Organic Process Research & Development **2005**, *9*, 719–729

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during July and August 2005

Summary

The current review of 21 patents has been culled from an initial list containing 219 that fitted the search criteria. One thing that struck me in this collection is that there are a large number of patents that contain experimental work using dichloromethane (DCM) either as a solvent for the reaction or for extraction during workup. Since there is supposed to be a move to greener, more environmentally friendly processes, this strikes me as a retrograde step. On the subject of solvents, a process for the preparation of a range of anticoagulants known as oxabispidines is disclosed that involves at least five different solvents including the use of DCM. These compounds are not readily prepared so perhaps such methods are necessary. A range of bipiperidine salts is described whose optical activity is due to restricted bond rotation rather than the presence of chiral centres. Careful choice of solvent and salt can give specific diastereoisomers of these so-called rotamers. The restoration of damaged brain cells is a goal in neurology, and a range of tetrahydropyridines has been synthesised that offer hope in this area. The desire to have sweet, low-fat foods drives the search for safe sweeteners, and new derivatives of aspartame have been described that may satisfy this market. Improved methods of aromatic nitrations are described, including one for making halonitrobenzoic acids. A second patent describes an improved method of nitrating bis(trifluoromethyl)benzenes. Although the patent title is the nitro compound itself, the actual subject matter is somewhat different and more interesting. The patent describes a method for preparing compounds that can be used to treat baldness or an enlarged prostate. Both problems may in future be of direct personal interest to older male readers. This latter patent is an example of a misleading or incomplete title, and another relates to a so-called low-pressure hydrogenation process. It may not be appreciated by everyone, but any word or term in a patent can be defined as meaning whatever the authors (or more likely the patent agents) desire. In the patent referred to, low-pressure is defined as applying to a process operating at 100 bar as opposed to 130 bar needed in earlier work. The production of highly stereospecific polyolefins has been radically changed in the past few years by the use of metallocene catalysts. The methods used to prepare the complex ligands owe much to skill of synthetic organic chemists, and a range of novel thiophene-based ligands is disclosed. In another patent a range of benzothiophenes is prepared by acid-catalyzed cyclodehydration reactions. Liquid acids cause the reaction and side-reactions to proceed so quickly that some useful intermediates cannot be isolated. Using less reactive but more selective acid clay improves the ability to obtain the desired products. An enantioselective Reformatsky reaction is described that is used to prepare a range of chiral alcohols using a recyclable cyclic diamine as a key reagent. Fewer patents in this selection contain details of experiments larger than bench scale, but this not mean that the process is not at an advanced stage of development. No legal or commercial significance should be inferred from the patents chosen, and any advantages are usually those claimed in the patent unless this reviewer has personal knowledge of the subject.

Patent No. U.S. 6,916,924

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

Title or Subject: Process for the Synthesis of Heteroarylureas that Are Useful as Antiinflammatory Agents

The title compounds **7a** and **7b** are useful in inhibiting cytokine production in various inflammatory and autoimmune diseases. A range of methods is available for synthesising these compounds, but these are described as nonconvergent and hence unattractive for commercial processes. The patent describes a method of preparing **7a** and **7b** that is shown in Scheme 1. The initial step is reaction of the chloroformate **1** with the naphthylamine **2** to give **3**. No information is given regarding the preparation of **2**. The treatment of the amine **4** with **3** in the presence of a base gives the urea **5**, and this is coupled with the boronic acid **6** to give **7**.

The key is the final step that provides the desired urea **7** via the coupling of **5** with the boronic acid **6** in the presence of $Cu(OAc)_2$ and base. This reaction takes place under very mild conditions, is not air sensitive, and uses commercially available boronic acids. It is stated that this type of reaction was originally described as being suitable for the coupling of a NH heterocycle to an aryl group. ^{1}H NMR data are given for the intermediates and final products.

Advantages

The process uses a mild procedure for the key step in the synthesis and thus provides the opportunity for a highly selective process.

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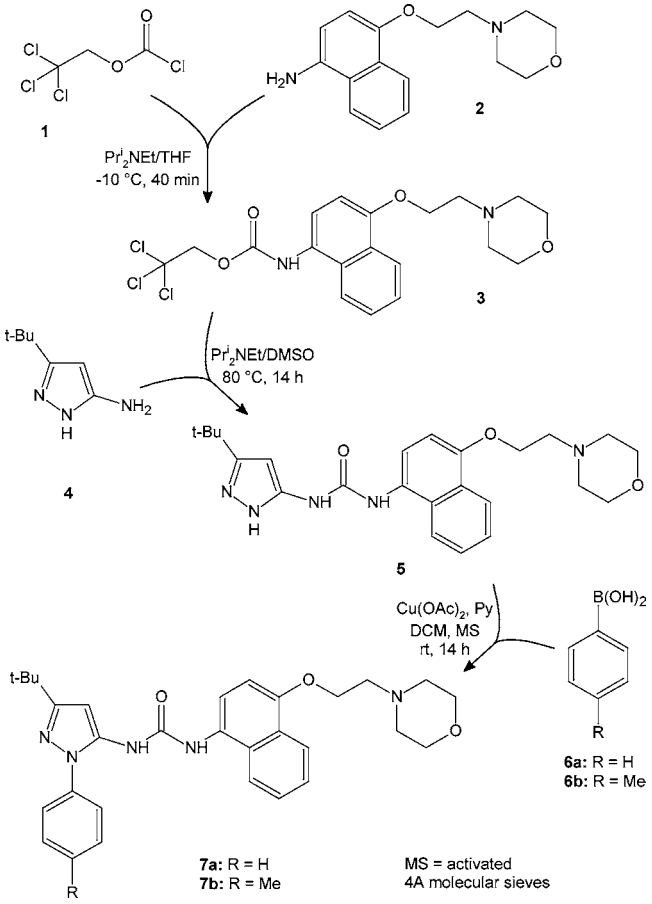
Scheme 1



Patent No. U.S. 6,916,929

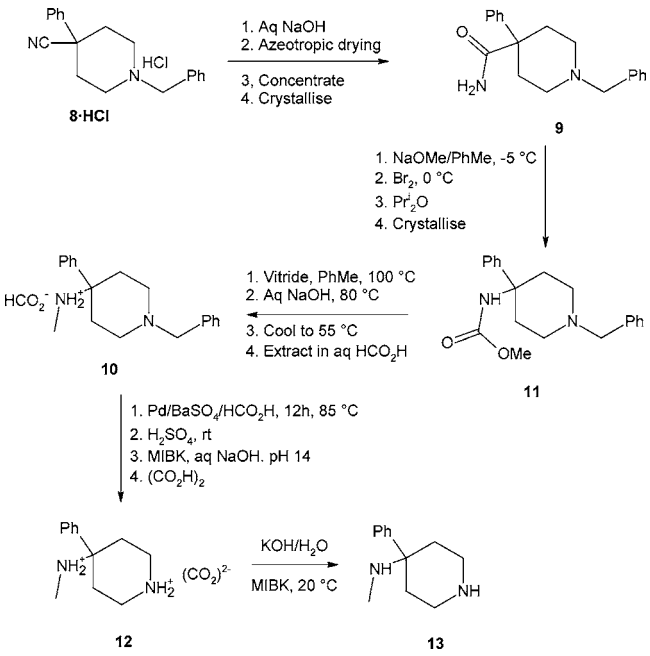
Assignee: Sanofi-Synthelabo, Paris, France

Title or Subject: Method for Preparing 4-Methylamino-4-phenylpiperidine

This patent describes a process for preparing **13** and its salts that are used as intermediates for synthesis of tachykinin antagonists. Alternative methods for preparing **13** are very lengthy but do give good yields. The new process uses a commercially available starting material **8** that is available as the HCl salt. The free base **8** is released by heating the salt with NaOH, and the base is then used in a one-pot reaction to make the amide **9**. Scheme 2 shows how **9** can be converted to **13** via the carbamate **11**. The formation of **11** in yields >80% may be carried out without isolation of the amide **9**, and the reactions are all carried out sequentially in the same vessel. Reduction of **11** to give **10** is carried out using vitride or similar reducing agents. The product is isolated as the formate salt **10** by extraction into formic acid. The benzyl group is removed from **10** by hydrogenolysis using Pd/$BaSO_4$ in formic acid, and treatment with oxalic acid gives the dioxalate salt **12** that is converted to the free base **13** using KOH.

The examples in the patent use kilo quantities of reagents thus indicating the advanced stage of process development.

Scheme 2



Advantages

The process has fewer steps and takes much less time than the alternative method and does not require isolation of intermediates. In addition the use of commercially available starting material improves the economics of the method.

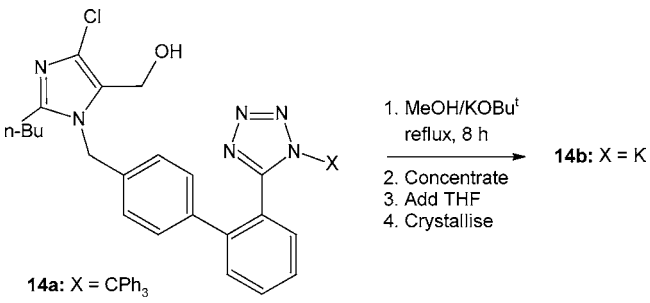
Patent No. U.S. 6,916,935

Assignee: Ipca Laboratories, Mumbai, India

Title or Subject: Losartan Potassium Synthesis

Losartan potassium **14b** is an angiotensin II receptor antagonist that is used to prevent the narrowing of blood vessels and to treat high blood pressure. **14b** can be prepared from the acid form (**14c:** X = H) by reaction with KOH. **14c** can be prepared from **14a**, and it is claimed that this requires extensive purification using large volumes of mixed solvents that are difficult to recover and reuse. Alternative procedures convert to **14a** to **14b** by refluxing KOH in a mixture of MeOH and THF for 18 h. The use of mixed solvents again causes purification problems. The current patent describes a method of preparing **14b** from the trityl derivative **14a** by refluxing in MeOH containing KO-*t*-Bu followed by crystallisation from THF or *i*-PrOH (Scheme 3). The reaction time is only 8 h, and a single solvent is used in the first stage.

Scheme 3



Advantages

The process is simpler than the alternatives and affords higher yields of the product in less time.

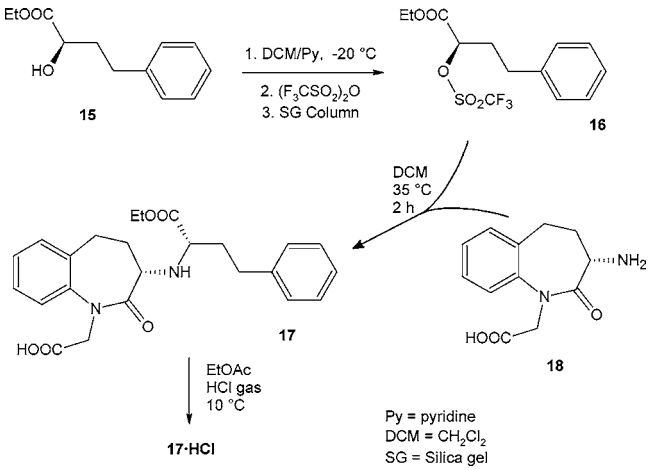
Patent No. U.S. 6,919,450

Assignee: Ranbaxy Laboratories Limited, New Delhi, India

Title or Subject: Process for the Preparation of Benazepril

The title compound **17** is an ACE inhibitor that is used in the treatment of hypertension and was first reported in 1983.The process for the preparation of **17** is shown in Scheme 4 and is similar to alternative methods that also use pyridine as base. It has been found that the pyridine reacts with triflic anhydride giving rise to significant amounts of the corresponding pyridinium salt. The presence of this salt reduces the overall yield of the process and makes recovery of **17** more difficult. To overcome this problem alternative bases to pyridine may be used; these can be costly. This patent uses the same reagents but solves the problem by using column chromatography to purify the product and remove the salts. Thus, the first stage is preparation of the ester **16** that is treated with the lactam **18** to give **17**. The product is isolated as the HCl salt by treating **17** with dry HCl gas.

Scheme 4



Advantages

The process may indeed make product recovery easier, but the use of DCM is not an attractive solvent for commercial operation.

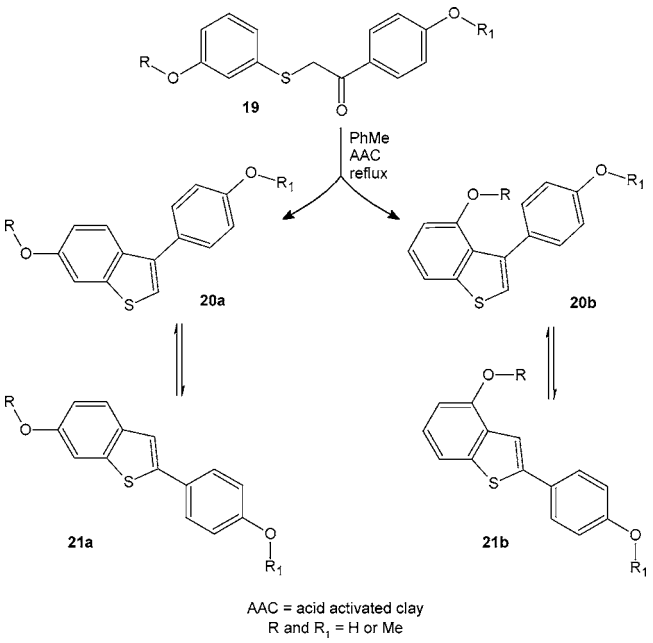
Patent No. U.S. 6,921,827

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

Title or Subject: Process for Preparing 3-Arylbenzo[b]thiophenes

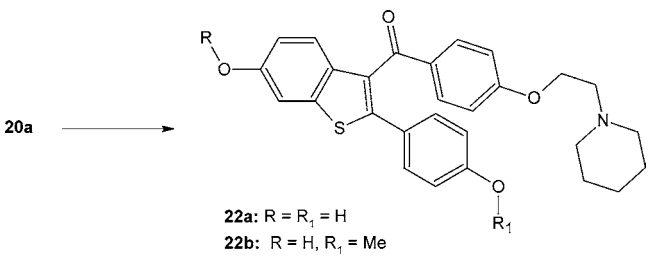
The compounds of interest in this patent such as **20a** are used as pharmaceutical intermediates. There are several references given to the preparation of compounds such as **20a** from acetophenones such as **19** by acid-catalyzed cyclodehydration. The type of acid catalysts dictates the product distribution, and a number of byproducts can be produced. The reaction scheme for conversion of **19** is shown in Scheme 5, and the initial reaction produces two possible isomers **20a** and **20b**. When phosphoric or methanesulphonic acids are used, the ratio of **20a**:**20b** is from 3:1 to 4:1 when R and R_1 are both Me. However, the rearrangement to give **21a** and **22a** takes place quickly so that the initial products **20a** and **20b** are not easily isolated. BF_3 is also suitable, but the reaction needs to be run without solvent to give good yields. If an ion-exchange resin (IER) is used, the rearrangement is up to 100 times slower, and the intermediates **20a** and **20b** can be isolated in a ratio of about 7:1. When R and R_1 are both H or are different, then different ratios of products are obtained. Thus, to produce high yields of **20a** the acid used must be carefully selected. The patent discloses an improved method giving high yields of **20a** by the use of acid-activated clay (AAC) or zeolites. These types of catalyst give selectivities >92% to the 6-isomer **20a** when R and R_1 are both Me.

Scheme 5



The patent also mentions that the compounds **22a** and **22b** can be produced by acylation of **20a** shown in Scheme 6. Presumably compounds **22a** and **22b** are those of interest as APIs. However, no details for this conversion are given in the patent although patent references to the procedure are provided.

Scheme 6



Advantages

The process allows production of the desired intermediates with higher selectivity than alternative processes,

thereby simplifying the purification and separation of products.

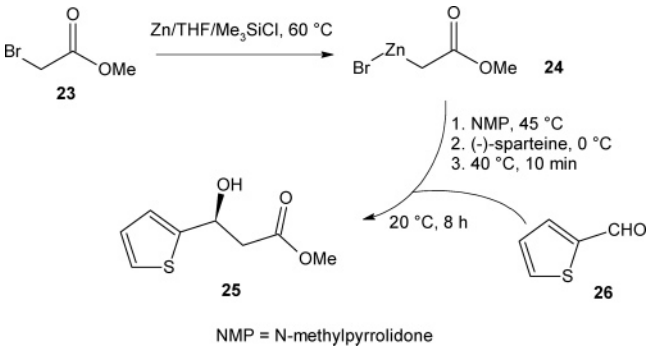
Patent No. U.S. 6,924,386

Assignee: Consortium für Elektrochemische Industrie GmbH, Munich, Germany

Title or Subject: Enantioselective Reformatsky Process for Preparing Optically Active Alcohols, Amines and Derivatives Thereof

This patent states that the preparation of chiral alcohols and amines by the asymmetric Reformatsky reaction is of ever increasing importance. However, it is claimed that known methods are not suitable for industrial scale use for a variety of reasons with low enantioselectivity being a major problem. The patent describes a process for the preparation of chiral alcohols such as **25** in high chemical and optical yields. The key is the use of a chiral auxiliary that is a diamine containing at least one cyclic group. In addition the pK_a of protons on the auxiliary must be >18. The examples describe the use of (−)-sparteine as the auxiliary. The patent states that the properties of the auxiliary limit the flexibility of the transition state intermediate so that the optical yield of the product is enhanced. Scheme 7 shows a route to make **25** from the aldehyde **26** by reaction with the intermediate Zn compound **24**. This intermediate is not isolated, and the second reaction is carried out in the same reaction vessel. The patent claims that it is surprising that high chemical and optical yields could only be obtained if the aldehyde is added to the mixture of **24** and the diamine at temperature <15 °C. Higher temperatures give less pure product. The process also says that sparteine can be recovered by distillation and reused.

Scheme 7



The patent also describes several experiments in which a range of other aldehydes is used. It is claimed that the process is applicable to the reaction of imines to give amines although no examples are given.

Advantages

The method gives high chemical and optical yields of products and does enable the chiral agent to be recovered and reused so that the potential for commercialisation is increased.

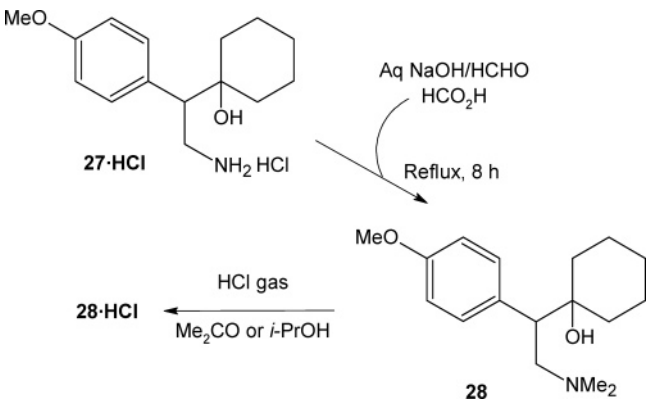
Patent No. U.S. 6,924,393

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

Title or Subject: Processes for Preparing Crystalline Venlafaxine Base and Novel Polymorphs of Its Hydrochloride Salt

Venlafaxine **28** and its salt are antidepressants that were initially reported in 1985. This patent discloses two new polymorphs of **28**, two novel solvate forms, an improved method of preparing solid **28** as a free base, plus two new forms of the HCl salt **28·HCl**. Scheme 8 shows how solid crystalline **28** can be produced from **27** by methylation using $HCHO/HCO_2H$ in aqueous NaOH. The crude HCl salt of **28** can be prepared by treating **28** with gaseous HCl. Two polymorphs of **28·HCl** were then obtained trituration with acetone followed by drying in a vacuum. If the drying is conducted with stirring, then Form I is produced, but static drying gives Form II. The solvates of **28** that were produced are from DMF or DMSO.

Scheme 8



The patent includes DSC and XRD spectra for the novel forms of the drug.

Advantages

Novel forms of the established drug have been prepared thereby opening up the possibility of new commercial opportunities.

Patent No. U.S. 6,924,394

Assignee: Invista North America S.r.l., Wilmington, Delaware, U.S.A.

Title or Subject: Low Pressure Process for the Manufacture of 2-(Aminomethyl)-1-cyclopentylamine

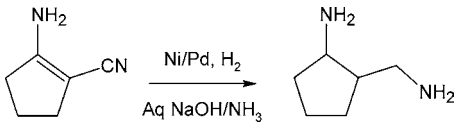
The subject of this patent **30** is useful as a chemical intermediate and also in the formulation of epoxy curing agents, and as a cross-link and polyamide modifier. **30** is generally produced by catalytic hydrogenation of **29** as shown in Scheme 9. The first reported of this conversion was in 1942 and used pressures in excess of 130 bar with Ni/alumina or Co catalysts. Other catalysts and process improvement have been made over the years, but all processes quire high pressure of H_2 and large quantities of aqueous NaOH. This combination can give major problems with the failure of the equipment by corrosion and stresses.

The new process is said to produce **30** from **29** at much lower pressure and temperatures. The process involves an initial catalysts activation step that is followed by the hydrogenation reaction. The catalyst used in the examples is a combination of two commercially available catalysts such as Pd/C and a Raney Ni type. The catalyst activation procedure is summarised as follows:

1. suspend the catalysts in 1,4-dioxane and water under N_2
2. admit H_2 at 20 bar maintain at 35 °C for 3 h
3. cool to room temperature and purge with N_2

After activation **29** is added to the reactor with aqueous NaOH and dry NH_3, and then the system is maintained at 100 bar pressure with H_2 and heated for 12 h at 75 °C. The product **30** is an oil that is vacuum distilled and obtained in purity >99%.

Scheme 9



29 **30**

The patent gives examples of using catalysts that are either Ni or Pd, and these give little or no reaction even at temperatures up to 150 °C.

Advantages

The process does give high conversion and high yields of the product, but I for one would not describe 100 bar as low-pressure hydrogenation, and hence this does not seem to be a significant improvement on earlier processes.

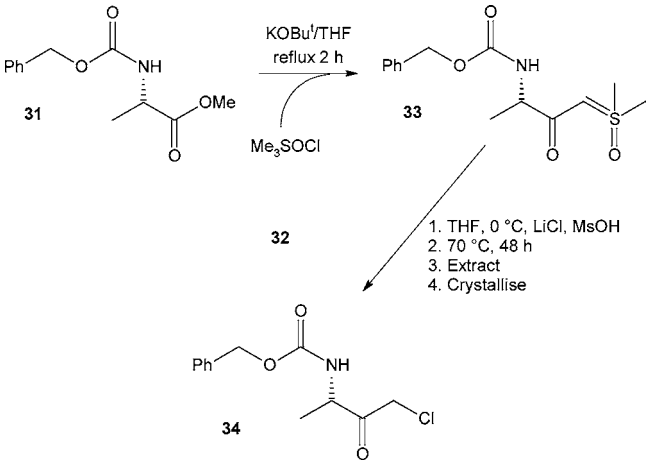
Patent No. U.S. 6,924,397

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

Title or Subject: Process for the Preparation of a-Chloroketones from Alkyl Esters

Chloroketones are very useful intermediates for the synthesis of ACE inhibitors, and renin or HIV proteases. The patent summarises some of the methods that are used for the preparation of the compounds, and as is common with many chlorosubstituents, some of them involve the use of hazardous or dangerous techniques or reagents. This patent describes a method for preparing the desired chloroketones such as **34** from alkyl esters and sulphoxonium ylides. The patent refers to reports concerning the use of phenyl esters to prepare chloroketones using sulphoxonium ylides, but these reports apparently do not refer to alkyl esters as being suitable. Scheme 10 shows the procedure for preparing **34** from **31** via the intermediate ylide **33**. The route begins with the reaction of the sulphoxonium chloride **32** with the protected alanine ester **31** to give the ylide **33**. This is isolated in 97% yield and then used in the second stage of the process to give the final product **34.** The production of **34** from **33** is by reaction with HCl, and this is formed in situ from LiCl and MsOH. **34** is obtained in 70% yield with an ee of 99%. A summary of the ^1H and ^{13}C NMR data is provided for both **33** and **34**.

Scheme 10



The patent provides a number of examples of the application of the reaction to the preparation of other chloroketones.

Advantages

The process provides a novel way of preparing the chloroketones in good yields that avoids the use of some of the hazards of alternative methods.

Patent No. U.S. 6,927,300

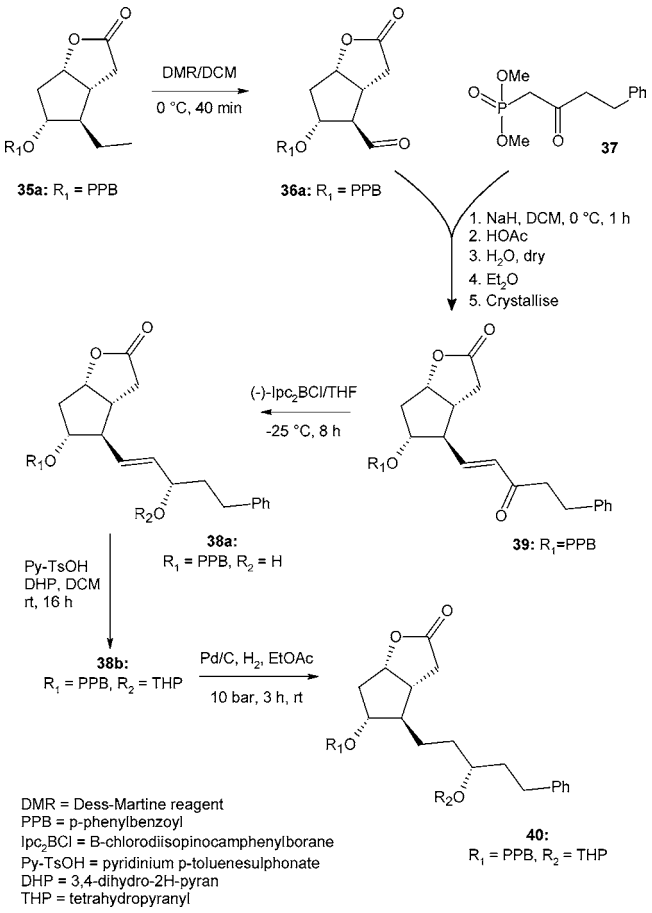
Assignee: FineTech Laboratories LTD, Nesher, Israel

Title or Subject: Process for the Preparation of Latanoprost

Latanoprost **43c** is used in the treatment of glaucoma, and one difficult step in the synthesis is a low-temperature reduction of a lactone ring. This is similar to the conversion of **40** to give **41** shown in Scheme 12 where R_1 and R_2 are both H. It is said that this exothermic reaction is difficult to scale up to a commercial scale without reducing selectivity. This patent describes an improved approach to this conversion by protecting the OH groups in **40** and **41** and thereby providing a novel route to **43c**. This extensive patent covers a multistep route with a number of variations. The first part of the synthesis is the preparation of the lactone **40** as shown in Scheme 11. The protected starting material **35a** is converted by a series of steps to **40.** The key reaction in converting **35a** to **40** is the stereoselective reduction of the keto-group in **39** to give **38a** using a chiral borane reagent. The patent also describes variations on the main scheme and conversion of some intermediates to other novel compounds. For example the hydroxy forms of compounds **38**, **39**, **40**, and **41** are described in which R_1 and R_2 are H in all compounds.

The second stage of the process is shown in Scheme 12 in which **40** is converted to the racemic alcohol **41**. In the production of **43a** from **41** and **42** the reaction is shown as being stereoselective. Although no mention of the reason for this is made in the patent, it is presumably due to steric factors and the influence of the adjacent groups. The final step is the production of the acid that is esterified before the last protective group is removed to give **43c**.

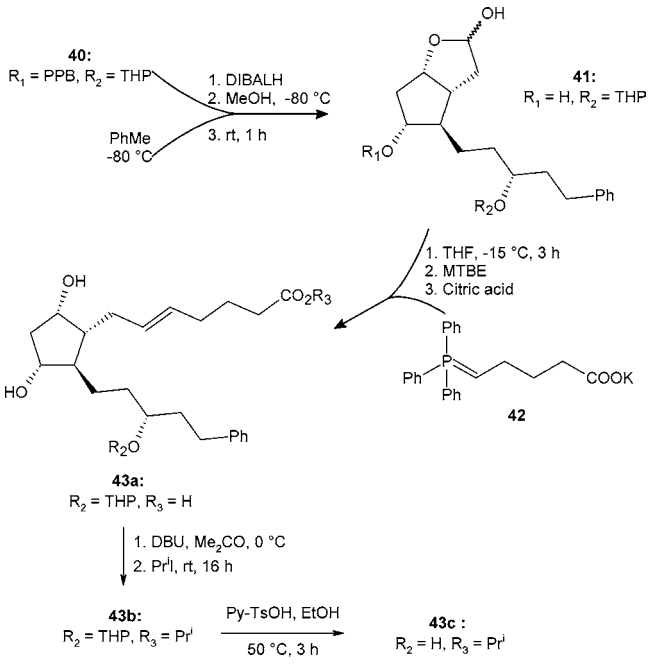
Scheme 11



Advantages

The process is said to be more efficient than alternative procedures, but it does involve the use of DCM as solvent in several steps.

Scheme 12



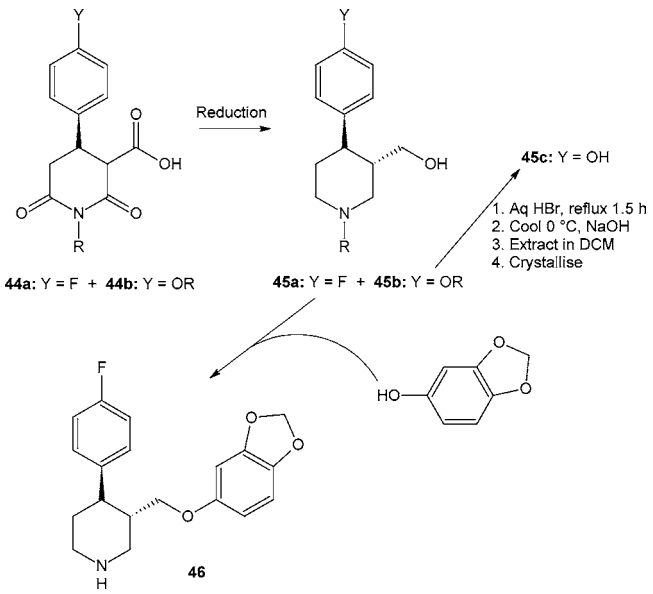
Patent No. U.S. 6,930,186

Assignee: Teva Pharmaceutical Industries Ltd., Petah-Tiqva

Title or Subject: Process for the Preparation of Paroxetine Substantially Free of Alkoxy Impurities

New synthetic routes to the widely used antidepressant paroxetine **46** are the subject of research by several companies after its main patents expired, and the subject has been reviewed (*Org. Process Res. Dev.* **2004**, *8*, 311). This patent is aimed at the removal of the impurity **45b** that is formed during the synthesis of **45a**; a key intermediate in the synthesis of **46** as shown in Scheme 13. **45b** is formed by defluorination of **44b** that itself is produced during the preparation of **44a** in the presence of a strong base such as KOBu^t. The mixture of **44a** and **44b** is not separated before reduction, and hence a mixture of **45a** and **45b** is obtained.

Scheme 13



The removal of **45b** from **45a** is carried out by cleavage of the ether linkage in **45b** with HBr to form the phenol **46c** (Y = OH). The phenol is then extracted into aqueous basic solution leaving **45a** that is crystallised from DCM. Purified **45a** was obtained containing <0.5% **45b** from an initial mixture containing 2.6% **45b**.

Advantages

The process improves the purification of a key intermediate in the production of paroxetine but again uses DCM as solvent.

Patent No. U.S. 6,930,190

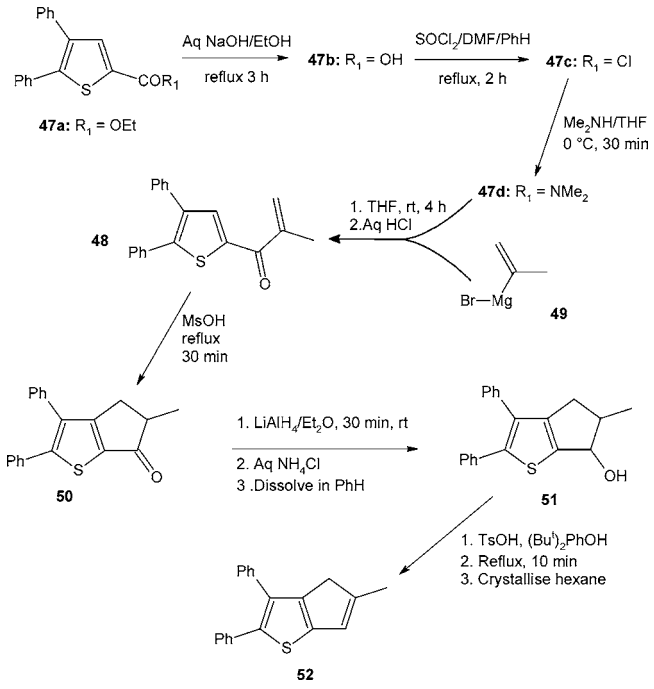
Assignee: Basell Polyolefine GmbH, Wesseling, Germany

Title or Subject: Process for the Preparation of Heterocyclic Pentalene Derivatives

The compounds of interest in this patent are used in the preparation of highly active metallocene catalysts of Zr or Hf for the polymerisation of olefins. Scheme 14 summarises the route used to prepare **52**. The first stage is the preparation of the amide **47d** by conventional means from the ester **47a**.

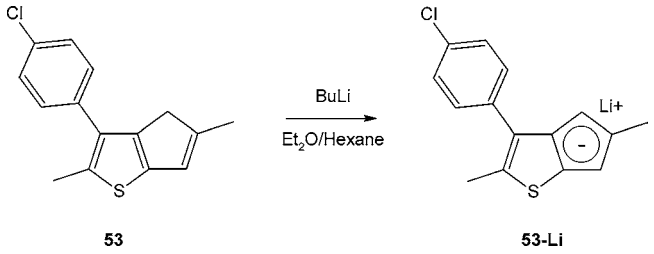
The amide **47d** is then treated with the vinyl Grignard reagent **49** to produce **48** that is treated with MsOH to effect cyclisation giving **50**. The final stage is reduction of **50** with $LiAlH_4$ to give **51** and dehydration using TsOH in the presence of $(But)_2PhOH$. The reason for adding this hindered phenol is not mentioned although it may be used as a polymerisation inhibitor or an antioxidant.

Scheme 14



The compounds described in the examples are all thiophenes although the patent does claim that pyrroles and furans can be prepared by analogous methods. In one example in the patent the final thiophene product **53** is treated with one mole of BuLi so that the Li salt **53-Li** is obtained as shown in Scheme 15. In the patent claims this reaction is specifically claimed to be a method of purifying the thiophene. Since the thiophenes are used to prepare metallocenes, it possible that the Li salt is actually used to prepare the metallocene complex.

Scheme 15



Advantages

This patent provides a novel method of preparing thiophenes that are valuable ligands in metallocenes. Some are said to be difficult to prepare by alternative procedures.

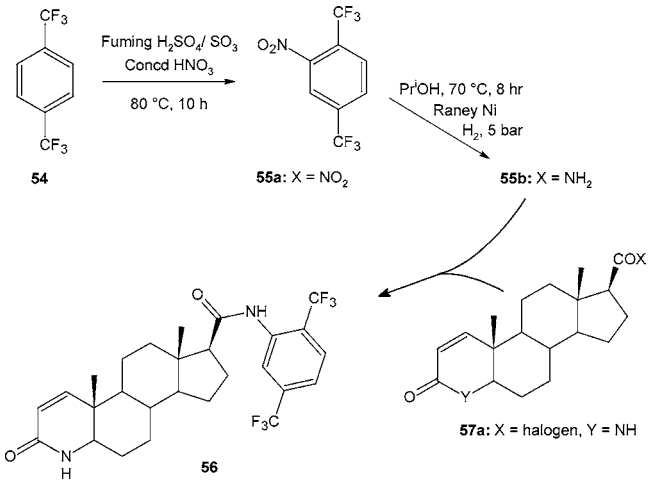
Patent No. U.S. 6,930,214

Assignee: Asahi Glass Company Limited, Tokyo, Japan

Title or Subject: Process for Producing 2,5-Bis(trifluoromethyl)nitrobenzene

The patent title is misleading since the actual subject of the patent is the production of the compound **56**. This compound is said to be a promising therapeutic agent for treating baldness or prostate enlargement. The title compound is also useful in the preparation of other pharmaceuticals and agrochemicals. Two of the alternative processes mentioned for preparing **55a** are said to be commercially unattractive because of the need to use expensive reagents. A third method uses cheaper reagents but involves direct nitration using fuming H_2SO_4 at high temperature and is said to be very exothermic and difficult to control. The process described in this patent involves nitration of the readily available compound **54** in a solvent consisting of 91−100% H_2SO_4 and fuming H_2SO_4 containing up to 20% SO_3 as shown in Scheme 16.

Scheme 16



It should be pointed out that most of the examples do not include nitric acid in the reaction mixture so the introduction of a nitro group is somewhat surprising. How this serious mistake was allowed to happen only confirms what many chemists think about the contents of patents.

As mentioned above, the main subject of the patent is the preparation of **56**, and this is by reaction of **55b** with **57a** (Y = NH). An alternative route to **56** is by using the **57b** (Y = CH_2), and the NH group is introduced separately. There are no experimental details of either of these two routes to **57**; they are summarised in main body and also the in the claims of the patent.

Advantages

The process for producing the nitrobenzene is an improvement on alternative methods using a readily available starting material. The production of **56** may be novel, but this is not mentioned in the patent.

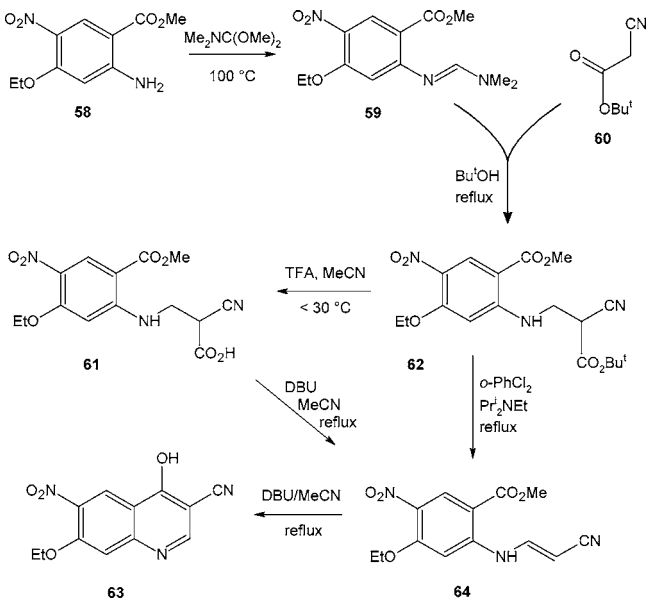
Patent No. U.S. 6,933,388

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

Title or Subject: Process for the Synthesis of 3-Cyano-6-alkoxy-7-nitro-4-quinolones

The quinolone **63** is an intermediate in the preparation of a protein tyrosine kinase inhibitor that is used to treat cancer. The synthesis of quinolones by intramolecular Friedel−Crafts ring closure of anilines is usually effective except when electron-withdrawing groups are present. Thermal cyclisation processes often require temperatures >240 °C, and low yields of products are encountered. Hence, the need for an improved method to produce quinolones from anilines that contain electron-withdrawing groups. Scheme 17 summarises the process for producing **63** from the anthranilate **58**. This is converted to the amidine **59** by refluxing **58** with DMF acetal. The next step is a condensation reaction between **59** and the cyanoester **60** to give **62**. This can be converted to **64** by two possible routes. In the first **62** is hydrolyzed to give **61** using TFA in MeCN at and then decarboxylation is carried out by addition of DBU and refluxing to give **64**. The second method of producing **64** is by refluxing **62** in *o*-$PhCl_2$ containing Pri_2NEt. The final step is cyclisation of **64** to give **63** using a base, and DBU is preferred. The reaction is carried out in refluxing MeCN followed by quenching with aqueous HCl.

Scheme 17



The yields of each of the steps are generally >90%, and the patent includes ^1H NMR data for the intermediates and product shown in the scheme.

Advantages

The process gives much higher yields and a higher purity product than the alternative thermal cyclisation procedure.

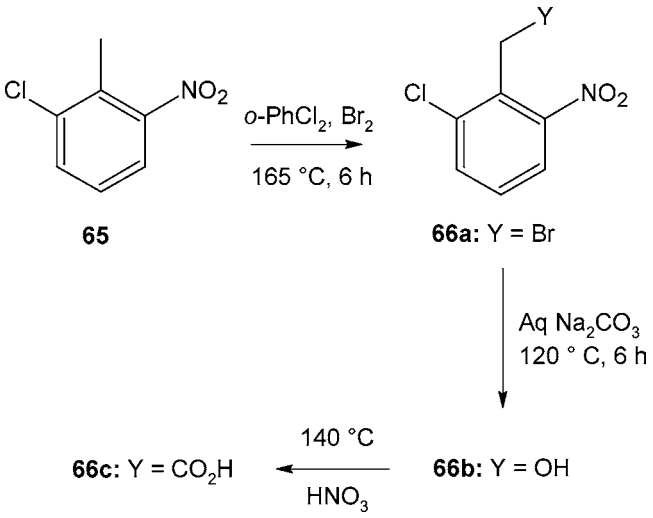
Patent No. U.S. 6,933,406

Assignee: Bayer AG, Leverkusen, Germany

Title or Subject: Method for Producing 2-Halo-6-nitrobenzoic Acids

The title compounds are intermediates in the preparation of haloanthranilic acids that are in turn used to prepare a range of chemical products. The patent describes a route to **66c** by the oxidation of **66b**. Alternative oxidation processes are described, and these are said to suffer from several disadvantages such as the use of low-concentration solutions or needing expensive or toxic reagents. The new process is shown in Scheme 18 and starts with bromination of **65** to give **66a** that is hydrolyzed to give the alcohol **66b**. The reactions are carried out in without isolation of intermediates, and the solvent is not removed. The oxidation of **66b** to the acid **66c** is carried out using 65% HNO_3 at 140 °C. There are two modes of carrying out the reaction. In the first the nitric acid is added to the hot alcohol over 4 h and stirred for a further 2 h before cooling to precipitate the **66c** in 60% yield. In the second mode most of the solvent is distilled off, and this residue is added to the hot nitric acid over 8.5 h. Aqueous nitric acid is removed by vacuum distillation, and the product is obtained in 78% yield after cooling.

Scheme 18



The second mode of oxidation gives higher yields but does take considerably longer.

Advantages

The process gives greatly improved yields compared to alternative methods.

Patent No. U.S. 6,933,408

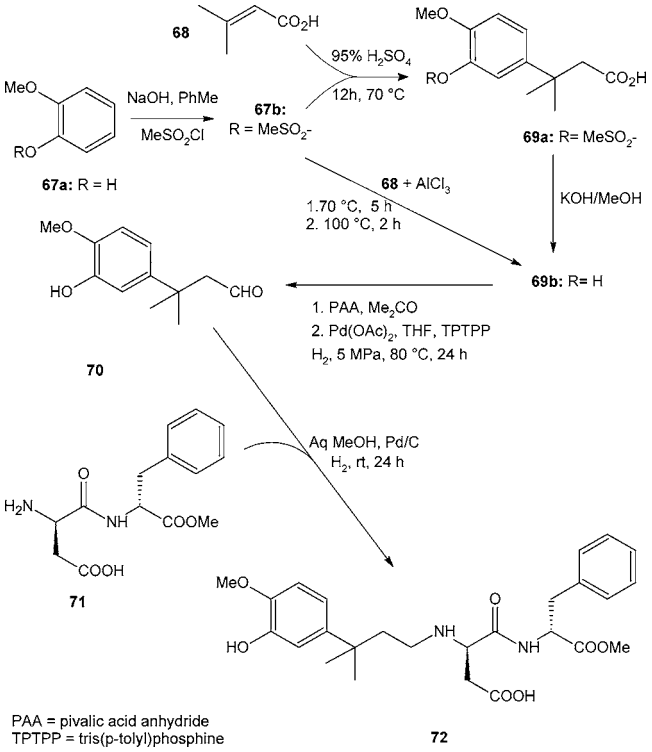
Assignee: Ajinomoto Co. Inc., Tokyo, Japan

Title or Subject: Process for Producing and Intermediate for a Sweetener with High Sweetness

The production of low-calorie, artificial sweeteners is of great interest, and the subject has been previously reviewed (*Org. Process Res. Dev.* **2005**, *9*, 244). The patent mentions that the popular sweetener aspartame **71** is somewhat unstable, and it is reported elsewhere that it can cause cancer hence alternatives are being sought. The actual subject matter

and main claim of the patent is a method for the synthesis of the acid **69b**. This is reduced to the aldehyde **70** that is used in the preparation of **72**, a safer alternative to **71**. Scheme 19 shows the route used to prepare **69b** and **70** from the *o*-methoxyphenol **67a**. The first step is protection of the OH group in **67a** by conversion to the mesyl ester **67b**. Reaction of **67b** with crotonic acid **68** in 95% H_2SO_4 gives the acid **69a**, and this is converted to the phenol by treatment with base. An alternative and preferred method of forming **69b** is a Friedel−Crafts reaction of **67b** with **68** in the presence of $AlCl_3$. The aldehyde **70** is obtained by reduction in the presence of pivalic acid anhydride (PAA) and $Pd(OAc)_2$ plus a phosphine. The sweetener that is obtained is **72** that has a high level of sweetness, and this is produced by condensation of **71** with **70** in the presence of a reducing catalyst.

Scheme 19



The aldehyde **70** and acid **69b** are both novel compounds, and the patent provides ^{1}H NMR for all intermediates and products.

Advantages

The process provides a novel sweetener that is a replacement for aspartame that is known to have stability and potential health problems.

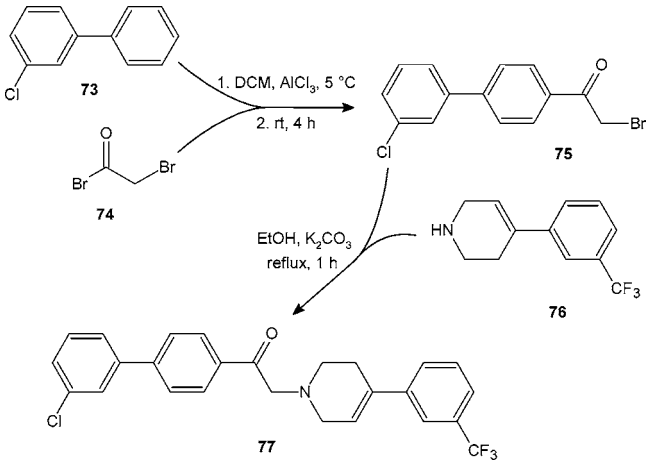
Patent No. U.S. 6,936,621

Assignee: Sanofi-Aventis, Paris, France

Title or Subject: Use of Benzoylalkyl-1,2,3,6-Tetrahydropyridines

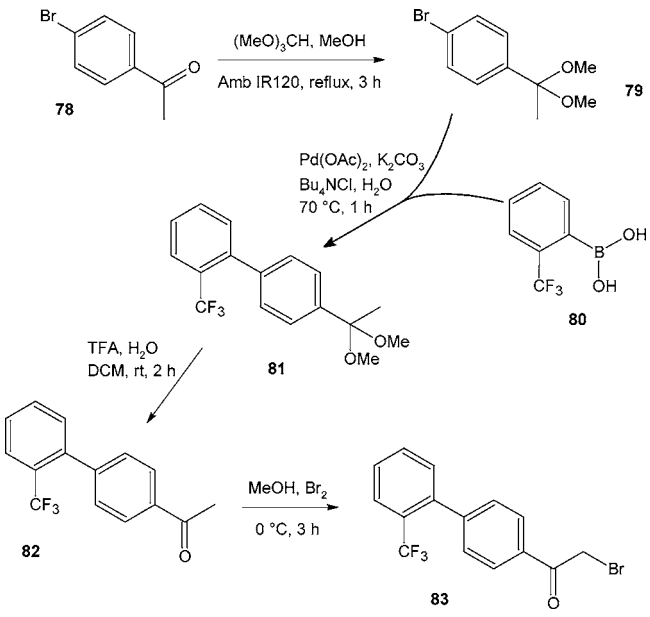
The compounds of interest in this patent are neurotrophic and neuroprotective agents that may have the capability of restoring the function of damaged cells and treating cerebral and neuronal disorders. An example of the range of compounds prepared by the process in the patent is **77**, and the synthetic route is shown in Scheme 20. The first step is a Friedel−Crafts reaction between the bromide **74** and **73** to give **75**. This is then reacted with **76** in a condensation reaction in the presence of K_2CO_3 to form **77**. The product is actually isolated as the HCl salt by acidification of the reaction mixture with HCl/EtOH.

Scheme 20



The patent includes examples covering a number of analogous compounds in which **73** is replaced by a number of aryl compounds including the 2- or 4-chloroisomers, Ph_2O, or alkylbenzenes. These reagents are used in an identical manner to that used for **73**. The patent also describes the preparation of the bromoketone **83** that is also used to prepare the corresponding final product, and the synthesis of this is shown in Scheme 21. There is an interesting use of an IER in the first step to effect the condensation reaction and give **79**. The formation of the biphenyl molecule **81** is carried out using the boronic acid **80**.

Scheme 21



Advantages

The process is used to prepare a variety of novel compounds that have potential in treating various neurological disorders.

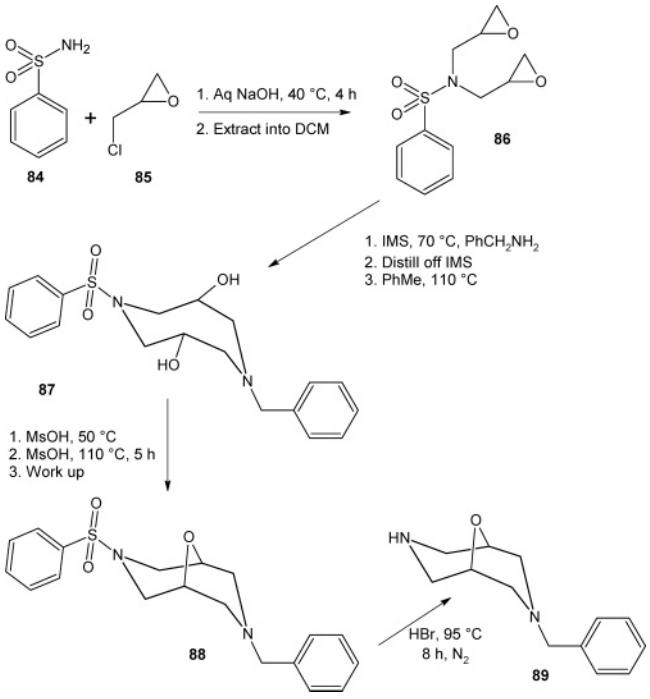
Patent No. U.S. 6,936,712

Assignee: AstraZeneca AB, Sodertalje, Sweden

Title or Subject: Process for the Production of Oxabispidines

The title compounds such as **88** are used as anticoagulants and antiarrhythmic agents for treating irregular heart rhythms and other coronary problems. There are apparently few reports of such compounds, and hence the process described in this patent has been developed to provide a commercially viable synthetic route. The route to prepare **88** is shown in Scheme 22 and starts with the reaction of the sulphonamide **84** with **85** in aqueous NaOH. The product **86** is extracted into DCM and the solution used in the next step. In this step IMS is added, the DCM is distilled off, and benzylamine is added in two stages with solvent removal between each addition. Before the final reaction stage the solvent is changed again, and the solution used without isolation of **87**. The bridgehead ether group is formed to give **88** by treating **87** with MsOH in stages. The solvent is gradually removed during the reaction, and it is stated that the temperature must be kept as low as possible during this procedure with vacuum being preferred. The final workup involves more solvent exchange with DCM and IMS being used. The crude product is finally obtained and recrystallised from MeCN.

Scheme 22



There a number of experiments describing the preparation of other examples of these compounds, and ^{1}H NMR data are provided for them all. The patent also describes the method for the removal of the protecting sulphonyl group so that **88** is converted to **89**.

Advantages

The process provides a novel route to these compounds that is said to be commercially viable. However, given the large number of solvent changes involved, this remains to be seen.

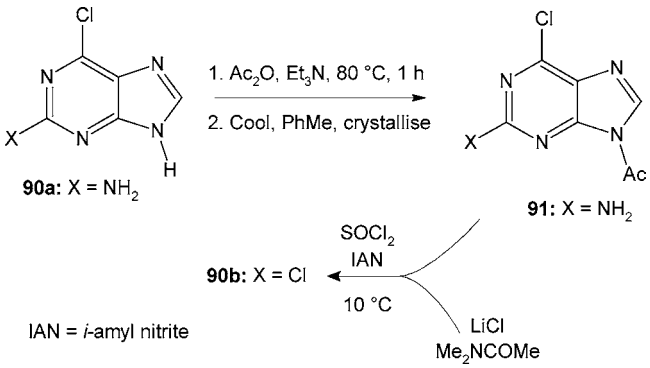
Patent No. U.S. 6,936,713

Assignee: Sumitomo Chemical Company, Osaka, Japan

Title or Subject: Process for Producing 2,6-Dihalogenopurines

Purine derivatives are used as intermediates for preparing a variety of pharmaceutical agents, and some of these have recently been reviewed (*Org. Process Res. Dev.* **2005**, *9*, 244). The patent describes the preparation of **90b**, shown in Scheme 23, and this involves the replacement of the 2-amino group in **90a**. Alternative routes to **90b** can involve chlorination reactions using pyrophosphoryl chloride, and this necessitates special corrosion resistant equipment. The method in this process uses a diazotisation reagent (IAN) to convert the 2-amino group, but before this can be used, the 9 position in **90a** is protected by forming the acetyl compound **91**. After diazotisation the chlorination is carried out using $SOCl_2$. The acetylation reaction produces **91** in 100% yield, and the recovered yield of **90b** is >70% in some cases.

Scheme 23



Advantages

The process starts from **90a** that is a commercially available material and uses milder processing conditions so that expensive equipment is not required.

Patent No. U.S. 6,936,718

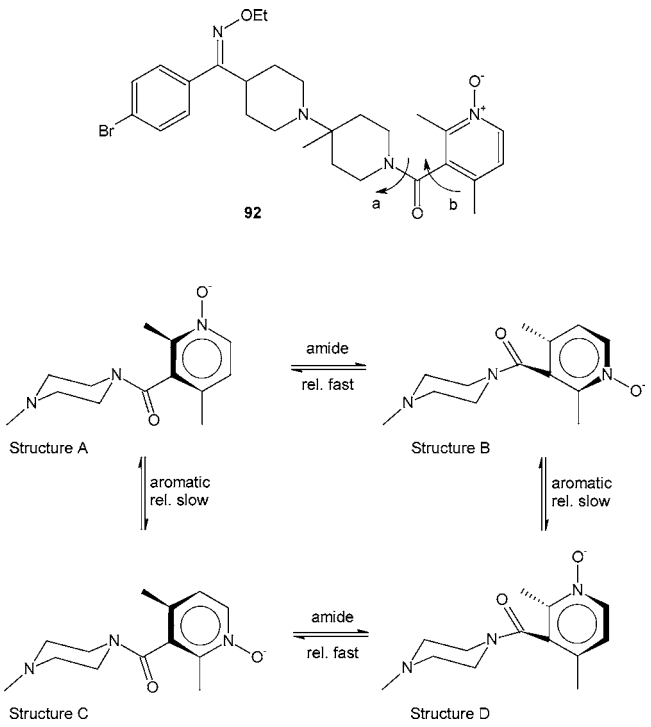
Assignee: Schering Corporation, Kenilworth, New Jersey, U.S.A.

Title or Subject: Preparation of Rotamer Mixtures of Pharmaceutical Salts

The compound of interest in this patent **92** exists as two pairs of diastereoisomers but does not have a chiral centre. The isomers exist because of restricted rotation about two

single bonds shown as *a* and *b*. The four isomers and their relationship are shown in Scheme 24. A and B are diastereomers as are C and D. **92** is of use in the treatment of AIDS and related HIV infections and may also have application in a range of inflammatory diseases. It is stated that the geometry of the oxime is controlled during its synthesis, but there are no details about the route used to prepare **92**.

Scheme 24



The patent contains a substantial number of experiments that describe the formation of a range of salts of **92** in different solvents. The patent claims that it is possible to adjust the ratio of the diastereoisomeric pairs from 99:1 to 7:93 by changing the solvent when producing tosyl salts. It is also possible to obtain only one enantiomer of a salt instead of the pair. For example, the dibenzoyl tartrate salt of A can be made as the single enantiomer in 95% yield if the reaction is performed in a ketone solvent.

Advantages

The process offers the opportunity to prepare a specific rotamer or a pair of rotamer salts by careful choice of salt and solvent.

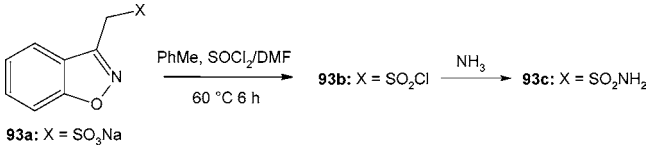
Patent No. U.S. 6,936,720

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

Title or Subject: Method for Preparing Benzisoxazole Methanesulphonyl Chloride and Its Amidation to Form Zonisamide

Zonisamide **93c** is used as an antiepileptic agent that has anticonvulsant and antineurotoxic effects. An earlier patent on this compound from the same company which was reviewed recently, focussed on the sulphonation step in the synthesis (*Org. Process Res. Dev.* **2005**, *9*, 244). The current patent looks at replacing $POCl_3$ in a chlorination step since this compound poses a number of problems including waste disposal and handling. The synthesis of **93c** is by using $SOCl_2$ in the presence of DMF as shown in Scheme 25. The use of SO_2 has its own problems in that it produces gaseous byproducts that need to be controlled. The patent describes three modes of carrying out the reaction. The first method does not use extra solvent, the second uses excess $SOCl_2$ that acts as solvent, and the third uses an inert solvent; the patent uses PhMe.

Scheme 25



The chloro compound **93b** is then used to prepare **93c** by an amidation reaction using NH_3. Here again there are three methods of carrying out the reaction, and these are:

1. biphasic reaction with aqueous NH_3 in PhMe at room temperature for 20 h
2. use of an NH_3 precursor such as $(NH_4)_2CO_3$ in refluxing MEK for 1 h
3. use of anhydrous, gaseous NH_3 in PhMe at 15 °C

The final product is then purified by crystallisation from aqueous EtOH and obtained in 90% yield with <0.02% of the ammonium salt **93d** ($X = NH_4$).

Advantages

The process gives an improved route to **93c** without the problems of handling $POCl_3$, but whether this outweighs the difficulties of handling $SOCl_2$ is another matter.

Keith Turner

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