Organic Process Research & Development **2010,** *14,* 759–769

Highlights from the Patents

Review of U.S. Patents in the Field of Organic Process Development Published During February and March 2010

Summary

The current review contains 22 patents from an original list that contained 316 that fit the search criteria. Four patents cover the preparation of high purity oxycodone, the semisynthetic opioid analgesic that is used to relieve severe pain. The patents contain details of the purification and analysis as well as formulation and packaging details, along with another patent focusing on purification of anastrozole, a drug used to treat advanced breast cancer. The method, involving four crystallisations to reduce an isomer down to acceptable levels, has been scaled up. Purification is also the subject of a patent on the anti-inflammatory drug meloxicam. The method is able to reduce a particular impurity from 0.78 to 0.02%, which is well within the desired specification. The production of the anaesthetic robivacaine from optically pure L-pipecolic acid is described. The method unusually incorporates a resolution step that uses both enantiomers of tartaric acid to achieve the desired optical purity of the product. Quetiapine fumarate is an antipsychotic agent used in the treatment of schizophrenia and a faster new process for its preparation gives higher purity product, avoiding the need to use flash chromatography in its purification. A new process for making the dye intermediate croconic acid is reported. Quite separately and perhaps coincidentally, the acid has been found to have unusual ferroelectric properties that may allow its use in the fields of both electronics and photonics. Two separate patents disclose new processes for the production of imiquimod, the active ingredient in the skin cream Aldara. One of these patents is very similar to an earlier patent from the same company, but no mention is made of the earlier work within the patent. The second patent goes via a new route that provides several novel intermediates. A process to make the antihypertensive drug valsartan is described that includes milling and drying examples on a kilo scale. The process avoids the use of the hazardous reagent $Bu_3^nSnN_3$, although this is made in situ in the new process. A MnO_2 catalyst is described that can be used to oxidise CN groups in compounds that have other oxidisable groups. The catalyst is doped with $CePO_4$ and K and is used to prepare an intermediate for methionine production. Pioglitazone is used to treat type II diabetes, and a new synthesis of this material is disclosed in a patent that contains 101 detailed examples. The process gives several new intermediates, and many examples are carried out on a kilo scale. Long-distance travelers who suffer from jet lag may be interested in a new process for making melatonin and its derivatives. This is another comprehensive patent containing over 90 novel compounds, and some derivatives of melatonin are claimed to be more effective than the parent compound. Levofloxacin is the *S*-enantiomer of the antibacterial agent ofloxacin that exists in three anhydrous forms and two hydrates. A new method of preparing the hemihydrate is described that relies on adjusting the water content of the crystal slurry in a long sequence of steps that could be difficult on a commercial scale. Allergies and hay fever seem to be more common, and a new method of making the antihistamine drug desaloratadine is described. The patent reports that an impurity found when an ester is hydrolysed using a base is not present when the hydrolysis is carried out under acidic conditions. Oddly enough, the actual identity of the impurity is not revealed. The tartrate salt of rivastigmine is used to treat mild Alzheimer's disease, and a new process for the preparation of the free base is described. The process involves resolution of an intermediate and then uses the pure enantiomer to give the desired product with high optical purity. Ethyleneimine is used to prepare polymers and a patent outlines a continuous process for its preparation but does not contain any specific examples. A patent for the preparation of several pyridine derivatives containing electron withdrawing groups is described. The process uses phosphorus ylid-type reagents to make the pyridines that are used to prepare agrochemicals. A very comprehensive patent describes a range of novel chloropyridine Baylis−Hillman adducts that have activity against chloroquine-resistant malarial parasites. Although the worldwide outbreak of swine flu seems to have abated, there is still interest in new methods of making Tamiflu. A new process uses gaseous H_2S in an azide reduction process, and despite this, it claims to be cleaner than an alternative procedure. A number of the patents describe experiments carried out on a kilo or multikilo scale, and this may suggest an advanced stage of development or even commercial operation. However, there is no legal or commercial significance in the choice of patents in this review. The advantages mentioned in this review are those claimed in the patent, unless this reviewer has personal knowledge of the subject.

Patent No. U.S. 7,655,806

Assignee: Synthon BV, Nijmegen, Netherlands

Title or Subject: Process for Purification of Anastrozole

Anastrozole **3** is a nonsteroidal aromatase inhibitor used as a hormonal therapy in the treatment of advanced breast cancer in postmenopausal women. It is used in the free base form and available as Arimidex. Processes for the preparation of **3** are reviewed, and the most important ones use **2a** in the synthesis. A major byproduct of the reaction is isoanastrozole **4** and its removal can be problematical. The patent describes a method for purifying **3** by crystallisation that reduces the level of **4** to <0.1%. The preparation of **3** from **1a** is shown in Reaction 1. Compound **1a** is dissolved in Me_2NAc and then chlorinated using $SOCl_2$ to give **1b**, which is isolated and recrystallised

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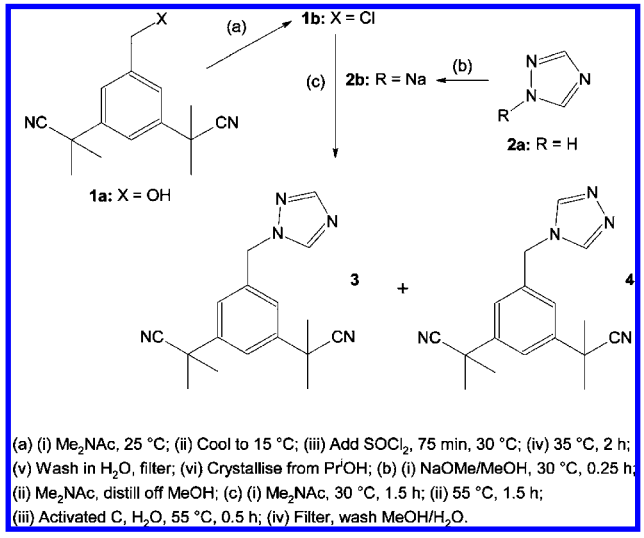
from *i*-PrOH to give an 87% yield. Compound **1b** is reacted with **2b**, which is obtained by treating **2a** with a 30% solution of NaOMe in MeOH. After completion of the reaction, the MeOH is distilled off and replaced by Me_2NAc. The crude mixture of **3** containing **4** is then treated with activated C in H_2O, and the filtrate was recovered for the purification steps. The first step is acidification with HCl at 25 °C, followed by seeding with pure **3**. Cooling to 0 °C gives crystals of purified **3**, and these are further purified in three crystallisation stages to give pharmaceutical grade product. The crystallisation steps involve the dissolution in MeOH/H_2O acidified with HCl and involve seeding with pure **3** and crude **3**. The second crystallisation is carried out without acidification, and the product contains <0.2% of **4**. The final step also contains no HCl and gives pharmaceutical grade **3**. The preparation of **3** and its subsequent purification produce over 4 kilos of product, thus, indicating the commercial status of this procedure.

Reaction 1



(a) (i) Me_2NAc, 25 °C; (ii) Cool to 15 °C; (iii) Add $SOCl_2$, 75 min, 30 °C; (iv) 35 °C, 2 h; (v) Wash in H_2O, filter; (vi) Crystallise from Pr^iOH; (b) (i) NaOMe/MeOH, 30 °C, 0.25 h; (ii) Me_2NAc, distill off MeOH; (c) (i) Me_2NAc, 30 °C, 1.5 h; (ii) 55 °C, 1.5 h; (iii) Activated C, H_2O, 55 °C, 0.5 h; (iv) Filter, wash MeOH/H_2O.

Advantages

The process is efficient and suitable for commercial production.

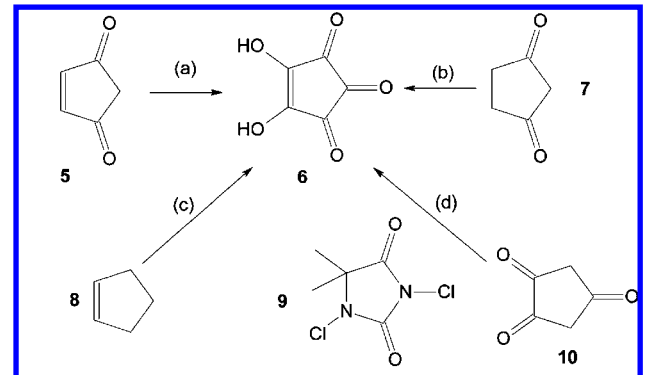
Patent No. U.S. 7,655,814

Assignee: Fujifilm Corporation, Tokyo, Japan

Title or Subject: Process for Producing Croconic Acid or Salt Thereof

Croconic acid **6** and its salt are used in the manufacture of dyes and are useful intermediates for agrochemicals. It has also been reported by Japanese researchers in a very recent paper (*Nature* **2010**, *463*, 789−792) that **6** exhibits stable ferroelectricity properties and has a ferroelectric phase transition temperature of 150 °C, the highest of any simple organic molecule. Ferroelectrics are used to perform various functions in the fields of both electronics and photonics and are used in memory, capacitors, piezoelectric devices, and optical devices. The patent mentions that **6** is produced when inositol is oxidised with fuming HNO_3 and is also obtained by oxidation and decarboxylation of tetrahydrobenzoquinone. In neither case is there any mention of how the product is obtained, and it is claimed that an inexpensive and simple process is desired. The basis of the method for preparing **6** is the reaction of a five-membered ring compound with a halogenating agent in the presence of a base. A number of ring compounds and a variety of halogenating agents are used, and Reaction 2 shows those covered in the patent examples. Each reaction is carried out by treating the ring compound with the halogenating agent below rt and then allowing to stand for different periods of time and at temperatures up to 50 °C before passing HCl gas through the solution. The precipitate is collected, washed, and then recrystallised from water. The reported yields are 88% for method (a), 66% for (b), 83% for (c), and 63% for (d). The Na salt of **6** is prepared in 76% yield by using method (a) and not acidifying. The purity of the product obtained is not reported for any of these methods. The claims of the patent cover the use of several different ring compounds and halogenating reagents, but examples are not provided for them all.

Reaction 2



(a) (i) Br_2, aq NaOH, 15 °C, 40 min; (ii) rt, 1 h; (iii) HCl gas, 10° C, filter; (b) (i) Cl_2, aq K_2CO_3, 15 °C, 3 h; (ii) 50° C, 3 h; (iii) HCl gas, 10° C, filter; (c) (i) Br_2, KOH, PhH, H_2O, <20° C, 1 h; (ii) rt, 2 h; (iii) 60 °C, 2 h; (iv) HCl gas, 5° C, filter; (d) (i) EDC, <10 °C, 1 h; (ii) rt, 1 h; (iii) Aq NaOH, <10° C, 0.5 h; (iv) rt, 1 h; (v) 50 °C, 3 h; (vi) HCl gas, <10° C, filter.

Advantages

The process gives high yields of a product that is not easy to prepare.

Patent No. U.S. 7,659,398

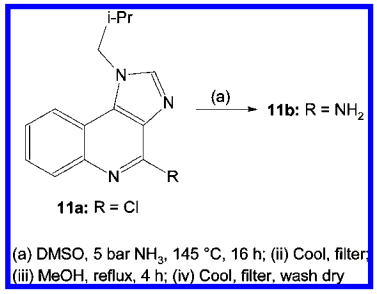
Assignee: Chemagis Ltd., Bnei Brak, Israel

Title or Subject: Imiquimod Production Process

This is the first of two patents covering the compound imiquimod **11b**. This is an immunomodulator that is used to treat genital warts, small superficial skin cancers and actinic keratoses on the face or scalp and is the active ingredient of the cream Aldara. An earlier patent on the synthesis of **11b** from this assignee has been reviewed (*Org. Process Res. Dev.* **2008**, *12*, 369.). The earlier patent describes the preparation of **11b** by the reaction between $HCONH_2$ and **11a** in the presence of NH_3, whereas the current patent covers the preparation of **11b** by the reaction of **11a** and NH_3 in DMSO as solvent. Other polar solvents are claimed in the patent, but no examples are given. It is tempting to speculate that the previous patent could describe the formation of **11b** from **11a** and NH_3 with $HCONH_2$ being a solvent. It is interesting to note that there is no reference in this patent to the earlier work. This newer process is carried out by heating **11a** with NH_3 in a closed vessel at 150 °C. The system generates a pressure of about 5 bar and the reaction is

monitored by stopping it and analysing by HPLC. In one example, after 10 h, the mixture contained 51% **11b** and 49% **11a**. After additional NH_3 was admitted and the process continued for a further 12 h, the product contained 99.93% **11b** and 0.07% unreacted **11a**. In an example that was stopped after 10 h then continued for a further 6 h the final mixture contained 92% **11b** with 8% **11a**. It is this mixture that is then used to prepare pure **11b** by refluxing in MeOH followed by hot filtration and cooling. The crystals are collected and washed in MeOH and this step is covered by one of the claims. The final product was obtained in 95% yield with purity 99.89% (HPLC). The patent contains a summary of using other solvents to purify **11b**, and the use of these is covered by the claims. The solvents are PhMe, MeCN, THF, 2-MeTHF, EtOAc, *n*- and *i*-PrOH, and Me_2CO, and they all give high purity **11b** with yields in the range 80−95%.

Reaction 3



Advantages

The process claims to give high yields of product with purity of >99.8%.

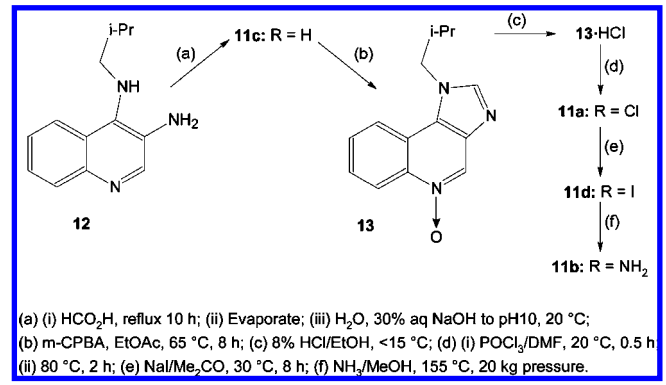
Patent No. U.S. 7,678,912

Assignee: USV Ltd., Mumbai, India

Title or Subject: Process for the Preparation of Imiquimod

This patent, covering another synthesis of **11b**, summarises the alternative routes and concludes that a simpler and more efficient method is needed. The new route is shown in Reaction 4 with the cyclisation of **12** to produce **11c** (R = H) by refluxing in HCO_2H. The product is recovered in 98% yield after the solvent is removed in vacuum and then the mixture is basified to pH 10−11. In the next step, **11c** is oxidised with mCPBA to give the *N*-oxide **13** that is recovered by evaporation of the organic reaction layer. Treatment of the crude mass with HCl/EtOH forms the salt **13·HCl** that is isolated in 94% yield. Chlorination of the salt using $POCl_3$/DMF forms **11a** that is isolated from the reaction mixture in 74% yield after basification to pH 10. Halogen exchange of **11a** with NaI gives the novel compound **11d** (R = I) and this is heated with NH_3/MeOH in an autoclave at 155 °C to form crude **11b**. The patent reports that the reaction is carried out at pressure of 20 kg without further explanation of the meaning of this unit. Purification of the crude product is carried out by conversion to the maleate salt **11b·maleate** that is recovered in 91% yield. Heating the maleate salt with charcoal in MeOH/H_2O at 75 °C, followed by addition of NH_4OH to the cooled filtered solution, precipitates **11b** in 89.7% yield but the purity is not reported. The patent provides ^1H NMR data for the compounds **11a**, **11b**, **11c**, **11d**, **11b·maleate**, and **13·HCl**.

Reaction 4



Advantages

The process gives high yields of intermediates and final product but the purity of the final product is not known.

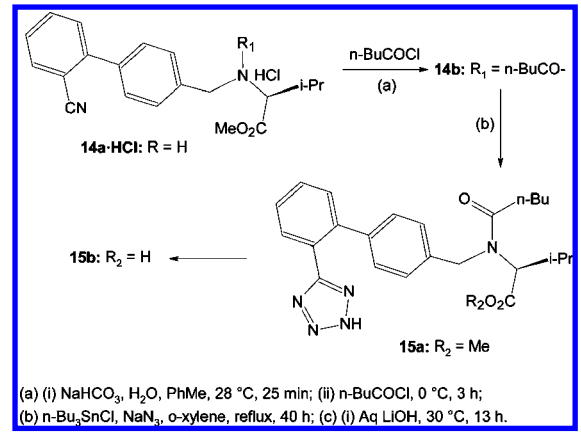
Patent No. U.S. 7,659,406

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

Title or Subject: Process for Preparing Valsartan

Valsartan **15b** is used to treat hypertension especially in patients with diabetes and is available as Diovan. A previous patent describing an alternative process for its synthesis has been reviewed (*Org. Process Res. Dev.* **2009**, *13*, 371.). The current patent discusses an early process for preparing **15b** that uses Et_3N and *n*-Bu_3SnN_3 and states that the use of these reagents make the process difficult to operate on an industrial scale. The new process is shown in Reaction 5 and begins with the condensation of the HCl salt of **14a** with *n*-BuCOCl in the presence of $NaHCO_3$ to form **14b**. The reaction was followed by TLC and after workup with aq $NaHCO_3$ the product was obtained by concentrating the organic layer to give a 97% yield of **14b** with 98.9% purity (HPLC). In the next step **14b** is refluxed with *n*-Bu_3SnCl and NaN_3 for about 40 h to form the ester of the tetrazole **15a**. This is not isolated and the reaction mixture is cooled to 30 °C and stirred with aqueous LiOH for 13 h to hydrolyse the ester and give **15b**. After extraction into DCM and washing with aq HOAc, H_2O, and brine, the organic layer is concentrated then dissolved in cyclohexane. Further concentration, redissolution in cyclohexane and evaporation gives **15b** in % yield with 96.6% purity. After recrystallisation from DCM **15b** is obtained in 59.3% yield and 98.99% purity (HPLC).

Reaction 5



The patent also includes an example of the commercial scale drying and milling of **15b** in which 9.5 kilo of wet material is dried and milled and this indicates that the synthetic route has been scaled up. The patent describes an example of how **15b** can be esterified to give **15a** by treatment with MeOH and $SOCl_2$. There is no discussion of this reaction in the patent and the reason for doing this is not clear and there is no mention in the patent as to how to prepare the key starting material **14a**.

Advantages

The patent provides an alternative process for preparing this drug in high yield.

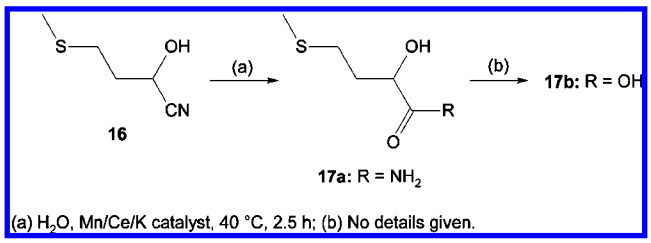
Patent No. U.S. 7,670,986

Assignee: Degussa AG, Dusseldorf, Germany

Title or Subject: Manganese Dioxide Catalyst for the Hydrolysis of Carbonitriles

The patent describes a catalyst that is used to hydrolyse nitriles containing readily oxidisable groups such as thiols or thioethers. The catalyst is particularly suitable for the hydrolysis of **16** to **17a**. This is a valuable intermediate in the preparation of **17b**; the hydroxy analogue of the amino acid methionine that is used as an animal feed supplement. The patent states that the hydrolysis of cyanohydrins, such as **16**, with strong bases gives an aldehyde and HCN and acid hydrolysis on an industrial scale is not known. Hence, there is a need for an improved method of hydrolysis such compounds. The patent obviously focuses on the preparation of the catalyst that may be made on a commercial scale by the assignee, a catalyst manufacturer. Details for preparing the catalysts are provided in the patent but are not included because this review focuses on their use. MnO_2 catalysts have powerful oxidation capability, and the objective of the patent is to inhibit this while maintaining the catalytic hydrolysis of the desired functional group while leaving other groups untouched. This has been achieved by producing a MnO_2 catalyst containing a lanthanide metal and an alkali metal with La or Ce salts being preferred. A number of catalysts are prepared and these are used for the oxidation of **16** to **17a**. When a catalyst prepared from $CePO_4$ and α-MnO_2 containing 1.6% K is used, the selectivity to **17a** was 98.1%, with a conversion of 99.8% of **16**. The catalyst was reused and the selectivity increased to 99.8%, while the conversion remained at 99.8%. An example of using a nondoped MnO_2 catalyst gave a conversion of 95.2%, with selectivity of 94.8%. The patent also has an example of the hydrolysis of **16** to **17a** using a MnO_2 catalyst that is prepared according to patent JP 09104665. The reaction was carried out continuously for 100 h and gave 96.1% conversion of **16** with selectivity to **17a** of 83.0% thus showing that the doped catalysts of this invention are better.

Reaction 6



Advantages

The catalysts are highly selective for the hydrolysis of the nitrile that contains an easily oxidisable group.

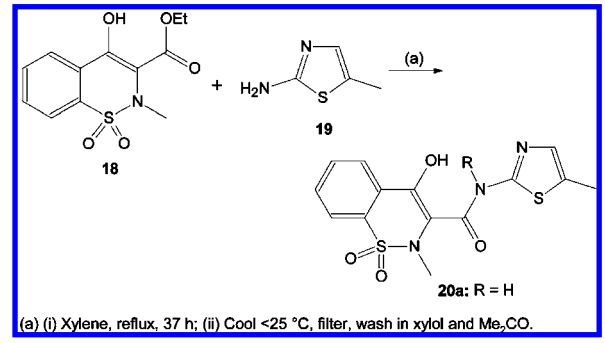
Patent No. U.S. 7,671,197

Assignee: A.M.S.A. Anonima Materie Sintetiche E Affini S.p.A., Milan, Italy

Title or Subject: Process for the Purification of Meloxicam

Meloxicam **20a** is a nonsteroidal anti-inflammatory drug that has a number of polymorphs and Form I is the form of the molecule is used in drug preparations. The preparation of **20a** is by the condensation of **18** and **19**, as shown in Reaction 7, that takes 37 h in refluxing xylene. During this time a flow of N_2 is passed through the mixture to remove the condensation products that are trapped in 4 Å molecular sieves. In methods for isolating and purifying **20a**, the main impurities are **18**, **19**, and **20b** (R = Et) formed during the reaction. Removal of **20b** is particularly difficult to <0.10%, and the requirement is <0.05% and, hence, an improved purification procedure is required.

Reaction 7



Following the completion of the reaction the wet product is collected and contains up to about 0.78% of **20b**. The purification method is summarised as follows: (1) suspend crude **20a** in MeOH at rt and add 30% NaOMe in MeOH (exotherm); (2) add activated carbon and then filter, wash solid, and add washings to filtrate; (3) add concd HCl to pH 2.3 to 2.4 to precipitate solid and stir for 1 h; (4) filter and wash in H_2O (HPLC analysis shows **20b** content = 0.21%); (5) suspend wet product in Me_2CO and reflux for 1 h; and (6) cool to rt, filter, wash in Me_2CO, dry under vacuum at 55−65 °C for 8 h.

The analysis of the dried product showed 0.022% of **20b** and the yield was 85% based on the wet product from step 4. The patent reports that the value of pH in step 3 is critical in the purification method and a table of results shows there is an optimum value of pH around 2.23, which gives a level of **20b** in the dried product of 0.020%. At pH 3.7, the amount of **20b** in the final product is 0.023% and at pH below 2 the amount of **20b** also rises so that at pH 1.52 it is 0.052% and at pH 1.12 it is 0.114%. Solvents other than Me_2CO are used in the purification step and only those that are polar and aprotic give the **20a** containing the required low levels of **20b**.

Advantages

The process removes the impurities to well within the required specification.

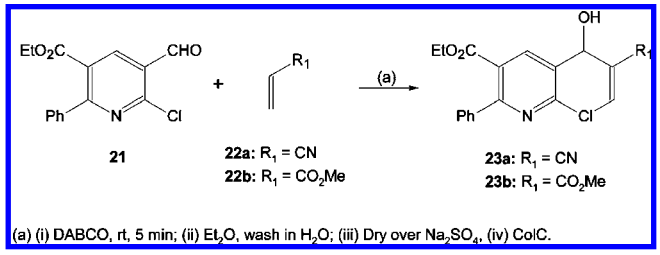
Patent No. U.S. 7,666,883

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

Title or Subject: Antimalarial Baylis-Hillman Adducts and a Process for the Preparation Thereof

This patent describes the synthesis of a number of chloropyridine compounds that have antimalarial activity against chloroquine-resistant malarial parasites. The patent contains experimental details for the preparation of a considerable number of compounds with two basic types of compounds being produced. These are exemplified by compounds **23a** and **23b** shown in Reaction 8 or **25** in Reaction 9. The formation of compounds **23a** and **23b** is carried out from **21** using DABCO without a solvent at rt. The reaction takes only 5 min after which time the mixture is diluted in Et_2O and washed in H_2O. The product is purified using ColC and isolated in almost quantitative yield.

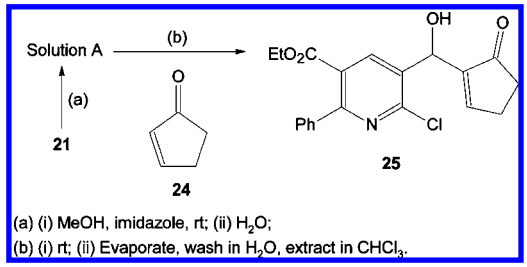
Reaction 8



The patent also describes details for the preparation of compounds **23a**, **23b**, and similar adducts using various solvents. Examples cover the use of EtOH, MeCN, THF, $CHCl_3$, and 1,4-dioxane with the products being obtained in quantitative yields after isolation by ColC.

The formation of **25** from **21** and **24** is carried out in MeOH and H_2O at rt using imidazole as catalyst (Reaction 9). The reaction is monitored by TLC, but the time required is not specified. After removal of MeOH, the product is extracted into $CHCl_3$, purified by ColC, and isolated in 97% yield. Replacement of **24** by cyclohexenone gives an identical reaction, and the product is isolated in 92% yield.

Reaction 9



The patent contains ^1H and ^{13}C NMR and MS data for 37 adducts made by the process described. There is also a summary of antimalarial activity tests using some of the compounds.

Advantages

The process gives excellent yields of a range of novel compounds that have antimalarial activity.

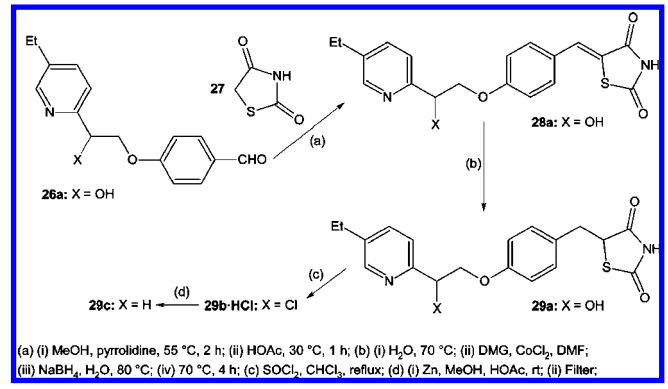
Patent No. U.S. 7,671,207

Assignee: Cadila Healthcare Limited, Gujarat, India

Title or Subject: Process to Prepare Pioglitazone via Several Novel Intermediates

Pioglitazone **29c** has antihyperglycemic properties and is used as the HCl salt to treat type II diabetes. A number of methods are known for preparing **29c** and a patent on its preparation along with other thiazolidinediones has been reviewed (*Org. Process Res. Dev.* **2009**, *13*, 669.). The current patent summarises some of the methods used to prepare **29c** and concludes that they lead to unwanted impurities that are difficult to remove, and some processes cause an evolution of HBr gas and so have adverse environmental impact. The patent discloses a new process for preparing **29c** and also includes a number of novel intermediates. The patent contains 101 examples that include details of the final steps shown in Reaction 10 and also different methods for preparing the key starting material **26a** and other intermediates. There is almost a spider's web of possible routes to the various intermediates in the patent, and hence, this review can only cover a small amount of the work. The final stages of the chemical process for preparing **29c** are summarised in Reaction 10, and the details shown are taken from examples in the patent that are carried out on a kilo scale. The first step is the condensation of the aldehyde **26a** with **27** to form **28a**. This is carried out in MeOH at 55 °C using an equimolar amount of pyrrolidine to that of **26a**, and after 2 h, HOAc is added in a equimolar amount to **27**. The precipitated product **28a** is filtered off, purified using MeOH, and recovered in 91% yield. In the next step, **28a** is reduced to **29a** using $NaBH_4$ in the presence of $CoCl_2$ and dimethylglyoxime (DMG), and workup with $CHCl_3$ gives the desired product in 95% yield. The OH group in **29a** is then converted to Cl using $SOCl_2$ in refluxing $CHCl_3$, and the product precipitates as the HCl salt **29b·HCl** in 95% yield. The Cl group is removed by treating with Zn and HOAc in MeOH to form **29c** and this is converted to the HCl salt using HCl in EtOH that is recovered in 84% yield.

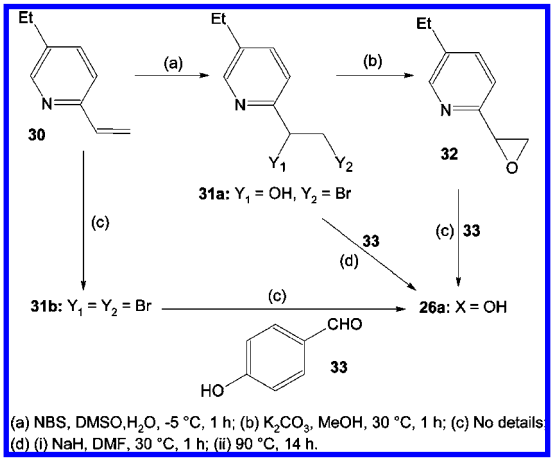
Reaction 10



The patent describes several methods for the preparation of **26a** from **30**, and Reaction 11 outlines some of them. Compound **30** can be converted to the bromohydrin **31a** and then the epoxide **32** or directly to the epoxide without isolating **31a** by a one-pot process that follows steps (a) and (b), with **32** being isolated in 80% yield. Bench-scale experiments are also described for preparing **32** from **30** or **32** using alternative

solvents or bases. The patent mentions that base catalysed condensation of **31a** or **32** with **33** produces **26a** and condensation of **33** with **31b** is also said to give **26a**. However, details of the reactions of **31b** or **32** are not described. The reaction of **31a** with **33** is carried out on the kilo scale by adding a solution of **31a** in DMF to a mixture of NaH and **33** in DMF at 30 °C followed by heating to 90 °C for 14 h. After extraction in Et_2O, **26a** is isolated in 69% yield. There are several smaller scale experiments for preparing **26a** using similar procedures that involve alternative solvents. They are reported as giving similar results.

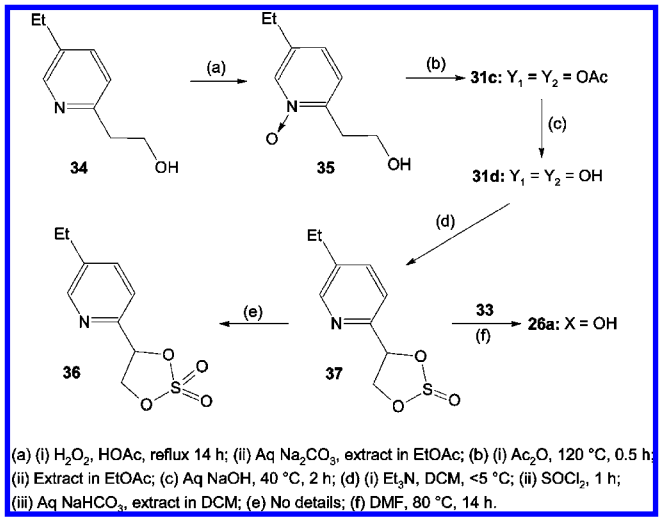
Reaction 11



(a) NBS, DMSO,H_2O, -5 °C, 1 h; (b) K_2CO_3, MeOH, 30 °C, 1 h; (c) No details; (d) (i) NaH, DMF, 30 °C, 1 h; (ii) 90 °C, 14 h.

Another sequence of reactions is described for the preparation of **26a** with a different class of intermediates being produced. Reaction 12 shows this route that starts from the pyridylethanol **34**, which is oxidised using H_2O_2 to give **35** that is isolated in 81% yield. Acetylation of **35** with Ac_2O produces the diacetoxy compound **31c** in 26% yield, and this is then hydrolysed to give the diol **31d**. This is recovered in 68% yield and then reacted with $SOCl_2$ to form the dioxathiolane **37** in 90% yield. Heating **37** with the aldehyde **33** in DMF promotes a condensation reaction to produce **26a**, which is recovered in 47% yield. The patent reports that **37** can be oxidised to **36** but no details are given.

Reaction 12



(a) (i) H_2O_2, HOAc, reflux 14 h; (ii) Aq Na_2CO_3, extract in EtOAc; (b) (i) Ac_2O, 120 °C, 0.5 h; (ii) Extract in EtOAc; (c) Aq NaOH, 40 °C, 2 h; (d) (i) Et_3N, DCM, <5 °C; (ii) $SOCl_2$, 1 h; (iii) Aq $NaHCO_3$, extract in DCM; (e) No details; (f) DMF, 80 °C, 14 h.

The patent reports details for the preparation and properties of derivatives of many of the intermediates described above. For example, details are given for analogues of **26a**, **28a**, and **29a** in which X = OMs, OTs, Br, or OSO_3H. The patent contains much more information than can be covered here and is worth reading in detail.

Advantages

The process provides a variety of novel intermediates and a new method of preparing the drug that has been successfully scaled up.

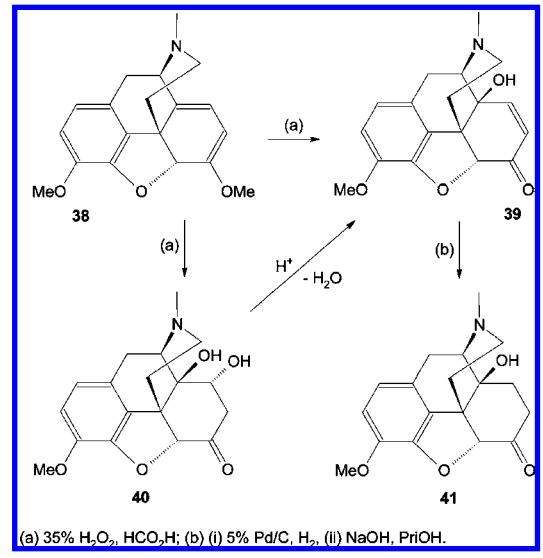
Patent Nos. U.S. 7,674,798 to 800 and 7,683,072

Assignee: Purdue Pharma L.P., Stamford, Connecticut, U.S.A

Title or Subject: Oxycodone Hydrochloride Having <25 ppm of 14-Hydroxycodeinone

Oxycodone **41** is a semisynthetic opioid analgesic used to relieve severe pain, particularly cancer pain or after-surgery pain. It is available as the HCl salt as OxyContin or OxyNorm and is obtained by the oxidation of thebaine **38**, which is derived from opium. The reaction proceeds via 14-hydroxycodeinone **39** and gives rise to several byproducts, including **40**, as outlined in Reaction 13. Compound **40** is carried through the process with **41**, and during production of the HCl salt of **41**, **40** is dehydrated to give **39**, which is present in the final product at levels up to 100 ppm. This is deemed too high, and hence, the objective of the work in the patent is to produce **41** containing <25 ppm of **39**. The claims of three of these four patents cover the formulation and packaging of a dose of **41**, whereas the claims of the fourth (7,674,800) cover the actual chemical process of producing the desired salt of **41** salt with <25 ppm of **39**. The removal of excess **39** from the HCl salt of **41** is carried out by catalytic hydrogenation at 40−85 °C and 45 psig pressure of H_2 using Pd/C catalyst. One example uses H_2O containing about 5% HCO_2H, and the process reduces the level of **39** from 154 to 6.8 ppm. Other examples use mixtures of *i*-PrOH and H_2O, and the hydrogenation process reduces the amount of **39** to <5 ppm from salts that contained up to 4000 ppm.

Reaction 13



(a) 35% H_2O_2, HCO_2H; (b) (i) 5% Pd/C, H_2, (ii) NaOH, PriOH.

The patents include details of two HPLC methods for the analysis of **39** in the salt and also contain details of the preparation of various formulations of the drug.

Advantages

The process gives a significant reduction in the level of the undesired impurity in the active drug product.

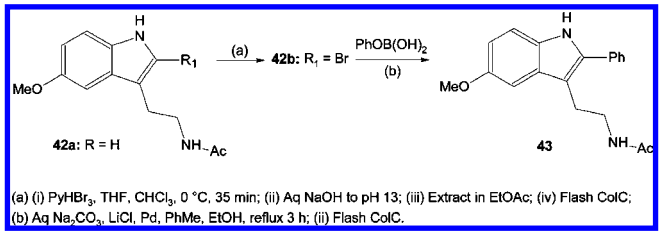
Patent No. U.S. 7,674,816

Assignee: Abraxis BioScience LLC, Los Angeles, California, U.S.A

Title or Subject: Process for the Preparation of Substituted Melatonin Derivatives and Methods of Their Use

The compounds of interest in this patent are used as anaesthetics and to treat sleep disorders such as those caused by jet lag. The main claim of the patent covers a range of over 90 novel compounds exemplified by **43** that is prepared from melatonin **42a** in a two-step process shown in Reaction 14. The first step is bromination using pyridinium tribromide ($PyHBr_3$) in THF/$CHCl_3$ at 0 °C. The reaction only takes 35 min, and the product is extracted from the mixture into EtOAc after addition of NaOH. Purification by flash ColC affords **42b** as a colourless solid in 71% yield. The bromide is then used to prepare **43** by reaction with $PhOB(OH)_2$. The reaction takes place in the presence of Pd in refluxing PhMe and EtOH containing LiCl and aq Na_2CO_3. The product is purified by flash ColC and obtained in 53% yield.

Reaction 14



(a) (i) $PyHBr_3$, THF, $CHCl_3$, 0 °C, 35 min; (ii) Aq NaOH to pH 13; (iii) Extract in EtOAc; (iv) Flash ColC; (b) Aq Na_2CO_3, LiCl, Pd, PhMe, EtOH, reflux 3 h; (ii) Flash ColC.

The bromide **42b** is used to prepare several other compounds by reaction with suitable aryl boronic acids $ArOB(OH)_2$. Examples are given where Ar = 4-fluorophenyl (yield 76%), 4-methoxyphenyl (yield 90%), 4-tolyl (yield 83%), 4-*t*-butylphenyl (yield 52%), 3-trifluoromethylphenyl (yield 56%), and 4-trifluoromethylphenyl (yield 49%). ^1H NMR data are given for the melatonin derivatives of these reactions. The patent describes tests carried out to determine the effectiveness of the new compounds and they appear to be better than melatonin itself.

Advantages

The patent provides a process for preparing number of novel compounds that are more effective than the parent compound.

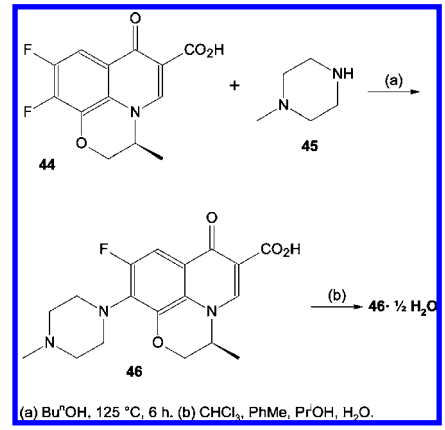
Patent No. U.S. 7,678,903

Assignee: Matrix Laboratories Limited, Bolloram, India

Title or Subject: Process for the Preparation of Levofloxacin Hemihydrate

Levofloxacin **46** is the *S*-enantiomer of the antibacterial agent Ofloxacin. The patent states that there are three anhydrous polymorphic forms of **46** designated α, β, and γ and two hydrates: a hemihydrate and a monohydrate. Processes are already known for crystallising each hydrate free of the other hydrate from aqueous EtOH but the patent claims to have surprisingly found an alternative method of crystallising the hemihydrate free from the monohydrate by adjusting the water content of the crystal slurry. **46** is obtained from **44** by heating with **45** in *n*-BuOH at 125 °C for about 6 h. The next stage is removal of the solvent under vacuum followed by addition of PhMe to remove the remaining solvent by azeotropic distillation. The mixture is then treated with a 20/80 mixture of PhMe and $CHCl_3$ at 65 °C, and these solvents are distilled off. Refluxing with *i*-PrOH then follows, and after cooling, a solid is recovered and the wet solid is dissolved in PhMe/$CHCl_3$ and treated with active C at 30 °C. Another distillation under vacuum removes the solvents, *i*-PrOH is added, and then it is distilled off. More *i*-PrOH is added, and it is refluxed followed by addition of H_2O. Cooling to 25 °C followed by filtration gives the hemihydrate that is dried, recovered in 68.5% yield, and found to have a water content of 2.54%.

Reaction 15



(a) Bu^nOH, 125 °C, 6 h. (b) $CHCl_3$, PhMe, Pr^iOH, H_2O.

This process involves a long series of steps of dissolutions and distillations using four organic solvents and water. There seems to be a considerable amount of scope for error during the process and a potential problem in the disposal of the used solvents.

Advantages

The process gives the desired hemihydrate, but may not be feasible on a commercial scale.

Patent No. U.S. 7,678,908

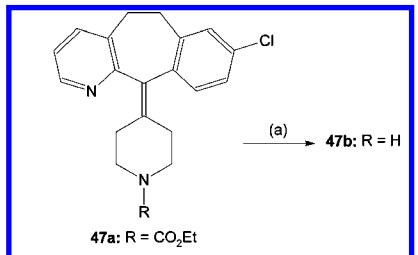
Assignee: Sun Pharmaceutical Industries Limited, Mumbai, India

Title or Subject: Process for Preparing Desaloratadine

Desaloratadine **47b** is an antihistamine drug and is available as Neoclarityn for treating seasonal hay fever and other allergic reactions. Methods for preparing **47b** are based on the alkaline hydrolysis of the ethyl ester **47a**, and the patent reports that when following these methods, HPLC analysis of the product shows a peak for an impurity that is at a higher level than the discard limit of <0.025% of the total area. The identity of the impurity is not discussed except to mention that its retention time is 0.85−0.99 relative to the retention time of **47b** of 25 ±

5 min using the HPLC method described in the patent. The patent discloses a method of preparing **47b** using acid hydrolysis of **47a** that gives **47b**, which does not contain this impurity. Reaction 16 outlines the method used to prepare pure **47b**. After heating **47a** in 50% H_2SO_4, the mixture is cooled and adjusted to pH 5 using what is described as liquor ammonia. Whether this means liquid NH_3 or NH_4OH is not made clear. An adsorbent such as charcoal may be added and then the pH is adjusted to >9.5 using the same reagent. The product is extracted into PhMe, and the crude **47b** is isolated in 96% yield with a purity of >99.0% and no sign of the impurity. Recrystallisation from a 1:14 v/v mixture of MeOH and cyclohexane affords product with purity of >99.92% and in a 90% yield.

Reaction 16



Advantages

The process gives high purity product and starts from the same starting material as alternative methods.

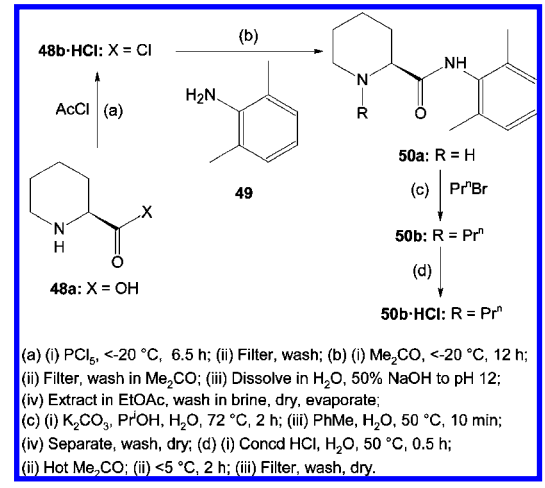
Patent No. U.S. 7,683,175

Assignee: Navina LLC, Ewing, New Jersey, U.S.A

Title or Subject: Process for Making Optically Pure L-Pipecolic Acid and Process of Making Anaesthetics and Intermediates Therefrom

L-pipecolic acid **48a** can be isolated from a variety of natural sources and is used as an intermediate in the synthesis of local anaesthetics such as levo-bupivacaine and robivacaine **50b**. The optically pure *S*-enantiomer of **50b**, or the L-form, is said to have lower cardio-toxic potential than the racemic mixture of the former and has equivalent analgesic effect, so it is clinically more beneficial. Despite the title of the patent, the claims actually refer to a process for preparing **50b** from optically pure **48a** that is obtained by resolution of the racemic acid using tartaric acid (TTA). Alternative resolution processes using either L-TTA or D-TTA are claimed to give **48a** that is only 90% optically pure. It is claimed that using these processes to obtain material with >99% optical purity is not economical. The patent describes a resolution process that is carried out in two stages that use sequentially L-TTA and D-TTA. In the first stage, the racemic acid is dissolved in EtOH/H_2O followed by L-TTA. The residual L-TTA is removed using an acid IER, crude **48a** is recovered by washing the resin with 10% NH_4OH, and the product is recovered with optical purity of about 85−90%. A second resolution is then carried out using D-TTA, and again an acid IER is used to remove the residual TTA. From 200 g of the racemic acid, 65 g of **48a** is recovered with a purity of 99.5%. The patent then describes using optically pure **48a** for the synthesis of optically pure **50a**, which is then used to prepare optically pure **50b**. Most processes for the preparation of **50a** are described as involving the condensation of **48** and **49** in the presence of a chlorinating agent such as PCl_5 or $SOCl_2$ at temperatures of 35 °C or more. These two materials are difficult to handle at such temperatures because of the liberation of acidic fumes, and so it is an objective to avoid using such conditions. Another problem identified is that the reaction solvent suggested for the condensation is a mixture of Me_2CO and *N*-methylpyrrolidone (NMP), and the presence of NMP gives a product that is difficult to isolate from the reaction medium, so it is an objective to avoid its use. The overall scheme for preparing **50b** is shown in Reaction 17; in the first step, **48a** is chlorinated using AcCl and PCl_5 at <−20 °C to produce the HCl salt of **48b**, which is recovered in 76% yield. This salt is then condensed with **49** in Me_2CO at <−20 °C, and **50a** is isolated in 71% yield. In an experiment in which both stages are carried out at 35 °C, the yield of **48b·HCl** is 36% and that of **51a** is 45%. The final step of the process is the preparation of the monohydrate of the HCl salt of **50b** that is isolated in yields up to 93%. The XRD spectra of three different samples of **50b·HCl** is provided.

Reaction 17



One of the claims of the patent covers a compound described as L-*N*-pipecolylxylidide, which is an alternative name for L-robivacaine. This is the *S*-enantiomer, and unfortunately, the formula shown in the patent claim is that of the *R*-enantiomer; there is absolutely no excuse for such a serious error in a legal document that could lead to unnecessary debate between patent attorneys.

Advantages

The process gives the desired drug product in high optical purity and does not have the acid emissions of alternative procedures.

Patent No. U.S. 7,683,205

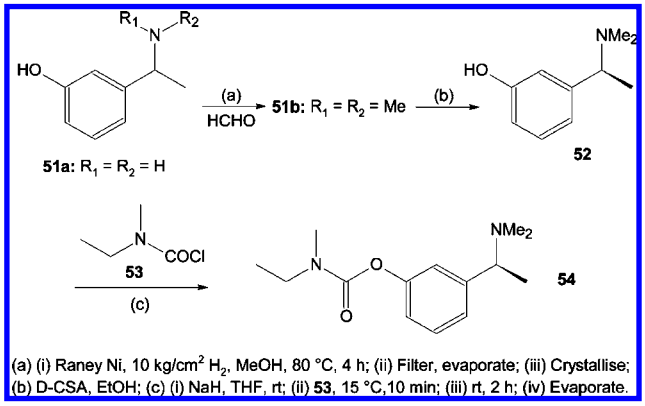
Assignee: Alembic Limited, Gujarat, India

Title or Subject: Process for the Preparation of Rivastigmine

The tartrate salt of rivastigmine **54** is available as Exelon for the treatment of mild Alzheimer's disease. Processes for preparing **54** are summarised, and the patent claims that an

improved method is required because of various shortcomings of the alternatives. The first part of the process to prepare **54** is the production of the *S*-enantiomer **52**, which is obtained by resolution of **51b** using D-camphorsulphonic acid (D-CSA). There is no mention as to whether the unwanted enantiomer of **51b** can be recovered and recycled. Compound **52** can be obtained by two methods, and one, shown in Reaction 18, starts from the aniline **51a** that is methylated using paraformaldehyde as a source of HCHO. The reaction takes place in MeOH under H_2 pressure in the presence of Raney Ni. After recrystallisation from PhMe/pet ether, the racemic methylated compound **51b** is recovered in 83 and 98% purity. The key step in preparing **54** is the condensation of the chiral phenol **52** with the carbamoyl chloride **53**. The reaction is carried out by addition of **52** to a suspension of NaH in THF to form the phenolate. To this is added **53** at 15 °C, and after 2 h at rt, the THF is removed under vacuum. Following workup with aq NaOH, the product is recovered by vacuum distillation to give **54** as a viscous oil in 80.5% yield and purity by GC of 99.6%. This is then converted to the tartrate salt using L-TTA in EtOH at 60−70 °C. After the reaction, EtOAc is added and the mixture is cooled to allow crystallisation of the tartrate salt that is recovered in 92.6% yield.

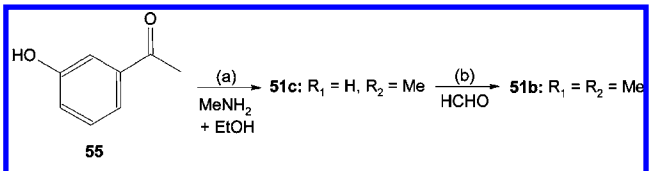
Reaction 18



(a) (i) Raney Ni, 10 kg/cm^2 H_2, MeOH, 80 °C, 4 h; (ii) Filter, evaporate; (iii) Crystallise; (b) D-CSA, EtOH; (c) (i) NaH, THF, rt; (ii) **53**, 15 °C,10 min; (iii) rt, 2 h; (iv) Evaporate.

An alternative procedure is described for the preparation of **51b**, and this is shown in Reaction 19. The process takes place in two steps, beginning with **55**, which is methylated with $MeNH_2$ using Raney Ni under unspecified H_2 pressure to give **51c**. The monomethyl product is reported as being recovered in yields from 64 to 90% and then methylated to give **51b** using HCHO, as described above. The yield of **51b** prepared by this route is 85% with 98% purity.

Reaction 19



(a) (i) Raney Ni, H_2, MeOH, 40 - 80 °C, 8- 16 h; (ii) Filter, evaporate; (iii) Wash in cyclohexane, filter dry; (b) (i) Raney Ni, 10 kg/cm^2 H_2, MeOH, 80 °C, 4 h; (ii) Filter, evaporate; (iii) Dissolve PhMe; (iv) Pet ether, crystallise.

Advantages

The process claims to give the desired pharmaceutical salt in high yield and in a cost-effective manner.

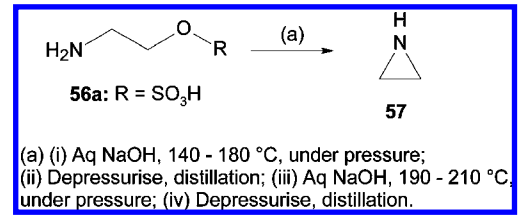
Patent No. U.S. 7,683,216

Assignee: BASF SE, Ludwigshafen, Germany

Title or Subject: Continuous Process for the Preparation of Alkyleneimines

This patent is mainly concerned with a process to produce ethyleneimine **57**. This is used in the production of polyethyleneimine polymers that are used to impart wet strength to paper. Such materials can be used in food packaging, and there are also types of the polymer that have application as fixation agents for enzymes and microorganisms. Alternative processes for preparing **57** include the catalytic dehydration of ethanolamine **56b** (R = H) or by treatment of the ester **56a** (R = SO_3H) with bases. These are claimed to require a long residence time, low yield, or poor catalyst on-stream time. An objective of the invention is to improve the energy balance and yield of making **57**, and the process disclosed in this patent is based on the reaction of the sulphuric acid monoesters of the amino alcohol **56a** with aqueous bases, as outlined in Reaction 20. The patent is not very specific on actual conditions and does not contain a formal example. It does not contain any quantities of flow rates and is written in the form of guidelines with wide ranges of temperature, pressure, and residence time. The process takes place in two stages under pressure with temperature in the first stage between 140 and 180 °C and pressure of 5−100 bar. After the first stage, the conversion to **57** is up to 90%, the pressure is released, **57** is distilled off, and the mixture is then passed to a second stage. In the second stage, under a similar pressure to the first and at temperatures from 190−210 °C, the conversion of **56** is up to 99.99%. After reducing the pressure of the second stage, the product is recovered by distillation. The product is claimed to be produced in 80% yield based **56a**.

Reaction 20



(a) (i) Aq NaOH, 140 - 180 °C, under pressure; (ii) Depressurise, distillation; (iii) Aq NaOH, 190 - 210 °C, under pressure; (iv) Depressurise, distillation.

The patent discusses the need for rapid heating of the reaction mixture and short residence times with continuous plug-flow through the reactor. It is recommended that this is carried out by using equipment with small volume and large internal surface area, therefore, spiral heat exchangers or plate heat exchangers are preferred.

Advantages

The process is claimed to give high yield and efficiency but the patent does not provide any evidence to support this.

Patent No. U.S. 7,687,632

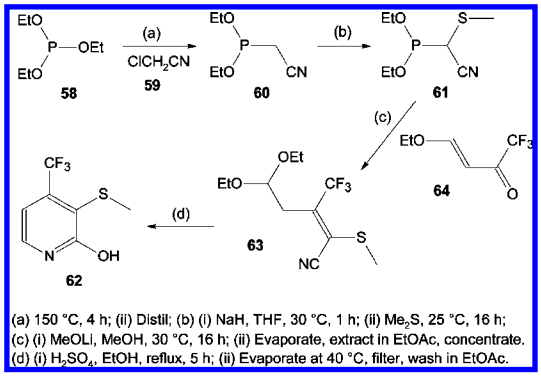
Assignee: Dow AgroSciences LLC, Indianapolis, Indiana, U.S.A

Title or Subject: Process for the Preparation of Pyridine Derivatives

The patent is concerned with the preparation of pyridine derivatives that contain an electron withdrawing group in the

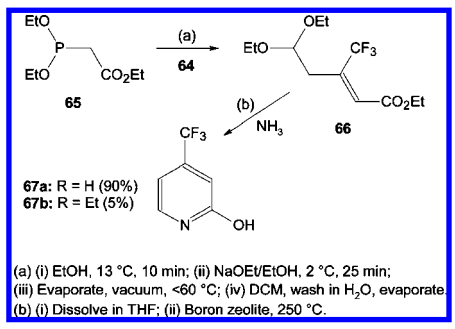
4-position of the ring, as well as substituents such as OH, EtO, or NH_2 in the 2-position. These compounds are said to be difficult to prepare because they tend to produce the 6-substituted derivative. The patent discloses a process for preparing a number of pyridine compounds involving the use of phosphorus compounds such as Wittig or Horner−Wadsworth−Emmons reagents. Reaction 21 outlines the procedure for preparing the pyridine **62** via the reagent **61**. In the first step, the reaction of **58** with **59** at 150 °C produces **60**, which is isolated by distillation in 99% yield, then treated with NaH, followed by Me_2S at 25 °C. After extraction into MTBE and evaporation, **61** is obtained in 87% yield. In the next step, **61** is reacted with **64** in the presence of MeOLi, and after workup, **63** is obtained as a mixture of *E*- and *Z*-isomers in 74% yield. Refluxing **63** in acidified EtOH followed by evaporation results in precipitation of the pyridine **62**, which is isolated in 77% yield.

Reaction 21



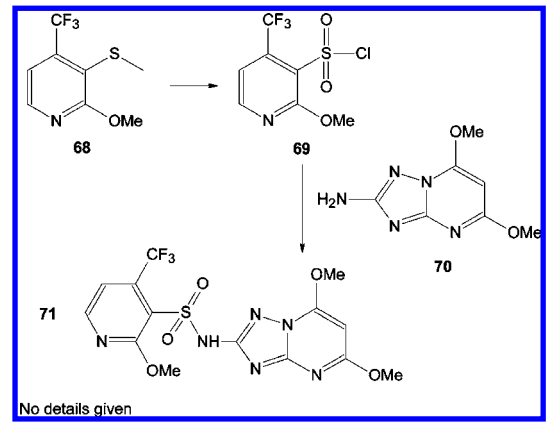
The pyridine **67a** is obtained by the process shown in Reaction 22, which begins with the reaction of **64** with the phosphonate ester **65** in the presence of NaOEt to form **66**. The product is actually a mixture of isomers that are isolated in 67% yield, and this product is used in the next step where it is dissolved in THF and passed over a boron-doped zeolite at 250 °C with NH_3 and N_2. The product is a mixture of 90% of **67a** containing 5% of **67b**. The other 5% is not identified, and the product yield is not disclosed. When this last step is carried out by dissolving **66** in EtOH, the reaction forms **67b** in 70% selectivity. Examples are also included in which the reaction is carried out in batch autoclave under a pressure of NH_3 at 230 °C for 30 min, and **67a** is obtained in 74% yield and 99% purity.

Reaction 22



The patent mentions that the pyridine compounds produced by this process can be used to prepare agrochemicals or pharmaceuticals. Specifically identified is the use of the pyridine **68** for the preparation the sulphonamide **71**, which is said to be a herbicide (Reaction 23). The process is outlined in the patent and said to proceed by the route shown where **68** is converted to **69**, which is then condensed with the triazole **70** to give **71**. Unfortunately, the preparation of **68** and its conversion to **71** are not described in the patent.

Reaction 23



Advantages

The process provides a method of preparing intermediates that would otherwise be difficult to prepare, and these can be used to prepare agrochemical products.

Patent No. U.S. 7,687,622

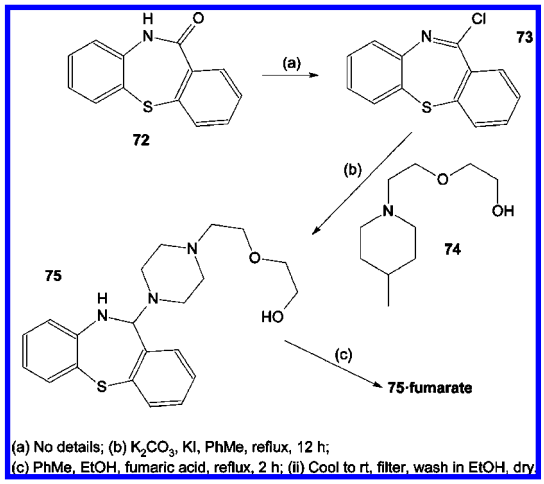
Assignee: Teva Pharmaceutical Industries Ltd., Petah Tiqva, Israel

Title or Subject: Process for Preparing Quetiapine Fumarate

The compound of interest in this patent, **75**, is an antipsychotic agent used in the treatment of schizophrenia and is available as Seroquel. The original process for preparing **75** is said to require a reaction time of 30 h and purification is by flash chromatography. An objective of the patent is to provide an improved process that takes less time and produces lower levels of impurities that can be more easily removed. The general reaction scheme used to prepare **75** that is mentioned in the patent is shown in Reaction 24. The patent claims and examples actually cover the synthesis of **75** that begins with **73**, and the conversion of **72** to **73** is not mentioned. The reaction of **73** with **74** to give **75** is carried out in the presence of a base plus an alkali halide or a phase transfer catalyst (PTC) and takes 12−14 h. The reaction scheme shows the use of the base K_2CO_3 and KI, and **75** is isolated as an oil in yields of about 78% after workup. Examples also describe the use of amines or inorganic bases such as $KHCO_3$, Na_2CO_3, and NaOH, and there are examples of using the amines Et_3N, $PhNMe_2$, and $EtPhN$*i*-Pr_2. The claims also cover the use of a silyl halide in place of an alkali halide, although the single example using Me_3SiI with Na_2CO_3

gives a very poor yield of <6% of **75**. Most of the examples do not use PTCs, and the two that do use *n*-Bu_4NBr with Na_2CO_3 and give a 78% yield of **75**. The oily product can be converted to the crystalline fumarate salt by treatment with fumaric acid in PhMe and EtOH.

Reaction 24



Advantages

The process does not require the use of chromatography and takes less time than the original method.

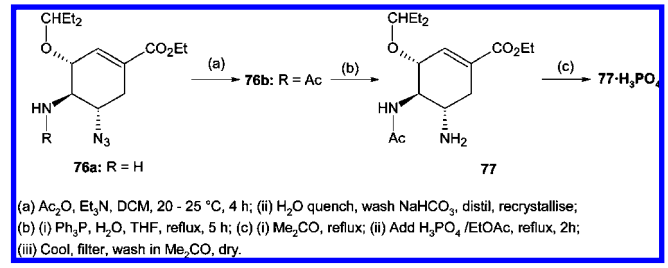
Patent No. U.S. 7,687,658

Assignee: Hetero Drugs Limited, Hyderabad, India

Title or Subject: Process for Oseltamivir Phosphate

Oseltamivir **77** is available as the phosphate salt and more commonly known as Tamiflu, the primary drug for the treatment of H1N1 avian influenza or swine flu. Two patents on this subject were reviewed last year at the height of the pandemic (*Org. Process Res. Dev.* **2009**, *13*, 829.). In some processes for preparing **77**, a key intermediate is the azide **76b**, which is obtained by acetylation of **76a** using Ac_2O in hexanes or DCM in the presence of aqueous $NaHCO_3$. The patent reports that surprisingly it has been found that this acetylation reaction can be carried out cleanly in an organic solvent in the absence of water. Reaction 25 summarises the process that begins with acetylation of **76a** by reaction with Ac_2O in DCM in the presence of an organic base such as Et_3N. The reaction takes place at rt and is then quenched with H_2O. After washing in $NaHCO_3$ and NaCl, the organic layer is distilled and the acetylated product **76b** is recrystallised from hexane and isolated in 53% yield. In the next step, **76b** is reduced to **77** by bubbling H_2S through a solution of **76b** in pyridine, and after removal of residual H_2S and solvent, the free base **77** is recovered but no yield is reported. The crude **77** is dissolved in Me_2CO and to the refluxing mixture is added H_3PO_4 in EtOH to form the phosphate salt. This is recovered in 61.8% based on **77** and has a purity of 99.8% (HPLC). An alternative procedure for reducing **76b** to **77** is by using Ph_3P in H_2O and THF, and the yield of the salt is 53.8% with a purity of 99.6% (HPLC). Despite the more hazardous nature of the procedure, the former method using H_2S is preferred.

Reaction 25



Advantages

The process is claimed to be a cleaner method of making oseltamivir, but this can only be said of the first step because the use of gaseous H_2S is not something normally viewed as a safe reagent on a commercial scale.

Keith Turner

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