Organic Process Research & Development **2008,** *12,* 13–22

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published During August and September 2007

Summary

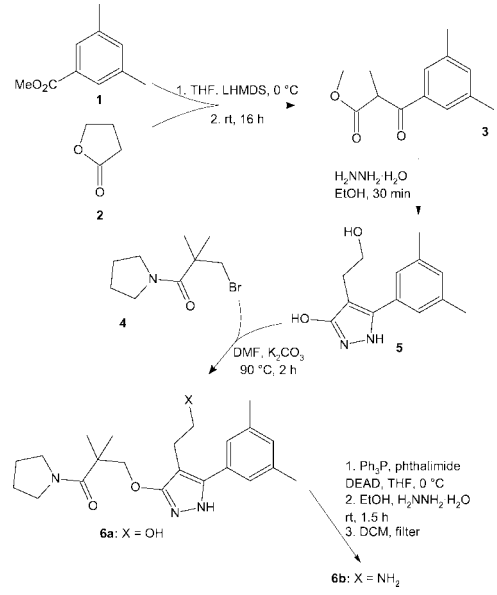
This month's selection of patents contains 21 from an original list of 222. A number of them report the synthesis of some novel compounds and intermediates and may be said to be preprocess development. However, most of the patents chosen report new processes or reactions to produce known compounds, and it is hoped that both types provide interesting reading. The safe production of any chemical is essential, and reports of safety issues are very important. A new process for the preparation of the drug balsalazide, for treating ulcerative colitis, is claimed to be safe since it uses soluble diazonium salts, thus preventing crystallisation without potential explosive results. Safety is a key issue in a patent for the production of pyrethroid-type pesticide intermediates. This avoids the use of OsO_4 by oxidation using Ru compounds in a redox system with periodates. 4-Fluoroethylene carbonate is used in the production of lithium batteries and is obtained using gaseous F_2. The process has a potentially dangerous exotherm that is prevented by controlling the size of the gas bubbles. On another safety issue a multistep process for producing quinolones avoids the use of NaCN and CuCN and thus removes several safety problems. The N-oxidation of pyridines is used to prepare compounds useful for cardiovascular treatments. The patent cautions against the potential of explosions since a perborate is used but then mentions that none occurred. Cancer treatments are vital, and two patents describe different types of compounds that are candidates for treating prostate cancer. One involves pyrazoles while the other describes novel arylindoles. Muscarinic receptor antagonists, used to treat respiratory diseases, are the subject of three patents from two companies. One company describes novel azabicyclo compounds, while the other covers biphenyl derivatives. A change of solvent in the preparation of the antipsychotic drug risperidone gave a much-improved yield. The solvent originally used, DMF, was replaced by MeCN or alkyl alcohols. The same patent also describes new polymorphs of the drug. A range of novel amino acid derivatives is reported that are prodrugs for treating other neurological disorders. The treatment of other mental disorders such as Alzheimer's disease is the subject of a patent describing novel indanylamines and aminotetralin derivatives. Drugs to treat inflammation are widely investigated, and one patent reports the stereoselective synthesis of some novel trifluoromethyl alcohols. Another patent describes novel compounds for the inhibition of the enzyme $CPLA_2$ that causes pain and inflammation. Two patents describe a range of novel azulenes that are of interest to treat rheumatoid arthritis. Methionine is an essential amino acid used in human and animal nutrition. A new method of preparing a key intermediate is reported that gives improved productivity so that smaller reactors can be used or more can be obtained from existing units. Novel, chiral aziridines are reported that can be prepared from natural and synthetic materials and thus offer the full range of optical isomers. A method of improving the production of the analgesic tilidine is described. This involves converting the major byproduct to one of the starting materials that is easier to remove and at the same time improves the process efficiency. Several of the current collection of patents contain serious errors that are not excusable and are entirely avoidable. For example, a three-valent O atom is shown in one formula, and in another patent the structure of a BOC-protected amine omits the NH group and an O atom for good measure. Careful reading of patent applications by chemists should prevent this happening. A number of the patents describe medium-to large-scale examples and this may suggest that the process is, or at least reached, an advanced stage of development. However, no legal or commercial significance is implied by the inclusion of any patent and the advantages mentioned are those claimed in the patent unless this reviewer has personal knowledge of the subject.

Patent No. U.S. 7,253,290

Assignee: AstraZeneca AB, Södertalje, Sweden

Title or Subject: Pyrazole Derivatives as GNRH Inhibitors

Scheme 1



This is the first of two patents relating to compounds such as **10** that are inhibitors of gonadotrophin-releasing hormones (GNRH). These compounds are of use in infertility treatment and are also of interest in treating prostate cancer. This first patent discloses work probably carried out in France and covers

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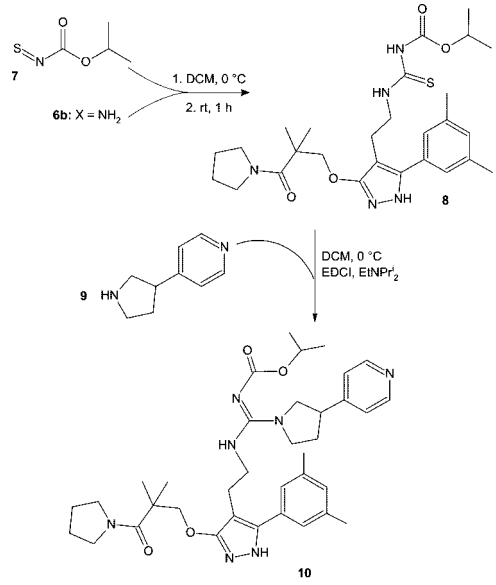
a large number of novel intermediates such as **6b** that are used to produce the desired drug candidates; their production is by the reaction sequence shown in Scheme 1. In the first stage the compound **3** is produced in 55% yield in a Claisen condensation of **1** and **2**. In the next step a cyclisation reaction of **3** with hydrazine produces a 90% yield of the pyrazole **5** that is selectively alkylated with **4** using a base to form compound **6a**. This is then converted to the amine **6b** in a Mitsunobu reaction using DEAD as an activation agent followed by deprotection using hydrazine.

The desired compound **10** is produced from **6b** using the route outlined in Scheme 2. The first stage is the reaction of **6b** with **7** to give a 94% yield of the thiourea **8**. In the next step **8** is reacted with the pyrrolidine **9** in the presence of the carbodiimide EDCI to form **10** in 84% yield.

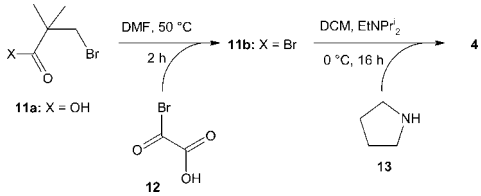
Scheme 2



EDCI = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

This patent contains a considerable number of compounds similar to **10**, and the interested reader is encouraged to examine the patent in detail. One of the key starting materials used in the patent, **4**, is prepared in 70% yield by the method shown in Scheme 3.

Scheme 3



The preparation of **4** is carried out by reaction of **11a** with oxalyl bromide **12** in the presence of DMF, giving **11b**. Reaction of **11a** with pyrrolidine **13** produces **4**, and this is obtained in 70% yield after purification by flash chromatography.

The patent provides ^{1}H NMR data for all intermediates and products and also includes some clinical test data.

Advantages

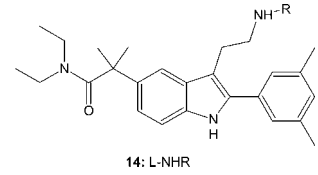
The process provides a novel range of intermediates and final products that have potential as GNRH inhibitors.

Patent No. U.S. 7,256,188

Assignee: AstraZeneca AB, Södertalje, Sweden

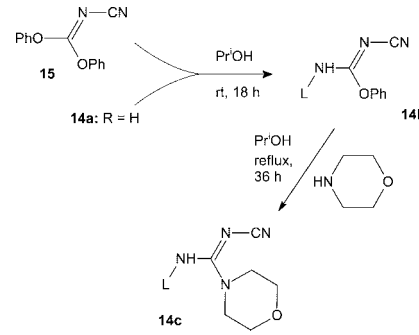
Title or Subject: Arylindole Derivatives as GNRH Antagonists

This is the second patent from the same company on GNRH inhibitors covering work that seems to have been carried out in the UK and covers a different range of compounds compared to those in the previous patent. As in the previous patent there are a considerable number of compounds covered and they all contain the basic nucleus L-NH- in compound **14**. The R group in **14** varies considerably, and the synthesis of **14c** is chosen as representative of the route described in the patent.



In the synthesis of **14c** (Scheme 4) the first step is the reaction of **14a** with **15** in Pr^{i}OH to give a 95% yield of **14b**. Refluxing **14b** with morpholine for 36 h produces **14c** and this is isolated in 46% yield.

Scheme 4



The amine **14a** is the starting material for the range of final products and is therefore a key compound. The patent does refer to a method for the synthesis of this compound. However, the method refers to intermediates identified by a letter in a series of reaction schemes that do not exist in the patent. Neither the structure nor names of these compounds are provided. Hence it is not possible to summarise how **14a** is prepared. How the examiner allowed this patent to be published without such details is a mystery.

Advantages

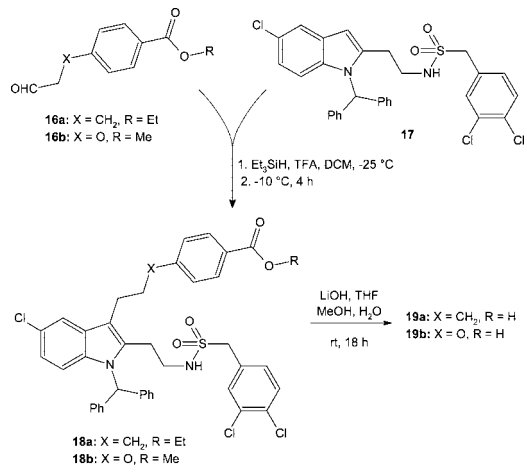
The patent claims that the final products are novel GNRH inhibitors.

Patent No. U.S. 7,259,277

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

Title or Subject: Advanced Route for the Synthesis of CPLA2 Inhibitors

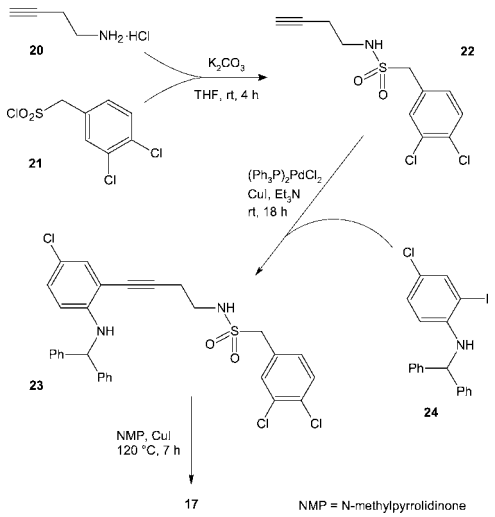
Scheme 5



This patent relates to inhibitors of the enzyme cytosolic phopholipase A_2 ($CPLA_2$); such compounds are of use for the relief of pain and inflammation. Scheme 5 shows the synthesis of the two novel compounds **19a** and **19b** that are $CPLA_2$ inhibitors. The first stage in the preparation is an alkylation of the indole **17** with the aldehyde **16a** or **16b** using Et_3SiH and TFA in dichloromethane (DCM) to give **18a** or **18b**. The yield of **18a** is 56%, and this is said to be higher than the yield of **18b**, which is not reported. Hydrolysis of **18a** or **18b** using aqueous LiOH in MeOH/THF gives the final products **19a** or **19b**. The yield of **19a** is reported as 96%.

The patent also describes the synthesis of the key intermediate **17**, and this is outlined in Scheme 6. Condensation of the HCl salt of **20** and **21** in the presence of K_2CO_3 produces **22** in 71% yield. Coupling of **22** with **24** in a Sonogashira reaction produces **23** in 81% yield, and then cyclisation of **23** using CuI in NMP forms **17** in 76% yield.

Scheme 6



^{1}H NMR data are provided for the compounds **17**, **18a**, **19a**, and **23**.

Advantages

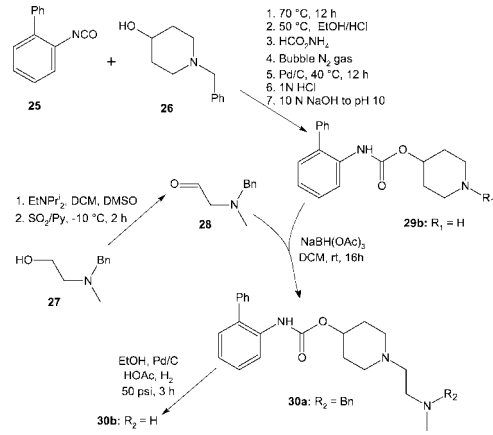
The patent describes a process for preparing these novel compounds that is claimed to be suitable for commercial production.

Patent No. U.S. 7,262,205 and U.S. 7,265,133

Assignee: Theravance Inc., San Francisco, California, U.S.A

Title or Subject: Biphenyl Compounds Useful as Muscarinic Receptor Antagonists

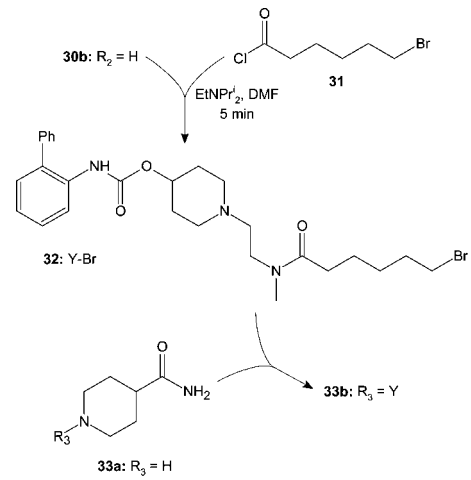
Scheme 7



Muscarinic receptor antagonists (MRA) are important in the treatment of respiratory and other diseases and are the subject of three patents from two companies. The first two of these patents disclose two ranges of novel compounds for the treatment of asthma. Such compounds are usually administered by inhalation and can have a short-lived duration of activity. The objective in these patents is to produce compounds that have high potency and long duration of activity. Both patents produce the final products using the same type of coupling reaction from a common starting material **30b**. This material is produced by the method shown in Scheme 7. The reaction of the isocyanate **25** with **26** forms the benzyl compound **29a** from which the protective Bn group is removed to give **29b** in 100% yield. These reactions for the conversion of **25** to **29b** are performed without isolating **29a** in a single pot. Compound **29b** is then reacted with the aldehyde **27** using $NaBH(OAc)_3$ to give **30a** in 95% yield, and upon hydrogenation **30b** is produced in 70% yield.

The patents then describe the synthesis of two ranges of compounds that are prepared from **30b**. The first patent converts **30b** to **33b** as shown in Scheme 8. The first step is condensation of **30b** with **31** to produce **32** in less than 5 min. The product

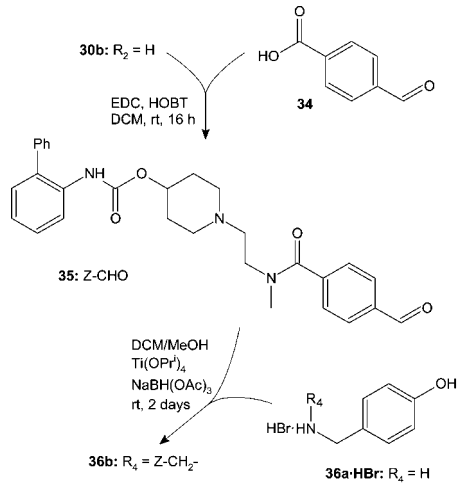
Scheme 8



32 is not isolated, and the reaction mixture is used directly in the reaction with the amide **33a** to form **33b**. The yield for this last step is not reported.

The products described in the second patent such as **36b** are produced by the reactions shown in Scheme 9. First **30b** is reacted with **34** in the presence of EDC and HOBT to give **35** in 92% yield and a purity of 85%. In the final stage **35** is reacts with the HBr salt of **36a** to form **36b** in 55% yield, and this is isolated as the TFA salt.

Scheme 9



EDC = N-ethyl-l-3-[3-(dimethylamino)propyl] carbodiimide hydrochloride
HOBT = 1-hydroxybenzotriazole hydrate

In both patents a large range of compounds is described with brief experimental details for each of them. Details of tests using the compounds are also described.

Advantages

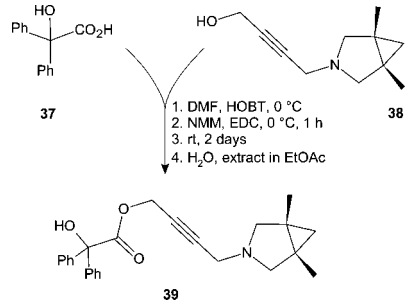
The patents provide methods for producing new drug candidates that have potential in treating asthma.

Patent No. U.S. 7,265,147

Assignee: Ranbaxy Laboratories Limited, Gurgaon, Haryana, India

Title or Subject: 3,6-Disubstituted Azabicyclo[3.1.0] Derivatives Useful as Muscarinic Receptor Antagonists

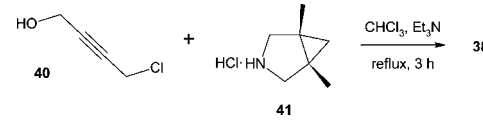
Scheme 10



This is the third patent on MRA, and it describes another novel range of compounds exemplified by **39** that is synthesised as shown in Scheme 10. The reaction used to prepare **39** is a condensation reaction between **37** and **38** using HOBT, EDC, and *N*-methylmorpholine (NMM) in DMF. The use of DBU in place of EDC is covered in the patent claims. There are 21 compounds analogous to **39**, and they are all prepared by the same condensation reaction. Experimental details are given for them all, but in no case is the product yield reported. ^{1}H NMR and limited IR data are provided for the products.

The patent also provides details for the preparation of the starting material **38** from **40** and **41**, and this is shown in Scheme 11. The preparation of compounds **37**, **40**, and **41** is by literature methods referred to in the patent.

Scheme 11



Advantages

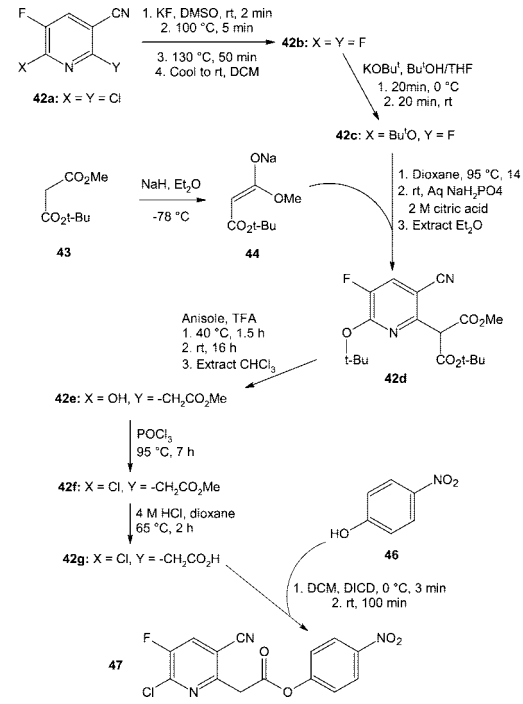
The patent provides a range of novel compounds that are claimed to be MRA, but the lack of yield data means an assessment of the commercial utility is not possible.

Patent No. U.S. 7,262,210

Assignee: Janssen Pharmaceutical N.V., Beerse, Belgium

Title or Subject: Fluorinated Pyridine-N-oxide Thrombin Modulators and Process for N-Oxidation of N-Containing Heteroaryls

Scheme 12

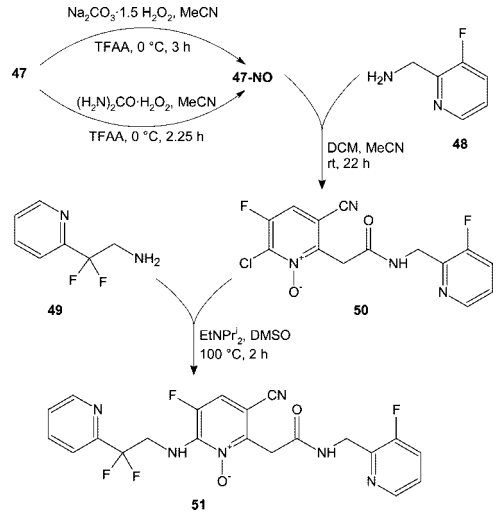


The compounds of interest in this patent have potential in treating cardiovascular diseases. The patent describes the synthesis of compounds such as **51** by a process involving N-oxidation of pyridines. The initial part of the process is the production of the 4-nitrophenyl ester **47**, which is produced in a multistep route that is outlined in Scheme 12. In the first stage **42c** (X = Bu^{t}O, Y = F) is produced from **42a** via **42b** by conventional means. The product yields in these two reactions are 76% and 85%. Compound **42c** is then reacted with **44** and

forms crude **42d** in 100% yield. Compound **42d** is then converted in a series of 3 steps to **42g** with the yields for each step being 51%, 96%, and 84%. The production of **47** by esterification of **42g** and **46** is carried out using 1,3-diisopropylcarbodiimide (DICD) and gives **47** in 84% yield. Many of the products in this scheme are oils even after purification.

The next stage of the process is the oxidation of **47** to give the *N*-oxide **47-NO**. This is carried out by either of two methods. In one the oxidation is performed using sodium percarbonate, and the other uses urea hydrogen peroxide. The former gives a 56% yield of the product containing 4 mol % of **47**, whereas the latter gives 84% yield of a product. The product is described as off-white in the former case and brown in the latter case. It is difficult to determine which is the preferred route, although the patent does mention that the reaction with the percarbonate is carried out behind a large Plexiglas shield without incident. The *N*-oxide **47-NO** is then used in the last section of the process as shown in Scheme 13.

Scheme 13



The reaction of **47-NO** with **48** is the first step to give **50** in a yield of 74%, and this takes 22 h with part of **48** added initially and the remainder after 10 h. In the next step **50** is reacted with the amine **49** to give **51** in 59% yield. Compound **51** is then converted to the dihydrochloride or the monohydrobromide salt. There are two procedures are given for the HCl salt. One uses HCl gas in MeCN and gives a yield of 57%, whereas the other uses 9.8 M HCl in MeCN and has a 94% yield. The patent gives basic ^{1}H NMR data for all compounds as well as results of elemental analysis.

The patent states that the procedure for *N*-oxide formation is applicable to a range of *N*-heteroaryl compounds. Brief details are given for a range of pyridines and pyrimidines containing electron-withdrawing groups such as CO_2alkyl, CF_3, or CN. Both oxidation methods are suitable and the reactions are carried out at 0 °C in MeCN with TFAA. The key aspect of this reaction is said to be the fact that it takes place in neutral to acid conditions and is applicable to acid sensitive groups.

Advantages

The process provides a multistep route to a potentially useful drug but with so many stages the overall yield appears to be quite low.

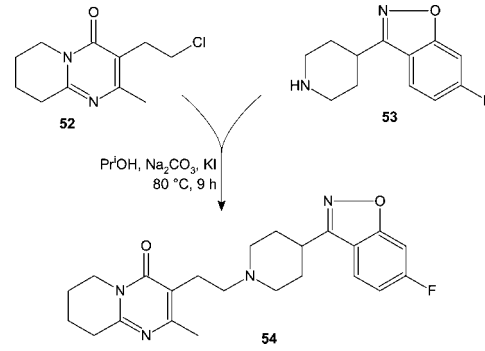
Patent No. U.S. 7,256,195

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

Title or Subject: Preparation of Risperidone

Risperidone **54** is an antipsychotic agent used in the treatment of schizophrenia as well as other mental disorders. This patent describes a method of making **54** that is based on the previously known process with a change of solvent. The original work used DMF, and it has been found that an improved method giving higher yields is possible by replacing DMF. The two solvents mentioned are MeCN or Pr^{i}OH, and the patent states that a yield of about 75% is possible. However, there are no examples where the yield exceeds 63%, and this is obtained when Bu^{i}OH is used as the solvent. Scheme 14 shows the new method in which the reactants **52** and **53** are refluxed in the solvent and the product is obtained in a yield of >60% at 99.7% purity. The product is recrystallised from hot Pr^{i}OH or Me_2CO.

Scheme 14



The patent also discloses methods for preparing three novel polymorphs of **54** designated Forms A, B, and E. These are obtained by recrystallising from a range of solvents and are characterised by XRD.

Advantages

The process gives novel forms of the known drug that may provide new, commercial opportunities.

Patent No. U.S. 7,256,217

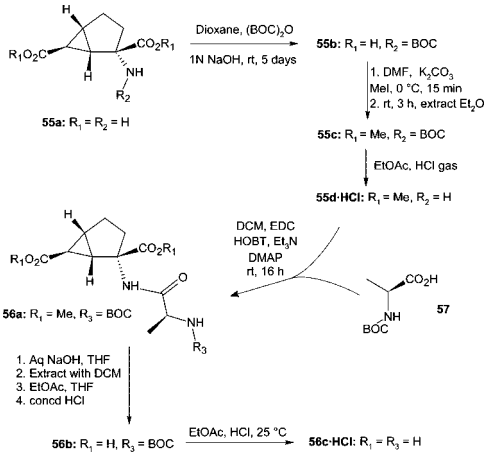
Assignee: Eli Lilly and Company, Indianapolis, Indiana, U.S.A

Title or Subject: Prodrugs of Excitatory Amino Acids

This patent describes the synthesis of a range of the compounds such as **56c** that are of interest in treating neurological and psychiatric disorders. The patent states that such disorders are linked to excitatory amino acid receptors and that **56c** is a prodrug for such compounds. The route to make **56c** is shown in Scheme 15 and starts from amino acid **55a**. The first step is the protection of the amino group by conversion to the BOC derivative **55b**. The yield is 77%, and the process takes 5 days with part of the $(BOC)_2O$ being added at the start and then the remainder after 2 days. The next stage is the

production of the HCl salt of **55d**. This is carried out via the ester **55c** that is isolated in 87% yield, and the HCl salt is obtained in 77% yield. In the next stage BOC-protected alanine **57** is coupled with **55d** to give **56a** in 50% yield. Hydrolysis of **56a** then gives **56b** in 84% yield of a 85:15 mixture of rotamers. After removal of the protective BOC group, the HCl salt of **56c** is obtained in 93% yield. The reaction to produce **56b** is carried out on a kilo scale, perhaps indicating the advanced stage of development of the process. The patent also describes the preparation of the mesyl salt and the free amine of **56c** and provides ^{1}H and ^{13}C NMR data for most of the intermediates and final products.

Scheme 15



Advantages

The process provides a novel compound that is a potential prodrug for the treatment of neurological disorders.

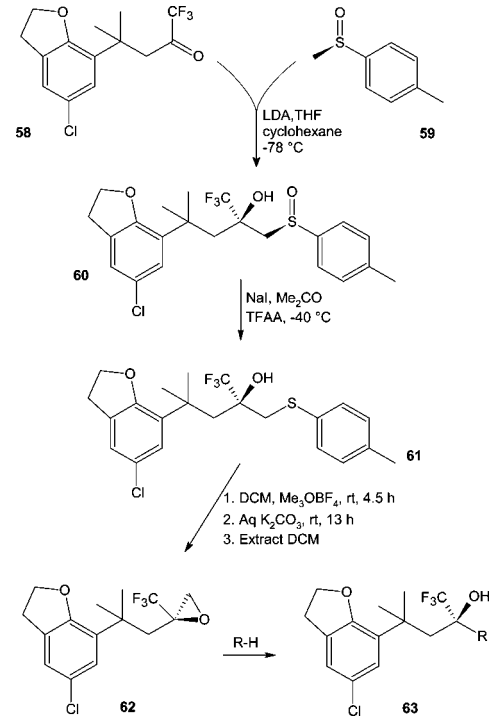
Patent No. U.S. 7,256,300

Assignee: Boehringer Ingelheim Pharmaceuticals Inc., Ridgefield, Connecticut, U.S.A

Title or Subject: Stereoselective Synthesis of Certain Trifluoromethyl-Substituted Alcohols

The patent claims cover a novel process to prepare CF_3 derivatives of epoxy compounds such as **62**. These compounds are key intermediates in the preparation of alcohols such as **63** mentioned in the title of the patent. The alcohols **63** are useful in treating diseases modulated by glucocorticoid receptors such as inflammatory, autoimmune, and allergic disorders. Scheme 16 shows the route used to prepare **62**, and this begins with the formation of **60** from **58** and *R*-**59** using LDA at –78 °C. The reaction produces a mixture of the two diastereoisomers with the desired isomer **60** being formed in 55% yield and the other in 25% yield. This is described as a key step, and yet there is no indication as to how the isomers are separated. In the next reaction the single diastereoisomer **60** is reduced to **61** using NaI in TFAA. In the last stage **61** is converted to the epoxide **62** in 95% yield by alkylation using Me_3OBF_4 followed by cyclisation with a base. The patent also describes the preparation of compounds analogous to **62** in which the benzofuran group is replaced by substituted aryls. Epoxide **62** can be converted to **63** by using a nucleophile R-H. The details are covered in a U.S. patent application, but the identity or nature of R-H is not revealed.

Scheme 16



Advantages

The process is provides a stereospecific route to the desired product

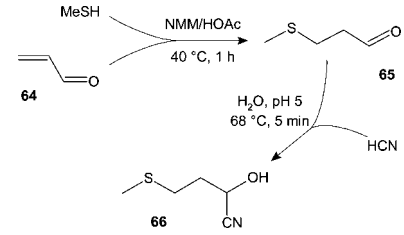
Patent No. U.S. 7,256,315

Assignee: Adisseo Ireland Ltd., Dublin, Ireland

Title or Subject: Process for the Production of 3-Methylthiopropanal

The title compound **65** is used to prepare **66** and the important amino acid methionine. Compound **65** is produced commercially in a liquid phase catalytic process from acrolein **64** and MeSH. The catalysts used are amines such as pyridine, Et_3N, or hexamethylenetetramine plus HOAc that is used to inhibit polymerisation of **64**. This patent describes that the process can be improved by using an *N*-alkyl morpholine as the catalyst with the methyl derivative (NMM) being preferred. Scheme 17 shows the method used to prepare **65** and how it can be converted to **66** in a yield >99%. The patent describes kinetic studies for preparing **65** using NMM or pyridine, and these indicate that the NMM is more effective from a kinetic

Scheme 17



point of view. NMM allows the reaction time to be reduced so that a commercial reactor would be smaller or it could be more productive. The data also indicate that the conversion is higher even when using less catalyst.

Advantages

The process has improved productivity and is more economical than alternatives.

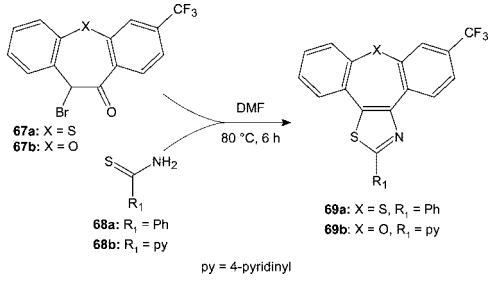
Patent No. U.S. 7,262,302 and U.S. 7,262,309

Assignee: GlaxoSmithKline Istrazivacki Centar Zagreb, D.O.O., Zagreb, Croatia

Title or Subject: The Preparation and Uses of 1-Thia-3-azadibenzoazulenes and 1- or 3-Thiabenzonaphthazulenes

These two patents describe many novel compounds that have potential as inhibitors of tumour necrosis factor-α production as well as the inhibition of interleukin-1. The patents specifically claim that the compounds can be used to treat inflammation caused by rheumatoid arthritis. The two patents use similar methods and reaction schemes to produce the desired compounds. The first patent covers a range of compounds including **69a** that is prepared from **67a** and **68a** by the route outlined in Scheme 18. The cyclisation reaction is carried out by heating the reactants in DMF followed by purification by extraction on a solid phase. The preparation of **69b** from **67b** and **68b** is carried out with the addition of K_2CO_3 and pyridinium perbromide to the reaction mixture. Using the same procedure, a number of products analogous to **69a** are made in which X = S and R_1 is an aryl or heteroaryl group.

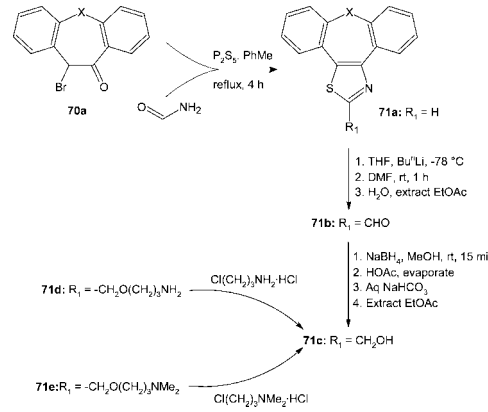
Scheme 18



There are also compounds described in the first patent that are made by the reaction **68b** with derivatives of **67b**. Examples are given in which X in **67b** is S, O, or CH_2 and in which the 6-CF_3 group is replaced by H, 5-Me, 6-Me, 7-Me, or halides at the 5-, 6-, or 7-position. A further range of compounds is described where X = S, O, or CH_2; they have a variety of substituents on one or both phenyl rings, and R_1 varies from H to CHO or -CH_2OCOMe.

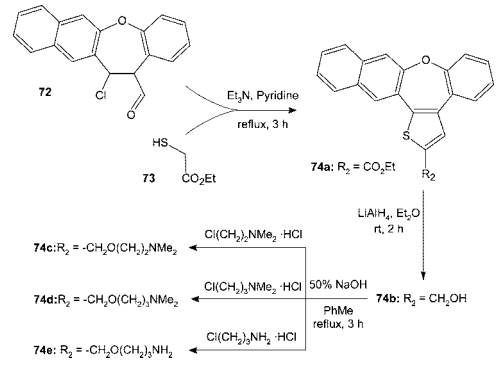
Scheme 19 shows the preparation of the **71a** and its conversion to the aldehyde **71b** that is then reduced to **71c** using $NaBH_4$. The alcohol **71c** reacts with chloralkylamines to produce **71d** or **71e**, which are described as oily products, but there are no experimental details for their preparation.

Scheme 19



The second patent describes the preparation and reactions of compounds such as **74a**. This is prepared as shown in Scheme 20 by refluxing a mixture of **72** and the ester **73** in pyridine containing Et_3N. **73a** is then reduced to the alcohol **73b** using $LiAlH_4$ and this is converted to a range of substituted amines **74c**−**e**.

Scheme 20



The two patents describe the preparation of over 150 compounds, and there are ^{1}H NMR data for most of them. Little if any details of yields are provided, and hence the process efficiency cannot be estimated.

Advantages

The patents provide a very large range of novel compounds that are claimed to be useful in the treatment of rheumatoid arthritis.

Patent No. U.S. 7,262,320

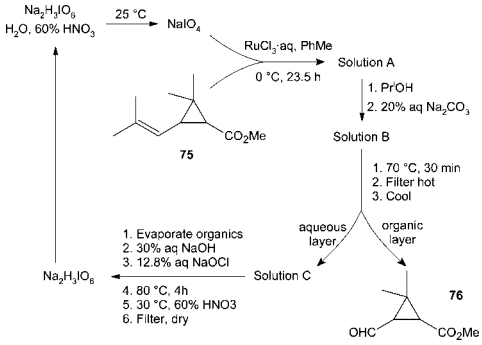
Assignee: Sumitomo Chemical Company Limited, Osaka, Japan

Title or Subject: Process for Production of 3,3-Dimethyl-2-formylcyclopropanecarboxylic Acid Derivatives

The title compounds are important intermediates for the production of pyrethroid-type pesticides. Processes for the production of compounds such as **76a** are known, and they involve the oxidation of **75** using OsO_4 and are therefore hazardous. The objective of this patent is to provide a safer and more efficient process of carrying out this reaction, and the method used is shown in Scheme 21. The oxidation of **75** is carried out using a mixture of sodium metaperiodate ($NaIO_4$) and a ruthenium compound. Several Ru compounds are used in the examples, and using

$RuCl_3$ hydrate gives a yield of 86%. The metaperiodate is produced from the paraperiodate ($Na_2H_3IO_6$) that is recovered from the reaction and then converted to the metaperiodate by treatment with NaOCl as shown in the scheme. The rate of recovery of iodates is 99%.

Scheme 21



The process allows reuse of the iodate oxidant compound by reoxidation of the paraperiodate using NaOCl. This is a readily available and much cheaper oxidising agent than the metaperiodate so that the overall raw materials costs will be lower. Variations on the basic process are described in the patent and use alternative iodine sources such as the K salt of H_5IO_6 or other Ru salts. All seem to give yields in excess of 75%.

Advantages

The process reuses the oxidant and offers a safer and potentially cheaper process than the alternative of using OsO_4.

Patent No. U.S. 7,262,326

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

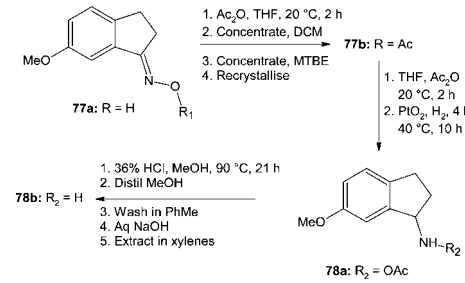
Title or Subject: Process for Synthesis of Indanylamine or Aminotetralin Derivatives and Novel Intermediates

The compounds described in this patent are useful in the treatment of depression, Alzheimer's disease, and other neurological disorders. Alternative processes for making the desired compounds are said to give low yields and low reproducibility. Hence the patent aims to overcome these problems, and the new process is divided into three steps. Scheme 22 shows these steps used for the preparation of compound **78b**. The route begins with the acylation of the oxime **77a** to produce the novel compound **77b** that is isolated in 77.6% yield. The acylated oxime is then hydrogenated using a PtO_2 catalyst to form the amide **78a** in 90% yield. In the final stage the hydrolysis of **78a** with HCl is done in three steps with cooling to 25 °C prior to adding further HCl and then reheating. This takes 21 h without the time needed to cool the batch before addition of more HCl. The final product **78b** is obtained in 65% yield on a kilo scale experiment, thus suggesting the advanced stage of development of the process.

Advantages

The process provides an effective method of synthesising the desired compounds via some novel intermediates.

Scheme 22



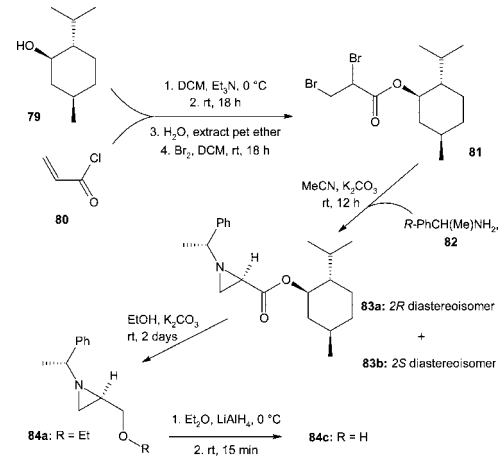
Patent No. U.S. 7,268,228

Assignee: Imagene Co. Ltd., Seoul, Korea

Title or Subject: Novel Optically Active Aziridine-2-carboxylate Derivatives and Process for Preparing Them

Aziridine compounds are useful for preparing many medicaments and fine chemicals. Methods available to produce such compounds from natural materials such as serine are claimed to be suitable for making only products with the same natural configuration as serine. Other methods use chiral sulfines that are difficult to prepare. This patent describes a series of products that have the alternative configuration from more readily available starting materials. A number of aziridine compounds are described in this patent that contain a (−) or (+) menthol group, so the full range of optical isomers can be produced. The production of **83a** and **83b** is carried out by reaction of the menthol ester **81** with **82** in the presence of Et_3N (Scheme 23). Also shown is the formation of the ester **81** from (−)-menthol **79** and acryloyl chloride **80** followed by treatment with Br_2. The reaction of **81** and **82** produces a mixture of the diastereoisomeric pair **83a** and **83b**. These are separated by crystallisation from MeOH or EtOH, giving the **83a** crystals while **83b** remains in solution and is crystallised from alkane hydrocarbon solvents. Transesterification of the menthol esters **83a** using alkyl alcohols gives the alkyl ester **84a** with the same configuration. Reduction of this ester using $LiAlH_4$ produces the hydroxymethyl aziridine **85c**.

Scheme 23



The patent also describes the preparation and separation of other diastereoisomeric pairs of esters from (+)-menthol in the same manner. ^1H NMR data are given for all products.

Advantages

The process provides a method of making a full range of enantiomers of a series of useful intermediates.

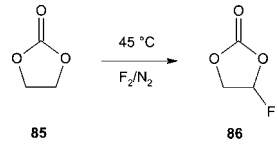
Patent No. U.S. 7,268,238

Assignee: Ulsan Chemical Co. Ltd., Ulsan, Korea

Title or Subject: Method and Apparatus for Manufacturing 4-Fluoroethylene Carbonate

The compound of interest of this patent, **86**, is claimed to be the best additive for improving the performance of the organic solvent in rechargeable lithium ion batteries. It reduces the decomposition of the electrolyte and improves thermal stability of the battery. The required purity of **86** is in excess of 99.8% with a moisture content <20 ppm. Various methods of producing **86** that meet this specification are summarised, and a few are claimed to be suitable for commercial operation. The patent describes a process that is said to be capable of the manufacture of **86** of the required high quality that employs a direct reaction between liquid **85** and a gaseous mixture of N_2 and F_2. It is noted in the patent that the size of the bubbles is critical to safe operation of the process. Large bubbles were found to give a rapid reaction that caused localised explosions and degradation of **85**, making purification difficult. The process therefore regulates the bubble size, contacting the liquid and gas in a packed column. This produces a smooth reaction and a much improved purification procedure. Vacuum distillation is the method used to separate **86** from the byproduct HF and the difluorinated product plus unreacted **85**.

Scheme 24



One of the patent claims refers to the use of column packing that is a cylinder that has a particular shape. Rather than describe the shape the claim is unusual in that it contains a small drawing of the cylinder.

Advantages

The process gives an efficient method of making this important product at the required high purity.

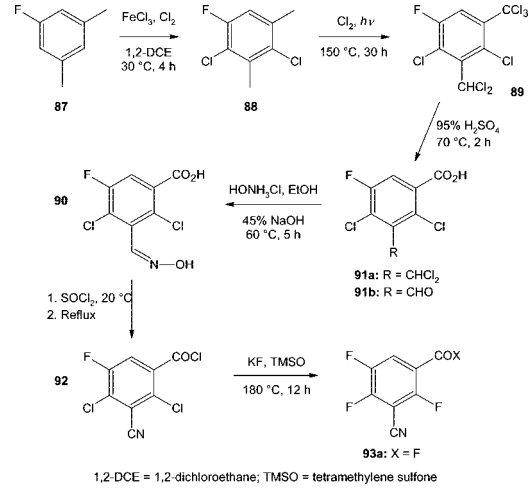
Patent No. U.S. 7,268,248

Assignee: Bayer AG., Leverkusen, Germany

Title or Subject: 3-Cyano-2,4,5-trifluorobenzoyl Fluoride and Intermediate Products for the Production Thereof

The title compound **93a** is used to prepare quinolones that are anti-infectives and antimicrobial reagents. One method available to produce **93a** using NaCN and CuCN is deemed unsafe on large scale. The production of **93a** described in this patent is a multistage process that starts from **87** and is summarised in Scheme 25. The first stage may be carried out without using 1,2-dichloethane, and both methods are described in the patent. The example using the solvent is carried out on a much larger scale than the solvent-free method. As is usually the case, ring-chlorination reactions give mixtures, and using the solvent gives 81% selectivity to **88** compared with 58% without solvent. The product is purified by vacuum distillation. The next step is again carried out at kilo scale and gives 71% of **89** and 28% of other chlorinated products; vacuum distillation is used in the purification step. Hydrolysis of **89** produces **91b** in two stages via **91a**. It is possible to stop the reaction and isolate **91a**. The oxime is formed from **91b** and then converted in one step to **92**. This is a key step in the process and involves simultaneous chlorination of the acid and dehydration of the oxime and is carried out using $SOCl_2$. In the final step fluorination is performed using KF at 180 °C in tetramethylene sulfone (TMSO) as a solvent, and **93a** is obtained. This can be converted to **93b** (X = Cl) using $AlCl_3$ and $SiCl_4$.

Scheme 25



There are several novel compounds that are obtained in the production of **93a**, and **90** is specifically covered in the patent claims, as is its conversion to **92**.

Advantages

The process provides a potentially safer process for producing the desired compound on a commercial scale. However, the large number steps and the formation of many byproduct in the early stages will decrease the overall process efficiency.

Patent No. U.S. 7,268,249

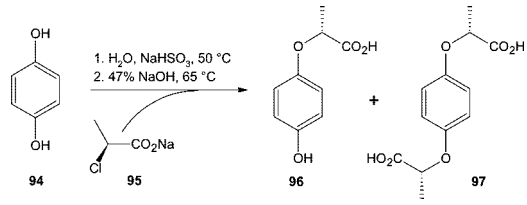
Assignee: Syngenta Limited, Huddersfield, United Kingdom

Title or Subject: Production Process for Optically Pure 2-(4-Hydroxyphenoxy)-propionic Acid Compounds

The particular acid of interest, **96**, is used to make herbicidal products and is usually produced from hydroquinone **94**. The major problems are overalkylation giving the bis-acid **97** and oxidation giving coloured byproduct that are difficult to remove. The process described in the patent overcomes these problems by using a mild reducing agent such as $NaHSO_3$ and by performing the reaction under N_2 to prevent oxidation. Scheme 26 indicates the basic procedure that is actually carried out in two stages. After addition of the first portion of **95**, the mixture contains 8.6% of the Na salt of **96** equivalent to an 85% yield. Acidification with H_3PO_4 and H_2SO_4 produces the acid form **96**, and the mixture is extracted with MIBK to remove the unreacted **94**, leaving the product in the aqueous solution. The MIBK solution is then recycled and used in another reaction

after fresh **94** is added. In the final step the acid is converted to the K salt for purification by addition of 32% HCl. The final product is obtained in 63% yield and determined to be 99.4% pure containing 0.3% of **97**. There is but a single example in the patent describing a kilo scale experiment.

Scheme 26



94 **95** **96** **97**

Advantages

The process produces high purity product by avoiding the formation of the byproduct bis-acid and coloured oxidation products.

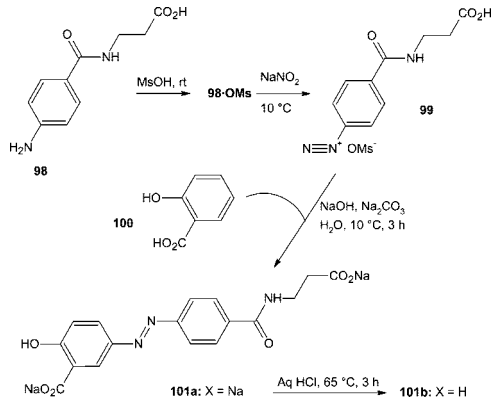
Patent No. U.S. 7,271,253

Assignee: Apotex Pharmachem Inc., Brantford, Ontario, Canada

Title or Subject: Safe Process for the Preparation of Balsalazide

Balsalazide **101b** is a gastrointestinal anti-inflammatory drug used for treating ulcerative colitis. It is usually administered as the Na salt **101a** and is available as colazal in the USA or colazide in the U.K. It was first reported in 1983, and the patent states that there is little information on its preparation. The original patent describes a synthesis of **101a** that involves the formation and use of a poorly soluble diazonium salt. It is known that diazonium salts can be very unstable especially if they are in the solid form. Hence poorly soluble compounds may appear as crystals during the process and result in a hazardous situation. The new process overcomes this potential problem by using a more soluble diazonium salt and ensuring that the reaction intermediates remain in solution. The method used is outlined in Scheme 27 and begins with **98**, which is converted to the diazonium mesylate salt **99** via the mesylate salt **98**·MsO. Compound **99** is then coupled with the Na salt of **100** to form the disodium salt **101a**. Although the Na salt is the usual form of the drug, the patent indicates that the acid form **101b** can be obtained from **101a** by using HCl.

Scheme 27



The solubility curve of **99** is provided, and this shows that the solubility of **99** is sufficiently high that the reaction can be carried out at increased concentrations, thus reducing the reaction volumes required. The patent reports results of decomposition experiments using DSC and also reports the use of batch and continuous experiments.

Advantages

The use of a soluble diazonium salt reduces the danger of explosions and improves process operability.

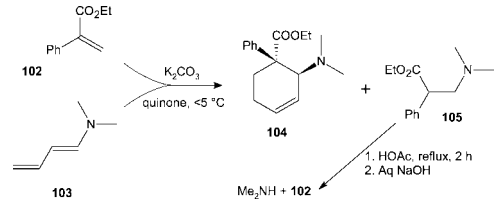
Patent No. U.S. 7,273,947

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Method for Increasing the Purity of an Intermediate Used in the Preparation of Tilidine

Tilidine, **104**, is a synthetic opioid analgesic that can be produced from **102** and **103** as shown in Scheme 28. The reaction to produce **104** actually gives a so-called mixture of *cis*/*trans* isomers with **104**, the active form, being described in the patent as the *trans* isomer. The stereochemistry defines the relative positions of the amino and ester groups. There are other methods available for producing **104**, but they all give **105**. The presence of K_2CO_3 inhibits its formation, but it is difficult to separate it from **104**. The patent describes a method for removal of **105** by converting it to **102** without affecting the amount of the *cis* isomer of **104**. This removal of **105** is achieved by dissolving the mixture in cyclohexane and adding up to 2 mol of an acid such as HOAc per mole of **105**. This releases the Me_2NH and produces **102**, which can in principle be recovered and reused, although it is probably not economic to do this. The patent describes how a mixture containing 1% **105** can be reduced to a level of 0.05%. It is also claimed that a mixture of HOAc and HCO_2H can be used. The desired *trans* isomer **104** can be recovered by selective complex formation with Zn ions or by salt formation with oxalic acid. These separation methods tend to enrich the amount of **105**, and so it is necessary to start with a **105** level of <0.1% in order to carry out the *cis*/*trans* separation step.

Scheme 28



Advantages

The process removes the byproduct and converts it to the starting material that is not difficult to remove.

Keith Turner

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