Organic Process Research & Development **2009,** *13,* 669–682

Highlights from the Patents

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

Summary

In the current review there are 19 patents from an initial list of 285 that met the search criteria. Despite there being slightly fewer than usual, there is probably more chemistry described because several of the patents contain some detailed process schemes. Antidepressants are regular subjects in patents, and an enantioselective hydrogenation is described for preparing aminoalcohols that are used as intermediates in producing duloxetine and related drugs. A second patent on antidepressants describes a new demethylation method that can be used in the preparation of desvenlafaxine, the active metabolite in venlafaxine. Those readers who are trying to stop smoking may be interested in two patents. One is a process to produce chinazoline alkaloids that can be used to treat nicotine addition. The second one is a synthetic route to lobelin that is found in certain plants and also helps with smoking cessation as well as treating asthma attacks. Simulated moving bed methods are usually found in the separation of close boiling isomers in the petrochemicals industry or, more recently, enantiomers. A patent uses the technique in a novel reactor for the preparation of acetals using ion-exchange catalysis. Processes for preparing drugs for the treatment of a number of neurological disorders are described in a number of patents. One covers the isolation of aminoindane intermediates for the production of Azilect, a drug used for treating Parkinsonism. The process describes various crystallisation methods. In another patent improvements in the yields of tetrafluorobenzylanilines are described that claim to give lower levels of a dimer impurity without providing analytical details. Olanzapine is used to treat schizophrenia, and a method of preparing the compound is described that avoids using expensive or toxic reagents employed in alternative processes. The HCl salt of atomoxetine is available as the drug Strattera and is used to treat hyperactivity; a high yield process to produce the salt is disclosed that includes a racemisation step. Drugs to treat or prevent coronary problems are covered in this selection of patents, and a very comprehensive one deals with intermediates for producing statins. It describes the stereoselective preparation of a C7 side chain that is common in the statins. A stereoselective process for the preparation of chiral azetidinones is described, and these can be used to treat atherosclerosis. Factor Xa inhibitors are also used to treat coronary diseases, and a patent describes the production of pyrrolidine carboxylic acids that can be useful in preparing these important drugs. The process uses the cheap bulk chemical urea although half of it is wasted. Patents are reviewed that describe processes to prepare drugs for the treatment of viral infections. One of these covers a very large amount of work on entecavir for hepatitis B and involves preparing several novel intermediates using a C−Si oxidation step. The other describes dioxolones that are HIV integrase inhibitors. It uses a K-containing base in a coupling reaction that would normally be expected to require a stronger base. The drug Gleevec is used for treating leukaemia, and the usual synthetic methods require the use of the toxic reagent, cyanamide. A new process avoids using this compound, and like another one mentioned above, uses urea. A very long and detailed patent describes a new method for producing the antihistamine carebastine. Despite the amount of information on the proposed process there is a lack of experimental detail to support many of the claims. Another detailed patent describes an improved method of producing the veterinary antibiotic ceftiofur. Methionine is a very important amino acid, and a new preparation of a α-hydroxyketone is described using a carbene-catalysed umpolung reaction of aldehydes. An interesting feature of this patent is that from over 3.6 million U.S. patents issued since 1976 this is the only one containing the word umpolung in the title. A patent details improvements in preparing pioglitazone and rosiglitazone, drugs that are used for treating type II diabetes. A catalytic hydrogenation process for reducing a C═C bond is replaced by using dithionite in water and reduces the safety issues associated with H_2 under pressure. There is no legal or commercial significance in the choice of patents in this review although a number of patents describe experiments on kilo scale and above. One in particular has only one example, but it does report making 50 kilo of material, and so it is clearly at an advanced stage of development if not in commercial operation. 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. 7,488,833

Assignee: Merck Patent GmbH, Darmstadt, Germany

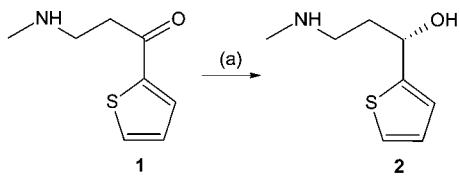
Title or Subject: Process for the Production of Aminoalcohols by Enantioselective Hydrogenation

The patent describes the use of transition metal complexes, containing chiral phosphine ligands compounds, as hydrogenation catalysts in the preparation of **2**. This and the 1-phenyl analogue compound are said to be useful in the preparation of

10.1021/op900144u CCC: $40.75
Published on Web 07/17/2009

antidepressants such as duloxetine, fluoxetine, and tomoxetine. Alternative enantioselective processes for preparing chiral aminoalcohols are claimed to give poor ee values or require a resolution step, thus reducing overall yield. Reaction 1 shows the preparation of **2** by catalytic hydrogenation of the ketone **1**.

Reaction 1



1 **2**

(a) MeOH, PhMe, $(COD)Rh_2Cl_2$, *S*-BINAP, 50 °C, 60 bar H_2, 8 h.

Isolation of the product followed by crystallisation in MTBE/PhMe gives **2** with ee of >99% although the final yield is not given. The patent also describes the use of alternative chiral phosphine ligands to S-BINAP. The claims also cover the preparation of 1-phenyl analogue of **2** in which the 2-thienyl group is replaced by Ph. but no experimental details are provided.

This actual title on this patent is the enantioselective hydrogenation of aminoalcohols, whereas it is clearly concerned with their production by enantioselective hydrogenation. Whether this is due to a mistake in translation or not there can be no excuse.

Advantages

The process gives higher enantioselectivity than alternative methods.

Patent No. U.S. 7,488,851

Assignee: Universidade Do Porto, Porto, Portugal

Title or Subject: Industrial Process for Acetals Production in a Simulated Moving Bed Reactor

Simulated moving bed (SMB) adsorption processes have been used since the early 1960s for large-scale separation of hydrocarbon mixtures such as *p*-xylene from C8 aromatics. Over the past 10 years SMB chromatography has been commercialised on more modest scales for the separation of enantiomers. The current patent applies the SMB concept to the preparation of acetals using a reactor containing an ion-exchange resin (IER) as catalyst. The single example in the patent describes the preparation of $MeCH(EtO)_2$ from MeCHO and EtOH in a SMB reactor using the cationic IER Amberlyst 15 as catalyst. SMB systems use a liquid as desorbent to regenerate the solid adsorbent, and in this process the alcohol used to prepare the acetal is used as desorbent. A comparison of the conversion of the MeCHO using different reactor configurations shows that the SMB reactor achieves 99.7% conversion whereas a fixed bed adsorptive (FBA) type has only 54.5%. The product from the SMB reactor contains 71% of acetal with 99.7% purity, whereas the FBA gives a product containing only 48% acetal that has a purity of 37.1%. The large improvement is because in the operation of the SMB reactor the product is continuously removed and the equilibrium is shifted towards product formation. This is an innovative method of overcoming equilibrium-limited reactions that could be applied to other reactions.

Advantages

The operation of any SMB device requires a complex, multivalve switching device with a sophisticated control system, but there are clearly large advantages in overcoming equilibrium limitations.

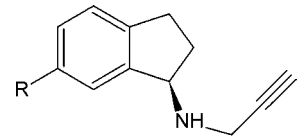
Patent No. U.S. 7,491,847

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

Title or Subject: Method for Isolating Propargylated Aminoindans

This patent is concerned with the isolation of **3a**, rasagiline, which as the mesylate is known as Azilect and is used in treating Parkinson's disease. **3a** is also used to produce ladostigil **3b**, which is used as the tartrate salt for the treatment of Alzheimer's disease.

Aminoindanes



3a: R = H; rasagiline
3b: R = $EtN(Me)CO_2$-; ladostigil

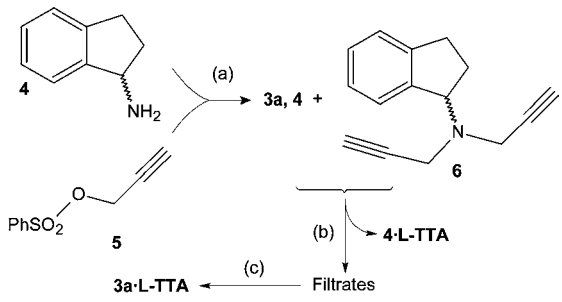
The production of **3a** is from the indane **4** and **5** as shown in Reaction 2, and this also produces a racemic mixture plus the byproduct dipropargyl compound **6**. The recovery of the desired pure enantiomer from the reaction mixture involves several stages including separation from **6** and then resolution of the racemic mixture to obtain the desired isomer. The patent states that all separation methods have shortcomings, and it discloses an improved method of recovering the desired enantiomer from the reaction mixture. The patent describes several experiments using a range of methods to recover the pure desired isomer from the reaction mixture. The methods cover extraction, direct precipitation, and two methods covered by the patent. The first is termed the aminoindane crystallisation method (ACM) and the second is the water recrystallisation method (WRM).

The extraction method requires many steps and uses a great deal of acidified solvents, and the precipitation method gave product that is contaminated with **4** and the *S*-enantiomer. The two new methods were applied to the isolation of both **3a** and **3b** and a key finding is that the final crystallisation of **3a** or **3b** should not be carried out when residual **4** is present.

The ACM as applied to isolation of the L-tartaric acid (L-TTA) salt of **3a** is summarised in Reaction 2. After the completion of the reaction between **4** and **5** a solution of L-TTA is added to the hot solution, and this precipitates the L-TTA salt of unreacted racemic **4** containing 0.1% **3**. This salt can be reused in the synthesis step to improve the process yield. After

removal of unreacted **4** more L-TTA is added to precipitate the salt **3a·L-TTA** with 0.4% **4** and an ee of 96%. This process is carried out using H_2SO_4 in the first step to remove **4** as its sulphate salt.

Reaction 2



(a) (i) PhMe, NaOH, H_2O, 45 °C, 4 h; (ii) Evaporate PhMe;
(b) (i) Pr^iOH, L-TTA, H_2O, reflux; (ii) Filter hot, wash, dry;
(c) (i) L-TTA, H_2O, reflux; (ii) Cool 25 °C, filter, wash dry

Using the WRM it is possible to obtain a pure salt of **3a** from crude material recovered by the extraction and direct precipitation methods. The procedure involves taking the crude material and recrystallising it from water heated to 60−80 °C. Not only does this give an improvement in the product purity, it also gives crystals with improved morphology. The crystals obtained from extraction and direct precipitation are needles, whereas recrystallisation from water gives rodlike crystals that are easier to handle.

Advantages

The method gives crystals with improved purity and morphology.

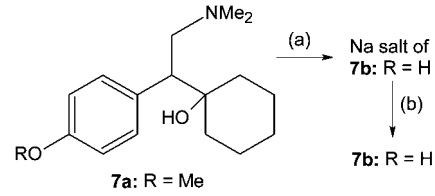
Patent No. U.S. 7,491,848

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

Title or Subject: Process for Making Desvenlafaxine

Desvenlafaxine **7b** is an active metabolite of the antidepressant venlafaxine **7a**, and is being tested as a substitute for **7a**. A process for a key step in the preparation of **7a** was reviewed recently (*Org. Process Res. Dev.* **2009**, *13*, 381). **7b** is usually prepared from **7a** by a demethylation procedure, and the patent mentions that the methods using $LiPPh_2H$, L-selectride and PhSH are inefficient. The patent therefore discloses a new demethylation process using a metal sulphide that may be combined with Se. Reaction 3 shows the procedure without using Se and this gives yields of up to 77%. When Se is used the yield falls to 60%. The advantages of using Se for this improvement against the disadvantages of using a toxic material are not clear. The reaction initially forms the Na salt of **7b** but this is not isolated and addition of water in the second step decomposes the salt to give the free base. This is said to be surprising but it does avoid the use of an acid. The two-step process is carried out in one reactor. The use of *N*-methylpyrrolidone (NMP) as solvent allows the crystallisation of **7b** to take place quite easily when a nonpolar antisolvent is added with the water. The use of sulphides other than Na_2S is covered in the claims in the patent although it is stated that K polysulphide is slower. The process can use hydrated Na_2S rather than the anhydrous material since it is cheaper, and the water is removed during the heating stage.

Reaction 3



(a) $Na_2S·H_2O$, NMP, 145 °C, 33.5 h;
(b) (i) Cool, add EtOAc, H_2O; (ii) Refrigerate, filter, dry.

Advantages

The process is claimed to be more efficient than alternatives but uses less than desirable reagents.

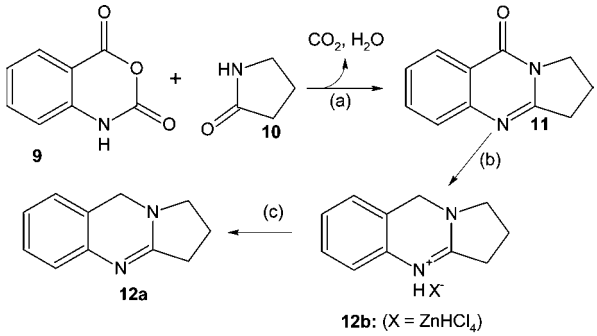
Patent No. U.S. 7,495,096

Assignee: HF Arzneimittelforschung GmbH, Werne, Germany

Title or Subject: Process for the Production of Chinazoline Alkaloids

The patent describes a process for producing intermediates in the preparation of **12a**, that is known as deoxypeganine. This compound occurs in some plants and is a reversibly active cholinesterase inhibitor and hence of interest in the treatment of drug and nicotine addiction and Alzheimer's dementia. A number of methods for preparing **12a** are summarised, and these tend to produce large amounts of byproducts and use environmentally unacceptable reagents and solvents such as $CHCl_3$ or PCl_3. In addition, to obtain high-purity product it is necessary to use expensive recovery methods such as high-vacuum distillation. The new process is aimed at overcoming such problems by the route shown in Reaction 4. The first step is the production of **11** by reaction of the anhydride **9** with excess of **10** at temperatures up to 180 °C. A surprising finding is that the use of excess of **10** reduces byproduct formation and allows ready crystallisation of **11**. The crystallisation requires up to 100 h at rt but can be reduced to about 72 h by increasing the temperature to at least 25 °C. The conversion of **9** to **11** is >90%, and **11** is obtained as crystals containing up to 30% of **10**. The wet crystals are used in the next stage where a Clemmensen reduction of **11** is carried out with the Zn dust being added in small portions over an unspecified time. The product is the salt **12b** that is recovered in 90% yield. Treatment of **12b** with hot NaOH solution gave the free base **12a** that was crystallised from hot H_2O and isolated in 90% yield at 99.9% purity by NMR.

Reaction 4



(a) (i) 100 °C, 1 h; (ii) 160 °C, 5 h; (iii) 180 °C; (iv) 50 °C, seed; (v) rt, 100 h; (b) (i) HOAc, 50 °C; (ii) Zn, 60 °C, 1 h; (iii) Concd HCl over 2 h; (iv) 60 °C, 5 h; (v) Filter, seed, crystallise; (c) (i) Aq NaOH, 100 °C; (ii) Separate; (iii) Dissolve in hot H_2O, crystallise.

The patent also describes carrying out the reduction of **11** in the presence of H_2SO_4, and this produces the salt **12c** (X = HSO_4). This can also be converted to **12a**. The effect of using excess **10** is shown in a comparative example using equimolar amounts of **9** and **10** when the yield of **11** was only 21%.

Advantages

The process provides higher-purity product in a more efficient process, and examples describe kilo-scale experiment, thereby suggesting a process at an advanced stage of development.

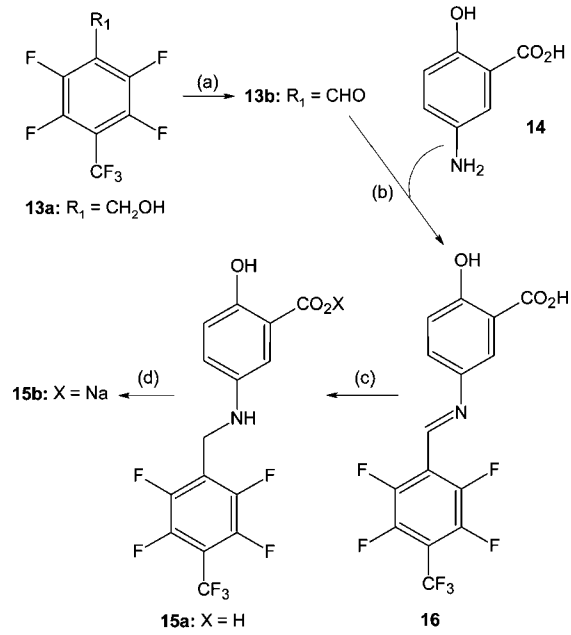
Patent No. U.S. 7,495,126

Assignee: Choongwae Pharma Corporation, Seoul, Korea

Title or Subject: Process for the Preparation of a Tetrafluorobenzylaniline Compound and its Pharmaceutically Approved Salts

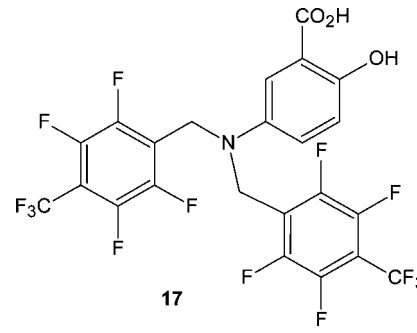
The compounds of interest in this patent are the acid **15a** and metal salts such as **15b** that are used to treat neurodegenerative diseases. One process for preparing **15a** uses the bromomethyl compound **13c** (R_1 = $BrCH_2$) with aniline compounds such as **14** but produces the byproduct dimer **17** at levels >1%, and it is not easy to reduce this to 0.1%. The patent therefore describes a process that uses alternative reagents giving **15a**, containing much lower levels of **17**. Reaction 5 shows the method to prepare **15a** starts from the alcohol **13a** that is oxidised to the aldehyde **13b** using PCC. **13b** is recovered as an oil in 98% yield and is then reacted with **14** in the presence of 4Å mol sieves in a condensation−dehydration to give **16**. This can be recovered as a solid in 88% yield or used directly in the next stage in which it is hydrogenated to give the amine **15a**. The example describes using an unidentified Pt catalyst and omits any mention of H_2, although it does report that the reaction is carried out at a pressure of 4 atm. After workup **15a** is recovered as crystals in 85% yield and with purity by HPLC of 99.8%. The acid can then be converted to the Na salt **15b** in 100% yield. Examples also describe the preparation of the Li and K salts by the same procedure. Alternatively, all three salts may be prepared using the 2-ethyl hexanoic acid metal salt, but this gives slightly lower yields.

Reaction 5



(a) (i) PCC, DCM, rt; (ii) Reflux, 4 h; (b) DCM, 4A mol sieve, rt, 16 h; (c) Pt catalyst, EtOH, 25 °C, H_2, 4 atm, 2 h; (d) 1M NaOH, H_2O, pH 7, 10 °C, 2 h.

Dimer



Advantages

The process gives very good yields of product with low levels of the byproduct dimer although the patent does not actually report any analytical data for the levels of **17** found in the product.

Patent No. U.S. 7,498,431

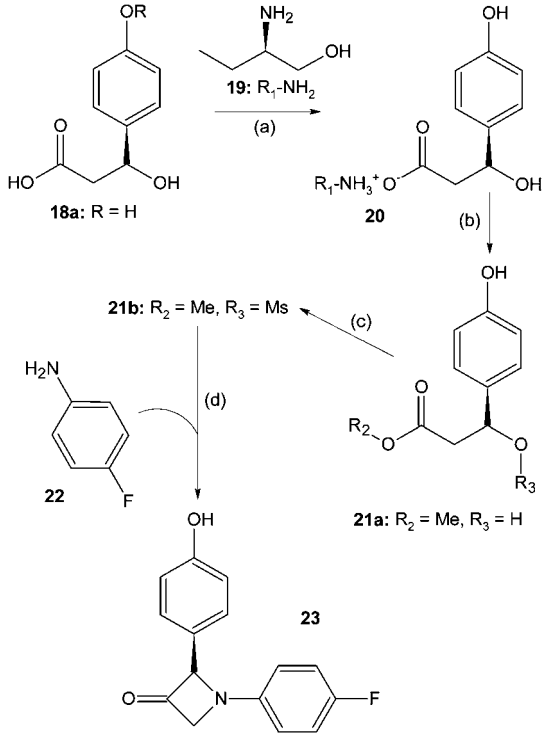
Assignee: Bomi Patel Framroze, Mumbai, India

Title or Subject: Process for the Preparation of Chiral Azetidinones

This patent, that is not assigned to any organisation, is concerned with azetidinone compounds such as **23** that are

intermediates in the preparation of drugs used to treat atherosclerosis. Patents covering other azetidinones for such uses have been reviewed previously (*Org. Process Res. Dev.* **2004**, *8*, 10). This patent discloses a novel stereospecific procedure for preparing a range of azetidinones. The preparation of **23** is outlined in Reaction 6 and begins with the production of the chiral amine salt **20** from the amino alcohol **19** and **18a**. The salt is recovered and dried before conversion to the methyl ester **21a** using HCl/MeOH. Treatment with MsCl produces **21b** that is isolated in 90% yield, and then reaction with aldehyde **22** in the presence of NaI produces **23** that is isolated in a yield of 65.6%. The patent also describes the preparation of other esters analogous to **21b** in which R_2 = Et and R_3 = Ms or Ts or R_2 = Me and R_3 = Ts or Ac. ^{1}H NMR data are given for all of these compounds that can be used to prepare **23**. The patent also describes the preparation of the azetidinone formed from **21b** and 3,5-dichloroaniline.

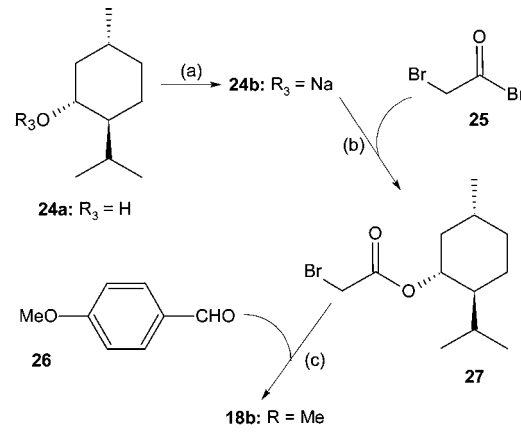
Reaction 6



(a) EtOH/H_2O, 78°C; (b) (i) 5% HCl/MeOH, reflux, 2 h; (ii) Evaporate; (c) Et_3N, THF, 35°C, 2 h; (d) NaI, Me_2CO, reflux, 8 h.

The patent describes the preparation of the chiral methoxy compound **18b** by the route shown in Reaction 7. It is presumed that **18b** can be used to prepare **18a** although details are not provided. The first step in the preparation of **18b** is the production of the L-menthol Na salt **24b**, and this is isolated and then treated with **25** to form the bromoacetic ester **27**. This is not isolated and treated directly with **26** in the presence of Zn/Cu pellets (ratio 9:1) and $CuCl_2 \cdot 2H_2O$ to form **18b**.

Reaction 7



(a) NaOH, H_2O, reflux, 4 h; (b) PhMe, rt,10 h; (c) (i) Zn:Cu pellets, reflux; (ii) $CuCl_2 \cdot 2H_2O$, reflux, 3 h; (iii) Aq NaOH; (iv) 2N HCl; (v) Extract in PhMe, evaporate, dry.

Advantages

The process is claimed to be a more efficient and highly stereoselective procedure for preparing the azetidinones.

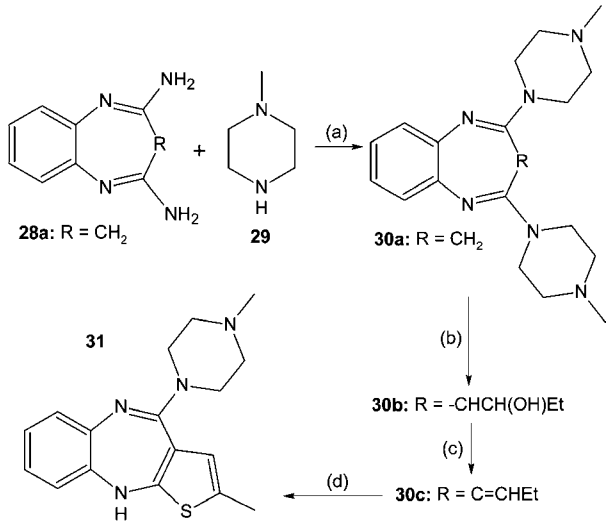
Patent No. U.S. 7,498,433

Assignee: KRKA, Tovarna Zdravil, D.D., Novo Mesto, Slovenia
Title or Subject: Process and Intermediates for the Preparation of Olanzapine

Olanzapine **31** is a drug used for treating patients with schizophrenia and manic episodes associated with bipolar disorder and a patent on its synthesis was reviewed last year (*Org. Process Res. Dev.* **2008**, *12*, 556). A number of processes for preparing **31** are summarised and are claimed to have many problems such as high costs because of low yields in the initial steps, large amounts of waste products, and the use of expensive catalysts or toxic reagents. Reaction 8 summarises the process described in the patent that starts with the formation of **30a** from heating **28a** and **29** at 120 °C for 16 h. The total yield of **30a** after workup was 82%. In the next step **30a** is treated with the strong base LDA, and the alkali salt is reacted with EtCHO to give the alcohol **30b** that is recovered in 92% yield. **30c** is obtained in 84% yield from **30b** by dehydration but it is also possible to convert **30a** to **30c** without isolation of **30b** and the yield of **30c** is 89%. In the final stage **30c** is heated with sulphur in the presence of quinolinium tosylate (TsQ) to give **31** in 69.5% isolated yield. Using alternative tosylates in this reaction the conversion of **30c** to **31** gives lower yields of between 51% and 67%.

The patent gives basic ^{1}H NMR data for the intermediates shown in Reaction 8.

Reaction 8



(a) (i) DMSO, PhMe, 120 °C, 16 h; (ii) Cool, filter; (b) (i) LDA, THF, -30 °C; (ii) -5 °C; (iii) EtCHO, THF, -30 °C; (iv) 10 °C, H_2O, extract in $CHCl_3$; (c) (i) Et_3N, pyridine, TFAA, THF, 0°C,1 h; (ii) MeOH; (iii) Aq NaOH, 10 °C; (iv) Extract in DCM, dry, evaporate; (d) (i) TsQ, S, PhCN, 140 °C, 13.5 h; (ii) evaporate at 80 °C; (iii) DCM, 2M HCl, pH 0.9; (iv) Extract in DCM, dry evaporate.

Advantages

The process gives high yields in the various steps and does not use expensive catalysts.

Patent No. U.S. 7,498,443

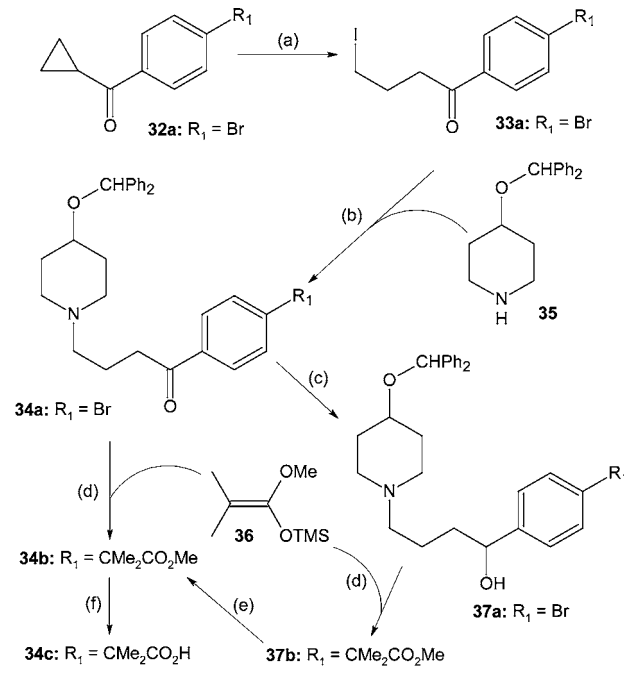
Assignee: Albany Molecular Research Inc., Albany, New York, U.S.A

Title or Subject: Process for Production of Carebastine

Carebastine (**34c:** $R_1 = CMe_2CO_2H$) is a non-sedating antihistamine that is used to treat various allergies. Processes to make **34c** often include a Friedel−Craft reaction step, and it is claimed that these have major shortcomings. One problem is that only acyl halides or anhydrides can be used, and another is that CS_2 is used as reaction solvent. Methods that do not use Friedel−Craft reactions are also known, and the patent makes no comments on the efficacy of these. The patent describes processes to make **34c** and also other related piperidine derivatives. The patent covers a substantial number of reactions and reaction schemes although experimental details are not included for many of them. Reaction 9 summarises a complex series of reactions used to prepare **34c** and intermediates in its preparation. The first step involves opening of the cyclopropyl ring of **32a** using Me_3SiI to form the iodo compound **33a** in up to 98% yield. Base-catalysed condensation of **33a** with the piperidine **35** gives **34a** that is isolated in 54% yield after flash chromatography. The conversion of **34a** to **34c** is possible by alternative routes, and there are examples for those shown in Reaction 9.

One route involves the coupling of **34a** with **36** to give the isobutyrate **34b** that is catalysed by $Pd(dba)_2$ and a phosphine in the presence of ZnF_2. The product is isolated in 67.8% yield and then hydrolysed in NaOH/MeOH to give the **34c** that is isolated by extraction into $CHCl_3$ but no yield is given. In an alternative route from **34a** the alcohol **37a** is initially formed by reduction of **34a** using $NaBH_4$ and **37a** is then coupled with **36** using the same Pd, phosphine, ZnF_2 catalyst to produce **37b**, and this is oxidised to give **34b** using MnO_2. There are no yields reported for any of the steps in this route from **34a** to **34b** via **37a**.

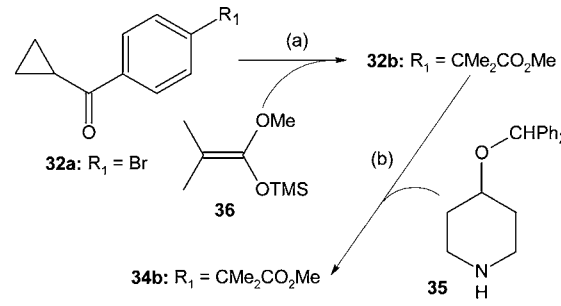
Reaction 9



(a) (i) Me_3SiI, DCM, 0 °C, 30 min; (ii) Aq $NaHSO_3$, rt; (b) K_2CO_3, DMF, rt, 2 h; (c) $NaBH_4$, MeOH, 0 °C, 1 h; (d) ZnF_2, $P(Bu^t)_3$, $Pd(dba)_2$, DMF, 80 °C, 2h; (e) MnO_2, DCM; (f) NaOH, H_2O/MeOH, reflux, 1 h.

Another method of making **34b** is shown in Reaction 10. However, no experimental details are given for this route that starts with the Pd-catalysed coupling of **32a** with **36** to give the isobutyrate **32b**. Condensation of **32b** with **35** then produces **34b**.

Reaction 10

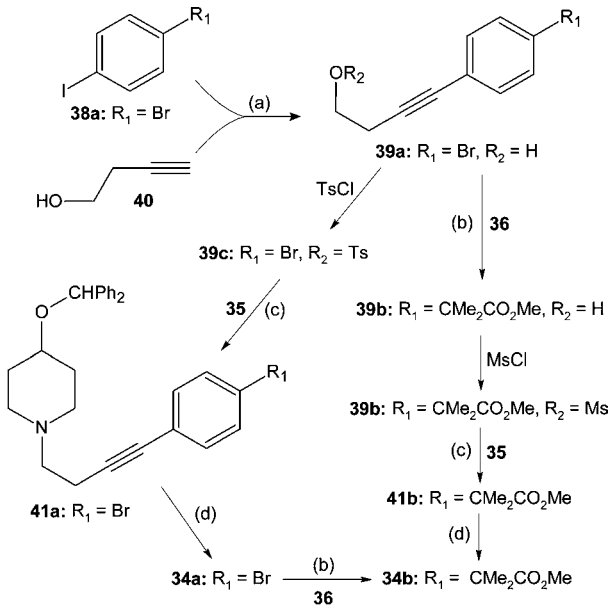


(a) ZnF_2, $P(Bu^t)_3$, $Pd(dba)_2$, DMF, 80 °C, 2h; (b) TsOH, PhMe.

Another reaction scheme described in the patent is shown in Reaction 11 and relates to the production of a series of acetylenic compounds. No actual experimental details are given in the patent although the reactions used are identical to those

shown in Reaction 9. This scheme begins with the formation of **39a** from **38a** and the acetylenic alcohol **40** using a Pd/Cu catalyst system. The acetylenic alcohol **39a** can then be converted via two routes to compound **34b**. In one case the isobutyrate **39b** is formed first, and in the other the benzhydryl compound **41a** is formed initially.

Reaction 11



(a) $PdCl_2(PPh_3)_2$, CuI, piperidine; (b) ZnF_2, $P(Bu^t)_3$, $Pd(dba)_2$, DMF, 80 °C; (c) Solvent, base; (d) HgO, H_2SO_4,

The patent also describes other series of piperidines, but yet again there are no experimental details and the interested reader is encouraged to consult the patent.

Advantages

The patent discloses new procedures for producing a range of piperidine intermediates, and the desired but the commercial viability of these cannot be assessed.

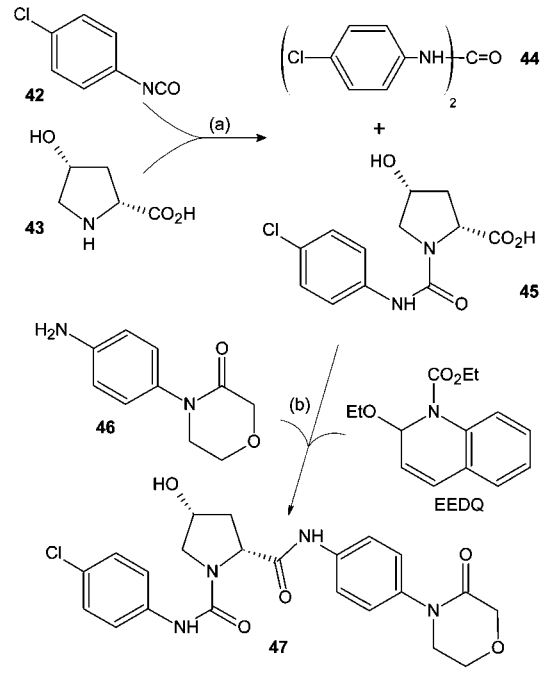
Patent No. U.S. 7,504,500

Assignee: Merck Patent GmbH, Darmstadt, Germany

Title or Subject: Method for the Production of Pyrrolidine-Carboxylic Acid Derivatives as Intermediates in Preparing Factor Xa Inhibitors

Factor Xa inhibitors can be used both to treat and to prevent several coronary disease, and this patent describes a process for producing compounds such as **47** that can be used to prepare Factor Xa inhibitors. The known processes used to prepare **47** and related compounds are said to have several steps, and this patent discloses a route to **47** that is shorter and more efficient. Reaction 12 summarises the method used to make **47** that begins with the reaction of the isocyanate **42** with **43** in water in the presence of $NaHCO_3$ to form **44** that is isolated in 81.8% yield plus the urea **45** that is precipitated from the solution and filtered off. In the second stage of the process **44** is coupled with the amine **46** in the presence of an equimolar amount of the reagent EEDQ to form **47** that is isolated in 69% yield.

Reaction 12



(a) (i) $NaHCO_3$, H_2O, 80 °C, 1 - 10 h; (ii) conc HCl, filter; (b) THF, rt, 20 h.

In the production of **44** the amount of **45** formed is considerable because the reaction uses 2 mol of **42** per mole of **43**. Although **42** is presumably relatively cheap, half of it is wasted in the formation of **45**, and this is a byproduct that requires disposal.

Advantages

The process has a poor atom yield of one starting material but it does have only two steps.

Patent No. U.S. 7,504,532

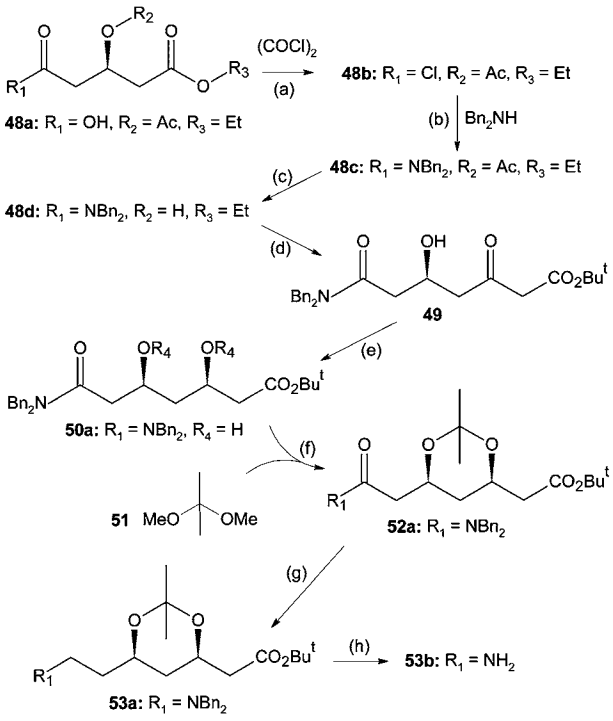
Assignee: Teva Pharmaceutical Industries Ltd., Petah Tiqva, Israel

Title or Subject: Process for the Preparation of 7-Amino syn-3,5-Dihydroxyheptanoic Acid Derivatives and Intermediates

There are three claims in this patent, and they cover compounds exemplified by **53b** that is an intermediate in the production of statins, the cholesterol-lowering drugs. These compounds have the common structural feature of a C7 side chain, and a key step in their synthesis is the introduction of the correct stereochemistry (*R*) at the C3 position. The patent covers a very substantial amount of work and specifically mentions the use of the intermediates in the production of atorvastatin. The route used to prepare **53b** and several intermediates is outlined in Reaction 13 although only the main reaction conditions are included because of space limitations. The initial stages of the process are the conversion of the acetoxyglutaric ester **48a** to the carboxamide **48d** by standard methods that give high yields. ^1H NMR data are given for each product in this sequence. By starting from **48a** the stereochemistry is assured from the outset. In the next stage **48d** is then treated with Bu^tOAc in the presence of a strong base to give **49**. The syn-selective hydrogenation of **49** is carried out using

a Pt/C catalyst in the presence of $Mg(OAc)_2$, and this forms **50a**. This experiment is carried out on a kilo scale, and **50a** is obtained in 98% yield with a syn/anti ratio of 7.6. When **50a** is treated with **51** the product **52a** is isolated in 98% and is described as pure by NMR. Reduction of the carboxamide group in **52a** using $NaBH_4$ gives **53a** that is converted to **53b**. This is carried out by catalytic hydrogenolysis using Pd/C with **53b** being obtained as a solution in hexane.

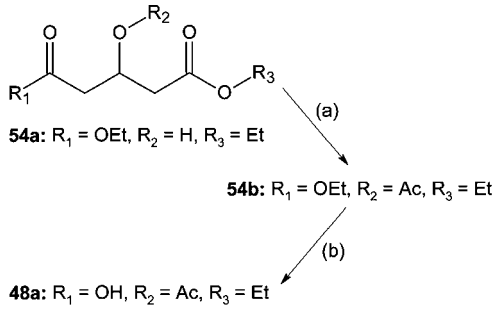
Reaction 13



(a) DMF, DCM, 0 °C; (b) Et_3N, DCM, rt, 2h; (c) HCl/EtOH, rt, 12h; (d) (i) Bu^nLi, Pr^i_2NH, THF, -20 °C; (ii) Bu^tOAc, -20 °C, 2 h; (e) Pt/C, $MgOAc_2$, MeOH, H_2, 25 bar, 35 °C, 18 h; (f) HCl/dioxane, rt, 2 h; (g) (i) $NaBH_4$,diglyme, Me_3SiCl, rt,1 h; (ii) $NaHCO_3$, hexane, reflux, 3 h; (h) Pd/C, MeOH, H_2, 10 bar, 70 °C, 3 h;

The key starting material **48a** is prepared by the method shown in Reaction 14. Initially **54a** is acetylated to give **54b**, and then α-chymotrypsin is used to induce the correct stereochemistry during the hydrolysis of **54b** to form **48a** in 97% yield.

Reaction 14



(a) Pyridine, Ac_2O, rt, 12 h; (b) (i) H_2O, buffer pH 7, rt;
(ii) α-chymotrypsin, NaOH, pH 7.8, rt;
(iii) Extract in EtOAc, HCl to pH 1; (iv) Extract in EtOAc, evaporate;

Advantages

The process maintains the required stereochemistry by starting from a pure material having the correct configuration at a key C-atom.

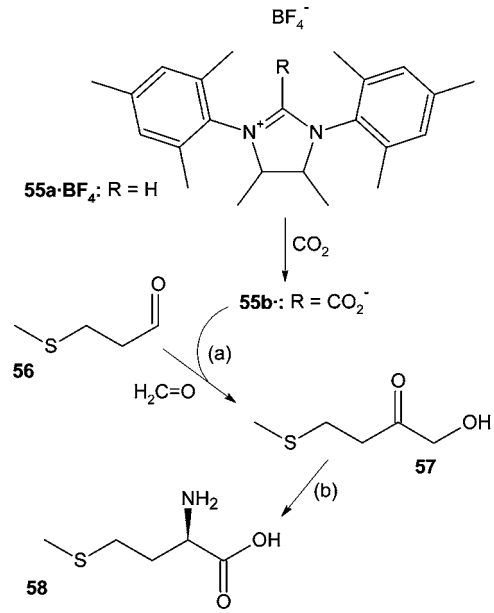
Patent No. U.S. 7,504,542

Assignee: Evonik Degussa GmbH, Essen, Germany

Title or Subject: Preparation of α-Hydroxyketones via Carbene-Catalyzed Umpolung Reaction of Aldehydes

The subject of interest in this patent is the α-hydroxyketone **57** that is used as an intermediate in the preparation of the important amino acid methionine **58**. The stated objective of the patent is to prepare the desired compounds using the acyloin condensation reaction without using the usual alkaline bases. It is well-known that aldehydes in the presence of bases can undergo aldol condensation reactions and byproducts are common if two different aldehydes are used. To avoid such problems the patent uses carbene precursors such as **55b** that is an adduct of the imidazolinium salt **55a** and CO_2. Such imidazolinium salts are known compounds, and the patent refers to several reports of them including their use in polymerisation of isocyanates. Other catalytic uses are said to be unknown. In the current process for preparing **57** the catalyst **55b** is used in the presence of DBU, and it is prepared in situ in the process of producing **57** without the need for it to be isolated as shown in Reaction 15. The catalysts are formed by carrying out the reaction under an atmosphere containing CO_2. This particular aspect is covered in one of the claims of the patent. Large numbers of imidazolinium catalyst salts are prepared and used to prepare **57** by the same route with yields of up to 93%. The patent also describes the preparation of a number of other α-hydroxyketones, and NMR data are given for many of them.

Reaction 15



(a) **55a**, CO_2, DBU, THF, 60 °C, 4 h; (b) No details provided.

Advantages

The process avoids unwanted condensation reactions taking place and hence gives very good yields of the desired product.

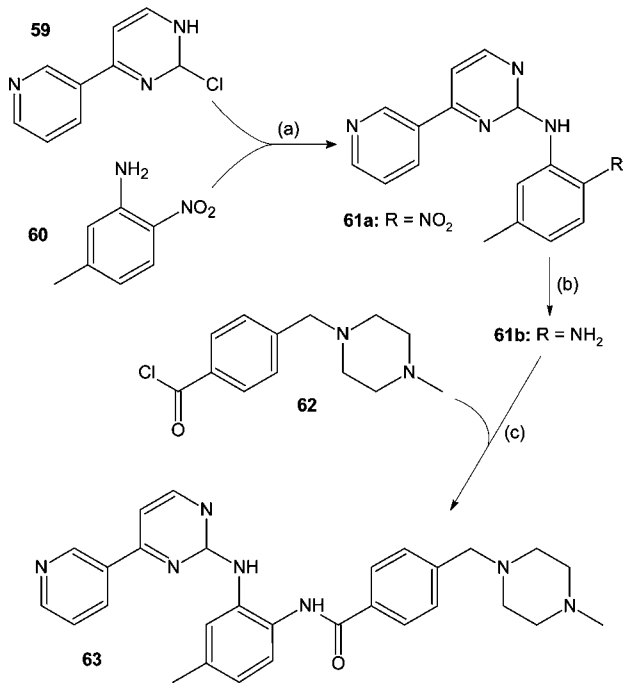
Patent No. U.S. 7,507,821

Assignee: Chemagis Ltd., Bnei-Brak, Israel

Title or Subject: Process for Preparing Imatinib

Imatinib **63** is used to treat leukaemia and is available as the mesylate under the name Gleevec. The patent summarises several routes that can be used to produce **63** using cyanamide that is a highly toxic material. It is also corrosive and there are difficult handling problems and material compatibility issues to address in its use. The patent discloses a process for preparing **63** that avoids the use of cyanamide. Reaction 16 outlines the method used to prepare **63** that begins with the condensation of the chloropyrimidine **59** with the nitroamine **60** giving **61a** ($R = NO_2$). The process is carried out in acidified Bu^nOH and requires refluxing for 38 h. The purity of **61a** is 80% but the yield is not reported. In the next step **61a** is catalytically reduced using a Pd/C catalyst to give **61b** ($R = NH_2$) in 94% yield and 96% purity. The final step is the condensation of **61b** with the benzoyl chloride **62** to produce **63** as the free base in 70% yield and 97% purity.

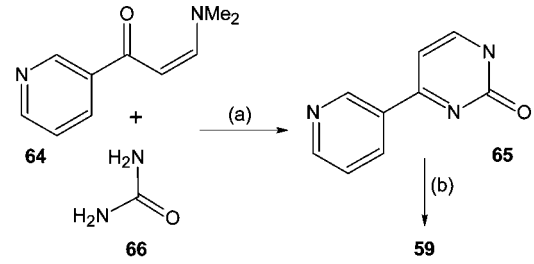
Reaction 16



(a) Concd HCl, Bu^nOH, reflux, 38 h; (b) Pd/C, EtOAc, H_2, 25 °C, 4 atm; (c) (i) Pyridine, 50 °C, 4.5 h.

The patent claims that the surprising finding is that **59** can be used to prepare **63** and Reaction 17 outlines the method used to prepare this key starting material. This shows that the first step is the preparation of **65** by heating **64** with urea **66**, in the presence of MsH. The patent states that the use of urea in this reaction is highly advantageous. Inexplicably, the example actually fails to mention the urea. A yield of 60% of **65** with a purity of 99.4% is reported, and then chlorination of **65** using $POCl_3$ produces **59** in 56% yield and 97% purity.

Reaction 17



(a) (i) MsH, 150 °C, 4.5 h; (ii) Cool to 90 °C; (iii) Pr^nOH, 80 °C, 1 h; (iii) Cool, 15 °C, filter; (iv) H_2O, 80 °C; (v) Cool to 20 °C, 2 h, filter, wash, dry; (b) (i) $POCl_3$, 50 °C, 4.5 h; (ii) Cold aq NaOH; (iii) Extract in EtOAc, dry, evaporate.

Advantages

The patent removes the need to use the hazardous reagent cyanamide and replaces it by urea that is very much safer, readily available, and cheap.

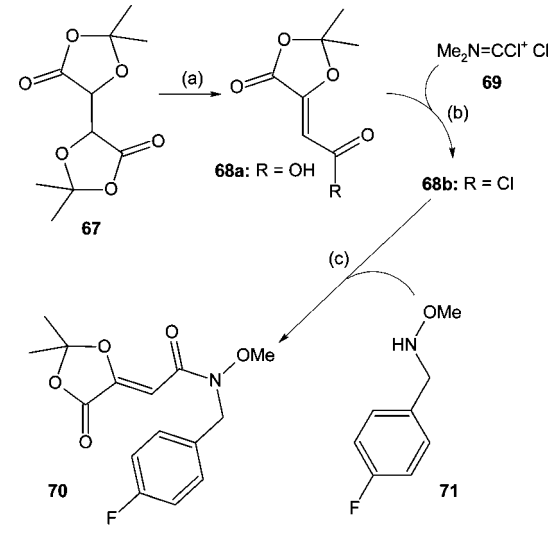
Patent No. U.S. 7,507,838

Assignee: Bristol-Myers-Squibb Company

Title or Subject: Process for the Preparation of Z-5-Carboxymethylene-1,3-dioxolan-4-ones

The main claim of this patent covers the production of **68a** ($R = OH$) that is used to prepare the acetamide **70**, a HIV integrase inhibitor. Several methods are described for preparing compounds such as **68a** and the patent discloses a novel process that is part of the scheme used to prepare **70** as shown in Reaction 18.

Reaction 18

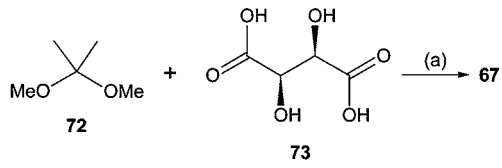


(a) (i) $KOBu^t$, THF, -40 °C, 15 min; (ii) Dry HCl, -40 °C; (iii) Warm to rt; (iv) Extract in EtOAc, crystallise; (b) EtOAc, 1 h, rt; (c) (i) Aq K_2CO_3, EtOAc, <5 C, 30 min; (ii) Wash in 1M HCl, H_2O; (iii) Solvent exchange with Pr^iOH, crystallise.

The preparation of **68a** is by treatment of the bis(acetonide) **67** with a strong base. The key finding is that the use of potassium-containing bases is more effective than bases such as NaH or LDA. Neither of these bases produced any reaction, and this finding is said to be surprising since the K-bases are nominally weaker bases. $KOBu^t$ or KHMDS are both used with the former being used in a kilo-scale example, and the conversion to **68a** was around 70%. The acid **68a** is then converted to **68b** by using the Vilsmeier reagent **69**. The chloride **68b** is not isolated and coupled with **71** using K_2CO_3 to give **70** that is isolated in 81% yield. The chloride **68b** was also isolated in quantitative yield by reaction of **68a** with $(COCl)_2$ and DMF.

The patent also describes the preparation of the two key reagents **67** and **71**. Reaction 19 shows the route used to prepare **67** from **72** and L-tartaric acid **73**. The reaction is carried out over a period of 4 h by adding **72** and more solvent in three portions. Between additions of **72** the mixture is concentrated by evaporation to remove the solvent and the MeOH to drive the reaction equilibrium. The pure **67** is obtained in 74% yield as a crystalline solid.

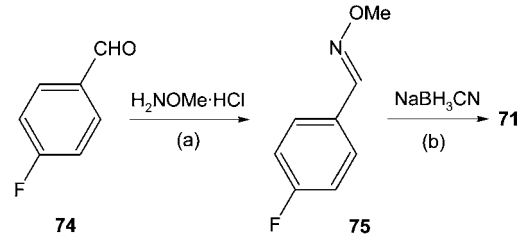
Reaction 19



(a) (i) $BF_3{\cdot}Et_2O$, Me_2CO, 50 °, 4 h; (ii) Evaporate; (iii) MTBE;
(b) (i) Aq $NaHCO_3$, rt, 30 min; (ii) Extract in heptane, evaporate, crystallise.

Also described in the patent is the preparation of the hydroxylamine **71**, and this is shown in Reaction 20. The first step is formation of the oxime **75** by treatment of the aldehyde **74** with $H_2NOMe{\cdot}HCl$. The oxime is obtained as a clear oil that is then treated with $NaBH_3CN$ to produce **71**. Column chromatography was used to purify the product that was isolated as an oil in 41% yield. ^1H and some ^{13}C NMR data are given for many of the intermediates.

Reaction 20



(a) (i) H_2O/THF, NaOAc, 22 °C, 4 h; (ii) Wash in NaCl;
(iii) Evaporate; (b) (i) DCM, rt; (ii) 2M HCl, MeOH, 30 min, rt;
(iii) 22 °C, 96 h; (iv) Evaporate, wash in aq NaOH;
(v) Extract in DCM, evaporate.

Advantages

The patent provides a novel process for the preparation of a drug intermediate in good yields.

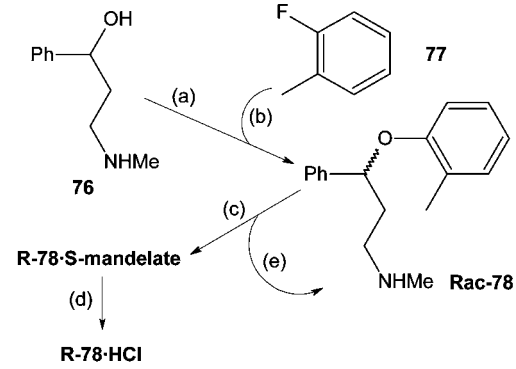
Patent No. U.S. 7,507,861

Assignee: Teva Pharmaceutical Fine Chemicals, S.r.l., Bulciago, Italy

Title or Subject: Process for the Preparation of Atomoxetine Hydrochloride

The title compound **R-78·HCl** is marketed under the name Strattera for the treatment of attention deficit hyperactivity disorder in adults and children. An earlier patent on impurities in its synthesis has been reviewed previously (*Org. Process Res. Dev.* **2008**, *12*, 797). Alternative processes for manufacturing the compound are summarised and said to give low yields or require operations incompatible with commercial production. The new process includes a racemisation procedure to recover the unwanted *S*-enantiomer and hence gives improved atom efficiency. Reaction 21 shows the basic reaction used to synthesis the racemic form **Rac·78** from **76** and **77**.

Reaction 21



(a) (i) KOH, DMSO, 110 °C, vac distil; (ii) Cool to 80 °C;
(b) Reflux, 1 h; (ii) Cool to 90 °C, extract in PhMe;
(c) (i) Evaporate; (ii) S-mandelic acid, PhMe, MeOH, 70 °C;
(iii) Cool, filter; (d) (i) PhMe, H_2O, 40 °C, (ii) 30% aq NaOH, separate; evaporate; (iii) EtOAc, HCl gas, 15 - 20 °C, 2 h, filter, wash, dry; (e) (i) 2% aq NaOH, evaporate;
(ii) DMSO, KOH, 90 °C; (iii) Extract in PhMe.

The amine **76** is initially heated with KOH, and it is interesting to note that the examples specify the use of 92% bulk industrial-grade solid material. After removal of about 9% of the solvent, the aldehyde **77**, is added and after workup the racemic product is obtained as a solution in PhMe. This is used in the resolution step where the *S*-mandelate salt of the *R*-enantiomer of **78** is obtained. The crude product is crystallised, and the final product yield is 38.7% with 99/1 *R*:*S* ratio. The PhMe solution from the resolution step is racemised by treatment with base, and again industrial grade KOH is specified. The mandelate salt of **R-78** is converted to the HCl salt that is isolated in a yield of 97%. A key feature of the patent,

covered by two separate claims, is that the formation of the HCl salt can be carried out with or without H_2O. An example in which EtOAc containing H_2O is used gave a yield of 84% of the HCl salt compared to the 97% in the absence of H_2O.

Advantages

The patent affords high yields of the product and has a racemisation step to improve atom efficiency.

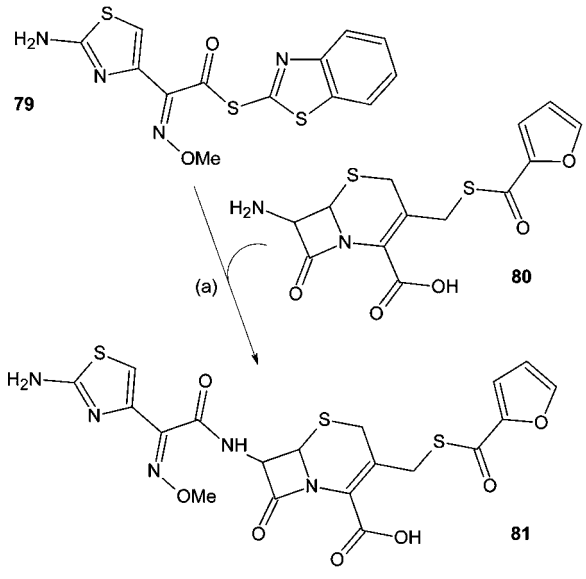
Patent No. U.S. 7,511,135

Assignee: Lupin Limited, Maharashtra, India

Title or Subject: Method for Manufacture of Ceftiofur

Ceftiofur **81** is a broad spectrum antibiotic primarily for veterinary use. The patent describes in some detail three methods that are used to make **81**. The complexity of the molecule necessitates several steps in the synthesis, and costly and time-consuming protection and deprotection stages are involved. There are also issues regarding the removal of impurities, and so the patent concludes that an improved process is required for commercial manufacture. The process is shown in Reaction 22 and is described as the amidification of the 7-amino position in **80** with the 2-benzothiazolyl ester **79**. This reaction is carried out in DCM and in the presence of a base such as Et_3N. The subsequent workup produces a biphasic mixture and then involves three further organic solvents, H_2O, brine, and H_3PO_4. There is also an optional decolourising step, and so the overall process looks to be extremely laborious. Despite this, the final product yield of **81** is 66.95%, and the purity is 98.5%. The patent includes a table comparing this method with others reported elsewhere, and this not surprisingly shows the new process gives the product with higher quality and better yield.

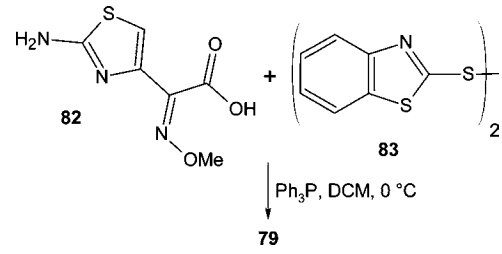
Reaction 22



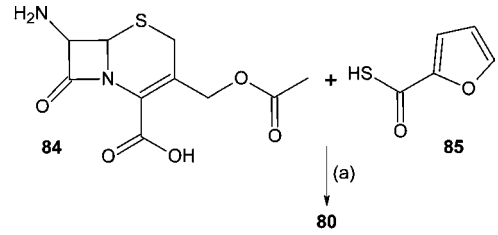
(a) Et_3N, DCM, < 5 °C, 1 h; (b) (i) < 5 °C, 15 min; (ii) H_2O, 15 °C; (iii) Wash in DCM; (iv) MeCN/EtOAc, H_3PO_4 to pH 3.0; (v) Brine; (vi) Extract in MeCN/EtOAc; (vii) Wash in brine, evaporate; (viii) EtOAc/cyclohexane, 25 °C, 1 h; (viii) Filter, wash in cyclohexane, dry.

The patent mentions that the starting materials can be prepared by procedures reported in other patents. Although there are no examples described in this patent Reactions 23 and 24 show the general reaction schemes said to be used for preparing **79** and **80** respectively.

Reaction 23



Reaction 24



(a) (i) EtOAc/H_2O, 65 °C; (ii) pH 6.4; (iii) Mineral acid, 40 °C; (iv) Filter, dry at 40 °C.

Advantages

The process does give a better-quality product, but the workup method involves several different solvents and so creates handling difficulties.

Patent No. U.S. 7,511,139

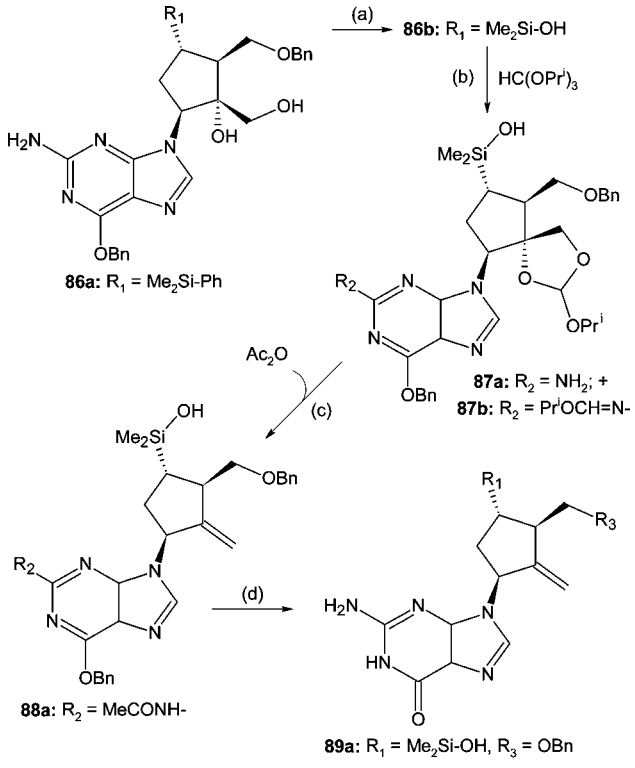
Assignee: Bristol-Myers Squibb Company, Princeton, New Jersey, U.S.A

Title or Subject: Process for the Preparation of Entecavir and Novel Intermediates via Carbon−Silicon Oxidation

Entecavir **89c** is used to treat hepatitis B viral infections, and this patent discloses a process for making **89c** and methods for the preparation of intermediates that are used in the synthesis. The patent title refers to the use of silylation to protect alcohol groups during the synthesis and subsequently their cleavage by oxidation. The many schemes shown in the patent differ in the point at which the silyl group is oxidised and then removed, and a specific synthetic route for **89c** is covered in the claims. However, experimental details are not reported for all the reactions in the route covered in the claims. Hence, the reaction schemes in this review are based on the route covered by the patent claims and the experimental details shown are taken from analogous reactions described in the patent.

The key feature of the synthesis is described in the patent as a protodesilylation reaction. This step is shown in Reaction 25 in the conversion of **86a** to **86b** in which the Si−Ph bond is converted to Si−OH by treatment with KOBu^t in DMSO. The patent also states that this may be achieved by using BF_3/HOAc or Bronsted acids such as TFA, MsH, and TfH. Only the latter reagent is described as being used in the examples. The reaction mixture is treated with HCl to a pH of 8.2, and after further workup **86b** is obtained in a yield of 72%. The next stage of the process is the preparation of the amide intermediate **88a** by reaction of **86b** with an orthoformate in the presence of TFA. The reaction produces a mixture of **87a** and **87b** that is not isolated but treated with Ac_2O in the presence of the antioxidant BHT to form the olefinic compound **88a**. This is also not isolated and in the last step of this stage the amide **88a** is converted to **89a** by acid hydrolysis. The crude product is then washed six times with heptane to remove the BHT, extracted with EtOAc, and then purified using column chromatography. The isolated yield of **89a** at this point is only 20% yield, and it was found to contain an impurity identified as a dimer of **89a**. Further washing with EtOAc/heptane removed the dimer, but the final yield of **89a** was not reported. The BHT having been removed it is tempting to suggest that the attempted purification may have resulted in the dimerization.

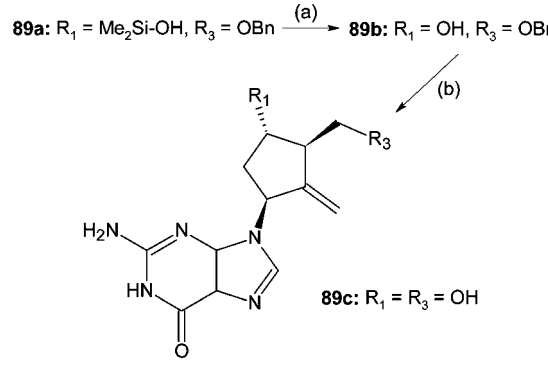
Reaction 25



(a) (i) KOBu^t, DMSO, 13 °C; (ii) rt, 2 h; (iii) H_2O, 6M HCl to pH 8.2, 15 °C; (iii) Filter, wash in H_2O, dry 40 °C, 60 h; (b) TFA, PhMe, rt, 1 h; (c) BHT, HOAc, 116 °C, 14 h; (d) (i) 6M HCl/MeOH, rt; (ii) 68 °C, 5 h.

The next phase of the process is shown in Reaction 26 in which **89a** is converted to **89c** by oxidation using H_2O_2 in the presence of KF and $KHCO_3$ to convert the silyl-protecting group to the alcohol. In the last step the Bn protection is removed using a Lewis acid such BCl_3. These two reactions are those for which precise details are not provided.

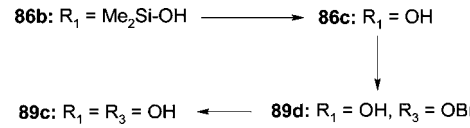
Reaction 26



(a) H_2O_2, $KHCO_3$, KF, MeOH, 65 °C; (b) BCl_3, DCM, -20 °C

However, there are examples given, and these follow the route in Reaction 27 in which **86b** is converted to **89c** by the same type of reactions described above. First **86d** is oxidised to **86c** that is isolated in quantitative yield and used immediately in the next step to give **89d** that is obtained in 44% yield, and finally **89c** is isolated in 44% yield.

Reaction 27



There are several other reaction schemes included in the patent forming other related intermediates. Overall there is a considerable amount of detail in this patent, and interested readers are strongly encouraged to read it carefully.

Advantages

The process provides an alternative route to the desired drug compound and includes several novel intermediates. However, some steps seem to be laborious and give poor yields, and so whether the overall process is commercially viable remains to be seen.

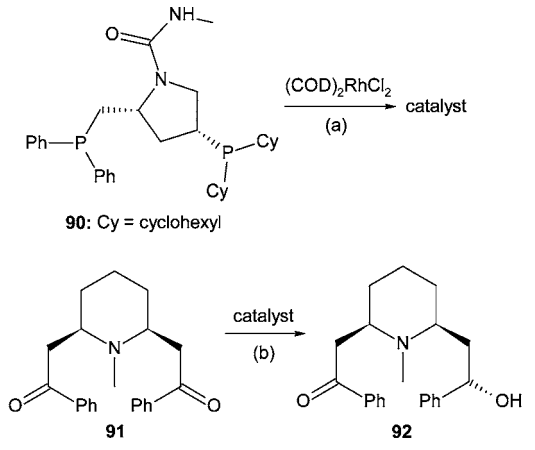
Patent No. U.S. 7,511,147

Assignee: Boehringer Ingelheim Pharma GmbH and Co. KG, Ingelheim, Germany

Title or Subject: Process for Manufacturing Chiral Lobelin

Lobelin **92** is found in lobelia plants in the eastern and central states of the U.S.A and Canada. It is a respiratory stimulant when taken parenterally but ineffective if inhaled and has been used to treat asthma attacks and as a slow-release drug to help people to stop smoking. Synthetic procedures are known for preparing **92**, but they generally require a high number of steps. The patent claims to provide a process with fewer steps for making **92**, and this is outlined in Reaction 28. The process described is the asymmetric hydrogenation of the HCl salt of lobelanine **91** using a chiral Rh catalyst prepared from **90** and $Rh(COD)_2Cl_2$. The hydrogenation is carried out at MeOH in the presence of a weak base such as Et_3N at a temperature of up to 53 °C and at 20 bar pressure of H_2. There is a detailed isolation procedure that is the subject of one of the patent claims. It involves removal of MeOH, acidification, and extraction into PhMe then crystallisation from Pr^iOH. Although there is only one example, it does use 90 kg of **6** from which **92** is obtained in yields up to 35%, and so the process is clearly viable on a large scale.

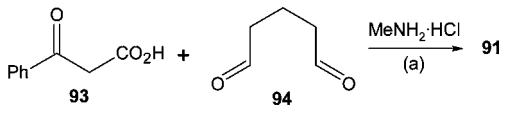
Reaction 28



(a) MeOH, argon, < 25 °C, 30 min; (b) Et_3N, MeOH, 53 °C, H_2, 20 bar.

The claim of a reduced number of steps for this process is an exaggeration since there are no details given for the preparation of **91**. However, the patent does mention that **92** can be produced from **93**, **94**, and $MeNH_2HCl$, but no details are provided (Reaction 29).

Reaction 29



(a) Me_2CO, citrate buffer

Advantages

The process is clearly suitable for large-scale production.

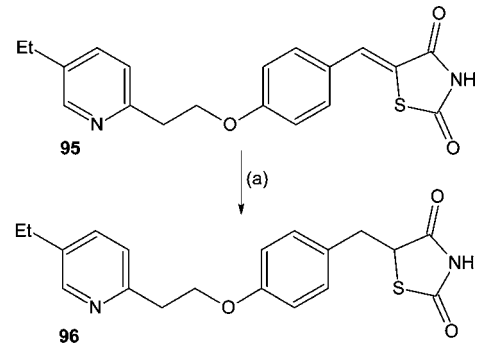
Patent No. U.S. 7,511,148

Assignee: Sandoz AG, Basel, Switzerland

Title or Subject: Process for Preparing Thiazolidinediones

The patent describes a process for preparing compounds such as pioglitazone **96** and rosiglitazone **107** that have antihyperglycemic properties and are used to treat type II diabetes. Methods for the preparation of **96** and **107** involve the hydrogenation of an exocyclic C═C bond at the 5-position on the thiazolidinedione moiety. The patent claims that the use of catalytic hydrogenation for this reaction is relatively expensive, has safety and environmental issues, and solves these problems by using a dithionite for this reduction. The preparation of **96** from the precursor **95** is shown in Reaction 30 and takes place in aqueous systems such as H_2O and dioxane. **96** is obtained in 82% yield with a purity of 97.2% (HPLC). Examples also describe alternative bases such as K_2CO_3 or solvents such as EtOAc, DMF, or H_2O which all give slightly lower yields. The use of Bu^n_4NBr as phase transfer catalyst (PTC) is also described in $PhMe/H_2O$, and this gives a 98% yield of **96** with purity of only 80%. Using the PTC in $EtOAc/H_2O$ gives a 70% yield of **96** at 90% purity.

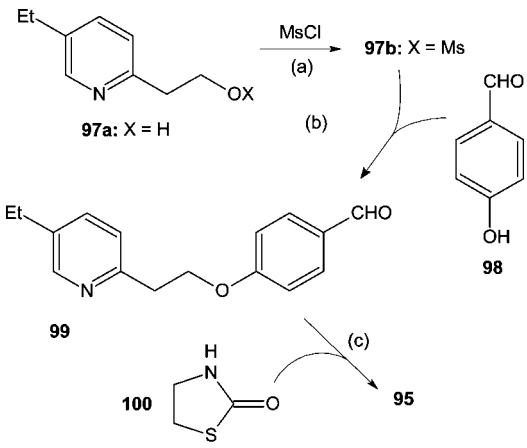
Reaction 30



(a) (i) Na_2CO_3, H_2O, dioxane, 80 °C; (ii) $Na_2S_2O_4$, H_2O, 1 h; (iii) 80 °C, 1 h; (iv) 50 °C, 1 h; (v) Cool to 10 °C; (vi) HOAc to pH 6, 30 min; (vii) Filter, wash in H_2O, dry.

The patent describes the preparation of **95**, and this is outlined in Reaction 31. In the first step the mesylate **97b** is prepared and then condensed with **98** to form the ether **99** that is recovered as an oil. Treatment of **99** with **100** forms **95** in a yield reported as 110% and HPLC purity of 98%.

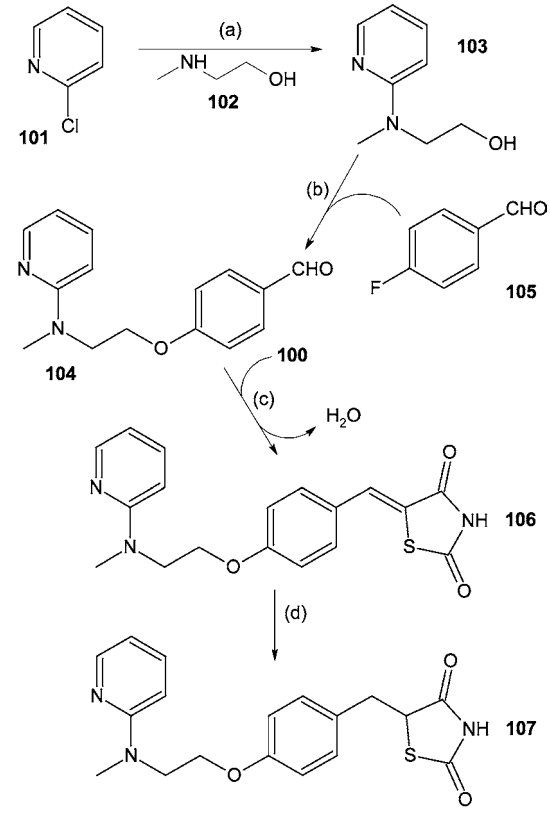
Reaction 31



(a) Et_3N, PhMe, rt, 1 h; (b) (i) PEG200, K_2CO_3, 80 °C, 4 h; (ii) rt, aq NaOH; (iii) Distil PhMe; (c) (i) Pyrrolidine, MeOH, 50 °C, 6 h; (ii) 10 °C, 2 h, filter.

The patent also describes the preparation of **96** by the route shown in Reaction 32. This begins with the reaction of **101** and **102** to produce **103** that is isolated as an oil. The ether **104** is also obtained as an oil by reaction of **103** and the fluorobenzaldehyde **105**. Reaction of **104** and **100** produces the unsaturated compound **106** that is reduced by using dithionite to give **107** in 60% yield and 99% purity by HPLC. The preparation of the maleate of **107** is also described by reaction with maleic acid in H_2O or mixtures of H_2O and solvents such as THF, EtOH, DMF, MeOH, or dioxane.

Reaction 32



(a) (i) 120 °C, 24 h; (ii) Distil off **102**; (b) (i) KOH, DMF, rt, 1 h; (ii) 40 °C, 24 h; (c) (i) PhMe, piperidinium acetate, reflux, 5 h; (ii) Cool, filter, dry; (d) (i) K_2CO_3, DMF, 80 °C; (ii) $Na_2S_2O_4$, H_2O, 80 °C, over 1 h; (iii) 80 °C, 2 h; (iv) 50 °C, 2 h; (v) Cool to 10 °C, 2 h; (vi) Filter, wash in H_2O, dry.

Advantages

The reduction procedure avoids the use of expensive catalysts and reduces the safety problems associated with H_2 under pressure.

Keith Turner

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