Organic Process Research & Development **2006**, *10,* 866–875

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during May and June 2006

Summary

There are 21 patents reviewed from an original list of 324, a significant increase in the number over recent searches. A wide selection of subjects is again covered with some good examples of process development included. An interesting example is shown in the use of a distillation using a divided wall column in the purification of oxazoles. The patent uses the same chemistry as before but improves the process using good engineering practice. A number of patents provide new routes to known compounds, but some would not seem to be commercially attractive. For example a method of preparing an intermediate for frovatriptan claims that halogenated solvents are needed to improve the process. Several other patents continue to use such solvents, and this seems to be against the trend for developing green processes. New methods are disclosed in two patents to prepare the antihypertensive drugs losartan and nisoldipine. There are improved processes described for the antinausea drug ondansetron and also for the drug pantoprazole that is used to treat gastric ulcers. A new method for the synthesis of the cephalosporins cefpodixime proxetil is described that removes the need for an expensive chromatographic separation technique. There seems to be a number of patents in this selection that coincidentally cover hazardous materials. Two quite different patents describe methods of making the stable high explosive TATB. The justification for each is different, and one is aimed at disposing of less stable explosives such as picric acid and picrates. Another dangerous material is monochloramine, and one patent describes its preparation that reduces the formation of hydrazine, a difficult product to remove. A method for the production of sulfamoyl chloride is described that involves a highly exothermic reaction. It is stated in the patent that this reaction produced an explosive gas release on a 100 g scale. The danger of this reaction is reduced by controlled addition, but whether this has been reported in the open literature is not known. The preparation of chemical sensors that are used to detect pesticide or nerve gas residues is the subject of one patent. The compounds are β-diketones that are prepared by aldol condensation reactions. Methods for preparing novel intermediates for the synthesis of the antitumour drug neplanocin A are disclosed, and two patents provide extensive details of these. Cilastazol is a competitor to the well-known Viagra, and one patent describes a new method for its synthesis. Interestingly the patent does not mention its use to treat erectile disfunction and focuses on its use in treating other blood circulation problems. There is no legal or commercial significance in the choice of patents reviewed, and it is hoped that the readers find some points of interest. The advantages noted are those claimed in the patent unless this reviewer has personal knowledge of the subject.

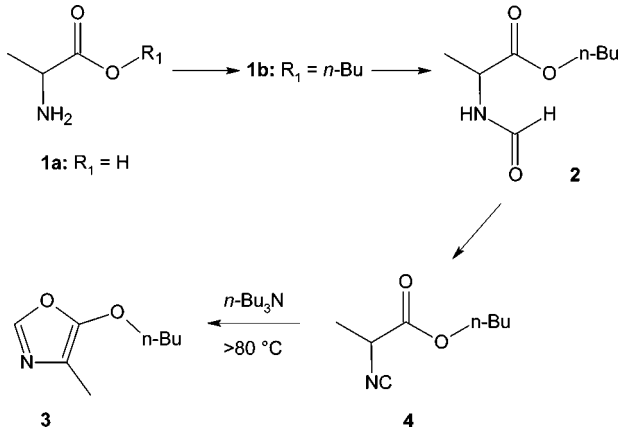
Patent No. U.S. 7,038,058

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Continuous Preparation of Substituted Oxazoles in a Divided Wall Distillation Column

The main subject of this patent is the compound **3**, and this is used in the preparation of vitamin B6. There are several methods available to prepare **3** from esters such as **4**, but these are all said to have low selectivity and hence give low yields of **3**. This is ascribed to the batch nature of the processes. This patent uses these same esters to prepare **3** and improves the yield by operating the process continuously in a divided wall distillation column. The cyclisation reaction is effected by using reaction assistants that are preferably bases, and examples are given using Et_2NPh and *n*-Bu_3N. The amines form a minimum boiling azeotrope with **3** and this is removed from the top of the distillation column. The azeotrope of **3** and *n*-Bu_3N at 800 mbar contains 10% *n*-Bu_3N, and at 10 mbar the azeotrope contains 30% *n*-Bu_3N. Hence by distilling the azeotrope at the lower pressure it is possible to remove more of the *n*-Bu_3N. The high boiling fraction is pure **3**, and this is obtained as a sidestream from the column. Scheme 1 shows the route for producing **3** that starts from the amino acid **1**, although the patent only provides details for the conversion of **4** to **3**.

Scheme 1



This patent uses methods that are probably unfamiliar to many R&D chemists. However, it is an excellent example of applying good chemical engineering practice to solving a problem.

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10.1021/op0601666 CCC: $33.50

Advantages

The process provides an effective and efficient method of improving known chemistry.

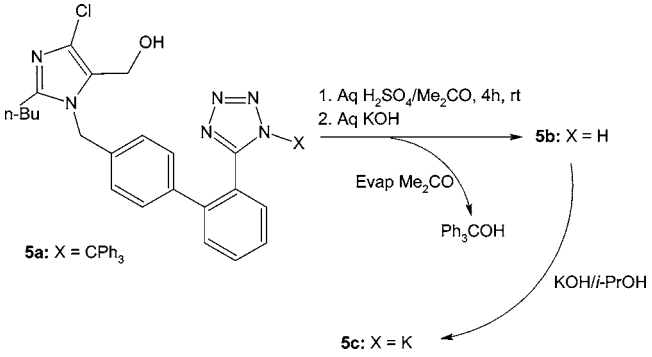
Patent No. U.S. 7,041,832

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

Title or Subject: Processes for Preparing Losartan and Losartan Potassium

Losartan **5b** is an angiotensin II receptor antagonist that prevents the narrowing of blood vessels, and the K salt **5c** is used to treat high blood pressure. Interest in new methods of preparing the K salt has increased since the original patents have expired. This patent provides a method of obtaining **5b** and **5c** from the trityl substituted compound **5a** by acid cleavage. An earlier patent covering the preparation of **5c** from **5a** using basic cleavage has already been reviewed (*Org. Process Res. Dev.* **2005**, *9*, 719). Scheme 2 outlines the process for preparing **5b** and **5c**. The first stage is formation of **5b** from **5a** by acidification followed by addition of KOH and evaporation of the solvent. As the solvent is removed, the trityl alcohol precipitates and acidification of the filtrate produces **5b** in 91% yield. The conversion of **5b** to the K salt is carried out by treatment with KOH in *i*-PrOH giving **5b** in 85% yield and purity 99.7% (HPLC).

Scheme 2



Advantages

This patent provides a simple process for preparing both the desired K salt and the free base.

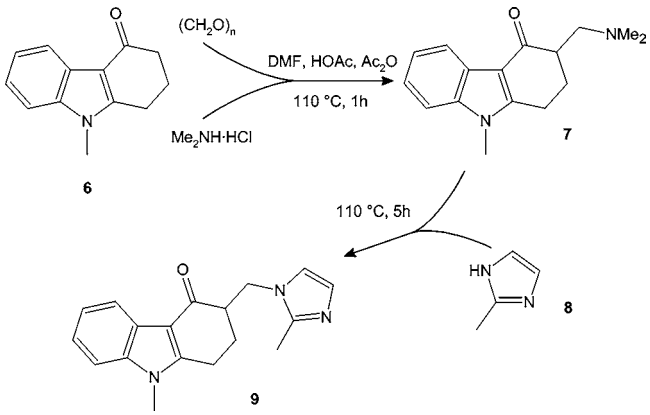
Patent No. U.S. 7,041,834

Assignee: Synthon IP Inc., Gainsville, Virginia, U.S.A.

Title or Subject: Process for Making Ondansetron and Its Intermediates

Ondansetron **9** is used to prevent nausea and vomiting during cancer chemotherapy treatments. **9** can be formed by a transamination reaction using **8**, but it is claimed that the overall reaction time needs to be improved for commercial scale operation. The patent describes a method of preparing **9** from the intermediate **7** by reaction with **8**. The first step is a condensation reaction of paraformaldehyde, $Me_2NH{\cdot}HCl$, and **6**. This is carried out in the presence of a water-binding agent that reacts with water such as Ac_2O. The second step of the process is carried out by adding the imidazole **8** to the mixture. The crude product is then treated with activated C in MeOH, and purified **9** is obtained by crystallisation.

Scheme 3



The patent states that by using the water-binding agent the condensation reaction time is decreased. For example without Ac_2O the reaction gave 90% conversion in 3 h, and when using Ac_2O the reaction took less than 1 h.

Advantages

The process improves the efficiency of the overall process by reducing the reaction time of the first step.

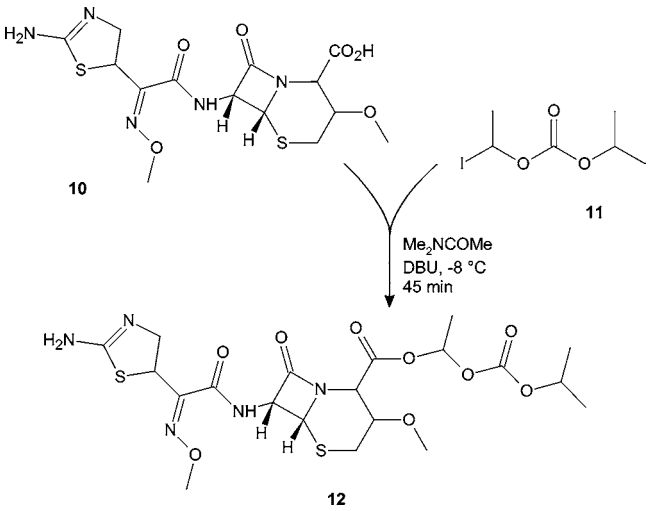
Patent No. U.S. 7,045,618

Assignee: Ranbaxy Laboratories Limited, Haryana, India

Title or Subject: Process for Preparing Cefpodixime Proxetil

The title compound **12** is a third generation cephalosporin that has activity against gram-positive and gram-negative bacteria. Several methods are known for preparing esters such as **12**, but they are said to suffer problems because the reaction impurities are difficult to remove without recourse to chromatographic methods. The problems arise when starting from the acid such as **10**, and this gives rise to a number of isomers of **12** that cannot easily be removed. These methods are said to be unsuitable for commercial processes. This patent describes a method for preparing **12** that is claimed to remove the need to use complex purification techniques. The process is shown in Scheme 4 and starts from the acid **10** that is esterified using the iodo-carbonate **11** in the presence of DBU. No mention is made of the stereochemistry of **11**, and the product is a mixture of diastereoisomers in which the more polar isomer predominates slightly (52%). After reaction the product is then purified by a procedure that is claimed to be key to the success of the process. This involves pouring the reaction mixture into a polar solvent that is immiscible with water such as EtOAc, and the product is then precipitated using a nonpolar solvent such as cyclohexane. The solid is then dissolved in a water-miscible polar solvent such as MeOH and precipitated using water.

Scheme 4



10 11 12

Advantages

The method removes the need for chromatographic separation thereby improving its industrial potential.

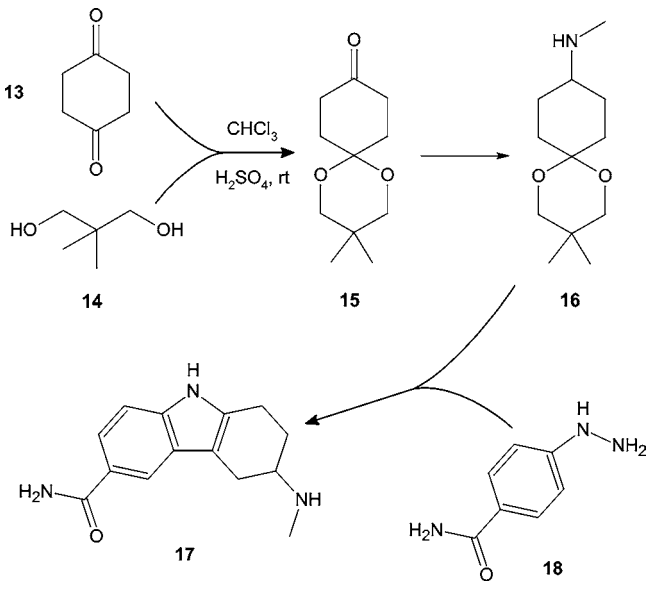
Patent No. U.S. 7,049,448

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

Title or Subject: Process for Preparing Monoketals of 1,4-Cyclohexanediones

A specific compound covered by this patent is **15**, and this is used to prepare frovatriptan **17**, an antimigraine drug. Although there is a range of methods for preparing this compound, they are said to be in need of improvement for commercial scale production. The route used is shown in Scheme 5, and this is the reaction between the diol **14** and the dione **13** in a halogenated solvent in the presence of a strong acid. The recovery of the product involves washing with a weak base, and $NaHCO_3$ is preferred. The organic phase is concentrated under a vacuum and then cooled to give the solid product.

Scheme 5



13 14 15 16 17 18

The patent also claims that **15** can be used to prepare **16** by reductive amination, and this can then be reacted with **18** to give **17**. However, no experimental details of any of these steps are given in the patent.

Advantages

The process is claimed to give a higher purity product than alternative methods. However, the retrograde step of using halogenated solvents will probably put off any competitors and leave the field open to the inventors.

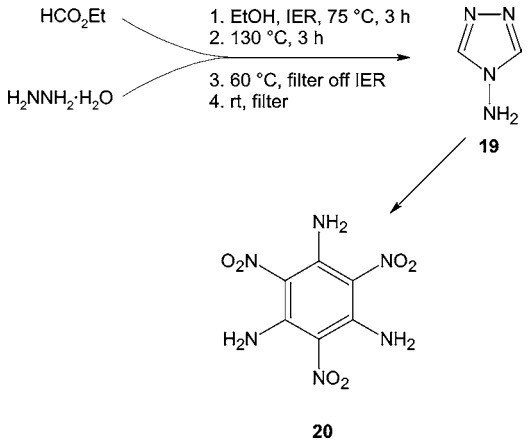
Patent No. U.S. 7,045,635

Assignee: BWXT Pantex LLC, Amarillo, Texas, U.S.A.

Title or Subject: Process for the Synthesis of 4-Amino-4H-1,2,4-Triazole

This is the first of two quite different patents describing processes for producing the explosive TATB **20**. This short patent actually covers a process for preparing the intermediate **19** (known as ATA) used in synthesising **20**. The patent consists of a single claim for synthesising **19** by the simple route shown in Scheme 6. **19** is used to make the explosive TATB **20** that is very powerful yet is shock resistant and hence safer to handle than other explosives. An alternative method for making **19** reacts H_2NNH_2 and HCO_2H with the same strong acid ion-exchange resin (IER) catalyst as that used in this patent. The earlier patent is said to claim that HCO_2Et is not suitable in the reaction, and yet the current work shows that this is not the case. Such findings are very useful in gaining a valid patent.

Scheme 6



19 20

Advantages

The patent disproves earlier work and provides a simple method of producing the important intermediate.

Patent No. U.S. 7,057,072

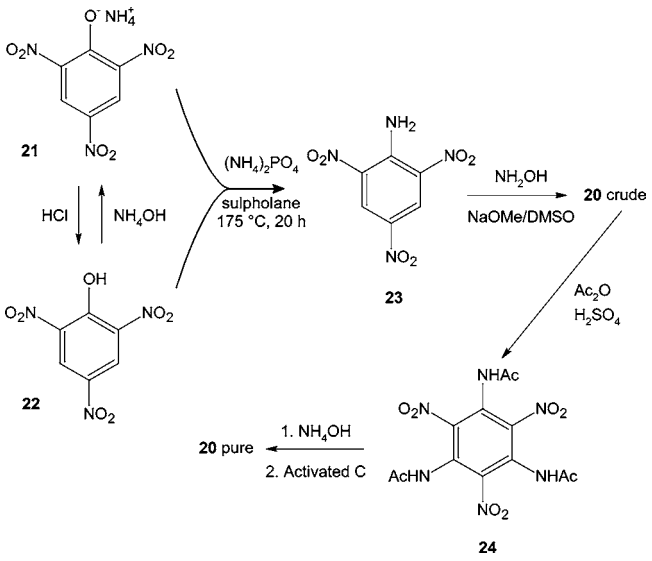
Assignee: The Regents of the University of California, Oakland, California, U.S.A.

Title or Subject: Synthesis and Purification of 1,3,5-Triamino-2,4,6-Trinitrobenzene

The second patent on the production of TATB claims to be addressing the problem of the disposal of surplus

nitroarene explosives such as picric acid **21** and its ammonium salt **22**. These materials are less stable than **20** and hence more difficult to handle. The process can be applied to both **21** and **22** and involves the initial formation of picramide **23** by heating **21** or **22** in sulpholane with $(NH_4)PO_4$. This conversion can also be carried out using urea, but this reaction forms cyanuric acid that can be difficult to remove from **23**. The next step is described as a vicarious nucleophilic substitution (VNS). For those readers such as this reviewer who are unfamiliar with the term VNS the patent gives several references to papers and patents from about 1986. This VNS reaction uses NH_2OH to give crude **20**. The reaction also produces disubstituted products, and these are removed by a purification process that involves acetylation. The acetylation forms **24** and other acetylated compounds. By treating the mixture with activated C the various acetylated impurities are removed. The purified **24** is then converted to **20** by ammonolysis. This purification procedure is used because the acetylated product **24** is much more soluble than **20**, and hence it can be purified more easily. The patent states that although NH_2OH is the least reactive VNS reagent it is inexpensive and readily available. It is claimed that ATA **19**, also a VNS reagent and used in the previous patent, is more costly and not available in bulk quantities.

Scheme 7



Advantages

The process couples a method of disposing of unstable explosives with a cheap procedure for making more stable explosive materials. It uses a reagent that is readily available in bulk quantities and hence it is relatively cheap.

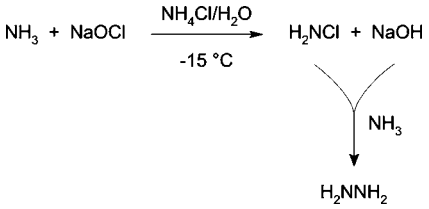
Patent No. U.S. 7,045,659

Assignee: Isochem, CNRS and Universite Claude Bernard, Lyon, France

Title or Subject: Process for the Synthesis of Monochloramine

Monochloramine H_2NCl is useful in the preparation of hydrazines that are used as propellants or for preparing agrochemicals and pharmaceutical intermediates. The established method of preparing H_2NCl is by the Raschig process using NH_3 and NaOCl as shown in Scheme 8. The reaction is carried out in the presence of NH_4Cl. A problem that is encountered is that the product reacts further with NH_3 and gives hydrazine that can be difficult to remove. Hence it is desirable to limit the concentration of NH_3 and reduce the formation of hydrazine. The improvement described in this patent is to add a base to the NaOCl solution beforehand and run the process continuously. This change means that lower quantities of NH_4Cl are required so there is less NH_3 present and the subsequent chloramine is of a higher purity and obtained in yields around 99%. A comparative experiment is said to give only yields of 50%.

Scheme 8



Advantages

The process significantly improves the yields of the product, and by operating continuously, it reduces the byproduct formation.

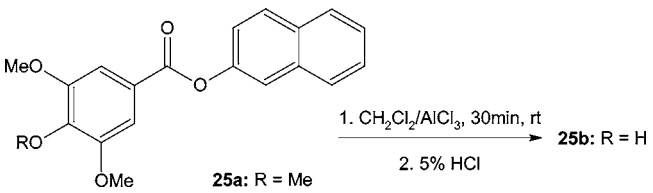
Patent No. U.S. 7,053,218

Assignee: Council of Scientific & Industrial Research. New Delhi, India

Title or Subject: Process for Regioselective Demethylation of p-Methoxy Groups of Aryl Esters and Ketones

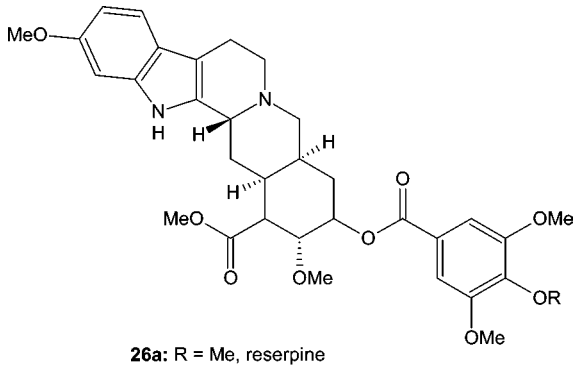
The object of this patent is the manufacture of a compound such as **25b** by demethylation of **25a**. It is claimed that this is the first reported method for the regioselective demethylation of *p*-methoxy groups in a 3,4-dimethoxy or 3,4,5-trimethoxybenzoic acid esters or diaryl ketones. The process is carried out using $AlCl_3$ in CH_2Cl_2 followed by addition of dilute HCl (Scheme 9).

Scheme 9



The process is also applied to the demethylation of a natural product known as reserpine **26a** that can be converted to **26b** by the same procedure. **26a** historically has been used to treat hypertension, but it has a number of serious side effects and is no longer used in Europe or the U.S.A. The

significance of the production of **26b** from **26a** is not mentioned in the patent.



26a: R = Me, reserpine
26b: R = H, O-desmethylreserpine

Advantages

The process introduces a novel procedure, and it is claimed that it does not require the use of toxic reagents and solvents so can be used to prepare pharmaceutical products. How the use of CH_2Cl_2 in preparing such compounds can be reconciled with these claims certainly escapes me.

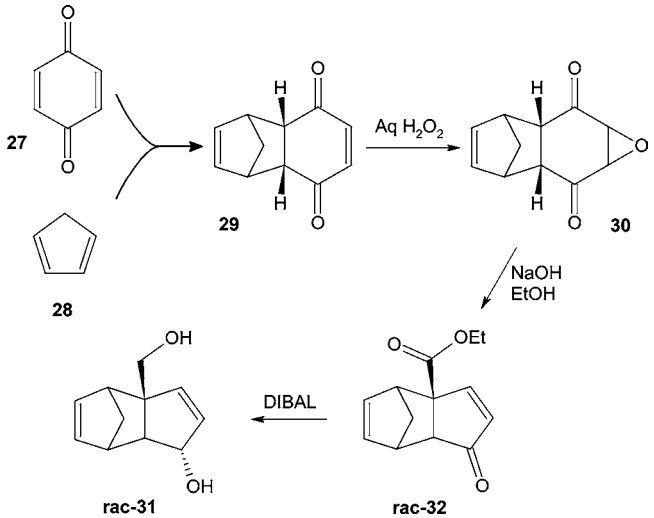
Patent No. U.S. 7,053,224 and 7,053,225

Assignee: Chisso Corporation, Osaka-fu, Japan

Title or Subject: Intermediates and Improved Process for the Preparation of Neplanocin A

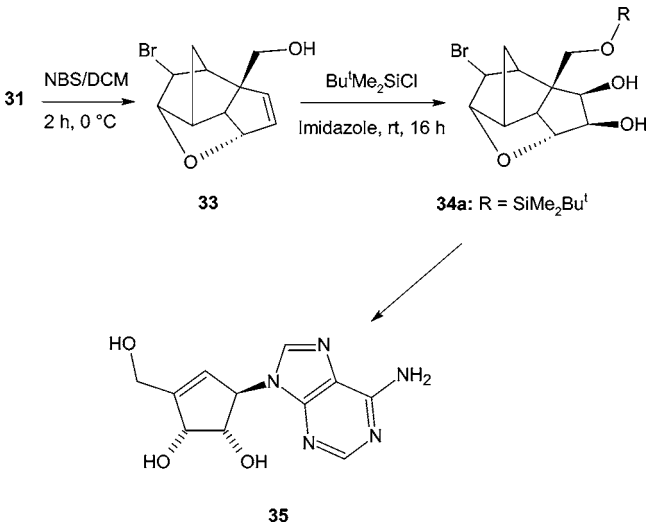
The claims of these two patents cover the novel compounds **33** and **34a** that are intermediates in preparing neplanocin A **35**. This is a carbanucleoside with strong antitumour activity. The patents cover a vast range of other compounds that are intermediates in the synthesis of **35** in seven steps starting from **34a**. In view of the extensive amount of work described in the patent, only a portion is covered here. The key compound appears to be **31**, and this is prepared by the route shown in Scheme 10. This begins with Diels−Alder reaction of **27** and **28** to give **29** followed by epoxidation using H_2O_2 to give **30**. A Favorski rearrangement of **30** then produces racemic **32**, and reduction with DIBAL gives racemic **31** that can be resolved via acylation.

Scheme 10



The two compounds **33** and **34a** are the subject of the claims of the two patents; they are produced from the pure enantiomers of **31** by the route shown in Scheme 11. The first reaction is the bromination of **31** using NBS to give **33**, although other reagents are claimed to be suitable. In the next step **34a** is produced by silylation of **33**. The experimental details for the conversion of **34a** to **35** are given in the patent.

Scheme 11



Advantages

The process produces novel intermediates in the synthesis of **31**, and these are claimed to afford a higher yielding and more efficient route for this compound.

Patent No. U.S. 7,060,833 and 7,064,208

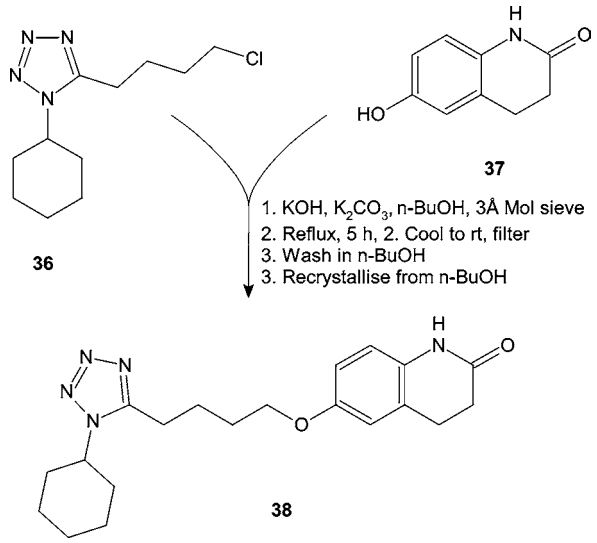
Assignee: Teva Pharmaceutical Industries Ltd., Petah Tiqva, Israel

Title or Subject: Substantially Pure Cilastazol and Processes for Its Manufacture

Cilostazol **38** is used to treat erectile dysfunction, although this is not mentioned in the current patent. The patent does mention that **38** is used to treat intermittent claudication, and this is a circulation problem that causes pain during exercise. A similar patent on the synthesis of **38** has recently been reviewed (*Org. Process Res. Dev.* **2006**, *10*, 703). These two current patents are concerned with producing **38** that has a reduced particle size from the normal material. The smaller particles are useful in preparing pharmaceutical formulations. The synthetic route used to prepare **38** is shown in Scheme 12. This route uses the same chemical reaction between **36** and **37** to obtain **38**, and the key difference between this patent and the work reviewed previously is the fact

that the current method uses a biphasic mixture and phase transfer catalysis. The biphasic system separates the base from the base-sensitive compound **36**.

Scheme 12



The patent gives 33 examples, and some show yields of **38** of >99%. The product is reduced in particle size by passing through a pin-mill, and a >90% amount was obtained with a diameter of <60 micron.

Advantages

The process improves the yields and purity of product made by the known synthetic route and provides a method producing small particle sized crystals.

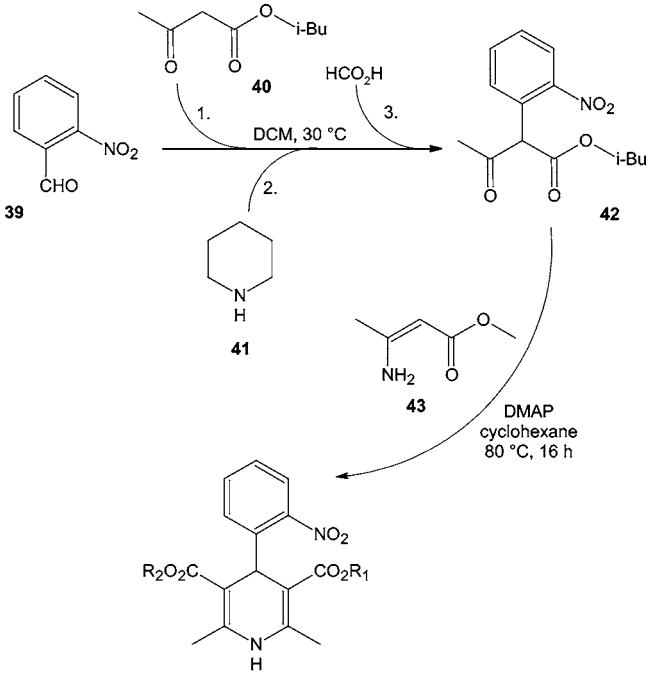
Patent No. U.S. 7,060,838

Assignee: Erregierre S. P. A., San Paulo D'Argon, Italy

Title or Subject: Industrial Process for the Synthesis of Nisoldipine

The subject of this patent **44a** is active as a calcium antagonist and antihypertensive and is used to treat high blood pressure. The patent claims that using one of the known syntheses for **44a** produced a material containing 3% of **44b** and 2% of **44c** as impurities. It is stated that the great similarity of these impurities to **44a** means that their removal is difficult. Hence the objective of the patent is to develop a better route to make **44a** with lower levels of impurities. The route used is shown in Scheme 13 and is an unexpected method involving the reaction between **42** and **43** in an apolar solvent in the presence of DMAP. The level of impurities is significantly less using this procedure, and the product purity exceeds 99% by HPLC.

Scheme 13



The intermediate **42** is prepared by stepwise addition of **40** to **39** followed by **41** and then finally HCO_2H. The catalyst for this reaction is piperidine formate that is formed in situ.

Advantages

The process gives a much higher purity product, and since the patent describes experiments that involve multi-kilo quantities, it suggests that the process is at an advanced stage of development.

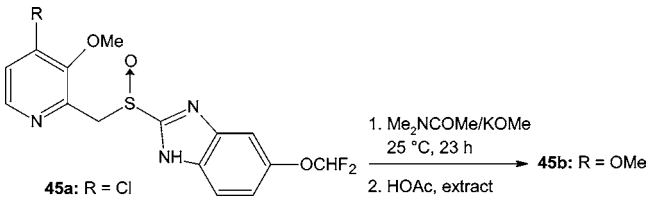
Patent No. U.S. 7,060,839

Assignee: Dinamite Dipharma (Dipharma S. P. A.), Basiliano, Italy

Title or Subject: Process for the Preparation of Pantoprazole and Intermediates Therefor

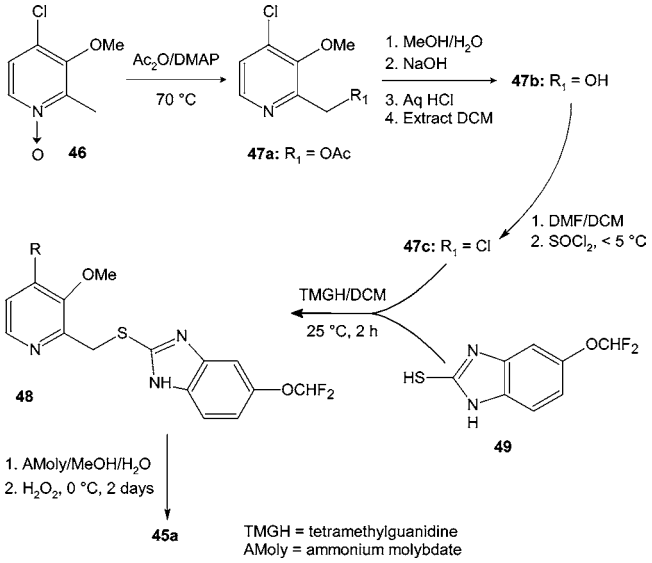
The sodium salt of pantoprazole **45b** is used to treat gastric ulcers. There are a number of methods known for the synthesis of **45b**, and they are claimed to have several shortcomings. Some of the reasons given are nonselective methylation reactions or inaccessible intermediates. This patent describes methods to prepare **45b** and also the novel intermediates **45a** and **48**. Scheme 14 shows how **45b** is prepared from **45a** by treatment with KOMe in either DMF or Me_2NCOMe. The crude product is obtained in 90% yield and is purified to remove coloured impurities giving a final yield of purified **45b** of 67%.

Scheme 14



The main aspect of the patent is the synthesis of **45a** and **48** (Scheme 15), and this is probably the subject of a separate patent. The route to **45a** starts by acetoxylation of the *N*-oxide **46** to form **47a** using the acetate salt of DMAP. This is formed in situ from Ac_2O and DMAP. Hydrolysis of **47a** produces **47b**, and then chlorination using $SOCl_2$ gives **47c**. The next stage is the coupling reaction of **47c** and the imidazole **49** to give **48**, and this is oxidised to produce **45a**.

Scheme 15



The patent claims that the reaction steps in Scheme 15 can be carried out without isolation of the intermediates, and the experimental details would appear to confirm this.

Advantages

The process provides a route to novel intermediates, and these can be easily transformed into the desired product.

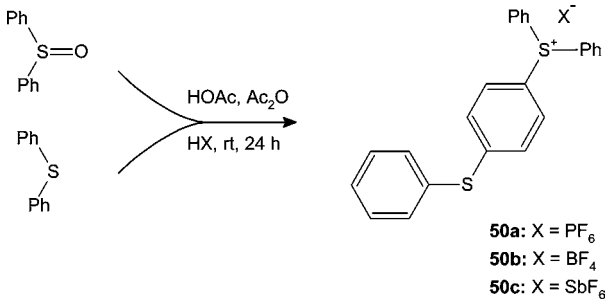
Patent No. U.S. 7,060,858

Assignee: San-Apro Limited, Kyoto-Fu, Japan

Title or Subject: Method of Manufacturing Sulfonium Salts

The particular sulfonium salts of interest are **50a,b** and **c**, and these are used as photocationic polymerisation initiators in lithography. The patent states that conventional processes for preparing the desired compounds involve the condensation of a sulfoxide or sulphide requiring excessive amounts of strong acids such as H_2SO_4. This means that product recovery and purification are difficult and large quantities of waste are formed. The objective of the work was to produce the desired compounds without using vast amounts of strong acids and without invoking a metathesis reaction. The current process involves the conventional condensation between a sulfoxide and a sulphide in the presence of a strong acid and a dehydrating agent. The preferred acids are HBF_4, $HSbF_6$, or HPF_6, while the preferred dehydrating agent is Ac_2O. Scheme 16 shows the reaction sequence involved in the preparation of **50** from Ph_2SO and Ph_2S.

Scheme 16



This reaction is carried out in the presence of HPF_6 and Ac_2O. As an alternative the HPF_6 can be prepared from KPF_6 and H_2SO_4 before adding Ph_2SO and Ph_2S. In both cases the yields are better than 99%. Modifications include the use of MeCN as solvent in place of HOAc and using the Na salt instead of the K salt. By similar procedures the SbF_6 and BF_4 salts are also prepared. To show how much more effective the process is compared to the conventional method an example using H_2SO_4 is described. This gave **50a** in only 80% yields and 90% purity.

Advantages

The process gives better yields and a product of higher purity than alternatives. It also produces less waste products.

Patent No. U.S. 7,064,200

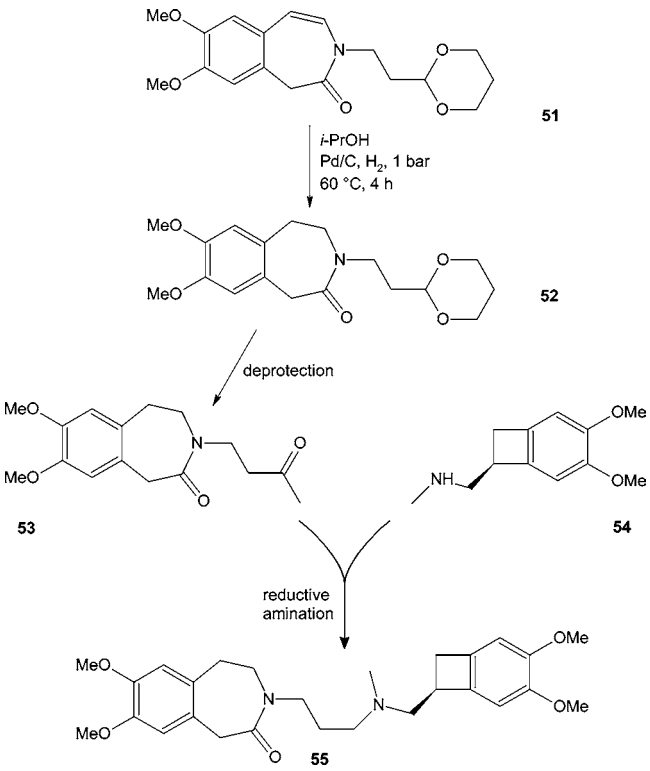
Assignee: Les Laboratoires Servier, Courbevoie, France

Title or Subject: Process for the Synthesis of Benzazepin-2-one Compounds and Their Application in the Synthesis of Ivabradine

The patent specifically claims a process to prepare **52** from **51** by catalytic hydrogenation. **52** is then used in the synthesis of ivabradine **55**, a drug used to treat various coronary diseases. Several processes for preparing **55** are reviewed, and these are described as giving only a low yield. One particularly difficult step in the synthesis of **55** is a catalytic hydrogenation reaction of the 1,3-dihydro-2H-3-benzazepin-2-one moiety to give the final product. The route to **55** selected in this patent is shown in Scheme 17 and involves the coupling of **53** and **54** in a reductive amination reaction. The patent claims that in view of the difficulty of the hydrogenation step referred to above the conversion of **51** to **52** was expected to be difficult. However, it has been found that by judicious selection of solvent and reaction conditions a very good yield (88%) of **52** can be obtained. Compounds **51**, **52**, and **53** are novel, and the patent does not give specific details for the production of **55** by the route

shown in Scheme 17. Since the focus of this patent is novel compounds, it is possible that the reaction of **53** and **54** is in another patent.

Scheme 17



Advantages

The process provides an alternative route to the known drug via novel intermediates.

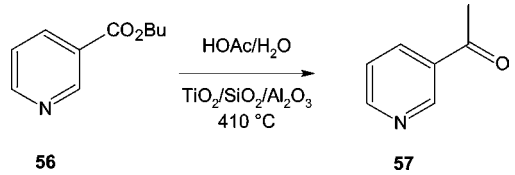
Patent No. U.S. 7,067,673

Assignee: Lonza AG, Basel, Switzerland

Title or Subject: Process and Catalyst for the Preparation of 3-Acetylpyridine

The title compound **57** is a useful intermediate that is usually prepared from nicotininc acid. A major byproduct is pyridine formed by decarboxyation at up to 40% of the product. The purpose of this work is to reduce the formation of pyridine. This is done by passing an ester of nicotinic acid **56** over a TiO_2 catalyst supported on silica−alumina (Scheme 18). Although the objective appears to have been met, the reaction conditions are rather severe since the reaction temperature is 410 °C and this would necessitate expensive reactor materials. However, it is stated in the patent that one alternative process requires an even higher temperature (520 °C). The process is carried out in the gas phase in the presence of HOAc and H_2O.

Scheme 18



The patent discusses the use of alternative esters to simplify the separation of the product and reactants. It is concluded that lower alkyl esters boil close to **56**, and so the butyl or higher esters are preferred. Compound **56** boils 32 °C higher than **57**, and so separation by distillation is straightforward.

Advantages

The process does reduce the amount of pyridine formed, but at such high temperatures it is not possible to avoid a certain amount of decarboxylation.

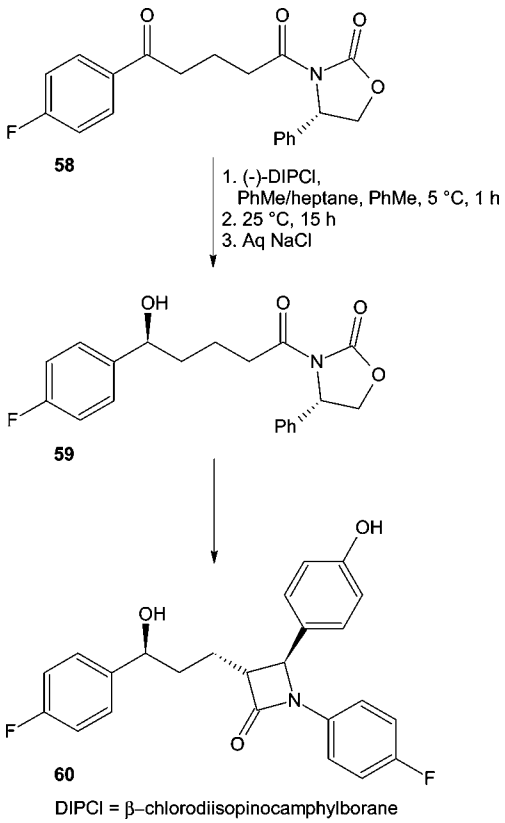
Patent No. U.S. 7,067,675

Assignee: Hetero Drugs Limited, Hyderabad, India

Title or Subject: Process for Ezetimibe Intermediate

Ezetimibe **60** is in a class of lipid-lowering compounds that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. This patent describes the preparation of the compound **59** that is an intermediate in the preparation of **60**. **59** is prepared in a 96% yield by a stereoselective reduction of **58** using a chiral borane reagent (−)-DIP chloride. Alternative methods for this conversion use the reagent borane Me_2S or use microbial reduction. The former reagent is difficult to handle and the latter is said to be expensive, whereas the reagent used in this patent is said to be less expensive.

Scheme 19



The patent outlines the route from **59** to **60** but does not give experimental details.

Advantages

The patent uses a less expensive chiral reagent than alternative synthetic procedures and gives an excellent yield of product.

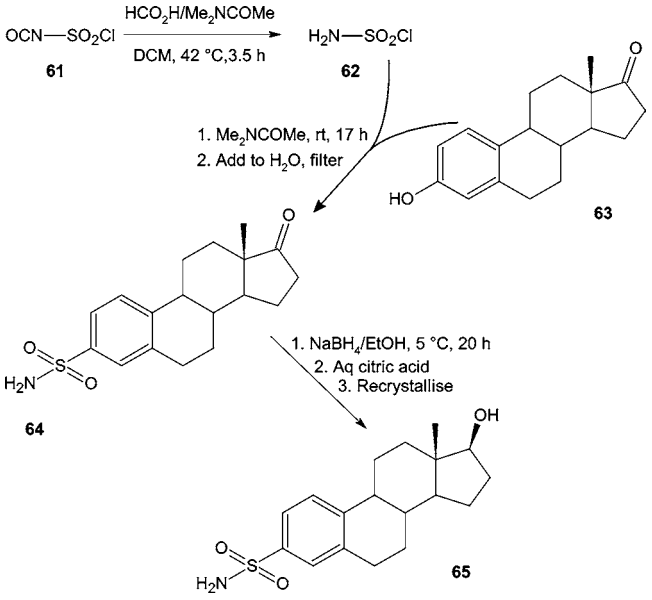
Patent No. U.S. 7,067,683

Assignee: Schering AG, Berlin, Germany

Title or Subject: An Industrially Applicable Process for the Sulfamoylation of Alcohols and Phenols

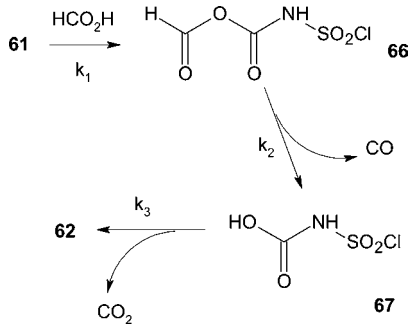
The patent is primarily concerned with the preparation of **64** that is an intermediate in the synthesis of **65**, a sulfatase inhibitor. Sulfamates are obtained by the reaction of sulfamoyl chloride **62** with alcohols or phenols. Usually excess **62** is used, and problems can arise with solvents that react with the reactive **62**. In DMF an adduct is formed and this causes problems in product recovery. The patent states that industrial scale processes using **62** are not feasible and so alternative sulfamoylation methods have been sought. The problems are claimed to have been solved by using Me_2NCOMe as solvent for the reaction, allowing the use of much lower quantities of **62**. Scheme 20 shows the route used to prepare **64** from **62** and estrone **63** and then the reduction of **64** to **65**.

Scheme 20



The patent describes an improved method for the preparation of **62** by reaction of **61** with HCO_2H. It is proposed that this proceeds via the mechanistic route shown in Scheme 21. The formation of **62** is highly exothermic and involves a decarbonylation and a decarboxylation reaction. It is stated in the patent that some experiments as small as 100 g exhibited uncontrolled runaway behaviour and explosive gas evolution. Thermal safety measurements confirmed a tendency for heat accumulation and hence the potential for a very dangerous process on a large scale. This danger is said to stem from the fact that the formation of **66** is faster than its subsequent decomposition to **67**. The problem is reduced by the controlled addition of HCO_2H containing a carboxamide catalyst to **61**. This allows the heat of reaction to be safely and efficiently removed. DMF or Me_2NCOMe is the preferred catalyst for this reaction.

Scheme 21



The patent shows figures that depict the thermal safety measurements of the process to prepare **62**, and these show gas evolution volumes over the time of the reaction. It is most unusual to have this sort of important information in a patent, and this finding should be reported in the open literature.

Advantages

The process gives not only an improved process for preparing the sulfamate, but it also describes a safe procedure for preparing sulfamoyl chloride.

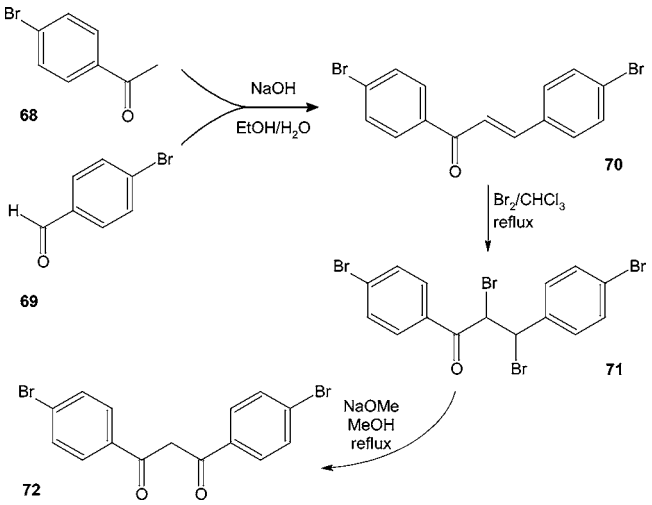
Patent No. U.S. 7,067,702

Assignee: The John Hopkins University, Baltimore, Maryland, U.S.A.

Title or Subject: Process for Preparing Vinyl Substituted β-Diketones

The patent covers compounds that are used in the production of a molecular imprinting polymer (MIP). An MIP is a chemical sensor that is used to detect specific molecules; the patent refers to the detection of organophosphorus pesticides and nerve agents. The MIP is made by adding the detecting molecule of interest to a solution of binding compounds that may be held in a polymer matrix. Vinyl-substituted β-diketones form complexes with a lanthanide ion, and these have a significant enhancement of luminescence intensity so the complexes are used in MIPs. The process to produce the diketones involves a Heck coupling reaction to prepare a range of vinyl compounds. The patent gives details of the preparation of some of the starting materials, and the synthesis of one of these, **72**, is shown in Scheme 22.

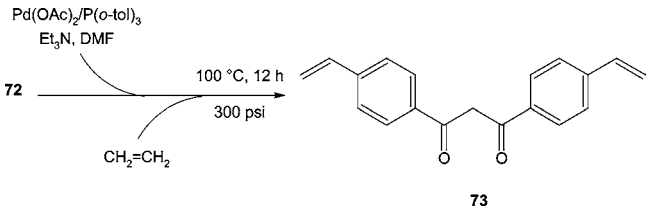
Scheme 22



The starting point for this is base-catalyzed aldol condensation of **68** with **69** to give **70**. Addition of Br_2 then produces **71**, and treatment with NaOMe forms **72**. These three reactions all take place readily and give yields in excess of 95%.

The Heck coupling reaction of **72** with $CH_2{=}CH_2$ to give **73** in 62% yield is shown in Scheme 23.

Scheme 23



A range of symmetrical and mixed diketone products is described, and the patent also provides details of the preparation of the starting compounds by condensation reactions. The preparation of the lanthanide complexes and MIPs are also described.

Advantages

The process provides some interesting diketone compounds that are of use in producing sensitive chemical detectors.

Keith Turner

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

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