Organic Process Research & Development **2010,** *14,* 8–18

Highlights from the Patents

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

Summary

The current review covers 20 patents from an original list containing 267 that fitted the search criteria. A wide selection of subjects is covered that is hoped to be of some interest to readers. Multistep processes are usually essential for the synthesis of complex molecules, and patents claim that this justifies the development of new simplified procedures. Sometimes the new process does not seem to contain fewer steps, and its advantages are not always clear. A novel formylation reaction of 1H-tetrazole compounds gives such low yields that, although it is novel, does not seem to be commercially viable. The use of large numbers of solvents in any process can give rise to significant handling and potential safety problems. For example, a process to extract the anticancer compound brevioliol from plant leaves uses at least four solvents and two chromatographic separations. Another patent covering extraction is that of the recovery of epothilones from a biochemical process. This procedure uses at least six solvents and also uses a chromatographic separation. At the other end of the scale a new process is described for preparing a critical reagent for the manufacture of a fluoroquinolone-based antibiotic. The method has four steps that can be carried out in one vessel and uses only a single solvent that simplifies the handling problems of alternative processes. An improved method is described for the removal of a CN group by catalytic hydrogenolysis from a fluorinated benzodinitrile. The use of a zeolite in conjunction with a Pd catalyst significantly reduces the Pd catalyst usage. Improved catalysts are found in a number of other patents. An example is in a cyclisation process for the production of an aldehyde, used in fragrances, using particular Lewis acids in place of H_3PO_4. This gives improved product yield and purity. A process for producing the important amino acid methionine, using a catalytic amidocarbonylation reaction, includes recycling of the catalyst and byproduct. The direct catalytic production of phenol from benzene has been a major objective within the chemical industry for many years. A patent claims to have achieved this using a vanadyl phosphate catalyst and H_2O_2. Oxazaborolidine compounds are precursors for catalysts used in enantioselective reductions of prochiral ketones, and a new process for their production is described. Producing chemicals and fuels from renewable biomass sources is a topic of major interest. Two patents cover the production of furans from sugars using catalysts to effect dehydration. One uses solid acid catalysts, while the other uses liquid acids. A new process for preparing an intermediate in the synthesis of montelukast sodium is described. One key intermediate was found to be unstable, and the improvement involves the preparation of a stable precursor to the desired intermediate. A number of patents describe the production of various types of indoles that have different applications. A highly selective asymmetric hydrogenation process is described, that takes place under very mild conditions, for preparing cycloalkaneindoles that are used in the treatment of allergic rhinitis. 7-Acryloylindoles have been reported as being useful in treating atherosclerosis, and a method involving successive cross-coupling reactions for preparing one particular compound is disclosed. A very comprehensive patent describes new processes for preparing a series of oxindoles and thio-oxindoles that are precursors for unspecified pharmaceutical compounds. A new process is described for preparing rocuronium bromide, the pre-anaesthesia muscle relaxant. The method gives improved yields with lower level of impurities. A number of the patents in this collection describe experiments carried out on a kilo or multikilo scale, thus suggesting an advanced stage of development or even commercial operation. However, there is no legal or commercial significance in the choice of patents in this review. The advantages mentioned in this review are those claimed in the patent, unless this reviewer has personal knowledge of the subject.

Patent No. U.S. 7,569,687

Assignee: Sicor Inc., Irvine, California, U.S.A

Title or Subject: Process for the Synthesis of Rocuronium Bromide

The title compound **8** is used as a muscle relaxant in general anaesthesia and is available as Zemuron in the U.S.A. and Esmeron elsewhere. Processes for the preparation of **8** are described as having several steps and involve the purification of intermediates that reduce the final yield of the desired product. The patent claims to provide a more efficient synthesis of **8** by improving the methods for the preparation of key intermediates and minimising byproduct. The first stage of synthesis of **8** is shown in Reaction 1 in which the first step is conversion of the 16,17-epoxy group to **2a** by base hydrolysis. **2a** is not isolated but converted to the pyrrolidinyl compound **2b** by treatment with 2 mol equiv of **3**. The enantiomer **2b** is formed with 82% stereospecificity, and it is claimed that there are minimal amounts of products resulting from the breaking of the 2,3-epoxy link, but actual analytical details are not provided. The reduced level of impurities is, in part, ascribed to the use of the minimum amount of **3** in preparing **2b**. The impurities that are mentioned are formed mainly by attack of the pyrrolidinyl group

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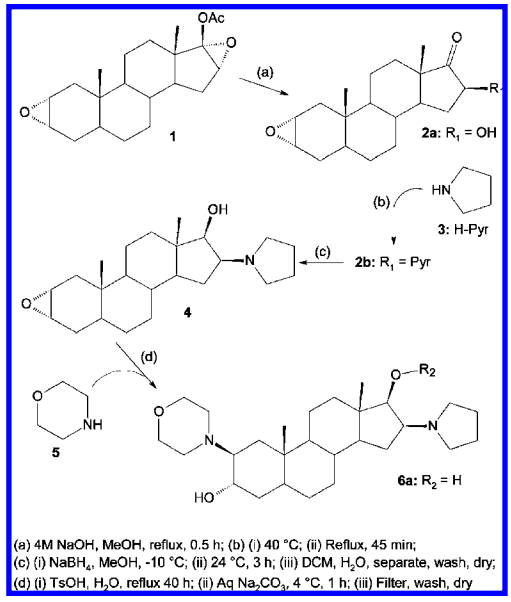
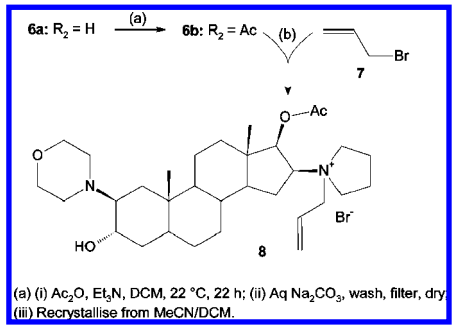
at the 2,3-epoxy group. The ee of crude **2b** can be increased to 98.2 by refluxing in MeOH followed by heating in MeOH/H_2O. In the next step **2b** is reduced to **4** using $NaBH_4$ and **4** is isolated in 80% yield compared to yields as low as 57% using alternative procedures. The reason for the improved yield in the current patent is not obvious since the alternative methods use the same reagent under very similar conditions. After isolation of **4** the morpholinyl compound **6a** is prepared by refluxing **4** with **5** in H_2O in the presence of an acid catalyst such as TsOH. The reaction takes up to 40 h, and the crude **6a** is isolated in almost 90% yield with 94% purity.

Reaction 1



The next stage of the process is shown in Reaction 2 where crude **6a** is acetylated to give **6b**, and the example in the patent describes this being carried out by using 2 kg of **6a**. The reaction takes place in DCM at 22 °C using Ac_2O in the presence of Et_3N and after purification **6b** is isolated in 99.9% purity and 68.8% yield. The final step to produce **8** is reaction of **6b** with about 2 mol of **7** in the presence of an inorganic base that inhibits undesired side reactions leading to a range of byproducts. The preferred base is Na_2CO_3, and the patent describes an example for the preparation of almost 10 kg of **8** that is isolated in 90% yield and 99.9% purity by HPLC.

Reaction 2



The patent lists a substantial number of impurities that can be formed during the different stages of the process. Their structures are shown in the patent, but these have been omitted here because of a lack of space. The patent contains DSC, TGA data, plus detailed ^1H and ^{13}C NMR data for compound **2b** plus NMR assignment data for **4** and its enantiomer.

Advantages

The process gives lower levels of impurities and higher yields than alternative procedures and has been scaled up to a kilo scale.

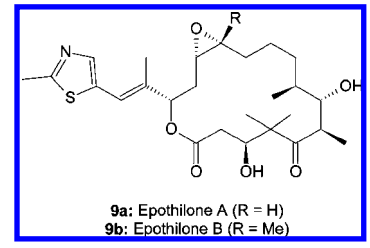
Patent No. U.S. 7,569,698

Assignee: Novartis AG, Basel, Switzerland

Title or Subject: Process for the Purification of Epothilones

The epothilones **9a** and **9b** are 16-membered macrolides having cytotoxic properties and are of interest in treating cancers. They can be extracted from natural sources by myxobacteria and a patent on the synthesis these two compounds, designated A and B, has been reviewed (Org. Process Res. Dev. 2008, 12, 556.). The current patent discloses an improved method for the purification of these materials. The epothilones can be produced by biochemical processes followed by absorption of the epothilones onto synthetic resin absorbents. Examples of these are commercially available styrene/divinylbenzene copolymer resins. The subsequent desorption from the resins is the basis of the process described in the patent. Alternative desorption procedures require the use of alcohols as desorption solvents and involve molecular filtration or adsorption chromatography. It is said that there are difficult phase separations and the processes are time-consuming. The key finding is that by using weakly polar or apolar solvents, in place of alcohols, many of the difficulties can be overcome, and a higher product yield is achieved. An example in the patent describes the desorption of **9b** from almost 600 kg of resin using two 720 L portions of PhMe as the desorption solvent. After concentrating the extract solution under vacuum, 4 kg of solution is obtained containing 209 g of **9b**. This solution is then dissolved in a mixture of MeOH and cyclohexane, and after addition of H_2O a mixture of **9a** and **9b** is recovered. These compounds are separated by reversed-phase chromatography using MeCN/H_2O as eluant, and 150 g of **9b** is subsequently recovered in 98.4% purity by crystallisation from a mixture of Pr^iOH and cyclohexane. Examples are also given of the use of other desorption solvents such as DCM or Pr^iOH. The former solvent is preferred because it is more selective, requires half the extraction time, and takes less time to remove by distillation. One of the claims of the patent covers the use of simulated moving bed chromatography to separate **9a** from **9b**.

Epothilones



Advantages

The process is efficient at recovery of the epothilones from biochemical processes and has been carried out on a substantial scale. Unfortunately, it does use a large number of solvents.

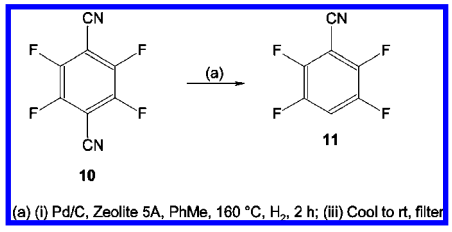
Patent No. U.S. 7,569,718

Assignee: Showa Denka K. K., Tokyo, Japan

Title or Subject: Production Process of a Fluorinated Benzonitrile

The patent describes the synthesis of **11** that is claimed to be an intermediate for preparing unspecified cyclopropanecarboxylic acid esters having insecticidal activity. Reaction 3 shows the route used to prepare **11** by the removal of one CN group from **10** in a hydrogenolysis reaction. This is similar to alternative processes for the preparation of **11** although these are claimed to require such large quantities of catalyst that they are not economically acceptable although the actual catalyst usage is not specified. This patent describes a process that reduces the amount of catalyst needed by carrying out the reaction in the presence of a zeolite. The reaction is carried out using Pd/C catalyst and zeolite 5A at 160 °C in PhMe under H_2 that is admitted after heating. The mixture contains about 15% w/w of **10**, 0.3% w/w catalyst and about 23% of zeolite. In some examples the reagent **10** and catalyst were initially both wet, and so the water was removed by azeotropic distillation with PhMe before the hydrogenolysis stage. After this the zeolite is added, and the mixture is heated to 160 °C before H_2 is admitted. Analysis showed that the conversion of **10** was up to 99.4% and yield as high as 89.4%. When no zeolite was used, the reaction stopped after about 3 h, and the conversion was only 50.4% and yield 20.7%.

Reaction 3



Advantages

The use of the zeolite gives a large improvement in the process efficiency with much higher yield and lower catalysts usage.

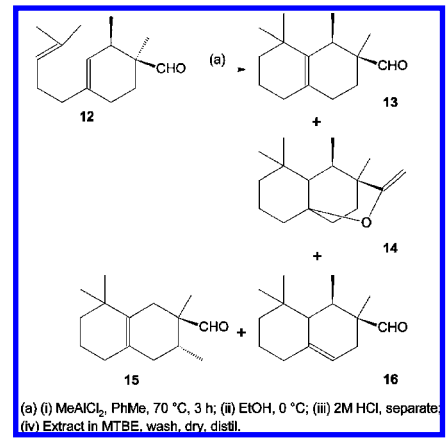
Patent No. U.S. 7,569,732

Assignee: Givaudan SA, Vernier, France

Title or Subject: Cyclisation Process

This patent describes a process for the preparation of the compound **13** that is the main isomer of a fragrance known as Georgywood. The other enantiomer of **13** is less potent, and so any preparation of this compound is aimed at increasing the amount of the desired isomer. Cyclisation of **12** using H_3PO_4 is known to produce **13** plus the products **14**, **15**, and **16** shown in Reaction 4. Formation of **15** is not desirable since it cannot be converted to **13**, unlike **14** and **16** which can. The patent discloses that a particular class of Lewis acids gives improved yield and selectivity for this reaction, and these catalysts are $RAlCl_2$ where R = Me or Et. The reaction is carried out by heating a solution of **12** in PhMe with $MeAlCl_2$ at 70 °C for 2−3 h. After workup the mixture is isolated by distillation in 80% yield and contains about 90% of **13**. Using a mixture of $AlCl_3$ and $MeAlCl_2$ a 70% yield of 80% pure **13** was obtained. These results compare well with the use of BBr_3 at −50 °C that produced a 40% yield of **13** with purity of 90%.

Reaction 4



The patent refers to an alternative patent application (WO 2005/0016938) for the preparation of **13** from **12** that also uses $MeAlCl_2$. However, that patent describes a particular method of preparing $MeAlCl_2$ from Al, $AlCl_3$, $Me_3Al_2X_3$ (X = Br or I) and MeCl, and the current patent excludes the use of $MeAlCl_2$ prepared by this procedure.

Advantages

The process gives an improved yield and higher purity product than the alternative.

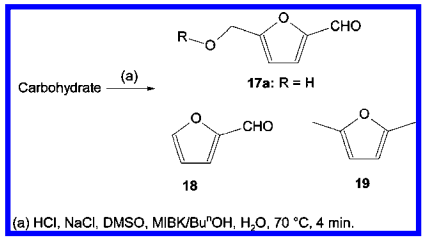
Patent No. U.S. 7,572,925

Assignee: Wisconsin Alumni Research Foundation, Madison, Wisconsin, U.S.A

Title or Subject: Catalytic Process for Producing Furan Derivatives in a Biphasic Reactor

This is the first of two patents dealing with the production of furan derivatives from biomass sources. This patent describes a process for the selective dehydration of carbohydrates to yield furan derivatives such as **17a**, **18**, and **19**. Over the past few years there has been considerable interest in obtaining various chemical raw materials and fuels from renewable sources. However, this strategy is under severe criticism where the renewable sources are foods themselves or are grown on land that could be used for food. Furan derivatives are themselves useful starting materials for a variety of chemicals and polymeric materials. The process for producing the derivatives is carried out by heating the carbohydrate in the presence of an acid in a two-phase system consisting of water, an inorganic salt, and a modifier plus an immiscible organic extracting solvent. The preferred carbohydrate is fructose, and the acid may be HCl, H_2SO_4, or H_3PO_4 and an example of the salt is NaCl. The so-called modifier is DMSO, and the extracting solvents are DCM, MIBK, Bu^nOH, Bu^sOH, or mixtures of two or more of these. The reaction is carried out at about 70 °C, and the time in some cases was 4 min for 100% conversion, but in others 2.5 h or more was required. There is a substantial amount of experimental work described in the patent with several variables studied and their effects reported graphically.

Reaction 5



The patent also describes the hydrogenolysis of **17a** to give **19** in both vapour-phase and liquid-phase reactions. The catalysts used was CuRu/C that was found to be more stable to deactivation by Cl ions than a $CuCrO_4$ catalyst. The interest in forming **19** is that it has a higher H/C ratio than **17a** and hence a higher energy value so it is more suitable for use as a fuel.

Advantages

The process produces good yields of chemical intermediates and fuel additives from biomass sources.

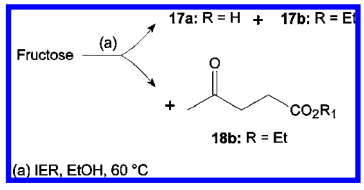
Patent No. U.S. 7,579,489

Assignee: Archer-Daniels-Midland Company, Decatur, Illinois, U.S.A

Title or Subject: Process for the Preparation and Purification of Hydroxymethylfurfuraldehyde

This is the second patent describing the preparation of **17a** and similar furan compounds from biomass sources that also uses fructose as the starting material. The production of furans from fructose involves acid-catalysed dehydration, and the current patent uses ion-exchange resins (IERs) as the acid catalysts, whereas the previous one used mineral acids. The reaction is carried out by heating the fructose source and solvent in the presence of an acid IER. The examples describe experiments carried out in a batch mode in which the IER is stirred in the mixture. This method physically degrades the IER and is not recommended for large-scale use. An improved procedure is to pass a solution of the fructose through a column of IER, and several examples describe this procedure. In fact the claims of the patent exclusively cover this method for the production of the ethoxy derivative **17b** (R = Et). In an example of this the fructose is dissolved in EtOH and passed over a column containing Amberlyst 131. At 60 °C complete conversion of the fructose was achieved, and the product was a mainly **17b** with **17a**. When the IER was changed to Amberlyst 35, a macroporous strong acid resin, the conversion fell to 85% and the product was again mainly of **17b** with **17a**, but the mixture also contained the ester **18b** (Reaction 6). This finding seems to have resulted in further development work for the preparation of the acid **18a** (R = H) directly from fructose.

Reaction 6



The preparation of **18a** is carried out by heating an aqueous solution of fructose with Amberlyst 35. At 150 °C for 4.5 h the yield of **18a** was 62% as a dark-brown oily material. After 18 h at rt the yield of **18a** was 41.2%, and by heating fructose and Amberlyst 35 in polyethyleneglycol dimethylether at 100 °C **18a** was formed in a yield of 45.3%. In each case the product yield is based on analysis of the mixture, and there are no details of the recovery of the product. The patent describes the preparation of **17a** from fructose by using an IER in either *N*-methylpyrrolidone (NMP) or Me_2NCOMe as solvents. The purification of **17a** is carried out by extraction into MIBK or by chromatography.

Advantages

The use of a solid catalyst does simplify the product separation and allows a continuous process to be operated efficiently.

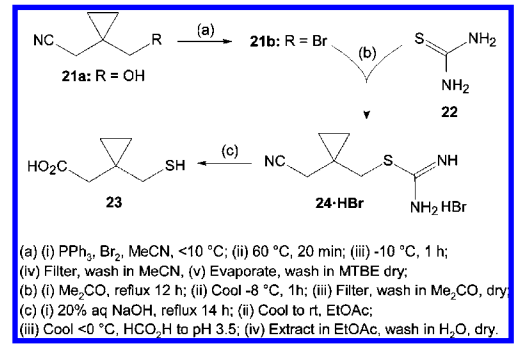
Patent No. U.S. 7,572,930

Assignee: Chemagis Ltd., Bnei-Barak, Israel

Title or Subject: Process for Preparing 1-(Mercaptomethyl)-cyclopropaneacetic Acid: A Montelukast Intermediate

Montelukast sodium is used in the treatment of asthma and allergic rhinitis and is available under the name Singulair. A patent covering a stage towards the end of the synthesis of montelukast sodium from this company has been reviewed (Org. Process Res. Dev. 2009, 13, 829.). The current patent describes a process for preparing an important intermediate **23** that was found to be very air sensitive and degraded from 98.1% purity to 97.6% after only six months even when packed in an airtight container in the dark in a refrigerator. Hence, it was decided to prepare **23** only when needed,and the patent describes a method of making a precursor to **23** that is stable at rt and can be stored until it is needed. This precursor is the novel HBr salt of **24**, and the overall route for preparing **24** and then **23** is shown in Reaction 7. This begins with the bromination of **21a** using PPh_3 and Br_2 to give **21b** that is isolated as an oil in 87% yield with a purity of 97%. **21a** is commercially available, and hence **21b** is then refluxed with **22**, and the novel HBr salt of **24** is produced and isolated as a solid in 91.1% yield and 99.2% purity. This salt **24·HBr** can then be converted to **23** by treatment with NaOH and is isolated in 76.7% yield and purity of 97.9%.

Reaction 7



Advantages

The patent provides a method of preparing a stable crystalline intermediate in very good yield that can be used to produce the desired active pharmaceutical ingredient (API) with fewer degradation problems.

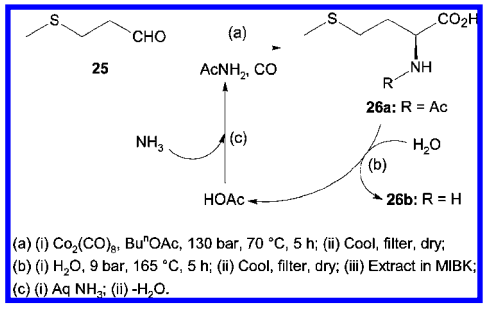
Patent No. U.S. 7,572,937

Assignee: Evonik Degussa GmbH, Essen, Germany

Title or Subject: Process for Preparing Amino Acids by Amidocarbonylation

The focus of the work described in the patent is the production of the important amino acid methionine **26b**. Amino acids can be produced by both biochemical and chemical methods including using the amidocarbonylation reaction that forms an *N*-acylamino acid by the catalysed reaction of an aldehyde, an amide, and CO. The use of this reaction for the preparation of **26b** outlined in this patent is shown in Reaction 8 and initially produces **26a** from **25**, $AcNH_2$, and CO in the presence of $Co_2(CO)_8$. The reaction is carried out in Bu^nOAc under 130 bar of CO/H_2 at 70 °C. After 8 h the reaction was analysed by HPLC and showed 100% conversion of **25** with 92.2% selectivity to **26a** and 5% $MeSCH_2CH_2CH_2SMe$. The **25a** precipitates from solution and is washed; the washings contain catalyst residues that are recycled. It is stated that the loss of activity of the catalyst is only 10−15% although there are no experimental details provided to substantiate this. Hydrolysis of **26a** at 165 °C and 5 bar pressure gave 93% conversion after 5 h, and **26b** is precipitated from the mixture and isolated by filtration in 60% yield. The HOAc is extracted into MIBK and treated with aq NH_3 in a counterflow extraction column to produce NH_4OAc. Dehydration of this gives $AcNH_2$ that is recycled to the first step although how this is carried out is not described. The novel aspects claimed by this patent are that of recycling of the catalyst and recovery of the HOAc for conversion to $AcNH_2$.

Reaction 8



Advantages

The process provides an efficient method of preparing methionine and, if operated continuously, would take advantage of the recycling aspects.

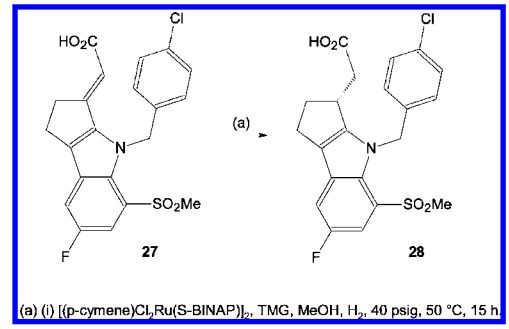
Patent No. U.S. 7,576,118

Assignee: Merck & Co., Rahway, New Jersey, U.S.A

Title or Subject: Asymmetric Hydrogenation Process

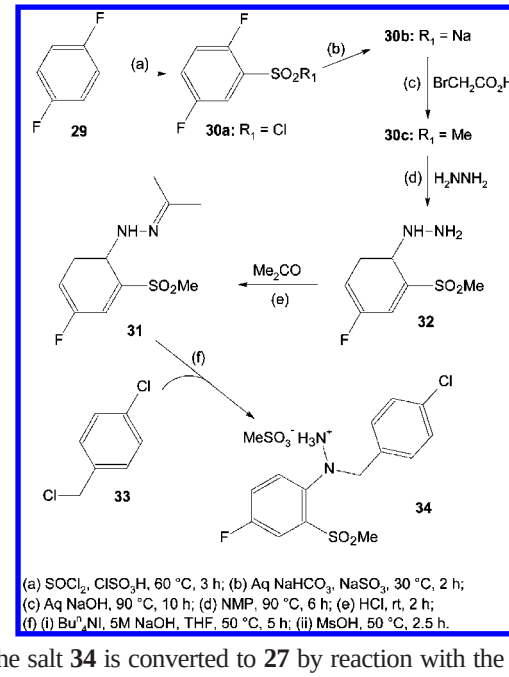
This patent discloses an asymmetric hydrogenation process for the preparation of the cycloalkaneindole compound **28** that is a DP receptor antagonist and useful in treating allergic rhinitis. The hydrogenation reaction to make **28** is carried out using Ru phosphine catalysts, and one example is shown in Reaction 9. The reaction is carried out in MeOH containing **27** and an equimolar amount of tetramethylguanidine (TMG) so that the product is the TMG salt of **28**. The conversion is up to 100%, and the ee of the product is 91%. Similarly prepared is the Pr^iNH_2 salt. The free acid **28** can be recovered from the hydrogenation mixture by acidification using HCl. The catalyst concentration used is around 1.4 mol %, and a range of other catalysts including Rh complexes is claimed to be suitable. These cover several different types of chiral phosphine ligands.

Reaction 9



The patent also outlines the synthesis of the acid **27**, and for clarity this is shown in Reactions 10 and 11. The first stage is the preparation of **34** that begins with the formation of the mesyl derivative **30c**. This transformation is carried out in three steps beginning with **29** that is converted to **30a** using $SOCl_2$ and $ClSO_3H$. **30a** is not isolated but treated with an aqueous solution of $NaHCO_3$ and Na_2SO_3 to produce **30b** that is isolated as a crystalline solid. Reaction of **30b** with bromoacetic acid produces **30c** that is recovered by crystallisation at rt and then reacted with H_2NNH_2 in NMP. This gives the hydrazine **32**, and this is treated with Me_2CO at rt forming the hydrazone **31** that easily crystallises from solution. In the next step **31** is reacted with **33** in a biphasic mixture in the presence of $Bu^n{}_4NI$ as PTC and NaOH. The organic phase of the mixture is then treated with MsOH, and addition of seed crystals gives the salt **34**.

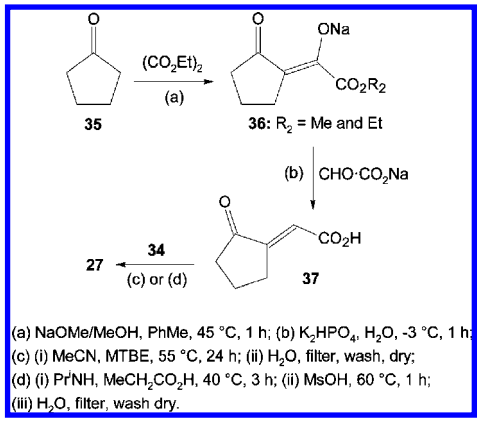
Reaction 10



The salt **34** is converted to **27** by reaction with the acid **37** (Reaction 11), and this can be carried out in two ways. In one method a slurry of **34** in MeCN is heated with a solution of **37** in MTBE followed by addition of water. After cooling, the product precipitates and is filtered off, washed, and dried. The

alternative method is to heat **34** with the $Pr^{i}_{2}NH$ salt of **27** in $MeCH_2CO_2H$ followed by addition of MsOH. Reaction 11 also outlines the method of preparing **37** from **35**. This proceeds via **36** that is a mixture of Me and Et esters formed by treatment of **35** with $(CO_2Et)_2$ using NaOMe and MeOH. Reaction of **36** with the Na salt of glyoxylic acid in the presence of K_2HPO_4 forms **37**. The steps shown in Reactions 10 and 11 are described in some detail in the patent, especially reaction times, although there are actually no details of amounts of reagents used or yields obtained. The patent describes the preparation of various salts of **27** such as salts of TMG, DBU, and K, and experimental details are given for their preparation.

Reaction 11



Advantages

The hydrogenation step is very selective and takes place under mild conditions. The efficiency of the preparation of the unsaturated acid cannot be assessed because of the lack of experimental detail.

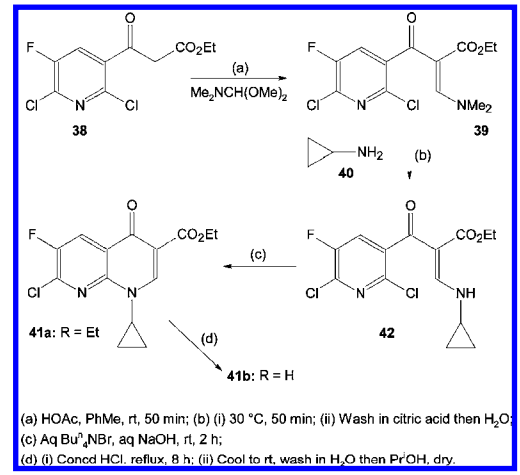
Patent No. U.S. 7,576,214

Assignee: LG Life Sciences Ltd., Seoul, Korea

Title or Subject: Process for Preparing 7-Chloro-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic Acid

The patent states that the title compound **41b** is a critical reagent for the manufacture of a fluoroquinolone-based antibiotic. One of the alternative processes for preparing **41b** requires three steps with separation of intermediates between each step. A second method does not require the separation of intermediates but uses $(EtO)_3CH$ in an early stage that if not removed gives problems later in the synthesis. Hence, the objective of the patent is to develop a process that is more efficient than the alternatives. Reaction 12 shows the route developed to produce **41b**, and this is a four-step, one-pot process that uses PhMe as the only solvent. The first step is the formation of **39** by reaction of **38** with $Me_2NC(OMe)_2$. The reaction is carried out at in 50 min at rt in the presence of 0.2−0.3 mol of HOAc per mole of **38**. In the next step **40** is added at the same temperature, and after 50 min **42** is obtained. After the reaction is complete, the mixture is washed with 10% citric acid solution and then water to remove traces of HOAc, **40**, and the MeOH released in step 1. The next step is the cyclisation of **42** to produce **41a**, and this is performed using aq $Bu^{n}_{4}Br$ and 25% NaOH at rt over 2 h. The final step is hydrolysis of the ester group using concd HCl under reflux for 8 h. Water is added, and after removal of the aqueous layer the desired acid **41b** is recovered in 90% yield and 99.5% purity. This procedure is carried out to give 77 kg of product, thus indicating the advanced commercial status of the process. The patent also describes bench-scale examples that use $Bu^{n}_{4}OH$ with or without NaOH to effect the cyclisation of **42** to **41a**. These methods both give excellent yields >92% and purity of 98.6−99.9%.

Reaction 12



Advantages

The process gives both excellent yield and product purity in a one-pot process that is clearly commercially viable.

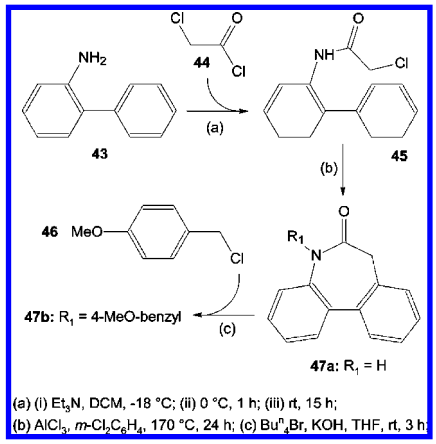
Patent No. U.S. 7,579,464

Assignee: Hoffmann-La Roche Inc., Nutley, New Jersey, U.S.A

Title or Subject: Process for Enantiomerically Pure Compounds

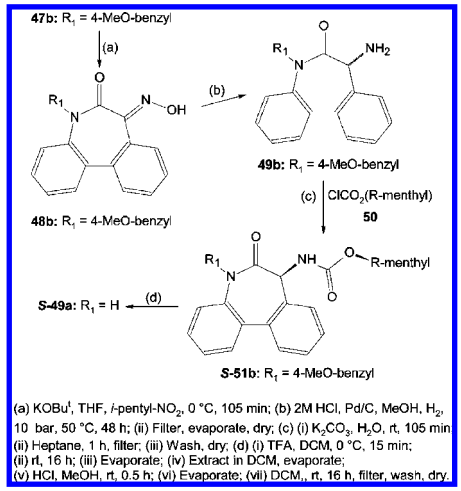
This patent describes a process for the preparation of dibenzoazepinones such as **49a** that are intermediates in the synthesis of drugs used to treat Alzheimer's disease. The patent reports that **49a** can be produced enantiomerically pure by using chiral HPLC, but this is not a commercially acceptable process. The process for producing the desired enantiomer is shown in Reactions 13 and 14. The first phase is the preparation of **47b** (Reaction 13) and starts with the formation of the chloroacetamide **45** by reaction of **43** with **44** at −18 °C. After extensive workup involving extraction, precipitation, and evaporation steps the product is recovered in three batches from the mixture in a total yield of 85.8% (purity not given). In the next step **45** is heated at 170 °C for 24 h with $AlCl_3$ to effect cyclisation and produce **47a** that is recovered in 82.5% yield. The amino group is then protected by reaction of **47a** with **46** in the presence of $Bu^{n}_{4}Br$ to form **47b** as a brown oil in 100% yield. This is used directly in the next stage that is outlined in Reaction 14.

Reaction 13



Treatment of **47b** with *i*-pentylnitrite in the presence of KOBu^t forms the oxime **48b** as a yellow foam that is used without further purification. Catalytic reduction of **48b** takes 2 days at 50 °C and 10 bar H_2 pressure using a Pd/C catalyst. The product **49b** is a racemic mixture and can be recovered in 96% yield as a solid as the HCl salt or as the free base as a yellow oil in 91% yield by adding NaOH during workup. In the next step the *S*-enantiomer of the *R*-menthyl carbamic ester ***S*-51b** is prepared from **49b** and **50** and recovered as a solid in 45% yield having an ee of 99.8. The reaction also gives the ***R*-51b** that is obtained as a foam and can be converted to the *S*-isomer by treatment with LDA and Me_3SiCl at −75 °C. The *S*-enantiomer ***S*-49a** is obtained in 94% yield by hydrolysis of ***S*-51b** using TFA.

Reaction 14



Advantages

The process provides a method of obtaining the desired enantiomer from readily available reagents and also allows the recovery use of the undesired enantiomer.

Patent No. U.S. 7,579,478

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

Title or Subject: Process for the Purification of Substituted Benzoxazole Compounds

The compounds covered by this patent such as **53** are described as oestrogenic agents and are of interest in treating a wide variety of diseases. The preparation of the benzoxazole compounds is covered in a 2004 patent from Wyeth (U.S. Patent 6,794,403), and the current patent describes an improved method of purifying the product from that work. The process is applied to the crude product **53** obtained from the vinylation of **52** shown in Reaction 15. The process of the patent consists of the following steps:

(i) The crude **53** is recrystallised from Me_2CO and MeCN and recovered in 71.5% yield.

(ii) Dissolve the partially purified product in EtOAc at 75−80 °C.

(iii) Cool to <45 °C and treat the hot EtOAc solution with a clarifying agent such as charcoal.

(iv) Filter off the charcoal and concentrate the clarified solution.

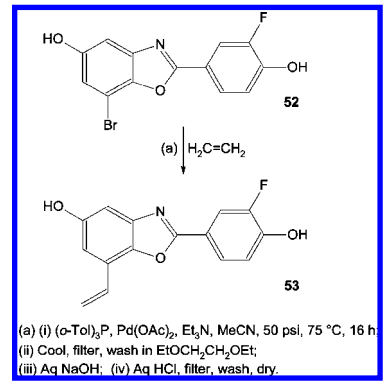
(v) Heat the concentrated solution to 80 °C and add heptane.

(vi) Cool the solution to <50 °C for 0.5 h then to <5 °C for 1 h.

(vii) Filter off the solid and dry.

The example in the patent is carried out using 300 g of crude **53**, and the final material is obtained in 87% yield and 99.4% purity.

Reaction 15



Advantages

The process gives very high purity product and presumably is an improvement on the original procedure.

Patent No. U.S. 7,579,480

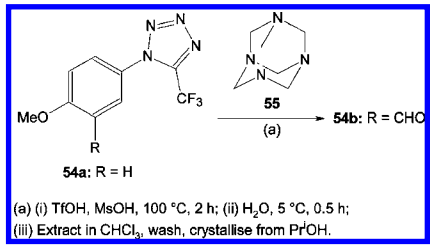
Assignee: Toyo Kasei Kogyo Co. Ltd., Osaka, Japan

Title or Subject: Alkoxy(tetrazol-1-yl)benzaldehyde Compounds and Process for Their Production

The title compounds are said to be useful intermediates in the production of analgesics or anti-inflammatory compounds. The object of the patent is to produce the desired compounds by the formylation of 1H-tetrazole compounds, and it is claimed that this is not a well-known reaction. The method used to prepare a compound such as **54b** is shown in Reaction 16 and uses 2 mol equiv of **55** as the formylating agent in sulphonic acid solvents. The solvent is an 50:50 mixture of MsOH and TfOH, and the reaction takes place at 100 °C over about 3 h. After this, the mixture is cooled and hydrolysed by pouring into iced water. The product is extracted and crystallised from Pr^{i}OH and recovered in 69.7% yield. There are several examples describing the preparation of other aldehydes, and **54b** is produced in the highest yield. All examples give low yields with the EtO analogue of **54b** being formed in 22.8%, and the

3-methoxy derivative is formed in only 14.9% yield. The formylating agent **55** is a commercially available material, but its use is very wasteful and the yield of reaction is not particularly high.

Reaction 16



Advantages

The process does provide a novel formylation method of preparing the desired compounds but is very inefficient.

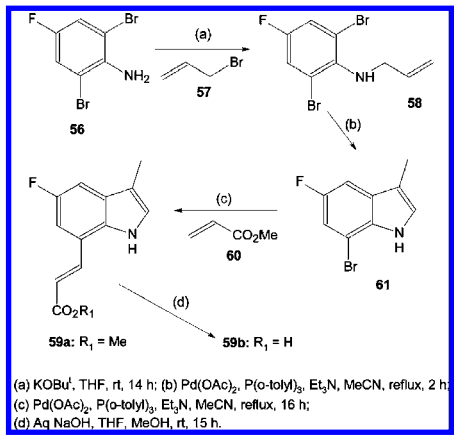
Patent No. U.S. 7,579,483

Assignee: deCODE Genetics ehf, Reykjavik, Iceland

Title or Subject: Process for Preparing 7-(Acryloyl)indoles

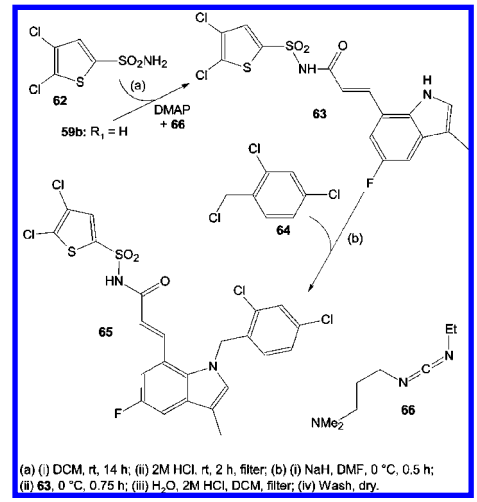
The title compounds have been reported as being useful in treating atherosclerosis. Compound **67** is specifically mentioned in the patent, and its preparation is the subject of one of the claims. The process is described as consisting of two sequential cross-coupling reactions. The first stage in the process is the preparation of acrylate **59a** as shown in Reaction 17. This begins with the reaction of aniline **56** and **57** in the presence of $KOBu^t$ to produce **58** that is isolated as a yellow oil in 97% yield. In the presence of $PdP(p\text{-tolyl})_3$, **58** rearranges to give the indole **61** that is obtained in 77% after purification by column chromatography. **61** then undergoes a Heck coupling with **60** in the presence of $Pd(OAc)_2$ and $P(o\text{-tolyl})_3$ producing **59a** that can be isolated in 73% yield. It is also possible to convert **58** directly to **59a** without isolation of **61** by reacting **58** with **60** also in the presence of $Pd(OAc)_2$ and $P(o\text{-tolyl})_3$.

Reaction 17



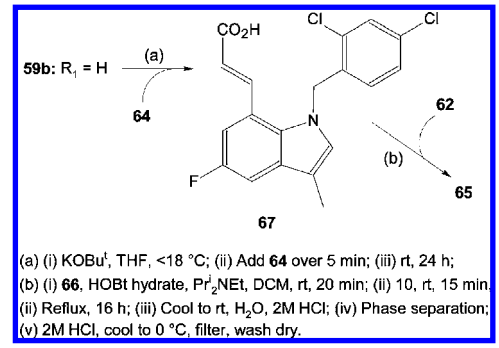
Base hydrolysis of **59a** forms **59b** that is isolated in 91% yield and used in the next stage of the process (Reaction 18). The acid **59b** is reacted with the sulphonamide **62** in DCM in the presence of DMAP and carbodiimide **66** (EDCI). The reaction gives **63** that is recovered in 71% yield and then dissolved in DMF containing NaH. After 30 min **64** is added, and the desired product **65** is obtained as a DMF solvate in 93% yield. Recrystallisation from EtOH affords the pure product, but the final yield is not reported.

Reaction 18



An alternative procedure for the synthesis of **65** is described and summarised in Reaction 19. In this method the acid **59b** is reacted with **64** in the presence of $KOBu^t$ to form **67**. This is recovered in 70% yield and then reacted with **62**. The reaction takes place in refluxing DCM in the presence of EDCI, Pr^i_2NEt and HOBt hydrate. After workup **65** is isolated in 60% yield and then recrystallised from EtOH.

Reaction 19



The method shown in Reaction 18 is carried out at kilo scale, whereas that shown in Reaction 19 is at a much smaller scale. This indicates that one method at least can be scaled-up and perhaps is the preferred route.

Advantages

The process is clearly capable of being carried out at kilo scale and gives good yields of the desired compound.

Patent No. U.S. 7,579,491

Assignee: Council of Scientific and Industrial Research, New Delhi, India

Title or Subject: Process for Preparing Brevifoliol

Brevifoliol **68** is found in the leaves of the plants of the genus *Taxus* and is useful as an anticancer agent. This patent describes a method of extracting **68** from the leaves of the plant *Taxus wallichiana* (*Tw*) Alternative methods are known for extracting **68** from *Tw* but they are said to suffer from several disadvantages. These include partitioning of an aqueous extract with hexane and $CHCl_3$ and the repeated use of chromatography to obtain the purified compound. The partitioning is said to work well on a small scale, but on a large scale thick emulsions are formed. Hence, the objective of the work in this patent is to

provide a process that can be operated on a large scale. The process developed comprises the following steps:

(i) Dry and pulverize the leaves of the plant.

(ii) Extract the dried leaves with an alcohol such as MeOH or EtOH at 20−40 °C over 3 days.

(iii) Concentrate the alcoholic solution and adsorb the extract onto Celite.

(iv) Dry the Celite adsorbate at 20−50 °C for up to 48 h.

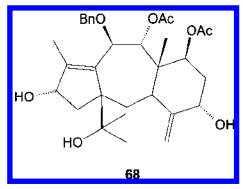
(v) Extract the dried adsorbate with 60−80 petroleum ether then $CHCl_3$ and concentrate the $CHCl_3$ extract.

(vi) Subject the concentrated mixture to gross fractionation over a column of silica gel using $CHCl_3$ add 2% MeOH in $CHCl_3$.

(vii) Subject the later eluate to further chromatography over alumina in petroleum ether using 10% EtOAc in petroleum ether.

(viii) Recrystallise **68** from EtOAc/petroleum ether as needles.

Brevifoliol



Advantages

The patent claims that the solvents can be recycled so that the process is cost-effective. Certainly it is true that avoiding water removes the emulsification problem, but two chromatographic steps are involved, and the use of so many solvents would seem to create handling problems on a commercial plant.

Patent No. U.S. 7,586,014

Assignee: Council of Scientific and Industrial Research, New Delhi, India

Title or Subject: Process for the Liquid-Phase Selective Hydroxylation of Benzene

Phenol is produced commercially by the oxidation of cumene in a process that also produces equimolar amounts of acetone. The production of phenol by the direct and selective conversion of benzene has been a major objective within the chemical industry for many years. There have been many attempts to develop such a process, and this patent claims to achieve this objective using H_2O_2 as the oxidant in the presence of a vanadium catalyst. The reaction is carried out in MeCN at 60 °C using an optimum molar ratio of H_2O_2 to benzene of 3.5:1 and an optimum catalyst/benzene ratio of 1:800. The catalyst is vanadyl pyrophosphate, and this is obtained from $VOHPO_4 \cdot 0.5H_2O$ that is prepared from V_2O_5. The H_2O_2 is added in two equal portions, and the reaction is completed in about 8.5 h. The selectivity to PhOH is 100% at a benzene conversion of 53%, and the yield of PhOH increases as the amount of H_2O_2 is increased. One example demonstrates using the catalyst in consecutive reactions. The conversion dropped from 53 to 43 then to 41% at 100% selectivity. The patent does not describe the recovery of the PhOH from the mixture although distillation would probably be a suitable method.

Advantages

This process is very promising and has excellent selectivity with relatively low catalyst costs. The major cost is likely to be the large amount of H_2O_2 required.

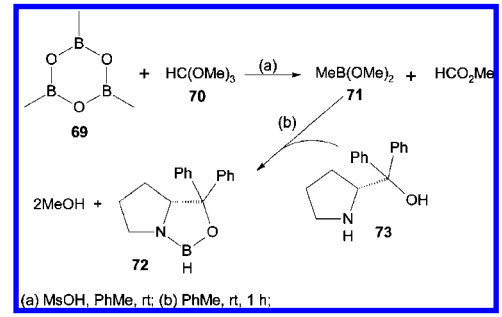
Patent No. U.S. 7,586,015

Assignee: Zach System, Avrille, France

Title or Subject: Process for the Preparation of 1,3,2-Oxazaborolidine Compounds

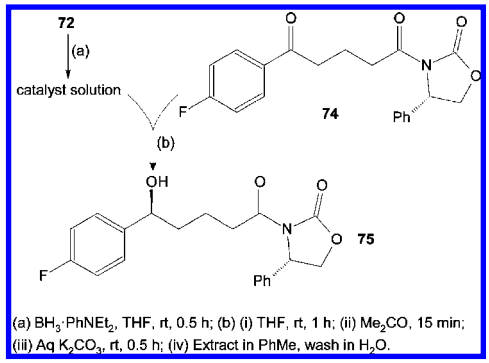
The title compounds are well-known precursors for the synthesis of catalysts used in enantioselective reductions of prochiral ketones. Processes used to prepare such compounds involve reactions that produce water. The water is usually removed by azeotropic distillation, and its removal is necessary to maintain high stereoselectivity of the catalysts obtained from the compounds. The objective of the work described in the patent is to avoid the use of azeotropic distillation to remove water during the preparation of the catalyst precursors. It is also an objective to reduce the amount of boronic acid residues that also affect the stereoselectivity of the catalysts. Reaction 20 shows the method used to prepare **72** in which the first stage is the formation of the boronate ester **71** by reaction of **69** with **70** at rt in PhMe using MsOH. By using an excess of **70** equal to the amount of water present in the reaction mixture, the anhydrous nature of the system is maintained because hydrolysis of **70** gives MeOH. This first stage results in an exotherm, and after the mixture is cooled to rt a solution of **73** in PhMe is added. After 1 h, PhMe is distilled off and replaced by an equal amount of dry PhMe. The patent does not explain why this is done, but MeOH does form an azeotrope with PhMe so it is possible that this distillation is carried out to remove the MeOH formed in both steps of the process. The mixture is then concentrated to obtain a PhMe solution containing about 15−20 w/w% of **72**. An alternative preparation of **72** is carried out by reacting **70** and $MeB(OH)_2$ in place of **69**. The final solution is concentrated to give 45 w/w% of **72** in PhMe.

Reaction 20



A catalyst solution is prepared by adding **72** in PhMe to a THF solution of the $BH_3 \cdot PhNEt_2$ complex. A solution of the ketone **73** in THF is then added to the catalyst, and the reaction produces **74** as shown in Reaction 21. After workup the product is obtained with diastereoisomeric excess of 98.1%.

Reaction 21



Advantages

The process produces high-quality anhydrous catalyst precursor by making use of a simple chemical method of removing water.

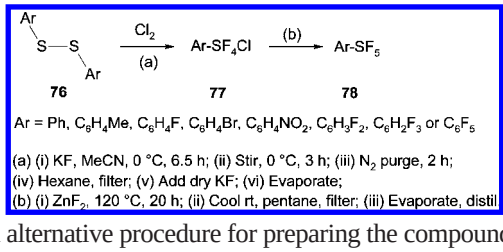
Patent No. U.S. 7,592,491

Assignee: IM&T Research Inc., Denver, Colorado, U.S.A

Title or Subject: Process for Producing Arylsulfur Pentafluorides

This patent covers the production of a wide range of compounds that can be used to introduce SF_5 groups into organic molecules. The resulting molecules are said to be useful in the preparation of liquid crystals and bioactive chemicals such as fungicides, herbicides, and insecticides. The known methods for producing the arylsulfur pentafluorides are claimed to be impractical. For example, they involve expensive reagents such as XeF_2, use materials that are toxic, and in general give low yields of products. Reaction 22 summarises one of the methods used to prepare the pentafluorides **78**. The process is carried out in two stages with the first being the chlorination of the disulfide **76** using Cl_2 gas in the presence of KF to give **76** that in the case of Ar = Ph is obtained as an oil in 88% yield. In the workup of this stage, dry solid KF is added to the filtrate to prevent possible decomposition of the product. Other yields vary from 60% for $C_6H_4NO_2$ to 86% for C_6F_5P. The compound **77** had the *trans*-configuration, and this was confirmed by ^{19}F NMR. In the second stage **77** is heated with ZnF_2, and the desired product **78** is recovered by vacuum distillation. For Ar = Ph the yield is 75%, and yields for other derivatives vary from 36% for $C_6H_4NO_2$ to 79% for C_6H_4Br. An alternative for the second stage is the use of HF in pyridine. For Ar = Ph, the reaction was carried out at rt for 1 h and then for 3 h at 50 °C. ^{19}F NMR showed the product **78** was produced in 93% yield.

Reaction 22



An alternative procedure for preparing the compounds is by using a thiophenol as the starting material in place of a disulfide. The procedure is identical to the first method where chlorination using Cl_2 gives **77** in 83% yield for Ar = Ph. Procedures are also described for the second stage using alternative fluoro salts to ZnF_2. Examples are given for the use of SbF_3, SbF_5, TiF_4, SnF_4, and CuF, but the yields were lower and varied from 33 to 57%. The use of BF_3 with **77** (Ar = Ph) gave a polymeric residue and no detectable **78**, while HBF_4·OEt_2 gave a 40% yield.

The patent contains over 30 examples, and ^{19}F NMR data are provided for all of the compounds prepared.

Advantages

The process avoids the use of expensive or toxic reagents and can be applied to a wide range of substrates.

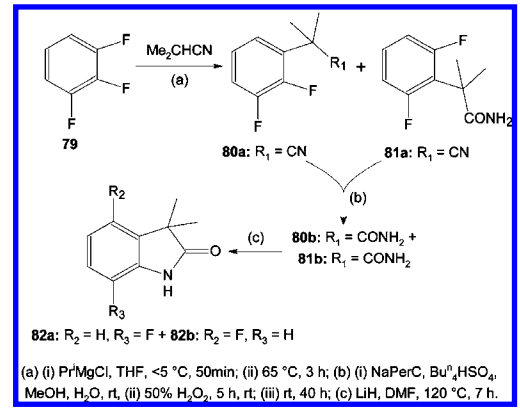
Patent No. U.S. 7,595,338

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

Title or Subject: Process for Preparing 3,3-Disubstituted Oxindoles and Thio-oxindoles

The title compounds are described as being useful precursors to various unspecified pharmaceutical compounds. Compounds containing a 3,3-disubstituted oxindole backbone are said to be especially useful, with **84** being specifically mentioned as well as **82a** and **83** specifically named as desirable intermediates. The patent states that an alternative route to make **84** involves six steps and gives an overall yield of 6%, whereas the current patent discloses a process that is claimed to be simpler and more efficient. The new process involves three basic reactions to prepare a 3,3-oxindole compound **82a** that can then be transformed to **84** and its derivatives. Reaction 23 summarises the route used to prepare **82a**, and Reaction 24 shows the preparation of **84**. The first step in the process is the formation of the nitriles **80a** and **81a** by reaction of **79** with Me_2CHCN in the presence of Pr^iMgCl. These isomers are produced in the ratio of 79:21. After workup, the mixture of isomers is recovered as an oil in 86% yield and then used in the next stage in which the amide mixture is produced by base hydrolysis of the nitriles. One method is by using sodium percarbonate (NaPerC) and H_2O_2. The crude amide isomers are recovered initially as an oil that formed a waxy solid after treatment with hexane (Yield = 100%). An alternative method for the hydrolysis of the nitriles uses NaOH and H_2O_2. The final stage is cyclisation of the amides by heating with LiH in DMF at 120 °C over 7 h, and the product is a mixture of the oxindole **82a** (81%) and **82b** (19%) that is isolated in 76% yield.

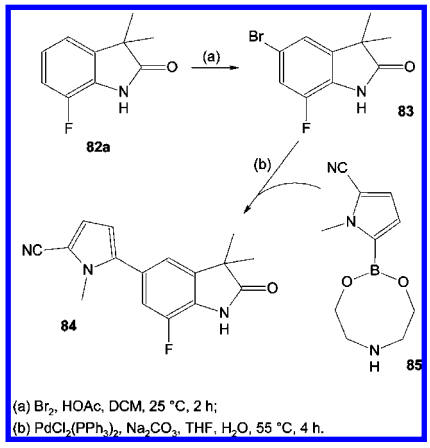
Reaction 23



The patent includes a reaction scheme for the preparation of **84** from **82a**, and this is shown in Reaction 24. The first step is bromination of **82a** to give **83** followed by the coupling reaction of **83** with the cyanopyrrole **85** in the presence of

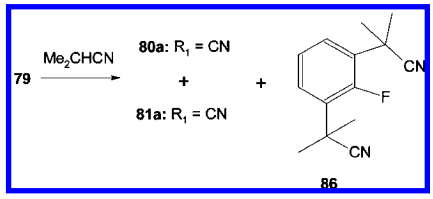
$PdCl_2(PPh_3)_2$. Unfortunately, there are no experimental details for this scheme, and the only information on the method of separating **82a** from **82b** is for analysis by chromatography.

Reaction 24



The formation of **80a** and **81a** is more complicated than that shown in Reaction 23 because a third isomer **86** can also be formed (Reaction 25). A number of experiments describe the investigation of the product distribution using alternative bases or solvents. Examples of bases are LHMDS, KHMDS, LDA, alkyl lithium, and Grignard reagents, and alternative solvents are THF, Et_2O, hexane, and PhMe. It was found that the use of Grignard reagents minimised the quantity of **86** that is formed.

Reaction 25



The patent contains several examples of the reaction of other *sec*-nitriles (R_3CN) with fluoroarenes analogous to the first stage shown in Reaction 23. There are examples of nitriles, where R_3 = cyclohexyl, cyclopropyl, and 2-norbornyl, reacting with a number of fluoroarenes. These are then transformed to the oxindoles via the amides. The patent title indicates that it covers thio-oxindoles, but there are no examples describing the preparation of these. Reference is made in the patent to their formation from the oxindoles by the use of Lawesson's reagent or by using P_2S_5. The patent does contain a substantial amount of information with around 30 examples, and interested readers should consult the patent for full details.

Advantages

The patent gives high yields of the key intermediate **82a** and is applicable to the preparation of several other analogous compounds that can be converted to the desired oxindoles.

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