Organic Process Research & Development **2007,** *11,* 940–950

Highlights from the Patents

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

Summary

The current review covers 22 patents from an initial collection containing 289 patents. As was the case in the last review, the patents have again been selected solely by the reviewer. The patents cover a range of subjects that it is hoped have some interest to readers. A number of patents disclose compounds that have proven or suspected activity in treating tumours. In one the synthesis of the compound rebeccamycin is described that involves the use of a novel catalytic oxidative cyclisation reaction. Pyrrolotriazine compounds have potential in treating tumours, and the patent provides details of some novel intermediates for the synthesis of these compounds. Two patents from the same company describe novel intermediates and a process to use them for the synthesis of tetrahydropteridines. The preparation of some novel nitrosopyrazoles and intermediates in their synthesis is described that provides much higher yields than alternatives. The key intermediate is produced using NOCl that is generated external to the reactor and used as needed. Improvements in the synthesis of compounds by using phase transfer catalysts (PTC) is becoming more common. An improved method of making a chlorocyclopropane is described that simply includes adding a PTC to a previously known reaction mixture. The process is speeded up significantly and can be run without solvents. In another patent a PTC is used to improve the production of cinacalcet, which is used to treat thyroid problems. A second patent covering this drug describes an improved method making the preferred crystalline, active form of the drug. The identification and extraction of drug molecules from natural sources is of great interest. One patent describes a stable derivative of pateamine A that is found in marine sponges. The parent compound is not very stable and cannot be used as a drug, although it does have use as a biochemical probe. The patent goes into great detail about the correlation between biochemical activity and molecular conformations. An extensive number of derivatives are described in the patent. A new method is described for the synthesis of the drug ropinirole, which is used to treat Parkinsonism. Another patent covers aporphine esters that are also used to treat this disease. The process may be hampered by some difficult material handling problems. Surfactants based on sulfones, sulfoxides, and sulfides are used to prepare multifunctional monomers. The synthetic methods have some interesting aspects, although the use of H_2S is not always welcome. One patent whose title refers to chromatographic analysis of the anaesthetic sevofirane is actually more concerned with synthesis that involves HF. The key problem to overcome in the analysis is developing a method that is fast enough to provide information that will allow control of the process, something that is not always considered in developing any process. The compound aminopterin, which has been known for over 60 years, has been the subject of recent reinvestigations into treating childhood leukaemia. A new method that produces higher purity material from folic acid is described. The patent reports that water is the key to the improvement. An improved method to prepare a morpholine derivative, used in pain relief, is described. The reaction rate is increased by using a sulfonic salt rather than a HCl salt of a semicarbazide in a key step. This allows the temperature to be increased and reduces the three days needed to complete the reaction in the original method. The increased incidence of allergies in western populations has seen new drugs to treat the problems. Two patents from the same company describe novel triazoles that are intermediates in making benzazepine antiallergy agents. A new method of preparing eletriptan for treating migraine is disclosed. A novel stable monohydrate form is reported that has benefits in the production of the pharmaceutical formulations. Imipenem is a broad-spectrum antibiotic, and an improved method is described for producing the stable form of this material. There is a new method of preparing the stimulant modafinil, but it unfortunately involves the use of $CHCl_3$ and hence is not particularly environmentally acceptable. Monomenthyl half-esters are used as coolants in flavours, oral care products and cosmetics, and an improvement in their synthesis is reported. Some of the patents describe experiments carried out on pilot plant scale or even larger, and hence the advanced state of development may be indicated. However, there is no legal or commercial significance to the patents selected, and the advantages listed are those claimed in the patent unless this reviewer has personal knowledge of the subject.

Patent No. U.S. 7,226,939

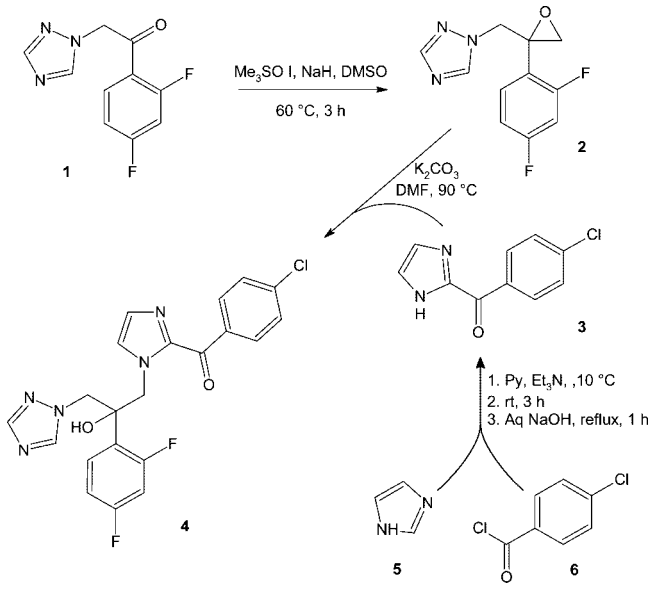
Inventors: M. A. Chandavarkar et al., Mumbai, India

Title or Subject: Thienopyridine Analogues with Antifungal Activity and Process for Their Preparation

This patent is unusual in not being assigned to an organisation even though the addresses of the various inventors indicate they are affiliated to universities or companies. The subject of the patent is a range of novel compounds such as **4** that have broad-spectrum antifungal activity. Scheme 1 shows how **4** is prepared by reaction of the imidazole **4** and the epoxide **2** in the presence of K_2CO_3 in dry DMF. The patent also describes the preparation of **2** in 63% yield by the reaction of **1** with an ylid formed from Me_3SOI, NaH and DMSO. The imidazole **3** is prepared from **5** and **6**, and this is also shown in Scheme 1. A range of compounds similar to **4** is described using imidazoles prepared from alternative aroyl chlorides to **6**.

10.1021/op7002216 CCC: $37.00
Published on Web 10/31/2007

Scheme 1



The patent also describes a range of compounds similar to **4** that are prepared by using benzimidazoles in place of **3**.

Advantages

The patent describes a range of novel compounds that have application as antifungal agents.

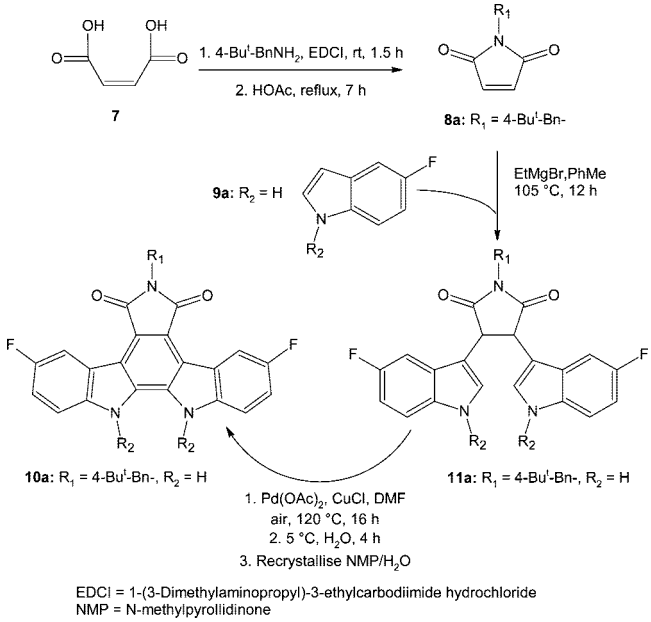
Patent No. U.S. 7,227,019

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

Title or Subject: Process for the Preparation of Rebeccamycin and its Analogues

The title compounds have potent activity in inhibiting tumour growth. The patent covers the method used for making the precursors of these compounds exemplified by **10a**. The process described for making **10a** is an oxidative cyclisation of a compound such as **11a**. Such reactions have been described and use $Pd(OAc)_2$, but they are said to require greater than stoichiometric amounts of the metal salt. The patent describes an improvement in which catalytic quantities of Pd salts are used. This is achieved by using a Pd/Cu system in the presence of air to reoxidise the Pd. The use of a Pd/Cu/air catalytic oxidation system is a well-known technique but has not previously been applied to this process. Scheme 2 outlines the route used to prepare **10a**. The initial step involves the preparation of the maleimide **8a** from **7** and the amine 4-Bu^t-$BnNH_2$ in the presence of EDCI. In the next stage **8a** reacts with **9** in the presence of EtMgBr to give **11a**, which is then converted to **10a** using the Pd/Cu/air system. It is suggested that the mechanism of cyclisation reaction of **11a** proceeds via a stabilised cation and that this is the rate-limiting step.

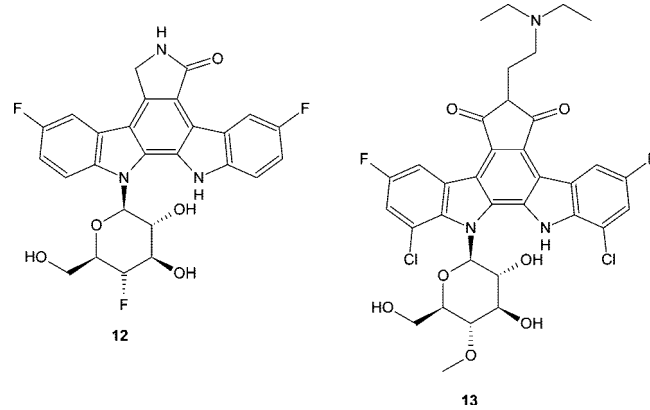
Scheme 2



EDCI = 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
NMP = N-methylpyrollidinone

The patent also states that one of the ketone groups in **10a** may be partially reduced to give an alcohol or completely reduced to the hydrocarbon using $NaBH_4$. The compound **10a** is a precursor to a range of rebeccamycin derivatives that are prepared from **10a** by reaction with glycosyl halides. Examples are covered in the patent claims given in which one R_2 group is H and the other a sugar moiety giving compounds such as **12** and **13** (Scheme 3). Experimental details for preparing **12** and **13** are not given, although general procedures are described.

Scheme 3



Advantages

This patent describes a novel process and intermediates that can be used to prepare tumour growth inhibitors.

Patent No. U.S. 7,227,032

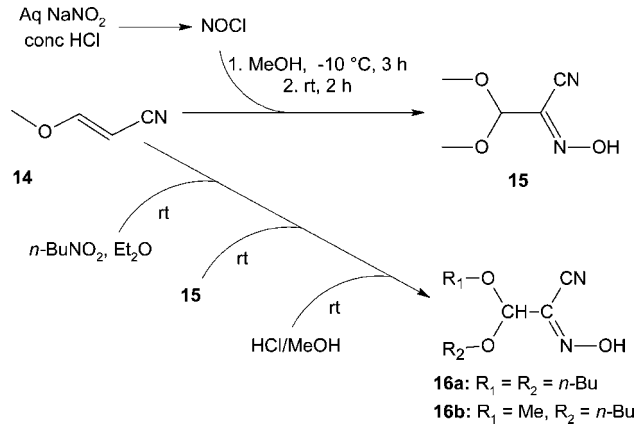
Assignee: Ube Industries Ltd., Ube-shi, Japan

Title or Subject: A Process for Preparing 3,3-Dialkoxy-2-hydroxyiminopropionitriles and 5-Amino-4-nitrosopyrazoles

The patent describes a method for preparing the novel compound **15**, **16a** and **16b** and their use as intermediates for making the pyrazole such as **18a**, a known, useful chemical intermediate. Alternative processes for preparing **18a** are described as using starting materials that are difficult to make and giving low yields. The compound **15** is prepared in 80% yield from **14** by reaction with NOCl, which is produced in a separate vessel. The patent also describes the preparation of a mixture of **16a** and **16b**. The yields are very poor (19% for **16a** and 4% for **16b**). This reaction is carried out by treating **14** with *n*-$BuNO_2$ followed by **15** and finally HCl. It is not

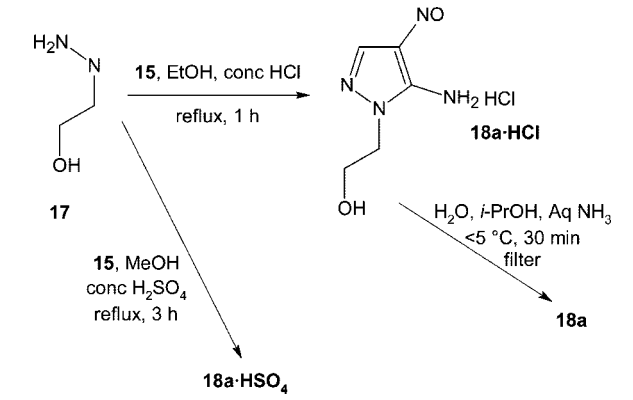
stated whether **16b** can be prepared directly from **14** in the same way as **15** is prepared.

Scheme 4



The patent also describes the conversion of **15** to **18a** and a range of its salts (Scheme 5). The yield of the HCl salt of **18a**

Scheme 5



can be as high as 94%. The patent also describes the preparation of other pyrazole derivatives in which the hydroxyethyl is replaced by benzyl, *p*-tolyl, 4-chlorophenyl or 4-methoxyphenyl. Basic ^{1}H NMR data are given for all of the novel compounds and pyrazoles.

Advantages

A range of novel compounds is produced in good yields that are suitable for making an important intermediate.

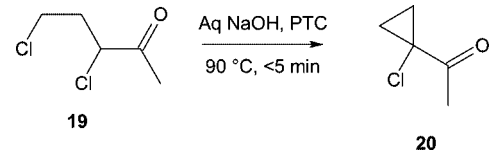
Patent No. U.S. 7,227,042

Assignee: Bayer CropScience, Monheim, Germany and North Carolina, U.S.A

Title or Subject: Method of Preparing 1-Acetyl-1-chlorcyclopropane

The title compound **20** is a useful intermediate, and the patent acknowledges that **20** can be prepared by heating **19** with a base, but this is known to give an unacceptable yield. Hence the objective is to improve this procedure, and this is achieved by carrying out the reaction in the presence of a phase transfer catalyst (PTC). The PTC used is Aliquat 336, the commercial form of Me(*n*-octyl)$_3$NCl. The reaction takes place very rapidly, and times of <5 min are common in the examples. Scheme 6 outlines the process that is carried out in the absence of a solvent

Scheme 6



in a batch or continuous manner. In a continuous process the equipment is described as a steam-distillation unit so that the product is obtained overhead as an azeotrope with water and then recovered by decanting. Yields of up to 86% are obtained.

The patent claims also cover the use of an organic solvent, and this has the effect of increasing the reaction time. However, it also reduces the amount of degradation of the product. The solvent mentioned is 1,2-dichlorbenzene, and it seems that when using this the process is carried out continuously.

Advantages

The process significantly improves the yield on a known procedure.

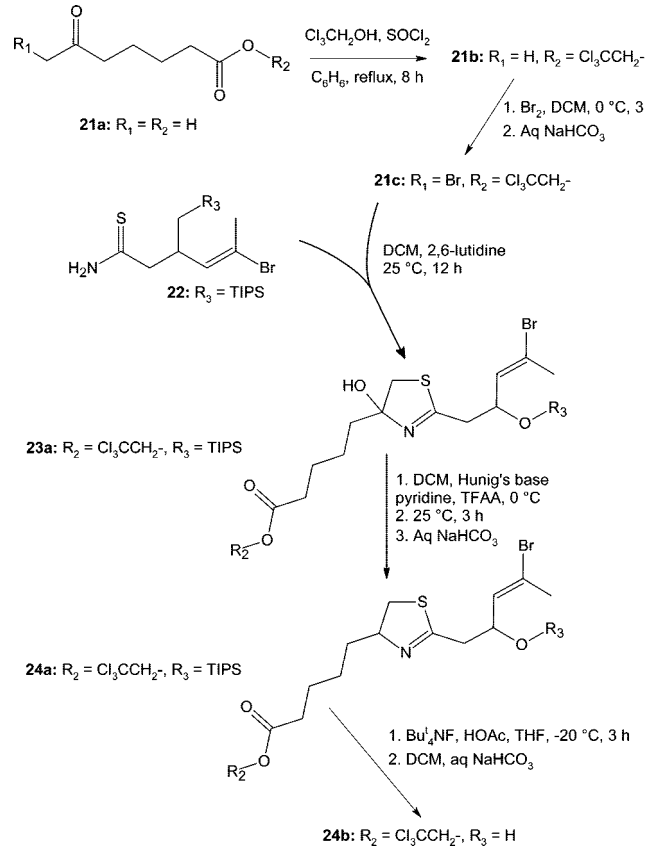
Patent No. U.S. 7,230,021

Assignee: The Texas A&M University System

Title or Subject: Potent, Simplified Derivative of Pateamine A

Pateamine A (**30a**) has been found to have potent immunosuppressive properties with low cytotoxicity and is useful as a biochemical probe. Compound **30a** was first isolated from a marine sponge living off the coast of New Zealand. Unfortunately the compound is not very stable, and hence derivatives

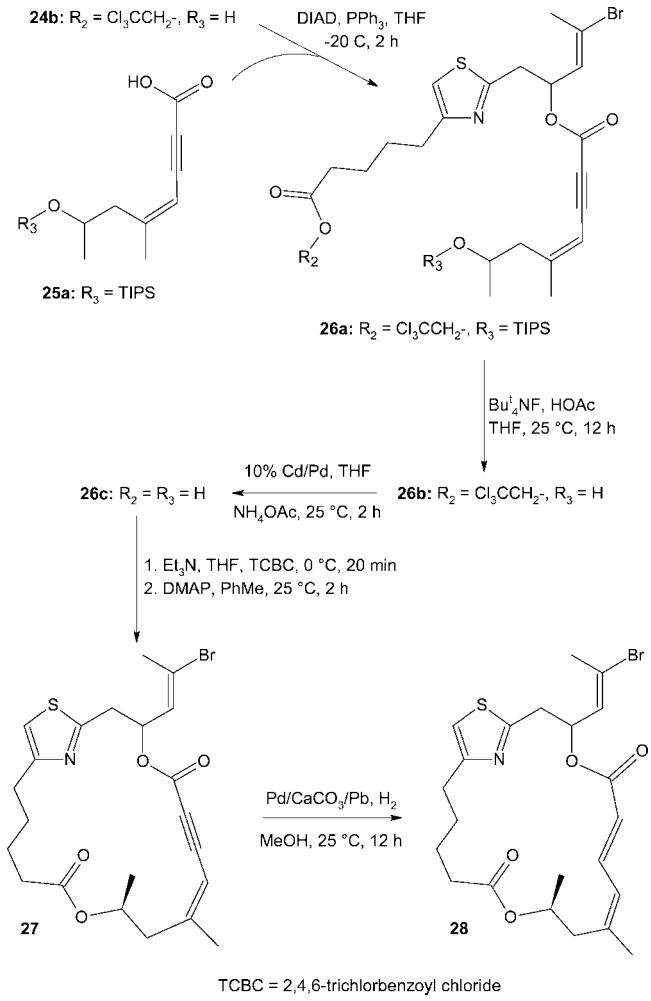
Scheme 7



are sought that may overcome this important shortcoming. The patent has an extensive discussion about **30a** and derivatives such as **30b** and in particular their conformation and molecular structure. The molecules have rigid and flexible portions, and these are studied by molecular modelling methods. These are then correlated with the biological activity. The patent describes the synthesis of several derivatives of **30a**, and an example is **30b**. The first stage of the synthesis of **30b** is the preparation of the thiazole **24a** by the route shown in Scheme 7. The key step in this synthesis is the reaction of bromoester **21c** with the thioamide **22** to form the thiazoline **23a** as a mixture of diastereoisomers. Before the next step it is important to purify **23a** to achieve an optimum yield of 80% of thiazole **24a**. This is then deprotected to give **24b**, which is used in the next stage of the synthesis.

In the next stage of the process, shown in Scheme 8, the

Scheme 8

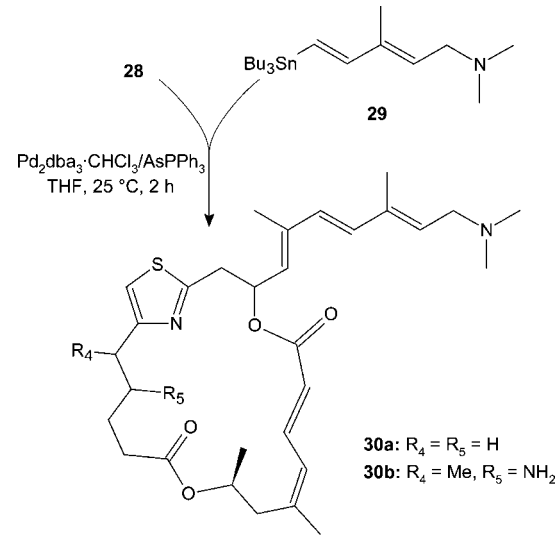


TCBC = 2,4,6-trichlorbenzoyl chloride

eneyne **26a** is prepared from **24b** and **25a** in a Mitsunobu reaction. Before the formation of the macrocyclic ring the ether and ester groups in **26a** are both deprotected to give **26c**. The formation of **27** is via a Yamaguchi macrocyclisation and conversion of **27** to **28** is carried out by a Lindlar reduction using Pb poisoned $Pd/CaCO_3$ catalyst. Compound **28** obtained as the *E/Z* mixture.

The final step is shown in Scheme 9 and involves a Stille coupling reaction between **28** and the stannane **29**.

Scheme 9



This is a very comprehensive patent describing a vast amount of information on these compounds. There is a large amount of ^{1}H and ^{13}C NMR data for the compounds, and some bioactivity details are also provided.

Advantages

Although the synthesis is long and complex, it does provide stable derivatives of a potentially useful range of drug molecules.

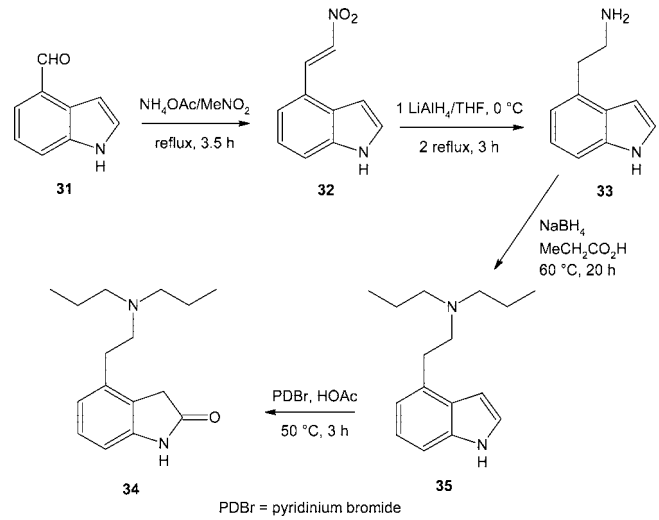
Patent No. U.S. 7,230,118

Assignee: Urquima S.A., Palau Solita I. Plegamans, Spain

Title or Subject: Process for the Preparation of Ropinirole

Ropinirole **34** is used as the HCl salt to treat Parkinson's disease, and this patent describes a new method that is suitable for its preparation on a commercial scale. Alternative methods for the manufacture of **34** are said to require a long synthesis or have other disadvantages for use on an industrial scale. A problem mentioned in one method is the use of MeCOCl and iron chloride, which can cause corrosion and necessitate the use of expensive equipment. The process described in this patent is shown in Scheme 10 and starts by the conversion of the aldehyde **31** to the nitrovinylindole **32** using NH_4OAc in

Scheme 10



PDBr = pyridinium bromide

$MeNO_2$ (yield 82%). The NO_2 group in **32** is then reduced using $LiAlH_4$ to give **33** in 81% yield, and alkylation gives **35**. There are two options described for this reaction. That shown in Scheme 10 gives **35** in a yield of 85%, and an alternative using *n*-PrI and $NaHCO_3$ in PhMe gives a yield of 83%. In the final step **35** is oxidised by PDBr to produce **34** in a 81% yield. The HCl salt of **34** can be produced by oxidation of **35** with *N*-chlorosuccinimide in PhMe and followed by treatment with aqueous NaOH and HCl to give the salt in a yield of 66%.

Advantages

The process is claimed to be simpler than alternatives and suitable for commercial production.

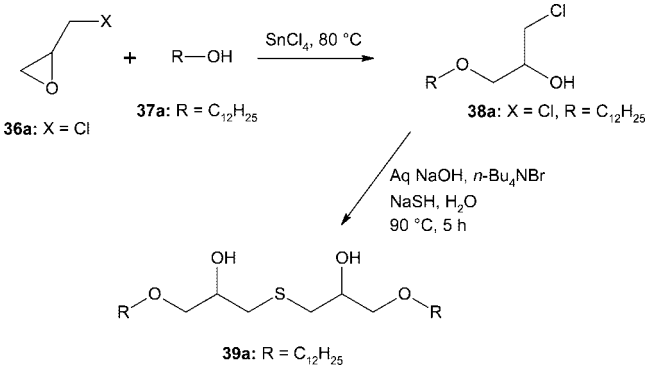
Patent No. U.S. 7,230,138

Assignee: Air Products and Chemicals Inc., Allentown, Pennsylvania, U.S.A

Title or Subject: New Preparative Methods for Bis(3-alkoxypropan-2-ol) Sulfoxides, Sulfides and Sulfones

The title compounds are used as surfactants, and having several OH groups, they are potential precursors to a range of multifunctional monomers and reagents. Two procedures are used to prepare these compounds, and Scheme 11 shows one

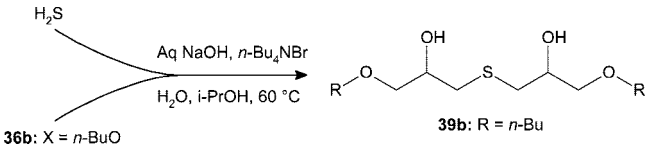
Scheme 11



used to make **38a**. The initial stage is the formation of **36a** with a long chain alcohol **37a** in the presence of $SnCl_4$. This reaction also produces bis, tris and higher alkoxylates, so controlling the ratio of alcohol and **36a** is critical to achieving a high yield of the desired monoalkoxychlorohydrin. The next step is essentially the reaction of H_2S with **38a**, and NaSH is used as the source of H_2S.

The patent describes an alternative method of producing compounds analogous to **39a**, but the only example is **39b**, which is prepared using the lower alcohol *n*-BuOH. Scheme 12 outlines this method that involves using H_2S gas with the

Scheme 12



glycidyl ether **36b**. The reaction is carried out by gradually allowing H_2S into the reactor while simultaneously feeding **36b**. The product **39b** contains approximately 0.8% excess **36b**.

Advantages

This process produces an interesting range of materials, although the use of $SnCl_4$ and H_2S would require very careful consideration regarding its safe containment.

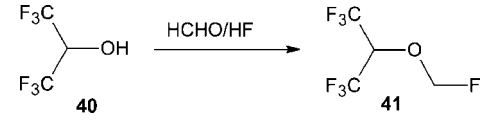
Patent No. U.S. 7,230,143

Assignee: Halocarbon Products Corporation, River Edge, New Jersey, U.S.A

Title or Subject: Chromatographic Method for the Analysis of Sevoflrane in the Process and in the Finished Product

Despite the title, the main claim of this patent covers the production of **41** as well as the analysis of the product within the process and also the finished product itself. The compound of interest **41** is used as an anaesthetic and is also an intermediate in the production of pharmaceutical and agricultural chemicals. The production process involves the use of HF, and hence this has considerable handling problems in the commercial plant that also impact on the analytical method and equipment. The patent discusses alternative production methods and analytical requirements. Scheme 13 outlines the method

Scheme 13



used to prepare **41** from **40** and HF with a source of HCHO. The HCHO can be formaldehyde itself or a precursor such as trioxane or paraformaldehyde. Reaction conditions are not disclosed within the patent. The crude reaction mixture is cooled to give two layers and then distilled to obtain an azeotrope containing **41** and HF. The HF is removed by extraction, and the final purified product is obtained by distillation. The preferred solvent for the extraction seems to be a mixture of tetrachlorobutanes produced by the assignee. The analytical improvement in the patent is the use of GC with a capillary column packed with trifluoropropylmethylpolysiloxane.

Advantages

The patent describes a analytical technique that is sufficiently rapid that it is suitable for control of the production of the product.

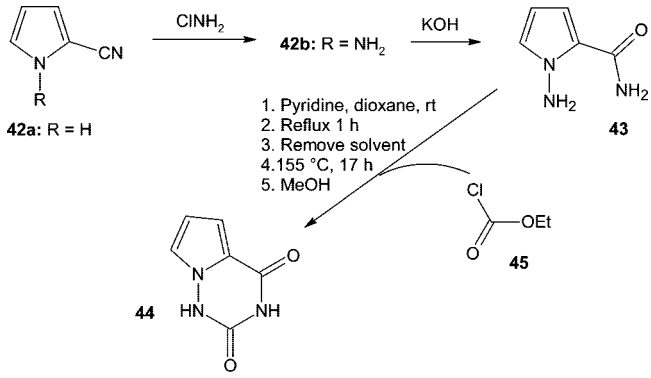
Patent No. U.S. 7,232,901

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

Title or Subject: Production of Novel Intermediates Useful in Preparing Certain Pyrrolotriazine Compounds

The patent main claim describes novel compounds such as **44**, which is an intermediate in preparing **52**, a protein kinase inhibitor (PKI) used to treat hyperproliferative diseases. Examples of such diseases are cancers, autoimmune diseases and Alzheimer's disease. The procedure used to prepare **44** from **42a** is outlined in Scheme 14, although the patent only gives

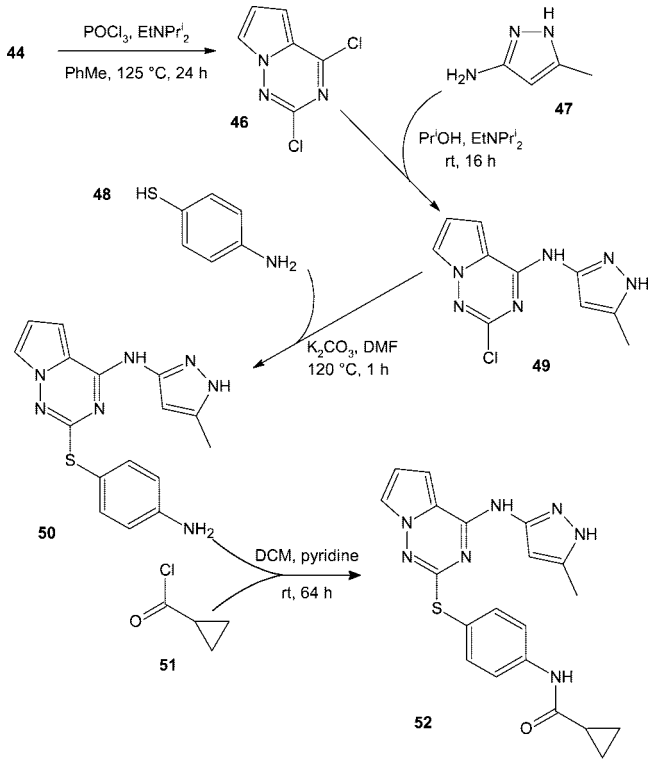
Scheme 14



experimental details for the preparation of **44** by reaction of **43** with **45**. The yield in this step is 63%. The reagents used for the preparation of **42** and **43** are mentioned in the patent, but no details are provided.

In the next stage, shown in Scheme 15, **44** is converted to

Scheme 15



46 in 81% yield by reaction with $POCl_3$ and condensation of **46** with **47** forms **49** in 86% yield. Reaction of **49** with **48** produces **50**, which reacts with **51** to form **52** in 27% yield.

A range of other pyrrolotriazines similar to **52** is also described that are prepared from **44**. Basic ^1H NMR data are given for all of the novel compounds and intermediates.

Advantages

The patent describes a process for preparing a novel intermediate and also shows how it is used to prepare a range of potentially useful drug molecules.

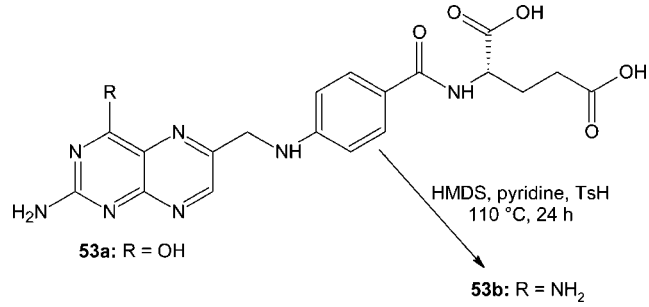
Patent No. U.S. 7,235,660

Assignee: John A. Zebala, Auburn, Washington, U.S.A

Title or Subject: Facile Process for the Preparation of High Purity Aminopterin

Aminopterin **53b** has been known for over 60 years and has been used in the treatment of childhood leukaemia, as a rat poison and to induce abortions. However, the molecule is unstable and difficult to purify. Many problems in its early use stemmed from the toxicity of impurities. Recently there has been renewed interest in the use **53b** for treating leukaemia, and this may be the reason behind the work in this patent. The original preparation of **53b** is by direct amination of folic acid **53a** using a silazane. Yields are said to be low, and the purity of the product is only 33.3% in one method and so would not be suitable for commercial production. The work described in this patent is based on the same method described in the original patent. However, the new process uses the surprising and unexpected finding that the amount water in the process is critical to the purity of the product obtained. The basic method is shown in Scheme 16 in which **53a** is heated with HMDS

Scheme 16



and TsH in pyridine. The example in the patent indicates that 1.08% water is present and then varying amounts of additional water were added. The highest purity product obtained was 96.9% using a mole ratio of water to **53a** of 3.19, and the preferred range in the patent claims is from 2.8 to 3.2.

Advantages

The process is a simple improvement on the original method and gives much higher purity product.

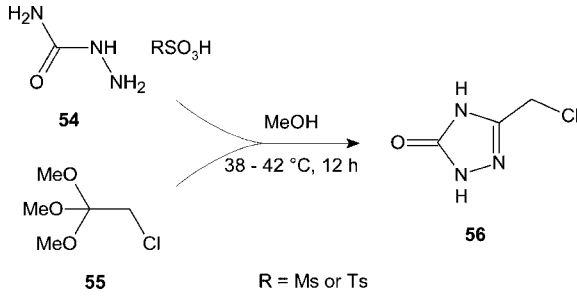
Patent No. U.S. 7,235,671

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

Title or Subject: Process for Preparing 3-Chloromethyl-1,2,4-triazolin-5-one

The title compound **56** is an intermediate in the preparation of a morpholine derivative that is a tachykinin receptor antagonist and used in pain relief. An alternative method for preparing **57** is said to be unsuitable for commercial production since the reaction takes three days at room temperature. The use of higher temperature causes decomposition of the product, and the rate cannot easily be increased. The reaction used is shown in Scheme 17, and the rate problem is overcome by using sulfonic acid salt of the semicarbazide rather than the HCl salt as in the original work. Examples are given using mesyl or tosyl salts. These salts are novel compounds, and their preparation is from the HCl salt by the addition of NH_3 to precipitate NH_4Cl followed by addition of the appropriate RSO_3H. Unfortunately there are no yield data given in the patent for this procedure or for the main process.

Scheme 17



Advantages

The process is claimed to be a better process for commercial operation than alternatives.

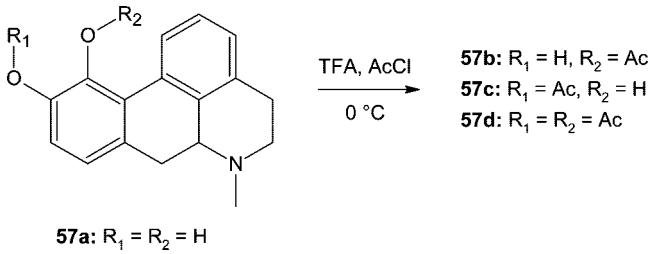
Patent No. U.S. 7,238,705

Assignee: Axon Biochemicals B.V., Groningen, The Netherlands

Title or Subject: Aporphine Esters and Their Use in Therapy

The compounds of interest in this patent are useful in the treatment of Parkinson's disease. Such compounds are known to be effective against this disease, but they have limited bioavailability. Scheme 18 shows the basic reaction that initially

Scheme 18



gives the mono derivatives **57b** and **57c**, and these are further reacted to give the diacetyl **57d**. The patent does not state the proportions of **57b** and **57c** that are obtained nor which is preferred. However, the yields reported are extremely low (5–21%). A range of derivatives is prepared containing alternative alkanoyl groups with butyroyl said to be the best. Separation of the product mixture is by column chromatography using solvents containing DCM. The patent states that **57a** is very sensitive to oxidation by air and handling without antioxidants is virtually impossible. If this is indeed the case, the process would seem to be unsuitable for preparing a drug molecule on a large scale.

Advantages

The patent describes novel compounds, but the commercially viability may be hampered because of material handling problems.

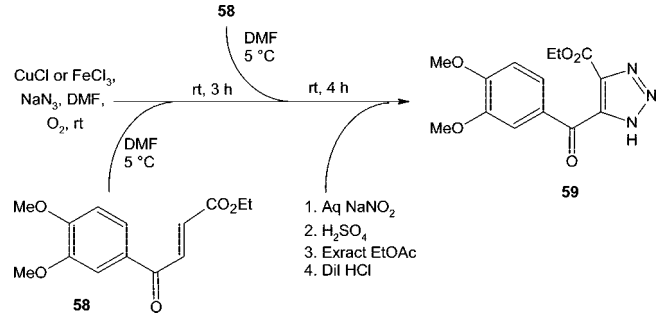
Patent No. U.S. 7,238,719

Assignee: Meiji Seika Kaisha Ltd., Tokyo-to, Japan

Title or Subject: Process for Producing 1,2,3-Triazole Compounds

This patent discloses a process for producing triazoles such as **59**, whereas the next patent claims cover the compounds themselves and is often described as a composition of matter patent. Hence there is much overlap in the content of the two patents. Compound **59** and its analogues are used as intermediates in preparing tricyclic triazolobenzazepines. These compounds are antiallergic agents, and a related patent covering the synthesis of such compounds is reviewed next. Alternative methods for the preparation of the triazoles are said to involve reacting acetylenes or olefinic compounds with an azide in a cycloaddition reaction. It is stated that using olefins without a leaving group gives poor yields; hence the objective is to prepare triazoles from olefins that do not contain leaving groups. The method described involves the use of a catalytic system comprising a metal salt and oxygen in the presence of an oxidising agent such as $NaClO_3$. Scheme 19 shows the method

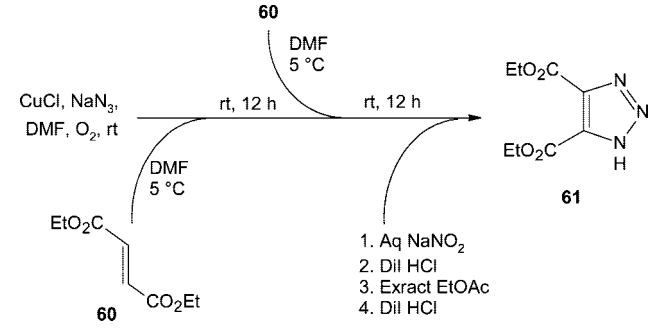
Scheme 19



used to prepare **59** from **58** using metal salts CuCl or $FeCl_3$. The reaction is carried out in two stages with half of **58** added at the start and the remainder later. The examples in the patent show that $FeCl_3$ without $NaClO_3$ gives the highest yield of **59** of 88%, with only 82.5% using $NaClO_3$. CuCl alone gives an 81% yield of **59**, and there are no examples of using $NaClO_3$ with CuCl.

The patent also describes the preparation of **61** from **60** in 96% yield using the same procedure, and this is shown in Scheme 20.

Scheme 20



Advantages

The process is fairly straightforward and gives high yields of the triazoles.

Patent No. U.S. 7,238,812

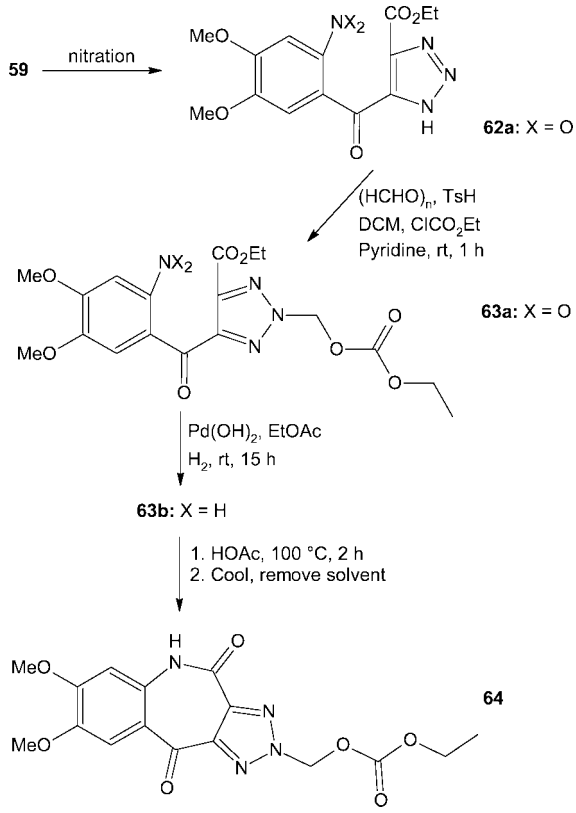
Assignee: Meiji Seika Kaisha Ltd., Tokyo-to, Japan

Title or Subject: Process for Producing Tricyclic Triazobenzazepine Derivatives and Their Use as Anti-Allergic Agents

The single claim of this patent covers compound **59** and its analogues, although the title relates to its use in preparing a

series of molecules that are antiallergic agents. A substantial amount of work is described in the patent, and space only allows a brief summary of this work. For full details it is suggested that the patent is read carefully. The patent describes the conversion of **59** to one of the antiallergic agents **64** as shown in Scheme 21. This is one of three methods used to prepare **64**

Scheme 21



and involves a catalytic reduction and cyclisation step very similar to that described in the next patent. Nitration of **59** gives **62a**, and then this is converted to **63a** using paraformaldehyde and $ClCO_2Et$. Reduction of the NO_2 group in **63a** produces **63b**, and this is cyclised by heating in HOAc to form **64**. A large number of analogues of **64** is described, and extensive experimental details are provided. As is often the case in patents, the examples are not laid out in a logical manner, and it is hoped that those skilled in the art are able to follow the stages of the process.

Advantages

The patent provides a route to some useful drugs and describes a range of novel compounds used in the synthesis.

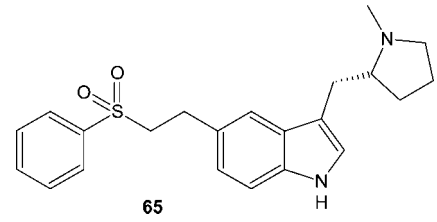
Patent No. U.S. 7,238,723

Assignee: Pfizer Inc., New York, New York, U.S.A

Title or Subject: Indole Derivatives

This patent is specifically aimed at the preparation of the drug eletriptan (**65**), which is used to treat migraine. There have been two forms of **65** known, and the α form is the stable form used as the anhydrous HBr salt. This patent describes a novel monohydrate form that may be formed by crystallisation of the anhydrous form from water or an organic solvent containing water. Suitable solvents are THF, Me_2CO. The procedure is to dissolve **65** in the solvent followed by addition of aqueous HBr, and cooling provides the crystalline hydrate. If the anhydrous HBr salt it needed, it can be produced by heating a slurry of the hydrate salt in PhMe and removing the water by azeotropic distillation. X-ray diffraction and DSC data are provided for the new form of the drug. Kilo scale experiments are described indicating the advanced nature of the process development.

Eletriptan



65

Advantages

The new form of this drug is stable and nonhygroscopic; hence it may be useful in pharmaceutical formulations.

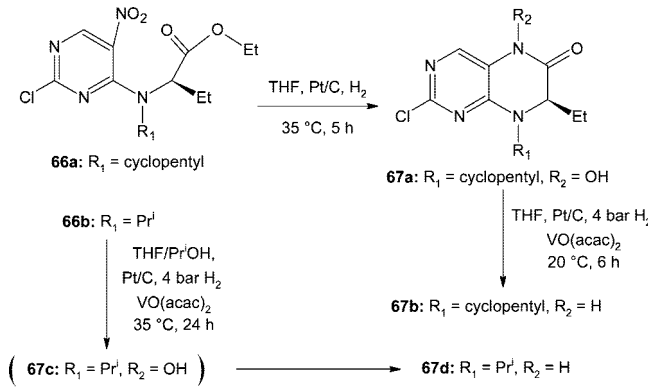
Patent No. U.S. 7,238,807

Assignee: Boehringer Ingelheim International GmbH, Ingelheim, Germany

Title or Subject: Process for the Manufacture of Fused Piperazine-2-one Derivatives

The compounds of interest in this patent, **67b** and **67d**, are intermediates in the production of tetrahydropteridine compounds that have antiproliferative activity. These compounds are used in treating tumours and are covered in another patent that is reviewed below. Alternative methods for producing compounds analogous to **67b** and **67d** are said to require hydrogenation of nitro groups, and it is stated that this results in strongly coloured products that are difficult to purify. This patent solves the colour problem by using an alternative strategy shown in Scheme 22. In the preparation of **67b** from **66a** the

Scheme 22



reaction is carried out in two hydrogenation steps, and in the first **67a** is formed. This is isolated and then converted to **67b** in another reduction in which $VO(acac)_2$ is used. The cyclisation step is the same type used an earlier patent in that it involves reduction of a NO_2 to an amine that cyclises by condensation with an ester group. For the production of **67d** the conversion of **66a** takes place in one step using Pt/C and $V(OAc)_2$. The patent does not describe if **67c** has been isolated, nor does it

state that **67d** can be made in one step. However, these possibilities are covered in the patent and also mentioned in the claims.

The patent does not describe how to prepare the starting materials **66a** and **66b** and refers to known literature and patents that cover their preparation.

Advantages

The process gives high purity products and avoids the formation of coloured byproduct by using an alternative synthetic route.

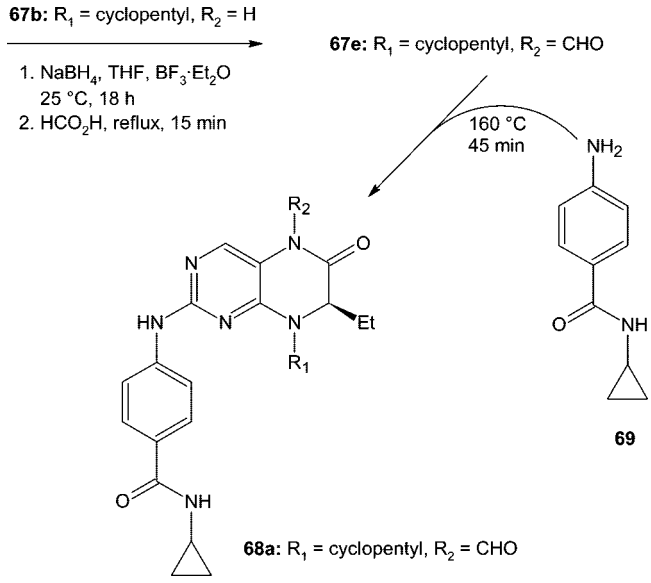
Patent No. U.S. 7,241,889

Assignee: Boehringer Ingelheim International GmbH, Ingelheim, Germany

Title or Subject: Process for the Manufacture and use of 6-Formyl-tetrahydropteridines

This is another composition of matter patent covering the actual compounds formed in the process of the previous patent. The patent extends the range of compounds described in the previous patent, and **68a** is a typical example. Scheme 23 shows

Scheme 23



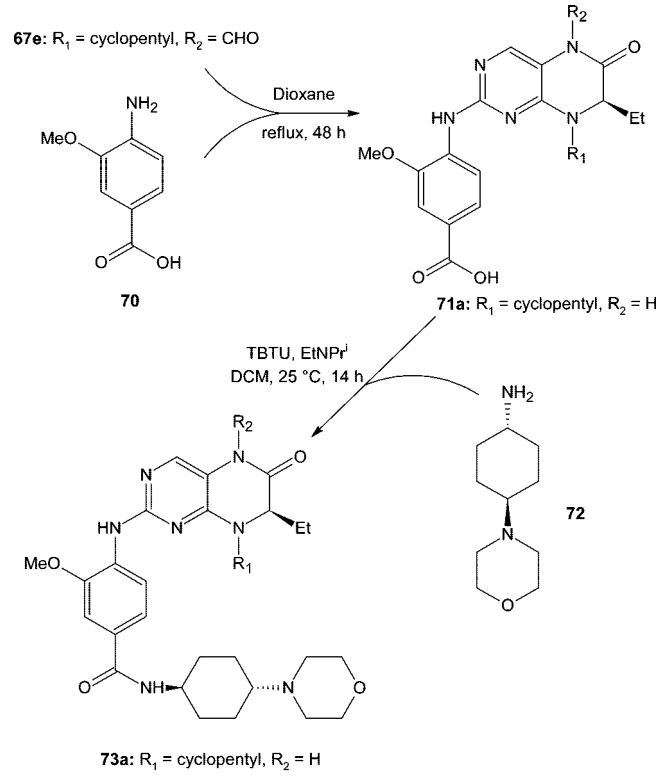
the method used to convert **67d** to **67e** by reduction using $NaBH_4$ followed by heating with HCO_2H; **67e** is then reacted with a range of amines to prepare compounds such as **68a**. In a similar manner compounds analogous to **68a**, in which $R_1 =$ $Me_2CHCH_2CH_2CH_2-$, are also prepared.

The patent further describes a series of derivatives such as **73a** as shown in Scheme 24. This is produced in a two-stage process that initially forms **71a** from the reaction between **67e** and the amine **71**. This is isolated but not purified and then reacted with **72** to give **73a**. The preparation of compounds analogous to **73a** is also described. The activity of some of the products in cytotoxicity test on tumour cells is also discussed.

Advantages

The patent describes a wide range of novel compounds that are active in the inhibition of tumours.

Scheme 24



TBTU = o-benzotriazolyl,N,N,N'N'-tetramethyluronium tetrafluroborate

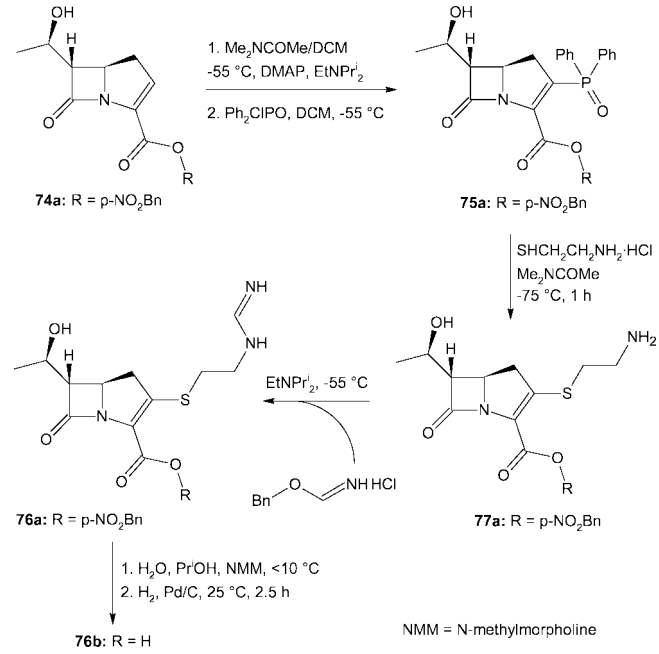
Patent No. U.S. 7,241,885

Assignee: Ranbaxy Laboratories Limited, Gurgaon, India

Title or Subject: Process for the Isolation of Crystalline Imipenem

Imipenem **76b** is a β-lactam antiobiotic that possesses broad-spectrum activity against Gram-positive and Gram-negative bacteria. The compound was first obtained by lyophilization and reported in 1980. This product was amorphous and thermodynamically unstable, and a more stable crystalline

Scheme 25



NMM = N-methylmorpholine

monohydrate was reported shortly after. The current patent claims that the production of this more stable form is not satisfactory on a commercial scale since it requires the use of column chromatography. Hence the objective of the work was to develop a simpler procedure for preparing and isolating **76b**, and Scheme 25 shows the method used to prepare **76b** from **74a**. The first stage produces the enol phosphate ester **75a** that is converted to the thienamycin ester **77a**. In the next step **77a** reacts with benzyl formididate to give the imipenem ester **76a**, and then finally the crystalline acid monohydrate is obtained. The isolation and purification step is then carried out, and this involves washing with solvents. The preferred system is not obvious from the patent since the examples specify Me_2CO although the claims specify using a ketone having six or more C atoms.

Advantages

The process is claimed to offer a more commercially suitable route to this important drug.

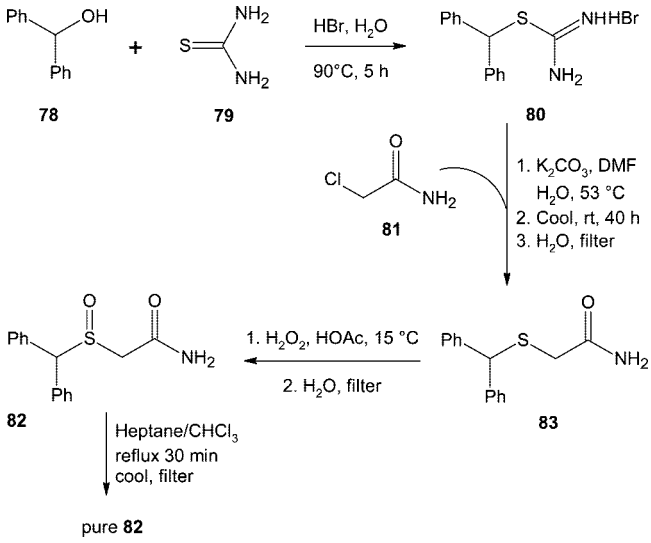
Patent No. U.S. 7,244,865

Assignee: Mallinckrodt Inc., Hazelwood, Missouri, U.S.A

Title or Subject: Process for Preparing Benzhydrylthioacetamide

The subject of this patent, **83**, is an intermediate in the production of modafinil (**82**), a stimulant used to overcome the effects of narcolepsy. The processes used to prepare **82** are said to require undesirable starting materials and give problematical byproduct. This patent describes an improvement in the preparation of **83** that has improved yield and gives a purity product over alternative methods. Scheme 26 shows the route

Scheme 26



used to prepare **83** an its conversion to **82** by oxidation using H_2O_2. The first stage produces the HBr salt of **80** by reaction between **78** and **79** in aqueous HBr. The yield in this step of 95% pure **80** is 90%. This is used in the next stage and reacted with **81** to prepare **83** in 98% purity. The final oxidation gives **82** as the racemic mixture. The crude product is purified by refluxing in *n*-heptane/$CHCl_3$, and the final product is obtained in 85% yield with a purity of 99.8%. The patent claims state that a halogenated solvent must be used for purification, and this must detract from the process's other improvements. The patent discusses the change in byproduct formation in going from small to commercial scale production. In so doing it was determined that water had a surprisingly beneficial effect on the course of the reaction. It was determined that residual **79** from the previous reaction impaired the oxidation reaction. Water reduced the formation of byproduct in the oxidation reactions; using a water-miscible solvent assisted in this, and the patent claims that the optimum ratio of solvent to water is 3:2. The use of water also allows the reaction to be conducted at room temperature, although this means that it does take 40 h.

Advantages

The process gives improved yield and purity of the product but does necessitate using halogenated solvents.

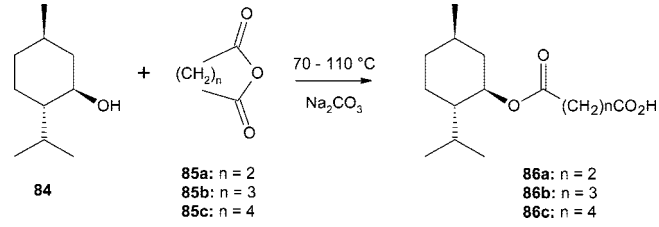
Patent No. U.S. 7,247,743

Assignee: Millenium Specialty Chemicals Inc., Houston, Texas, U.S.A

Title or Subject: Process for Making Monomenthyl Esters

The monomenthyl half-esters described in this patent are used as physiological coolants in flavours, oral care products and cosmetics. When preparing half-esters of dicarboxylic esters, it is often difficult to achieve high selectivity to the desired product. Alternative methods are discussed that start from diacids or anhydrides using TsH or without any catalyst. There is one method known that uses DMAP in pyridine, but it is said to be impractical because of the need to use a large excess of anhydride and both pyridine and DMAP are highly toxic. The products of interest in this patent are prepared by reacting *l*-menthol **84** with cyclic anhydrides **85** in the presence of basic catalysts. The process does produce the expected mixture of mono and diesters, and it can be controlled to maximise the ratio amount of mono to diester. The general method for producing the esters is shown in Scheme 27 and preferably uses

Scheme 27



l-menthol with or without solvent in the presence of bases such as Na_2CO_3 or NaOAc. The patent claims cover the preparation of **86a**−**c**, although there are no examples for **86c**. The ratio of the monoester to diester varied from 4.7 up to 21.3, and this is often double the value found when not using a catalyst. The catalysts also reduces the time needed for the reaction and so can increase productivity.

Advantages

The process improves the reaction selectivity and also reduces the reaction times.

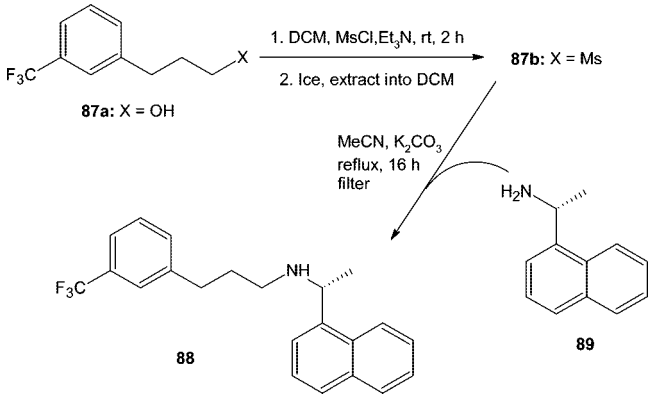
Patent No. U.S. 7,247,751 and 7,250,533

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

Title or Subject: Processes for Preparing Cinacalcet Hydrochloride

Cinacalcet (**88**) as the HCl salt is a calcimimetic and is used to treat hyperparathyroidism. The first of these two patents describes a process to prepare the crystalline Form I of the HCl salt of **88** that is the normally prescribed form of the drug. The second patent covers a process to prepare the molecule **88**. The first patent therefore discusses the method used to obtain **88** by crystallisation and provides XRD and thermogravimetric data to back up the claims. The second patent discloses the chemical reaction pathway developed to prepare **88**, and this is shown in Scheme 28. A number of known methods to prepare **88** are

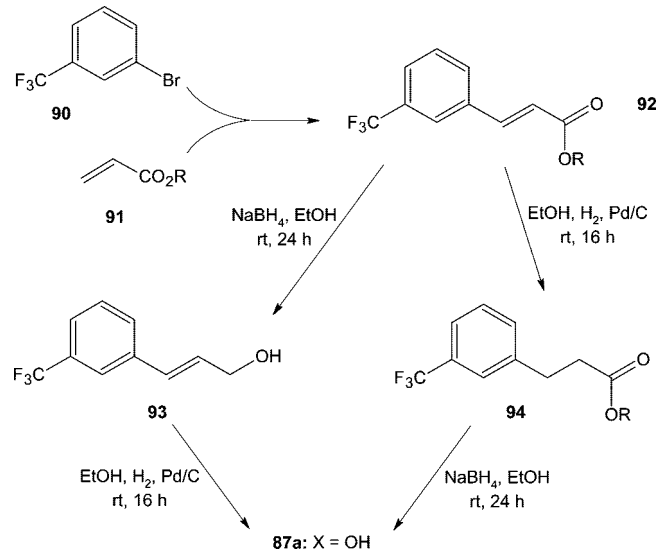
Scheme 28



discussed and said to be indirect, environmentally unfriendly and not suitable for industrial production. The process disclosed in the patent is claimed to offer all of these qualities. Compound **88** is prepared from **87a** via the mesylate **87b**, which is reacted with the chiral amine **89**. The time required to carry out the second reaction is said to be between 5 and 96 h. A variation of the synthesis is to prepare **87c** (X = Cl) using DMF/$SOCl_2$. When reacting **87c** with **89** KI is also added to improve formation of **88**. In some examples a PTC is also added in the formation of **88**, and NBu^t_4 is preferred.

The patent also covers the synthesis of the compound **87a**, and one method is outlined in Scheme 29. In the first stage **90** and **91** undergo a Heck coupling reaction to produce **92**, and

Scheme 29



this can be converted in two ways to the desired product. These methods differ in the order in which the C=C and C=O bonds are reduced. The C=C bond is reduced by catalytic means and the C=O by using $NaBH_4$.

There is no definitive information as to which is the preferred route to make **87a**.

Advantages

The process gives an improvement in yield of products and their purity compared to alternatives. It is also avoids the use of toxic and expensive reagents that are employed in other processes.

Keith Turner

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