Organic Process Research & Development **2008,** *12,* 146–155

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published During October and November 2007

Summary

The current review contains 23 patents from an original list containing 260, and it is hoped that readers will find something of interest. Changing reaction solvents can have such a dramatic effect, and this is shown in a Pd coupling of benzylamines and haloaromatics. By using a mixture of two solvents the yield of the product was increased from 40 to 76%. In an attempt to improve a process for preparing the drug perindopril, one patent reports using a mixture of three solvents. This mixture is used in a step following the use of chlorinated solvents, and hence the overall process does not look appealing. Another three patents on perindopril from a different company are also covered in this review. These cover novel intermediates and alternative coupling reagents to DCC (that gives byproducts that are difficult to remove). Handling several different solvents in a commercial process can be a logistical nightmare. A process for the preparation of soluble succinate derivatives of probucol, that is used to lower blood lipid levels, uses a very complex extraction process that may be inefficient on a large scale. Another patent that also describes the preparation of probucol succinates may also have similar product recovery difficulties. Both patents report forming mixtures of mono- and disuccinates and unreacted starting materials that are difficult to separate. Sometimes changing solvents is not feasible, and in a new preparation of the insecticide imidacloprid, an alternative approach is used. In this method a more soluble salt is used to speed up the key step in the synthesis. Reducing safety hazards is a major objective in any process development. In the production of a range of tetrazoles a patent reports on a process that avoids having to use hydrogen azide gas at 200 °C. This is achieved by a method that uses NaN_3 and gives improved yields as well as being safer. A safer method of preparing the active ingredient imiquimod, used in a skin treatment cream is reported. Interestingly this moves away from using NaN_3 by changing the synthetic route. Unfortunately the new method may be much less efficient and has several steps with low yields. A difficult reagent to handle is ozone, and a new process for preparing the anabolic steroid oxandrolone uses the gas in an oxidation step. The gas is also used in alternative methods, and so the new process does not seem to improve the safety aspects. Producing the correct physical form of a drug is vital in formulations and for long-term stability. A method of producing anhydrous stable crystals of the antidepressant mirtazipine is described. Another important antidepressant is sertraline, and a key step in the synthesis is an imine hydrogenation. This gives two pairs of enantiomers, and an improvement in the stereoselectivity of this step is reported. A comprehensive patent on the synthesis of spirolactams and their functionalisation discusses the theoretical aspects of the reaction pathway and makes a refreshing change from many patents. In fact, some of the current selection do not include experimental examples, and there are the usual assortment of errors. An interesting approach is taken in a patent on the purification of cinacalcet that is used to treat hyperparathyroidism. The patent covers a specific impurity and how to remove it. In fact the patent describes the synthesis of cinacalcet that is specifically contaminated with the impurity. Removal of a dimeric impurity during the production of the migraine treatment drug eletriptan can be a problem. By using an alternative synthetic route, that avoids the production of the dimer precursor, an improved process is described. Salmeterol is used to control asthma, and a new method of making the single active enantiomer is described that uses a widely available chiral auxiliary. In a new process for preparing the ulcer-control drug, pantoprazole, a chiral auxiliary is used in conjunction with Zr or Hf oxidation catalysts. Reducing wastes is highly desirable, and a method of making a vulcanisation inhibitor avoids producing amine HCl salts by taking care to use dry reagents and by using a stirring system that has multiple propellers on a common shaft. Terbinafine is used to treat athlete's foot, and during the synthesis, it is difficult to remove a Pd/Cu/phosphine catalyst that can be used in a coupling step. By changing to Pt/Cu/base catalyst the yield and catalyst recovery from the process was improved. Amlodipine as the besylate salt is used to treat various coronary problems. A method of making the nicotinate salt is described that has high activity and also good photostability, a known problem with other active salts of the drug. A number of the patents report the production of kilo-scale or even larger batches of material, and this may suggest the advanced commercial nature of the process. There is no legal or commercial significance in the patents reviewed, and the advantages are those claimed in the patent unless this reviewer has personal knowledge of the subject.

Patent No. U.S. 7,276,629

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

Title or Subject: Catalytic Hydrogenation of Imine Intermediates of Sertraline

Sertraline **2** is a widely used antidepressant drug, and patents on various aspects of its synthesis have been covered previously (Org. Process Res. Dev. 2005, 9, 537). The hydrogenation of **1** to **2** is a key step in the synthesis and produces two pairs of enantiomers; one *cis* and the other *trans* (Reaction 1). Only one of the *cis* isomers is active, and hence a stereoselective hydrogenation step is highly desirable. Some processes produce

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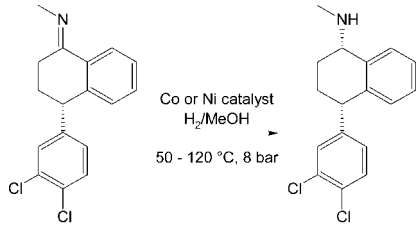
about 25% of the *trans* pair, and a further process loss arises by removal of one or both of Cl groups during hydrogenation. This patent describes the use of commercial Ni catalyst (e.g., G69 from Süd-Chemie) and also proprietary Co catalysts. The patent states that G69 is preferred although the claims cover both Ni and Co catalysts and the patent gives details of the preparation of the Co catalysts. The reaction is carried out in trickle-bed reactor or in a batch reactor with a variety of solvents being used. A process operated at 65 °C and 5 bar pressure using G69 in MeOH gave a 100% conversion of **1** with a selectivity to *cis*-**2** of 79.8%. This is understood to be less than other commercial catalysts.

Reaction 1



1 2

The option of using the racemic mixture of **1** is also covered in the patent. The resolution of **2** was carried out by preparation of the D-(−)-mandelate and crystallisation and isolation of (+)-sertraline mandelate.

Advantages

The process gives improved selectivity to the desired *cis*-isomers of this widely used drug.

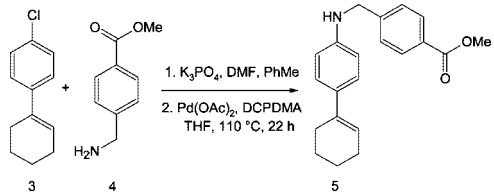
Patent No. U.S. 7,276,630

Assignee: Saltigo GmbH, Leverkusen, Germany

Title or Subject: Process for Coupling Benzylamines with Haloaromatics

Pd coupling reactions are valuable tools in chemical synthesis. The current patent states that it is very difficult to obtain arylated benzylamines from functionalised anilines and benzyl chlorides by Pd-catalysed coupling. It has been found that such a reaction is possible by using mixtures of nonpolar solvents with polar solvents. Reaction 2 shows the formation of **5** from **3** and **4** using a mixture of DMF and PhMe containing a base and a Pd catalyst that is formed *in situ* from $Pd(OAc)_2$ and the phosphine DCPDMA. The isolated yield of **5** was 76%. When using the same catalyst system and either PhMe or DMF, the yield of **5** fell to about 40% in both cases.

Reaction 2



3 4 5

DCPDMA = 2-dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl

Advantages

The use of a mixed solvent significantly improved the product yield in the coupling reaction.

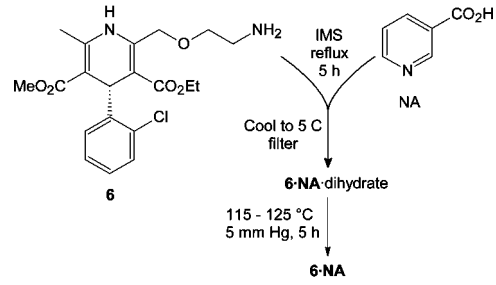
Patent No. U.S. 7,279,492

Assignee: Hanlim Pharmaceutical Co. Ltd., Seoul, Korea

Title or Subject: S-(−)-Amlodipine Nicotinate and Process for its Preparation

Amlodipine **6** is used for the treatment of hypertension, chronic stable angina, and vasospastic angina. It is commonly used as a salt, and the maleate is said to be preferable; however, it is stated that the besylate salt has some advantages over the maleate salt but it suffers from poor photostability. This patent describes the formation of a nicotinate salt **6-NA** that has improved photostability and high pharmacological activity. Reaction 3 shows that this salt is prepared from the dihydrate that is formed from **6** and nicotinic acid (NA) in refluxing IMS. Heating the dihydrate under vacuum then forms the anhydrous nicotinate salt **6-NA**. The patent provides ^{1}H NMR and XRD data plus the results of some clinical tests.

Reaction 3



Advantages

The novel salt is simple to prepare and has the desired activity and improved photostability.

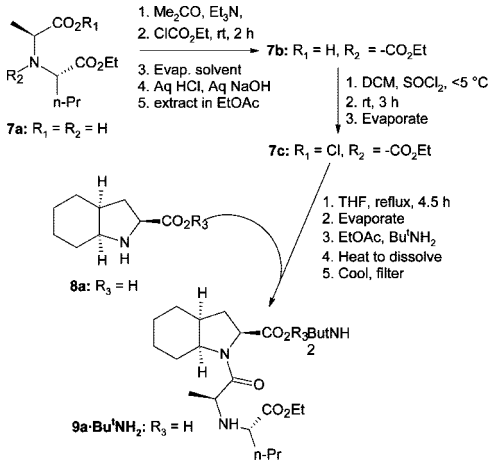
Patents Nos. U.S. 7,279,583, 7,279,595, 7,288,661

Assignee: Les Laboratoires Servier, Coubevoie Cedex, France

Title or Subject: Process for the Synthesis of Perindopril and Intermediates Used in Its Preparation

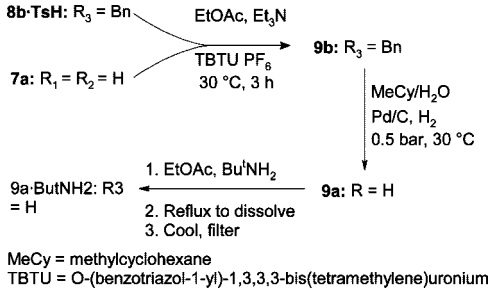
Perindopril **9a** is used in treating cardiovascular problems, and these three patents cover the synthesis of **9a** and intermediates used to prepare **9a**. It is stated that the usual synthesis of **9a** involves a coupling reaction that uses DCC, and this reagent is said to produce considerable amounts of benzyl esters that are difficult to remove. The process described in these patents overcomes these disadvantages by using alternative coupling agents and gives a high-purity product. The claims of the second patent cover the synthesis of the intermediate **7c** by acylation of **7a** using $ClCO_2Et$ in the presence of Et_3N (Reaction 4). This patent also describes the synthesis of the *tert*-butylamine salt of **9a** by reaction of **7c** with **8a**.

Reaction 4



The first patent focuses on the formation of **9a** via the coupling reaction of the tosylate of the benzyl ester **8b** with **7a** in the presence of the PF_6 salt of O-(benzotriaxol-1yl)-1,3,3,3-bis(tetramethylene)uronium (TBTU) in place of DCC (Reaction 5). This reaction produces **9b** that is then catalytically hydrogenated to give **9a**. The final step is the formation of the *tert*-butylamine salt.

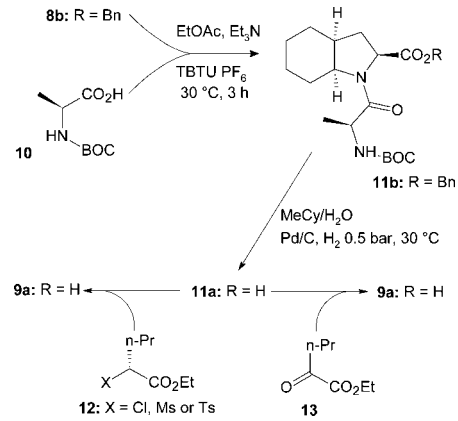
Reaction 5



MeCy = methylcyclohexane
TBTU = O-(benzotriazol-1-yl)-1,3,3,3-bis(tetramethylene)uronium

The third patent takes a different approach to synthesising **9a**, and this is shown in Reaction 6. The patent covers the synthesis of the compounds **11a** and **11b** that are used to produce **9a**. In this route the benzyl ester **8b** is coupled with the BOC-protected alanine **10** using TBTU PF_6 to produce the benzyl ester **11b** that is hydrogenated to give the acid **11a**. The final stage in which **11a** is converted to **9a** by reaction with **12** or **13** is mentioned in the patent, but there are no details provided.

Reaction 6



These patents refer to **9a·HCl** as perindopril eburmine, whereas the correct name is perindopril erbumine and this is used in the following patent.

Advantages

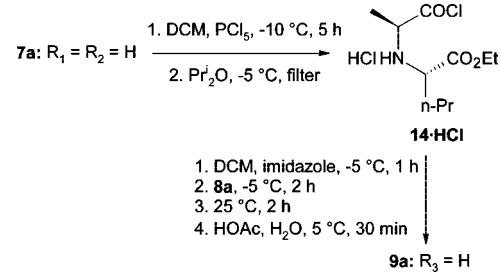
The process overcomes the disadvantages of using DCC as a coupling agent and provides a high-purity product. No mention is made as to the cost or availability of the TBTU salt used.

Patent No. U.S. 7,291,745

Assignee: Glenmark Pharmaceuticals Limited, Mumbai, India
Title or Subject: Process for the Preparation of Perindopril

This is the fourth patent on this drug, and it summarises a number of methods for the synthesis of **9a**. These are said to be time-consuming, not cost-effective, and use expensive or toxic reagents, necessitating the application of stringent standards. Hence, it is claimed that an improved procedure is needed, and so the patent discloses a process for the synthesis of **9a** using the reaction of the HCl salt of alanoyl chloride **14** with **8a** or the ester **8c** (R = Me_3Si) as shown in Reaction 7. The **14·HCl** is prepared from **7a** and PCl_5, and this is then reacted with **8a** in dichloromethane (DCM) and in the presence of base with imidazole being used in the example. This gives **9a** that is not isolated but converted directly to the *tert*-butylamine salt. This conversion to the salt involves removing the DCM by distillation and then heating Bu^tNH_2 and **9a** in a solvent mixture comprising Pr^iOH, Me_2CO and MeCN. The reason for such a mixture is not clear. One of the patent claims specifically states that the solvent used in the coupling reaction is a chlorinated hydrocarbon and others mention aliphatic or aromatic hydrocarbons. No examples are given using nonchlorinated hydrocarbon solvents, and hence the process cannot be termed environmentally friendly.

Reaction 7



Advantages

The process is claimed to be an improvement although the use of chlorinated solvents and solid PCl_5 are not usually recognised as such.

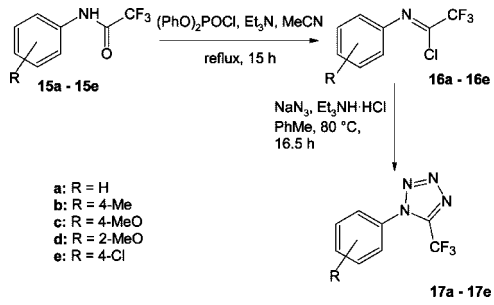
Patent No. U.S. 7,282,609

Assignee: Toyo Kasei Kogyo Co. Ltd., Osaka, Japan
Title or Subject: Process for Production of 1-Aryl-5-(trifluoromethyl)-1H-tetrazoles

The compounds described in this patent are intermediates for a variety of pharmaceuticals. Methods for the preparation of such compounds are summarised and include the use of hydrogen azide gas at temperatures of 200 °C. This creates considerable safety hazards, and it is an objective of the patent

to provide a synthesis that is less hazardous and can be operated on a commercial scale. Reaction 8 shows the method used to prepare the range of compounds **17a–17e** from the amides **15** via the imidoyl chlorides **16**. The imidoyl chlorides **16** are produced using $(PhO)_2POCl$ or $POCl_3$. in the presence of a tertiary amine, and Et_3N is preferred. In the second step cyclisation is achieved using NaN_3 with $Et_3N \cdot HCl$ to form **17**. The compounds **16** and **17** are all yellow oils, and they are purified by column chromatography. The yield of all products is very good. In the first step the yields are generally 80–85%, and in the second they are as high as 98% in some cases. ^1H and ^{13}C NMR and IR data are provided for all examples. In addition basic DSC data are also given that indicate the compounds are thermally stable to >300 °C.

Reaction 8



Advantages

The process improves the safety of producing these compounds and gives high yields that have potential for commercial operation.

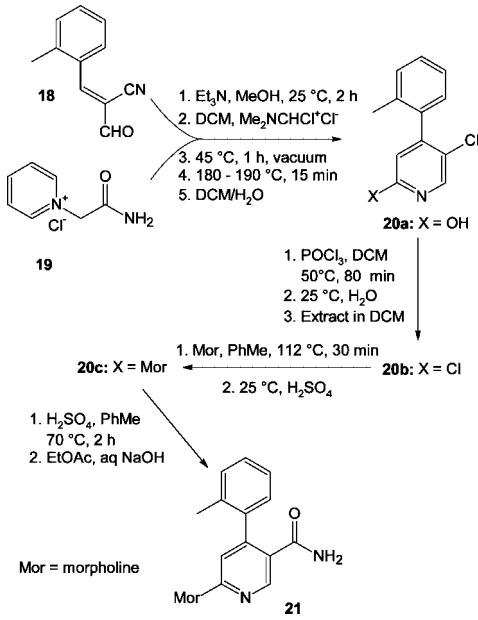
Patent No. U.S. 7,288,658

Assignee: Hoffmann-La Roche Inc., Nutley, New Jersey, U.S.A

Title or Subject: Process for Preparation of Pyridine Derivatives

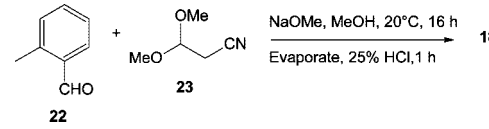
The specific pyridine derivatives covered by this patent are exemplified by **21**, and this and related compounds are intermediates in the production of NK-1 antagonists. Such compounds are useful in treating a range of inflammatory conditions and diseases of the central nervous system. In the methods available for preparing the desired compounds, a Grignard reaction is often used. However, the presence of electron-withdrawing groups in the aromatic ring prevents the desired substitution reaction. The objective of this patent is to provide a route to compounds containing such groups. Reaction 9 shows the route used to prepare **21** that begins with the formation of **20a** by reaction of **18** and **19**. In the first step of this reaction Et_3N is added in an alcohol followed by treatment with the Vilsmeier reaction reagent and heating the residue to 190 °C. **20a** is then converted to **20b** using $POCl_3$, and then the morpholinyl compound **20c** is produced that on hydrolysis gives the desired amide **21**. The patent also describes the preparation of analogues of **21** by the same process.

Reaction 9

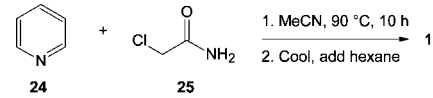


Also described in the patent are the methods used to prepare **18** and **19**. Reaction 10 shows the preparation of **18** from **22** and **23**, and Reaction 11 summarises the route used to prepare **19**.

Reaction 10



Reaction 11



The patent provides ^1H NMR data for all intermediates and products plus basic MS data.

Advantages

The process provides a route to compounds that are difficult to prepare by other means.

Patent No. U.S. 7,288,660

Assignee: Taro Pharmaceutical Industries Limited, Haifa Bay, Israel

Title or Subject: Process for Preparing Ondansetron Hydrochloride Dihydrate Having a Defined Particle Size

The compound of interest in this patent is used to alleviate the nausea caused by chemotherapy in the treatment of various cancers and is available as Zorfran. As is often the case, the physical form of drugs is important in the production of suitable formulations, and additionally particle size is frequently critical. An alternative method for producing the appropriately sized particles is said to be nonconventional and takes a prolonged period of time. The patent refers to another patent on this topic, and the number of the patent referred to is actually about a type of child's car seat. Although clearly a typographical error such an important mistake should be checked before submitting the patent.

The procedure described in this patent involves preparing a solution of the HCl salt dihydrate in H_2O/Pr^iOH and heating to 70 °C. The hot solution is then added to cold Pr^iOH and maintained at <40 °C for <1 h. The solid product is collected by filtration and found to have particles with a size <250 μm. There are several examples describing the procedure, and they all use kilo quantities of product. The patent also states that several batches of tablets were produced that met the U.S. specification for the product. These reports indicate the commercial status of the process.

Advantages

The process gives the desired particle size using a simple procedure.

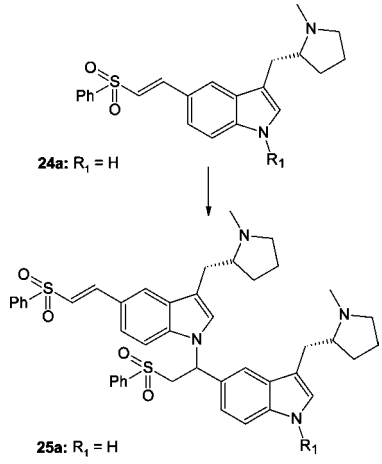
Patent No. U.S. 7,288,662

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

Title or Subject: Process for the Preparation of Eletriptan

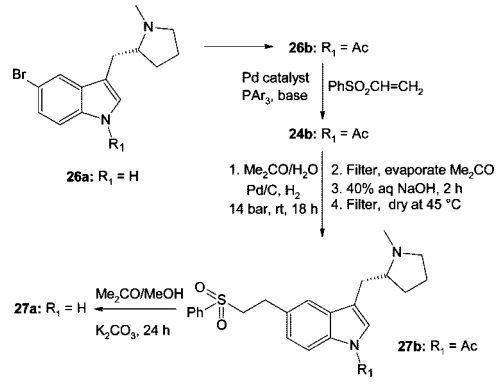
The HBr salt of **27a** is known as eletriptan and is used to treat migraine. A patent covering a novel polymorph of **27a** was reviewed recently (Org. Process Res. Dev. 2007, 11, 940). One major problem in the preparation of **27a** is the elimination of a dimer that is difficult to remove. The dimer **25a** is produced by reaction of the amine group in the intermediate **24a** as shown in Reaction 12.

Reaction 12



The problem of the dimer is overcome by avoiding the production of **24a**, and this is done by formation of the acetyl compound **24b** in order to protect the amine group. Reaction 13 shows the route used to prepare **24b** by acetylation of **26a**, giving **26b**, followed by reaction with $PhSO_2CH{=}CH_2$. The details of these reactions are not provided and are covered in earlier patents. Catalytic reduction of **26b** gives **27b**, and base hydrolysis then produces **27a** in 91.8% yield, and this can be converted to the HBr salt. The four claims of the patent cover only the last step of the synthesis in which **27b** is hydrolysed.

Reaction 13



Advantages

The process improves the overall production efficiency by eliminating the dimer by avoiding the production of the intermediate that causes the problem.

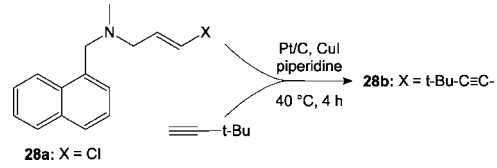
Patent No. U.S. 7,288,678

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

Title or Subject: Process for Preparing Terbinafine by Using Platinum as Catalyst

Terbinafine **28b** is an effective antifungal compound used to treat athlete's foot. In the final stage of one method for the synthesis of **28b** a Pd/CuI/tertiary phosphine catalyst is used in a coupling reaction. However, it is said that this requires an expensive purification stage to remove traces of the Pd catalyst and the phosphine. Attempts at improving this process have been patented, but they are said to require long reaction times. This patent discloses an improvement to the coupling process that has a short reaction time and requires less complex purification methods. Reaction 14 shows the method used to prepare **28b** by coupling **28a** with *tert*-butylacetylene in the presence of Pt/Cu catalyst and in the presence of a base. The base can be used as the solvent as shown in the scheme with piperidine. In one example pyridine is used as the base, and PhMe is the solvent. A yield of up to 97% is obtained, and the product purity by HPLC is 95%. The patent also describes the use of the oxalate salt of **28a**, and this is prepared from **28a** and oxalic acid in MeOH at room temperature. The patent claims cover the use of other Pt-containing catalysts although there are no examples given. After recovery and purification the product is said to have catalysts residue levels of <1 ppm.

Reaction 14



Advantages

The process provides higher-purity product in almost quantitative yields without recourse to expensive purification methods.

Patent No. U.S. 7,291,741

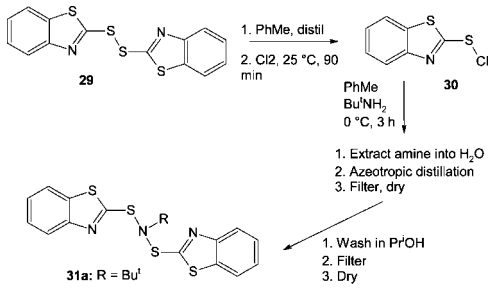
Assignee: Duslo A.S., Sal'a, Slovakia

Title or Subject: Equipment and Process for the Production and Purification of N-Alkyl-2-Benzothiazolylsulfeneimides

The title compounds such as **31a** are used as vulcanisation accelerators for rubber, giving better stability and improved physical properties. Such compounds have been known for many years, and there are several processes for their preparation. In many processes there is a chlorination step that requires anhydrous solvents to avoid HCl production and results in the production of amine hydrochlorides. The objective of the patent is to reduce the disposal problems of the hydrochloride salts and increase the purity of the product by an improved method. Reaction 15 summarises the method used to prepare **31a**. In the first step **30** is formed by chlorination of **29** using dry Cl_2. The reactant **29** used is only 96.5% pure and is initially heated in PhMe until 10% of the solvent has been removed. This is presumably done to remove any moisture before reaction with the Cl_2. In the second step **30** is treated with Bu^tNH_2 to form **31**. This reaction is carried out at 5–15 °C in a reactor containing multiple propeller mixers on a common shaft. Unreacted Bu^tNH_2 is removed from the mixture by extraction into water, and the solvent, PhMe, is removed by azeotropic distillation with water. The crude **31a** is purified by washing with Pr^iOH. The yield of final product is 89%, and in one example the process is carried out using 700 kg of **29**, thus indicating the commercial viability of the process.

The patent also describes the production of **31b** (R = cyclohexyl).

Reaction 15



Advantages

The process eliminates the disposal problem of hydrochloride salts and gives high yield of product in a commercially viable process.

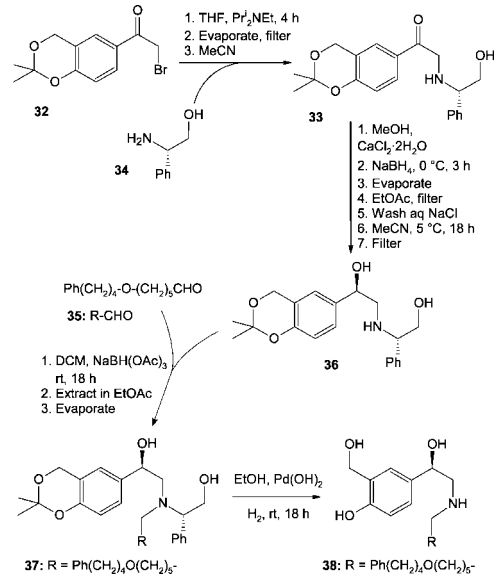
Patent No. U.S. 7,294,725

Assignee: SmithKline Beecham Corporation, Philadelphia, Pennsylvania, U.S.A

Title or Subject: Process for Preparing Salmeterol

Salmeterol **38** is a bronchodilator used to treat asthma and chronic bronchitis. It is used as the 2-naphthalenecarboxylate salt of the single enantiomer, and hence it is desirable to either make this directly or recycle the unwanted enantiomer. The process described in this patent produces the single enantiomer directly from the widely available chiral auxiliary **34**. The process is shown in Reaction 16 and begins with the preparation of **33** by the condensation of **32** and **34** in the presence of Pr^i_2NEt. The ketone group is then reduced using $NaBH_4$ to give **36**. Condensation of **36** with **35** in the presence of $NaHB(OAc)_3$ then forms **37**, and in the final stage the pure enantiomer **38** is formed by hydrogenolysis of **37** using Pearlman's catalyst. The desired salt can then be produced by treatment of **38** with 2-naphthoic acid in MeOH.

Reaction 16



Advantages

The process is claimed to give both savings in cost and time plus a high ee by using a readily available chiral starting material. However, since the auxiliary is discarded, this must be taken into account.

Patent No. U.S. 7,294,735

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

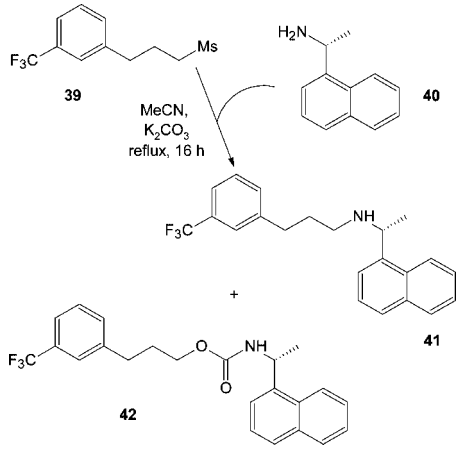
Title or Subject: Purification of Cinacalcet

Cinacalcet **41** as the HCl salt is a calcimimetic and is used to treat hyperparathyroidism. Patents on novel methods to produce this compound were reviewed recently (Org. Process Res. Dev. 2007, 11, 940). This patent builds on the earlier ones and describes an impurity **42** called cinacalcet carbamate and how to remove it. This patent is quite unusual in that it discusses the synthesis of **41** that is substantially contaminated with **42** as measured by HPLC. Normally patents claim products that are substantially free from impurities, and this may be a legal strategy covering a specific synthetic route during which **42** is produced. In fact the first claim in the patent is the impurity itself, and other claims cover the use of this impurity as a reference marker or standard. **42** is produced during the synthesis of **41** from **39** and **40** as shown in Reaction 17, and it is formed in various amounts, depending upon the solvent used in the process. The conversion to **41** was 93% and the amount of **42** was 2.9% when MeCN was solvent. When PhMe and a phase transfer catalyst (PTC) were used, the conversion to **41** was 81%, and the amount of **42** was 12%. Other solvents used with % conversion and % **42** are Me_2CO (60, 1.6), MIBK

(81, 11.5), Pr^{i}OH (88, 4.4), EtOAc (80, 7.0), EtOH (68, 10.0), and PhMe with no PTC (81, 12.0). When viewing the variation in these figures it has to be remembered that the reaction is carried out in refluxing solvent, and the differing reaction times may be dependent on the solvent boiling point as well as any other solvent effect.

The excess **42** is removed during the conversion of **41** to its HCl salt by passing HCl gas through a solution of **41** in MTBE. Final amounts of **42** are at a level of between 0.03 and 0.15% by HPLC.

Reaction 17



Advantages

The focus of the patent is the impurity, and the advantages appear to be the ability to identify and reduce it to acceptable levels.

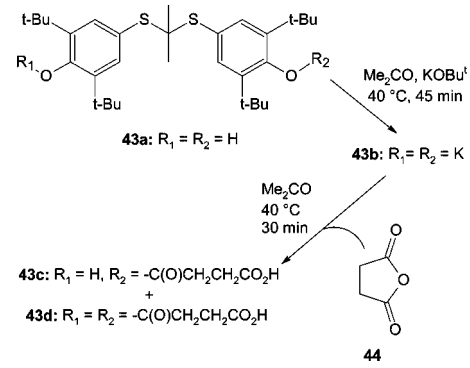
Patent No. U.S. 7,294,736

Assignee: Cambrex Charles City, Inc., Charles City, Iowa, U.S.A

Title or Subject: Process for Preparation of Probucol Derivatives

This is the first of two patents from different companies covering the preparation of Probucol **43a** or its derivatives. **43a** is a well-known antioxidant, approved for use in food, and because it is can lower lipid levels in blood, it is therefore useful in the treatment of cardiovascular diseases. However, the compound and many derivatives have poor solubility in body fluids, and so efforts are aimed at improving this. This patent discloses a process for producing water-soluble derivatives of **43a** by treatment with metal alkoxides followed by reaction with anhydrides. Reaction 18 shows the synthesis of succinate derivatives of **43a** in which the first stage is formation of the potassium salt **43b**. It is specifically stated that this reaction is carried out in a ketone with Me_2CO being preferred. The K salt is then treated with **44** and forms a mixture that contains 67% **43a**, 29% **43c**, and 4% **43d**. The mixture is then treated with aqueous KOH and, after a complex series of extractions and washings using heptane, aqueous KOH, and H_3PO_4, the solid that is obtained in 16% yield is **43c**.

Reaction 18



Advantages

The process claims to produce soluble derivatives, but the extraction and washing method requires a very large number of operations. It is debatable whether it would be a very efficient or robust process in commercial operation.

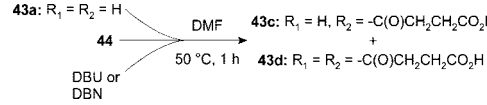
Patent No. U.S. 7,294,737

Assignee: AtheroGenics Inc., Alpharetta, Georgia, U.S.A

Title or Subject: Process for Preparing Esters and Ethers of Probucol and Derivatives

The second patent on this topic also provides a method for preparing the soluble succinate derivatives **43c** and **43d**. In this case the method used involves the reaction of **43a** with the anhydride **44** and DBN or DBU and gives a mixture of **43a**, **43c**, and **43d**. Solvents used for the reaction are DMF, MeCN, THF, dioxane, or PhMe. A base such as an alkaline carbonate or $(Me_2N)_2CO$ may also be present. The reaction temperature varied from 20 to 50 °C, and the time was up to 1 h. There are over 50 examples described, and the conversion is rarely more than 50%. There are no examples given in which the product **43c** is isolated although there is generally more present than there is **43d**. All yield data are from HPLC analysis.

Reaction 19



Advantages

The process claims to produce the desired soluble derivatives, although no data are provided for the method of isolating the final products from the reaction mixture.

Patent No. U.S. 7,297,788

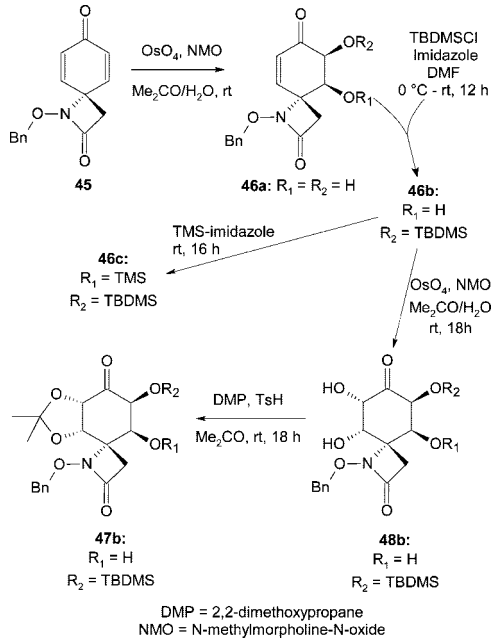
Assignee: Laboratorios Del Dr. Esteve S.A., Barcelona, Spain

Title or Subject: Regioselective Hydroxylation, Functionalisation and Protection of Spirolactams

The spirolactams covered in this patent have biological activity and it is stated that functional derivatives of such compounds are difficult to prepare in high yield. The work builds on an earlier patent (EP 1,595,865) in which novel spirolactam compounds such as **45** are described. The current patent uses **45** as a starting point for a variety of functionalised compounds. The patent contains a very large amount of work and hence only a small fraction is reviewed. Reaction 20 shows

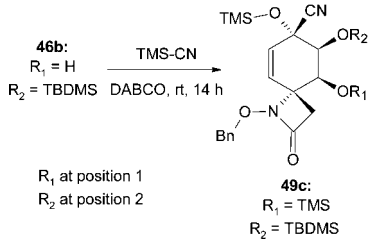
how **45** is converted to the dihydroxy derivative **46a** and then this is transformed to give **46b**. **46b** can be converted to **46c** using TMS-imidazole derivative or it can be dihydroxylated to form **48b**, and cyclisation of **48b** produces **47b**. Clearly the protective group **47b** and **48b** can be removed to form the dihydroxy derivatives **47a** and **48a** in which $R_1 = R_2 = H$.

Reaction 20



In another series of reactions shown in Reaction 21 a stereoselective addition to the carbonyl group in **46b** can be carried out using TMSCN and DABCO to produce the silylcyanohydrin **49c**. By starting from **46a** and using the same procedure **49d** ($R_1 = R_2 = TMS$) can be prepared. The conversion of **45** to the corresponding nonhydroxylated silylcyanohydrin is also described using the same method.

Reaction 21



The patent discusses the ability to selectively protect the OH groups in **46a**. When using TBDMS-Cl the OH group at the 1-position in **46a** does not react until all OH groups at position 2 are protected. This is ascribed to the existence of C−H π interactions between the H at position 2 and the benzyl group. It is suggested that this means that the conformation of the 2-OH is equatorial and more reactive than that of the 1-OH group that is axial. The patent indicates that because of this it is possible to use different protecting groups for protection of the OH groups. The ability to stereoselectively add to the carbonyl group is also partly explained by this conformational effect. Unusually for a patent there is a considerable amount of discussion to explain the course of the reactions. The patent includes ^{1}H NMR and MS data for all compounds.

Advantages

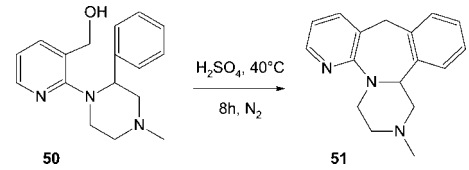
The patent provides a wide range of spirolactams that have biological activity and have potential as antibiotics and in the treatment of tumours.

Patent No. U.S. 7,297,790

Assignee: Sumitomo Chemical Co. Ltd., Osaka-shi, Japan
Title or Subject: Anhydrous Mirtazipine Crystals and Process for Preparing Them

Mitrazapine **51** is used as an antidepressant and it is said that it is difficult to purify by crystallisation because the crystals are often obtained in an oily state. Additionally the crystals have hygroscopic properties and need to be stored under dry conditions. This patent is a divisional application of an earlier patent that has been reviewed (Org. Process Res. Dev. 2004, 8, 553). The route used to prepare crude **51** is by dehydration of **50** using H_2SO_4 as shown in Reaction 22. The crude **51** is then converted to the hemihydrate form by dissolving in hot EtOH or MeOH containing water and decolourising carbon. The crystalline material obtained was then pulverised and dried by heating in a vacuum to obtain the anhydrous form. The patent provides detailed IR, XRD data of the anhydrous crystalline material. The first claim of the patent states that the anhydrous form has <0.5 wt % water and this increases to no more than 0.6% after 500 h at 25 °C in air with a relative humidity of 75%. One example is carried out using 84 kilo of crude **51** thus indicating the advanced commercial status of the process.

Reaction 22



Advantages

The process produces stable anhydrous crystals, suitable for commercial use, in a straightforward manner.

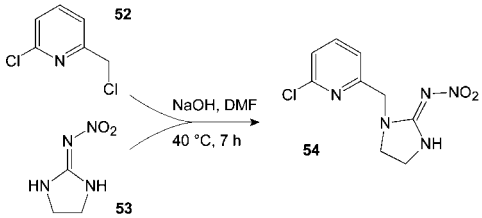
Patent No. U.S. 7,297,798

Assignee: Excel Crop Care Ltd., Mumbai, India
Title or Subject: Process for the Preparation of the Insecticide Imidacloprid

Imidacloprid **54** is a neonicotinoid insecticide that is used to protect seeds after planting. The insecticide has been blamed for the loss of significant numbers of bees and in 1999 was banned for use on sunflowers in France. This resulted in extensive legal battles between the French beekeepers and Bayer, the manufacturers. Interestingly another neonicotinoid insecticide was in the news in the UK for the same reason at the time of writing this review. Methods for the preparation of **54** involve the use of alkali metal–carbonates in solvents in which they are not very soluble. This means that the reaction is incomplete and requires extended reaction times and poor product recovery. This patent attempts to improve the process by using alkali metal hydroxides that have improved solubility. Reaction 23 shows the reaction between **52** and **53** that takes place in DMF containing NaOH. Acidification with HCl precipitates the **54** that is obtained in 78% yield and a purity of 96%. By adding the NaOH and **52** in two portions the

yield and purity of **54** are increased compared with adding everything at the start in a single portion. The first portion of each is added at the start and the second after 4 h.

Reaction 23



Advantages

The process takes less time and gives higher yield and purity product than the alternative method.

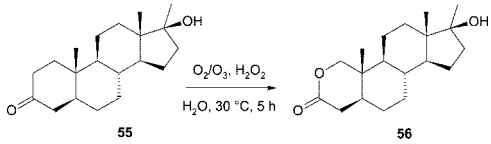
Patent No. U.S. 7,297,801

Assignee: Barr Laboratories Inc., Woodcliff Lake, New Jersey, U.S.A

Title or Subject: Process for the Production of 2-Oxa-3-One Androstane Derivatives

This patent discloses methods for producing a range of anabolic steroids such as oxandrolone **56**. The compound is used with a diet and exercise program to cause weight gain in patients who have lost too much weight due to surgery, injury, or long-lasting infections such as AIDS. It is also used by body-builders and can have serious side effects if used at high doses. **56** is also used to treat bone pain in patients with osteoporosis. The method described in this patent is shown in Reaction 24 and is carried out by bubbling a mixture of O_2 and O_3 through an aqueous solution of mestanolone **55** containing H_2O_2. The patent does not provide a formal example but gives rather nonspecific information regarding times and temperatures for the reaction, and yield details are not provided. It is not surprising that the patent states that the reaction should be carried out in an explosion-proof vessel. The product can be extracted using DCM although, again, no firm details are given.

Reaction 24



Advantages

The patent does not claim specific advantages, and since other methods also use ozone, it is not possible to comment on the utility of the process.

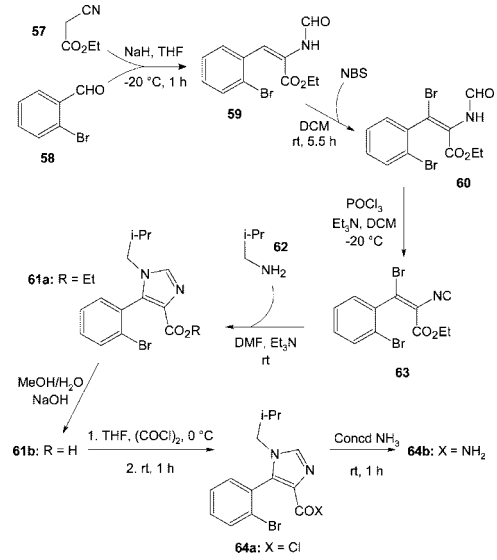
Patent No. U.S. 7,301,027

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

Title or Subject: Process for the Preparation of Imiquimod and Intermediates Thereof

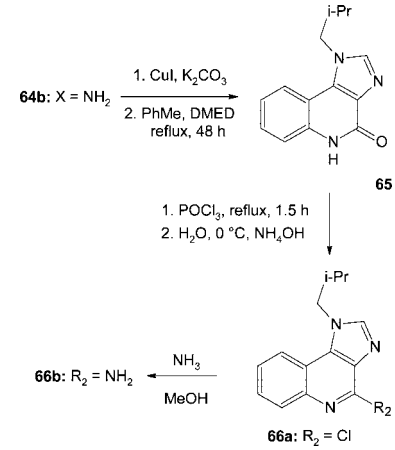
Imiquimod **66b** is an immunomodulator that is used to treat three different skin conditions: genital warts, small superficial skin cancers and actinic keratoses. It is available as a cream under the name aldara. A number of methods used to prepare **66b** are reviewed and said to be time-consuming and complex requiring the use of toxic or hazardous reagents such as NaN_3. The process described in this patent is said to be simpler, safer and commercially viable compared to other methods. The patent claims cover the synthesis of **66b** from the intermediate **64b**, and the synthesis of **64b** is outlined in Reaction 25. The patent examples only cover the synthesis of **64b** and do not describe its conversion to **66b**. The route to **64b** begins with the addition of **57** to **58** in the presence of NaH to give **59** as a dark, brownish oil. Bromination of **59** using NBS gives **60** in 40% yield, and then treatment with $POCl_3$ produces **63** in quantitative yield. The crude product is used in the next step in a reaction with **62** to give **61a** in a yield of 71% after purification by flash chromatography (FC). Base hydrolysis of the ester group then gives an 87% yield of **61b**, and this is converted to **64a** that is not isolated and used directly to form the amide **64b** by reaction with NH_3.

Reaction 25



The crude product **64b** is used in the synthesis of **66b** as shown in Reaction 26 although examples in the patent are given for all reactions apart from the final step. The first step in Reaction 26 forms **65** from **64b** by an intramolecular aromatic substitution that is effected by using CuI and $MeNHCH_2CH_2NHMe$ (DMED). The yield in this step is 36%, and the product is then chlorinated using $POCl_3$ to give **66a** that is isolated in 30% yield after purification by FC. For the final step no details are given although the patent refers to other routes to **66b** from **66a** that use NH_3 in MeOH to convert the Cl to NH_2.

Reaction 26



There are several novel compounds reported in this patent, and basic ^{1}H NMR data are given for them. It is also reported that chlorophenyl analogues of **59**, **60**, **61**, **63**, etc. can also be prepared by the processes described, but no experimental details are given.

Advantages

The patent does use safer methods than other processes to produce the desired product, but the yields in some steps are quite low, and hence the overall process efficiency may be poor.

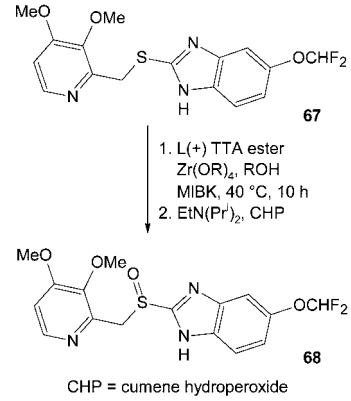
Patent No. U.S. 7,301,030

Assignee: Nycomed GmbH, Konstanz, Germany

Title or Subject: Process for Preparing S-Pantoprazole

Pantoprazole **68** is one of a class of drugs known as proton pump inhibitors that are used to control gastric acid levels and ulcer formation in the stomach. A key step in synthesising **68** is the oxidation of a thioether group to a sulfinyl group. Several methods are known, and new processes have been reviewed previously (Org. Process Res. Dev. 2007, 11, 318). Reaction 27 shows the reaction of interest in preparing **68** from **67**, and the patent provides a new oxidation process using Zr of Hf alkoxides with chiral auxiliary agents. Several alternative reagent mixtures are described in the patent consisting of the metal alkoxide and alcohol, a chiral agent, cumene hydroperoxide (CHP) and a *tert*-amine. The alkoxides used are *i*- or *n*-propoxide or *tert*-butoxide with the corresponding alcohols. The chiral agent is L-(+)-tartaric acid or its amide or ester derivatives and the amine used in the examples is $EtNPr^i_2$. The reaction is carried by adding the amine and CHP to an MIBK suspension of everything else at room temperature. The reaction takes between 5 and 10 h, and after extraction the product is obtained at up to 80% yield and an optical purity of 95%. If the amine is omitted, the yield falls to 65%.

Reaction 27



CHP = cumene hydroperoxide

Advantages

The process provides an alternative process in the key oxidation step for preparing this widely used drug.

Keith Turner

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