paraformaldehyde, rt, 14 h;
(2) Aq NaOH, 30 °C, 2 h, filter, wash MeOH, dry.
(b) (1) 36% aq HCl, aq HCHO, 50 °C, 5 h;
(2) NaOH, extract into PhMe, concentrate;
(3) Me_2CO, 2 h, filter dry.

Advantages

The process uses commercially available materials to produce the novel starting reagent and the desired product in good yield.

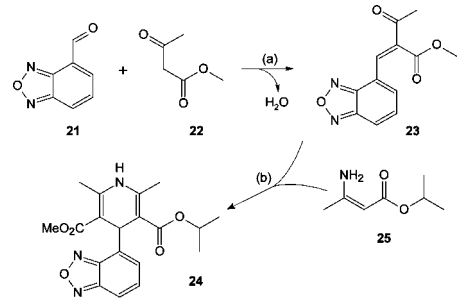
Patent No. U.S. 7,329,756

Assignee: Shasun Chemicals and Drugs Limited, Chennai, India

Title or Subject: Process for the Manufacture of Isradipine

Isradipine **24** is another drug used to treat a range of coronary diseases and also high blood pressure. The methods used to prepare the drug are discussed, and their drawbacks are related to the separation of the desired isomer from the reaction mixtures. Chromatographic methods are sometimes needed, and the objective is to avoid such procedures. The patent discloses a two-stage process for preparing **24** shown in Reaction 7. In the first stage **21** is reacted with **22** in the presence of HOAc and piperidine to form the acrylate ester **23**. The water is removed as the reaction proceeds, and this increases the reaction rate. The crude product can be used in the next stage or can be purified by crystallisation using one of two methods that are described in the patent. The preferred method uses EtOH for crystallisation. A 90% yield of **23** can be obtained with a purity of >99%. In the second stage of the process **23** reacts with the crotonate **25** in EtOH to give **24**. The purification of **24** involves distilling off EtOH followed by dissolution in EtOAc and then redissolving in EtOH prior to crystallisation. The yield of **24** using crude **23** is around 54%, but when using purified **23** the yield of **24** increases to 67%.

Reaction 7



The patent cannot have been proof read since one scheme shows a three-valent O atom instead of an N atom in compounds **23** and **24**. Such mistakes are easily avoided and not acceptable.

Advantages

The process avoids complex purification methods and gives good product yields without the formation of isomers that are difficult to separate.

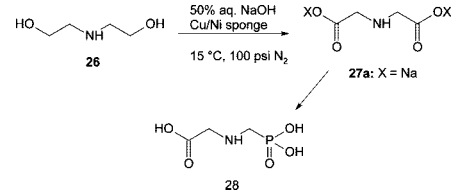
Patent No. U.S. 7,329,778

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

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

The process described in this patent is aimed at primary alcohols that contain other reactive functional groups that are susceptible to side reactions. The real focus of the patent is the production of the popular weed killer glyphosate **28**, and a related patent from the same company has been reviewed (*Org. Process Res. Dev.* **2007**, *11*, 318). The current patent focuses on the Cu catalysts used in the process of making the salt **27a** that is a precursor to **28**. The patent has 147 claims that primarily relate to various physical properties of the catalysts as well as to their preparation. Reaction 8 shows the dehydrogenation reaction that is the main subject of the patent, and it is clearly not aimed at simple primary alcohols. There are a number of catalysts discussed in the patent, and they consist of Cu supported on a metal sponge. Ni is the preferred support, but other metals are also covered including Zn, Co, Sn, and Fe. The reaction is carried out in water in the presence of a strong alkaline base at a pH > 11.

Reaction 8



Advantages

The patent describes new catalysts that may extend the commercial life of the process to make glyphosate.

Patent No. U.S. 7,329,789

Assignee: Phasex Corporation, Lawrence, Massachusetts, U.S.A.

Title or Subject: Method for Extraction and Concentration of Carotenoids using Supercritical Fluids

The use of supercritical fluids (SCFs) for the purification of organic chemicals has increased dramatically in the past few years, and the process is no longer a laboratory curiosity. The development of the technology in which liquefied CO_2 is used with organic solvents has driven this growth. The organic component is often used mixed with the CO_2 to alter the polarity of the solvent mixture thereby increasing the utility of the technique. Carotenoids are natural pigments that are used as dietary supplements for both human and animal consumption, and hence there are strict limits on the levels of solvent residues in final products. A great advantage of using SCFs and especially materials that are normally gaseous at atmospheric pressure is that the residues are virtually zero, and of course in the case of CO_2 it is nontoxic. This patent describes a two-stage method of extracting the carotenoid astaxanthin from the microalgae *Haematococcus pluvialis*. Astaxanthin is a powerful biological antioxidant and exhibits strong free radical scavenging activity. It protects against lipid peroxidation and oxidative damage of LDL-cholesterol, cell membranes, cells, and tissues and hence is of considerable interest. The process for its extraction involves the use of CO_2 and Me_2O. The CO_2 is used to extract lipids for the algae, and the Me_2O extracts the carotenoids. The extractions can be performed in any order. A fraction containing up to 14.5% astaxanthin was extracted in a two-stage process, and the yield obtained was as high as 98%. The process actually extracts all carotenoids, and so further purification is required to obtain the desired component but details of this are not covered.

Advantages

The process is very selective, and although the pressure may be high, the temperature is low so that the process can be used with thermally sensitive materials.

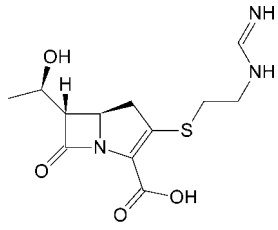
Patent No. U.S. 7,332,600

Assignee: Ranbaxy Laboratories Limited, Gurgaon, India

Title or Subject: Process for the Preparation of Crystalline Imipenem

Imipenem **29** is a β-lactam antiobiotic that possesses broad-spectrum activity against Gram-positive and Gram-negative bacteria. The compound, first reported in 1980, was amorphous and thermodynamically unstable, and a more stable crystalline monohydrate was reported shortly after. A patent in 2007 from the assignee of the current patent disclosed a process for preparation of crystalline **29** that did not require the use of column chromatography, and this was reviewed (*Org. Process Res. Dev.* **2007**, *11*, 941). The current patent states that the process described in the earlier one gives products that contain polymeric and coloured impurities and in effect is not a commercially suitable method. The current patent bemoans the fact that it is difficult to detect these impurities and qualitative HPLC did not find them. A quantitative assay found impurity levels of 5−10%, and in the eyes of this reviewer this suggests that the original experimental work and especially the analysis were both extremely poor. The solution to the problem is claimed to be to dissolve the crude **29** in warm water and to add activated carbon (AC) followed by Me_2CO to precipitate the "pure" product. Without wishing to pass a legal judgment on this patent, it is difficult to see why this should be granted a patent since coloured impurities are usually removed using AC.

Imipenem



29

Advantages

The process corrects a method that was unsuitable for commercial use.

Patent No. U.S. 7,332,612

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

Title or Subject: Preparation of Amorphous and Crystalline Forms of Losartan Potassium

This is the first of two patents on the K salt **30b** of the compound Losartan **30c** (X = H) that is an angiotensin II receptor antagonist that prevents the narrowing of blood vessels and is used to treat high blood pressure. Interest in new methods of preparing the K salt has increased since the original patents have expired, and patents on the subject have been reviewed (*Org. Process Res. Dev.* **2006**, *10*, 866). This patent provides a process to make a novel amorphous K salt, two novel crystalline K salts designated Forms IV and V, plus a novel method for making the known crystalline Forms I and II. The majority of the patent examples, and all of the claims cover the new process to make Form I. There is one example each for the preparation of Forms IV and V, and XRD data are provided for these polymorphs that are presumably the subject of other patents. The production of all of the Forms involves dissolving the K salt in EtOH, cooling, adding a second solvent and then allowing the material to crystallise. Solvents used include PhMe, EtOAc, Me_2CO, MEK, hexane, MeCN and dichloromethane (DCM). By changing the temperatures of the different stages of the process, the final Form obtained can be changed. However, the variations described did not seem to be sufficiently different to allow good control over the polymorph that is produced.

Advantages

The patent claims to provide novel polymorphs of this important drug plus a new method of making a known polymorph.

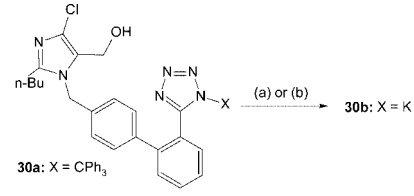
Patent No. U.S. 7,345,071

Assignee: IPCA Laboratories Limited, Mumbai, India

Title or Subject: Process for the Synthesis of Losartan Potassium

This is the second patent covering the compound **30b**, and it describes an improved method for preparing the polymorph Form I. An alternative method for preparing **30b** begins with the trityl compound **30a** that is converted to the acid form **30b** and then the K salt using a strong base such as KOH in Pr^iOH. The removal of H_2O by azeotropic distillation or antisolvents is said to cause operational problems. The current assignees have attempted to use $KOBu^t$ in powder form but concluded this created handling problems for operators. Hence the current patent attempts to improve the production of **30b** by finding a base that avoids the use of solid $KOBu^t$. The process developed uses either a solution of $KOBu^t$ in Bu^tOH or surprisingly a weaker base such as K_2CO_3. Reaction 9 outlines the method used to convert **30a** to **30b**. After the reaction the mixture is filtered to remove solid byproduct, the MeOH is replaced with a second solvent that is Pr^iOH or THF, and then the product is isolated by crystallisation after cooling to <5 °C. The yield of **30b** varies from 78% to 90% with the best yield obtained using K_2CO_3 as base and THF as the second solvent.

Reaction 9



(a) $KOBu^t/Bu^tOH$, MeOH, reflux 9h; (b) Anhyd K_2CO_3, MeOH, reflux 12 h

It should not be a surprise to find a simple solution to a problem. Perhaps the use of a weak base had not previously been tried because it was assumed that it would not work.

Advantages

The process avoids handling problems and gives very good yields using a readily available weak base.

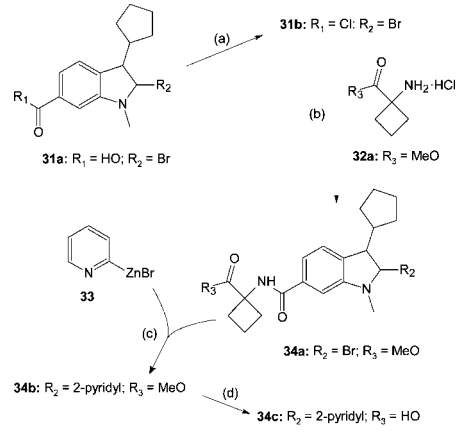
Patent No. U.S. 7,332,614

Assignee: Boehringer Ingelheim International GmbH, Ingelheim, Germany

Title or Subject: Process for Cross Coupling Indoles

This patent covers a Pd-catalysed cross-coupling reaction of indoles such as **34a** with **33** in the production of compounds such as **34b** and **34c**. The claims cover the reaction of a very large number of compounds, and in addition they also specifically cover the compounds **31b** (R_1 = MeO, R_2 = Br or Cl) and **34a** (R_2 = Br or Cl and R_3 = HO or MeO). A specific application mentioned is the production of 25 kilo quantities of **34b** that can be used in the treatment of hepatitis C viral (HCV) infections. Reaction 10 summarises the route used to produce **34b** and **34c**. In the first stage of the process the acid **31a** is converted to the acyl chloride **31b** in 77% yield using $SOCl_2$ then condensation of **31b** with the HCl salt of **32** forms the ester **34a** in 86% yield. The Pd-catalysed coupling reaction of **34a** with **33** then produces **34b**, and hydrolysis gives **34c** in a 74% yield.

Reaction 10



(a) (1) THF, Et_3N; (2) $SOCl_2$, 5 °C, 1 h; (3) rt, 16 h
(b) (1) rt, 4 h; (2) HOAc/H_2O, distil off THF
(c) THF/N-methylpyrrolidinone, $PhCO_2Me$, $Pd(OAc)_2$, PPh_3, 90 °C, 3 h
(d) (1) Aq NaOH, Pr^iOH, relux 90 °C, 1 h; (2) Cool 60 °C, HOAc, 1 h; (3) Cool rt, filter, Pr^iOH, dry

34c can also be prepared by a coupling reaction between **33** and **34a** (R_2 = Cl, R_3 = MeO). There is also a description of the coupling reaction of **31c** (R_1 = MeO, R_2 = Cl) with **33** to give **31d** (R_1 = MeO, R_2 = 2-pyridyl). An alternative in some coupling reactions is to use di(2-pyridyl)zinc in place of **33**. *N*-methylpyrrolidone is a solvent in step (c), and the importance of this is indicated by its use being the subject of one of the claims.

Advantages

The patent provides novel intermediates and a new process for making the drug candidate.

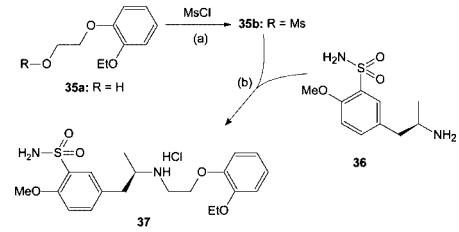
Patent No. U.S. 7,332,621

Assignee: Scinopharm Taiwan Ktd., Taiwan

Title or Subject: Process for Preparing Tamulosin

Tamulosin **37** is an α-adrenergic blocker that causes the blood vessels to relax and expand so that blood passes through them more easily. The HCl salt of the (*R*)-enantiomer is available as Flomax and is used to treat benign prostatic hyperplasia or enlarged prostate, and a patent on the subject has previously been reviewed (*Org. Process Res. Dev.* **2005**, *9*, 235). The claims of this patent actually cover the preparation of **35b** that is used to synthesise **37** although the patent does give an example of how to prepare **37**. A number of synthetic routes to **37** are summarised in this patent, but no comments are made as to their shortcomings. Reaction 11 shows the novel process described in this patent in which the mesyl compound **35b** is first made by reaction of **35a** with MsCl in pyridine. The product is isolated in 85% yield and 99.83% purity. The HCl salt of **37** is obtained at up to 70% yield by reaction of **35b** with **36** in the presence of KI with $NaHCO_3$ as an acid scavenger. The product is crystallised from EtOH.

Reaction 11



(a) (1) Pyridine, <0 °C, 4 h; (2) H_2O, < 5 °C; (3) Filter , wash in H_2O, dry
(b) (1) KI, NaHCO3, DMF, 65 °C, 11 h; (2) Cool, filter, extract in EtOAc (3) Distil off EtOAc, add EtOH; (4) Aq HCl, rt, filter

Advantages

The patent describes a novel process for making this drug that gives higher yields than alternative methods.

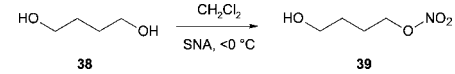
Patent No. U.S. 7,335,789

Assignee: Dipharma S.p.A., Mereto di Tomba, Italy

Title or Subject: Process for the Mononitration of Alkanediols

The patent is concerned with the production of compounds such as **39** that are used in the synthesis of important nonsteroidal anti-inflammatory drugs. Methods for producing **39** are said to be poorly selective and have problems claimed to be similar to those encountered when handling nitroglycerine. The patent describes a nitration method that uses stabilised nitric acid (SNA). This is nitric acid that contains about 85% HNO_3 and <10 ppm of nitrogen oxides, and it is prepared by treating 84.7% HNO_3 with about 0.7% w/w urea for about 90 min. To determine if the acid is sufficiently stabilised it can be titrated against $KMnO_4$. It should be used in the nitration process within about 3 h because after this time the levels of nitrogen oxides increase, and their presence reduces the selectivity of the acid. As an alternative to using urea in this procedure the patent also mentions the use of sulfamic acid but there are no examples using this compound. Reaction 12 shows the preparation of **39** by reaction of SNA with the diol **38** in a chlorinated solvent below 0 °C and DCM is preferred. The mixture is neutralised with NaOH, and the organic phase contains **39**, unreacted **38** and the dinitrated compound. The selectivity to **39** is around 75%. The patent does not disclose how this mixture is separated.

Reaction 12



Advantages

The process provides a safer and more selective method of nitrating the diol.

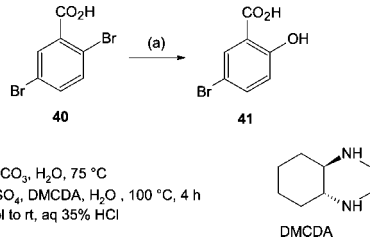
Patent No. U.S. 7,335,791

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

Title or Subject: Process for the Synthesis of Hydroxy Aromatic Acids

The compounds of interest in this patent are useful intermediates in the preparation of pharmaceuticals, agrochemicals and monomers. Typical processes for the synthesis of such compounds are characterised by long reaction times and low conversion and are said not to be commercially viable. The process disclosed in this patent involves the reaction of a halogenated aromatic acid with a Cu salt and a diamine ligand such as alkyl, cycloalkyl, aryl or aralkyl diamines. Reaction 13 shows the method used to prepare **41** from **40** using $CuSO_4$ and the diamine DMCDA. After the reaction the product is isolated in one of two ways. The first involves extraction into EtOAc followed by evaporation of the solvent. In the second method the product is filtered off, washed in water and dried. A number of other reactions were carried out using this method, and in most case the conversion and selectivities were >99%.

Reaction 13



Reactions were also carried out in which CuBr was used in place of $CuSO_4$, and in fact CuBr is specifically mentioned in the claims of the patent. Several other diamines were also used, and the patent describes 50 examples. Comparative examples are included that use no ligand or a tetramine, and these gave very poor yields of products.

Advantages

The method gives very high yields of products in a potentially useful process.

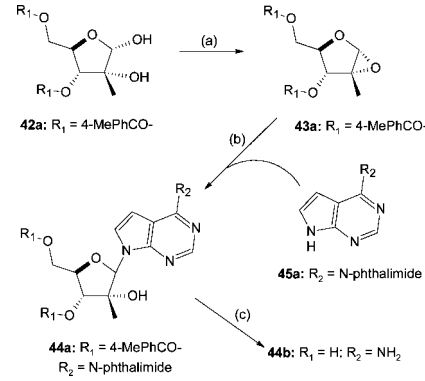
Patent No. U.S. 7,339,054

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

Title or Subject: Process for Preparing Branched Ribonucleosides from 1,2-Anhydroribofuranose Intermediates

The compounds such as **44b** covered by this patent are used in treating HCV infections. References are made to alternative methods of preparing the ribonucleosides that are said to be unsuitable for kilo-scale production because of low yields. A summary of the synthetic route used to prepare **44b** is shown in Reaction 14. The patent gives quite detailed experimental information, and this is much simplified in the scheme. The first step is the formation of the epoxide **43a** by reaction of **42a** with MsCl in the presence of a base. The product is extracted with MTBE, the solvent exchanged for PhMe, and this solution is used in the next step. Reaction of **43a** with **45** in the presence of NaH produces **44a**. After extraction into EtOAc there is another solvent exchange to PhMe, and the solution is used in the next step. Treatment of **44a** with Bu^nNH_2 in MeOH/PhMe produces **44b** that is isolated as the PhMe solvate at a purity of 94%. A final crystallisation from Pr^nOH gave nonsolvated **44b**.

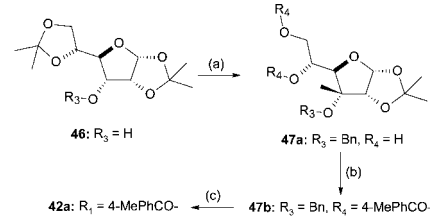
Reaction 14



(a) (1) Et_3N, DCM, MsCl, 30 °C, 1 h; (b) NaH/THF, Me_2NCOMe, 0 °C;
(c) PhMe, MeOH, Bu^nNH_2, 64 °C, 24 h

The patent also claims the preparation of analogues of **44b** in which **45a** is replaced by other purine or pyrimidine nucleobases such as cytosine, uracil or thymine but there are no details provided. The examples describe the production of **44a** on a multikilo scale thus showing that the process has commercial potential. The patent includes details of the preparation of **45a** from **45b** ($R_2 = NH_2$) and phthalic anhydride. There is also included the synthesis of **42a** from **46** that is summarised in Reaction 15.

Reaction 15



(a) No details given; (b) 4-MePhCOCl, pyridine, MeCN, 55 °C, 12 h;
(c) (1) Aq HBF_4, 55 °C, 2 h; (2) Aq H_6IO_6, 0 °C; (3) Pr^i_2NH, MeOH, 0 °C, 48 h;
(4) Aq HCl, aq $NaHCO_3$; (5) Azeotropic distillation of H_2O;
(6) H_2, Pd/C, Pr^iOAc, 45 psi, 50 °C, 24 h

A literature reference is given for the conversion of **46** to **47a**, but details are provided for the production of **42a** from **47a** and **47b**. Again this process is carried out on a large scale. The patent includes DSC, TGA, XRD and ^{13}C NMR data for the final product and also NMR data for **42a**.

Advantages

The patent provides a process that can be carried out on a commercial scale.

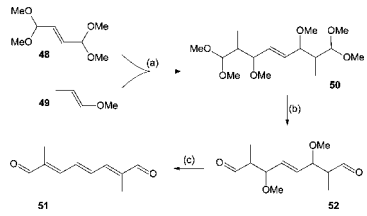
Patent No. U.S. 7,339,085

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Method for Producing 2,7-Dimethyl-octa-2,4,6-trienedial

The title compound **52** is an important intermediate for the production of carotenoids, and several methods are mentioned. They are all claimed to give unsatisfactory yields of product that is insufficiently pure for direct use in carotenoid synthesis. The patent therefore claims to provide a high yield synthesis of **51** that has high purity, and the route is shown below.

Reaction 16



(a) $FeCl_3$, PhMe, 25 °C, (b) 2% H_2SO_4, 80 °C; (c) 5% $NaHCO_3$, 85 °C

This begins with a double enol ether condensation of **48** with **49** in a water immiscible solvent in the presence of anhydrous $FeCl_3$ to give **50**. The reaction is carried out by feeding **49** into a solution of **48** in PhMe, and the product is not isolated but undergoes acid hydrolysis to give **52**. This product is also not isolated but treated with aqueous base to give **51** in 77.3% yield and 100% purity by concentrating the organic phase. The yield can be increased by recovery of additional product from the concentrated mother liquor and from washings by recycling these to the next batch.

The claims also cover the use of other Lewis acids such as $ZnCl_2$ or BF_3. Experiments are described in which **50** and **52** are isolated. For example **50** can be converted to **52** using 2.5% H_3PO_4 and it is isolated in 89% purity. Treatment of **52** with Et_3N produces **51** that is obtained in 98.5% purity.

The structure of **52**, shown several times in the patent, is actually incorrect. It is shown as having three C═C bonds instead of the single one shown. This seems to be another example of a patent being written, submitted, presumably examined, and then published without a chemist actually being involved.

Advantages

The process gives high yield of the desired product, and it is also possible to isolate potentially useful intermediates.

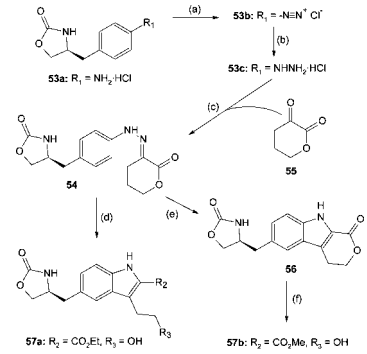
Patent No. U.S. 7,342,035

Assignee: Inke S.A., Barcelona, Spain

Title or Subject: Process for Preparing Zolmitriptan

Zolmitriptan **57f** is used for the acute treatment of severe headaches and migraine attacks. One method for the preparation of **57f** involves the use of the toxic reagent tin chloride and gives a yield of only 18% while another avoids toxic reagents but only gives yields of 30%. The process disclosed in this patent contains several steps, and these are shown in Reactions 17 and 18. Reaction 17 shows the formation of the intermediate **54** that can be converted via one of two pathways to give precursors to **57f**. The initial stages in Reaction 17 involve the formation of the diazonium salt **53b** that is converted to the hydrazine **53c** by reduction with Na_2SO_3 followed by acidification. The next step is carried out in the same pot without isolating **53c**. This is reacted with **55** to produce **54** that is isolated in 87% yield after crystallisation. **54** is then treated with dry HCl in EtOH and converted to **57a** that is isolated in 89% yield. **54** can also be converted to **56** via a Fisher indole reaction using dry HCl in HOAc, and the product is obtained in 92% yield. A transesterification reaction of **56** using MeOH and MsH produces **57c** in 93% yield after crystallisation.

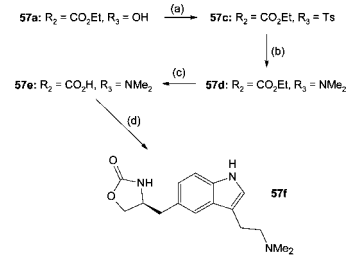
Reaction 17



(a) Aq $NaNO_2$/HCl, 0 °C;
(b) (1) Aq Na_2SO_3, 0 °C, (2) 65 °C, 1.5 h; (3) Concd HCl, 65 °C, 3 h;
(c) (1) rt, 12 h; (2) 0 °C, filter, dry;
(d) (1) 2N HCl in EtOH, 75 °C, 35 min; (2) Evaporate, aq K_2CO_3;
(3) Extract in DCM; (4) Evaporate, recrystallise from PrOH;
(e) (1) HCl/HOAc, rt, 16 h; (2) H_2O, 0 °C, 20 min, filter, dry;
(f) (1) MsH, MeOH, reflux, 3 h; (2) Evaporate, aq $NaHCO_3$;
(3) Extract in DCM; (4) Evaporate, recrystallise from EtOH

Reaction 18 shows the next stage of the process. The examples only describe the use of the ethyl ester **57a** for this, but it should also be applicable to the methyl ester **57b**, and the patent claims cover this. The first step is to replace the OH group using TsCl and DMAP to give **57c** that is isolated in 95% yield and converted to **57d** with Me_2NH in EtOH. The isolated yield of **57d** is 91%. Saponification of **57d** using KOH/EtOH produces **57e** that is isolated in 94% yield after purification using ion-exchange resins (IER). Last the decarboxylation of **57e** is carried out using Cu_2O at 200 °C to give **57f**, and despite this high temperature the yield of the final product was 90%.

Reaction 18



(a) (1) TsCl, DMAP, pyridine, DCM, rt, 20 h; (2) 3N HCl, 0 °C;
(3) Extract in DCM; (4) Dry, evaporate; (5) Crystallise from PrOH;
(b) Me_2NH, EtOH, 50 °C, 20 h; (2) Evaporate; (3) 2N HCl;
(4) Aq NaOH to pH 12, extract in DCM; (5) Evaporate;
(6) crystallise from EtOAc
(c) (1)KOH/EtOH, reflux 1 h; (2) Cool, evaporate; (3) H_2O, 5 °C;
(4) HOAc >pH 6, 30 min; (5) Treat with IER; (6) Evaporate to dryness
(d) (1) Cu_2O, dry quinoline, 200 °C, 20 min; (2) Cool, filter, distil solvent;
(3) Succininc acid/H_2O; (4) Wash in DCM; (5) Aq NaOH >pH 12;
(6) Extract in DCM; (7) Evaporate; (7) Crystallise from PrOH

The patent gives IR, ^1H and ^{13}C NMR data for all of the isolated intermediates. As can be seen from the reaction schemes there are a large number of steps involved in the overall synthesis of **57f**, and fortunately most of them give high yields.

Advantages

The process gives a high yield of the intermediates and

product without using toxic tin compounds although there is considerable use of DCM in many of the stages.

Patent No. U.S. 7,342,121

Assignee: Cognis Corporation, Ambler, Pennsylvania, U.S.A.

Title or Subject: Method of Producing High Density Tocopherol Acid Succinate

The subject of the patent is a vitamin E derivative that is an antioxidant and used as a dietary supplement, but it also has a variety of therapeutic uses. The compound can be produced as needles, and such materials are often difficult to handle in the production of formulations, and this patent describes a process for making high-density powder material The method is to dissolve the pure compound in hexane to obtain a solution of about 40% by weight and then remove the solvent under vacuum <30 °C, and the product begins to crystallise. The hexane is completely removed by bleeding in dry nitrogen gas to fluidise the particles and cause agglomeration. Finally the particles are then sprayed with hexane while they are fluidised with nitrogen, and this results in larger, denser material being produced. Considering the claims of this patent, inexplicably, it does not report any data on the density of the new material or that of the needles.

Advantages

The process claims to give high-density material that is more suitable in producing formulations.

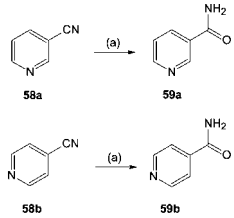
Patent No. U.S. 7,345,176

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

Title or Subject: Process and Catalyst for the Conversion of Cyanopyridines to Nicotinamides

The amides **59a** and **59b** are used to prepare vitamin B12 and the drug isoniazid that is used to treat tuberculosis. The hydrolysis of a cyano group is a known reaction for preparing an amide but some processes require alkaline or acid conditions that present subsequent separation difficulties. In processes for preparing **59b** a high yield of nicotinic acid is formed that is a loss to the process. The main focus of the patent is the use of an MnO_2 catalyst that is prepared by a redox method involving heating an aqueous solution of $KMnO_4$ with $MnSO_4$ or $MnCl_2$.

Reaction 19



(a) (1) MnO_2, H_2O, 100 - 115 °C, 8 h; (2) Cool, filter, wash in H_2O, dry

The MnO_2 is filtered off and then dried at 110 °C for 3 h before use in the hydrolysis of the cyanopyridines **58a** or **58b**. Using this catalyst the hydrolysis reaction can be carried out in neutral solution thus simplifying the product recovery and avoiding the formation of nicotinic acid. Reaction 19 shows the method used to prepare **59a** and **59b**. The yield of the amides reached 92% with almost 100% selectivity.

The patent states that role of the MnO_2 has not been elucidated although the catalyst is nonstoichiometric and contains H_2O with IR spectroscopy, suggesting that there are OH groups present that are linked to Mn.

Advantages

The process gives high selectivity of the amides using a simple catalyst in a straightforward procedure.

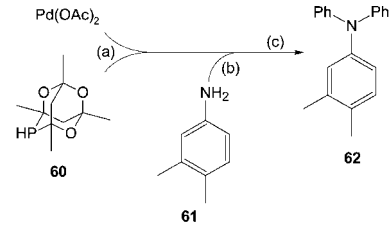
Patent No. U.S. 7,345,203

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

Title or Subject: Cost Effective Method for the Synthesis of Triarylamines from Aniline and an Aryl Chloride

Triarylamines are used in the manufacture of various layer components of electrophotographic imaging systems. It is claimed that the production of triarylamines can involve the use of costly intermediates such as aryl iodides in multistep processes that are time-consuming. The patent overcomes such problems and describes the use of a Pd/ligand catalyst in the alkylation of anilines with aryl chlorides. The patent contains one example, and this describes the preparation of **62** from **61** and PhCl (Reaction 20). The reaction is carried out by stirring a mixture of the phospha-adamantane ligand, **60** and $Pd(OAc)_2$ in PhCl before adding **61**, more PhCl and a strong base ($NaOCH_2Bu^t$). The product is obtained in <75% yield, and the purity as measured by HPLC is >99%. The ligand **60** is a commercially available as Cytop-216, and it is claimed that the reaction can be carried out using a solvent such as xylene although no details are given. The reaction uses about 1.8 wt % each of the Pd salt and the ligand in the mixture. There is no information as to whether the catalyst is reusable, and this seems quite a high catalyst to substrate ratio for a method purporting to be low cost.

Reaction 20



(a) PhCl, 30 min; (b) PhCl, $Na(OCH_2Bu^t)$, 130 °C, 6 - 18 h; (c) (1) Distil off PhCl; (2) Cool to rt, MeOH/H_2O, filter, dry

Advantages

The process uses the readily available aryl chloride rather than the iodide and gives the desired arylamine in a procedure that is more cost-effective than alternatives.

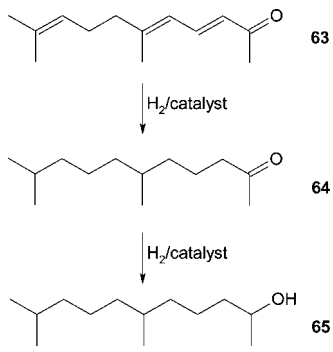
Patent No. U.S. 7,345,205

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Method for the Production of Tetrahydrogeranylacetone

The title compound **64** is used as a starting material for the preparation of isophytol that is itself a reactant in the synthesis of vitamins E and K. The patent states that in principle **64** should be accessible by hydrogenation of **63** but the presence of a ketone group makes the selective hydrogenation reaction of the three olefinic bonds difficult, and this leads to the formation of **65**.

Reaction 21



The problem is overcome by the use of catalyst in a continuously operated liquid phase hydrogenation reaction in a column that is filled with structured packing. This latter material is very widely used in distillation columns and can give problems if solids are present in the liquid since they can block the flow of liquid through the packing. However, this problem seems to be turned to advantage because the solid particles of catalyst are held back more than the liquid, and this is claimed to improve the selectivity of the process. The catalyst that is preferred is a Pd on activated C, and the process is carried out at 10 bar pressure of H_2 at 100 °C. The patent contains specific details about the size of the orifices and channels in the structured packing, and this is related to the size of the catalyst particles. The process gives a conversion of **63** of >99.9% with a selectivity to **64** of >96%.

Advantages

The process provides a highly selective method of preparing the desired ketone.

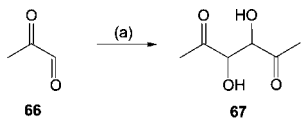
Patent No. U.S. 7,345,206

Assignee: Firmenich S.A., Geneva, Switzerland

Title or Subject: Process for the Dimerisation of Alkyl Glyoxals

The patent describes a novel process for the preparation of **67** that is used in the synthesis of perfumes and flavours. The process disclosed is the reductive dimerisation of **66** that is promoted by $HOCH_2SO_2Na$; a commercially available material under the name Rongalit. It is stated that **67** can be made from tartaric acid or by oxidation of 2,5-dimethylfuran. The dimerisation of glyoxals has been reported as a route to **67**, but is claimed that the processes give yields less than 70% and require the use of heavy metals salts. This causes difficulties in product purification and waste treatment. Reaction 22 outlines the process described in this patent, and it is notable that it does not involve heavy metal salts.

Reaction 22



(a) (1) H_2O, Na_2CO_3, 40 °C, pH 5.5; (2) $HOCH_2SO_2Na{\cdot}2H_2O$, H_2O, 40 °C, 6 h; (3) 85% H_3PO_4 to pH 5; (4) Distil off H_2O; (5) Extract in EtOAc, distil

The process is carried out in aqueous solution with a base to buffer the solution and ensure slightly acidic conditions. After workup the product is obtained by vacuum distillation in 72% yield. Several experiments are described with varying amounts and types of base. Although the stoichiometry of the reaction requires a ratio 2 mol of **66** per mol of Rongalit, it is reported that excess of the promoter is beneficial. The patent does not discuss whether the reaction is the sterospecific.

Advantages

The process gives a cleaner reaction than alternatives giving slightly better yields without the need for heavy metal salts.

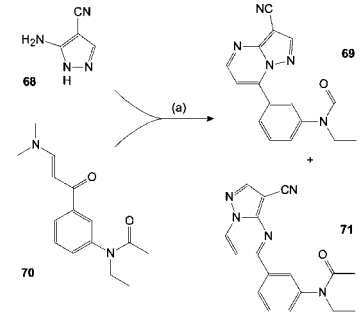
Patent No. U.S. 7,348,429

Assignee: TEVA Gyógyszergyár Zrt., Debrechen, Hungary

Title or Subject: Process for Purifying Zaleplon and for Preparing Novel Crystalline Forms

Zaleplon **69** is available as Sonata and is used to treat insomnia. This patent describes five polymorphic forms of the molecule (of which four are claimed to be novel) plus improved purification methods. This patent is a continuation of a patent reviewed previously (*Org. Process Res. Dev.* **2005**, *9*, 244), and hence the polymorphs have already been described. The patent describes the synthesis of **69** containing **71** that is a regioisomer of **69** and is an undesirable impurity. The synthetic route used is identical to the work described earlier and is shown in Reaction 23. The reaction is an acid-catalysed condensation of **68** with **70** and apart from H_3PO_4 it can also be carried out using HCl or HOAc. The two claims of this patent cover the purification of a specific polymorph of **69** having a particular XRD pattern. The patent therefore appears to be a composition of matter patent for a specific polymorph. The purification of the polymorph is carried out by dissolving crude **69** in MeOH, EtOH, Pr^iOH or MeCN followed by addition of iced water to induce crystallisation. The synthesis produces **69** containing 0.21% of **71**, and examples show that up to 84% of this impurity can be removed.

Reaction 23



(a) (1) H_2O/EtOH, 85% H_3PO_4, rt, 8 h; (2) Cool 5 °C, filter, wash, dry

Advantages

The process provides a method of preparing zaleplon with low levels of the regioisomer impurity.

Keith Turner

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