Organic Process Research & Development **2008,** *12,* 1031–1040

Highlights from the Patents

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

Summary

The current review includes 22 patents from an initial list containing 264 that fitted the search criteria. In this collection there are five patents covering the production of antiepileptic drugs including three covering the drug gabapentin. One of these discloses a novel process for the synthesis of a key intermediate, a second covers a novel tannate salt of gabapentin, and the third describes a method of purifying the drug using ion-exchange resins. The other patents on antiepilepsy drugs cover the drug lamotrigine. One describes a novel polymorph, and the second describes a novel dimesylate salt in a new synthesis of the drug. The advantages claimed in patents are often somewhat exaggerated. A patent for the production of 3-aminophenylacetylene claims that the known processes have so many problems that it should not be possible to operate them. The new method obviously claims to overcome such difficulties. Grignard reagents are very widely used, but one patent claims that they are dangerous on a commercial scale and describes a synthesis of phenyltetrazoles that does not use them. Using carcinogenic reagents is sometimes unavoidable, and a process for producing arylamines for electrophotographics tries to avoid them. A derivative of the carcinogen 1-biphenylamine is prepared by a process that does not begin with the amine. The process uses a modified Ullman reaction that is sped up by a ligand-modified Pd catalyst. The production of an antihistamine to replace the obsolete drug terfenadine is described. The synthesis of one key intermediate involves six different solvents, various aqueous solutions, and diazomethane. Its commercial attractiveness is dubious. Stereoselective processes are important in the synthesis of many molecules, and enzymatic reagents are attractive unless low concentrations or product are obtained. An oxidoreductase is used to produce a pyrrolotriazine anticancer agent at concentrations up to 100 g/L. Another biochemical process is described for the production of the antibiotic rapamycin. This includes a chemical purification step involving silylation that is an improvement on the crystallisation method used in alternative procedures.Another patent on rapamycin gives details of the preparation of the solvent-free amorphous form that is used as a coating for medical implants. The production of the amorphous form of the platelet inhibitor drug clopidogrel is claimed not to be reproducible, and the product can be unstable. An improved crystallisation method gives reproducible product. Another platelet inhibitor is cilostazol, and a new process for producing this is described. This uses a continuous circulating pulverising technique and phase transfer catalysts to give small particles of the desired product. Many reactions can be inhibited or even stopped because of changes in the physical properties of a mixture such as an increase in viscosity. A patent for producing an intermediate for an antibacterial molecule improved the original process that used DMSO as solvent. The original process took several days because it gave rise to a very high increase in viscosity, whereas the new process takes a matter of hours. Cefdinir is another antibiotic, and an intermediate for this compound can be difficult to purify. An improved procedure is described that proceeds via amine salts that can be isolated in high purity. Most patents are assigned to companies or academic institutions, but there is one from an unaffiliated group in France. It describes a process for preparing fluoroquinolines that are intermediates for antibacterial agents, and some examples are on a kilo scale. The conversion of glycerol to useful high-value products is a key aim of biodiesel producers. A patent describes how to convert pure and crude glycerol to a starting material for the amino acid, methionine. Improvements in the *Z*/*E* ratio of an oxime intermediate enable higher yields of the drug resperidone to be obtained. This is done by salt formation allowing the *Z*-isomer to be recovered. The market for hair dyes is vast, and improvements in the synthesis of key intermediate, nitroanisoles, give higher-purity products under conditions milder than those of alternative procedures. Several of the patents describe experiments carried out on a kilo scale or greater, thus suggesting that the process is at an advanced state of development. However, the inclusion of a patent has no legal or commercial significance, and the advantages described are those claimed in the patent unless this reviewer has personal knowledge of the subject.

Patent No. U.S. 7,381,823

Assignee: Serichim S.R.L., Torviscosa, Italy

Title or Subject: Process for Preparing Cyclohexanediacetic Acid Monoamide

The title compound **7a** is a key intermediate in the production of gabapentin **7b** ($R_2 = NH_2$) that is used as the HCl salt to control epilepsy. This is one of three patents covering **7b** in the current review, and there are also two further patents describing alternative antiepilepsy drugs. The previously reported methods for synthesising **7a** are summarised in this patent and are said to be difficult and onerous to apply industrially. One step is said to require a reaction time of 72 h, and a hydrolysis step uses concd H_2SO_4 at high temperature and

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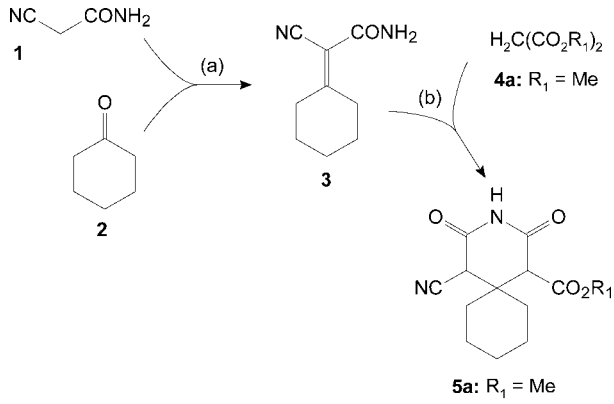
produces large quantities of waste. The new process is based on a novel intermediate ester such as **5a** that can be transformed into **7a** and Reaction 1 shows the synthesis of the methyl ester **5a** by two condensation reactions. In the first of these **1** reacts with **2** in the presence of NH_4OAc to form **3**. The water produced is constantly removed, and then **3** is reacted with **4a** in the presence of a strong base to give **5a**. The ethyl and benzyl esters **5b** (R_1 = Et) and **5c** (R_1 = Bn) are also prepared by reacting **3** with the corresponding malonates. For the preparation of **5a**, the strong base is NaOMe; for **5b**, Na in EtOH is used; and for **5c**, the base is NaH. The patent states that the two reaction steps can be carried out in a single pot without isolation of **3**. The patent also describes the preparation of the acid **5d** (R_1 = H) by catalytic hydrogenation of **5c** using Pd/C.

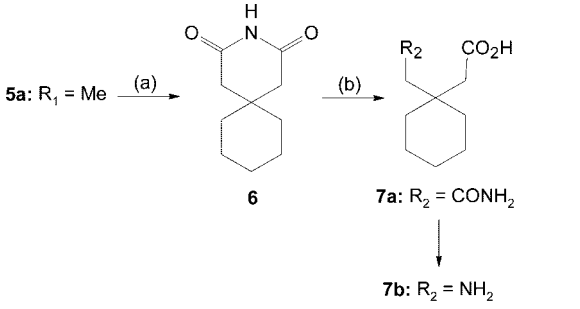
Reaction 1



(a) (1) NH_4OAc, HOAc, PhMe, reflux, - H_2O, 2 h;
(2) Cool to 70 °C, aq $NaHCO_3$, filter, dry
(b) (1) NaOMe/MeOH, 25 °C, 1 h; (2) 5% HCl, filter (3) MeOH, dry

The transformation of **5a** to **7a** is shown in Reaction 2 and proceeds under mild conditions using classical methods of base hydrolysis and decarboxylation of **5a** to form **6**. The reaction is carried out without isolating **6** that is hydrolysed to produce **7a**. The patent also describes a one-pot reaction that starts with **3** and **4a** producing **5a** that is not isolated but converted to **7a** by the method shown in Reaction 2. The overall yield for this is 42%.

Reaction 2



(a) (1) NaOH, EtOH/H_2O, reflux, 1.5 h; (2) 5% HCl, reflux, 2 h;
(3) Cool to 20 °C, filter, wash in H_2O, dry.
(b) (1) 10% NaOH, reflux, 1 h; (2) Cool to 25 ° C, 36% HCl,
(3) Filter, wash in H_2O, dry.

Advantages

The process provides a simple procedure of preparing a novel intermediate for an important drug.

Patent No. U.S. 7,390,922

Assignee: Kiel Laboratories Inc., Gainesville, Georgia, U.S.A.

Title or Subject: Phenolic Acid Salts of Gabapentin in Liquid and/or Semi-Solid Dosage Forms

The usual dosage form of gabapentin **7b** ($R_2 = NH_2$) is the HCl salt, and this patent reports on the preparation of a novel tannate salt of **7b**. There are apparently no reports of this salt, and it is stated that its formation is unexpected because of the close proximity of the carboxylic and amino groups on the molecule. The novel salt is prepared from synthetic or natural tannic acid and **7b**. Tannic acid comprises of a mixture of compounds that have molecular weights in the range 500−5000 Da. The tannin molecules generally contain a central polyol such as D-glucose in which the OH groups are partially or totally esterified by phenolic groups. The examples in the patent describe the preparation of aqueous suspension formulations containing the tannate salt. The suspensions also contain preservatives, sweeteners, etc.

Advantages

The patent describes a novel salt form of an important drug, but it is not clear if it offers higher bioavailability than other salts.

Patent No. U.S. 7,393,975

Assignee: ZACH System s.p.A., Bresso, Italy

Title or Subject: Process for the Purification of Gabapentin

This is the third patent on gabapentin, and it describes a method for purifying **7b** using ion-exchange resins (IERs). Previously described methods for purification of **7b** are said to require a final step involving column chromatography (CC) of an aqueous HCl salt using either acidic or basic IERs. One process uses large quantities of NH_3 solution as eluent so that the solution of **7b** that is obtained is only about 3−4%. The concentration of this weak solution before crystallisation takes significant time and energy. The new process reduces the volumes of liquid handled and therefore reduces the time and costs involved. The process involves passing a solution of the HCl salt of **7b** through a strong cationic IER, followed by demineralised water, a solution containing of 3% NH_3 and 7% NaOH, and finally DI demineralised water. The eluate is then acidified before concentrating, and **7b** is crystallised from MeOH and Pr^iOH. The substitution of most of the NH_3 by NaOH reduces the processing time and also the volume of liquid by about 20%. A point to note is that the presence of Na^+ can destabilise **7b**, and so careful monitoring of the acidification step is required. The final purity of **7b** was >99%.

Advantages

The process reduces liquid volumes and hence processing times.

Patent No. U.S. 7,381,833

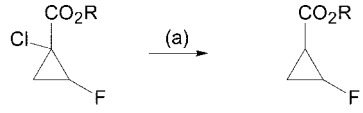
Assignee: Daiichi Pharmaceutical Co. Ltd., Tokyo, Japan

Title or Subject: Process for Producing a 1,2-cis-2-Fluorocyclopropane-1-carboxylic Ester

The compounds of interest in this patent, such as **9a**, are used to prepare quinolones that have strong antibacterial activity. The method for the preparation of **9a** involves the dechlorination

of **8a** as shown in Reaction 3. Commercial processes use DMSO as solvent, and a major problem with such a reaction is said to be the increase in viscosity that occurs during the process, and this causes poor mixing. This increases the reaction time, and on a commercial scale this can be several days. In addition DMSO degrades to produce Me_2S that has a very offensive odour and obviously is not environmentally acceptable. The improved process described involves the use of three essential materials. The first is $NaBH_4$ as reducing agent with an aprotic solvent and a Lewis acid. The preferred solvents are DMF, Me_2NCOMe, or *N*-methyl-2-pyrrolidone (NMP), and the Lewis acids are chlorides of Al, Fe(II), Co(II), Pb(II), Ag, or In. A large number of examples is provided, and in one $CoCl_2$ gave a yield of 96% after 1 h. The product is obtained as a solution in PhMe, and the yields are reported as being determined by HPLC of the solution. There are no details of the methods used to isolate the products. Other examples show that without all three key materials there is little or no reaction. The reaction gives a selectivity to the *cis* configuration of >90%. Alternative esters, such as **9b** (R = Et), **9c** (R = Me), are also produced although most examples relate to **9a**. The patent does not give details of the preparation of **8a** and refers only to a Japanese patent. Regarding the stereochemistry of **8a** the patent only points out that it can exist with the F and the ester groups *cis* or *trans* to one another. The examples are carried out with **8a** that contains a mixture of *cis/trans* isomers in the ratio 62:38.

Reaction 3



8a: R = Bu^t **9a:** R = Bu^t

(a) (1) $NaBH_4$, NMP, $CoCl_2$, 50 °, 1 h; (2) H_2O, 5M HCl; (3) Extract in PhMe

Advantages

The process is reported to be more efficient and takes much less time than alternatives.

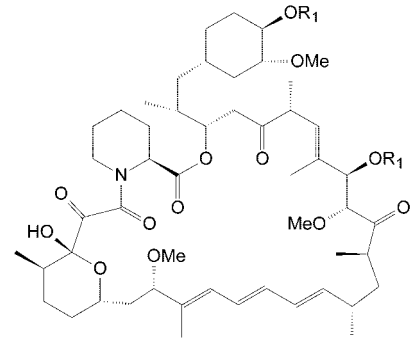
Patent No. U.S. 7,384,953

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

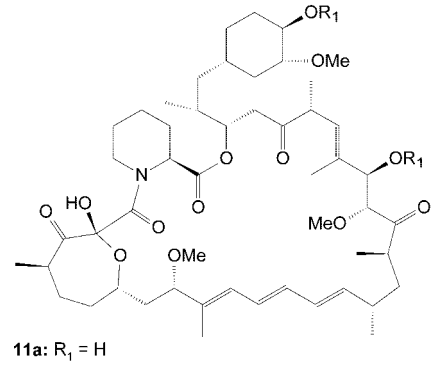
Title or Subject: Purification of Rapamycin

Rapamycin is an antibiotic that has antitumour and immunosuppressant effects and is produced from *Streptomycin hygroscopicus* by fermentation. This is the first of two patents on this compound that consists of the two isomers **10a** and **11a** that are designated Isomer B and C, respectively. Isomer B, **10a**, is preferred, and a ratio of >23:1 is required. In addition a yellow index of <2 is required, and impurities tend to significantly increase this to 20 or more. Since the product is obtained by fermentation, it is obtained in low concentration, and extensive purification by crystallisation is used to meet the required specification of the API. The objective of the patent is to develop a chemical purification method that will give higher yields from the crude product or that can be applied to recovering additional product from mother liquors.

Rapamycin



10a: R_1 = H



11a: R_1 = H

The process initially involves the silylation of the OH groups at positions 31 and 42 to give **10b** as shown in Reaction 4. The mixture containing the silylated compound is filtered, extracted into heptane and treated with charcoal to remove the impurities. Acidification of the purified silylated isomer mixture removes the protective groups and **10a** is recovered in 98.7% purity. The recovery yield is 87.6% with a ratio of isomer B to C of 35:1 and a yellow index of 0.73. Isomer C, **11a** behaves in an identical manner although at a pH < 5.5 it is converted to **10a** and so the ratio of isomer B to isomer C is increased during the deprotection stage of **11b**.

Reaction 4

10a: R_1 = H $\xrightarrow{(a)}$ **10b:** R_1 = Me_3Si-

(a) Imidazole, EtOAc, Me_3SiCl, <5 °C, 1 h

Advantages

The process provides an efficient and simple method of purifying the product while at the same time improving the level of the desired isomer.

Patent No. U.S. 7,393,952

Assignee: Cordis Corporation, Miami Lakes, Florida, U.S.A.

Title or Subject: Solvent Free Amorphous Rapamycin

The second patent on this compound describes in great detail the method of coating medical implants with therapeutic agents and, in particular, coatings that are solvent-free and amorphous. Almost as an afterthought, the patent mentions the preparation of amorphous rapamycin, and the single claim in the patent actually covers this procedure. The amorphous form is prepared by dissolving rapamycin in Pr^{i}OH and then adding water to precipitate the product. The process is carried out in an inert atmosphere, using solvents that have low peroxide content. These precautions are to prevent autoxidation by free radicals.

There are no experimental details of the process although there are copies of the IR, DSC, TG, and HPLC traces of the product.

Advantages

The process enables production of the amorphous form that is presumably more suitable for application by implants.

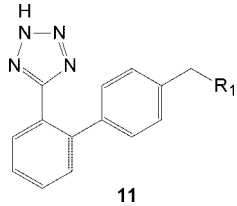
Patent No. U.S. 7,385,062

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

Title or Subject: Process for the Preparation of Phenyltetrazole Derivatives

The compounds of interest in this patent, such as **12b** to **12e**, are intermediates in the synthesis of compounds containing the biphenyltetrazole moiety **11** that are angiotensin II antagonists (AIIA). These are used to treat hypertension, kidney damage due to diabetes, and congestive heart failure. Some AIIA have recently been found to have some effect on the development of Alzheimer's disease.

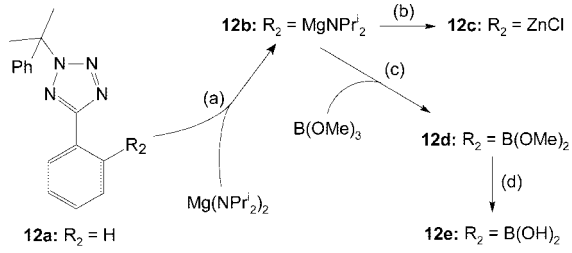
Tetrazoles



11

The major finding reported in this patent is the development of a process to prepare the range of compounds **12b**−**12e** without using Grignard reagents that are described as potentially dangerous on a commercial scale. Reaction 5 summarises the stages that are used to prepare compounds **12b**−**12e**. The starting material for all of these is **12a** that is converted to the Mg amide **12b** by reaction with $Mg(NPr^i_2)_2$. This can be isolated or converted to the Zn chloro compound **12c**, and ^{1}H NMR shows that the conversion to **12c** is >96%. **12b** can also be transformed to **12d** by treatment with $B(OMe)_3$, and again this can be isolated or hydrolysed using H_3PO_4 to give **12d**. The patent also describes the preparation of some other derivatives in which the $PhMe_2C$- group is replaced by Bu^t or Na. The patent states that **11** can be prepared from some or all of the compounds **12b**−**12e**. There are no details given as to which one is used apart from references to two patents.

Reaction 5



(a) THF, reflux, 3 h; (b) $ZnCl_2$, THF, reflux 2 h; (c) (1) THF, < 5 °C, 20 min; (2) rt, 2 h; (3) H_2O, extract in PhMe; (4) Evaporate; (d) (1) H_3PO_4, 35 °C, 2 h; (2) H_2O, PhMe, rt, 3 h; (3) Filter, wash, dry

Advantages

The process avoids the use of Grignard reagents and hence claims to improve the safety aspects.

Patent No. U.S. 7,390,807

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

Title or Subject: Crystal Forms of Lamotrigine and Processes for Their Preparation

This is the first of two patents covering the drug lamotrigine **16**, used to treat epilepsy. The original patents have expired so that market opportunities for new manufacturers exist. The patent describes almost 20 new crystal forms of **16** and also methods for their preparation. The new forms are all solvates that contain varying ratios of different solvents such as alcohols, ketones, ethers, or DMF. The patent also describes a novel hydrate and an anhydrous form D. The claims of this patent cover only two forms designated E and O, and presumably the others are the subjects of further patents. The preparation of the various forms is by crystallisation, and the anhydrous form is obtained by heating some of the crystalline forms. The XRD patterns of several of the new forms are provided.

Advantages

The new forms could provide improved formulations of the drug and enable new entrants to establish a position in the market.

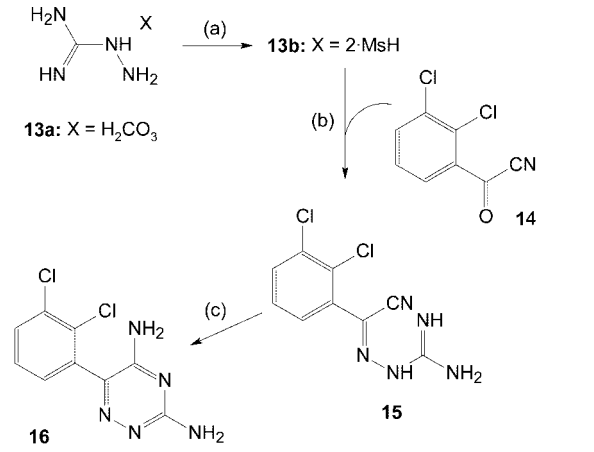
Patent No. U.S. 7,390,899

Assignee: Richter Gedeon Vegyeszeti Gyar, RT, Budapest, Hungary

Title or Subject: Process for the Synthesis of High Purity 3,5-Diamino-6-(2,3-dichlorophenyl)-1,2,4-triazine

This is the second patent on lamotrigine **16**, and it describes a new synthesis. The patent states that the problems with the known processes are low yields, use of aggressive reagents, and long process times. Hence, the objective of this patent is to simplify the process so that **16** can be obtained in high yield and high purity. Reaction 6 summarises the route used, and this begins with the production of a new dimesylate salt, **13b**, that is obtained in 88.1% yield from the hydrogen carbonate salt **13a**. This salt forms the adduct **15** in almost quantitative yield when treated with **14** in MeCN. The adduct **15** is not isolated but cyclised using MgO to give the desired product **16** in 93% yield. The use of MgO for this step is claimed to be in contrast to other cyclisation processes that use strong bases. The product is recrystallised from Me_2CO and recovered in a yield of 70%.

Reaction 6



(a) (1) MsH, MeOH, <22 °C, 1.5 h; (2) 70 °C, 15 min; (3) <5 °C, 1 h; (4) Filter, MeOH, dry; (b) MeCN 70 °C, 1 h; (c) (1) MgO, H_2O, 70 °C, 3 h; (2) Filter, H_2O; (3) <5 °C, filter, wash, dry.

Advantages

The main advantage is the high yield of high-purity product using relatively mild conditions.

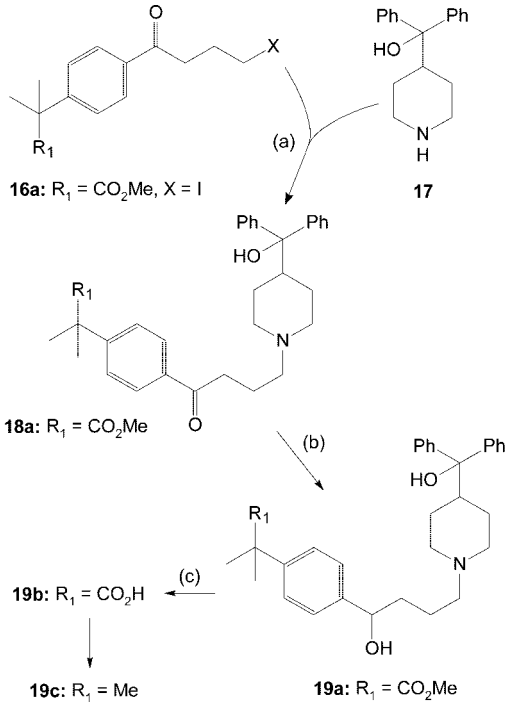
Patent No. U.S. 7,390,906

Assignee: AMR Technologies Inc., Manchester, Vermont, U.S.A.

Title or Subject: Piperidine Derivatives and Process for Their Production

The compounds covered by this patent are antihistamines that are replacements for the drug terfenadine, previously found to cause cardiac arrhythmia after prolonged use; it has now been withdrawn. Piperidine compounds related to terfenadine **19c** (R_1 = Me) have been described, but it is said that their preparation gives inseparable mixtures of aromatic regiosiomers. Hence, the objective of this patent is to develop a process to produce the desired isomer in high yield. Reaction 7 shows the route used to prepare **18a**, a typical compound covered by this patent. This is a straightforward reaction between the iodo-compound **16a** and the piperidine **17** that is catalysed by K_2CO_3. The product **18a** is recovered in 79% yield. The ketone group in **18** can be reduced using $NaBH_4$ to give **19a** is recovered in 70% yield as a foam. Base hydrolysis of **19a** gives the acid **19b** (R_1 = CO_2H) that is purified by chromatography.

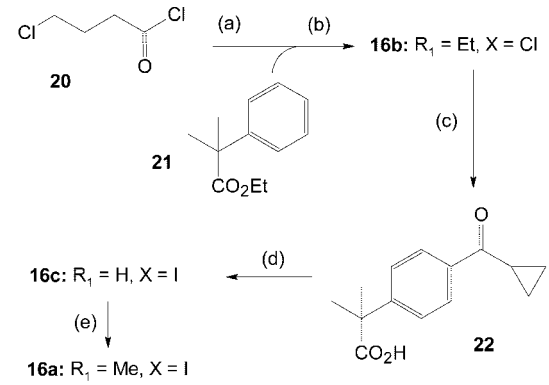
Reaction 7



(a)(1) K_2CO_3, PhMe, reflux, 7 h; (2) Cool, filter, evaporate; (3) Et_2O, HCl, evaporate; (4) EtOAc, filter, dry; (b) (1) $NaBH_4$, MeOH, 0 °C, 1 h; (2) Evaporate, extract in EtOAc, wash in aq NaCl, dry, filter, concentrate; (c) Aq NaOH

The patent also describes methods for the preparation of **16a**, and one of these is shown in Reaction 8. This is a critical reaction because of the importance of isomers, and it is in this stage that the desired isomers are obtained. In the procedure the first step is acylation of **21** with **20** in a Friedel−Crafts reaction that takes place in CS_2 to form **16b**. This reaction actually gives a mixture of the 3- and 4-aryl-substituted isomers that is used in the next step. The mixture of isomers of **16b** is then hydrolysed to give a mixture of isomers of the cyclopropylcarbonyl compound **22**. The desired 4-isomer shown is recovered as a salt by fractional crystallisation from EtOAc containing cinchonidine. The salt is then converted to the pure **22** that is isolated in 33% yield as an oil. Treatment of **22** with Me_3SiI produces **16c** that is recovered in 77% yield. Esterification using CH_2N_2 gives **16a** that is recovered in 96% yield.

Reaction 8



(a) (1) $AlCl_3$, CS_2, -10 °C, 15 min; (2) rt, 15 min;
(b) (1) -10 °C, CS_2, 3 h; (2) rt, 16 h; (3) Extract in $CHCl_3$, wash aq $NaHCO_3$, filter, evaporate; (4) DCM, filter; (5) EtOAc/hexane, evaporate;
(c) (1) Aq NaOH, MeOH, reflux, 1 h; (2) Evaporate off MeOH; (3) H_2O, concd HCl, extract in EtOAc; (4) Cinchonidine, rt, 16 h; (5) Filter, wash in EtOAc, 2N HCl, extract in EtOAc; (6) Evaporate;
(d) (1) Me_3SiI, DCM, <0 °C, 1 h; (2) rt, 1 h; (3) Aq $NaHSO_3$; (4) Extract in DCM, wash aq NaCl, dry, filter, evaporate;
(e) (1) CH_2N_2, Et_2O, 0 °C, 2 h; (2) Filter, evaporate.

During the process for preparing **16a** six different solvents are used plus various aqueous solutions, and the hazardous reagent CH_2N_2 is employed. In addition one intermediate is isolated as an oil, and hence the process as described does not seem to be particularly robust. Whether it could be optimised for large-scale use remains to be seen.

The patent also describes the preparation of other piperidines analogous to **18** and **19a** from **16a** and other piperidinemethanol reactants.

Advantages

The process does enable the desired isomers of the key reactant to be obtained. However, the process involves many solvents and may not be easily carried out on a commercial scale.

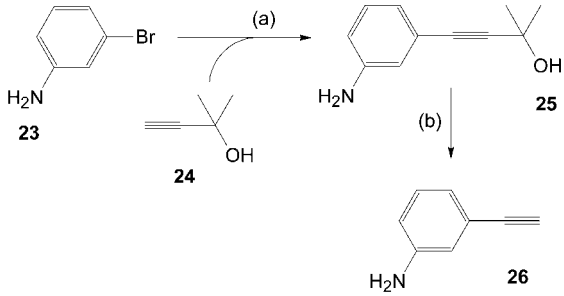
Patent No. U.S. 7,390,927

Assignee: Fujifilm Corporation, Tokyo, Japan

Title or Subject: Process for Preparing 3-Aminophenylacetylenes

The compounds covered by this patent are described as useful chemical intermediates. Processes for their preparation are said to have so many problems that commercial operation would not seem possible. The patent claims to overcome these difficulties and describes a process for the preparation of **26** that is summarised in Reaction 9. In fact the only compound described in the examples is **26**. The reaction proceeds in two steps in which the first is the formation of **25** by coupling of **23** with **24**. This is carried out using a catalyst system comprising salts of Pd and Cu with PPh_3 in the presence of Et_3N. The yield of **25** is 75% after recovery by crystallisation, and in the second step it is treated with base to form **26**. This is recovered by distillation in 88% yield.

Reaction 9



(a) (1) PPh_3, $Pd(OAc)_2$, CuI, Et_3N, reflux, 7 h; (2) Cool, filter off residue; (3) Concentrate filtrate, Pr^iOH, hexane, heat; (4)Cool to 10 °C, filter, wash, dry; (b) (1) NaOH, PhMe, reflux, 3 h; (2) Cool to rt, filter; (3) Wash filtrate in aq Na_2EDTA, H_2O; (4) Distil

Advantages

The patent provides a simpler process for preparing the acetylene without the problems associated with alternative methods, such as handling acetylene.

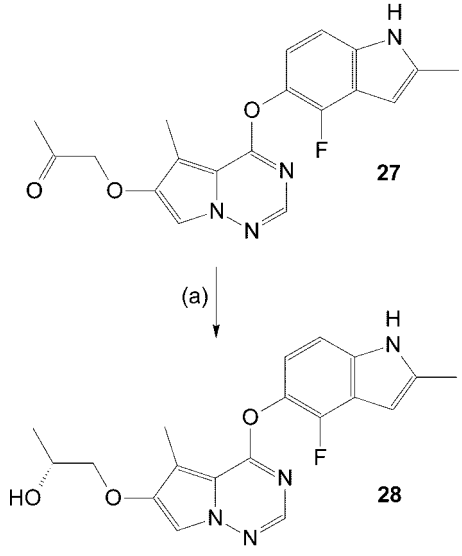
Patent No. U.S. 7,393,667

Assignee: Bristol-Myers Squibb Company, Princeton, New Jersey, U.S.A.

Title or Subject: Stereoselective Reduction Process for the Preparation of Pyrrolotriazine Compounds

The chiral alcohol **28** is an intermediate for the preparation of inhibitors of vascular endothelial growth factor receptor-2, useful as anticancer agents. The process for the production of **28** is carried out by enzymatic reduction of corresponding ketone **27**, shown in Reaction 10. The enzyme used is an oxidoreductase obtained from cell extracts. Much of this patent focuses on the biochemical aspects of the process, and these are not covered here since they are outside of the expertise of this reviewer. It is interesting to note that, although the desired enantiomer is **28**, by using alternative enzymes the other isomer can also be produced. The reaction is carried out at concentrations of up to 100 g/L and gives the product with ee of >93% and in a yield of 70%.

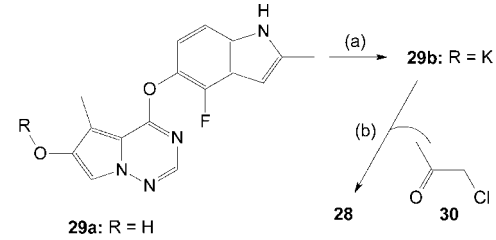
Reaction 10



(a) Oxidoreductase enzyme

The patent also gives details for the preparation of **27** by the reaction of **29b** with **30** in the presence of K_2CO_3 (Reaction 11). The preparation of **29b** from **29a** proceeds without isolation of **29b**, and the mixture is immediately used in the second step. After recrystallisation **28** is recovered in 86.3% yield and shown to be 99.1% pure by HPLC. The reaction can also be carried out using Na_2CO_3, Cs_2CO_3, or DBU as base and in MeCN as solvent.

Reaction 11



(a) KOMe, MeOH, rt, 2 h; (b) (1) K_2CO_3, DMF, rt, 17 h; (2) H_2O, 20 min; (3) Cool to 15 °C, filter, wash H_2O/DMF, dry; (4) Recrystallise THF/H_2O

Advantages

The process provides high yields of the chiral alcohol that is a key intermediate in drug synthesis.

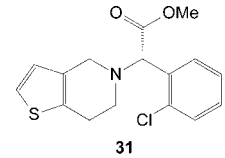
Patent No. U.S. 7,396,931

Assignee: Egus Gyógyszergyár RT, Budapest, Hungary

Title or Subject: Process for the Preparation of Amorphous Form of a Platelet Aggregation Inhibitor Drug

This patent describes a novel method of preparing the amorphous form of the hydrogen sulfate salt of the drug clopidogrel, **31**. This drug is used in preventing blood clots that may lead to heart and circulation problems. The patent states that the production of the amorphous form does not always produce a stable material and it is not possible to predict whether the material produced will be stable or not. The stability refers to the spontaneous formation of crystalline forms. Hence, the objective is to develop a reproducible process for the formation of the amorphous form of **31**. The procedure is to dissolve the base form of **31** in one solvent, adding H_2SO_4, and then adding a second solvent to precipitate the salt. The examples show that the first solvent can be DCM or acetone, and the second solvent, EtOAc, cyclohexane, or Pr^i_2O. The yield of the amorphous salt varied from 82% to 92.8% with the best results obtained using DCM and cyclohexane. The patent gives ^{13}C and ^1H NMR data for the salt. The patent does not mention how the amorphicity or stability is measured.

Clopidogrel



Advantages

The process enables the amorphous form of the drug to be produced in a reproducible manner.

Patent No. U.S. 7,396,934

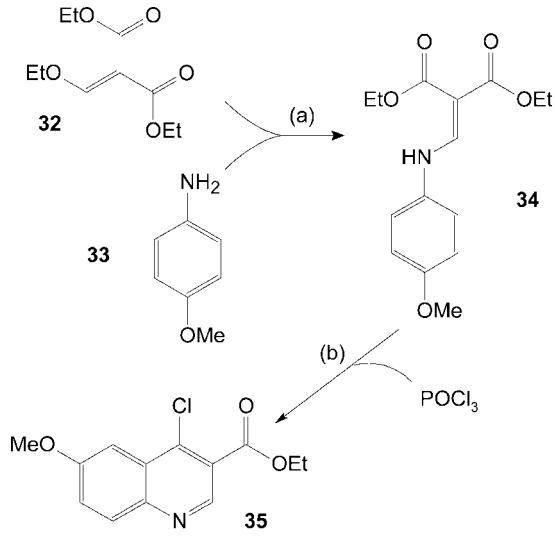
Assignee: Youssef El-Ahmad, et al., France

Title or Subject: Process for Preparing 3-Fluoroquinolines

This patent is from a group of individuals in France with no specified affiliation. The compounds covered by the patent,

such as **36d**, are said to be useful as intermediates for the preparation of chemicals having antibacterial activity. The preparation of **36b** takes place in several stages, and the first stage is the preparation of **35** that is shown in Reaction 12. This begins with the condensation of **32** and **33** to form **34** that is recovered as a viscous oil in quantitative yield. The reaction of **34** with $POCl_3$ followed by base hydrolysis produces **35** that is isolated in 61% yield.

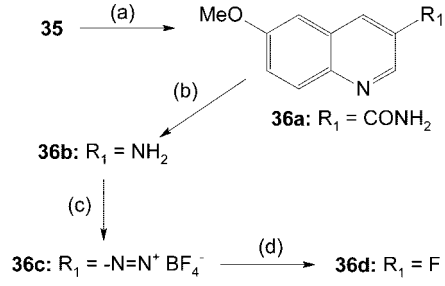
Reaction 12



(a) (1) 14 - 59 °C, 125 min; (2) 95 °C, 1 h; (3) Distil off EtOH, cool to 45 °C; (b) (1) 25 °C, 15 min; (2) 100 °C, 4.75 h; (3) 125 °C, -$POCl_3$; (4) DCM, 47% NaOH, 25 °C; (5) EtOH, 82 °C; (6) Cool <5 °C, filter, wash, dry;

In the next stage of the synthesis, **35** is subjected to a hydrogenolysis reaction using Pd/C, followed by treatment with ammonia, to give a 71% yield of the carboxamide **36a**. A Hofmann degradation reaction of **36a** using NaOH/Br_2 and pyridine produces the amine **36b** that is converted to the diazonium salt **36c**. In the final step, gradual heating in PhMe followed by addition of NaOH gives **36d** after workup in a 76% yield.

Reaction 13



(a) (1) EtOH, 45 °C, 0.5 h; (2) Cool 20 °C, Et_3N, Pd/C, 0.8 bar H_2, 33 °C, 48 h; (3) Filter, aq NH_3, 25 °C, 4 days; (4) Distil off EtOH; (5) <5°C, 3 h; (6) Filter, wash H_2O, dry; (b) (1) Aq NaOH, Br_2, pyridine, 0 °C, 3 h; (2) 60 °C, 7 h; (3) Cool 20 °C, evaporate to dryness; (1) EtOH/H_2O, reflux, 1 h; (2) Cool <5 °C, 2 h, filter, wash H_2O, dry; (c) (1) THF, -15 °C, $BF_3{\cdot}Et_2O$, 15 min; (2) Bu^tNO_2, THF, -15 °C, 1 h; (3) 15 °C, 1 h; (4) Filter, wash hexane, dry (d) (1) PhMe, 60 °C, 85 min; (2) 72 °C, 90 min; (3) 85 °C; (4) Cool to rt, 16 h; (5) H_2O, EtOAc; (5) 47% NaOH pH 7.5, (6) Extract in EtOAc, wash H_2O, evaporate, distil

Some of the stages in this synthesis are carried out on a kilo scale, and this is indicative of the advanced stage of development. Examples are also given for the preparation of the 3,7- and 3,8-difluoro-6-methoxyquinolines by analogous procedures.

Advantages

The patent does claim specific advantages over alternatives and may be suitable for large-scale use.

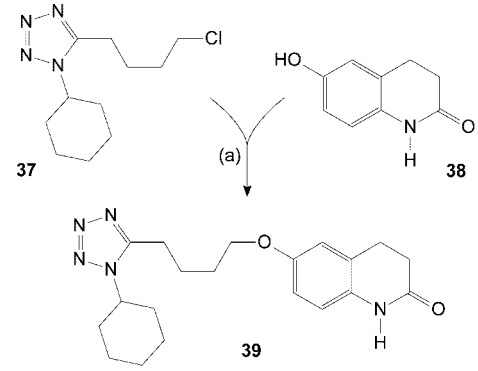
Patent No. U.S. 7,399,864

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

Title or Subject: Process for Producing Carbostyril Derivatives

This patent describes a process to produce the compound **39** known as cilostazol that inhibits platelet aggregation. The drug dilates the arteries supplying blood to the legs and relieves the pain caused by the reduced circulation. Alternative processes to produce **39** are said to give low yields because of a number of problems such as the removal of impurities and disposal of waste. Reaction 14 shows the procedure to prepare **39** by the condensation of **37** with **38**. The reaction mixture is circulated in a continuous disperser, pulverising the mixture and forming small particles <200 μm. The process is carried out in water in the presence of a base and a phase transfer catalyst (PTC) plus Na_2SO_3. The latter reagent is used to prevent discolouration caused by oxidation. The process is carried out to produce >10 kg of product at a yield of 95.6% and purity by HPLC of 99.7%. One example is given in which PhMe/water is used as solvent, and this also gives high yield.

Reaction 14



(a) (1) K_2CO_3, NaOH, But_4NCl, Na_2SO_3, H_2O, 85 °C, 6 h; (2) 50 °C, MeOH; (3) Reflux, 0.5 h; (4) Cool <20 °C, 0.5 h, filter; (5) Wash H_2O, MeOH, H_2O, dry 80 °C

Advantages

The process gives an excellent yield of product that is of high purity.

Patent Nos. U.S. 7,402,699 and U.S. 7,402,700

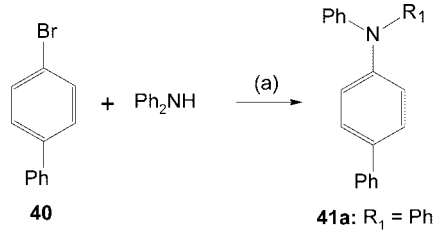
Assignee: Xerox Corporation, Norwalk, Connecticut, U.S.A.

Title or Subject: Processes for Arylamine Production

These two patents cover processes to produce arylamines that are used in electrophotographic imaging systems. The first patent is concerned with the preparation of **41a** and explains that the desired compound is a derivative of 1-biphenylamine; however, this compound is carcinogenic. Hence, it is an objective to avoid preparing this amine, thus removing the need to handle it in an industrial environment. The method used to

synthesise **41a** is by a modified Ullmann reaction of **40** and Ph_2NH. It is stated that **40** is not normally sufficiently reactive to be used in this reaction economically. However, by using a ligand-modified Pd catalyst the reaction between **40** and Ph_2NH can be carried out in a period of time that is acceptable on a commercial scale, and Reaction 15 summarises the process using the ligand PBu^t_3 in the first patent to prepare **41a** in 95.1% yield at a purity of 99.5%. The patent also discusses the preparation of a large number of arylamines derived from **41a** containing siloxane groups attached to the para position of the two phenyl rings. However, no experimental details are described for the synthesis of these compounds.

Reaction 15

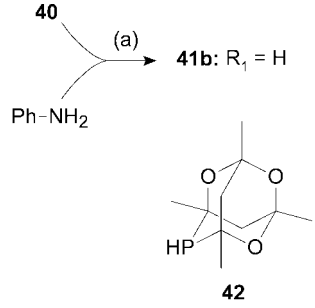


40 **41a:** R_1 = Ph

(a) (1) $Pd(OAc)_2$, PBu^t_3, $NaOBu^t$, PhMe, 70 °C, 1.75 h
(2) PhMe, filter insolubles; (3) Evaporate; (4) Pr^iOH;
(5) MeOH; (6) Filter, wash MeOH, dry

In the second patent the focus is on the preparation of **41b** (Reaction 16) and **43b** (Reaction 17) using a Pd catalyst with the phospha-oxa-adamantane ligand **42**. The process conditions and workup for these reactions are similar to those used for **41a** except that in the preparation of **41b** the base used is NaO(*tert*-pentyl).

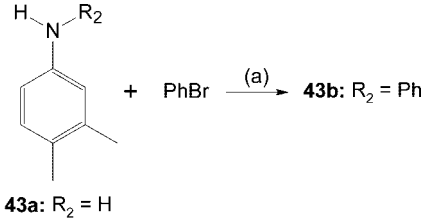
Reaction 16



42

(a) $Pd(OAc)_2$, **42**, $NaOPn^t$, PhMe, 110 °C, 6 h

Reaction 17



43a: R_2 = H

(a) $Pd(OAc)_2$, **42**, $NaOBu^t$, PhMe, 110 °C, 6 h

Advantages

The process avoids the preparation of a carcinogenic intermediate and gives high yields by a more acceptable route.

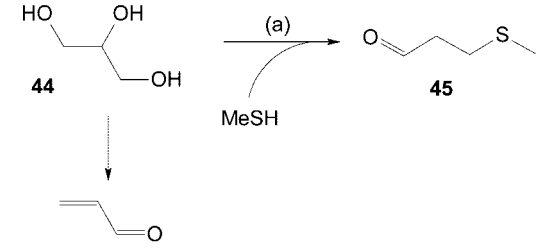
Patent No. U.S. 7,402,705

Assignee: Evonik Degussa GmbH, Essen, Germany

Title or Subject: Production of 3-(Alkylthio)propanal

The title of the patent covers a range of compounds although the main subject is the methyl compound **45** that is used to produce the essential amino acid methionine and its derivatives. **45** is usually produced by the acid-catalysed addition of MeSH and acrolein **46**, but the process described in this patent uses glycerol **44** as the starting material, and this has not previously been reported. However, it is known that pyrolysis of **44** does produce **46**, and so the new process effectively reacts **46** as it is formed from **44** (Reaction 18). It is tempting to speculate that this process has been developed to use some of the large quantities of **44** that are available from the increased quantities of biodiesel being produced. The reaction is carried out by heating **44** with MeSH in an autoclave in MeOH in the presence of a zeolite. Both HZSM-5 and an ammonium-type zeolite are used at 300 °C and at pressure of up to 60 bar. The isolation of the product was not described, and its presence was confirmed by GC. Using HZSM-5 the concentration of **45** was 6% after 1 h, whereas only 0.8% was present after 0.5 h using the other zeolite. The process is a long way from commercialisation, but it may have some potential.

Reaction 18



44 **45** **46**

(a) MeOH, zeolite, 300 °C

Advantages

The process uses a potentially cheap raw material to prepare an important compound, but the commercial viability is unproven.

Patent No. U.S. 7,402,709

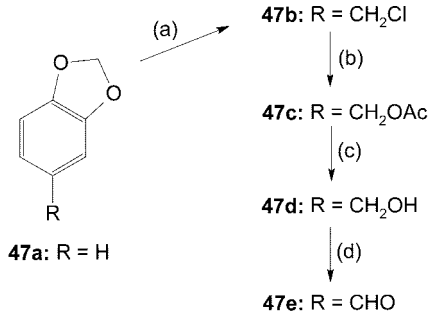
Assignee: Endura S.p.A., Bologna, Italy

Title or Subject: Process for Synthesizing Heliotropine and Its Derivatives

The aldehyde **47e** is known as heliotropine and is used in the production of perfumes. There are a number of methods for producing **47e** from **47a**, but the patent claims that they are not particularly efficient and require purification of intermediates. The patent aims to address this shortcoming with the process summarised in Reaction 19 that takes place in four steps. In the first step the chloromethylation of **47a** is carried out using a mixture of paraformaldehyde and HCl to give **47b** with a 50.9% yield and at a selectivity of 89%. In the next stage, the acetate **47c** is formed, and the crude product is used in the third step where hydrolysis using NaOH in the presence of a PTC gives **47d** in a yield of 97.6%. The

overall conversion of **47b** to **47d** is reported as 100%. In the last step the alcohol is catalytically oxidised to **47e** using air and a Pt/C catalyst. The yield of crude **47e** is 82.3%, and it is purified by distillation and crystallisation to give an 89.3% recovered yield with a purity of 99.2% w/w. The patent does not the address the safety issues that are inherent in the chloromethylation step where carcinogenic compounds will be formed. Dealing with these may in fact outweigh any advantages of the process.

Reaction 19



(a) HCHO, 37% HCl, PhMe, <25 °C, 4 h; (b) NaOAc, H_2O, 85 °C, 4 h; (c) Bu^n_4NCl, NaOH, 85 °C, 2 h; (d) NaOH, H_2O, Pt/C, 85 °C, air, 10 h

Advantages

The process may provide a route to a valuable intermediate without the need to purify the various intermediates in the synthesis.

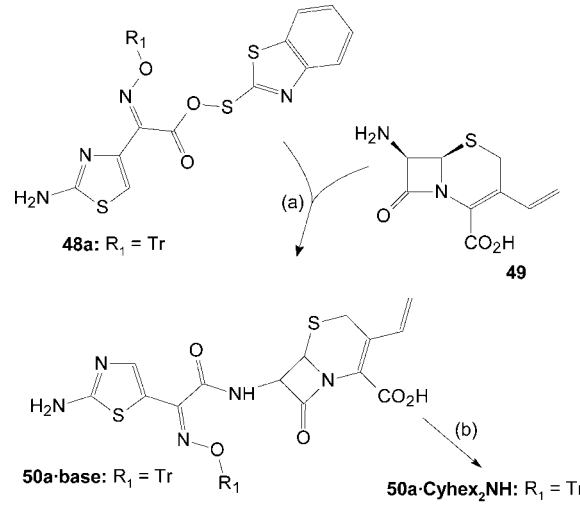
Patent No. U.S. 7,405,294

Assignee: Antibioticos S.p.A., Rodano, Italy

Title or Subject: Intermediate Cefdinir Salts

Cefdinir **50b** (R_1 = H) is a cephalosporin antibiotic having broad-spectrum activity against *Staphylococci* and *Streptococci*, two commonly found and virulent bacteria. Several methods for synthesising **50b** are summarised and said to have numerous drawbacks for commercial operation. In particular, the recovery of intermediates is said to be difficult. The patent discloses a process that enables the salt of a key intermediate, **50a**, to be recovered in high yield and purity. The production of the intermediate salts of **50a** is from reacting **48a** with **49** as shown in Reaction 20. There are a number of amines used, including Et_3N, 1,1,3,3-tetramethylguanidine (TMG), and MeBnNH. There are also alternative procedures described for the recovery of the salts of **50a**. In each case the acid is not isolated but recovered as a salt of the base used. In one method a simultaneous silylation is also carried out, and this procedure is one of the two favoured methods. The other preferred procedure is to extract the salt from the reaction mixture and hydrolyse it to give the acid. This is then extracted and precipitated from the mixture using the base. The salts are isolated and then converted to the dicyclohexylamine salt of **50a** that can then be used to prepare **50b**.

Reaction 20



(a) Base, DMF or Me_2NCOMe, 10 - 25 °C
(b) (1) EtOAc, aq HCl, pH 3.0, (2) $Cyhex_2NH$.
$Cyhex_2NH$ = dicyclohexylamine

Advantages

The process enables the formation and isolation of the important intermediates to be produced in a commercially viable procedure.

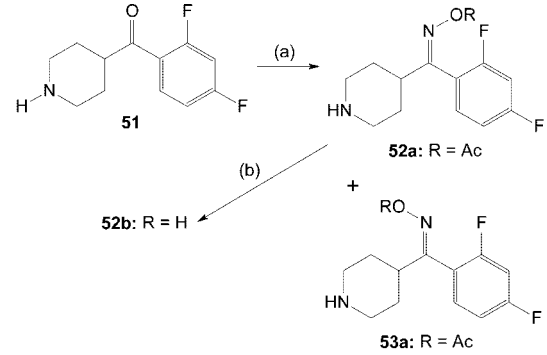
Patent No. U.S. 7,405,298

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

Title or Subject: Process for Making Resperidone and Intermediates

The title compound, **56**, is used to treat schizophrenia, and several methods for its preparation are known. These generally involve the cyclization of an oxime intermediate to form the benzisoxazole ring, and these are summarised. It is the objective of this patent to provide an improved method of making the oxime intermediates that have an increased amount of the desired *Z*-isomer, **52b**. It is only this *Z*-isomer that undergoes the cyclization reaction, and so increasing the *Z*/*E* ratio increases the yield. The patent reports that it is possible to separate the *Z*- and *E*-oxime isomers by conversion to an acetate salt, and Reaction 21 shows this for the formation of the oximes from **51**. Initially the acetate salts **52a** and **53a** are formed, and the *Z*-isomer, **52a**, preferentially crystallises from the reaction mixture after acidification using HOAc in a 75.7% yield. **52a** is then hydrolysed using NaOH to give the oxime, **52b**, that is recovered in 60.5% yield. The acetate salt of *E*-isomer **53a** is obtained from the solution in a 28.5% yield.

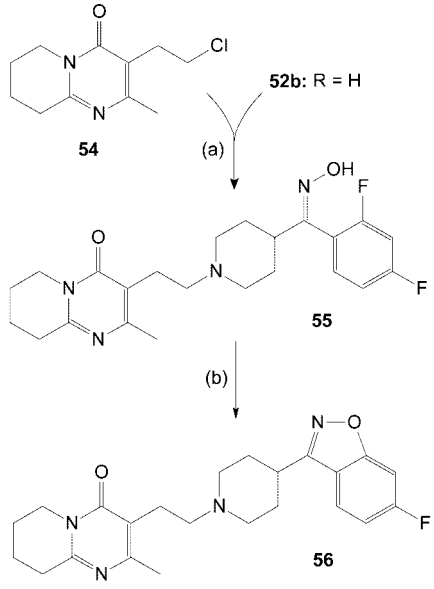
Reaction 21



(a) (1) $H_2NNOH{\cdot}HCl$, EtOH, aq NaOH, 10 min, rt; (2) NH_4OAc, 10 h, 60 °C; (3) HOAc; (4) -15 °C, 4 h, filter, wash EtOH, dry;
(b) Aq NaOH, 1 h, rt, filter, wash H_2O

The next step in the production of **56** is the formation of the intermediate **55**. This is shown in Reaction 22 and involves the alkylation of **52b** with the HCl salt of **54**. The product **55** is isolated in 93.6% yield with purity (HPLC) of 96.2% and then converted to **56** by base-catalysed cyclisation. The final product can be crystallised from alcohols or DMF and is isolated in yields of up to 93%. The cyclisation is complete in less than one hour and can be carried out with KOH or NaOH but prolonged heating causes degradation of **56**.

Reaction 22



(a) (1) KI, K_2CO_3, MeCN, reflux, 3.5 h; (2) Cool rt, aq KOH, pH 10, rt, 4 h; (3) Filter, wash H_2O, dry;
(b) (1) NaOH, EtOH, 70 °C, 30 min; (2) 40 °C, H_2O;
(3) 2 h, rt; (4) Filter, wash H_2O, dry.

Advantages

The process gives an improved atom yield of the key oxime isomer.

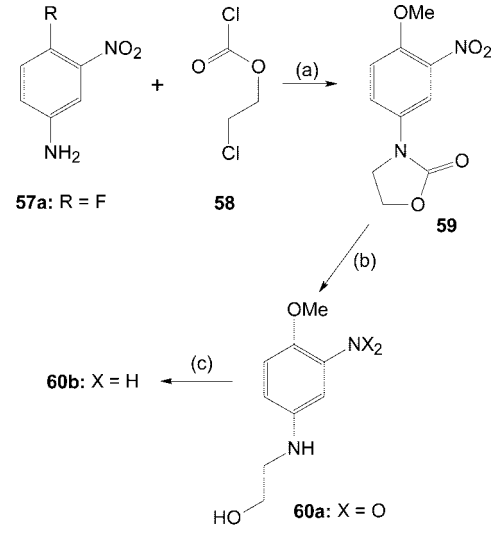
Patent No. U.S. 7,405,325

Assignee: The Proctor & Gamble Company, Cincinnati, Ohio, U.S.A.

Title or Subject: Process for the Preparation of 4-Hydroxyalkylamino-2-nitroanisoles

The compounds covered by this patent, such as **60a**, are intermediates for the synthesis of hair dye couplers such as **60b**. The synthesis of **60a** can result in residual levels of up to 500 ppm of **57b** (R = OMe), and when **60a** is reduced to **60b**, residual **57b** produces the corresponding amino compound that cannot be removed very easily from **60b**. Hence, the objective of this patent is to prepare **60a** with low levels of **57b**, and Reaction 23 shows the route used to achieve this objective. The initial step is condensation of **57a** and **58** to form a carbamate that is not isolated but cyclised to give **59** using NaOMe. The crude product is recovered in 82% yield and then treated with base to give **60a** (X = O) that can be reduced to give **60b** (X = H). Details of this reduction are not given in the patent. The preparation of the 3-hydroxypropyl analogue of **60a** is also given, and this is reported to contain <10 ppm of the undesirable **57b**.

Reaction 23



(a) (1) NMP, <60 °C, 30 min; (2) NaOMe/MeOH, <40 °C; (3) H_2O, 0.5 h; (4) Filter, wash dry; (b) (1) KOH, MeOH, reflux, 5 h; (2) Aq HOAc, <5 °C, filter dry; (c) Pd/C, H_2

Advantages

The process is performed under milder conditions than alternatives and gives a higher purity product.

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