Organic Process Research & Development **2009,** *13,* 371–380

Highlights from the Patents

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

Summary

The current review contains 19 patents from an original list of 262 that fitted the search criteria. Macrolide mycins are antibiotics with several uses, and three patents describe new polymorphs or processes for their preparation. The cholesterol-lowering drug fluvastatin is attracting great interest, and another polymorph has been described. The use of ionic liquids is increasing, and their use in breaking a large number of azeotropes has been covered. A patent describes the use of an enzyme to prepare a chiral intermediate that is used in the synthesis of the antidepressant duloxetine. Solid acid catalysts are widely used in preparing esters, but solid base catalysts are not so common. A patent discloses the use of such materials for the synthesis of vitamin E acetate from tocopherol. Materials to control pests and parasites are disclosed in a number of patents. Two describe artemisinin derivatives for malaria control, and another describes over 300 novel phenacylamine compounds that kill mammalian pests without harming the animal. Elimination of toxic reagents is a desirable goal in any process. A patent describes the preparation of the antihypertension drug valsartan that avoids the use of Bu_3Sn. This is achieved by developing an alternative route involving the preparation of several novel intermediates. In another case of avoiding toxic reagents a new synthesis is described for the drug temozolomide that is used to treat aggressive brain tumours. One known route uses MeNCO, and this is avoided in a new process in which several steps have been carried out on kilo scale. A process for the preparation of *N*-formylhydroxylamine antibacterial agents is disclosed that is said to be safer than alternatives in avoiding the use of H_2O_2. Another patent cites safety problems as a reason to develop a better method of making α-aminoindans that are used to produce drugs for treating bipolar disorders. The use of cheap and readily available reagents is a desirable objective with NH_3 and HCHO fulfilling both criteria. A thiazole used as an intermediate for agrochemicals is prepared in high yield and with fewer impurities in a synthesis using both of these commodity chemicals via a novel hexahydrotriazine. The elimination or removal of impurities is often the make-or-break aspect of a synthesis. The drug darifenacin is used to treat urinary incontinence, and a Mitsunobu reaction using Ph_3P is involved in one synthesis. The byproduct Ph_3PO can be difficult to remove, and a new route is described that proceeds via an alternative pathway that produces a novel intermediate enamine. High doses of the analgesic paracetamol are known to cause liver damage and fatalities, and so safer derivatives are sought. A process for the preparation of a nitrate derivative of paracetamol is described that uses commercially available reagents. The high incidence of allergies has resulted in the search for improved antihistamines or better processes. A novel route for the preparation of loratadine is disclosed that does not require purification of some of the intermediates obtained in the multistep route. Supercritical fluids (SCF) are becoming more widely used, and a process for the purification of tetrahydrocannabinol is described using the technique of SCF chromatography. The inclusion of a patent in this review does not imply any commercial significance. Some patents do however describe kilo scale preparations indicative perhaps of an advanced stage of development. The advantages cited are those claimed in the patent unless this reviewer has personal knowledge of the subject.

Patent No. U.S. 7,432,380

Assignee: Ciba Specialty Chemicals Corp., Tarrytown, New York, U.S.A

Title or Subject: Crystalline Form of Fluvastatin Sodium

This patent describes yet another polymorph of fluvastatin sodium that is used to treat high cholesterol levels and is available as Lescol. Recent patents on this compound from another company have been reviewed (*Org. Process Res. Dev.* **2008**, *12*, 1355) and claim 105 polymorphs of this drug. Whether this latest polymorph, designated Form G, is the same as any of the others will probably result in extensive debate between lawyers. The form described in this patent is obtained by suspending a crystalline or amorphous form in water for 18 h at ambient temperature followed by filtering and drying the solid. XRD data are provided.

Advantages

The new polymorph is suitable for preparing pharmaceutical formulations.

Patent No. U.S. 7,435,318

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Ionic Liquids as Selective Additives for Separation of Close-Boiling or Azeotropic Mixtures

The separation of mixtures of close-boiling compounds or azeotropes is a frequently encountered problem in organic chemical processes. Extractive and azeotropic distillations are techniques that are used and involve the addition of an extra component or entrainer to form new azetropes or break existing ones. The addition of these entrainers increases the costs and complexity of the desired separation. Hence, the objective is to

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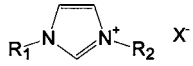
add the minimum amount of the cheapest entrainer. This patent claims that a surprising discovery is that mixtures of some ionic liquids can be used as entrainers. A great advantage of ionic liquids is that they have very low vapour pressure, are nonflammable and noncorrosive, and have low viscosity. These are all usually very desirable properties for entrainers. The patent naturally claims the use of a huge number of possible ionic liquids for separating a wide range of mixtures with the main types being imidazolium salts as shown below:

Ionic Liquids



1a: R_1 = n-Octyl, R_2 = Me, X = BF_4
1b: R_1 = Et, R_2 = Me, X = BF_4
1c: R_1 = R_2 = Me, X = BF_4
1d: R_1 = Et, R_2 = Me, X = PF_6
1e: R_1 = Et, R_2 = Me, X = Ms
1f: R_1 = R_2 = Me, X = Ms
1g: R_1 = Et, R_2 = Me, X = $N(CF_3SO_2)$
1h: R_1 = Et, R_2 = Me, X = Tetrafluorotoluene sulphonate

The examples in the patent cover the separation of the following mixtures that are commercially important using the ionic liquid indicated:

(1) butene/butane - **1a**
(2) cyclohexanol/cyclohexanone - **1b** or **1d**
(3) acetone/methanol - **1a**, **1b**, **1d**, **1f** or **1g**
(4) ethanol/water - **1b**
(5) THF/water - **1b** or **1h**
6) Pr^{n}OH/water - **1b**
7) Pr^{i}OH/water - **1b**

The molecules of the ionic liquid interact with one component in the mixture more than the other, and this affects the relative vapour pressure of the components in the original mixture. This is known as extractive distillation, and the entrainer breaks the original azeotrope, thereby allowing the distillation of the mixture. Since the ionic liquid is nonvolatile, it can then easily be separated from the other component by evaporation. The technique is very effective, especially in continuous distillation but less easy to operate with a batch distillation.

Advantages

The process enables the separation of azeotropes or close-boiling mixtures on a continuous basis.

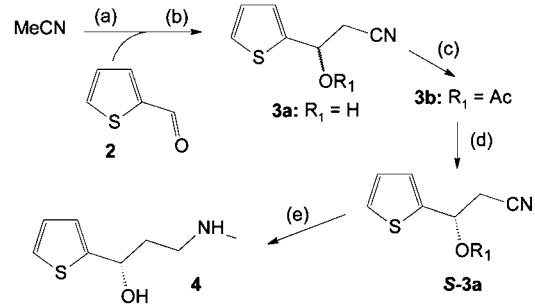
Patent No. U.S. 7,435,563

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Method for the Production of (S)-3-Methylamino-1-(thieny-2-yl)-propan-1-ol)

The title compound **4** is an important intermediate in the preparation of the antidepressant duloxetine. It is claimed that alternative methods for preparing duloxetine are laborious and require the use of chiral reagents. This patent describes a process for preparing **4** from a racemic intermediate **3a**. Reaction 1 summarises the reaction conditions in the process used to prepare **4** that begins with the base-catalysed reaction of **2** with MeCN. This reaction can also be carried out using KOBu^t at a temperature of −50 °C. The reaction gives a racemic mixture of the alcohol **3a** in 97% purity at 100% yield. The racemic mixture of alcohols is then acylated using vinyl hexanoate or propionate or succinic anhydride and the racemic mixture **3b** is then hydrolysed in the presence of a lipase enzyme. *Pseudomonas* sp. DSM 8246 is used in the example, but many others are covered in the claims. Hydrolysis of the *S*-enantiomer of **3b** gives ***S*-3a**, and this is separated from the acylated *R*-isomer of **3b** by flash chromatography (FC). ***S*-3a** is obtained in a yield of 48% with an ee of >99%. The ***R*-3a** is also obtained pure and can be recycled to the acylation step. The acylation and hydrolysis are carried out simultaneously in a one-pot process. In the last stage of the process **4** is produced by catalytic hydrogenation in the presence of $MeNH_2$ and recovered by recrystallization in 79% yield and >99% ee. Raney Ni catalyst can also be used for this reaction in place of Pd/C at pressure of 50 bar.

Reaction 1



(a) (i) NaOBu^t, THF, 30 min, <35 °C; (ii) rt, 30 min; (b) rt, 3.5 h;
(c) Acylation, MTBE, rt; (d) (i) Lipase, rt;
(e) Aq $MeNH_2$, MeOH, Pd/C, H_2, 60 °C, 100 bar, 24 h;

Advantages

The process allows the use of an enzyme to prepare the desired enantiomer, and although it gives the product in high optical purity, the yield is <50% and the unwanted enantiomers are not racemised.

Patent No. U.S. 7,435,836

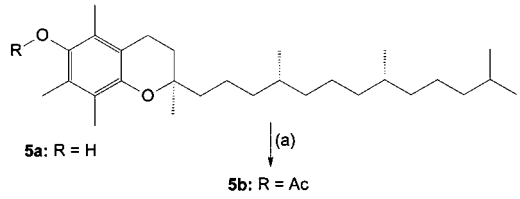
Assignee: DSM IP Assets B.V., TE Heerlen, Netherlands

Title or Subject: Process for the Manufacture of Tocopheryl Acylates

This patent describes a novel process for preparing the acetate **5b**, the usual form of vitamin E manufactured on a large scale. There are known processes for the esterification of tocopherol **5a** using Ac_2O or HOAc in the presence of solid acid catalysts or soluble basic catalysts. The patent states that there are no references to the use of solid basic catalysts in the acylation of **5a** to give **5b**, and it is this topic that is covered by this patent. The process is shown in Reaction 2 and is carried out by heating **5a** with an acylating agent such as Ac_2O or AcCl in the presence of a supported basic catalyst at about 100 °C. The catalysts were commercial materials containing Cs, K, Na,

or Mg salts supported on Al_2O_3 or SiO_2 although an example is given for the preparation of a Ca/Al_2O_3 catalyst. The yield of **5b** for all catalysts was between 92 and 97% after purification by distillation, and examples are given for the use mixtures of tocopherol isomers as well as individual α- and γ-stereoisomers. The use of an insoluble catalyst helps in product recovery, and the fact that a solvent is not required in the process simplifies the overall process.

Reaction 2



(a) (i) Ac_2O, catalyst, 100 °C, 4 - 21 h; (ii) Cool, Na_2CO_3, filter; (iii) Wash in heptane, evaporate, vacuum distillation

Advantages

The process gives high yields of the acetate, and the purification is straightforward.

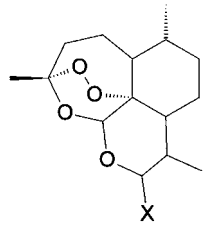
Patent No. U.S. 7,439,238 and 7,452,915

Assignee: The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong

Title or Subject: Antiparasitic Artemisinin Derivatives (Endoperoxides)

Artemisinin derivatives are used to treat parasitic diseases such as malaria. The various derivatives work in different ways with some having poor bioavailability so the objective of this patent is to provide derivatives that have good bioavailability. The two patents are very similar in their content with the claims covering the use of artemisinins for treating diseases. Each patent specifies a different parasite. The compounds covered are C-10 derivatives as exemplified by **6** where the main substituents appear to be X = F or an amino group.

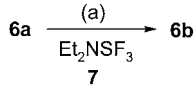
Artemisinins



6a: X = OH; **6b:** X = F;
6c: X = Ph; **6d:** X = NR_2

The preparation of the range of compounds starts with dihydroartemisinin **6a**, and Reaction 3 shows the method used to prepare **6b**. This uses **7** as fluorinating agent and gives a 50% yield of **6b** after purification by flash chromatography.

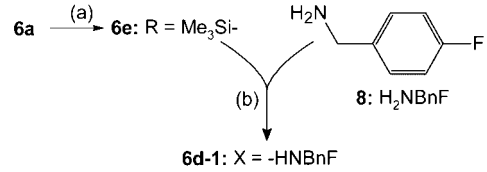
Reaction 3



(a) (i) DCM, 0 °C, (ii) rt, 24 h.

The patents contain over 50 examples of derivatives with ^1H NMR and MS data plus elemental analysis for all of them. The preparation of **6c** (X = Ph) proceeds via initial formation of the Me_3Si derivative in a 78% yield and this is then converted to **6c** using PhMgCl. The product is isolated in 45% yield. An example of the preparation of one of the amino derivatives **6d-1** is shown in Reaction 4. The first stage is to prepare the TMS derivative **6e** from **6a** and Me_3SiCl in 78% isolated yield and then treat with Me_3SiBr. This is followed by the addition of **8** in THF giving **6d-1** in 53% isolated yield after purification by flash chromatography.

Reaction 4



(a) (i) Et_3N/Me_3SiCl, DCM, 0 °C; (ii) rt, 1 h;
(b) (i) Me_3SiBr, DCM, 0 °C, 30 min; (ii) **8**, THF, 0 °C; (ii) rt, 16 h

The patents also contain details of activity testing against parasites of the compounds.

Advantages

The process provides a route to the preparation of many compounds with antiparasitic activity.

Patent No. U.S. 7,439,252

Assignee: Teva GZMR, Debrecen, Hungary

Title or Subject: Novel Crystalline Forms of Ascomycin and their Preparation

This is the first of three patents on macrolide mycins that are antibiotics with a variety of uses including that of immunosuppressants in organ transplant surgery. This first patent covers the compound ascomycin, and it describes three crystalline forms designated A, B, and C. In the examples in the patent it is not clear about the origin of the starting materials used. For example it stated that Form A is obtained by dissolving crystalline Form A and then obtaining crystals by using an antisolvent. The procedure is described as follows

1. Dissolve Form A in EtOAc, evaporate to dryness, and repeat twice

2. Dissolve oily material in one volume of EtOAc and add six volumes of cyclohexane

3. Add water over 3 h, or water and DMF over 1.5 h at rt to obtain crystals; filter, wash in cyclohexane, and dry at 70 °C under vacuum.

Form B is obtained by dissolving crude ascomycin in EtOAc at rt, evaporating to reduce the volume and leaving at 0 − 8 °C for 24 h, filtering, washing, and drying.

Form C is obtained in a manner similar to that for Form A using either DMF or DMSO as the antisolvent. Form C is also obtained when Form A is kept at 150 °C for 1 h.

The patent contains XRD, DSC, TGA, and FT-IR data for the three new forms.

Advantages

The new forms of the compound are used to prepare pharmaceutical formulations with desirable properties.

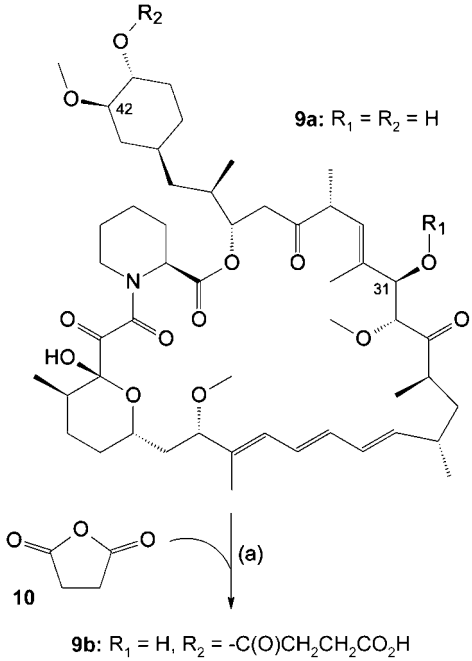
Patent No. U.S. 7,445,916

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

Title or Subject: Process for Preparing Rapamycin 42-Esters and FK-506 32-Esters with Dicarboxylic Acid

The second patent on these antibiotics describes a series of 42-substituted esters of rapamycin **9b** and 32-substituted esters of the related compound designated in the patent as FK-506 but also known as fujimycin or tacrolimus. The desired products are half-esters of dicarboxylic acids, and the difficulty in preparing them can be maintaining regioselctivity and avoiding the production of the 31,42-diesters in which the R_1 and R_2 groups are both esterified. Reaction 5 shows the method used to prepare **9b** from **9a** and the anhydride **10**. The reaction is carried out in the presence of an enzyme such as *Candida antarctica*, and the product is obtained in 91% yield after purification by column chromatography. Examples are also given for the preparation of the analogous half-esters of adipic and suberic acids that are prepared using the divinyl esters. There are no examples given for the preparation of the 32-esters of FK-506 although it is stated that similar methods are employed.

Reaction 5



Advantages

The process gives high regioselectivity and good yields of the desired mono half-esters.

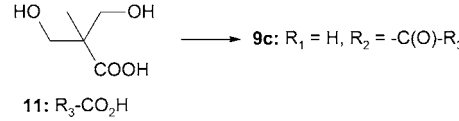
Patent No. U.S. 7,446,111

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

Title or Subject: Amorphous Rapamycin 42-Ester with 3-Hydroxy-2-(hydroxymethyl)-2-methylpropionic Acid and Its Pharmaceutical Compositions

The second patent on rapamycin esters describes the preparation of an amorphous form of the 42-ester of the acid **9c**. Although the patent does not mention how the ester is made, based on the previous patent this is probably by the reaction of the acid **11** with **9a** as shown in Reaction 6. The ester **9c** is designated as CCI-779 and is used in the treatment of renal cancer as the drug Torisel or Temsirolimus. The patent states that the crystalline form of the drug has poor solubility, and hence the objective is to produce an amorphous form with improved solubility. There are four methods used that begin with the crystalline form. In the first method a solution of crystalline **9c** is prepared using anhydrous EtOH containing the antioxidants, butylated hydroxytoluene (BHT) and butylated hydroxyanisole (BHA). The solvent is removed under vacuum and evaporated at 25 − 30 °C, and the amorphous solid is then dried. The second method involves grinding the crystalline form in a ball mill, while the third uses a jet-mill to give **9c** as a micronized amorphous solid from the crystalline form. The last method is a precipitation of **9c** from a solution in EtOH using water at temperatures down to around 8 °C. The solid is then dried under vacuum for up to seven days. The patent shows that the solubility of the amorphous form produced by micronization is 3 times that of the crystalline form at 25 °C.

Reaction 6



Advantages

The process provides a more soluble form of the drug that improves its suitability in formulations.

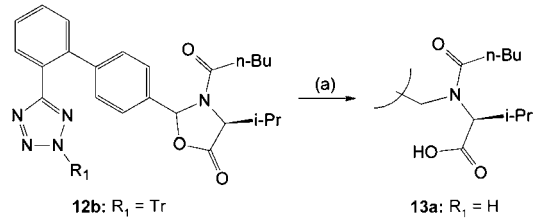
Patent No. U.S. 7,439,261

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

Title or Subject: Process for the Preparation of Valsartan and Intermediates

Valsartan **13a** (R_1 = H) is used to treat hypertension especially in patients with diabetes. One of the known processes for preparing **13a** is described and said to be very complex and unsuitable for industrial-scale production because it uses toxic reagents such as Bu_3Sn-derivatives and azides. The novel process consists of opening the oxazolidinone ring in the novel compound **12b** (R_1 = Tr) by catalytic reduction using Pd/C and HCO_2NH_4 as hydrogen transfer reagent (Reaction 7). The product is obtained in 70% yield and at a purity >99.5% with azide levels of <20 ppm. The ring-opening can also be carried out under a pressure of H_2, but the yield is lower at 53%.

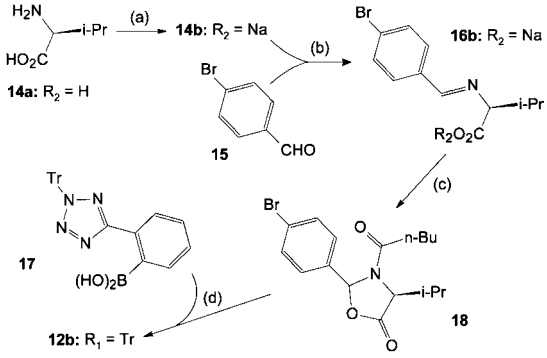
Reaction 7



(a) HCO_2NH_4, Pd/C, Me_2NCOMe, 90 °C

The method used to prepare the novel intermediate **12b** is described in the patent and outlined in Reaction 8. The route begins with the formation of reaction of the Na salt **14b** of L-valine **14a**. Reaction of **14b** with the bromo-aldehyde **15** forms the Na imine salt **16b** that is reacted with valeroyl chloride to give **18** in a yield of 34% after an extensive workup procedure. Coupling of the boronic acid derivative **17** with **18** produces **12b** in a yield of 80% using a Pd catalyst used prepared from $Pd(OAc)_2$ and PPh_3. The catalyst is not isolated before use nor is it characterized.

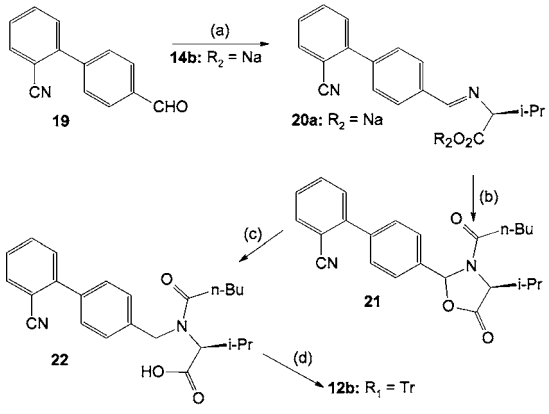
Reaction 8



(a) NaOH, MeOH, 25 °C, 10 min; (b) (i) rt, 1 h; (c) Bu^nCOCl, DCM, reflux, 2 h; (d) (i) $(EtO)_2CH_2$, H_2O, K_2CO_3, 25 °C, 30 min; (ii) Pd catalyst, 79 °C, 2 - 6 h.

The patent also describes the preparation of further novel compounds by the route outlined in Reaction 9. In this route **20a** is isolated in 90% yield and **21** in 50% yield. No yield is given for the formation of **22** and the conversion of **22** to **12b** is mentioned in the patent claims, but there are no experimental details other than a mention of hydrogenolysis. There are ^1H NMR data for all intermediates.

Reaction 9



(a) (i) PriOH, rt, 1 h; (ii) Evaporate at 60 °C; (iii) 50 °C, vacuum, 3 h; (b) Add Et_3N then step (c) in Reaction 8; (d) No details given

Advantages

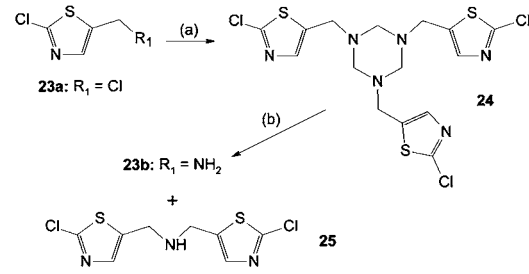
The process has potential for industrial use but probably still uses toxic reagents such as azides even though it does not use tin compounds.

Patent No. U.S. 7,439,357

Assignee: Sumitomo Chemical Company Limited, Tokyo, Japan
Title or Subject: Process for Preparing a Thiazole by Aminomethylation

The compound of specific interest in this patent is **23b**, an intermediate for preparing agrochemicals and pharmaceuticals. One method for preparing **23b** has the advantage of using low-priced NH_3, but unfortunately produces a considerable amount of the byproduct **25**. The objective of this patent is to develop a process for producing **23b** that also uses NH_3 but does not form **25**. The process that has been disclosed is shown in Reaction 10 and initially produces the novel hexahydrotriazine compound **24** by the reaction of **23a** with NH_3 and HCHO added as paraformaldehyde. In the second step acid hydrolysis of **24** produces **23b** at yields of up to 94.5% with levels of **25** between 1.2 and 8.9%. The patent does describe the isolation of **24**, and brief details of its ^1H and ^{13}C NMR spectra are given. When trying to convert **23a** to **23b** directly without the addition of HCHO, the yield of **25** was 24.5%, and that of **23b** was only 41.4%. The patent also describes the preparation of an aqueous solution of the HCl salt of **23b**.

Reaction 10



(a) (i) HCHO, NH_3/MeOH, 70 °C, 3 h; (ii) Concentrate in vacuum; (b) (i) Concd HCl, 50 °C, 30 min; (ii) Cool rt, H_2O

Advantages

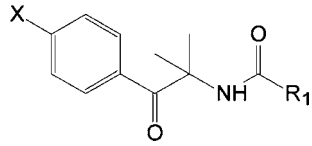
The process uses cheap raw materials and gives improved yields of the desired product with substantially lower levels of impurity.

Patent No. U.S. 7,439,366

Assignee: Ishihara Sangyo Kaisha Ltd., Osaka-shi, Japan
Title or Subject: Process for the Production of Phenacylamine Derivatives and Pesticides Containing Them

This patent describes a number of novel phenacylamines such as **29** that are highly effective against a variety of animal pests and which have little effect on the mammals themselves or fish. There are over 300 novel phenacylamine compounds, listed in the patent, that it is claimed can be made by the process covered by the patent and they of the types shown below:

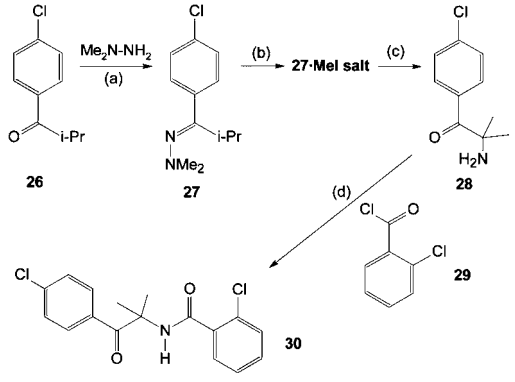
Phenacylamines



X = H, alkyl, halo, CN, Ms, NO_2, Tf
Range 1: R_1 = substituted Ph
Range 2: R_1 = substituted pyridyl
Range 3: R_1 = substituted pyrazole
Range 4: R_1 = alkyl or cycloalkyl

The patent examples cover compounds of Range 1 only, and Reaction 11 outlines the method used to prepare **30**. This starts with the formation of the hydrazone **27** from **26** and Me_2NH_2 using molecular sieves as dehydrating agent. The hydrazone **27** is an oil and is converted to the MeI salt that can be converted to the α-amino compound **28** by treatment with NaOMe. **28** is also obtained as an oil but can be isolated as the HCl salt although it is only the free base that is used in the next step in which it is condensed with **29** in dichloroethane (DCE) in the presence of Et_3N to produce **30**. The compounds **27**, **27·MeI**, **28**, and **30** are all claimed to be novel, and the patent contains ^1H NMR data for them. The patent states that **28** can be produced from **26** by reaction with NH_3 in the presence of an oxidising agent such as $K_3Fe(CN)_6$ at 50−100 °C for up to 20 h although precise details are not provided. The formation of **28** is suggested to proceed via a cyclic imine that on acid hydrolysis gives **28**. The patent describes the preparation of various formulations and their testing for activity against various animal pests.

Reaction 11



(a) 3A mol sieve, 100 °C, 110 h; (b) MeI, EtOH, rt, 15 h; (c) MeONa/MeOH, reflux, 3 h; (d) Et_3N, DCE, rt, 15 h.

Advantages

The patent provides a wide range of novel compounds that have activity for the treatment of animal pests.

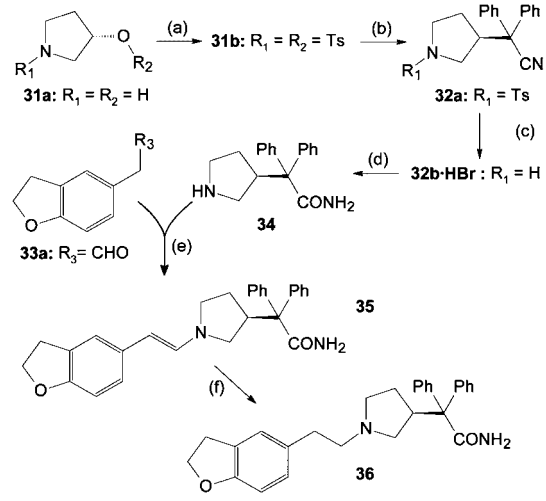
Patent No. U.S. 7,442,806

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

Title or Subject: Process for Preparing Darifenacin Hydrobromide

Darifenacin **36** is used as the HBr salt to treat urinary incontinence and is available as Enablex. Methods for preparing **36** use Ph_3P in a Mitsunobu reaction, and oxidation of the phosphine during the process results in the contamination of the product with Ph_3PO that is difficult to remove. A number of hazardous reagents are also used, and it is the objective of the patent to devise a safe and economical industrial process for the production of **36**. Despite the title of the patent and its stated objectives, the single claim of the patent does not mention the process of making **36** but instead covers the novel compound (*S*)-darifenamine **35**. The patent describes a substantial amount of work with alternative routes to prepare **36** and also details of methods used to prepare several intermediates such as **33a** and derivatives. Hence, only very brief details of these are included here. Reaction 12 shows the method used to prepare **35** that begins with the conversion of **31a** to the ditosyl compound **31b** in 94% yield. The ditosylate then reacts with Ph_2CHCN in the presence of Bu^tONa to give **32a**. This is recovered in 86.5% yield and 99.3% purity by HPLC and then converted to the salt **32b·HBr** that is recovered in 87.4% yield. The reaction uses PhOH as a bromide acceptor although β-naphthol is also used. It may be significant that in the solvent exchange procedure for the production of **32b·HBr** the temperature steps are described in great detail. The **32b·HBr** salt is then converted to the free base of the amide **34** that is reacted with the aldehyde **33a** to form the novel enamine **35**. The examples do not indicate that this is isolated, and it is reduced using $NaBH_4$ to give **36** that can be converted to its HBr salt. The overall yield of **36** from **34** appears to be around 22%.

Reaction 12

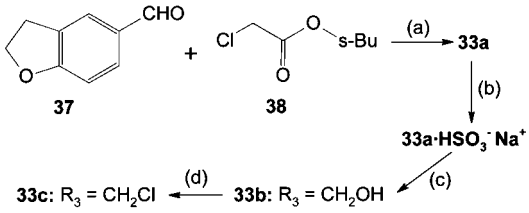


(a) (i) Bu_4NBr, TsCl, PhMe, <40 °C; (ii) 30% NaOH, 60 °C, 6 h; (b) Ph_2CHCN, DMF, Bu^tONa, 20 °C; (ii) 75 °C, 4 h; (c) 48% HBr, PhOH, reflux, 1 h; (d) (i) Aq NaOH, DCM, 30 °C; (ii) 90% H_2SO_4, 102 °C, 15 h; (e) rt, 15 h; (f) $NaBH_4$, EtOH, rt, 3 h; (ii) Bu^nOH, 48% HBr.

The patent also describes methods for the preparation of **33a**, its bisulphite complex, and also analogous derivatives such as the alcohol **33b** (R_3 = CH_2OH), chloride **33c** (R_3 = CH_2Cl, and ester **33d** (R_3 = CO_2Me). The methods used to prepare **33a**, **b**, and **c** are shown in Reaction 13. **33a** is produced by treating **37** with **38** in the presence of strong base such as $KOBu^s$. After workup

the product is obtained as an oil with purity by GC of 91%. The bisulphite complex is then prepared and isolated as a solid wetted with PhMe. The wet solid is then reduced with $NaBH_4$ to form the alcohol **33b** that is obtained initially as an oil that does solidify. When **33b** is treated with $SOCl_2$ and after extensive workup **33c** is isolated in 92% yield with a purity of 99.2% (HPLC).

Reaction 13



(a) (i) Bu^sOH, $KOBu^s$, 45 °C, 2 h; (ii) Aq KOH, 45 °C, 1 h; (iii) PhMe, H_2O, < 5 °C; (iv) 75% H_3PO_4, pH 5.8, $-CO_2$; (b) PhMe, aq $Na_2S_2O_5$, rt, 3 h; (c) (i) Aq NaOH, pH 10.2, rt; (ii) Na_2CO_3, PhMe, <10 °C; (iii) $NaBH_4$, H_2O, pH 10, <10 °C, 1 h; (d) (i) $SOCl_2$, PhMe, <25 °C; (ii) 60 °C, 14 h.

These compounds can be used to prepare **36** by alternative procedures to that shown in Reaction 12 and interested readers are recommended to read the patent for further details.

Advantages

The process provides a new route to the compound from a commercially available material, and it also allows the production of a novel intermediate.

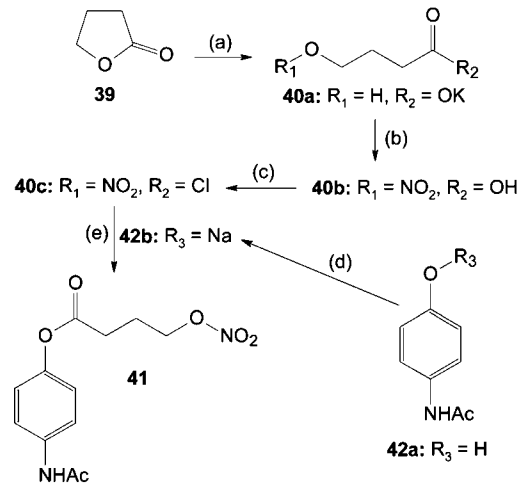
Patent No. U.S. 7,442,826

Assignee: Nicox S.A., Sophia Antipolis, France

Title or Subject: Process for the Preparation of Nitrooxy-derivatives of Paracetamol

The analgesic paracetamol **42a** is very widely used, but it is known to cause liver damage and can be fatal if high doses are taken. Hence, alternative, safer derivatives are sought. This patent describes a process for preparing the nitrate **41** that is a nitric oxide-donating analgesic with reduced liver toxicity compared with that of **42a**. Alternative methods of preparing **41** use $AgNO_3$ as a nitrating agent in greater than stoichiometric amounts, thus making the process expensive and not commercially attractive. The new process involves the reaction of **42b** with the nitrate **40c** as shown in Reaction 14. This reaction is said to be surprising since **40c** is a strong oxidant and **42b** a reductant; so it may have been expected that redox reactions would have resulted. This proved not to be the case, and additionally products from the nucleophilic substitution of the nitrate group were also not obtained. The patent also describes the preparation of **40c** from **39** via **40a** and **40b**. The final yield of **41** is 40% based on the conversion of **42a**. The patent claims also cover the reaction of **42a** with **40b** in an aprotic dipolar solvent and a dehydrating agent such as DCC, DCC with an aminopyridine, Amberlyst 15 ion-exchange resin, or DEAD with Ph_3P. However, there are no experimental details for this procedure. Nitrates are not usually considered to be safe materials, and the hazards associated with handling some of the intermediates are not discussed in this patent.

Reaction 14



(a) MeOH, KOH, 25 °C, 4.5 h; (b) (i) HNO_3/H_2SO_4, DCM, <5 °C; (ii) 25 °C, 6 h; (c) (i) $SOCl_2$/DMF, Et_2O, 0 °C; (ii) 20 °C, 5 h; (d) NaH,THF, 0 °C, 40 min; (e) (i) THF, 0 °C; (ii) rt, 18 h;

Advantages

Since both **39** and **42a** are readily available commercial materials, this is an inexpensive route to prepare the alternative analgesic.

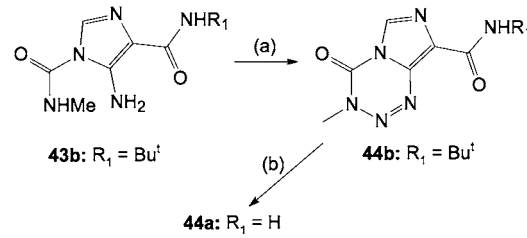
Patent No. U.S. 7,446,209

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

Title or Subject: Synthesis of Temozolomide and Analogs

Temozolomide **44a** was first discovered about 30 years ago but has only been approved to treat aggressive brain tumours in the past few years. One method of preparing **44a** uses MeNCO, and in view of this chemical's association with the disaster at Bhopal it is not surprising that alternative commercially viable syntheses are sought. The patent describes a process for preparing **44a** although the claims actually cover the compound **43b**. Reaction 15 summarises the route used to prepare **44a** beginning with diazotisation of **43b** and subsequent workup involving extraction into DCM producing crude **44b**. This is then hydrolysed using H_2SO_4, and the solid **44a** is obtained by precipitation in 84.5% yield with purity of 98.4%. An additional 9.7% of **44a** is present in the mother liquors.

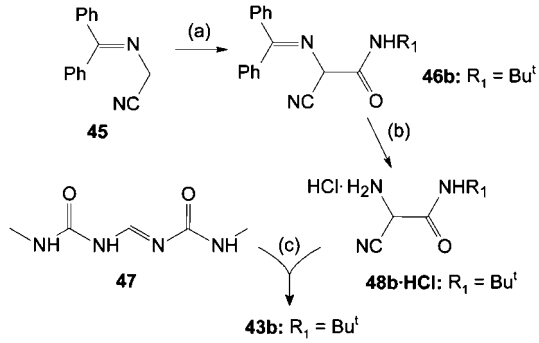
Reaction 15



(a) (i) LiCl, H_2O, HOAc, rt, 30 min; (ii) $NaNO_2$, 0 °C, 1 h; (iii) 5 h, rt; (iv) Extract in DCM, wash in aq $Na_2S_2O_4$, aq $NaHCO_3$; (b) (i) Concd H_2SO_4, rt, 2 h; (ii) EtOH, 0 °C, filter, wash, dry.

The patent also contains details of the synthesis of various intermediates, and Reaction 16 outlines a method used to prepare **43b**. The imine **45** is reacted with Bu^tNCO in the presence of $KOBu^t$, and from the reaction mixture the amide **46** is obtained in 90% yield. The amide is then heated with 1 M HCl, and the salt **48b·HCl** is isolated in 90.7% yield. Reaction of the salt with the urea **47** in the presence of HOAc produces **43b** that is isolated with a purity of 93%. The reaction is carried out on kilo scale, and it is interesting that the patent mentions that higher yields of higher purity product can be obtained on smaller-scale experiments. A similar route is described for the preparation of **43a** (R_1 = H) from the free base **48a** and **47**.

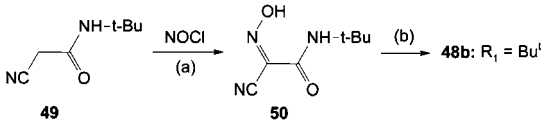
Reaction 16



(a) Bu^tNCO, $KOBu^t$/THF, DCM, 0 °C, 5 h;
(b) 1M HCl, EtOAc, 60 °C, 4 h; (c) HOAc, DCM, rt, 18 h.

The patent also describes a method for preparing the free base **43b** (R_1 = Bu^t) via the novel oxime **50**. This route is shown in Reaction 17, and the first step is the formation of **50** by bubbling NOCl through a solution of the amide **49** in DCM. The oxime is isolated as a white solid in 76% yield and then reduction with an Al/Hg amalgam affords **48b** as an oil in 88% yield.

Reaction 17



(a) (i) DCM, 0 °C; (ii) rt, 18 h; (b) Al/Hg amalgam, H_2O, <10 °C, 2.5 h.

The patent provides a method for the purification of the free base **48a** (R_1 = H) and references for its preparation and that of **45**. Brief ^1H NMR data are provided for all compounds.

Advantages

An improved process for preparing this important drug is described that is safer than alternatives. Some steps have been performed at kilo scale, suggesting the advanced stage of development.

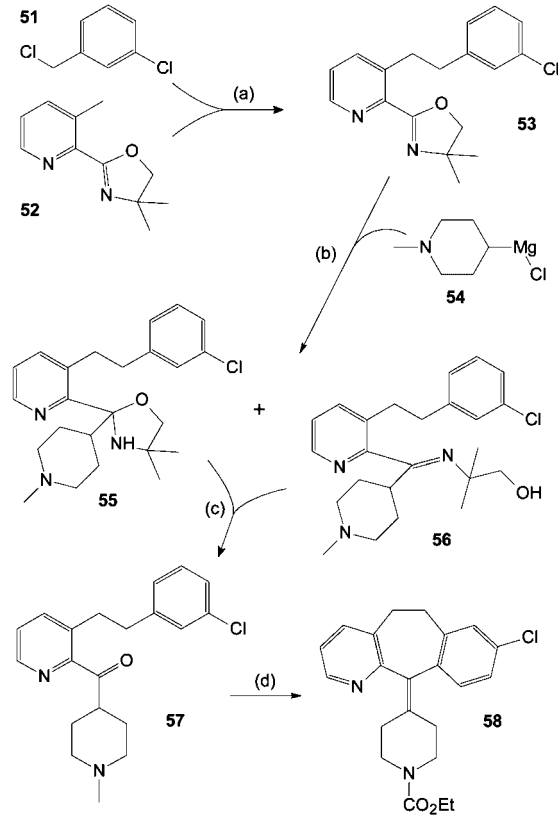
Patent No. U.S. 7,449,583

Assignee: ZaCh System S.p.A., Bresso, Italy

Title or Subject: Process for the Preparation of Loratadine

Loratadine **58** has antihistamine activity and is used to treat hay fever and other allergies. The processes that are known for preparing **58** are claimed to have a large number of steps and give side reactions that reduce the overall yield for industrial scale use. The patent describes a process to prepare compound **57** that is a known intermediate in the production of **58**. The preparation of **57** starts from the pyridine compound **52** as the preferred starting material, and the route used is outlined in Reaction 18. The first stage is the preparation of **53** by coupling of **51** with **52** in the presence of the strong base LDA. The reaction produces **53** as an oil with HPLC purity of 79% and an overall yield of 80.2%. The crude **53** is then reacted with the Grignard **54** to give a dark oil consisting of **55** containing a small, unspecified amount of **56**. The mixture is used in the next stage in which acid hydrolysis produces **57** that is recovered as a dark oil with HPLC purity of about 58%. The crystalline HCl salt of **57** may be obtained, but no details are provided. The conversion of **57** to **58** is known and not described in this patent.

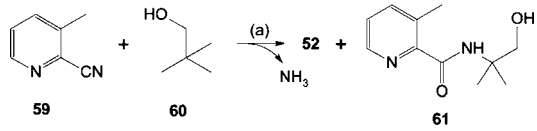
Reaction 18



(a) LDA, THF, 0 °C, 2.5 h; (b) (i) THF, -20 °C; (ii) rt, 16 h;
(iii) PhMe, aq HOAc, 1 h; (c) (i) 10% HCl, reflux, 14 h;
(ii) rt, DCM, aq NaOH, pH 8.5; (d) Known methods

The preparation of the pyridine **52** is also described in the patent and shown in Reaction 19. The reaction of **59** with **60** in the presence of $ZnCl_2$ produces a red oil containing 95.3% of **52** containing **61**. NH_3 is also produced, and this is removed by passing reaction vapours through aq HCl. It is stated that the byproduct **61** can be converted to **52** by treatment with MsCl and Et_3N in DCM at −5 °C and that **52** can be purified by vacuum distillation. There are no experimental details given for these steps although **52** is obtained in 98.5% yield and its bp is given.

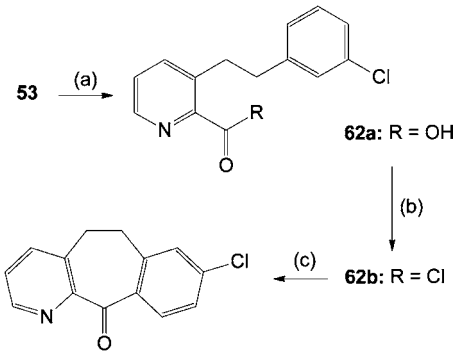
Reaction 19



(a) (i) $ZnCl_2$, 140 °C, 18 h; (ii) Cool to 60 °C, filter; (iii) Cool to rt, PhMe, aq NaCl; (iv) Evaporate organic phase

The patent also provides details for the conversion of **53** to the acid **62a** by acid hydrolysis and then chlorination using $SOCl_2$ to give **62b** as shown in Reaction 20. The product acid **62a** is recovered as a dark oil with purity of 80%, and this can be obtained as a white solid after crystallization from PhMe at 0 °C. The acyl chloride **62b** is obtained as a solid that is obtained in 62% yield and 99% purity. After crystallization from Pr^i_2O, it can used to prepare **58** by known techniques, but specific details are not given.

Reaction 20



(a) (i) Aq HCl, reflux, 8 h; (ii) Cool to 60 °C, PhMe, aq NaOH, pH 5; (b) (i) $SOCl_2$, rt; (ii) 60 °C, 3 h; (c) (i) DCE, $AlCl_3$, 0 °C, 16 h; (ii) 1N HCl, <15 °C.

Basic ^1H and ^{13}C NMR data are given for some of the intermediates.

Advantages

The patent provides a number of novel routes for making a key intermediate in the synthesis of the desired drug. Purification of intermediates is not always necessary, and this may simplify the overall process.

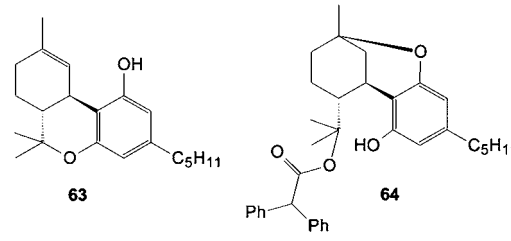
Patent No. U.S. 7,449,589

Assignee: Johnson Matthey PLC, London, United Kingdom

Title or Subject: Process for Purifying (−)-Δ⁹-trans-Tetrahydrocannabinol

The title compound **63** is the active ingredient of marijuana and does have a number of legal medical uses such as appetite stimulation in AIDS and cancer patients. It is also used to relieve pain in patients with severe arthritis and rheumatism although not always under medical supervision. This patent describes a method of purifying **63** by using supercritical fluid chromatography (SFC). The patent claims to describe the first preparative chromatographic process for the production of quantities of enantiomerically pure **63** that can be incorporated in pharmaceutical products. The objective is to obtain quantities of **63** from mixtures of cannabinoids and especially from **64**. The examples refer to purifying synthetically produced material although the claims also cover naturally occurring **63**. The patent states that when **63** is prepared by a particular synthetic route disclosed in patent WO02/096899 from the same company, the particular byproduct **64** is difficult to remove. When using displacement chromatography and a mobile phase of heptane/EtOH, the byproduct elutes on the tail of **63**, and hence it is difficult to separate the two compounds. However, it has been found that by using EtOH and liquefied CO_2 as the mobile phase then **64** elutes first, making its removal much easier. There are a number of examples using SFC processes using a chiral stationary phase that is a derivatised polysaccharide and the mobile phase is a mixture of EtOH and liquefied CO_2. A second achiral stationary phase is also used in a two-step procedure. There are examples of separation processes that have been scaled up and use columns with internal diameter of 100 mm and mobile flow rates of up to about 1 kg/min. The product is obtained at up to 99% purity although there is no information regarding productivity of larger-scale examples.

Cannabinoids



Advantages

The process allows the separation of a particular byproduct and gives high purity **63**.

Patent No. U.S. 7,452,999

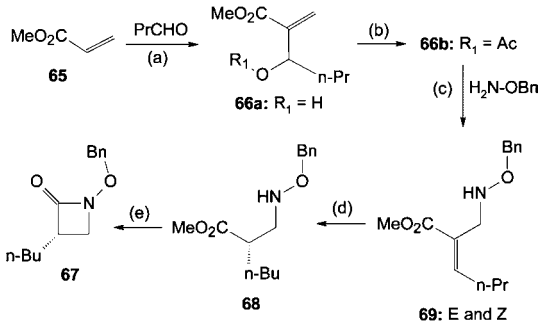
Assignee: Novartis AG, Basel, Switzerland

Title or Subject: Process for the Preparation of Intermediates for N-Formyl Hydroxylamine Compounds

The patent describes an improved process for the preparation of compounds such as **71c** that are used to prepare antibacterial agents. Alternative methods are said to have safety problems because of the use of H_2O_2 and also have waste disposal issues due to a nonselective debenzylation step. The first stage of the process is the preparation of azetidinone **67** that is outlined in Reaction 21. In the first step the hydroxyl ester **67a** is recovered in a 61% yield after a Bayliss−Hillman reaction between **65** and PrCHO in the presence of DABCO. In the experimental section of the patent it is mistakenly reported that butanol reacts with **65** to give **66a**. The claims and main body of the patent, however, do state that **65** reacts with an aldehyde. In the next stage acetylation of the hydroxyl group gives **66b** in 97.5% yield, and this reacts with the hydroxylamine H_2NOBn. This results in addition to the methylene group and formation of 1:1 mixture of *E*- and *Z*-isomers of the unsaturated ester **69** in 76% yield. The asymmetric hydrogenation of **69** uses a chiral phosphine with a Rh complex to give **68** in 94% yield with ee

of 98%. Both *R*- and *S*-forms of **68** are prepared separately by this method using the appropriate chiral phosphine. The cyclisation of **68** to form **67** is carried out using MeMgCl, and the product is obtained in 50% yield after purification by flash chromatography.

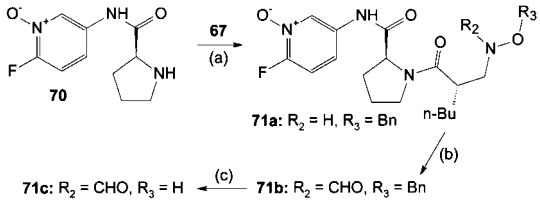
Reaction 21



(a) DABCO, rt, 7 h; (b) DMAP, PhMe, Ac_2O, <5 °C, 0.5 h; (c) THF, rt, 48 h; (d) nor_2RhBF_4, TangPhos, MeOH, H_2, 50 psi, rt, 24 h; (e) MeMgCl, THF, 0 °C, 1 h;

Reaction 22 shows the route for the conversion of **67** to **71c**. There are incomplete experimental details given for this reaction scheme with the production of **71a** from **67** and **70** only broadly discussed in the patent. The reaction is said to be carried out using an acid as an activator in aqueous alcohol or alternatively without an activator in THF, dioxane or DME. No preference is stated. Formylation of **71a** to give **71b** can be carried out using HCO_2H/Ac_2O or $HCO_2CH_2CF_3$ and debenzylation of **71b** to give **71c** is by hydrogenation that can result in partial reduction of the amine oxide. This is inhibited by performing the reaction at H_2 partial pressure below 1 atm using a mixture of N_2 and H_2 at 1 atm pressure. The selectivity to **71c** of the hydrogenation is 98 − 99%. A hydrogen transfer reaction can also be used to convert **71b** to **71c** and this is done using HCO_2H and Pd/C.

Reaction 22



(a) RCO_2H, aq alcohol, pH 5 - 11, 60 - 80 °C; (b) HCO_2H/Ac_2O, EtOAc, <25 °C; (c) EtOH, Pd/C, N_2/H_2, 1 atm, rt, 3 h.

Advantages

The process is claimed to be safer and less wasteful than alternative procedures.

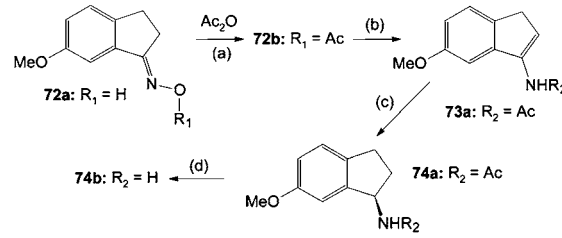
Patent No. U.S. 7,456,320

Assignee: ZaCh System, Avrille, France

Title or Subject: Process for the Synthesis of Optically Active Substituted α-Aminoindan Derivatives

The title compounds such as **74b** are intermediates that are used to prepare drugs for the treatment of bipolar disorders. An alternative method, that is used to prepare the intermediates and involves a Friedel−Craft and a Bayer−Villiger reaction, is said to give low yields and have safety issues. The new process disclosed in this patent is outlined in Reaction 23 and begins with the acylation of the oxime **72a** to form **72b** in 77% yield. The next step is heterogeneous catalytic hydrogenation of **72b** using Ir/C catalyst to form the ene-amide **74a** in 84% yield. The conversion of **72a** to **73a** can be carried out with or without isolation of **72b**, and both options are described in the patent. The key aspect of the invention is the asymmetric hydrogenation reaction of **73a** to give **74a** using Ru catalysts containing a chiral phosphine ligand. The mole ratio of **73a** to catalyst is up to 500:1. A wide range of ligands is described as being suitable including diphosphines, bisphospholanes, and ferrocenylphosphines. Yields for this reaction are 80% with ee values >98%. Treatment of **74a** with HCl in MeOH produces **74b** that is isolated in 65% yield. This hydrolysis is carried out by adding the MeOH/HCl in three stages at 25 °C so that between each addition the batch is cooled then reheated to 90 °C. For a commercial process an improved procedure for this operation would probably be desirable.

Reaction 23



(a) THF, 20 °C, 2.25 h; (b) 5% Ir/C, H_2, 7.4 bar, 80 °C, 2.25 h; (c) H_2, 8 bar, MeOH, *R*-$Ru(OAc)_2$diphosphine, 40 °C, 27 h; (d) HCl/MeOH, 90 °C, 21 h.

Advantages

The process gives good yields of product with high ee and without the safety issues of the alternative method.

Keith Turner

Kappa Tau Consulting, 12 The Avenue, Fairfield, Stockton-on-Tees TS19 7EY, U.K. Telephone/fax: +44 (0)1642 653484. E-mail: keith@kappa-tau.co.uk

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