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Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published During June and July 2009

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Summary

The current review of patents covers 20 from an original list of 287 that fitted the search criteria. Patents regularly claim that there is a need for a new process because of major problems with alternatives despite the fact that the alternatives may have been in successful commercial operation for many years. The real reason is often that the original patents have expired and a new market opportunity exists for the applicant. Unfortunately, this is not an acceptable reason for a patent being granted, and so at times the reasons given are somewhat exaggerated. Patents covering drugs to treat various neurological diseases and disorders are regularly published. One describes a series of tropane derivatives for treating Parkinsonism and Alzheimer's disease, and unusually the patent has some very specific claims rather than the general all-embracing ones regularly found. A method for the production of the antipsychotic drug ziprasidone is disclosed that gives a product free from the pink coloration that is often formed. The resolution of the antidepressant citalopram has been the subject of intense debate in this journal, and another patent on this topic is described and uses HCHO to improve the resolving process with L-tartaric acid. Cancer treatments are the subject of a many investigations, and several patents covering different anticancer drugs are reviewed. New processes for treating prostate cancer are reviewed with one covering bicalutamide and another covering finasteride that is also of interest for treating male-pattern baldness. Two patents describe the synthesis of different quinolinecarboxamides that are of interest in cancer treatments. One of the treatments for leukaemia is imatinib; a new process is disclosed, but it uses so many mixtures of solvents that its claims of being environmentally friendly may prove to be unsubstantiated. Topotecan is used to treat tumours, and an improvement in a hydrogenation step in its synthesis is described that is claimed to be cheaper than alternatives. The antiemetic ondansetron is used to control vomiting in patients receiving chemotherapy, and a one-pot process for its production is described. The drug gimeracil is used to prevent degradation of the anticancer drug 5-fluorouracil, and a new method for its preparation is described. Unfortunately, it uses some rather unpleasant reagents that may prove difficult to handle on a large scale. A very comprehensive patent describes a complex synthesis for the preparation of diphenylazetidinone analogues of ezetimibe that are useful in lowering blood cholesterol levels. The preferred treatment for anyone who swallows antifreeze is Antizol, and a procedure for producing ultrapure material is described that reduces the level of toxic components of this important antidote. The increase in obesity in society brings new drugs to treat the problem, and one patent describes a method of preparing *trans*-aminocyclohexane carboxylic acids that are intermediates for such drugs. The process includes a method of isomerising the unwanted *cis*-isomer. A new procedure for the oxidation of oximes to nitro groups is described using a Mo peroxo catalyst that is applicable to compounds containing other oxidisable groups. The process is applicable in the production of antithrombotic drugs. The use of microreactors is very common, and a patent describes their use in a Buchwald−Hartwig amination for the preparation of triarylamines used in electrostatic imaging systems. New methods are described for producing nitroisoureas that are intermediates for making nitroguanidine insecticides and pyridine derivatives that are useful in the preparation of fungicides. A new recrystallisation process in the production of the broad-spectrum antibiotic cefotetan is described that uses an ion-exchange technique to remove Na salts of an unwanted tautomer from the final product. An improved Oppenhauer oxidation reaction using HCHO as a hydrogen acceptor is described for the preparation of a range of aldehydes used as fragrances. Several of the patents in this collection describe experiments carried out on a kilo or multikilo scale, and this may indicate 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. 7,544,802

Assignee: Neurosearch A/S, Ballerup, Denmark

Title or Subject: Process for the Preparation of 2-Ethoxymethyl-Tropane Derivatives

The particular compound of interest in this patent, **1b**, is used in the treatment of central nervous disorders such as Parkinson's or Alzheimer's diseases. In one method for producing compounds similar to **1b** NaH is used as a base and Et_2SO_4 as ethylation agent. The patent claims that for safety reasons the use of NaH on an industrial scale is virtually impossible. In addition the process is not reproducible and does not give pure product. The new process is described as a surprising find and is shown in Reaction 1 in which **1a** is ethylated with EtBr in the presence of solid KOH and a phase transfer catalyst (PTC). The product **1b** is isolated as the citrate in 86% yield and 99.4% purity without isolation of the free base form. A comparative experiment using NaH and Et_2SO_4 gave **1b** in 70% yield. The purity of the final product is not given, but its mp of 153−155.5 °C is perhaps indicative of lower purity by this procedure.

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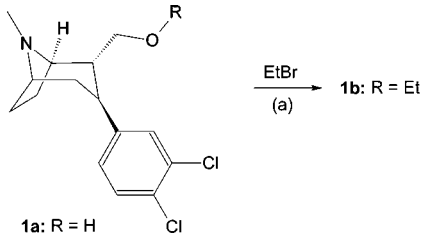
Reaction 1



(a) (i) KOH, $Bu^n_4NHSO_4$, DME, <31 °C,15 min; (ii) 60 °C, 1.5 h; (iii) H_2O, 60 °C, 1 h; (iv) Separate, evaporate; (v) Me_2CO, 55 °C; (vi) Citric acid, MeOH, 40 °C; (vii) Cool to <20 °C, 1 h, filter, dry.

Several of the claims in this patent state specific quantities of reagents and addition or reaction times to be used so that they read exactly like experimental details or operating instructions. The reason behind this is not clear, and being so specific in patent claims is very unusual.

Advantages

The process gives very high-purity product that does not require further purification, and it is also claimed to have a high space-time yield.

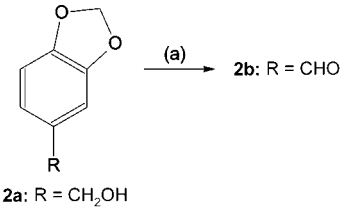
Patent No. U.S. 7,544,843

Assignee: Endura S.p.A., Bologna, Italy

Title or Subject: Process for Preparing 4,4-Dioxo-Substituted Aromatic Aldehydes

This patent describes a process of preparing aryl aldehydes such as **2b** by Oppenauer oxidation of the corresponding benzylic alcohol. These aldehydes are used in fragrances. The feature of the new process is the use of HCHO as hydrogen acceptor. It is claimed that the use of HCHO as an oxidising agent in such reactions is rare and usually ineffective. The patent reports that HCHO can be used effectively in Oppenauer reactions in the presence of common oxidation catalysts. The process for the preparation of **2b** is shown in Reaction 2 in which paraformaldehyde is the form of HCHO used. The scheme shown uses $Al(OPr^i)_3$ as a homogeneous catalyst, and this requires quenching with base. The conversion is 100%, and the GC yield of crude product is 99.3%. Alternative examples use commercially available heterogeneous catalysts such as a Zr hydrotalcite. These also give quantitative conversion with similarly high GC yield of crude product. The amount of catalyst used is about 10 mol % based on **2a** for the homogeneous method and about 25 w/w% for the heterogeneous catalyst.

Reaction 2



(a) (i) $Al(OPr^i)_3$, PhMe, reflux; (ii) HCHO, reflux, 2 h; iii) Cool, aq NaOH, separate, evaporate.

Examples are given in which alternative H acceptors are used such as PhCHO or cyclohexanone when the conversions were 95% and 70%, respectively. The GC yields were 83% for PhCHO and 58% for cyclohexanone. The reaction is also applied to 3,4-dimethoxybenzyl alcohol, and the aldehyde was obtained in 96.5% GC yield with conversion of 98.3%. The aldehyde product of this reaction is used to prepare the vasodilator Verapamil.

Advantages

This process does give excellent yields of products and is aimed at particular dioxo-substituted aldehydes presumably for specific products.

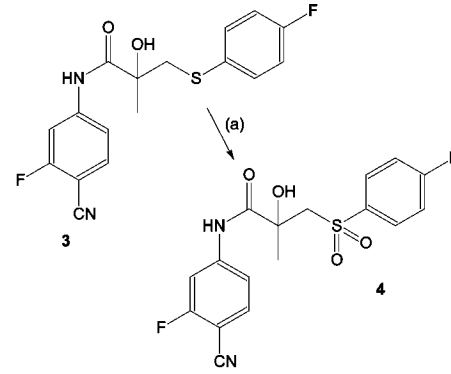
Patent No. U.S. 7,544,828

Assignee: Dabur Pharma Limited, Kolkata, India

Title or Subject: Process for the Preparation of Bicalutamide

The focus of this patent is **4**, a nonsteroidal antiandrogen used in the treatment of advanced prostate cancer. Several processes for preparing **4** are reviewed, and a key step is oxidation of the sulphide **3** to give **4** (Reaction 3). Several processes use halogenated solvents, and the oxidation uses peroxy acids. An objective of the patent is to avoid using such materials. The patent claims that all of the prior methods assert that peroxy acids are necessary for the oxidation of the sulphide. The new method avoids both halogenated solvents and peroxy acids by using $KMnO_4$ in a water or aqueous solvent system. Reaction 3 outlines the method used in which 3 equiv of $KMnO_4$ is used for the oxidation. The product is precipitated during the reaction and is relatively free from MnO_2. After completion **4** is collected and purified by extraction into MeCN followed by treatment with charcoal and recrystallisation. The yield of **4** is up to 74% with purity >99% compared with yields from alternative processes of between 41 and 67%.

Reaction 3



(a) (i) MeCN, H_2O, 45 °C; (ii) $KMnO_4$, 30 min, 45 °C; (iii) 45 °C, 5 - 8 h; (iv) Cool to 30 °C, $NaHSO_3$, H_2O, 7 h; (v) Filter, wash H_2O, dry.

Advantages

The process uses a safer and cheaper oxidising agent than alternatives, uses more environmentally friendly solvents and gives higher yields.

Patent No. U.S. 7,547,785

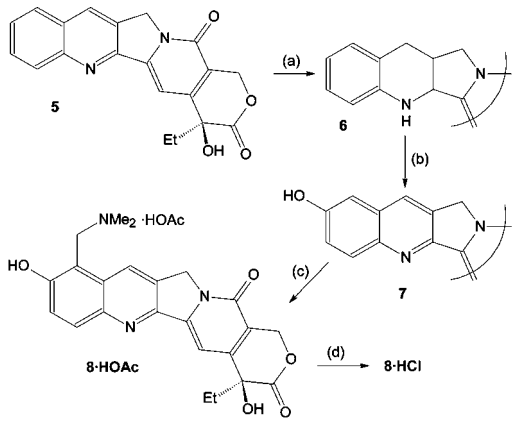
Assignee: Dr Reddy's Laboratories, Hyderabad, India and Bridgewater, New Jersey, U.S.A

Title or Subject: Process for Preparing Topotecan

Topotecan, an antitumour drug (**8**), is available as the HCl salt under the name Hycantin. **8** is a semisynthetic

derivative of camptothecin (**5**) that is extracted from the bark of the Asian tree *Camptotheca acuminate*. The patent claims that an alternative method for preparing **8** that starts from **5** involves the preparation of the intermediate **6** by hydrogenation using PtO_2 with DMSO and thiophene as catalyst moderators to inhibit overhydrogenation. A brief examination of the examples in that patent determines that they actually describe the use of Pt/C catalysts although there is reference to PtO_2. The process in U.S. Patent 5,734,056 is said to give low yield, uses expensive reagents, and is not suitable for industrial-scale production. The process described in the current patent is shown in Reaction 4 and uses PtO_2 as the catalyst in the hydrogenation of **5** with PhSMe as moderator in HOAc. The tetrahydro compound **6** is not isolated, and the reaction solution is used in the next stage where **6** is oxidised to **7** using iodobenzene diacetate. The crude wet solid is then washed in cold MeOH, hot DMF, then cold DMF/MeOH, hot MeOH, and finally cold MeOH. The final product **7** is recovered in 51% yield at 97.4% purity (HPLC). Treatment of **7** with Me_2NH and HCHO in HOAc affords the acetate salt **8·HOAc** in about 76% yield with purity of 98.9% (HPLC). In the final step the HCl salt of **8** is prepared and obtained in 99.65% purity. The HCl salt can be further purified to 99.94% by treatment with diatomaceous earth and hot Pr^iOH. The examples are all carried out on multikilo scale, thus indicating the advanced status of the process.

Reaction 4



(a) (i) PhSMe, PtO_2, HOAc, H_2, 63.7 °C, 64 psi, 6 h; (ii) 41.3 °C, 62 psi, 22 h, filter; (b) H_2O, $PhI(OAc)_2$, 27.5 °C, 18 h; (c) Aq Me_2NH, aq HCHO, HOAc, 45.3 °C, 2 h; (d) (i) 0.1 M HCl, H_2O, 15 min, filter.

The catalyst usage for the hydrogenation step in the example is 660 g of PtO_2 for a batch of 2000 g of **5**. This equates to around 283 g of Pt per kilo of **5**. The alternative process mentioned in the patent uses 500 g of 5% Pt on C for a 1000 g batch of **6**. This equates to only 25 g of Pt per kilo of **5**. The claim that the new process uses less expensive reagents does not seem true with regard to the catalyst.

Advantages

The process claims to give high yields of very high-purity product and does not require significant purification of intermediates. The process is suitable for larger-scale production.

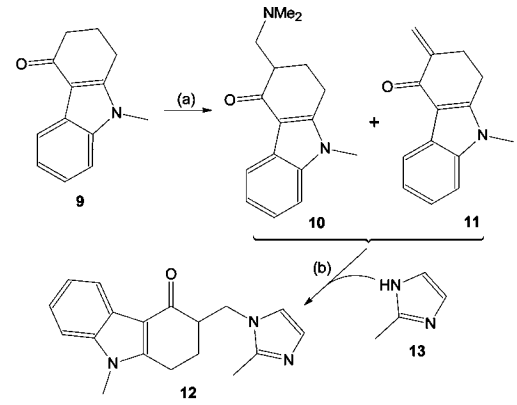
Patent No. U.S. 7,547,791

Assignee: IPCA Labratories Ltd., Mumbai, India

Title or Subject: One-Pot Process for the Preparation of Antiemetic Agent, 1,2,3,9-Tetrahydro-9-methyl-3-[2-methyl-1H-imidazole-1-yl)methyl]-4H-carbazol-4-one

The title compound **12** is known as ondansetron and is very widely used to treat the nausea and vomiting that is associated with chemotherapy in cancer treatments. Several processes for preparing **12** are reviewed in detail, and a major challenge is said to be the introduction of the 2-methylimidazole group. The original patents on the compound were first published in 1987, hence, the interest in alternative potentially viable commercial processes. The patent therefore discloses a one-pot process that does not require isolation of any of intermediates. Reaction 5 summarises the route that starts with a Mannich reaction of **9** with paraformaldehyde and $Me_2NH·HCl$ giving a mixture of **10** and **11**. The reaction is carried out in a mixture of glacial HOAc and PhMe, and according to the prior art the use of HOAc gives a sluggish reaction that produces polymeric tar-like materials. By using PhMe this is avoided, and the reaction takes only 6 h compared with 47 h when HOAc only is used. The solvents are distilled off from the reaction mixture, and the residue is used directly in the second step where **13** reacts with **10** and **11** in a 1:4 mixture of MeCN and H_2O. The crude product is filtered off, washed, and then purified by crystallisation from DMF. The yield of crude **12** is 92%, and the yield from crystallisation is 87%. There are four examples in the patent, and each describes the preparation of almost 70 kg of **12**, thus indicating the commercial status of the process.

Reaction 5



(a) (i) HCHO, $Me_2NH·HCl$, HOAc, PhMe, 105 °C, 3.5 h; (ii) Distil solvents; (b) (i) MeCN, H_2O, 85 °C, 6 h; (ii) Cool to <25 °C, filter , wash in H_2O, dry.

Advantages

The process is an efficient and commercially viable method for preparing this important drug.

Patent No. U.S. 7,547,800

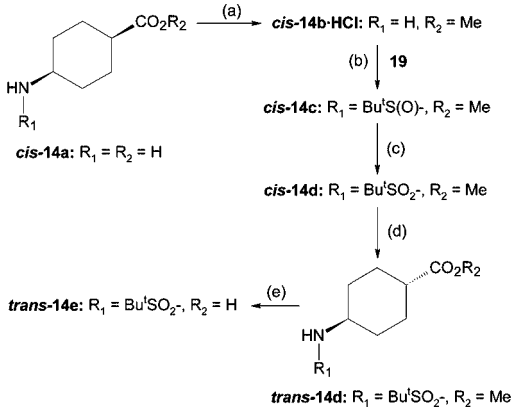
Assignee: Shionogi & Co. Ltd., Osaka, Japan

Title or Subject: Process for trans-4-Amino-1-cyclohexane-carboxylic acid Derivatives

The compounds covered by this patent are intermediates in the synthesis of NPY Y5 receptor antagonists that are of interest as antiobesity drugs. An alternative method for preparing the desired *trans*-compounds is said to afford only 40% yield because the *cis*-isomer does not isomerise smoothly even over extended reaction times. The current patent discloses a method of preparing the *trans*-isomer that includes an improved *cis*-to-*trans* isomerisation procedure.

The patent contains a substantial amount of experimental work, and because of limits on space the reaction schemes only contain pertinent details. Reaction 6 outlines the route used to prepare ***trans*-14e** beginning with the esterification of ***cis*-14a**. The HCl salt of the ester ***cis*-14b** is prepared by treating ***cis*-14a** with MeOH and $SOCl_2$. The reaction takes 3 days and gives a final yield of 88.6%. The ester salt is then treated with Bu^tSOCl, **19** in the presence of Et_3N, and the sulphinylamine ***cis*-14c** is recovered as an oil. Oxidation of this oil with H_2O_2 produces ***cis*-14d** that is obtained in 79% (based on the ester salt ***cis*-14b**). This is isomerised to give ***trans*-14d** in a yield of 70% containing 3% *cis* using NaOMe in PhMe. Base hydrolysis of the ester then gives the acid ***trans*-14e** in a yield of 87.2%. The acid can also be obtained in a one-pot process from ***cis*-14d** in 92.5% yield.

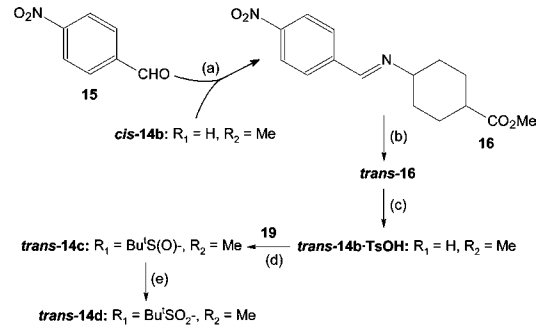
Reaction 6



(a) (i) $SOCl_2$, MeOH, rt, 78 h; (ii) Evaporate, Pr^i_2O, filter;
(b) (i) Et_3N, EtOAc, <9 °C, 1 h; (ii) Dil HCl extract in EtOAc;
(c) (i) Aq NH_4 Molybdate, DMF; (ii) 30% H_2O_2, ,43 °C, 2 h; (iii) H_2O, filter;
(d) (i) NaOMe, PhMe, HCO_2Me, rt, 1 h; (ii) Reflux, 145 min;
(e) (i) NaOH, MeOH, <12 °C, 0.5 h; (ii) 12 - 36 °C, 1 h;

An alternative route to ***trans*-14e** is also described and this is shown in Reaction 7. This also begins with ***cis*-14b** in a base catalysed condensation reaction with the aldehyde **15** to produce a *cis/trans* mixture of **16**. Treatment of the mixture with NaOMe gives ***trans*-16** in 82.7% isolated yield and this is treated with HCO_2Me and NaOMe in MeOH to give the TsOH salt of ***trans*-14b** in 94.1% yield. The conversion of ***trans*-14b** to ***trans*-14d** is performed using identical procedures to those used for the *cis*-isomers and the final yield of ***trans*-14d** is 100% based on ***trans*-14b**.

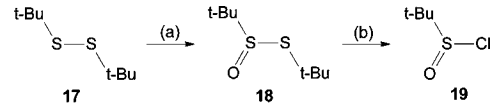
Reaction 7



(a) (i) Et_3N, MeCN, rt, 3 h; (ii) Evaporate, extract in MeOAc; (b) (i) NaOMe, HCO_2Me, MeOH, reflux, 4 h; (ii) Cool, 0 °C, filter; (c) TsOH, EtOAc, H_2O, rt, 1.5 h; (d), (e) Same as (b) and (c) in Reaction 6.

The patent also describes methods for the preparation of **19** by the method shown in Reaction 8. The disulphide **17** is oxidised with H_2O_2 and produces **18**. This reaction is carried out over a period of 8 h with the peroxide being added in three batches over about 1 h each. Between the additions of peroxide the mixture is stirred for up to 135 min. After the oxidation step both $NaHSO_3$ and NaOH are added to remove the unreacted peroxide. Finally **18** is treated with Cl_2 gas to give **19**, and this is distilled to obtain 92.1% yield based on **17**. The example in the patent for this step is carried out using 27 kg of **17**, and the chlorination stage is carried out in eight separate small batches, presumably because of equipment limitations.

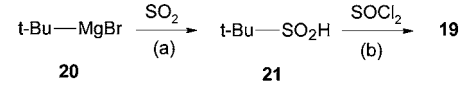
Reaction 8



(a) (i) HOAc, 35% H_2O_2, <37 °C, 8 h; (ii) Aq $NaHSO_3$, <28 °C;
(iii) 48% aq NaOH, <15 °C, 136 min; (iv) Extract in EtOAc, evaporate;
(b) (i) Cl_2, <17 °C, 145 min; (ii) <13 °C, 100 min; (iii) Distil.

An alternative small-scale example is described for the preparation of **19** that is shown in Reaction 9. The first step is reaction of the Grignard reagent **20** with SO_2 to produce **21** in 78.7% yield, and treatment with $SOCl_2$ forms **19** that is isolated as a solid of unspecified purity.

Reaction 9

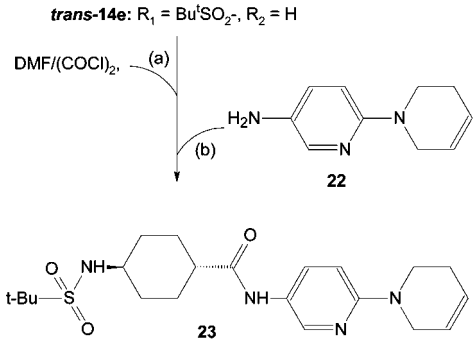


(a) (i) THF, < 20 °C; (ii) Ice, conc HCl, PhMe;
(iii) Extract, wash, dry; (b) (i) THF, 0 °C, 0.5 h; (ii) Evaporate.

Several of the examples in the patent are carried out on a kilo scale, indicating the advanced stage of development of the process. The patent also contains several laboratory-scale examples describing the preparation of amide derivatives such as **23** from the acid ***trans*-14e** by

the method outlined in Reaction 10. The acid ***trans*-14e** is initially treated with the Vilsmeier reagent formed from DMF and either $(COCl)_2$ or $SOCl_2$. The amine **22** then reacts with the intermediate acyl chloride in the presence of Et_3N to give the amide **23** that is isolated in 70% yield. Reactions using a wide range of other heteroaromatic amines and aniline derivatives are also described.

Reaction 10



(a) (i) DCM, <5 °C; (ii) rt, 1 h; (iii) Evaporate, (b) Et_3N, DCM, rt, 2.5 h;

Advantages

The process has obviously been extensively developed and may be in commercial operation to make the important intermediates.

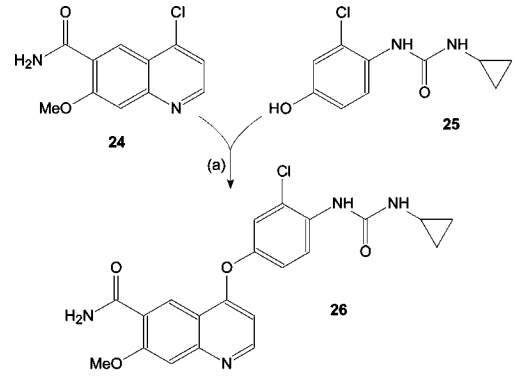
Patent No. U.S. 7,550,483

Assignee: Eisai R&D Management Co., Ltd., Tokyo, Japan

Title or Subject: Amorphous Salts of 4-(3-Chloro-4-(cyclopropylaminocarbonyl)aminophenoxy)-7-methoxy-6-quinolinecarboxamide and Process for Preparing the Same

This is the first of two patents on quinolinecarboxamides. Both patents describe compounds that have biological properties that render them of interest in the treatment of various cancers. This patent specifically mentions that the title compound **26**, is an angiogenesis inhibitor or a c-Kit kinase inhibitor. The objective of the work in this patent is to produce amorphous forms of various salts of **26** that have good physical and pharmacokinetic properties such that the salts can be used to prepare medicinal formulations. The preparation of **26**, shown in Reaction 11, is via the base-catalysed condensation of **24** and **25** and is disclosed in an earlier patent from the assignee. In the reaction the reagents are mixed together, and after 19 h portions of Me_2CO and H_2O are added periodically to the reaction mixture over a period of 6 h. After a further period of 16 h at 40 °C the product is precipitated and filtered off. After several washing steps the crystals are recovered in 96.3% yield. This step is carried out to produce 7.78 kg of **26** and hence is shown to be very efficient.

Reaction 11



(a) (i) KOBu^t, DMSO, 20 °C, 0.5 h; (ii) Heat to 65 °C; (iii) 65 °C, 19 h; (iv) Add Me_2CO + H_2O, 60 °C, 22 h; (v) Stir, 40 °C, 16 h; (vi) Filter, wash in Me_2CO/H_2O; (vii) Wash in H_2O; (viii) Wash in Me_2CO; (ix) Dry 60 °C, 22 h.

A number of crystalline salts of **26** are prepared on a mg scale including HCl, HBr, TsOH, MsH, and ethanesulphonate (**26·EtSO$_3$H**). This procedure is outlined for the latter salt as follows:

(i) Mix EtOH, $EtSO_3H$ and **26** at rt.
(ii) Heat to 65 °C to dissolve.
(iii) Cool to 22 °C and add seed crystals.
(iv) Filter and dry crystals.

A mg scale example then describes crystalline **26·EtSO$_3$H** being used to prepare an amorphous form of the salt by the following procedure:

(i) Dissolve crystalline **26·EtSO$_3$H** in EtOH and H_2O at rt.
(ii) Filter and concentrate solution by evaporation.
(iii) Freeze solution at −78 °C for 5 days to lyophilize the solid.

The amorphous **26·EtSO$_3$H** salt was characterised by XRD and IR spectra. The material was found to have a significantly increased rate of dissolution compared to the crystalline salt as measured by a rotating disk method. The rate was higher by a factor of 22.8.

Advantages

The process for preparing the crystalline material is clearly suitable for large-scale production, but it is not obvious that the process for preparing the amorphous salt has the same status.

Patent No. U.S. 7,560,557

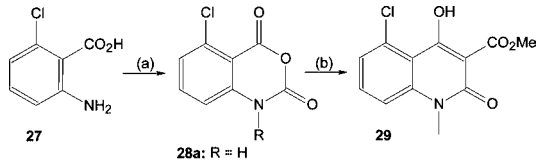
Assignee: Active Biotech AG., Lund, Sweden

Title or Subject: Process for the Manufacture of Quinoline Derivatives

This is the second patent on quinolinecarboxamides with an example being **31**. The patent discusses difficulties in preparing such compounds because of degradation of intermediates, leading to impurities such as **28b** in the final drug product. Reaction 12 shows the first stage of the process that is the production of the ester **29**. This begins with the formation of **28a** by treatment of **27** with $ClCO_2Et$ followed by MeCOCl. **28a** is isolated in 97% yield and then used directly in the next stage where it is treated with NaH followed by MeI. After

further treatment with NaH and then $H_2C(CO_2Me)_2$, the product is precipitated from cold water using HCl, and the final isolated yield of the ester **29** is 70%. The ethyl analogue is prepared in the same manner.

Reaction 12

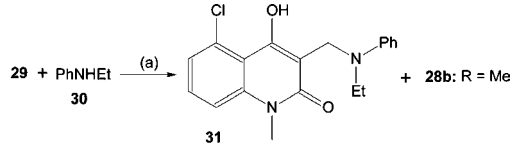


27 **28a:** R = H **29**

(a) (i) $ClCO_2Et$, 1,4-dioxane, reflux 1 h; (ii) Cool 50 °C, MeCOCl; (iii) 10 h, 50 °C; (iv) Filter, wash PhMe, dry;
(b) (i) Me_2NCOMe, 5 °C; (ii) NaH; (iii) MeI; (iv) rt, 18 h; (v) Remove MeI;
(v) NaH, $H_2C(CO_2Me)_2$, 85 °C, 3 h; (vi) Cool, H_2O, 5M HCl to pH<2; (vii) Filter.

The next stage of the process is the N-amidation of **29** to the give carboxamide **31** by reaction with **30** (Reaction 13). The key feature of this step is the choice of solvent. The claims of the patent specify using an alkane or cycloalkane with a bp between 80 and 200 °C. The solvents specified in the claims are *n*-heptane, *n*-octane, or decalin. The example uses *n*-heptane that gives a yield of **31** of 98% compared with only 90% using PhMe. The reason for this is attributed to the higher solubility of both the ester **29** and product **31** in heptane than in PhMe. In addition to higher yield using heptane there is also a lower level of the main impurity **28b**. Using PhMe the level of **28b** is 0.54% and with heptane the level is down to 0.03%.

Reaction 13



(a) (i) n-heptane, 6.5 h; (ii) Cool to rt, filter, wash, dry.

Advantages

The process gives excellent yields with lower impurities than alternative procedures.

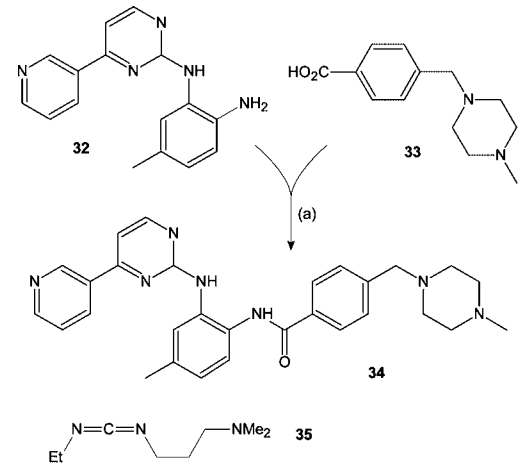
Patent No. U.S. 7,550,591

Assignee: Chemagis Ltd., Bnei Brak, Israel

Title or Subject: Imatinib Production Process

Imatinib **34** is used to treat leukaemia and is available as the mesylate under the name Gleevec. The patent summarises some of the known processes for producing **34** and states that there is a need for a less hazardous process that is more environmentally friendly and has fewer steps. Reaction 14 shows that **34** is produced by coupling the amine **32** and the benzoic acid **33** that is carried out in the presence of a carbodiimide such as **35** or its Cl salt. The reaction takes place at ambient temperature in aqueous THF. Work-up involves extraction into a 4-to-1 mixture of DCM and EtOH. The free base product is obtained in 76% yield at 99.3% purity by HPLC. This is then crystallised from DCM/EtOH to afford 99.8% pure base in 72% yield. The base can then be converted to the mesylate salt by treatment with MsOH in 4-methylcyclohexanone.

Reaction 14



32 **33** **34** **35**

(a) (i) THF/H_2O, rt, 20 min; (ii) **35**·**HCl**, rt, 1 h; (iii) DCM, EtOH, aq NaOH to pH 8 - 9, rt; (iv) Separate, extract in DCM/EtOH; (v) Concentrate, cool <5 °C, filter, wash in EtOH, dry.

The process to make the base involves the use of three solvents and water with one of the solvents being DCM. In addition a further solvent is needed to prepare the mesylate salt. The use of so many solvents that finish as a mixture is likely to give rise to costly waste-disposal issues.

Advantages

The process is claimed to have fewer steps than alternatives, but it is not known how the two reactants are prepared.

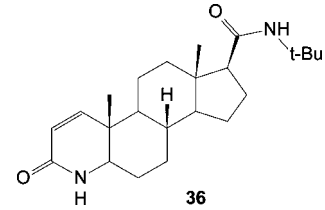
Patent No. U.S. 7,550,593

Assignee: Cipla Limited, Mumbai, India

Title or Subject: Process for the Preparation of Finasteride Form I

Finasteride **36** was initially developed to treat prostate enlargement but has also been studied as a cure for male-pattern baldness.

Finasteride



36

A new synthesis for **36** has previously been reviewed (Org. Process Res. Dev. 2007, 11, 663.). The new patent states that alternative syntheses of **36** use solvents that are difficult to remove from the crystalline product. The solvents mentioned are THF, EtOAc, PhMe, Pr^iOAc, and glacial HOAc, and the objective is to avoid using these materials. There are two processes that are described, and one consists of the following steps:

(i) Dissolve **36** in DCM.
(ii) Distill off the solvent and add water until vapour temperature is 80 °C.

(iii) Cool to rt and stir for 24 to 30 h.
(iv) Filter, wash in water, and dry.

The purity of Form I of the final product is 99.7%, but the solvent level is not disclosed.

An alternative method is to dissolve **36** in MeOH or DCM. Neutral alumina and activated charcoal are then added to remove any colour. After filtration, the solvent is replaced by an antisolvent such as PhMe or Pr^iOAc. Cooling and filtration provide the Form I crystals with purity of about 99.8%. The three examples in the patent all use 10−11 kg of **36**, thus indicating the commercial status of the procedure.

The patent claims that using PhMe and Pr^iOAc cause difficulties in alternative processes, and yet these are used in one version of the process.

Advantages

The use of water has operational and environmental benefits, although removing it is sometimes not easy.

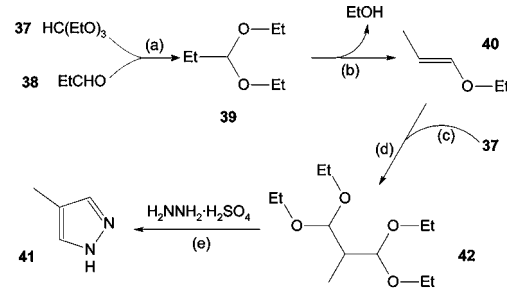
Patent No. U.S. 7,553,863

Assignee: Paladin Laboratories (Barbados) Inc., Barbados

Title or Subject: Ultrapure 4-Methylpyrazole

The title compound **41** is marketed under the brand name of Antizol as a specific antidote for the treatment of poisoning by ethylene glycol, the main constituent of antifreeze. **41** is also used to treat methanol poisoning. Unfortunately some of the synthetic routes used to prepare **41** also form byproducts that are themselves toxic such as pyrazole, hydrazine, or $PhNO_2$. Originally the accepted level of pyrazole was 0.5%, but the FDA has recently reduced this to 0.1%. Thus, there is a need to prepare **41** in a highly pure form, and the patent discloses a route to fulfill this need. The route used is shown in Reaction 15 and proceeds in four stages. In the first stage **37** and **38** are condensed in the presence of NH_4NO_3 to form **39** that is recovered by distillation in 81.6% yield. In the next step around 1 w/w% of MsOH is heated with **39**, and $(2\text{-Et-hexyl})_2NH$ is added while N_2 is bubbled through the mixture to help remove the EtOH. Following a water wash the liquid is dried and then distilled to give the ether **40** in 77.5% yield containing <0.01% $EtOCH{=}CH_2$. This ether can create problems in the subsequent stage, and the patent states that commercially available **40** cannot be used since the level of $EtOCH{=}CH_2$ is too high. In the next stage **40** is added to a mixture of **37** that has been treated with $BF_3{\cdot}Et_2O$. The reaction exotherm is controlled, and then the mixture treated with solid Na_2CO_3 for 1 h. After filtration **42** is recovered as a clear yellow-brown liquid by fractional distillation in 80% yield. The last step is carried out in sterile water containing $H_2NNH_2{\cdot}H_2SO_4$. After workup with 50% aqueous NaOH and $NaHCO_3$ the mixture is extracted with EtOAc, and the desired product is obtained as a clear, pale-yellow liquid by vacuum distillation in 84% yield based on **42**. GC analysis showed it contained <0.1% pyrazole and 10 ppm H_2NNH_2.

Reaction 15



(a) (i) NH_4NO_3, EtOH, < 36 °C, 1 h; (ii) rt, 16 h; (iii) Aq Na_2CO_3 to pH 7.5; (iv) Separate, distil; (b) (i) TsOH, $(2\text{-Et-hexyl})_2NH$, 160 °C; (ii) Wash H_2O, dry; (c) $BF_3{\cdot}Et_2O$, <25 °C; (d) (i) <25 °C, 1 h; (ii) Na_2CO_3, 25 °C, 1 h; (iii) Filter off solid, distil filtrate; (e) (i) Sterile H_2O, 80 °C, 3 h; (ii) 40 °C, remove volatiles; (iii) H_2O, $(HOCH_2)_2$, cool to 3 °C; (iv) Aq NaOH to pH 4 - 6, < 30 °C; (v) Aq $NaHCO_3$ to pH 7.0; (vi) Extract in EtOAc, dry, distil.

The patent does not make any comment about the required purity of the reactants **37** and **38**. The purity of **38** is especially important because it often contains MeCHO that would give problems in the condensation reaction.

Advantages

The process meets the recently prescribed lower levels of impurities in this important emergency medicine.

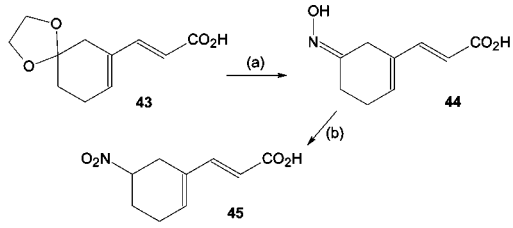
Patent No. U.S. 7,553,987

Assignee: Schering Corporation, Kenilworth, New Jersey, U.S.A

Title or Subject: Synthesis of 3-(5-Nitrocyclohex-1-enyl)acrylic Acid and Esters Thereof

The title compound **45** is an intermediate in the synthesis of compounds that are thrombin receptor antagonists (TRAs). Such TRAs are used to treat thromboses and inflammatory and atherosclerotic disorders. The patent discusses methods of making nitro compounds by oxidation of oximes and concludes that the known processes are not suitable for use with compounds that contain other functional groups. In particular any double bonds should not be oxidised or isomerised during the reaction. Hence, the objective is to convert an unsaturated oxime to an unsaturated nitro compound, and this is achieved by the use of a process using a Mo VI/VII peroxo catalyst. Reaction 16 outlines the method used to prepare **45** by oxidation of **44** that is produced from **43**. The first step is the removal of the protective group in **43** giving a ketone that is converted to the oxime **44**. This is isolated in 77% yield and then oxidised to **45** using an equimolar amount of Na_2MoO_4 in basic solution. The crude product **45** is isolated in a 69% yield and then purified by one of two methods. These both involve stirring **45** in $MeCN/H_2O$ under either acidic or basic conditions. The purified product is recovered in >88% yield with purity of 97−98%.

Reaction 16



(a) (i) TsOH, H_2O, 20 °C, 20 h; (ii) NaOH to pH 6.5, 0 °C, (iii) $H_2NOH{\cdot}HCl$, 0 °C;
(b) $Na_2HPO_4{\cdot}H_2O$, H_2O, aq NaOH, $Na_2MoO_4{\cdot}2H_2O$, MeCN, 50 °C;
(ii) 30% H_2O_2, 50 °C, 2 h; (iii) Aq Na_2SO_3, 20 °C, 0.5 h; (iv) Evaporate;
(v) H_2O, 5 °C; (vi) 37% HCl to pH 3, filter, wash, dry.

The patent claims that the reaction uses catalytic amounts of the Mo peroxo compound, but this is not the case in the patent examples. The oxidation uses an equimolar amount of the Mo complex to the oxime plus a 50% excess of H_2O_2. Hence, the cost of the catalyst is significant, and the disposal of the heavy metal residue is an additional problem and expense.

Advantages

The oxidation reaction is selective, but the catalyst cost and cost of disposal of the wastes could be high.

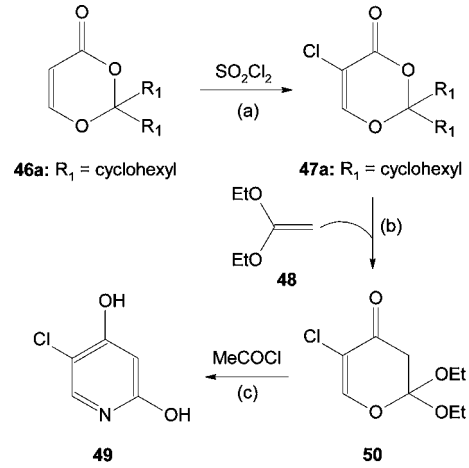
Patent No. U.S. 7,557,216

Assignee: Taiho Pharmaceutical Co., Ltd., Tokyo, Japan

Title or Subject: Process for Production of 5-Chloro-2,4-dihydroxypyridine

The title compound **49** is available as gimeracil and is an inhibitor of an enzyme that biodegrades the antitumour agent 5-fluorouracil. Several known routes for preparing **49** are summarised, and they are all said to be unsuitable for large-scale operation. The patent discloses that a pyrone such as **50** is a valuable intermediate in the production of **49**, and hence, the first aspect of this patent is the production of **50**. There are only two claims in this patent, and the second claims the novel pyrone **50** and its analogues. The reaction begins with the chlorination of the dioxinone **46a** to give **47a** using SO_2Cl_2. This is isolated as an oily substance in 65.9% yield. **47a** is then treated with the ketene acetal **48** in dry xylene to produce the pyrone **50**. This can be isolated 77.7% yield or used in the next step where it is dissolved in EtOH and treated with MeCOCl. After 1 h the mixture is concentrated, and more EtOH added followed by aqueous NH_3. After further concentrating the mixture, water and HOAc are added, and the product precipitates from solution. The yield of **49** based on **47a** is 72.4%. An alternative route using **46b** (R_1 = Me) is also described in which **47b** is produced and then reacted with $CH_2{=}C(OMe)OSiMe_2Bu^t$ in place of **48**. This gives the analogue of **50** that is converted to **49**. The yields of the intermediates and of the final product are lower by this route. The applicability of this process for commercial use cannot be assessed because the examples in the patent are only carried out on gram scale, and some of the reagents may not be suitable for large-scale handling.

Reaction 17



(a) (i) Pyridine, ice-cool, 0.5 h; (ii) rt, 2 h; (iii) H_2O,
(iv) Extract in DCM, dry, concentrate;
(b) (i) Xylene, reflux, 40 min; (ii) Cool rt, concentrate;
(c) (i) EtOH, rt, 1 h; (ii) Aq NH_3, EtOH, rt, 2.5 h;
(iii) Concentrate, H_2O, HOAc, rt, 1 h; (v)Filter, wash H_2O, dry.

Advantages

The process provides a new route to the desired product and also introduces a new intermediate but uses reagents such as SO_2Cl_2 that may cause handling difficulties on an industrial scale.

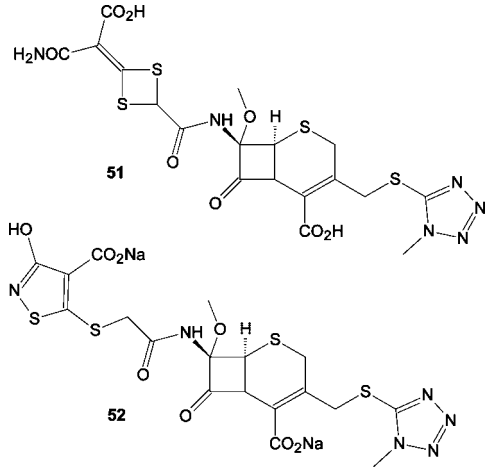
Patent No. U.S. 7,560,545

Assignee: ACS Dobfar S.p.A., Tribano, Italy

Title or Subject: Process for Obtaining Cefotetan with High Yield

Cefotetan **51** is a broad-spectrum antibiotic that is used for prophylaxis and treatment of bacterial infections. It was first produced in 1983 by Yamanouchi Pharmaceutical, and the story of its process development has been reported (Org. Process Res. Dev. 2004, 8, 915.). The Dobfar patent refers to an earlier process, from the same assignee, for preparing **51** that is admittedly rather lengthy with poor productivity. The current patent is said to be an improvement that is simpler and highly productive. The full details of this process are not covered in this patent whose focus is on the recrystallisation of **51** and the removal of the Na salt **52**. The purification process is an ion-exchange method that is based on the capacity of **52** to bind to Al^{3+} ions and produce an insoluble salt that can be easily removed. These ions can be provided in the form of $AlCl_3$ or neutral Al_2O_3. It is also claimed that Fe^{3+} or Cr^{3+} ions can be used although no examples are provided. The process is carried out by dissolving **51** containing **52** in water at pH 7.0−7.2 at <5 °C. This solution is then contacted with the Al^{3+} source to precipitate the Al salt of **52**. The filtrate is acidified to pH 1.3−1.5 to precipitate **51**; after drying, **51** is isolated in >99.0% purity with <0.2% of **52**. The neutral Al_2O_3 can be recovered and reused, thereby reducing waste, and the patent describes an example in which >300 kg are recovered. Hence, this would suggest that the process has been operated on a commercial scale.

Cefotetan



51

52

Advantages

The process is an efficient and simple method of purifying the desired compound that is suitable for large-scale operation.

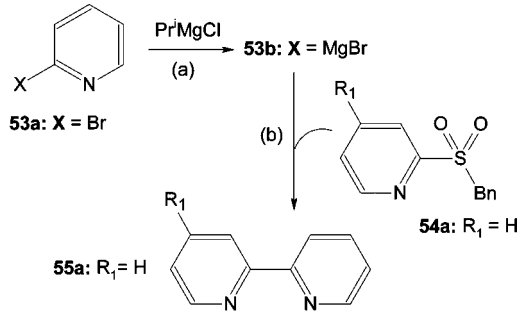
Patent No. U.S. 7,560,563

Assignee: Kuraray Co., Ltd., Kurashiki-shi, Japan

Title or Subject: Process for Producing 2-Substituted Pyridine Derivatives

The compounds of interest in this patent are said to be useful in the production of an unspecified antifungal agent. Methods for producing 2-substituted pyridine derivatives are said to require the use of expensive transition metal catalysts (TMCs) to give good selectivity and produce wastes that are difficult to dispose of. Without TMCs the selectivity is reduced because of the formation of bipyridine derivatives via homocoupling reactions. The key feature of the process is the reaction of a sulphonyl derivative such as **54a** (R_1 = H) with an organometallic compound such as **53b**. Reaction 18 outlines the preparation of **55** that take place at ambient temperature. The product is isolated as a solid by column chromatography (ColC) in 91% yield; also prepared by this method in 89% yield is 2,3-bipyridine from **54a** and 3-bromopyridine.

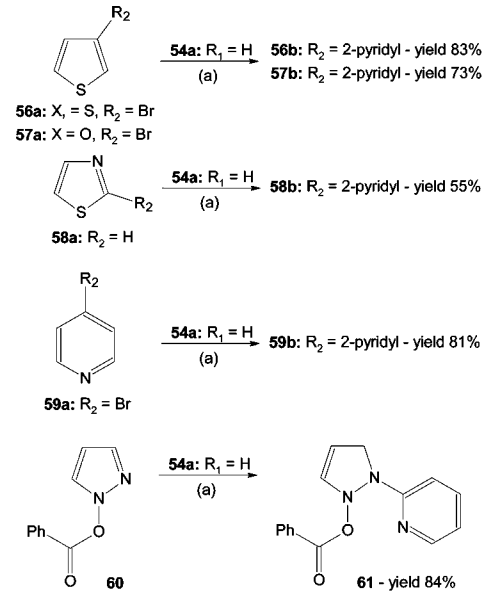
Reaction 18



(a) THF, rt, 1 h; (b) (i) THF, rt, 5 h; (ii) Pr^iOH; (iii) H_2O; (iv) Extract in EtOAc; (v) Concentrate; (vi) ColC.

A number of other 2-substituted pyridine derivatives are prepared in varying yields using Li organometallics. Reaction 19 shows a selection with the yields obtained. These include the thiophenes **56** and **57**, thiazoles **58**, and pyrazole **61**. These are all prepared using BuLi at a temperature of −78 °C and the appropriate halo compound which is obviously more costly than using the Grignard reagent at ambient temperature.

Reaction 19



(a) (i) BuLi/hexane, THF, -78 °C, 0.5 to 1 h; (ii) 3 h, -78 °C (ii) Pr^iOH; (iii) H_2O; (iv) Extract in EtOAc; (v) Concentrate; (vi) ColC

The patent gives brief ^1H NMR data for the compounds.

Advantages

The process gives high yields of the 2-pyridines without using TMCs, and if using the Grignard method is applicable, then there is no extra expense of low-temperature reaction.

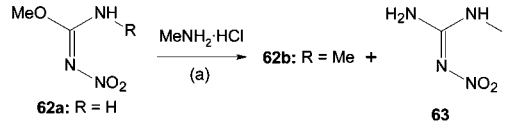
Patent No. U.S. 7,560,593

Assignee: Mitsui Chemicals Inc., Minato-Ku, Japan

Title or Subject: Process for Producing Nitroisourea Derivatives

This patent discloses details for preparing compounds that are intermediates in the production of nitroguanidines that have insecticidal activity. Alternative processes for producing nitroguanidine derivatives are said to produce mercaptans as byproduct, thereby causing environmental and health problem as well as being uneconomical. Reaction 20 shows the new process for the preparation of **62b** by reaction of **62a** with $MeNH_2 \cdot HCl$ in a solution of about 25% NaCl in water at 20 °C. After 8 h about 0.09 mol % of $NaHCO_3$ (based on **62a**) is added to the mixture, and it is stirred for a further 16 h.The product is isolated in yields of 61−67% with a purity of 99%. The use of $NaHCO_3$ suppresses the formation of byproduct such as the nitroguanidine **63**. When using $NaHCO_3$ the amount of **63** formed was 4 mol %, and without it 14 mol % was formed. The combination of $NaHCO_3$ and another inorganic salt in the procedure gives high productivity and removes environmental and health issues. The patent also describes the preparation of the *O*-ethyl analogue in yields of 70−73% by the same procedure.

Reaction 20



(a) (i) NaCl, H_2O, 20 °C, 8 h; (ii) $NaHCO_3$, 20 °C, 16 h; (iii) Concd HCl; (iv) Cool 0°C, filter, wash in H_2O, dry.

Advantages

The process as described is efficient and avoids producing hazardous byproduct, but there is no indication as to how **62a** is produced.

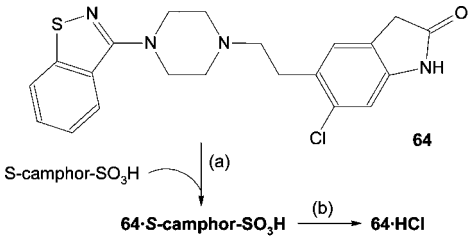
Patent No. U.S. 7,563,794

Assignee: Dipharma Francis S.r.l., Baranzate, Milan, Italy

Title or Subject: Ziprasidone Free from Colored Impurities and a Process for its Preparation

The HCl salt of ziprasidone **64** is available as Geodon and is used as an antipsychotic. Despite the purity of **64** and its salts generally being >99.9%, they frequently have a pink coloration. Hence, one objective of the patent is to provide a method of producing **64** that is free from the pink-coloured impurity. The HCl salt is also highly hygroscopic when the particle size is <85 μm, although whether this is because it is made via milling is not mentioned. A second objective is to prepare the anhydrous salt that has larger particles and is not so hygroscopic. The patent describes a procedure for the formation of the *S*-camphorsulphonate (*S*-Cam) salt of **64** that is then converted to the HCl salt (Reaction 21). The *S*-Cam salt is novel and is the subject of the single claim in the patent. The formation of the HCl salt is carried out by adding seeds of the anhydrous salt **64·HCl** very quickly to the *S*-Cam salt along with 37% HCl in MeOH. The experiments described only use 60 g of **64** to which is added 5.5 g of **64·HCl** seed in 10 s. The stirrer speed is then increased from 80 to 120 rpm, and more HCl is added. The final product is isolated, having a purity of 99.9% and is free from coloured impurities; the particle size is about 150 μm. The patent reports that by varying the addition time of the second quantity of HCl the particle size distribution can be changed with larger particles being formed if the time is increased.

Reaction 21



(a) (i) MeOH, 65 °C; (ii) Cool 5 - 20 °C, filter, wash in MeOH, dry; (b) (i) MeOH, H_2O, 71 °C; (ii) Stir 80 rpm, seed with **64·HCl**, 37% HCl, MeOH; (iii) Stir 120 rpm, 37% HCl, MeOH, 2 h; (iv) Cool 20 °C, filter, wash Me_2CO, dry.

Advantages

The process gives the required quality product on the small scale, but whether the results are reproducible on the large scale is debateable. The addition of seeds over a very short time to a commercial batch could be the critical factor.

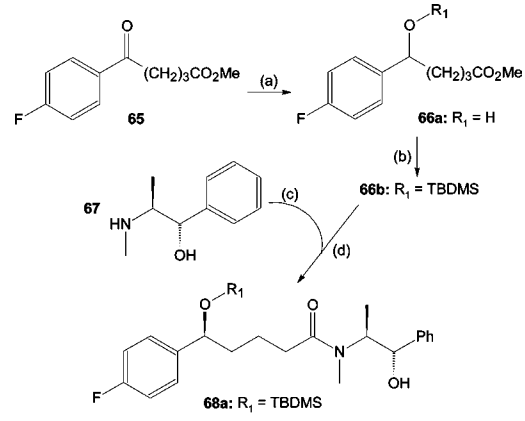
Patent No. U.S. 7,563,888

Assignee: Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany

Title or Subject: Process for the Preparation of Diphenyl Azetidinone Derivatives

The title compounds are useful in reducing high cholesterol levels in the blood, and one commercially known example is ezetimibe **76b** ($R_1 = R_4 = H$, $R_5 = F$). Reference is made to a number of methods for preparing the azetidinone compounds that use toxic reagents or have low stereospecificity and the objective therefore is to avoid these problems. The patent does not describe the actual synthesis of **76b** itself although the claims cover the synthesis of the general class of diphenylazetidinones. This patent is extremely comprehensive and covers a great deal of chemistry with some detailed experimental examples. This review concentrates on the synthesis of the compound **76a** that is presumably a precursor to **76b** although the patent does not describe how this is accomplished. For ease of understanding, the synthetic route to **76a** has been divided into several sections, and Reaction 22 outlines the first of these to produce **68a**. The first step is the stereospecific reduction of **65** to give **66a** that is carried out using the Corey oxazaborolidine reagent R-Me CBS. **66a** is obtained as a yellowish-oil in 92% purity with ee of 96%. In the next step the OH group is protected by conversion to the TBDMS derivative **66b**. This ester is used in the next step as an oil of 73% purity and is reacted with lithiated **67** to produce the amide **68a** as a pale-yellow resin in 92% yield.

Reaction 22

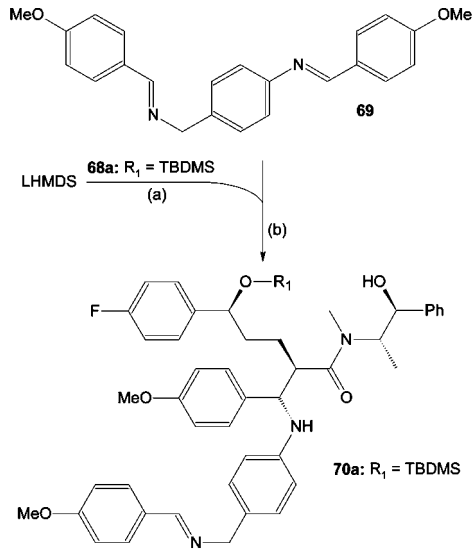


(a) R-Me CBS, DCM, -5 °C, 3 h; (b) Imidazole, TBDMS-Cl, DCM, <27 °C; (c) (i) LiCl, THF, <2 °C; (ii) BuLi/hexane, 5 °C; (d) THF, rt, 24 h.

The next stage of the synthesis is shown in Reaction 23 and very briefly outlines the production of **70a** by reaction of **68a** with the bis-imine **69** in the presence of LHMDS in a multistage reaction. This reaction takes place at −78 °C, and before addition of **69** there are difficulties with stirring; as a result, the reaction temperature is raised to −50 °C for a short time before being cooled again. The mixture is then warmed to 0 °C at which time **68a** is added. The crude product contains a

mixture of 57% of the protected Mannich product and 8% deprotected compound with an overall yield of 83%.

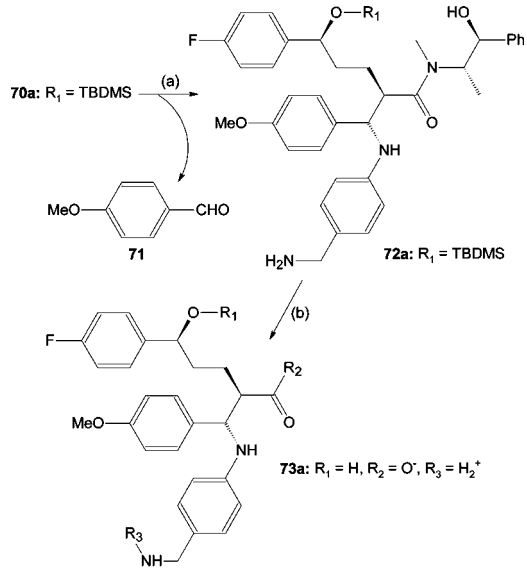
Reaction 23



(a) (i) THF, -78 °C, 1h; (ii) 0 °C, 15 min; (iii) rt, 5 min; (b) THF, 0 °C, 1h.

The next step is the complete deprotection of **70a** that is carried out in HOAc/NaOAc buffered to pH4.5 to give **72a** as shown in Reaction 24. Anisaldehyde **71** is also produced at this point and must be completely removed before work-up when base is added. Failure to remove **71** allows **70a** to be reformed. The product **72a** is obtained in 68% yield and is shown to be a mixture of two rotamers of the amide function in the ratio 2:1. ^{1}H NMR data are given for each rotamer. The amide **72a** is then hydrolysed by heating with NaOH in EtOH and **73a** is obtained in 72% yield with a purity of 95%.

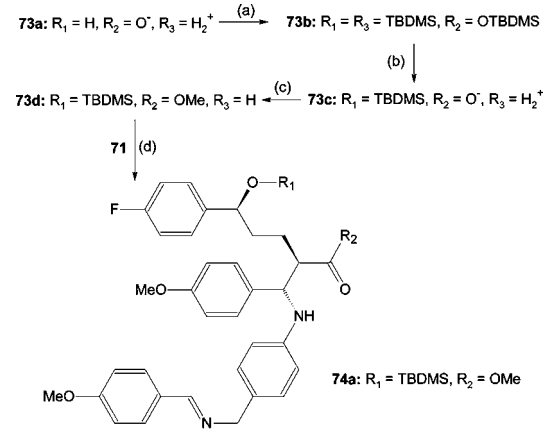
Reaction 24



(a) 20% HOAc/NaOAc, MeOH, rt, 0.5 h; (b) NaOH, EtOH, 75 °C, 19h.

Protection of the three acidic H atoms in **73a** is then carried out to give **73b** using TBDMS-Cl (Reaction 25). The protective groups are then removed from the amino and acid groups in **73b** to give **73c** that is treated with CH_2N_2 to give the methyl ester **73d**. The product is purified by flash chromatography and isolated in 79%. The final reaction in the stage is condensation of **73d** with **71** in PhMe to produce **74a** as a viscous yellow oil in 96% yield.

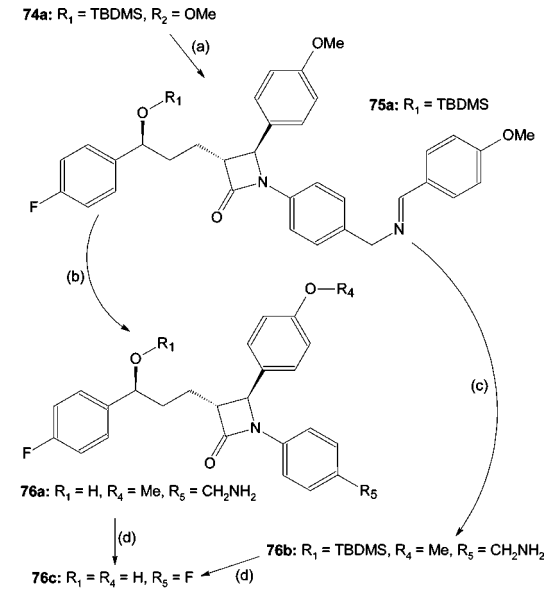
Reaction 25



(a) Imidazole, TBDMS-Cl, DCM, reflux, 4 h; (b) HOAc/MeOH, rt, 18 h; (c) CH_2NH_2/Et_2O, MeOH, rt; (d) PhMe, 30 °C

The next stage is the key cyclisation step and is carried out using LHMBDS in THF to form the β-lactam **75a** that is isolated as a yellow solid in 94% yield and is shown in Reaction 26. The imine protection and OH are removed using H_2SO_4 to give **76a** complete conversion. The patent also describes that by using HOAc the OH protection remains intact to give **76b**.

Reaction 26



(a) LHMDS, THF, -20 °C, 1 h; (b) 50% H_2SO_4, 1,4-dioxane, rt, 35 min; (c) HOAc, H_2O, MeCN, rt, 1 h; (d) No details in patent.

There is a great deal more information covered in the patent than reviewed here, but space restrictions prevent inclusion. The interested reader is strongly encouraged

to consult the patent. There are examples describing the preparation of **65**, **69**, and several intermediates that are analogues to those shown in the above reaction schemes. Many of the examples are carried out on mg scale, and several of the products are oils, so handling on a large scale may present difficulties.

Advantages

The process does provide a stereospecific route to the desired product and generally avoids the use of toxic reagents although CH_2N_2 is used in one stage. The large number of steps makes it difficult to evaluate the commercial potential of this route since the examples are carried out on mg scale.

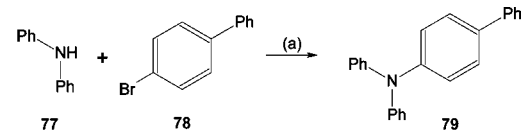
Patent No. U.S. 7,563,932

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

Title or Subject: Microreactor Technology For Buchwald–Hartwig Amination

This patent describes the preparation of triarylamines that are used in electrostatic imaging systems. The methods used to produce these materials are summarised and said to involve several steps and give a product of low purity, thereby necessitating costly purification steps. Such materials are clearly manufactured on a large scale, but this patent focuses on carrying out the reaction in a microreactor using a Pd catalyst. The use of microreactors is commonplace in process optimisation and screening when they can produce large amounts of useful data relatively quickly. One of their shortcomings is their intolerance to particulate matter; hence, they are not usually used when precipitates are formed. The patent states that the Buchwald synthesis of arylamines is known to precipitate salts, and so the use of microreactors to study this reaction would not be expected. The patent discloses an improvement in the reaction that avoids the formation of precipitates and so can be carried out in a microreactor. The preparation of **79** is shown in Reaction 27 and involves the reaction of a Pd/phosphine catalyst in a mixture of one or more solvents. The solvents used in the patent examples are PhMe and 1,3-dioxolane although the claims also cover the use of the ionic liquids with these two solvents. The ionic liquids mentioned are trihexyltetradecylphosphonium bis(trifluoromethylsulphonyl)amide or trihexyltetradecylphosphonium saccharin although no examples are described in which these materials are used. The first step in the process is the formation of the Pd catalyst system by reaction of a solution of PBu^n_3 in PhMe with $Pd(OAc)_2$ in 1,3-dioxolane followed by addition of $NaOamyl^t$ to give solution A. A second solution (B) is prepared by dissolving about 1.13 mol/L each of **77** and **78** in 1,3-dioxolane. The microreactor is maintained at 70 °C, and the two solutions A and B are pumped to the reactor using HPLC pumps at 1 mL/min each. The residence time in the microreactor is 23.5 min, and over a period of 18 min the conversion averaged 92%. Details of the recovery of **79** are not described, and so the final product yield is not known.

Reaction 27



77 78 79

(a) $Pd(OAc)_2$, PBu^n_3, $NaOamyl^t$, PhMe, 1,3-dioxolane, 70 °C, 23.5 min.

Advantages

The procedure gives a high conversion in a continuous process, but whether it is applicable to large-scale use is not known.

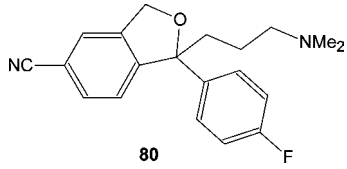
Patent No. U.S. 7,566,793

Assignee: Synthon BV, Nijmegen, Netherlands

Title or Subject: Process for Resolving Citalopram

Citalopram **80** is an antidepressant, and the racemic HBr salt is marketed under the brand name Celexa. The *S*-enantiomer is the more potent of the two isomers, and since the original patents have expired, interest in improved methods of resolution or synthesis has increased and a new synthesis has been reviewed (Org. Process Res. Dev. 2007, 11, 663.). More recently there has been a dispute over published methods for the resolution of **80** (Org. Process Res. Dev. 2009, 13, 23.). These papers do indicate the difficulty of resolving **80** and perhaps suggest that a practical solution to the problem has not been found. The latest patent on the subject may add more fuel to the fire and describes a process for the production of pure *S*-enantiomer from the racemic mixture by formation of the L-tartrate salt. L-tartaric acid (LTTA) is very widely used as a resolving agent for a whole range of mixtures, but it is claimed that it has not previously been applied successfully to resolving **80**. The inventive step claimed in this patent is the use of HCHO in conjunction with LTTA that greatly improves the resolution process. The precise mechanism for the improvement is said to be unclear, and one possible suggestion is that a hemiacetal is formed from the OH group on the LTTA and HCHO. This may occur before or after salt formation. An alternative proposal is that HCHO modifies the solvent and provides solubility discrimination between the tartrate diastereomers. It is claimed that the HCHO can be used in any convenient form although the examples use the standard 37% aqueous solution that contains up to 15% MeOH. The procedure is to stir a solution of LTTA, **80**, and HCHO in H_2O then seed and stir overnight at 4 °C. The solids are recovered and suspended in 37% HCHO, and the LTTA salt of the *S*-enantiomer is obtained with ee of 78.3%. A second treatment with HCHO solution increased the ee of the salt to 95%, and after a third treatment the ee increased to 97%. The tartrate salt can be converted to the free citalopram by treatment with base. One example describes the production of about 9 kg of the *S*-oxalate salt. Initially the tartrate salt is treated with concd NH_3 and the base recovered as an oily mass. Treating this with $(CO_2H)_2$ in EtOH solution at 5 °C gives the *S*-oxalate. This at least shows that the process can be scaled up successfully. There is no mention of recovery of the *R*-enantiomer and its racemisation to improve yield.

Citalopram



80

Keith Turner

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Advantages

The process claims to provide an effective method of resolving the racemate and thus of obtaining high yields of the more active enantiomer.

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