Organic Process Research & Development **2010,** *14,* 311–322

Highlights from the Patents

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

Summary

The present review covers 22 patents from an original list containing 226 and includes some patents having a considerable amount of information. The expiration of a patent for any well-known drug or chemical usually results in a number of patents describing new processes. Some of these may be less efficient or ecologically less desirable than the original. An example is a new one-step method of producing the antibiotic cefoxitin. Although the process does not require the isolation of intermediates, it does involve three chemical transformations and is extremely complex with considerable material handling. Prazoles are used to treat ulcers, and although a patent describes a new process for preparing a series of these compounds the yields are low. A method of avoiding the use of column chromatography in separating isomers of an indazole derivative contains conflicting details that suggest there may be no improvement. A new process is described for the preparation of ropinirole that is used to treat Parkinson's disease. The process is claimed to be environmentally friendly and in one stage uses NaCN that is more toxic than KCN that is used in an alternative process. There are patents that do seem to provide improvements. Rasagiline is another drug used to treat Parkinsonism, and a patent describes methods for detecting low levels of chloride impurities that degrade the drug. The preparation of nitro compounds can be a challenge, and a method of nitrating imidazoles without using strong acids is described. Another patent on imidazoles describes two novel compounds that are intermediates for an unspecified pharmacologically active agent. The antibiotic aztreonam is used when patients are allergic to penicillin, and a new one-pot process is described. Rapamycin is an antibiotic that is used in organ transplant surgery, and a new process for its production is disclosed that has been scaled up and is suitable for large-scale operation. Florfenicol is a veterinary antibiotic, and in an improvement of an established process, less acylating agent and catalyst are used to produce higher-purity product. A reduction in the usage of expensive reagents is described in a patent for the preparation of ziprasidone, an antipsychotic drug used to treat schizophrenia. Another patent focussing on reducing the usage of toxic or expensive reagents covers the antiepilepsy drug levetiracetam. A key step in the process is an intramolecular allylation reaction. An interesting method is described for producing the free base of the anticancer drug temozolomide from the HCl salt. The method takes place under acid conditions since the base is unstable at pH >7. A selective method for preparing Li derivatives of fluorochlorobenzenes is described that are then used to prepare a boronate that is an herbicide intermediate. Another patent covering boronates describes the production of heteroaryl compounds containing boronate substituents. These useful intermediates are prepared using iridium catalysts containing bidentate bipyridyl ligands. Producing acetate esters using Ac_2O is commonplace, but its use on a commercial scale is apparently not viable for preparing a butenyl ester. However, the addition of KOAc to the reaction and an improved purification scheme provides a commercially viable procedure. A new process is described for preparing aminopentadienoate compounds that are UV absorbers. The new method uses Ti alkoxides as transesterification catalyst and gives higher yields than processes using alternative routes. The use of chlorofluorocarbons is now a rarity, and any process that still uses them is under threat. A patent describes how to prepare a series of perfluorovinylether monomers that does not use CFCs. Improvements in the production of the drug sildenafil are disclosed in which reduced levels of byproducts are formed. This is done by reducing the amount of a cyclic amine that is used as a proton scavenger. The patent also describes a water adduct of the citrate salt. A very detailed and comprehensive patent describes a process for the synthesis of a DPP-IV inhibitor. The key feature of the patent is the selective introduction of a chiral centre into a desired drug molecule. Some of the patents describe experiments carried out on a kilo or multikilo scale, thus suggesting 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. 7,598,394

Assignee: Allergan Inc., Irvine, California, U.S.A

Title or Subject: Process for the Synthesis of Imidazoles

This patent has two claims, and these cover the novel imidazole **5** that is an intermediate for an unspecified pharmacologically active compound. The process used for the preparation of **5** is shown in Reaction 1 and begins with the formation of the formamide salt **2** that is reacted with **3a** to form **3b** that is isolated by distillation in 78% yield. Treatment of **3b** with Pr^i_2NH followed by $POCl_3$ produces the isonitrile **3c** that is purified by distillation and obtained in 55% yield. The formation of the imidazole is carried out by reaction of **3c** with the nitrile **6** in the presence of $KOBu^t$. The reaction produces a mixture of **4** (26%) and **5** (71%) that is refluxed with KF to convert **4**

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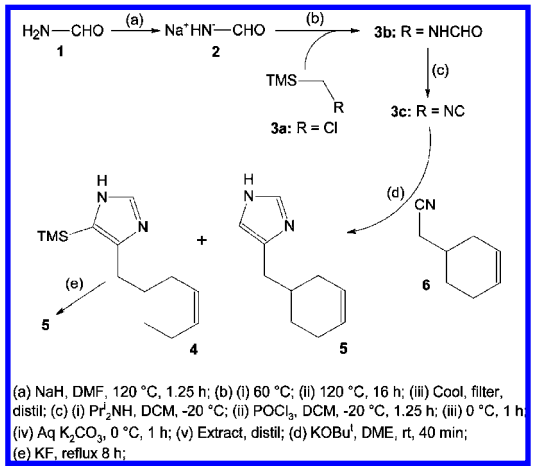
to **5**. The product is purified by flash column chromatography (ColC) and then crystallisation to give 52% yield of **5** in 100% purity by HPLC.

Reaction 1



The process is also used to prepare analogous cyclopentene derivatives and alternative nitriles to **6** to give a range of cyclohexenyl imidazoles. However, the patent specifically excludes the use of a number of nitriles that have benzylic or allylic H atoms at the α-position to the CN group. This is presumably to avoid infringing other patents.

Advantages

The process is applicable to synthesis of imidazoles that are intermediates for the synthesis of specific pharmaceutical agents.

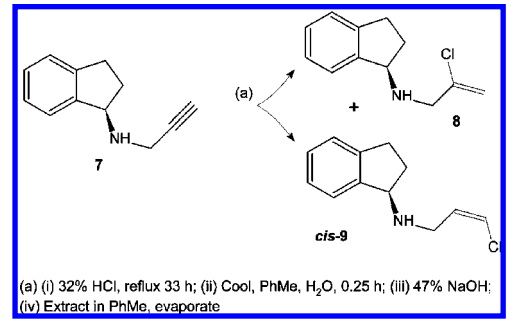
Patent Nos. U.S. 7,598,420 and U.S. 7,619,117

Assignee: Teva Pharmaceutical Industries Ltd., Petach-Tiqva, Israel

Title or Subject: Rasagiline Formulations and Processes for Their Preparation

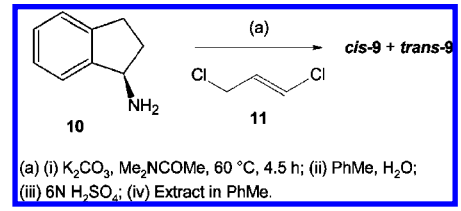
These patents cover the preparation of validated pharmaceutical formulations of rasagiline, **7**, that is used as the mesylate salt to treat Parkinson's disease and is available as Azilect. An earlier patent from Teva on the isolation of **7** has been reviewed (*Org. Process Res. Dev.* **2009**, *13*, 669). The two new patents report that under certain conditions, where even low levels of Cl^- ion are present, the triple bond in the mesylate salt of **7** is susceptible to chlorination to give **8** and *cis*-**9**, but *trans*-**9** was not formed. One objective of the work is to produce formulations of **7** that contain very low levels of Cl ions. It is also an objective to devise a suitable method for detecting the level of chlorinated compounds that could degrade the formulated drug product. The current patent claims a process for producing a validated batch of **7** that contains >0.7 and <30 ppm of any isomer of the compound **8** or any of the corresponding salts. These amounts are determined by LC/MS:MS, and the analytical method used is also part of the patent claims. The patent describes the manufacture of the various optical and geometrical isomers of **8** including ^{13}C-labeled compounds. Reaction 2 shows the method used to prepare **8** and *cis*-**9** by acid hydrolysis of **7**. The product of the reaction is a dark-brown oil that is subjected to ColC to give a 15% yield of **8** and 13% yield of *cis*-**9**, both pure. Treatment of **8** with HCl/EtOH in Et_2O produced the HCl salt of **8** in 90% yield. ^1H NMR data are given for this salt.

Reaction 2



The patents also describe the preparation of *cis*- and *trans*-**9** by reaction of **10** with a *cis/trans* mixture of **11** (Reaction 3). These isomers are separated by ColC, and the *trans*-isomer is converted to its HCl salt for which ^1H NMR data are given. The HCl salts of **8** and **9** can be converted to their mesylate salts by neutralisation followed by dissolution in Et_2O and addition of MsOH.

Reaction 3



The patents describe the use of GC/MS, HPLC/UV, and LC/MS:MS methods for the determination of the chlorinated compounds in **7**.

Advantages

The patents provides a method of detecting undesirable impurities that can degrade the drug during storage.

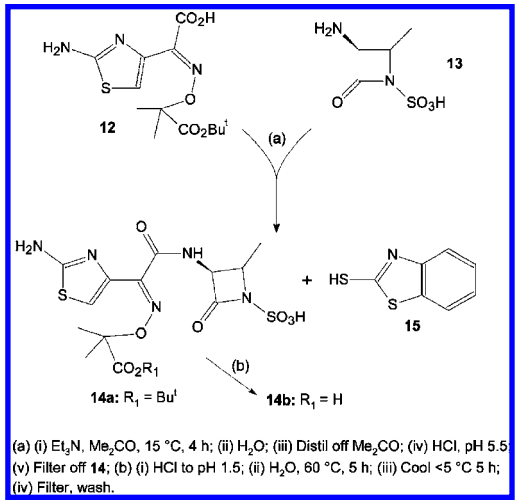
Patent No. U.S. 7,601,832

Assignee: Sicor Inc., Irvine, California, U.S.A

Title or Subject: Process for Making Aztreonam

This patent describes a one-pot process for making aztreonam **14b** a monobactam antibiotic that is useful if patients are allergic to penicillins. The process is summarised in Reaction 4 and involves the condensation of the azetidine **13** with **12** in the presence of Et_3N to give the Bu^t derivative **14a** and **15** as a byproduct. **12** is added in three portions over a period of 4 h after which time the reaction is quenched in H_2O. After removal of the solvent the mixture is acidified to precipitate **15** that is filtered off. Acid hydrolysis of **14a** at 60 °C produces **14b** that is recovered as a wet solid and purified by heating with NH_4OAc in EtOH. The final isolated yield of **14b** is about 50%. Alternative processes for preparing **14b** are described and said to use reagents that are toxic and expensive. One of these processes involves the same chemical reaction shown in Reaction 4 and uses different several solvents and requires the extraction of **14a** using EtOAc and H_2O. This procedure complicates the process, increases the production time, and reduces plant capacity.

Reaction 4



Advantages

The new process allows manufacture of the product to be carried out in a single vessel and improves the yield by avoiding the need to extract the intermediate from the reaction mixture.

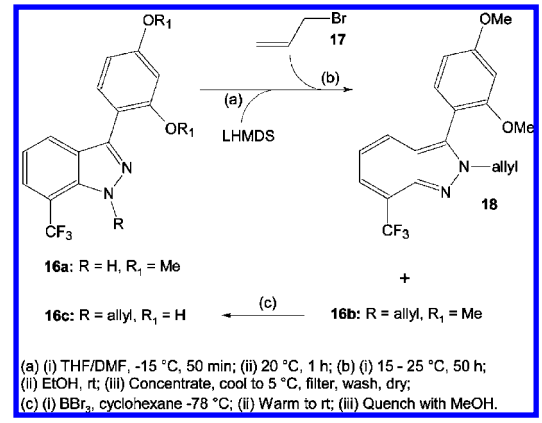
Patent No. U.S. 7,601,847

Assignee: Wyeth, Madison, New Jersey, U.S.A

Title or Subject: Preparation and Purification of 4-(Indanazol-3-yl)phenols

This patent is concerned with the production of diol compounds such as **16c** that are used to treat various inflammatory diseases. These compounds can be produced via the dimethoxy intermediates such as **16a** as shown in Reaction 5, but the process usually gives a mixture of two isomers, **16b** and **18**, in equal proportions. The separation of these compounds is typically by ColC that is expensive on a commercial scale. The objective of the patent is to develop an alternative method that does not require the use of ColC and hence is commercially attractive. The first stage in the process is to treat **16a** with a base followed by addition of **17** as the alkylating agent to give a mixture of the isomers **16b** and **18**. The ratio of **16b** to **18** is affected by changing the solvent and the base with LHMDS being the preferred base. The preferred solvent in this step is THF plus a polar solvent such as DMF. The conversion of **16a** is as high as 100% with selectivity to **16b** up to 79%. An anhydrous alcohol such as EtOH is added to this reaction mixture and the solution is then reduced in volume by about 50% and cooled. The precipitate is filtered off, and according to the experimental details the solid obtained contains both **16b** and **18**. However, the patent claims that the precipitated solid is **16b**, and logic would also suggest that this should be the case. If the process does not include a method of separating the isomers, then the process is no better than the alternative that uses ColC. The last stage of the process is the hydrolysis of **16b** in the presence of BBr_3 at −78 °C to give **16c** that is purified by recrystallisation from MeOH/H_2O.

Reaction 5



Advantages

The process gives higher selectivity of the desired precursor isomer and claims to avoid the use of ColC to separate the isomeric mixture.

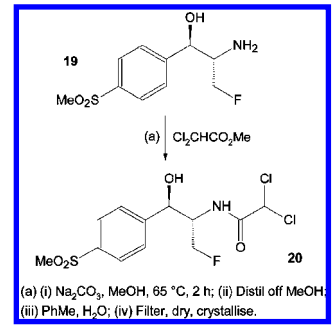
Patent No. U.S. 7,601,869

Assignee: Aurobindo Pharma Inc., Hyderabad, India

Title or Subject: Process for the Preparation of Florfenicol

Florfenicol **20** is a broad-spectrum antibiotic that is used in veterinary medicine. Alternative processes for the preparation of **20** are described that are based on the acylation of a fluoroamine compound. These are said to have various shortcomings such as giving low yield or low-purity product. The new process is claimed to provide high-purity **20** by improvements made to the usual preparative method. The route is shown in Reaction 6 and involves the reaction of the fluoroamine **19** with a 2.5 mol equiv (ME) of the Cl_2CHCO_2Me in the presence of an inorganic base such as anhydrous Na_2CO_3 (0.1 ME). The product is isolated in a yield of 79%, after crystallisation, with purity of 99.73% (HPLC). The patent states that an alternative process uses 5 ME of **20** and 1 ME of Et_3N as base to catalyse this reaction.

Reaction 6



Advantages

The process is very efficient using half the acylating agent and significantly less of a catalyst than alternative procedures.

Patent No. U.S. 7,605,256

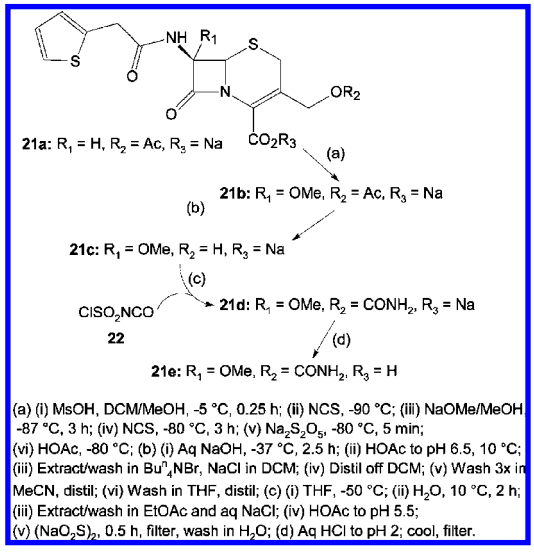
Assignee: ACS Dobfar S.p.A., Tribiano, Italy

Title or Subject: Process for Preparing Sodium Cefoxitin

Cefoxitin **21e** is a cephalosporin antibiotic that is administered by injection and used for the treatment of serious infections

caused by a variety microorganisms. There are a number of methods of preparing **21e** and these are said to require the separation of intermediates with resulting losses in yield. The route disclosed in the patent is summarised in Reaction 7. The experimental details in the patent are extremely lengthy with a considerable number of steps involved; thus, the scheme shown is abbreviated for clarity. The process uses six organic solvents plus various aqueous solutions and several different reagents during extraction and workup. Despite this the patent claims that **21e** can be prepared in a single step without separation of intermediates. The process starts from sodium cefalotin **21a** that is treated with NCS and NaOMe in MeOH at −80 °C to form **21b**. Deacetylation using NaOH gives the alcohol **21c**, and in the next stage **22** is used at −45 °C in a carbamoylation reaction to give **21d**. Acidification of **21d** with HCl produces the acid **21e**, and this is isolated by crystallisation in 48% yield with purity of 94.4% (98.6% on anhydrous basis). An alternative method is described that proceeds via initial silylation of **21a** and gives the final product in about the same yield and purity. In the conversion of **21c** to **21d** it is claimed that it is also possible to use Cl_2NCO_2Et in place of **22**, but no experimental details are provided.

Reaction 7



Advantages

The process claims to provide a single-step method of making **21e**. Whilst it is true that intermediates are not isolated, this statement is a considerable exaggeration based on the fact that three chemical transformations reactions are involved, and the experimental procedure described in the patent is extremely complex.

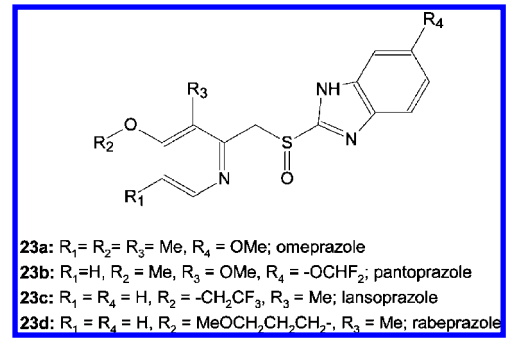
Patent No. U.S. 7,605,268

Assignee: Dipharma Francis s.r.l., Baranzate, Italy

Title or Subject: Process for the Preparation of Pyridine Compounds

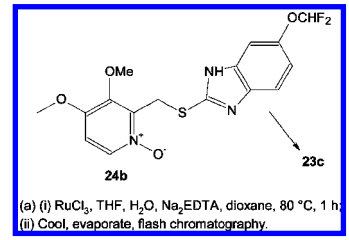
The subject of this patent relates to the group of compounds known as prazoles that inhibit gastric secretions and are used to treat ulcers. The patent describes a process that is applicable to the preparation of these compounds and gives examples for omeprazole, pantoprazole, lansoprazole, and rabeprazole. The structures of these compounds are shown below.

Prazoles



Alternative processes for the preparation of prazoles involve the oxidation of a thioether intermediate to a sulphinyl derivative. This can result in overoxidation and the production of sulphonyl compounds. This reaction has been the subject of previously reviewed patents (*Org. Process Res. Dev.* **2008**, *12*, 146). The current patent proposes to prepare the desired prazoles from novel pyridine-*N*-oxide compounds such as **24b** and **24d**, and the single claim of the patent covers these two molecules. The patent does not describe their preparation, and the focus is on their conversion to the prazoles by treating the pyridine-*N*-oxides with a Ru(III) catalyst. Reaction 8 shows the preparation of pantoprazole **23b** from **24b**. No yield is given for this reaction. Other experiments are described for preparing **23a**, **23c**, and **23d** from the respective *N*-oxides using Ru catalysts under similar conditions. The yield for preparing **23c** is 50%, and that for **23a** is only about 10%.

Reaction 8



Advantages

The process does offer an alternative method of preparing the desired prazoles, but the yield does not appear to be very high.

Patent No. U.S. 7,608,711

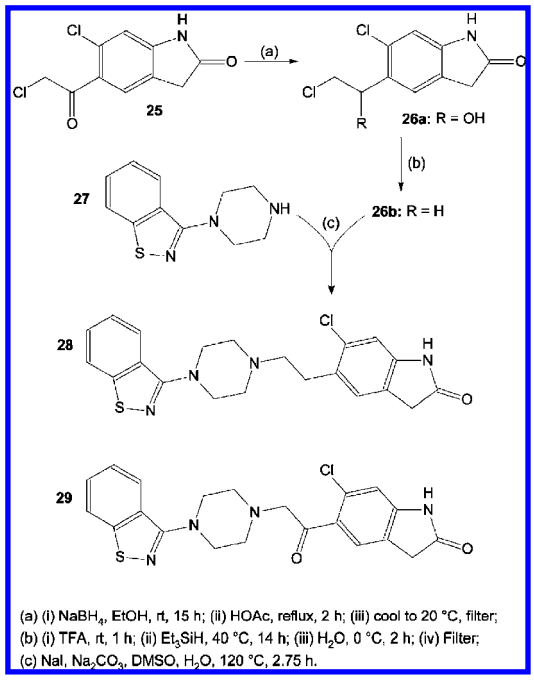
Assignee: Dipharma Francis Srl., Baranzate, Italy

Title or Subject: Process for the Preparation of Ziprasidone

Ziprasidone **28** is an antipsychotic drug used to treat schizophrenia. The original preparation of the compound is by the reaction of the amine **27** with **26b** that is obtained by reduction of the chloroketone **25**. The current patent states that the original method for the reduction of **25** to **26b** is carried out using TFA and Et_3SiH. These are described as expensive reagents, and an additional problem is caused by the reaction of **25** with **27** to form the impurity **29**. This is difficult to remove from **28**, and hence, it is essential that all traces of **25** are removed from **26b** before reaction with **27**. In the original process this is carried out by the use of excess of TFA and Et_3SiH, and clearly this adds to the process costs. The new process minimises the amount of these expensive reducing

reagents by carrying out the reduction in two steps. In the first step the alcohol **26a** is formed by reduction of **25** using the inexpensive $NaBH_4$ and isolated in 88% yield. The novel alcohol **26a** is then reduced in a second step using TFA and Et_3SiH, and the product **26b** is obtained in quantitative yield. The coupling of **26b** with **27** takes place in DMSO containing 10% H_2O and Na_2CO_3. The free base **28** is isolated in 72% yield and can be converted to its HCl salt. The patent claims that the final product **28** contains <100 ppm of the impurity **29**.

Reaction 9



Advantages

The process reduces the amount of expensive reagents and improves the purity of the final product.

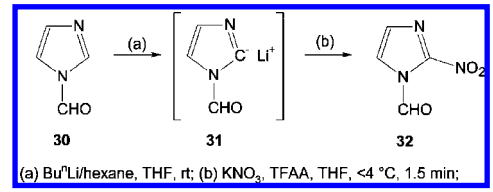
Patent No. U.S. 7,608,725

Assignee: The Richard Stockton College of New Jersey, Pomona, New Jersey, U.S.A

Title or Subject: Process for Nitration of N-Substituted Imidazoles

2-Nitroimidazoles have been identified as radiosensitisers and can be used to improve the effectiveness of radiotherapy treatment of solid tumours. These tumours are often hypoxic and hence have low O_2 content with the result that radiotherapy, that relies on sensitisation by O_2, is often ineffective in treating such tumours. The preparation of 2-nitroimidazoles is said to be challenging, and methods which use strongly acid conditions often give rise to 4- or 5-nitroimidazoles. The patent discloses a method for preparing the desired derivatives that uses milder conditions. The procedure involves the treatment of a N-substituted imidazole such as **30** with a strong base to give the anion **31** that is then reacted with a nonacidic acyl nitrate. The preparation of **32** is shown in Reaction 10, and this takes place very rapidly at about 0−4 °C. The anion **31** is initially produced and then treated with KNO_3/TFAA that forms $F_3C(O)ONO_2$, the active nitrating species. The reaction takes about 1.5 min, and **32** is isolated in 62% yield and 95% purity by flash ColC.

Reaction 10



The 1-Ts-2-nitro derivative was formed in 72% yield by a similar reaction, and the reaction is claimed to be applicable to N-substituted imidazoles where the substituent has a nonacidic H atom. A range of metal nitrate salts is also claimed to be suitable although there are no examples.

Advantages

The process is selective for preparing the 2-nitroimidazoles that are potential activators in radiotherapy treatment of solid tumours.

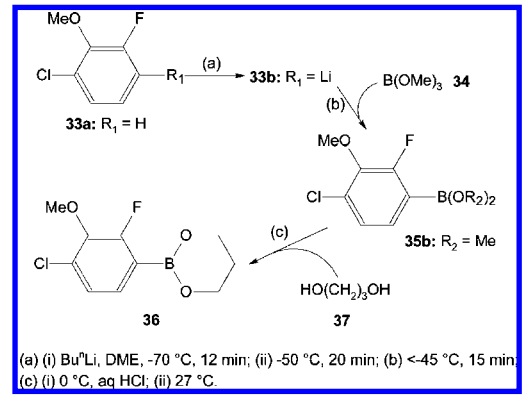
Patent No. U.S. 7,611,647

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

Title or Subject: Process for Selective Deprotonation and Functionalization of 1-Fluoro-2-Substituted-3-Chlorobenzenes

The main claim of this patent covers a process to prepare a Li compound such as **33b** from a fluorobenzene **33a**. The Li reagent **33b** is used in the preparation of the boronate **36**, an intermediate for preparing herbicides. After formation of **33b**, **34** is added to give **35b**, but this not isolated and the mixture is acidified and then treated with **37**. After workup the product is isolated as a colourless oil containing about 5% of **37**.

Reaction 11



The process is also used for the preparation of a number of other compounds. For example, **35a** (R_2 = H) is isolated as a white solid in 88% yield after treating **35b** with KOH followed by aq HCl. The acid **33c** (R_1 = CO_2H) is prepared as a solid in 80% yield by treating **33b** with gaseous CO_2 at −70 °C and the aldehyde **33d** (R_1 = CHO) is obtained in 75% yield as an oil when **33b** reacts with DMF at −75 °C. Crystallisation from pentane gives fine needles of **33d**.

Advantages

The process is very selective and allows the preparation of Li reagents that can be converted to a range of potentially useful products.

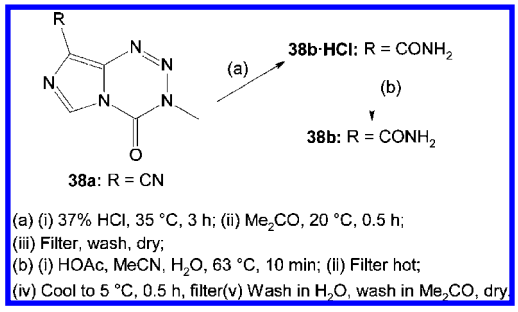
Patent No. U.S. 7,612,202

Assignee: Chemagis Ltd., Bnei Brak, Israel

Title or Subject: Process for Preparing Temozolomide

Temozolomide **38b** was first discovered over 30 years ago, and it is only in the past few years that it has been approved to treat aggressive brain tumours. A number of processes are reported for the preparation of **38b**, and one has been reviewed (*Org. Process Res. Dev.* **2009**, *13*, 371). The production of **38b** via its HCl salt followed by addition of strong base is not feasible because the free base is highly unstable >pH 7 and stable <pH 5. Hence, the objective of the patent is to provide a process for the conversion of the HCl salt of **38b** to the free base under acidic conditions. The process to form the salt **38b·HCl** is shown in Reaction 12 and involves hydrolysis of the nitrile **38a** using 37% HCl at 35 °C, whereas alternative processes are said to use 32% HCl at 60 °C. The salt is recovered in 89% yield with purity of 99.6% (HPLC). There is no information as to how **38a** is prepared. The conversion of the salt to the free base is carried out by heating a solution of the salt in a solvent that is miscible with water in the presence of HOAc. MeCN is preferred although Me_2CO is also used. The base is recovered in 86.7% yield with purity of 99.96% (HPLC). A further aspect of the process is that the yield of **38b** may be increased by passing the crystallisation mother liquors over a weakly basic ion-exchange resin (IER). The liquors are passed through the column of IER, and the eluate is then used in the next batch when **38b·HCl** is converted to the free base. In this way the overall yield of product is increased without negatively impacting on the product quality. The patent explains that, before use, the IER must be washed with MeCN and H_2O to swell the resin beads.

Reaction 12



(a) (i) 37% HCl, 35 °C, 3 h; (ii) Me_2CO, 20 °C, 0.5 h;
(iii) Filter, wash, dry;
(b) (i) HOAc, MeCN, H_2O, 63 °C, 10 min; (ii) Filter hot;
(iv) Cool to 5 °C, 0.5 h, filter(v) Wash in H_2O, wash in Me_2CO, dry.

Advantages

The patent claims that using stronger HCl and a lower temperature for the hydrolysis of **38a** is an improvement and the use of IER in the recovery of the free base increases the product yield.

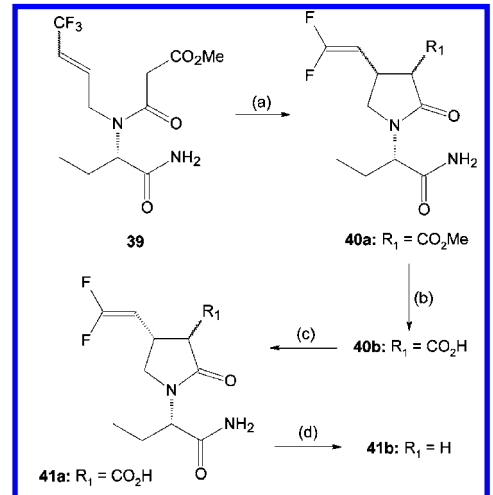
Patent No. U.S. 7,612,215

Assignee: UCB Pharma S.A., Brussels, Belgium

Title or Subject: Process for Preparing 2-Oxo-1-Pyrrolidine Derivatives by Intramolecular Allylation

This patent concerns a new process for the preparation of intermediates such as **41b** that are used to make levetiracetam, an antiepilepsy drug, although the production of the drug from **41b** is not described in the patent. The key step in the route to make **41b** is a base-catalysed cyclisation step that is shown in Reaction 13 where **40a** is prepared from **39** catalysed by DBU in MEK at rt. After acidification the product is extracted into Pr^iOAc, and crude **40a** is obtained in 99% yield. The ester **40a** is then hydrolysed using Na_2CO_3 to produce **40b**. This is obtained as a crude product in 69% yield, and recrystallisation from MeOH gives the pure enantiomer **41a** in 70% yield. Decarboxylation is effected by refluxing in MIBK to produce **41b** that is isolated in 71% yield after crystallisation from MTBE. The patent states that it is surprising that there is no racemisation during either the cyclisation of **40a** to give **39** nor in the decarboxylation of **41a** to give **41b**.

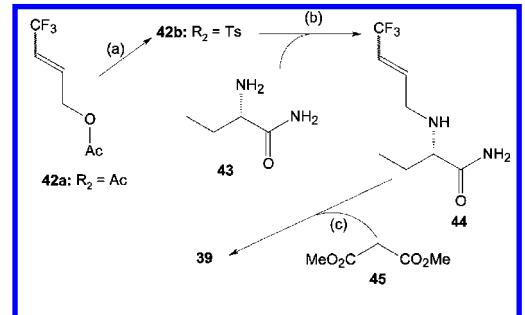
Reaction 13



(a) (ii) DBU, MEK, rt, 1 h; (ii) 1M HCl, <25 °C;
(b) (i) Na_2CO_3, H_2O, MeOH, 25 °C, 24 h; (ii) Extract in Pr^iOAc;
(iii) Aq HCl to pH 2, < 25 °C, 20 h; (iii) Filter, wash H_2O, dry;
(c) Recrystallise from MeOH; (d) (i) MIBK, reflux, 6 h; (ii) Cool to rt, evaporate; (iii) Crystallise from MTBE.

The patent also describes the preparation of **39** by the route shown in Reaction 14. In the first step the acetate **42a** is converted to the tosylate **42b** which is isolated in 89% yield and then reacted with **43** that is obtained from its tartrate salt by treatment with NH_4OH. This reaction between **42a** and **43** produces **44** and takes place in a 50:50 solvent mixture of Pr^iOH and Pr^iOAc in the presence of K_2CO_3 and $BnEt_3NCl$. The workup of the reaction mixture involves the addition of more Pr^iOAc then distillation to remove the azeotropic mixture of Pr^iOH and Pr^iOAc. This is followed by acidification with HCl and extraction into Pr^iOAc, addition of aq NaOH and further extraction into Pr^iOAc. After evaporation of the solvent the crude **44** is obtained in 71% yield. The final step is the reaction of **44** with **45** to form **39** that is carried out in a rotary evaporator, and the crude product is used directly in the preparation of **40a** (Reaction 13).

Reaction 14



(a) (i) Aq NaOH, $BnEt_3NCl$, PhMe, 20 °C, 20 h; (ii) TsCl, 20 °C, 3 h;
(iii) Add H_2O, separate, evaporate; (b) (i) K_2CO_3, Pr^iOH/Pr^iOAc, 60 °C, 17 h;
(c) 110 °C, 40 h, rotary evaporator.

^{1}H NMR data are provided for many of the compounds described.

Advantages

The process gives high-purity product without the use of toxic or expensive metal catalysts.

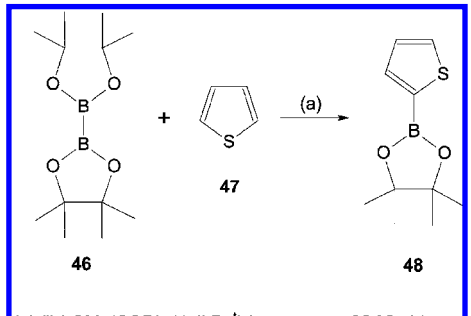
Patent No. U.S. 7,612,218

Assignee: Mitsubishi Rayon Co. Ltd., Tokyo, Japan

Title or Subject: Process for Production of Heteroaryl-Type Boron Compounds with Iridium Catalyst

The boron compounds covered by this patent are used as reaction substrates when producing biaryl derivatives that are useful chemical intermediates. Some of methods for the boronation of aromatics are summarised, but they are usually not applicable to aromatic heterocyclic compounds. The patent describes a process for producing a range of heteroaryl compounds containing boronate substituents. The route for the production of **48** is shown in Reaction 15 and is between the boron compound **46** (1 mol) and the heteroaryl **47** (10 mol) The reaction takes place in the presence of an Ir catalyst (0.03 mol) and bidentate ligand (0.03 mol). Using the Ir cyclooctadiene complex catalyst, IrOMe(COD) and that of the ligand (4,4′-Bu^t)$_2$bpy the product is obtained in 88% yield purified after distillation. Using IrCl(COD) as the catalyst, the reaction takes 16 h at 80 °C and gives a yield of 75%; when this catalyst is used with bpy under the same conditions the yield of **48** is 60%. Other mixtures of Ir catalysts and ligands are also described that give varying yields. The reaction is also applied to the synthesis of heterocyclic compounds using the substrates 2-methylthiophene, 2-methoxythiophene, 2-trifluoromethylthiophene, furan, pyrrole, pyridine, benzothiophene, benzofuran, indole, and quinoline,. These give varying product yields of 60−85%. When furan is reacted, the patent states that the ratio of 2-to-3-substitution is 92:8, but similar data are not given for other substrates.

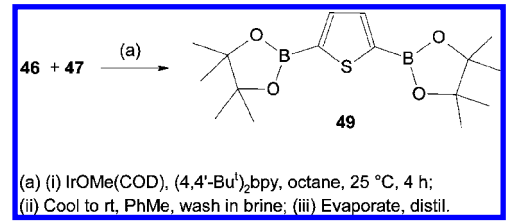
Reaction 15



(a) (i) IrOMe(COD), (4,4'-Bu^t)$_2$bpy, octane, 25 °C, 4 h; (ii) Cool to rt, PhMe, wash in brine; (iii) Evaporate, distil.

An extension of the work was applied to the synthesis of disubstituted heteroaryls. When using the same catalyst, ligand, and conditions as in Reaction 15 with a 1.1:1 mol ratio of **46**:**47** the product was **49** that was isolated in 80% yield by distillation (Reaction 16). This reaction was also applied to the synthesis of disubstituted heteroaryls from the substrates furan and pyrrole.

Reaction 16



(a) (i) IrOMe(COD), (4,4'-Bu^t)$_2$bpy, octane, 25 °C, 4 h; (ii) Cool to rt, PhMe, wash in brine; (iii) Evaporate, distil.

^{1}H and ^{13}C NMR data are provided for many of the products, but the patent does not report how to prepare **46**.

Advantages

The process enables a range of potentially useful, 2-substituted heteroaryl compounds to be produced in high yield.

Patent No. U.S. 7,612,227

Assignee: Sumitomo Chemical Company Limited, Tokyo, Japan

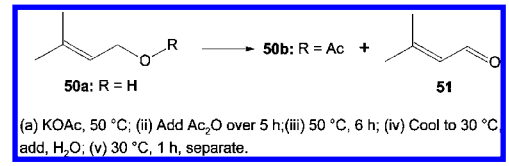
Title or Subject: Process for Producing 3-Methyl-2-butenyl Acetate

The title compound **50b** is an intermediate in the production of various agrochemicals and pharmaceuticals. Mention is made of **50b** as an intermediate in preparing a pyrethroid compound. The production of **50b** by esterification of the alcohol **50a** and Ac_2O is an obvious method to use, but it is claimed to be unsuitable for commercial production. This patent discloses a method using this reaction, but the key to the process, and the focus of the claims of patent, is the purification of the product that it is claimed and makes the overall process industrially viable. The method used to make **50b** from **50a** and Ac_2O is shown in Reaction 17. The reaction is carried out in the presence of an inorganic base such as KOAc, and after initial separation the mixture contains 92.67% **50b**, 6.49% HOAc, and 0.06% **51**. The purification steps are then carried out as shown below, and these first remove the HOAc before distilling the final product:

(1) Add an aqueous solution of $NaHSO_3$ at 30 °C, stir 1 h.
(2) Separate phases and add H_2O to organic phase, stir 0.5 h
(3) Cool to 15−25 °C, add 30% aq K_2CO_3, and then 5% Na_2CO_3; stir 0.5 h.
(4) Add H_2O, stir 0.5 h.
(5) Distill.

The purified product was obtained in 93.5% yield with 99.2% purity by GC and contained 0.01% **51** with no detectable HOAc.

Reaction 17

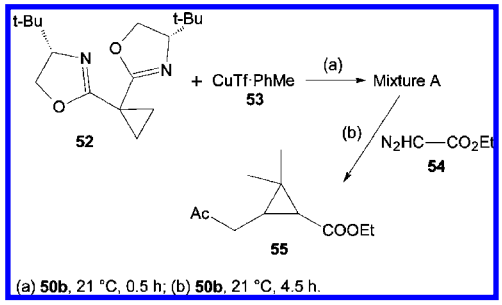


(a) KOAc, 50 °C; (ii) Add Ac_2O over 5 h;(iii) 50 °C, 6 h; (iv) Cool to 30 °C add, H_2O; (v) 30 °C, 1 h, separate.

The patent includes two experiments for preparing the cyclopropane compound **55**. This is probably the intermediate mentioned early in the patent used for preparing the pyrethroid. The preparation of **55** is outlined in

Reaction 18 and begins with the preparation of an asymmetric Cu catalyst (Mixture A) from a mixture of **52** and **53** dissolved in **50b**. To this is then added a solution of **54** in **50b** to give a 72% yield of **55**, the stereochemistry of which is not reported.

Reaction 18



Advantages

The process provides a facile method of producing the pure ester that can then be used to prepare a useful intermediate.

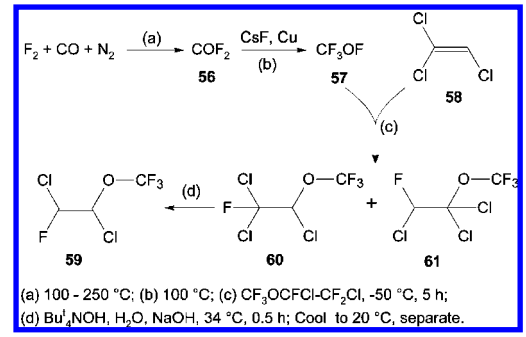
Patent No. U.S. 7,612,242

Assignee: Solvay Solexis S.p.A., Milan, Italy

Title or Subject: Process for Preparing Fluorohalogenoethers

The patent relates to a process for the preparation of perfluoroalkylvinylethers (PFAVEs) and uses precursors that are not chlorofluorocarbons (CFCs). The PFAVEs are very useful monomers used for preparing polymers and elastomers that have a variety of applications. A number of processes for preparing many of the desired monomers involve the use of CFCs, and hence alternatives are required. The patent claims to have surprisingly and unexpectedly found a process for synthesising PFAVEs that overcomes the need to use CFCs. The route used to prepare one such ether, **59**, is shown in Reaction 19. The first stage is the preparation of **56** that takes place by passing an equimolar gas mixture of F_2, CO, and N_2 through a steel pipe at 100 °C. The formation of **56** is highly exothermic, and the maximum temperature is maintained <300 °C with the outlet gas mixture <250 °C. A yield of **56** >95% is obtained, and the gas mixture is then cooled to 100 °C and passed through a bed of finely milled CsF (<0.1 mm) mixed with fine needles of Cu. Under these conditions **56** is converted to **57** in >98% yield. The next stage is the addition reaction of **57** with **58** that is carried out by bubbling a mixture of **57** and He gas into a solution of **58** in $F_3COCFCl-CF_2Cl$. The reaction forms a mixture of **60** and **61** in 96% yield and this is dehydrochlorinated by treatment with Bu^t_4NOH and NaOH in aqueous solution at 34 °C. The product **59** is recovered by phase separation in 92% yield with 99% purity.

Reaction 19



The addition step is also applied to the reaction of $F_3CCF_2CF_2OF$ and CHCl═CHCl at −90 °C to give $F_3CCF_2CF_2OCHClCHClF$ in 25% yield. The addition reaction of F_3CCF_2OF with CHCl═CCl_2 at −70 °C gives a mixture of $F_3CCF_2OCHClCFCl_2$ and $F_3CCF_2OCCl_2CHClF$ in 61% yield. The dehydrochlorination of any of these three ethers is not described. The patent also describes discontinuous and semi-continuous processes for the preparation of $F_3COCFCl-CF_2Cl$ that is used as the solvent in the addition step. The preparation is by reaction of **59** with F_2 gas in CF_3Cl at −70 °C. In the discontinuous method a 31.5% conversion of **59** takes about 10 min to give a 79% yield. In the semicontinuous process after 4 h a 100% conversion is achieved, and the product yield is 98.4%.

Advantages

The process does not require the use of CFCs to obtain the desired ethers and uses chloro-olefins that are commercially available.

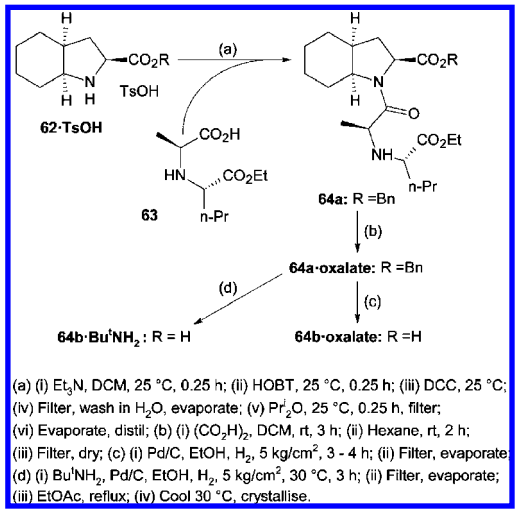
Patent No. U.S. 7,615,571

Assignee: IPCA Laboratories Ltd., Mumbai, India

Title or Subject: Process for the Manufacture of Perindopril and its Salts

Perindopril **64b** (R = H) is used in treating cardiovascular problems, and patents on this compound have been reviewed previously (*Org. Process Res. Dev.* **2008**, *12*, 556). The current patent summarises a number of methods of preparing **64b** and states that the key to a successful process depends on the purity of a benzyl ester **64a** (R = Bn) that is an intermediate in the synthesis of **64b**. Hence, an objective is to provide a process that produces this ester in high purity. The route used to prepare **64a** and **64b** is summarised in Reaction 20 and begins with the coupling of the benzyl ester **62** with the alanine **63** to give **64a**. The reaction takes place in the presence of peptide coupling agents DCC and 1-hydroxybenzotriazole (HOBT) plus a base such as Et_3N. The product **64a** is obtained as an oil in 90% purity and 99% yield and is then converted to the oxalate salt **64a·oxalate** (R = Bn) by treatment with oxalic acid in DCM. This produces a solid that has a mp of 108−118 °C and is clearly impure. The salt can then be debenzylated by catalytic hydrogenation to give **64b·oxalate** (R = H) using 5% Pd/C catalyst. Alternatively, the *tert*-butylamine or erbumine salt, **64a·Bu^{t}NH$_2$** (R = H), can be obtained by hydrogenation of **64a·oxalate** salt in the presence of Bu^tNH_2. The patent claims that the purity of the erbumine salt is >99.5%. Details are also provided for the preparation of (+)- and (−)-tartrate salts of **64a** and **64b**.

Reaction 20



Advantages

The process provides a method of producing the key intermediate with higher purity than alternative methods, and from this a higher-purity final product can be obtained.

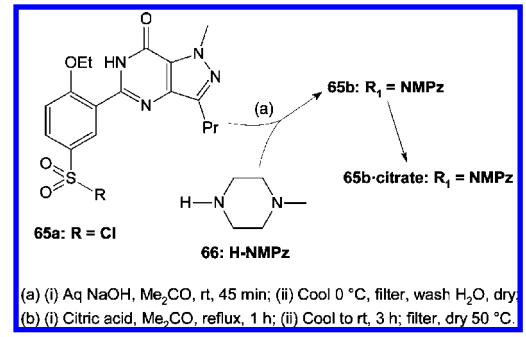
Patent No. U.S. 7,618,976

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

Title or Subject: Methods for the Production of Sildenafil Base and Citrate Salt

The title compound is the generic name for the well-known drug Viagra that is used as the citrate salt of **65b**. Processes for the production of **65b** involve reaction of a sulphonyl chloride with excess of a cyclic amine, and the resulting mixture may contain impurities that are difficult to remove from the desired product. One patent on the synthesis of **65b** was reviewed some time ago (*Org. Process Res. Dev.* **2001**, *5*, 350). The current patent focusses on reducing the amount of byproduct by minimising the amount of amine used as proton scavenger. The patent describes a series of experiments for the preparation of **65b** by condensation of the piperazine **66** (1.1 mol) with the sulphonyl chloride **65a** (1 mol) as shown in Reaction 21. The reaction is carried out in the presence of a base as proton scavenger and a series of examples is listed in which the solvents and proton scavengers were varied and product yield was measured. The solvents used were Me_2CO, MEK, MeOH, EtOH, Pr^iOH, MeCN, and PhMe, and the base is either Et_3N or NaOH. The most effective combination appears to be Pr^iOH and Et_3N that gave a yield of 95.5% although examination of the examples and the claims indicates that Me_2CO appears to be the preferred solvent and NaOH is the base. The patent also describes the preparation of the citrate salt of **65b** by treating equimolar amounts of the free base **65b** with citric acid in refluxing Me_2CO for 1 h. This gives a precipitate of the salt, and after cooling to rt over 3 h this is filtered off, and a yield of 94% is obtained. Alternatively, the citrate salt can be obtained by a method that uses a partially purified wet form of the base. In this procedure **65a** and **66** are dissolved in Me_2CO at rt for 1 h followed by 2 h at 5 °C. The precipitated base is washed in H_2O, and the wet base is recovered in 91% yield and then converted to the citrate by refluxing in Me_2CO as above. The salt is dried at 50 °C for 4 h and recovered in 98.8% yield with an overall yield is 83.3%, but the final water content of the salt is not reported. If the salt is further dried under vacuum at 100 °C, the final water content of the salt is 0.3%; however, if the salt is left at rt overnight in air, the water content increases to 1.2%. Further investigations show that the salt can be dried at temperatures <100 °C and residual water content of between 1.5 and 1.7% is obtained. In view of these findings the patent claims cover a citrate water adduct.

Reaction 21



Advantages

The process gives reduced levels of byproduct and minimises the amount of amine used. It also provides the citrate salt that is suitable for use in preparing pharmaceutical formulations.

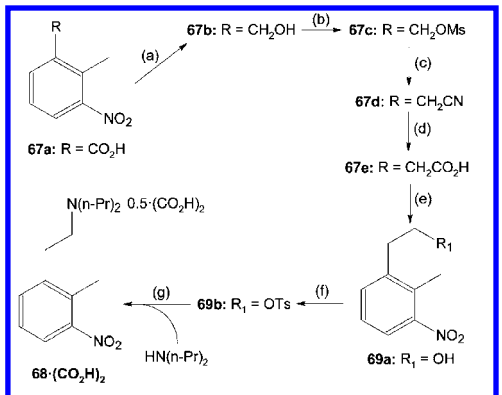
Patent No. U.S. 7,619,095

Assignee: Alembic Limited, Gujarat, India

Title or Subject: Process for the Preparation of Indolone Derivative

This patent relates to the preparation of ropinirole, **71**, that is used to treat Parkinson's disease, and a patent on an alternative preparation of **71** has been reviewed previously (*Org. Process Res. Dev.* **2007**, *11*, 940). Several alternative methods are summarised as are the disadvantages that make them unsuitable for industrial production. The difficulties range from the use of reagents that are lachrymators (2-methyl-3-nitrobenzyl chloride), toxic (KCN), or highly flammable (borane/THF). Other problems mentioned are the need for special, short-path distillation apparatus and low product yields. The current patent describes a new synthetic procedure for preparing **71**. This is a multistep synthesis, and for clarity it has been divided in two parts, shown in Reactions 22 and 23. The first stage of the process is the preparation of the amine salt **68·$(CO_2H)_2$** (Reaction 22). The process starts with the reduction of the acid **67a** with $NaBH_4$ to give alcohol **67b** in 84% yield that is converted to the Ms derivative **67c**. This is recovered as an oil, and reaction with NaCN produces **67d** that is hydrolysed to the acid **67e**. Reduction with $NaBH_4$ gives the alcohol **69a** as a brown oil and this is converted to the tosylate **69b**. These two compounds are novel and covered by the patent claims. The final step in this section is reaction of **69b** with $HNPr^n_2$ in water and after azeotropic removal of water using PhMe followed by reaction with oxalic acid in MeOH <10 °C. This forms the oxalate salt that is recovered for the next stage of the process shown in Reaction 23.

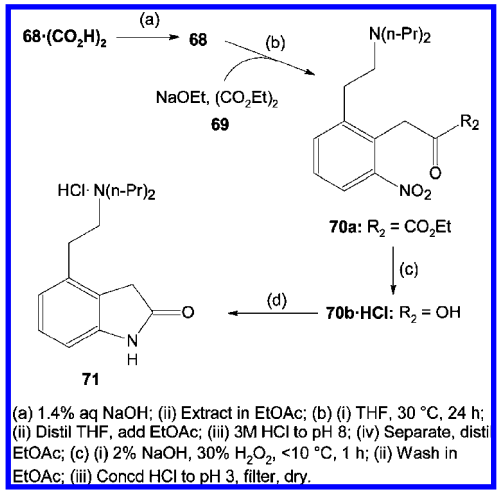
Reaction 22



(a) (i) $NaBH_4$, THF, rt, 0.5h; (ii) MsOH, rt; (b) (i) Et_3N, DCM, MsCl, rt; (ii) Distil DCM; (c) NaCN, MeCN, reflux; (d) Aq HOAc, H_2SO_4, reflux, 12 h; (e) $NaBH_4$, THF, MsOH, 60 - 75 °C; (f) (i) Et_3N, TsCl, DCM, 30 °C, 15 h; (ii) 5M HCl, extract in DCM; (iii) Distil DCM; (iv) Cyclohexane, rt, 0.5 h, filter (g) (i) H_2O, 60 - 90 °C, 8 -12 h; (ii) Separate, add PhMe, distil; (iii) MeOH, $(CO_2H)_2$, <10 °C; (iv) Precipitate, filter, dry.

The oxalate salt **68·(CO$_2$H)$_2$** is first converted to the free base **68** by treatment with aq NaOH. This is extracted into EtOAc, and then the solvent is removed leaving the free base. A freshly made solution of NaOEt in THF is added to $(CO_2Et)_2$, and then **68** is added to this mixture and left stirring for 24 h at 30 °C. After removal of THF, EtOAc is added followed by 3 M HCl; the organic layer is recovered and solvent removed to give the pyruvate **70a**. This is then treated with 2% NaOH and H_2O_2 at <10 °C for 1 h. After washing with EtOAc the aqueous mixture is acidified with HCl, and the HCl salt of **70b** is recovered. The final step to prepare the HCl salt of **71** is carried out by catalytic hydrogenation of **70b·HCl** using 10% Pd/C. Reaction conditions are not given for this step, and the yield is reported to vary between 75 and 87%. The patent also reports the conversion of the alcohol **69a** to the chloride **69c** and bromide **69d**, and these novel compounds are covered by the patent claims.

Reaction 23



(a) 1.4% aq NaOH; (ii) Extract in EtOAc; (b) (i) THF, 30 °C, 24 h; (ii) Distil THF, add EtOAc; (iii) 3M HCl to pH 8; (iv) Separate, disti EtOAc; (c) (i) 2% NaOH, 30% H_2O_2, <10 °C, 1 h; (ii) Wash in EtOAc; (iii) Concd HCl to pH 3, filter, dry.

The patent maintains that this process is environmentally friendly and criticises alternative processes for using KCN, and yet the process described here uses NaCN that is actually more toxic than the KCN.

Advantages

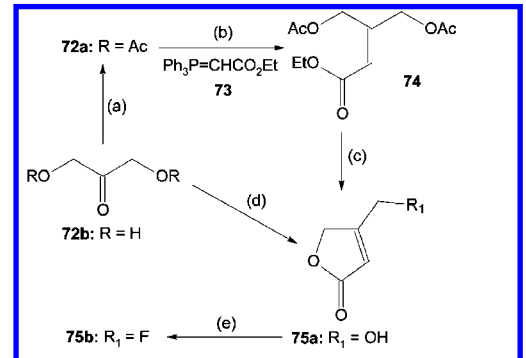
The process is claimed to be more economical and simpler than alternatives with no requirement for the use of specialised equipment.

Patent No. U.S. 7,619,101

Assignee: Hoffman-La Roche Inc., Nutley, New Jersey, U.S.A Title or Subject: Preparation of (S)-4-Fluoromethyl-dihydrofuran-2-one, an Intermediate Useful in the Synthesis of a DPP-IV Inhibitor

This very detailed and comprehensive patent describes a process for the synthesis of the novel compound **82** and its use in the preparation of **85b**. This compound is a DPP-IV inhibitor and is of interest for the treatment of diabetes and a number of other diseases. A major task in the synthesis of **85b** is said to be the introduction of the chiral (*S*)-4-fluoromethylpyrrolidino residue and is discussed in another patent from this applicant (WO 2005/000848). A problem with the synthesis of **82** is that a chromatographic separation is required, and so an improved procedure is desired. The synthesis of **82** is part of the improvement, and the last stage is the asymmetric hydrogenation of **75b** for which the patent describes several methods of preparation. Two routes start from **72b** and are outlined in Reaction 24. One of these begins by cyclisation of **72b** using the Wittig reagent **73** in DCM to give **74** that is obtained as a yellow oil and crystallised from DCM to obtain a 78% yield of solid with 90% purity. The Wittig reagent **73** is freshly prepared by treating $[Ph_3PCH_2CO_2Et]Br$ with aq NaOH. Reaction of **74** with AcCl at rt in MeOH resulted in the formation of **75a** that is isolated as a yellow oil then crystallised from DCM giving a 87% yield of **75a** with 98.6% purity. The conversion of **75a** to **75b** can be carried out using a number of fluorination methods and the scheme shows the use of Deoxo-Fluor that is added to a solution of **75a** in DCM at <−5 °C over 50 min. After workup **75b** is recovered by distillation in 58% yield and 99% purity. The other route to **75b** begins by converting **72b** to the diacetoxy compound **72a** that is refluxed with **73** in MTBE for 5 h then cooled. The MTBE is exchanged for heptane and PhMe is then added, the mixture is cooled and the solid removed and the filtrate concentrated to give a reddish oil. This was purified using ColC and **75b** obtained as a colourless oil in 98% yield with 99.9% purity.

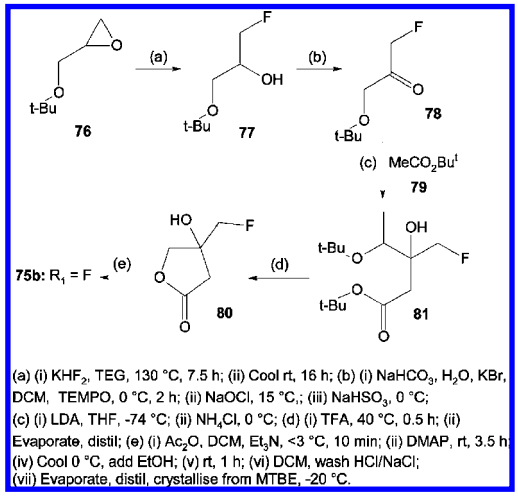
Reaction 24



(a) Ac_2O, pyridine, rt, 3 h; (b) (i) MTBE, reflux, 5 h; (ii) Solvent exchange to heptane, add PhMe, cool; (c) (ii) AcCl, MeOH, rt, 18h; (ii) 2 h, 50 °C; (d) (i) **73**, DCM, rt, 22 h; (ii) Extract in H_2O, evaporate; (iii) DCM, cool -5 °C, seed, filter wash, dry; (e) (i) Deoxo-Fluor, DCM, <-5 °C, 50 min; (ii) Wash in H_2O/EtOH, rt; (iii) Extract in DCM, wash 4M HCl; (iv) Evaporate, distil;

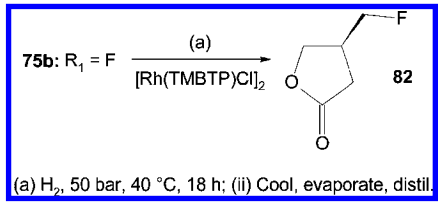
A quite different route to give **75b** is shown in Reaction 25, and this starts from the oxirane **76** that is heated at 130 °C with KHF_2 in triethylene glycol (TEG). After extraction and washing with H_2O and MTBE **77** is recovered as an oil and purified by distillation to give a 61% yield and 95.1% purity. The alcohol is then oxidised to the ketone **78** using TEMPO and the product isolated in 93.5% yield and 98.9% purity. Reaction of **78** with **79** in the presence of the strong base LDA gives **81**. The procedure involves initial treatment of **79** with LDA <−65 °C then warming to −20 °C and cooling back to −65 °C before addition of **78**. The crude product is recovered as a yellow oil then used for the next step where it is stirred in TFA at 40 °C to effect the cyclisation and form **80** as an oil that is purified by distillation and recovered in 96.6% yield. Dehydration of **80** to **75b** can be carried out using Ac_2O in the presence of Et_3N and DMAP. Alternatives methods described for this step include using $SOCl_2$/pyridine, MsCl/Et_3N or Ac_2O/NaOAc and experimental details are provided. A one-pot process is described for the preparation of **80** from **78** without isolation of **81** that gives **80** in 85.3% yield.

Reaction 25



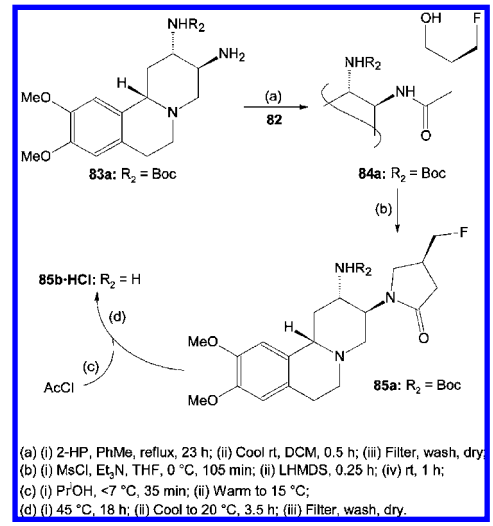
The catalytic asymmetric hydrogenation of **75b** to give **82** is carried out using a Rh or Ru catalysts containing a chiral diphosphine ligand. A large number of experiments is described using a range of ligands, and one example of the catalyst system used is shown in Reaction 26. The catalyst is prepared by mixing $[Rh(COD)Cl]_2$ and the diphosphine (*S*)-(+)-TMBTP in DCM at rt for 15 min. The hydrogenation is then carried out at 50 bar H_2 pressure at 40 °C for 18 h. After evaporation of the solvent, the residue is distilled at 0.05 mbar to give 76−94% yield of **82** with 96.3% ee and purity of 99.3% by GC.

Reaction 26



The final part of the patent covers the preparation of the HCl salt of **85b**, and again a number of options are provided. The method summarised in Reaction 27 is that which is referred to in the claims of the patent. This starts with the coupling of **82** and **83a** in the presence of 2-hydroxypyridine (2-HP) to form the hydroxymethyl derivative **84a** that is isolated in 94% yield and 100% purity. Cyclisation of **84a** is carried out by initial treatment with MsCl, and the patent reports that the mixture is a very thick suspension. Upon addition of LHMDS the suspension dissolves, and after workup a slightly brownish foam is obtained that is crystallised from MeOH to give **85a** in 77% yield and 99.5% purity. In the final step the Boc protection is removed and the HCl salt formed. The HCl is provided by a mixture of AcCl and Pr^iOH that is prepared separately then added to a solution of **85a** in Pr^iOH.

Reaction 27



The patent contains a considerable amount of detail, and for some transformations there is more than one synthesis described. It is not obvious which is the preferred option for some of these, and detailed scrutiny of the patent is recommended for the interested reader.

Advantages

The process provides a method of preparing a novel intermediate that is used to selectively introduce a chiral centre into a desired drug molecule.

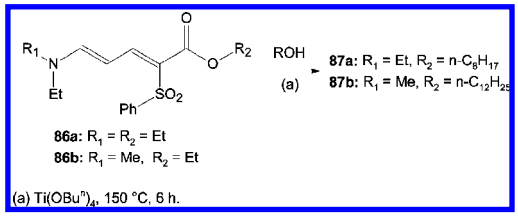
Patent No. U.S. 7,622,603

Assignee: Fujifilm Corporation, Tokyo, Japan

Title or Subject: Process for Producing a δ-Aminopentadienoate Compound

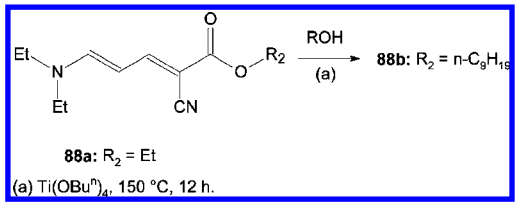
The compounds covered by this patent are said to be UV absorbers, but specific uses for them are not mentioned in the patent. The desired compounds are esters containing alkyl groups having eight or more C atoms. Alternative processes for preparing such compounds are said to give low yields of products, and the methods are not suitable for large-scale production. The new process is a transesterification reaction using Ti alkoxides as catalysts as shown in Reaction 28. The reactions are carried out by heating the alcohol, ROH, and the ethyl ester **86a** or **86b** with $Ti(OBu)_4$ at 150 °C for 6 h. The EtOH is stripped from the mixture by depressurising the reactor, and after extraction in *n*-hexane and purification by ColC the products **87a** or **87b** are obtained in >97% yield. The production of **87a** was also carried out using $Zr(acac)_2$ in place of $Ti(OBu)_4$, and the yield was 84%. ^1H NMR data are given for **87a**. Using an alternative process with DBU the yield of **87a** was only 40%.

Reaction 28



The reaction was also applied to the production of cyano-ester **88b** by reaction of the ester **88a** with *n*-$C_9H_{19}OH$, and the product was isolated in 99% yield after purification using ColC (Reaction 29).

Reaction 29



Advantages

The process gives high yields of the desired esters using well-established reagents for transesterification reactions.

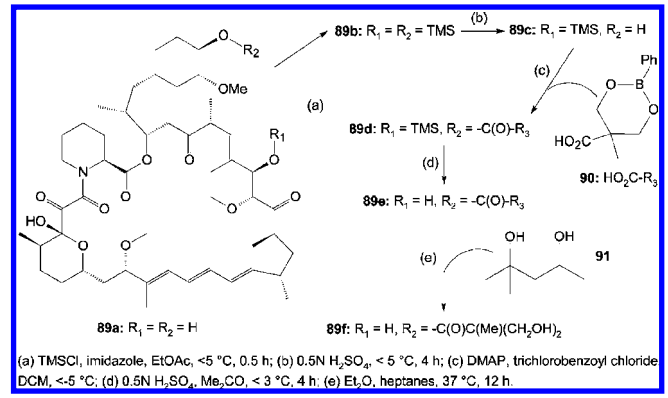
Patent No. U.S. 7,622,578

Assignee: Wyeth, Madison, New Jersey, U.S.A

Title or Subject: Scalable Process for the Preparation of a Rapamycin 42-Ester Boronate

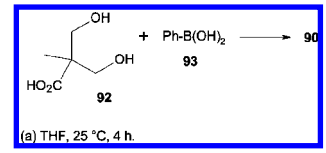
Rapamycin **89a** is a naturally occurring, macrocyclic triene antibiotic and is useful as an immunosuppressant in organ transplant surgery. The ester **89f** is designated as CCI-779 and is available for the treatment of renal cancer as the drug Torisel or Temsirolimus. Earlier patents from Wyeth covering these compounds have been reviewed previously (*Org. Process Res. Dev.* **2009**, *13*, 371). The current patent describes a process that is suitable for large-scale production of **89f** via the boronate ester of rapamycin **89d** (Reaction 30). The process gives **89d** with about 85% conversion of **89a**, and the first stage in the process is to convert **89a** to the bis-TMS derivative **89b** by treatment with TMSCl in the presence of imidazole, and **89b** is then hydrolysed to remove the C31 TMS group giving **89c**. Experimental details are not provided in this patent for these steps, and the method used is described in an earlier patent from Wyeth (U.S. 7,153,957). The boronate ester **89d** is obtained by reaction of **89c** with **90**, but again the actual details are not described The experimental details that are given in the patent relate mainly to the purification and isolation of **89e**. This reaction is carried out in Me_2CO, then the reaction mixture is concentrated to give a slurry of the crude solid in Me_2CO. The reactor vessel is washed with EtOAc, and the washings are mixed with the acetone slurry of **89e**. The purification of **89e** then involves addition of Et_2O, concentration, crystallisation, and filtration steps and further treatment with Me_2CO and Et_2O. Several methods are described for this, and **89e** is isolated in a yield of 63% with 0.95% of **89a** and total impurities of 1.8%. This reaction is carried out on a large scale and results in the preparation of 32.9 kilo of purified **89e**. The final stage of the process for preparing **89f** is the reaction of **89e** with the diol **91** in a mixture of Et_2O and heptanes at 33−37 °C over 12 h. After purification an 89% yield of **89f** is obtained with total impurity level of 0.98% of which 0.36% is **89a**.

Reaction 30



Although the preparation of the boronate **90** is not described in detail in the patent, the procedure that is used is the condensation of the diol acid **92** with the phenyl boronate **93** (Reaction 31).

Reaction 31



Advantages

The purification procedure described is quite complicated and uses several different solvents, but the fact that the process has been carried out on a large scale suggests it may be commercially viable.

Keith Turner

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