Organic Process Research & Development **2010,** *14,* 1061–1072

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published During April and May 2010

Summary

The current review covers 20 patents from an original total of 316 that fitted the search criteria. A number of these are quite extensive and contain a considerable amount of chemistry. One patent in particular is remarkable for containing no experimental evidence whatsoever for a proposed multistep process to prepare pyrazoles for treating type-2 diabetes. This situation would not be allowed in a reputable peer-reviewed publication. Two related patents cover the preparation of the penicillin tazobactam. One describes the preparation of a crystalline intermediate, and the other focuses on suppressing the formation of a byproduct. A patent describes a method of preparing an intermediate used in producing the antibacterial agent moxifloxacin. The new method avoids using NaH and DMF in a deprotonation step because of concerns that these reagents can give rise to explosive mixtures by release of H_2 gas. Interestingly, the new process involves a catalytic hydrogenation using H_2 gas. Two very detailed but different patents describe processes for producing CGRP antagonist compounds. One describes the preparation of benzodiazepinones and includes several isolated intermediates, while the second covers caprolactam compounds and has been scaled up to kilo scale. A process for preparing the antihypertensive drug telmisartan avoids the formation of an intermediate that is not readily available and requires the use of protective group chemistry. The new process proceeds via a novel intermediate and does not require protection and deprotection steps. A novel crystalline polymorph of the anthistamine drug fexofenadine is reported as well as an anhydrous form of its HCl salt. The patent also claims to be the first report of a method for separating the para and meta isomers of the drug molecule and the isolation of pure para isomer. Three patents disclose a process for preparing alkylthiopyridines that are used to prepare new insecticides. The three patents focus on preparing one particular compound, but each covers a different synthetic route with a kilo scale example for one route being described. A very comprehensive patent describes about 100 compounds containing a pyrazolyl group that are used to treat a variety of crops against fungi. The reductive alkylation of the C-3 group in indoles is the subject of one patent that uses a Lewis acid and silane reducing agent. The process is applicable to acid-sensitive groups. A fluoropyrazole that is an intermediate for fungicides is prepared by a halogen exchange reaction using phase transfer catalysis. The reaction uses polyglycol ethers as solvents, and without using the phase transfer catalysts no reaction is observed. Rebamipide is used to treat gastric ulcers, and a new process for its preparation is revealed. This avoids the formation of a troublesome intermediate by converting the intermediate's precursor to a compound that is an intermediate to rebamipide. A patent describes the heterogeneous catalytic oxidation of benzylic alcohols to aldehydes using Ru-catalysts with NaOCl. It is claimed that this is a surprising finding because the prior art reports low catalyst turnover numbers for such processes. Campholytic aldehyde is used in fragrance production, and a new process for its preparation starts from cheap, readily available reagents. Two related and comprehensive patents report on the preparation of nitrooxy derivatives of a number of well-known drugs that contain hydroxy or thiol groups. The drugs include paracetamol and losartan plus many others, and although the derivatives probably have bioactivities different from those of the parent compounds, there are no details in the patents. The contrast reagent iopromide exists as a mixture of two isomers, and a method of isomerising the less desirable isomer is described that increases the overall yield of the production process. The use of supercritical fluids has increased in recent years, and a patent describes a process using such materials for the extraction of the carotenoid astaxanthin from a microalgae. This material gives shrimp and salmon their pink colour and is said to be superantioxidant having many health benefits. On the subject of health, it is a major concern to see the continuing use of solvents that have been banned in many companies and countries. Examples are described using chlorinated solvents, and one patent uses benzene as a solvent in a chromatographic purification. 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. 7,692,003

Assignee: Otsuka Chemical Co. Ltd., Osaka-shi, Japan and Taiho Pharmaceutical Co. Ltd., Tokyo, Japan

Title or Subject: Penicillin Crystals and Process for Producing the Same

This patent describes a method of preparing **2a** that is an intermediate used in the preparation of tazobactam, a weak, penicillin antibacterial agent. This patent is related

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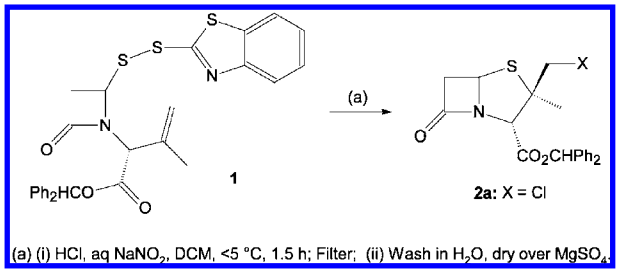
to the following one and one of the assignees is named on both patents. The objective of the work in this patent is to provide a method of producing crystals of **2a** that are stable. Alternative processes for preparing **2a** can give the product as an oil or give crystals that deteriorate in storage at ambient conditions. The solution to the problem is the use of column chromatography (ColC) in the product recovery stages. Reaction 1 shows the synthesis of the crude **2a** that is based on earlier work of the second assignee on this patent disclosed in U.S. 4,496,484. The reaction solution is concentrated under vacuum and then purified by ColC over silica gel using EtOAc/benzene (1:20). The use of benzene here is quite worrying since it has been banned many years ago in most companies. The fractions are collected and concentrated, and then Et_2O is added to give a solution to which *n*-hexane is added and crystals of **2a** are formed. When the earlier process was repeated, without the use of the ColC step, the product was recovered as an oil. The patent contains the XRD pattern of the crystalline product and a comparison of the stability data for the crystals and the oily material.

Reaction 1



Advantages

The process produces a stable crystalline product that can be used to prepare penicillins.

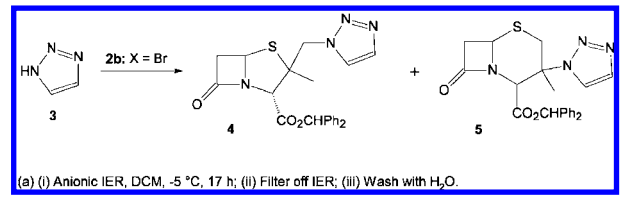
Patent No. U.S. 7,714,125

Assignee: Otsuka Chemical Co. Ltd., Osaka-shi, Japan

Title or Subject: Process for Producing a Penam Compound Useful for Preparing Tazobactam

The second patent on the topic of penicillins is aimed at suppressing the formation of the cepham **5** during the preparation of the compound **4**, an intermediate used in the production of tazobactam. The process described in the patent is shown in Reaction 2 in which **2b** is reacted with **3** in the presence of an ion-exchange resin (IER) as the base in a halogenated solvent. The improvement in the process is to use the Br derivative **2b** in place of the Cl compound **2a**; by making this change the amount of **5** produced is significantly reduced. Using **2b** the ratio of **4** to **5** is 6.34, and when **2a** is used, this falls to 4.55. Examples describe the use of DCM or $CHCl_3$ as solvents, and the **4** /**5** ratio can be improved by carrying out the reaction at lower temperature. The patent examples do not indicate how the desired product is recovered from reaction mixture. Although the two patents are clearly related, there is no mention of the method used to prepare **2b**.

Reaction 2



Advantages

The process gives an improvement in the preparation of an important drug intermediate.

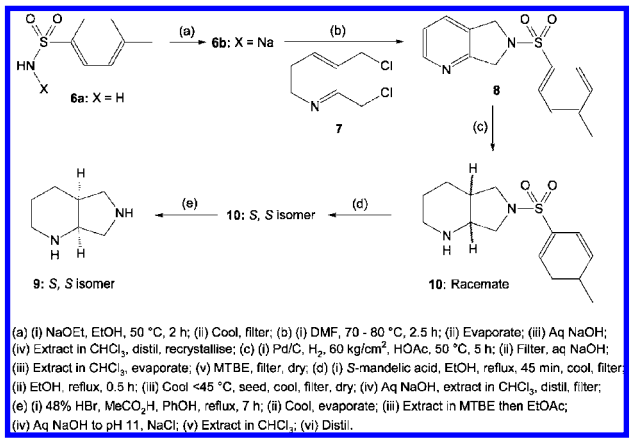
Patent No. U.S. 7,692,015

Inventors: Zheqing Wang (East Haven, Connecticut, U.S.A), Shushan Feng and Yongzhi Cheng (both of Lianyungang City, China)

Title or Subject: Economical Process for Preparing (S,S)-2,8-Diazabicyclo[4.3.0]nonane and Its Enantiomer

The compound of interest in this patent **9,** is an intermediate in the preparation of quinolone and naphthyridine antibacterial agents such as moxifloxacin. Methods of preparing **9** are summarised, and one disadvantage mentioned is that, in a deprotonation step, NaH and DMF are used. These two reagents have been reported to cause explosions, and so the current patent avoids this problem by not using those reagents and uses NaOEt in EtOH. The route disclosed in the patent is shown in Reaction 3, and after recovery of the Na salt **6b** in 90% yield it is reacted with the dichloro compound **7** in DMF to form **8a**. The recovery involves extraction into $CHCl_3$ and then azeotropic distillation to remove H_2O followed by crystallisation from EtOH. This gives the product **8a** in 80.5% yield, and in the next step the pyridine ring is reduced by catalytic hydrogenation with Pd/C to give racemic mixture **10** in 89.2% yield that is resolved using mandelic acid (MA). The patent uses (*S*)-(MA) to form the mandelate salt which, when treated with NaOH, affords the desired (*S*,*S*) isomer of **10** as the free base. It should be noted that the molecule shown in the patent is the (*R*,*R*)-enantiomer, whereas it is the (*S*,*S*)-enantiomer that is used to prepare moxifloxacin; hence, the reaction scheme presented here shows the chemistry to produce the desired molecule. The method described in the patent is capable of producing either enantiomer of **10**, and thus **9** and the product obtained depends on the resolution agent used. The sulphonamide group in **10** is removed using HBr and after several extractions and a distillation the product **9** is recovered in 80.1% yield with purity 99.8% (GC) and ee of 99%. The workup in many of the steps in this route involves extractions with $CHCl_3$ and evaporation to dryness. This solvent is not acceptable in many companies; however, in this process the formation of an azeotrope with water is used as a convenient means of removing water from the mixture.

Reaction 3



Basic ^{1}H NMR data are given for all compounds.

Advantages

The process gives good yields of the product and reduces safety hazards by avoiding the use of NaH and DMF.

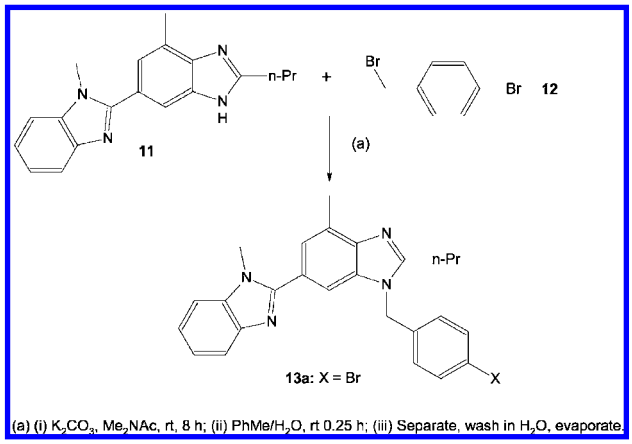
Patent No. U.S. 7,692,027

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

Title or Subject: Process for the Preparation of Telmisartan

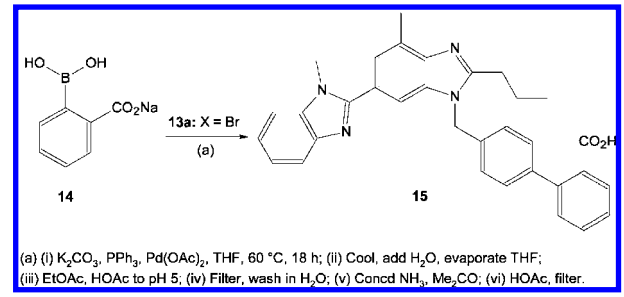
Telmisartan **15** is used to treat hypertension, and one method used in its preparation uses an intermediate that is not readily available, and its preparation requires several steps including protection and deprotection reactions. Hence, the patent aims to provide an alternative route using more readily available reagents in a reduced number of steps. The new method uses the novel intermediate **13a**, and it is synthesised by the alkylation of the benzimidazole **11** with **12** in Me_2NAc in the presence of K_2CO_3 (Reaction 4). The reaction occurs at rt over 8 h, and after workup **13a** is recovered in 69% yield.

Reaction 4



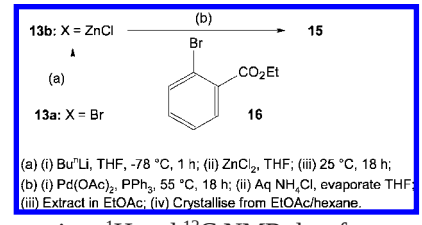
13a is then used to prepare **15** by reaction with the boronic acid salt **14** in the presence of a base plus a Pd catalyst with phosphine ligand (Reaction 5). The crude product is recovered in 46.7% yield and then purified by dissolution in concd NH_3 followed by Me_2CO and then precipitation using HOAc, but the final yield and purity are surprisingly not given.

Reaction 5



The patent also describes the preparation of various derivatives of **15** including the Et ester, Na salt, and HCl salt. The salts are prepared from **15** itself, whereas the Et ester is prepared by the method shown in Reaction 6. The first stage of this is treatment of **13a** with Bu^nLi at −78 °C followed by $ZnCl_2$. This provides **13b** that is treated with the bromoester **16** in the presence of Pd/phosphine catalyst system to form **15**. The reaction is stopped by addition of NH_4Cl solution, and then the product is recovered and crystallised to obtain **15** in 73.3% yield.

Reaction 6



The patent gives ^{1}H and ^{13}C NMR data for compounds **13a** and **15**.

Advantages

The patent claims that the starting materials are readily available and there is no need for protection and deprotection steps that reduce yield.

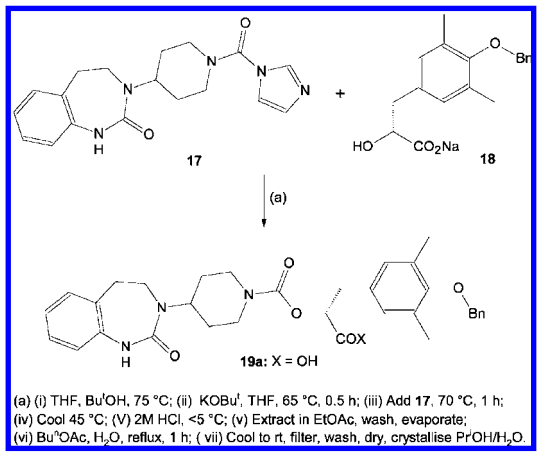
Patent No. U.S. 7,696,346

Assignee: Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany

Title or Subject: Process for the Production of CGRP Antagonist Compounds

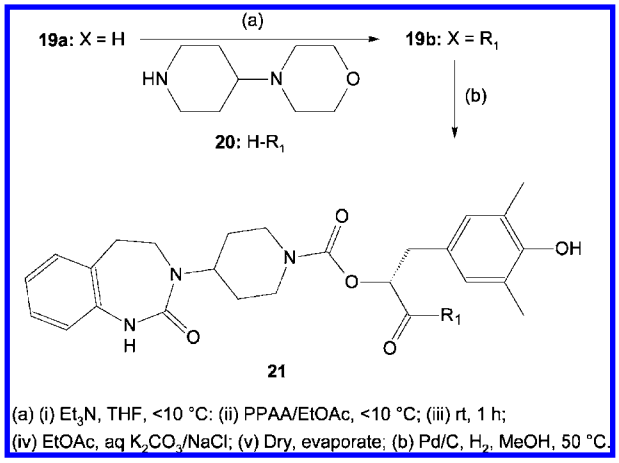
CGRP antagonists are used to treat migraine and cluster headaches, and this is the first of two patents covering the production of such compounds. This patent covers a range of compounds such as the acid **19a** that is an intermediate in the production of the amide **21**. The main claim of the patent covers a process to prepare **19a** by the base-catalysed coupling reaction of **17** and **18** as outlined in Reaction 7. The method involves heating a suspension of the reactants in THF and Bu^tOH to remove about 40% of the solvent before addition of the base, and after a short time more **17** is also added. The reaction proceeds for about 1.5 h before being quenched with cold HCl. After extraction into EtOAc and evaporation, the residue is refluxed in Bu^nOAc containing about 5% H_2O. The crude product is isolated in 87% yield with ee of 80%, and this is increased to 97.3% after crystallisation from Pr^iOH/H_2O.

Reaction 7



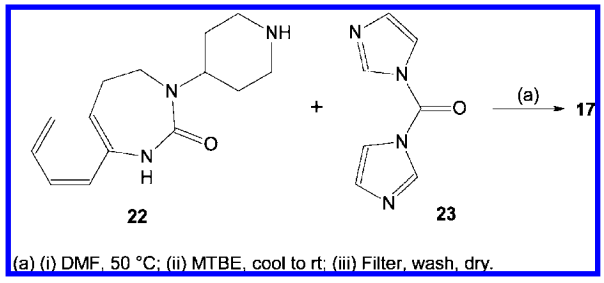
The acid **19a** is used to prepare the amide **21** by the scheme shown in Reaction 8. A mixture of **19a** and **20** in THF at <10 °C is treated with a solution of propane phosphonic acid anhydride (PPAA) in EtOAc. After 1 h at rt, EtOAc is added, and the mixture is washed in K_2CO_3/NaCl solution. After evaporation of the solvents, the amide **19b** is recovered in 94% yield with ee of 99.7% and purity 90.9% (HPLC). The benzyl group is then removed from **19b** by hydrogenation using Pd/C catalyst at 50 °C, and the crude amide **21** is isolated in quantitative yield and 92.4% purity with ee of 98.8%.

Reaction 8



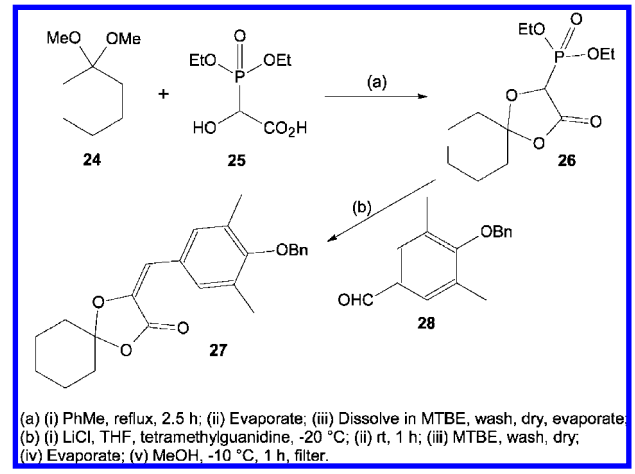
The patent also describes the methods used to prepare the reactants **17** and **18**. The piperidine **17** is obtained by the reaction of 1′1-carbonyldiimidazole (CDI) **23** with the benzodiazepinone **22** in DMF as shown in Reaction 9. The reaction is straightforward and gives a 93% yield of **17** with purity of 98.2%.

Reaction 9



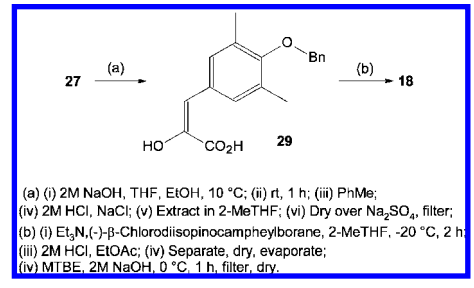
The preparation of **18** is described in more detail than **17** and is summarised in Reactions 10 and 11. The patent contains substantial details and because of space limitations the scheme shows only the main reaction conditions. The preparation begins with the reaction of the hydroxyacetic acid **25** with the acetal **24** in refluxing PhMe to form the phosphonate **26**. The MeOH produced in the reaction is removed as an azeotrope with PhMe, and all the solvent is evaporated after completion. The residue is dissolved in MTBE, and the workup involves washing with K_2CO_3 then $NaHSO_3$, and the crude product is isolated in 86% yield after evaporating the MTBE. In the next step **26** is reacted with the aldehyde **28** in the presence of LiCl and tetramethylguanidine at −20 °C to form the enone **27**. The product is extracted into MTBE and obtained as an oil that is stirred intensively in MeOH at −10 °C to give **27** as a white solid in 86% yield.

Reaction 10



In the next stage, shown in Reaction 11, the enone **27** undergoes base hydrolysis to give the hydroxy acrylic acid **29** that is recovered as a solution in 2-MeTHF. The solution is used directly in the next step that is an asymmetric reduction using (−)-β-chlorodiisopinocampheylborane. The reaction is carried out in the presence of Et_3N at −20 °C, and the Na salt **18** is isolated in 77% yield with quite a poor ee of 78% and 97.5% purity (HPLC).

Reaction 11



Advantages

The process provides very good yields for many of the intermediates, many of which are isolated as crystalline solids.

Patent No. U.S. 7,718,796

Assignee: Merck Sharp & Dohme Corp., Rahway, New Jersey, U.S.A

Title or Subject: Process for the Preparation of Caprolactam CGRP Antagonist

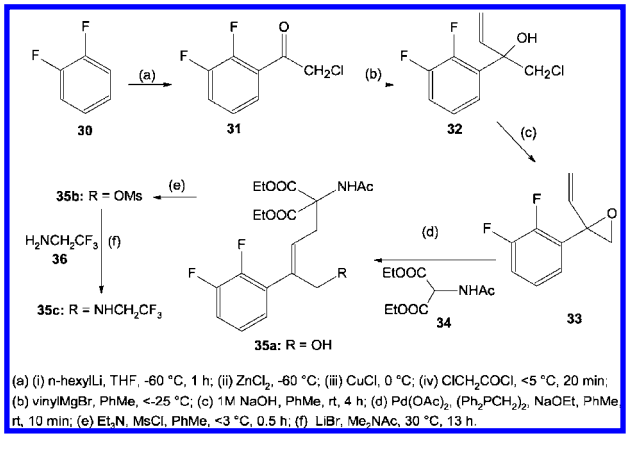
This is the second patent on CGRP antagonists and covers a range of compounds different from those dis-

closed in a previous patent. The claims of this patent cover a process for the preparation of compound *trans*-**41** that is an intermediate in the production of **43**, a known CGRP modulator. The patent summarises laboratory methods for preparing *trans*-**41** and **43** and claims that they are not efficient enough for use on a commercial scale. The patent contains a substantial amount of experimental information, and space limitations mean that this can only be briefly covered. Hence, workup details are omitted, and the interested reader is encouraged to consult the patent. The patent describes the overall reaction scheme to produce **41** as having four distinct phases as follows:

1 selective formation of the *Z*-allylic alcohol **35a** by Pd catalysis
2 use of crystallisation-driven asymmetric transformation to set the amine stereocentre in **39·DTTA**
3 cis-selective hydrogenation to give *cis*-**41·HCl**
4 epimerization to set the benzylic stereocentre and ensure *trans*-geometry.

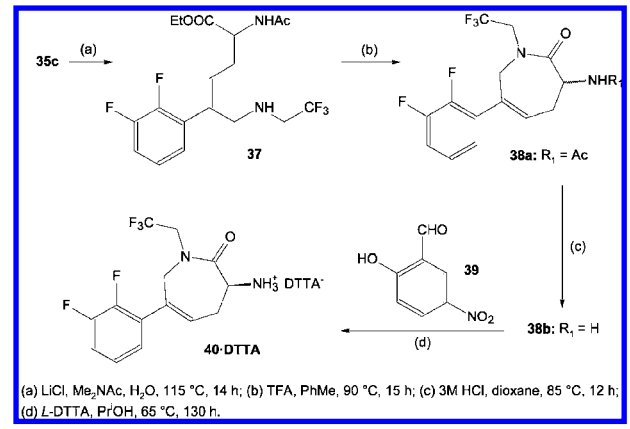
The synthesis of **41** as its HCl salt is outlined in Reactions 12, 13, and 14 and starts from the readily available **30**. The conversion of **30** to **31** takes four steps and initially produces an oil that is solidified by treatment with heptane. **31** is recovered in 71% yield and then converted via **32** to the oxirane **33** that is isolated in 89% yield. In this sequence **32** is also obtained as an oil but is used directly to give **33**. The formation of the key intermediate **35a** takes place by reaction of **33** with the malonate **34** in the presence of a Pd diphosphine catalyst system. The product **35a** is isolated in 70% yield and then converted to the mesylate **35b** that is recovered as a solution in Me_2NAc. This solution is treated with the amine **36** in the presence of LiBr to form **35c** that is also recovered as a solution in Me_2NAc in 92% yield.

Reaction 12



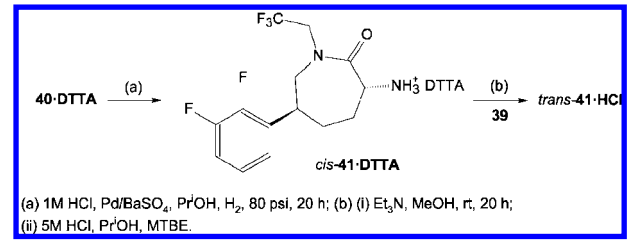
The next stage is outlined in Reaction 13 and begins with the decarboxylation of **35c** using LiCl. This produces **37** that is isolated as a solution in PhMe and treated with TFA to form the caprolactam compound **38a**. No yield is reported for this and in the next step **38a** undergoes acid hydrolysis to give the racemic amine **38b**. This is treated with L-ditoluoyl tartaric acid (DTTA) in the presence of the benzaldehyde **39** and converted to the salt **40·DTTA** after 130 h at 65 °C.

Reaction 13



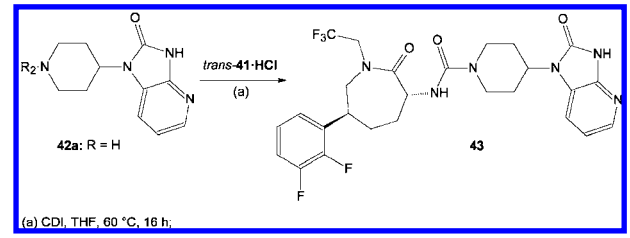
The yield of the tartrate salt is not reported, and the final step in producing **41** begins with the catalytic hydrogenation of **40·DTTA** as shown in Reaction 14. After extraction into MTBE and a solvent switch to MeOH, the mixture is treated with Et_3N and **39** to give a 20:1 ratio of the *trans:cis* DTTA salt of **41**. This is treated with HCl in PriOH and MTBE to form the HCl salt of **41** that is recovered as a MTBE solvate in 85% yield with 99% ee.

Reaction 14



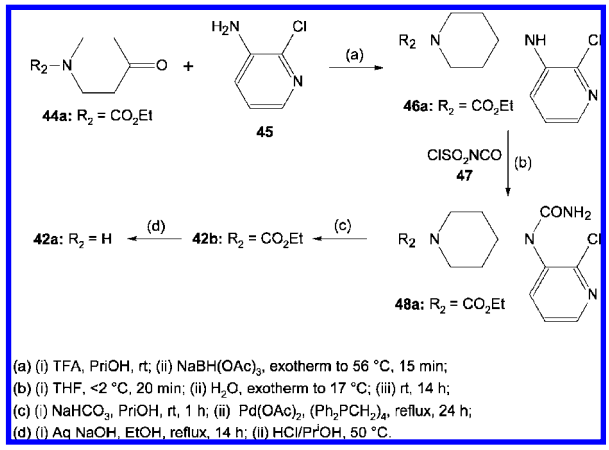
The preparation of the CGRP antagonist **43** is by the reaction of *trans*-**41·HCl** with the HCl salt of **42a** in the presence of CDI and Et_3N as shown in Reaction 15. The final product yield is 95.3% with purity reported as 98 area % by LC. The patent also gives details for the preparation of 8 kilos of the K salt ethanolate of **43** in 84% yield.

Reaction 15



The final aspect of this patent is the preparation **42a** that is shown in Reaction 16. The synthesis starts with the reductive alkylation of amine **45** by **44a** in the presence of TFA and $NaBH(OAc)_3$ to form **46a**. In the next step the urea **48a** is obtained in 96% yield by reaction of **46a** with **47**, and then **48a** is cyclised using a Pd catalyst to give **42b**. Finally the protective ester group is removed from **42b** by heating in NaOH/EtOH, and **42a** is recovered as the HCl salt in 89% yield.

Reaction 16



Advantages

The process seems to be efficient and is clearly amenable to large-scale production since there are a number of the patent examples describing kilo-scale preparations.

Patent No. U.S. 7,696,396

Assignee: Phasex Corporation, Lawrence, Massachusetts, U.S.A

Title or Subject: Method for Extraction and Concentration of Carotenoids Using Supercritical Fluids

The use of supercritical fluids (SCFs) as extraction solvents has been practised for decades, and the use of the technique for the extraction of compounds from natural products has increased significantly over the past 10 years. The use of SCFs, and particularly CO_2, for the extraction of pharmaceuticals, food additives, or dietary ingredients is of increasing interest because such processes do not leave solvent residues in the product. In addition the method uses low temperatures, avoiding the thermal decomposition of extracted materials. This patent focuses on a process to extract the carotenoid astaxanthin from the dried algae biomass of *Haematococcus pluvialis* (HP). This microalgae is part of the diet of fish and crustaceans such as salmon and shrimps and is responsible for the pink coloration of their flesh. Astroxanthin is said to be a superantioxidant that is reported to have many health benefits and hence is sold as a dietary supplement. The patent describes a two-step process using two SCFs for the extraction of astroxanthin from HP. The process can be carried out by first extracting with CO_2 at 60 °C and 2800 psi (193 bar) and then extracting with Me_2O at 40 °C and 1500 psi (103 bar) in the second step. Under these conditions both extracting solvents are liquid, and a 98% yield of the product was achieved. It is also possible to extract first with Me_2O at 45 °C and 1500 psi (103 bar) and then use CO_2 at 40 °C and 2800 psi (193 bar). This method gave a 97% yield of product and has the advantage of removing the organic reagent with the CO_2 and is the method covered in the patent claims. The patent mentions the fact that the Me_2O is a gas and hence is very easily removed after the extraction. The patent includes a process flow diagram and a schematic diagram of an extraction system for the process. Although the use of such high pressures is not the norm in most chemical operations and requires specialised equipment, SCF extraction is certainly a technique that is very suitable for the recovery or extraction of valuable or thermally sensitive materials.

Advantages

The process is very efficient and gives high yields of extracted materials without the use of liquid organic solvents.

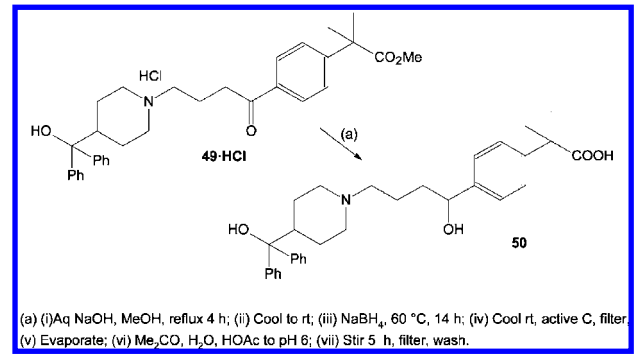
Patent No. U.S. 7,700,779

Assignee: Dr. Reddy's Laboratories, Hyderabad, India, and Bridgewater, New Jersey, U.S.A

Title or Subject: Crystalline Forms of Fexofenadine and Its Hydrochloride

Fexofenadine **50** as the HCl salt is an antihistamine and is used for the treatment of hayfever and similar allergic reactions. It was developed as a successor of and alternative to terfenadine, an antihistamine that was withdrawn from use because of potentially serious contraindications. The patent reports a novel polymorph of **50** that is crystalline and designated Form A and an anhydrous crystalline form of **50·HCl**, designated Form X. It is stated that **50** is actually a mixture of the para isomer (33%) and the meta isomer (67%) when it is obtained by processes described in the prior literature. Previously it has been claimed that these components are inseparable and it has also not been possible to obtain either isomer in the pure form. However, the patent discloses a method of producing the para isomer of **50** with purity of >99.5% containing <0.1% of the meta isomer and also describes the preparation of the novel polymorph of **50·HCl** from **50**. The process in the patent is outlined in Reaction 17 and starts with the preparation of crude **50** from the HCl salt of the ketone **49**. The ketone is actually a mixture of the para and meta isomers, but the actual composition is not given. This mixture is hydrolysed using NaOH/MeOH and then reduced with $NaBH_4$ to obtain crude **50**. The *p/m* ratio is not reported, and the crude solid is refluxed in MeOH for 1 h, then cooled to rt, and filtered to obtain crystals that are recrystallised from MeOH to afford **50** with HPLC purity of 99.85% containing <0.1% meta isomer. The novel Form A is then obtained by suspending pure **50** in refluxing PhMe for 2.5 h. This procedure is described as azeotropic refluxing, and this would imply the removal of H_2O; although if the **50** is pure, then the origin of the H_2O is not clear. The hot solution is cooled, and Form A crystals are obtained. These are then used to obtain crystals of Form X of the HCl salt by suspending them in PhMe and adding a solution of HCl in Pr^iOH to give a pH of 2. After 10.25 h the solid is recovered, washed in PhMe, and dried. This is then refluxed in EtOAc for 1 h and stirred at rt for 1.5 h; the recovered solid is the desired Form X of **50·HCl**.

Reaction 17



XRD, DSC, and IR data are provided for both polymorphs described.

Advantages

The process claims to provide the first example of the pure para isomer and its HCl salt of this well-known drug.

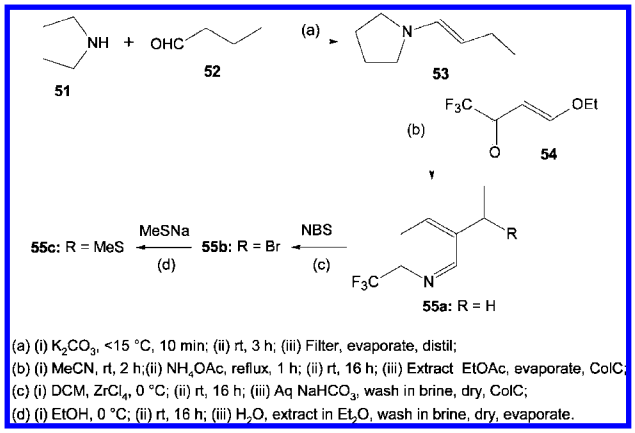
Patent Nos. U.S. 7,705,154, U.S. 7,709,648, and U.S, 7,709.650

Assignee: Dow AgroSciences LLC., Indianapolis, Indiana, U.S.A

Title or Subject: Process for the Preparation of 2-Substituted-5-(1-alkylthio)alkylpyridines

The compounds covered by these patents are used in the preparation of new insecticides that are the subject of other patent applications. Surprisingly, the patents do not describe any background information, nor do they mention alternative methods available for the preparation of these compounds. The three patents all relate to the synthesis of compound **55c** (R = MeS), but they each provide a slightly different synthetic route. In the first patent the route is shown in Reaction 18. This begins with the condensation of **51** and **52** to produce the enamine **53** that is isolated and purified by vacuum distillation, but no yield or purity data are provided. In the next step the enone **54** is condensed with the enamine **53** in a highly polar solvent such as MeCN. The product of this reaction is not isolated, nor is it identified, and the reaction mixture is treated with NH_4OAc as a source of NH_3 to effect a cyclisation reaction giving the pyridine compound **55a**. This product is purified by ColC and isolated as a red liquid in 59.9% yield. Bromination of **55a** is then carried out using NBS in the presence of $ZrCl_4$, and **55b** is isolated in 80% yield by ColC. It is stated that this reaction can also be performed using Bz_2O_2 although there are no details. In the final step, treatment of **55b** with MeSNa produces **55c**, and the crude product is isolated as a yellow liquid in 93% yield.

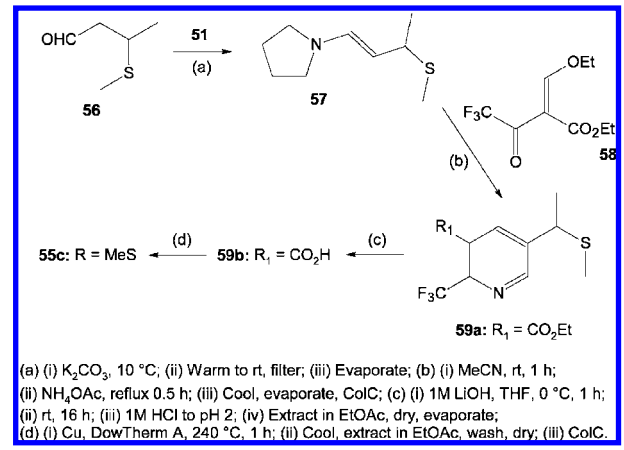
Reaction 18



(a) (i) K_2CO_3, <15 °C, 10 min; (ii) rt, 3 h; (iii) Filter, evaporate, distil;
(b) (i) MeCN, rt, 2 h;(ii) NH_4OAc, reflux, 1 h; (ii) rt, 16 h; (iii) Extract EtOAc, evaporate, ColC;
(c) (i) DCM, $ZrCl_4$, 0 °C; (ii) rt, 16 h; (iii) Aq $NaHCO_3$, wash in brine, dry, ColC;
(d) (i) EtOH, 0 °C; (ii) rt, 16 h; (iii) H_2O, extract in Et_2O, wash in brine, dry, evaporate.

The route described in the second patent is shown in Reaction 19 and involves the base-catalysed condensation of the aldehyde **56** with 100% molar excess of **51** to give **57** as a red liquid. The reaction is carried out on a kilo scale, and crude **57** is isolated in almost 100% yield based on **56**. In the next step **57** is treated with **58** in MeCN at rt followed by NH_4OAc to effect the cyclisation reaction and produce the ester **59a**. Hydrolysis of **59a** with LiOH gives the crude acid **59b** as a tan solid in 91% isolated yield. In the final stage the acid is heated at 240 °C with Cu powder in DowTherm A as solvent, and the product is obtained in 44% yield after purification by ColC.

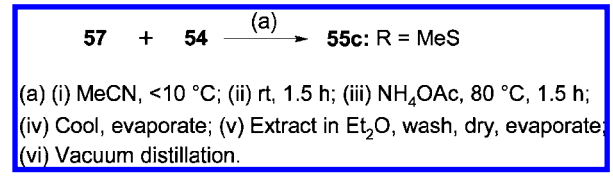
Reaction 19



(a) (i) K_2CO_3, 10 °C; (ii) Warm to rt, filter; (iii) Evaporate; (b) (i) MeCN, rt, 1 h;
(ii) NH_4OAc, reflux 0.5 h; (iii) Cool, evaporate, ColC; (c) (i) 1M LiOH, THF, 0 °C, 1 h;
(ii) rt, 16 h; (iii) 1M HCl to pH 2; (iv) Extract in EtOAc, dry, evaporate;
(d) (i) Cu, DowTherm A, 240 °C, 1 h; (ii) Cool, extract in EtOAc, wash, dry; (iii) ColC.

The route used in the third patent is shown in Reaction 20 and involves the condensation of the enamine **57** with **54** followed by NH_3-catalysed cyclisation to give **55c**. The product is purified by vacuum distillation, and a kilo-scale example is recovered in 59% yield. On a smaller-scale example, the product is purified by flash ColC and the isolated yield is only 44%.

Reaction 20



(a) (i) MeCN, <10 °C; (ii) rt, 1.5 h; (iii) NH_4OAc, 80 °C, 1.5 h;
(iv) Cool, evaporate; (v) Extract in Et_2O, wash, dry, evaporate;
(vi) Vacuum distillation.

Advantages

The patents claim to provide alternative routes to the desired compound, but the overall yield is quite low.

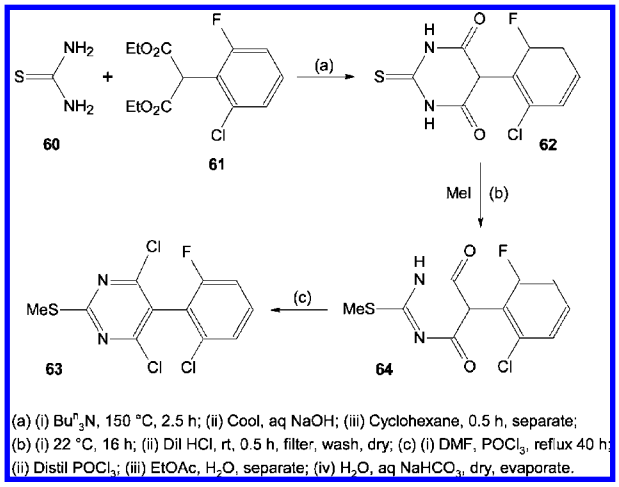
Patent No. U.S. 7,709,637

Assignee: BASF SE, Ludwigshafen, Germany

Title or Subject: The Preparation of 5-Phenylpyrimidines and Their Intermediates, and Their Use in Controlling Harmful Fungi

The patent describes a very large number of compounds that are used to treat a variety of crops against fungi. The fungicides discussed in this patent are compounds such as **67** that contain a pyrazolyl group and are claimed to be more active than other compounds used for the same purpose. The actual claims of the patent cover compounds such as **63**, **65a**, and **65b** that are intermediates used in the preparation of **67**. Reaction 21 outlines the preparation of **63** that begins with the cyclocondensation of thiourea **60** with the malonate **61**. This reaction takes place in Bu^n_3N at 150 °C to form **62** that is not isolated but treated with MeI at about 22 °C to give the thioether **64** that is isolated in 28% yield based on **61**. Chlorination of **64** using $POCl_3$ and a trace of DMF produces **63** that is isolated in 68% yield as an oil and used in the next stage without further purification.

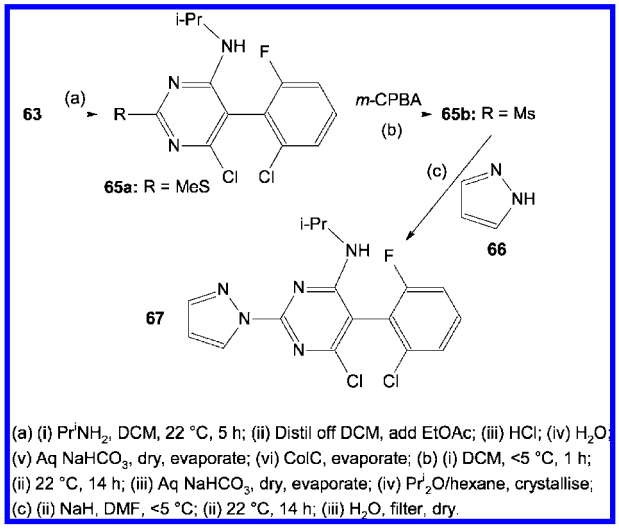
Reaction 21



(a) (i) Bu^n_3N, 150 °C, 2.5 h; (ii) Cool, aq NaOH; (iii) Cyclohexane, 0.5 h, separate; (b) (i) 22 °C, 16 h; (ii) Dil HCl, rt, 0.5 h, filter, wash, dry; (c) (i) DMF, $POCl_3$, reflux 40 h; (ii) Distil $POCl_3$; (iii) EtOAc, H_2O, separate; (iv) H_2O, aq $NaHCO_3$, dry, evaporate.

The crude **63** is treated with Pr^iNH_2 in DCM at about 22 °C for 5 h. After workup and purification by ColC, **65a** is isolated as colourless crystals that are used in the next stage without further purification. The crystals are treated with *m*-CPBA to oxidise the MeS group in **65a** giving the sulphone **65b**. This is isolated in 77.8% yield and then reacted with a solution of **66** in DMF that has been treated with NaH, and the final product **67** is isolated in about 46% yield after precipitation with H_2O.

Reaction 22



(a) (i) Pr^iNH_2, DCM, 22 °C, 5 h; (ii) Distil off DCM, add EtOAc; (iii) HCl; (iv) H_2O; (v) Aq $NaHCO_3$, dry, evaporate; (vi) ColC, evaporate; (b) (i) DCM, <5 °C, 1 h; (ii) 22 °C, 14 h; (iii) Aq $NaHCO_3$, dry, evaporate; (iv) Pr^i_2O/hexane, crystallise; (c) (ii) NaH, DMF, <5 °C; (ii) 22 °C, 14 h; (iii) H_2O, filter, dry.

The patent has a table containing 100 compounds prepared by this process and also includes details of tests on the fungicidal activity of some of them. The safety problems of NaH and DMF that are mentioned in an earlier patent are not discussed here.

Advantages

The process gives a novel range of compounds that have good fungicidal activity.

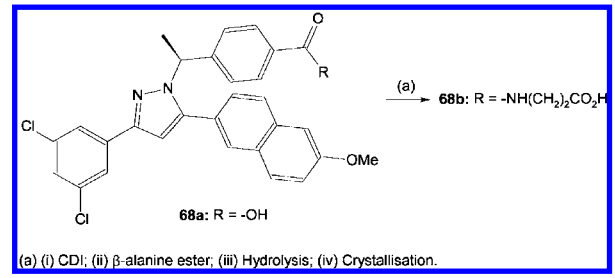
Patent No. U.S. 7,709,658

Assignee: Merck Sharp & Dohme Corp., Rahway, New Jersey, U.S.A

Title or Subject: Process for Synthesising a Substituted Pyrazole

The pyrazole covered in this patent, **68b**, is said to be suitable for treating type-2 diabetes, and the patent proposes a process for its preparation. There is a great deal of chemistry in this patent, and several reaction schemes are shown, but there are no experimental details given for any of them. The patent contains a synthetic methodology with some information about reagents and solvents, but there are no factual examples of any preparative work. How this is deemed to be acceptable in a chemical patent must be debatable. Objectives of the patent are to provide a process that removes protective groups without resorting to harsh conditions and also provide a selective deprotection method. The absence of any experimental details means that it is not possible to assess whether this objective is met. The patent claims cover a process for preparing **68b** shown in Reaction 23 plus processes for the synthesis of **68a** (Reaction 24) and **69** (Reaction 25). The process claimed for preparing **68b** is shown in Reaction 23 and involves the reaction of **68a** with an unspecified *β*-alanine ester in the presence of CDI followed by base hydrolysis and crystallisation from $MeCN/H_2O$.

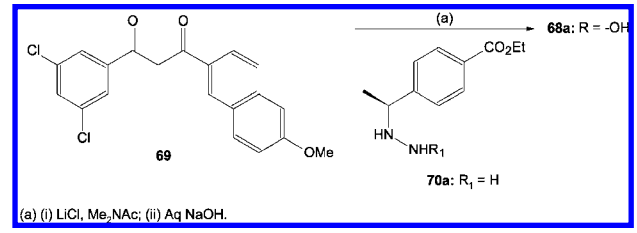
Reaction 23



(a) (i) CDI; (ii) β-alanine ester; (iii) Hydrolysis; (iv) Crystallisation.

The proposed preparation of **68a** is by a cyclisation of the hydrazine **70a** with **69** in the presence of LiCl in Me_2NAc or *N*-methylpyrrolidone (NMP) followed by base hydrolysis (Reaction 24).

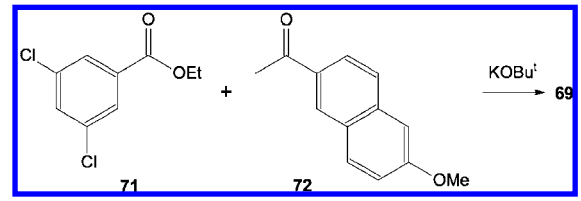
Reaction 24



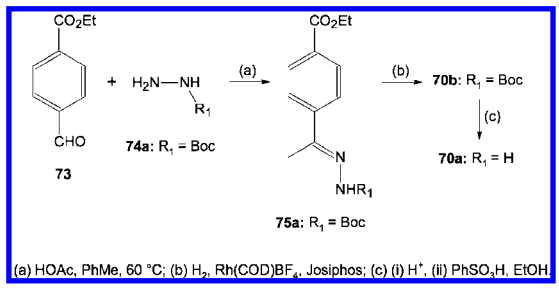
(a) (i) LiCl, Me_2NAc; (ii) Aq NaOH.

The preparation of the diketone **69** is by condensation of **71** and **72** using $KOBu^t$ as shown in Reaction 25, and the scheme for preparing the hydrazine **70a** is shown in Reaction 26. This starts with the condensation of the aldehyde with the protected hydrazine **74a** to form **75a**. Asymmetric hydrogenation, using a Rh catalyst containing a chiral ligand such as Josiphos, then gives the protected hydrazine **70b**. Acidification of **70b** is then used for removing the protection, giving **70a**, and this is said to be enantiomerically enriched to >99% ee using $PhSO_3H$/EtOH.

Reaction 25

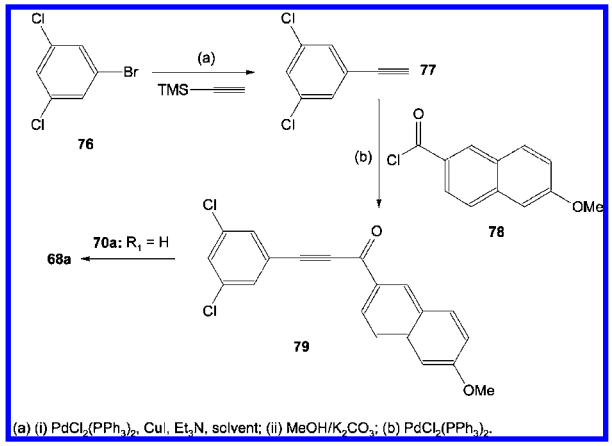


Reaction 26



The patent also suggests an alternative process for the synthesis of **68a**, and the basis of this is shown in Reaction 27. This proceeds by conversion of the Br group in **76** to the acetylene **77** that upon treatment with the naphthoyl chloride **78** gives the acetylenic ketone **79**. Reaction of this ketone with the hydrazine **70a** produces **68a**.

Reaction 27



Advantages

Without any experimental evidence it is not possible to assess if there are any advantages.

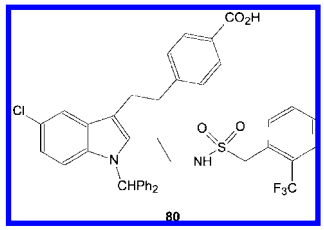
Patent No. U.S. 7,709,661

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

Title or Subject: Synthetic Methodology for the Reductive Alkylation at the C-3 Position of Indoles

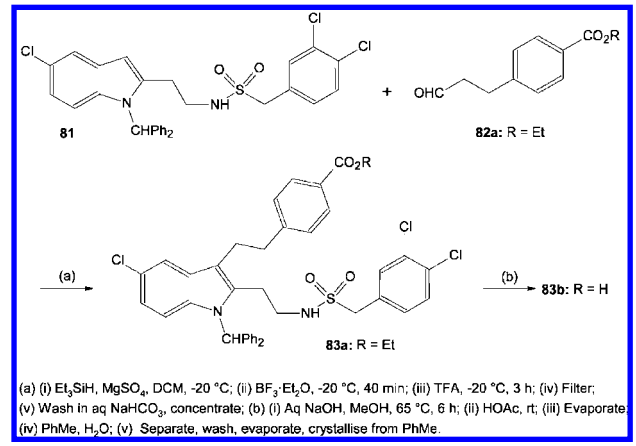
The single claim of this patent covers the indole compound **80** and a method for its preparation by reductive alkylation. The alkylation of indoles at the C-3 position can normally be catalysed by acids or bases although the presence of an acid-sensitive group on the N-atom in this case means certain acid catalysts cannot be used. The desired indoles are said to be useful for treating a range of inflammatory conditions and contain a *N*-benzhydryl group; hence, an acid such as TFA cannot be used to catalyse the alkylation. The patent overcomes this problem by carrying out the alkylation reaction in the presence of a Lewis acid and a silane reducing agent.

Indole



Although the patent claim covers the indole **80**, it actually omits any details of its preparation. Fortunately, details are included for the preparation of an analogous compound **83b**. This is shown in Reaction 28, and the first step is the reductive alkylation of **81** with the aldehyde **82a** to give **83a**. This is carried out at −20 °C by initial addition of Et_3SiH and $MgSO_4$ followed by $BF_3 \cdot Et_2O$ and finally TFA. The ester **83a** is then hydrolysed using NaOH/MeOH, and the acid **83b** is recovered by crystallisation in 52% yield.

Reaction 28



If the alkylation is carried out in the absence of the Lewis acid, the benzhydryl group is removed, and rearrangement may occur. In the absence of the silane a *bis*-alkylated dimer is obtained, and when TFA is absent, the dimeric compound is formed quickly but slowly converts to the desired compound **83a**. Hence, the optimal conditions involve the use of all three reagents. ^{1}H NMR data are given for **83b**.

Advantages

The process allows the alkylation of indoles that contain acid-sensitive groups and hence is applicable to the synthesis of the desired compounds.

Patent No. U.S. 7,714,144

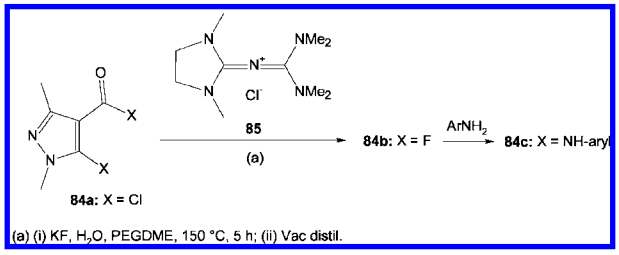
Assignee: Bayer CropScience AG, Monheim, Germany

Title or Subject: Method for the Production of 5-Fluoro-1,3-dialkyl-1H-pyrazol-4-carbonyl Fluorides

The title compounds are starting materials for the synthesis of amides that are used as fungicides. A specific example of the desired compound is **84b** that is used to prepare amides such as **84c** (Ar = aryl). The process for preparing **84b** is shown in Reaction 29 and involves the halogen exchange reaction of the corresponding chloro compound **84a** with KF and a phase transfer catalyst (PTC). The patent claims that an alternative process that is carried out in sulpholane has a low yield and is not suitable for industrial use. The process referred to is covered in a 1997 European patent (EP 0776,889 to Bayer AG). The preparation of **84b** is carried out in a polyethylene glycol dimethylether (PEGDME) as solvent that has been dried by azeotropic distillation to <0.1% H_2O (by Karl Fischer). The solvent has a bp >250 °C so that the product can be recovered directly from the reaction mixture by distillation in up to 83% yield. The reaction mixture also contains a trace of a protic compound, and in the examples water or sulpholane are used

although other compounds are covered in the patent claims. The PTCs used are Ph_4PBr or **85**. The patent reports that, when the reaction is carried out with a PTC, then no success was observed. Using a range of PTCs gave a yield of about 30% but when Ph_4PBr or **85** were used with a catalytic amount of a protic compound, an acceptable process was developed.

Reaction 29



Advantages

The process gives high yield of the product in high purity and is suitable for large-scale production.

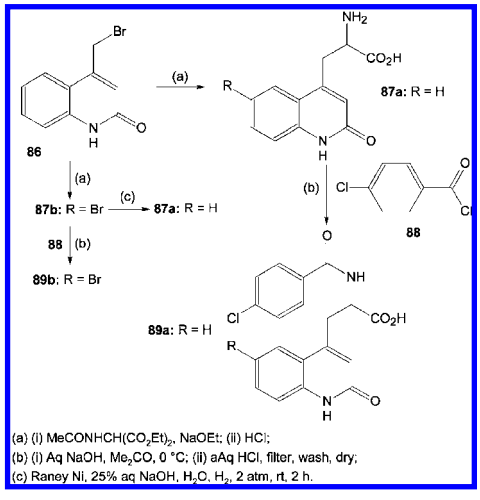
Patent No. U.S. 7,718,805

Assignee: Otsuka Pharmaceutical Co. Ltd., Tokyo, Japan

Title or Subject: Process for Preparing Rebamipide

Rebamipide **89a** is used to treat gastric ulcers, and a process used for its preparation starts from the bromomethyl compound **86** that is initially converted to **87a** (Reaction 30). However, during the preparation of **87a** the bromo derivative **87b** is also formed. **87a** is converted to **89a** by reaction with **88** in basic solution, and at the same time **89b** is formed from **87b**. It is difficult to remove **89b** from **89a**, and so the objective of this patent is to develop a method of reducing the amount of **87b** to avoid the formation of **89b**. This has been achieved by hydrogenating the mixture containing **87a** and **87b** and then reacting this with **88** to give **89a**. The hydrogenation is carried out at about 2 atm H_2 pressure using Raney Ni catalyst in basic aqueous solution at rt. A mixture containing 98.56% **87a** and 1.09% of **87b** was hydrogenated, and after 2 h only 0.01% **87b** remained. After removing the catalyst this mixture was treated with **88** in aq NaOH and Me_2CO and then acidified with HCl to give crystals of **89a**. The isolated yield was 96.2% with a purity of 99.6%.

Reaction 30



Advantages

The process gives improved yield and purity of the desired product without a complex purification procedure.

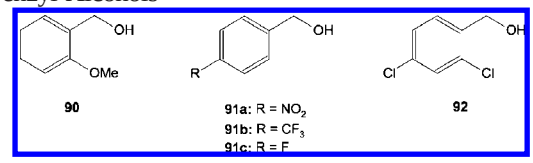
Patent No. U.S. 7,718,827

Assignee: Saltigo GmbH, Lagenfeld, Germany

Title or Subject: Process for the Ru-Catalysed Oxidation of Alcohols by Means of Hypochlorite

The patent describes a process aimed mainly at preparing aromatic aldehydes from benzyl alcohols although the patent claims also cover the oxidation of other alcohols. The oxidation of alcohols to give aldehydes can be carried out by a variety of catalytic or noncatalytic methods. However, it is stated that heterogeneous catalytic oxidations are not often used because they do not have high turnover numbers and are applicable to only a limited number of substrates. The patent reports that the new process does use a supported Ru catalyst, and this is said to be surprising in view of previous reports. The oxidation uses an alkali hypochlorite such as NaOCl and a Ru catalyst that may also contain a second metal selected from Cu, Mo, Mn, Fe, or Co. The reaction is carried out at rt over about 1 h in the presence of H_2O and a solvent that may be 1,2-dichloroethane (DCE) or Bu^tOH. The catalysts are generally prepared by conventional coprecipitation of solutions of $RuCl_3$ and a metal salt with a suitable supporting material. The patent also contains a procedure for preparing some catalysts that involve the use of a microwave plasma, but the commercial viability of this method is not known. Some of the alcohols for which the patent has examples are shown in the graphic, and the % conversion, % selectivity to the aldehyde, and % selectivity to acid are **90** (62, 98, 2), **91a** (100, 99, 1), **91b** (55, 91, 9), **91c** (67, 99, 1), **92** (62, 80, 20). Several experiments were carried out using BnOH as substrate with a range of catalysts, and the results varied from 42% conversion and 90% aldehyde to 100% conversion with 86% aldehyde selectivity. After the reaction is complete, the catalyst can be removed, and the product is extracted using DCE.

Benzyl Alcohols



Advantages

The process can give high yields of aldehyde using very mild conditions.

Patent No. U.S. 7,718,828

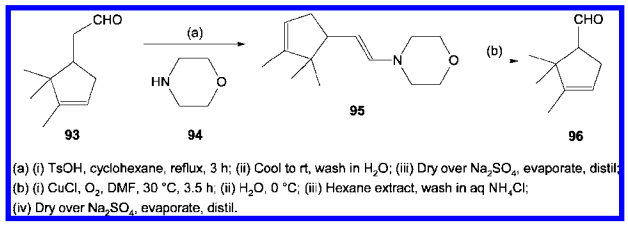
Assignee: Givaudan SA, Vernier, Switzerland

Title or Subject: Process for Producing 2,2,3-Trimethylcyclopent-3-enecarbaldehyde

The title compound is also known as campholytic aldehyde **96** and is said to be useful for preparing a new class of unspecified fragrance materials. The process to produce **96** is shown in Reaction 31 and proceeds via the formation of the enamine **95** by reacting **94** with the relatively cheap substrate campholenic aldehyde **93**. The reaction is catalysed by TsOH

in refluxing cyclohexane, and the water is removed over 3 h. The product is recovered in 93% yield as an oil by vacuum distillation. The enamine **95** is then dissolved in a protic solvent such as MeCN, DMF, or NMP and oxidatively degraded using CuCl catalyst while passing neat O_2 gas through the mixture. This produces **96** that is recovered as an oil by distillation in yields up to 81.5%. The patent gives ^1H and ^{13}C NMR data plus basic MS data.

Reaction 31



Advantages

The patent gives high yields of a valuable material from a readily available and cheap substrate.

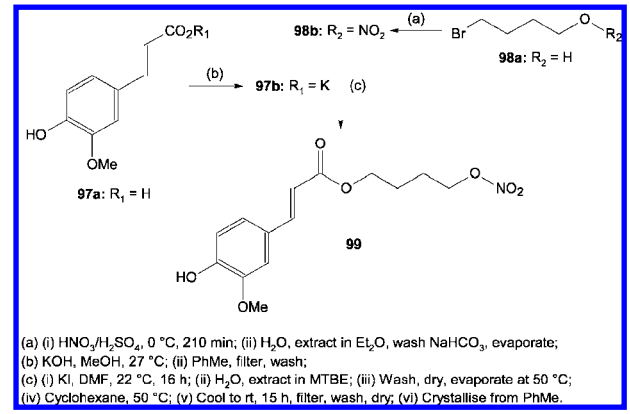
Patent No. U.S. 7,723,382 and U.S. 7,723,529

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

Title or Subject: Process for Preparing Nitrooxy Esters, Thioesters, and Carbonates and Intermediates in Their Preparation

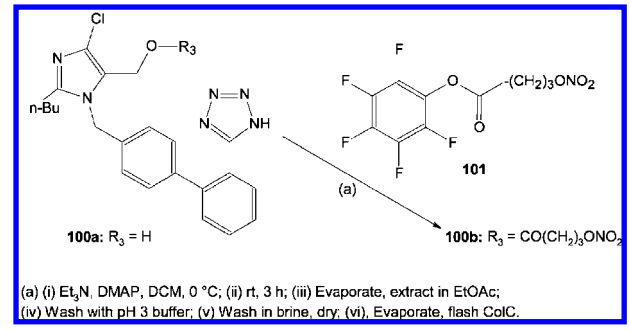
These two patents describe the preparation of nitrooxy derivatives of a number of well-known drugs that contain hydroxy or thiol groups. The list includes relatively simple molecules such as paracetamol and more complex examples such as losartan **100a**. Although the patents claim that a long list of molecules are suitable, there are examples for only a small number. For example, the first patent describes derivatives of ferulic acid **97a**, and the second has derivatives of paracetamol, **100a**, and captopril (**102a**). The bioactivity of the derivatives is not mentioned in the patents although it will presumably be different from that of the parent compounds. The basic reaction used to prepare the derivatives is the condensation of a nitrooxy ester and a thiol or hydroxy compound. The reaction is catalysed by DMAP or DMAP plus a Lewis acid, and the preferred Lewis acid is scandium triflate. Reaction 32 shows the preparation of the nitrooxy derivative **99** that is described in the first patent. The success of this reaction is described as a surprising finding, and it is postulated that the presence of two nucleophilic groups could be expected to form substantial amounts of the nitroxyalkylether. The synthesis is carried out by reacting the K salt **97b** and **98b** in DMF in the presence of KI at 22 °C. The crude product is initially recovered as a brown oil after evaporation of DMF. After heating in cyclohexane, a solid is obtained in 92% purity and 82.7% yield, and crystallisation from PhMe affords **99** as an analytically pure product. The salt **97b** is obtained in quantitative yield from KOH and **97a** in MeOH, and **98b** is obtained in 84.8% yield from the bromo compound **98a**. The preparation of **99** can also be carried out by reaction of **97a** and **98b** in DMF in the presence of Et_3N. However, the reaction is incomplete, and the reaction mixture containing **97a** and **98b** requires separation by flash ColC, providing the ester in 65% yield.

Reaction 32



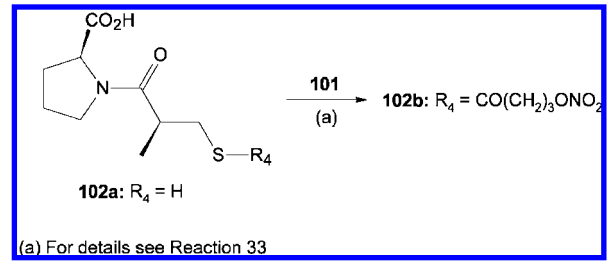
The second patent describes derivatives of **100a** and Reaction 33 shows the preparation of the nitrooxybutyrate **100b** by reaction of **100a** with the ester **101** in DCM containing Et_3N and DMAP. The product is isolated in 66% yield by flash ColC. The reaction may be carried out in DMF, and the final yield is 53%. The patent also describes the preparation of the nitrooxypentanoate ester and the 4-nitrooxymethylbenzoate ester of **100a**. The former is isolated as a pale-yellow oil in 50% yield and the latter is recovered in 88% yield as a white solid. An example is also described in which the condensation of **100a** and pentafluorophenyl 4-nitrooxymethylbenzoate is catalysed by $Sc(OTf)_3$ in conjunction with DMAP in DCM. The yield of the final product is 47%.

Reaction 33



The patent also describes how captopril **102a**, the antihypertensive drug, is converted to the nitrooxyderivative **102b** as shown in Reaction 34. The product is isolated in 20% yield as a white foam.

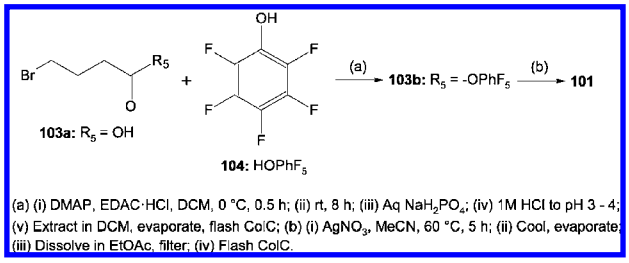
Reaction 34



The preparation of the nitrooxy compound **101** is described in the patent and outlined in Reaction 35. The first stage is formation of the 4-bromobutyrate ester **103b** by treatment of **103a** with the phenol **104** in the presence of DMAP and the HCl salt of the carbodiimide, EDAC. **103b** is recovered as a colourless oil in 86% yield and then converted to **101** by heating

with $AgNO_3$ in the absence of light. After purification by flash ColC, **101** is isolated in 80% yield as a colourless oil.

Reaction 35



(a) (i) DMAP, EDAC·HCl, DCM, 0 °C, 0.5 h; (ii) rt, 8 h; (iii) Aq NaH_2PO_4; (iv) 1M HCl to pH 3 - 4; (v) Extract in DCM, evaporate, flash ColC; (b) (i) $AgNO_3$, MeCN, 60 °C, 5 h; (ii) Cool, evaporate; (iii) Dissolve in EtOAc, filter; (iv) Flash ColC.

The patents contain examples covering the formation of other nitrooxyesters using the similar methods. Basic ^{1}H NMR data for many of the intermediates and final products are provided in the patents. Nitrooxy compounds may be expected to be thermally unstable, but this is not mentioned in the patents.

Advantages

The process provides a method of preparing a large number of derivatives of several known drug molecules that may have improved activity.

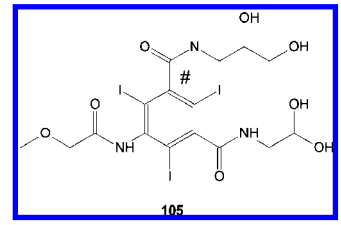
Patent No. U.S. 7,723,544

Assignee: Bayer Schering Pharma AG, Berlin, Germany

Title or Subject: Process for Recovery of Iopromide, Suitable for Pharmaceutical Purposes, from Mother Liquors

Iopromide **105** is an X-ray contrast medium that exists as two thermally stable isomers. The isomerism is caused by restricted rotation about the bond marked # (see structure in the graphic) by the two bulky I atoms, and the phenomena is referred to as atropisomerism. The two isomers have quite different physical properties, especially their solubility, and the specification of the composition of **105** for use as a contrast medium allows 40−51% of isomer 1 and 49−60% of isomer 2. **105** is purified by crystallisation from EtOH, and the mixture that is regularly obtained contains 48% isomer 1 and 52% isomer 2. The mother liquor contains about 60% of isomer 1 and hence crystals recovered from this are not acceptable so there is an overall yield loss. Hence, the objective of this patent is to provide a method of recovering crystals with an acceptably low level of isomer 1. The process that is disclosed involves heat treatment of the mother liquors to isomerise a proportion of isomer 1 to isomer 2. This is followed by rapid cooling to rt and crystallisation. The patent describes an example beginning with 12 kg of liquor with a solid content of 6.2% that is evaporated to 892 g and then dissolved in Pr^nOH at 65 °C. From this is recovered crystals of **105** that contain 62.2% of isomer 1. This solid is dissolved in water (280 g of **105** in 520 g water) and passed at 3 mL/min through a 5.5 m long tubular reactor with an internal diameter of 1.7526 mm at 208−209 °C. The solution obtained is purified by passage through a column of IER and then crystallised from EtOH. The crystals contained 49.4% of isomer 1 and hence are within specification. The yield of recovered crystals is reported to be about 80% of the amount of crystals present in the isomerisation feed.

Iopromide



Advantages

The process gives an overall improvement in the yield of the desired isomer.

Keith Turner

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