Organic Process Research & Development **2004**, *8,* 146–156

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during November and December 2003

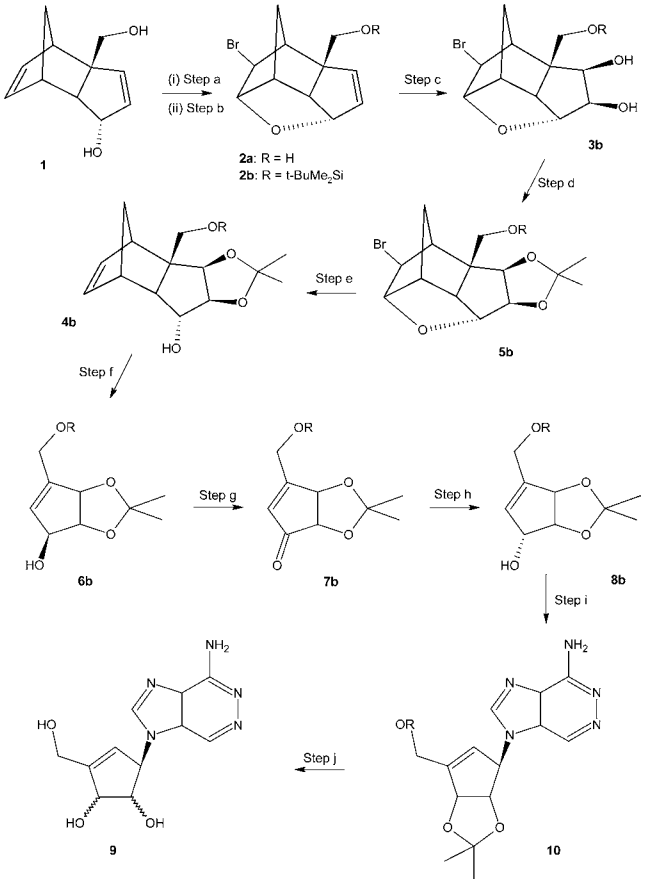
The selection of 20 patents for this review is taken from a total of 280 that fitted the original search criteria, and it is hoped some will be of interest to readers. The discovery of new polymorphs of known drugs continues, and two patents from different companies disclose new information on polymorphs of the important statin drugs. Another patent describes a new method for making a stable polymorph of the anti-bacterial agent finafloxacin. The preparation of two similar ranges of oximes is the subject of two patents from Bayer AG. One is for a range of pesticides, and the other, for use as fungicides. The use of reusable supported osmate catalysts for producing optically active *vic*-diols from olefins has been described which avoids the use of the extremely toxic OsO_4. An interesting approach to achieving concentrated solutions for crystallisation is the use of elevated pressure. This increases the temperature of the solvent without its boiling and avoids the need to change to a different solvent. Another novel development in crystallisation is the use of a peristaltic pump to induce nucleation in a solution by the normal squeezing manner of the pump on the delivery tube. This technique removes the need to add seed crystals in the commercial production of aspartame. A new range of chiral amines is described which are used to resolve a range of trifluoro acids more effectively. A new route to cilostazol is disclosed, and more information on a polymorph of the drug has also been published. A range of insoluble analogues of the useful oxidant TEMPO is described, and these are used in oxidation of alcohols with NaOCl. By the reversing the mode of the addition of reactants in the production of a sulphonamide from a sulphonyl chloride, the yield and purity was increased by 50%, thus showing how simple changes can give dramatic results. There is no legal or commercial significance in the selection, and the advantages are those claimed in the patent unless this reviewer has prior knowledge. As usual, some of the comparisons with prior work are very selective and chosen to make the new invention look more attractive and beneficial than it actually is. The occurrence of serious errors continues, and in one patent structural formulae are given which indicate that an O atom has a valency of 4. In fact what has happened is that the O is actually a C atom but the error exists in five formula in a patent and should have been picked up by any chemist reading the patent. Perhaps none did.

Patent No. U.S. 6,642,424

Assignee: Chisso Corporation, Osaka-Fu, Japan

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

Neplanocin A **9** has strong anti-tumour activity and is used in conjunction with other drugs to treat cancer. Alternative synthetic routes to **9** that are mentioned have at least nine steps and give yields of <15%. This patent claims to provide improvements in the preparation of **9**, some of its related compounds, and novel intermediates that are useful in the synthesis of **9**. Although the synthetic route shown below has 10 steps, it is claimed that the overall yield is much higher than alternatives. Only one enantiomer is shown in the scheme below, but it is claimed that the process can be carried out using either form. The (+) form of the diol **1** giving the (−) form of **9** and the (−) form of **1** gives the (+) form of **9**.



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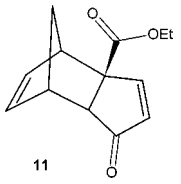
10.1021/op0499674 CCC: $27.50

The first step (a) in the process is the bromination of the diol **1** with NBS in CH_2Cl_2 to give **2a**. Step (b) is the protection of the hydroxymethyl group by reaction of **2a** with TBDMS chloride in DMF in the presence of a base such as imidazole to give **2b**. The next step (c) is the oxidation of **2b** with OsO_4/4-methylmorpholine oxide (NMMO) in THF/H_2O to give the diol **3b**. In step (d) a ketalizing agent such as dimethoxypropane is used in the presence of pyridinium *p*-toluenesulphonate (PPTS) to convert **3b** to **5b**. The next step (e) debrominates **5b** using active Zn in MeOH/HOAc to give **4b** which in step (f) undergoes the key reaction in the route. This is a retro-Diels−Alder reaction which is carried out by refluxing **4b** in Ph_2O for 30 min to give **6b**. Oxidation of **6b** in step (g) using pyridinium dichromate gives the ketone **7b** which is reduced in step (h) to **8b** using DIBALH. Thus, steps (g) and (h) are used to invert the configuration of the OH group. In step (i) a Mitsunobu reaction is carried out in which another inversion of the configuration occurs, resulting in the formation of **10**. The reaction is the condensation of the OH group in **8b** with adenine in the presence of diisopropylazocarboxylate and Ph_3P. The final step is the deprotection of the OH groups by treatment of **10** with HCl/MeOH to give **9**.

Compound **1** is novel, and a racemic mixture of **1** can be prepared by reduction of **11** using DIBAL. No details of the synthesis of **11** are provided, but the route is based on published work. The resolution of **11** is based on trans-esterification in the presence of a hydrolase, but again no details are given.



11

Advantages

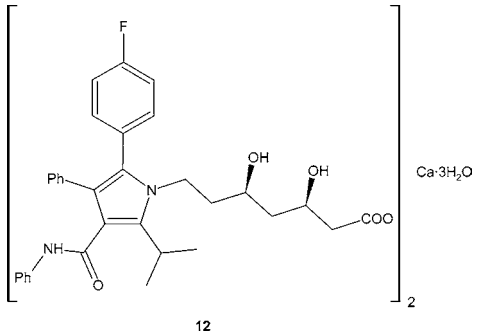
This procedure is claimed to give a 45% overall yield of **9**, and hence, this is a significant improvement over previous routes.

Patent No. U.S. 6,646,133

Assignee: Egis Gyogyszergyar Rt., Budapest, Hungary

Title or Subject: Process for the Preparation of Amorphous Atorvastatin Calcium

Statins are currently of great interest in treating cardiovascular diseases, and several patents have already been reviewed (*Org. Process Res. Dev.* **2003**, *7*, 784). This is the first of two patents in this review covering these compounds and deals with producing **12** in the amorphous form. **12** is known to exist as four polymorphs, but the amorphous form is preferred in pharmaceutical formulations. One alternative method of producing amorphous **12** from the crystalline Form I is said to be difficult to carry out. This is partly because the production of Form I itself cannot be accurately predicted. Hence, this patent attempts to overcome this problem by producing the amorphous form from the crude **12**.



12

The procedure consists of dissolving the crude **12** in a boiling alcohol such as *i*-PrOH and then cooling to room temperature. The mixture is then left at 4 °C for 4 h, and the solid is collected and dried in a vacuum at room temperature. The procedure is very simple and is said to be all the more surprising because a previous process for preparing amorphous **12** recommended only using solvents that did not contain a hydroxy group such as THF or PhMe. The alternative process also required drying of the crystals in specially manufactured apparatus which increased the costs of the procedure.

Advantages

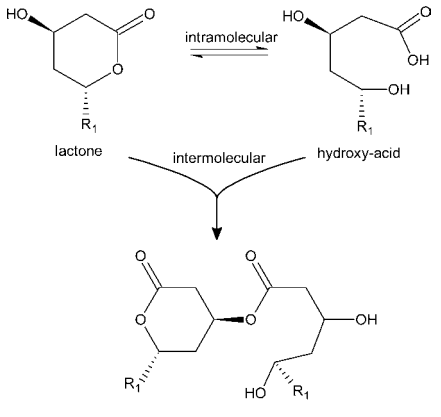
This procedure is extremely simple and does not require special drying equipment; hence, it seems to be a great improvement over the alternative process.

Patent No. U.S. 6,649,775

Assignee: Cheil Jedang Corporation, Seoul, Korea

Title or Subject: Process of Lactonisation in the Preparation of Statins

This is the second patent on statins and is concerned with lovastatin **15a** and simvastatin **15b**. The patent focuses on the key problem in dealing with statins, namely the intramolecular lactonisation reaction shown below which makes their recovery difficult. Another particular problem is an intermolecular reaction which can produce dimeric species such as **13** which can give further side reactions and more by-products.

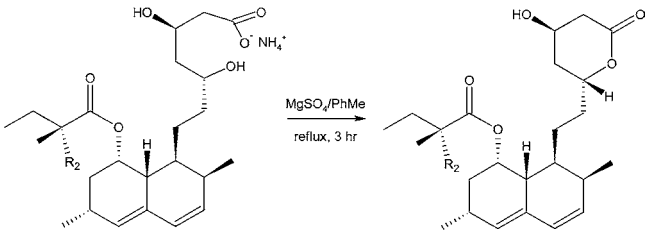


13

The drugs are said to be administered in the lactone form; hence, the objective of the patent was to provide an effective method for producing the lactone form of the statins, and

the patent discloses experimental details for producing both compounds.

The process is based on the use of a dehydrating agent to effect the lactonisation reaction. The reaction shown below is carried out using the ammonium salts **14a** or **14b** of the hydroxy acid form, and this is refluxed with $MgSO_4$ in PhMe. Recrystallisation from EtOH/H_2O at 30−40 °C gave the statins with <0.17% of the dimers. It is noted that the temperature of the crystallisation process is maintained between 30 and 40 °C. This is because below 30 °C it is difficult to remove contaminants and above 40 °C the crystallisation process is less effective.



14a: R_2 = H
14b: R_2 = Me

15a: R_2 = H; lovastatin
15b: R_2 = Me; simvastatin

Advantages

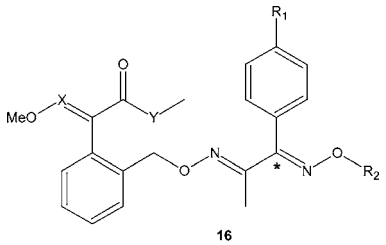
The process is claimed to produce a more efficient commercial method of obtaining these important drugs in high purity.

Patent No. 6,646,151

Assignee: Bayer AG, Leverkusen, Germany

Title or Subject: Process for the Preparation of Pesticides

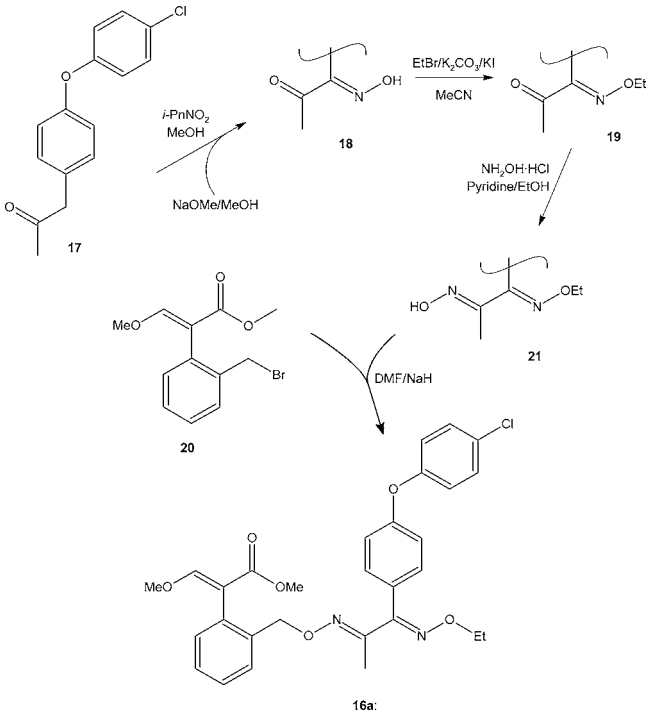
This is the first of two patents from Bayer on the subject of oximes. This patent describes pesticides, and the later one covers plant fungicides. The three ranges of pesticide described in the current patent are represented by the general formula **16** below. All of the compounds claimed in the patent have the *E* configuration at the C═N bond indicated. It is stated that the *E* and *Z* isomers have differing activity and the *E* is much preferred.



16

16a: Series 1; X = CH, Y = O
16b: Series 2; X = N, Y = O
16c: Series 3; X = N, Y = NH

The process described here is said to be an improvement over alternatives routes in that it gives pure *E* isomer. In total the patent includes a tabulation covering 924 combinations of R_1 and R_2. Experimental details are given for four compounds of series 1, one each of series 2 and 3. Melting point data are given for around 30 compounds and ^{13}C NMR data for two compounds. The basic synthetic route to all compounds is identical, and the scheme below shows the preparation of one compound from series 1 in which R_1 = 4-chlorophenoxy and R_2 = Et. Details are also given in the patent for preparing the analogous compounds from series 2 and 3.



17 **18** **19** **20** **21**

16a:

The route to **16a** begins with the formation of the *E*-oxime **18** from **17** in a two-step, one-pot reaction using isopentyl nitrite. This seems to be the key step of the process and is reported to proceed with selective formation of the 1-*E*-oxime. There is no suggestion as to why this step is selective. In the next step the 1-ethyloxime **19** is formed, and then the second ketone group is converted to the oxime **21** using NH_2OH. Reaction of the bromo compound **20** with **21** in the presence of a strong base such as NAH/DMF gives the desired compound **16a**.

Advantages

The selective formation of the desired *E*-isomer early in the synthesis means that the overall yield of the process is very much higher than alternative routes that require separation of the *E* and *Z* isomers at some stage of the process.

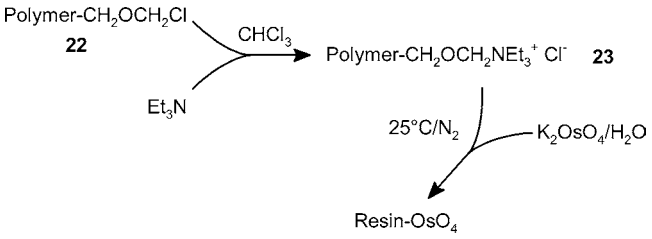
Patent No. U.S. 6,646,168

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

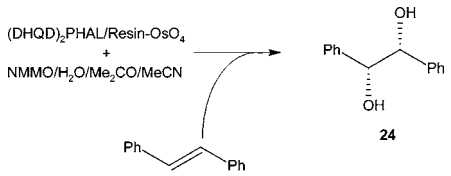
Title or Subject: Process for the Preparation of Supported Osmates and Their Use as Catalysts in Preparing Vicinal Diols

The patent is specifically aimed at preparing and using supported osmate catalysts to prepare *vic*-diols from olefins in the presence of chiral cinchona alkaloid compounds. This combination allows an asymmetric dihydroxylation reaction to be carried out. The use of supported osmates is claimed to avoid the use and potential losses of the highly toxic osmium tetroxide.

The supported osmate catalysts are prepared by an ion-exchange technique shown below. The first step is formation of the quaternary salt **23** by reaction of Et_3N with the chloromethylated polymer **22**. The polymer was a commercially available styrene/divinylbenzene material. Reaction of **23** with K_2OsO_4 resulted in the catalyst designated Resin-OsO_4. Silica supported osmates were also prepared.



The hydroxylation is carried out using a cinchona alkaloid as a chiral ligand, and the example used in the patent is hydroquinidine 1,4-phthalazinediyl diether $(DHQD)_2PHAL$. The scheme below shows the reaction using stilbene to give **24**. The catalysts and the alkaloid were mixed with NMMO as the oxidant in a solvent mixture consisting of equal parts of Me_2CO, H_2O, and MeCN. Alternative solvents mixtures also contain H_2O and either *n*-BuOH, Me_2CO, or MeCN. Experiments also described the dihydroxylation of styrene, *E*-methylstyrene, methyl *trans*-cinnamate with yields >93% and ee in excess of 95%, whereas experiments using allyl 1-naphthyl ether gave ee of only 77%.



The activity of the supported catalysts is higher than that of homogeneous counterparts, and this is attributed to the large positive potential of the OsO_4^{2-} which induces polarisation of the N→O bond in the NMMO, facilitating O transfer. The patent claims that the catalyst is capable of being recycled and reused several times without substantial loss in activity or product yield. Experiments are described using catalysts up to six more times which support this claim.

Advantages

This is claimed to be a selective and ecofriendly process since the catalysts are easily recovered and reused. This is a major improvement over the use of the more frequently employed soluble osmate catalysts.

Patent No. U.S. 6,646,169

Assignee: Chemetall GmbH, Frankfurt am Main, Germany

Title or Subject: Concentrated Stable Alkali Alkoxide Solutions

Alkali alkoxides are extensively used in many synthetic procedures, and solutions of the more commonly used materials derived from primary alcohols are widely available. This patent describes a method for preparing stable solutions of the *tert*-butyl and *tert*-amyl derivatives in aprotic solvents such as PhMe or MTBE. Details are given for the preparation of Na and K derivatives by dissolving the metal hydroxide and alkoxide in the solvent. The addition of the hydroxide is found to increase the solubility of the alkoxide and therefore gives more concentrated solutions.

When preparing a solution of Na *tert*-amyloxide in PhMe by simply dissolving Na pieces in *tert*-amyl alcohol the maximum content of alkoxide was 36.1% at 21 °C. However, by carrying out the procedure in the presence of NaOH pellets, the alkoxide content was increased to 46.6% at 23 °C. An alternative approach is to add alkali metal as pieces and an amount of water to give the required quantity of metal hydroxide. In this way a solution of the Na *tert*-amyloxide was obtained containing 53.2% of the alkoxide at 24 °C. The patent also claims that *n*-BuLi can be used to improve the alkoxide solubility, but no examples are provided.

Advantages

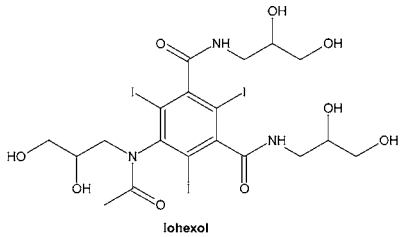
The method can give much higher concentrations of the alkoxides which are claimed to be more stable than those obtained by alternative procedures.

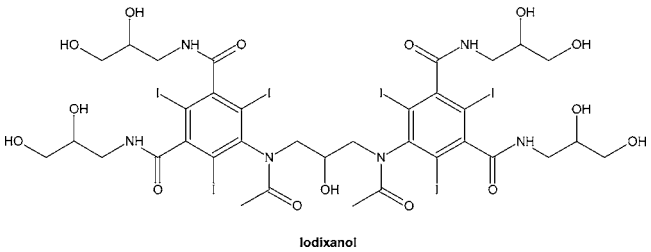
Patent No. U.S. 6,646,171

Assignee: Amersham Health AS, Oslo, Norway

Title or Subject: Process for Crystallisation of Sterically Hindered Compounds

This patent relates to two compounds known as iodixanol and iohexol which are iodophenyl compounds. They are both used as X-ray contrast agents in the diagnosis of problems in the kidney and other major organs. It is stated that these sterically hindered molecules are very slow to crystallise because of the time taken for transition of the various possible conformations. Hence, several days may be needed to obtain crystals. To increase the rate of producing crystals a high degree of supersaturation is often needed, but this often reduces the purity of the crystals. This subject has been reviewed previously (*Org. Process Res. Dev.* **2003**, *7*, 135).





This patent describes a process of accelerating the crystallisation of these compounds without the need for highly supersaturated solutions. The basis of the procedure

is to produce a supersaturated solution of the compounds under elevated pressure. This increases the boiling point of the solution so that a more concentrated solution can be obtained because of the higher temperatures that can be employed. In addition this reduces the amount of solvent that is needed. The procedure was applied to obtaining crystals by the use of seeding, anti-solvents, or controlled cooling. The pressure required is such that the boiling point of the solvent is increased by at least 10 °C above its boiling point at atmospheric pressure.

The effect of elevated pressures on crystallisation has been examined over a long period although it is probably not something that is routinely carried out by organic chemists. To obtain a more concentrated solution of a compound it may be a useful exercise to increase the pressure instead of changing to a solvent that has a higher boiling point. This is particularly the case if the solvent has other desirable properties and is already part of a standard and approved process. The patent does state that this process is applicable to any substance of low solubility as long as it is stable at the elevated temperature.

Advantages

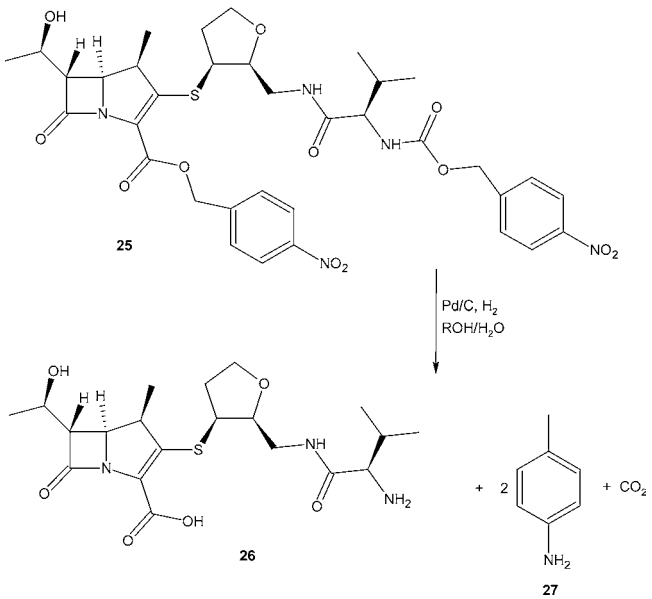
This process provides a relatively simple way of increasing solubility without having to change the solvent.

Patent No. U.S. 6,649,756

Assignee: Wyeth, Five Giralda Farms, Madison, New Jersey, U.S.A.

Title or Subject: Improved Process for the Preparation of a Carbapenem Antibacterial Agent

The patent relates to producing the compound **26** which is an anti-bacterial agent. The process is a biphasic hydrogenation of **25**, and the product is recovered from the aqueous portion by lyophilization (freeze-drying) or reverse osmosis. It is stated that carbapenems are difficult to produce and purify because they are thermally sensitive. This necessitates the use of protecting groups which can give unwanted contaminants that are difficult to remove. Commonly used protecting groups are *p*-nitrobenzyl or *p*-nitrobenzyloxycarbonyl, and they can be removed by hydrogenation in buffered aqueous solutions. The patent describes a biphasic hydrogenolysis process that removes the need for buffers and simplifies the product recovery.



The reaction scheme is shown below and is carried out in a mixture of a water and a solvent that is immiscible with water such as *n*-hexanol, *n*-pentanol, *n*-BuOH, or ethyl acetate using Pd/C catalyst. Analytical yields of up to 100% were obtained. The reaction produces CO_2 and **27** which is dissolved in the organic phase. The desired product is dissolved in the aqueous phase and is recovered by lyophilization or reverse osmosis although no experimental details are given as to the use of either recovery method.

Advantages

The biphasic process avoids the use of buffered solutions that create problems in product recovery common in alternative routes. Hence, it gives higher yields of the product.

Patent No. U.S. 6,649,762

Assignee: Bayer AG, Leverkusen, Germany

Title or Subject: Crystal Modification C of 8-Cyano-1-cyclopropyl-7-(1S,6S-2-8-diazabicyclo-[4.3.0]nonan-8-yl)-6-fluoro-1,4-dihydro-4-oxo-3-quinoline Carboxylic Acid

This patent focuses on an anti-bacterial agent commonly known as finafloxacin **29**. The normal method used to synthesise **29** is said to give a mixture of polymorphs in unpredictable proportions. An amorphous form of **29** is also known, but this is hygroscopic and hence not particularly suitable for pharmaceutical formulations. This patent discloses a method of producing a stable form of **29** that can be obtained in a predictable and controlled manner. This form is designated Form C and was characterised by X-ray diffraction (XRD) and differential thermoanalysis (DTA). Copies of these spectra and also the IR spectrum of the new form are shown in the patent.

The route to make **29**, shown below, is the reaction of the chloroquinoline **28** with **30** in the presence of a base. The initial solid from the reaction is then further treated as follows:

(a) suspend in EtOH/*i*-Pr_2NEt and reflux 3 hr;

(b) cool, filter to recover solid, wash in EtOH, and dry under vacuum at 60−70 °C;

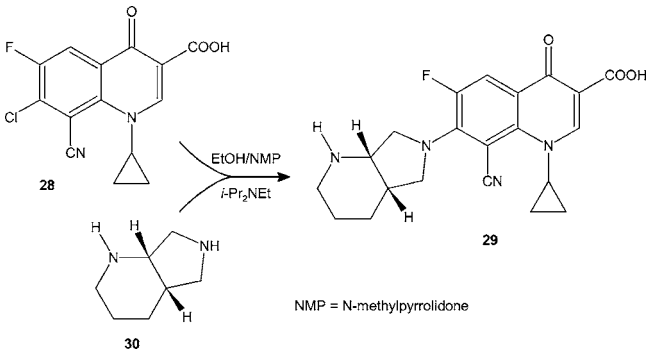
(c) store solid at room temperature in an atmosphere with a relative humidity of >92% until there is no weight increase. (The experiment in the patent states that this took 11 days.)

(d) The solid was dried at 100 °C in a vacuum over P_2O_5 for 24 hr

At this stage the amorphous form of **29** is obtained, and if this heated under N_2 at 180 °C for 2 h, the new form C is obtained.

The synthesis of the solid used in step a was carried out using >1 kg of **28**; hence, at least this step has been carried out on a reasonable scale. However, the subsequent steps described for the production of the new form were carried out using <500 mg of material, and it is not obvious how

this procedure can be scaled up. Since step c was reported as taking 11 days, the scale-up of this process would need to address this problem.



28 29 30

Advantages

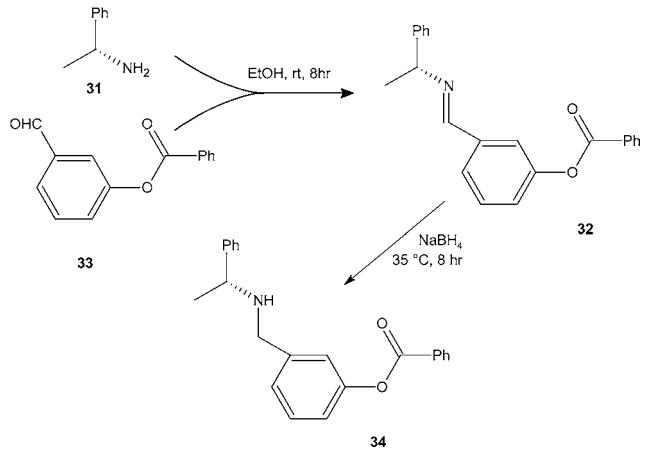
The procedure is claimed to be reproducible and to give a stable form of the active material, but it is debatable if the process, as described, can be carried out on a commercial scale.

Patent No. U.S. 6,653,507

Assignee: Sumitomo Chemical Company Limited, Osaka, Japan

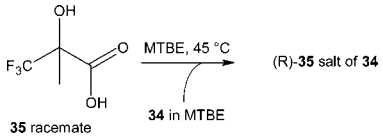
Title or Subject: Process for Producing Optically Active 3,3,3-Trifluoro-2-hydroxy-2-methylpropionic Acid and Salt Thereof

The title compound **35** is used to prepare a range of agrochemicals and pharmaceutical intermediates, and this patent describes a resolution process for producing **35** using a novel optically active amine **34**. In fact the claims of the patent actually cover the novel amines themselves, and the patent provides a method of preparing the amines, an example of which is **34**. This is prepared by reaction of the benzaldehyde **33** with the chiral amine **31** as shown below. This is a two-stage reaction that takes place via the imine **32** which is first formed but not isolated and then reduced to **34** using $NaBH_4$. A large number of amines are claimed which all contain the 3- or 4-benzyloxyphenyl group and which are prepared by this general method.



31 32 33 34

The resolution of the acid **35** is carried out as shown below by adding a solution of the amine in MTBE to **34** in MTBE at 45 °C. Upon cooling to 35 °C crystals of the *R*-form of **35** are precipitated as the salt of **34** with an ee of 95%. The patent contains >20 examples of the resolution of **35** by using a variety of the novel amines. Comparison with conventional resolving amines shows that they give much poorer results. For example using (−)-brucine the *ee* was 42% and with **31** the ee was only 5%. No details are provided for the isolation of the free acid **35**, and so it is not known if this is any more difficult than the standard methods using conventional amine-resolving agents.



Advantages

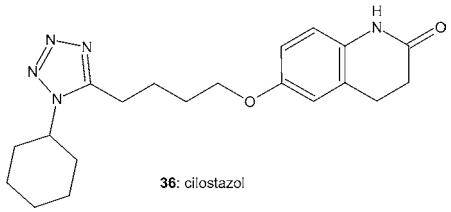
The use of these novel amines seems to give a more efficient process of resolving the desired compound. The patent does provide a new range of amines which may have potential as resolving agents for other materials.

Patent No. U.S. 6,657,061

Assignee: G. W. Stowell and R. R. Whittle

Title or Subject: Polymorphic Forms of 6-[4-1(1-Cyclohexyl-1H-tetrazol-5-yl)butoxy]-3,4-dihydro-2-(1H)-quinolinone

This and the next patent cover the drug cilostazol **36** that is used to treat erectile dysfunction. The current patent describes one of three polymorphs of **36**, and analogous patents on this subject from the patent authors have already been reviewed (*Org. Process Res. Dev.* **2003**, *7*, 784). The current patent provides extensive physical characterisation data based on XRD, FTIR, and FT-Raman spectra as well as differential scanning calorimetry of the B Form of **36**. The B form is the most stable and soluble form of **3**, hence, the interest in developing a method to produce it.



36: cilostazol

Advantages

The patent provides a method to produce the stable form of this drug.

Patent No. U.S. 6,660,773

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

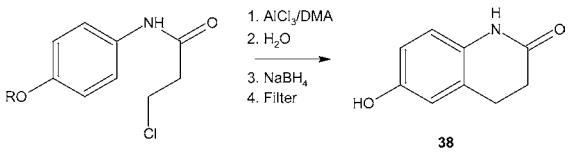
Title or Subject: Processes for Preparing 6-Hydroxy-3,4-Dihydroquinolinone, Cilostazol and N-(4-Methoxyphenyl)3-chloropropionamide

This patent describes a new process for preparing the quinolinone **38** that is an intermediate in the production of cilostazol **36**. The patent compares the new route to the original process for preparing **38** that was in a patent published about 30 years ago (U.S. Patent 3,819,637). The

original process also starts from **37a** as does the present route but is carried out in a melt of $AlCl_3$ and **37a** and does not use solvents. Not surprisingly, this is said to be unselective and gives low yields. Reference is also made to more recent work which improved on the earlier process but it does show how patents can be selective when comparing procedures. The new route to **38** is shown below and is also based on the cyclisation of the amide **37a** using $AlCl_3$ but is carried out in dimethylacetamide (DMA). It was claimed that an excess of DMA was required (30%) to give the highest yield of **38** (94.4%), but even using a equimolar quantity gave better quality product than alternative methods. The major by-product in the reaction is **37b** (R = H). The original method for producing **38** gave a 28% yield of **37b**, and the current process maintains this at <0.1%.

The DMA is described as being a diluent rather than a solvent, and in fact the concentration of **37a** is so high that the mixture is described as a slurry. However, it is claimed that it can be stirred easily; therefore, hot spots are prevented, and as a consequence, by-products are not formed.

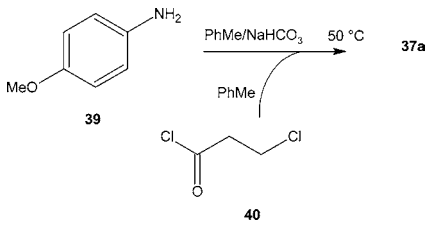
After the reaction is completed, the mixture is quenched in water, and then $NaBH_4$ is added to decompose the Al salts.



37a: R = Me

38

The patent also provides an improved preparation of the amide **37a** by an acylation reaction between *p*-anisidine **39** and **40** shown below The improvement arises from the use of a specific combination of base and solvent plus the control of the reaction temperature. The combination of $NaHCO_3$ and PhMe gave a yield of **37a** of 96% which compares with a yield of 95% using $NaOH/CH_2Cl_2$, 87% using NEt_3/MEK, or 77% using only DMF.



39

40

Advantages

The patent provides improved methods to prepare a key intermediate for a drug of great interest.

Patent No. U.S. 6,657,073

Assignee: Daesang Corporation, Kyungki-do. Korea

Title or Subject: Crystallisation of α-L-Aspartyl-L-phenylalanine Methyl Ester

The title compound is a low calorie sweetener commonly known as aspartame. The patent discloses a method of achieving maximum productivity of crystals with optimum crystal size distribution by crystallisation of aspartame from aqueous solution. As is common with any crystallisation process, there is a balance between the maximum production rate of crystals and the production of high-purity crystals. These two processes are incompatible; hence, a compromise is necessary between high production rate and high purity. The normal procedure for crystallising aspartame is to cool a hot, saturated solution either with or without the addition of seed crystals.

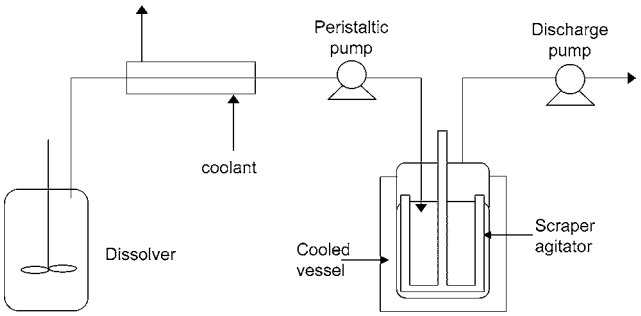


Figure 1. **Crystal nucleation using peristaltic pump.**

The process described here does not add seed crystals to the cooled solution. Instead, seeds are formed in situ by pumping the cooled solution with a peristaltic pump, and the squeezing action of the pump on the tube induces nucleation. The slurry is then transferred to an agitated cooled vessel in which the crystallisation process takes place. A problem common to cooled crystallisers is the reduction in heat-transfer capabilities as the crystals form on the vessel walls and cooling coils. This is avoided by using a ribbon-type impeller which scrapes the surfaces and maintains good heat transfer in the crystalliser. The process scheme is shown in Figure 1.

On a commercial scale the process is carried out in a continuous mode. One example in the patent describes a process flow of about 25 L/min, indicating that this is most probably in commercial operation. The key to this process is to control the nucleation process using the mechanical energy of the peristaltic pump. Although the process in the patent is aimed at a continuous process, it is not difficult to apply this procedure to batch process by simply circulating the saturated solution through a peristaltic pump until nucleation occurs.

Advantages

The procedure allows much better control of the whole crystallisation process from nucleation through to crystal production. Hence, the product can be produced more quickly and in higher quality.

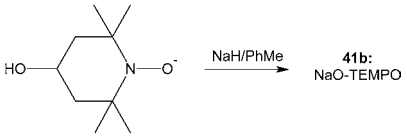
Patent No. U.S. 6,660,860

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

Title or Subject: Process for the Selective Oxidation of Alcohols Using Readily Removable Nitroxyl Radicals

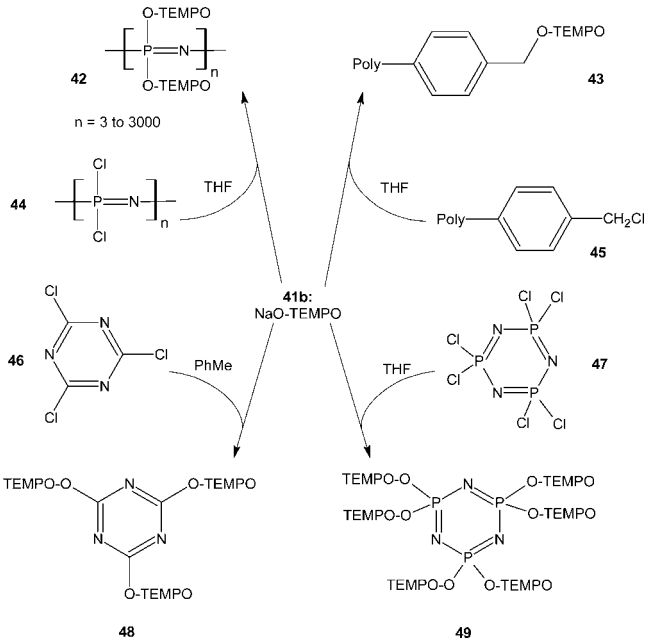
This patent describes the preparation of a number of heterogeneous oxidation catalysts (**42, 43, 48**, and **49**) that are based on compounds containing nitroxyl radicals derived from the well-known oxidant TEMPO. The patent has a single claim that covers the compound **42** and has experi-

mental details describing the preparation and use of the four related oxidation catalysts. The patent uses these insoluble catalysts for the oxidation of alcohols by NaOCl. The catalysts are prepared from the Na salt **41b** which is made by reaction of NaH with hydroxy TEMPO as shown below.



41a:
HO-TEMPO

Four different insoluble catalysts are described and they prepared by the same type of reaction between **41b** and chloro compounds as shown below.



The catalysts are then used in the oxidation of a range of primary and secondary alcohols to ketones. Examples of alcohols are 1,2-propanediol, *i*-PrOH, 2,4-pentanediol, benzoin, and phenylglycol. The oxidation is carried out by treating the alcohol with a mixture of $NaOCl/NaHCO_3$ in a Me_2CO/PhMe solution the presence of the novel catalysts. The ketones are obtained in virtually quantitative yield, and the catalysts are recovered by filtration.

Advantages

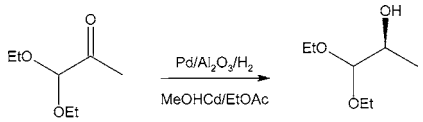
TEMPO is widely used; since it is soluble, it can be difficult to separate the products of the reaction. The use of insoluble forms of the useful oxidant gives high yields and more efficient product recovery.

Patent No. U.S. 6,660,890

Assignee: Solvias AG, Basel, Switzerland

Title or Subject: Production of Optically Active α-Hydroxyacetals

The subject of this patent is the hydrogenation of prochiral α-ketoacetals with supported Pt catalysts in the presence of cinchona alkaloids to give a chiral α-hydroxyacetal such as **51**. It is claimed that the use of this catalysts system is unique for these substrates and suitable for use on an industrial scale. The α-hydroxyacetal products are valuable intermediates in the production of pharmaceuticals and pesticides. An example of the reaction is shown below in which a solution of **50** in EtOAc is converted to the α-hydroxyacetal **51** using Pt/Al_2O_3 in the presence of methoxyhydrocinchonidine (MeOHCd). The ee of the product is >91%.



50 **51**

A variety of α-ketoacetals, alkaloids, and solvents was used, and the yields and ee of the products varied for each combination. The solvents used were PhMe, EtOH, HOAc, or EtOAc, and a feature of the process is that high concentrations of the substrate can be used. It is also claimed that it is possible to use no solvent.

Advantages

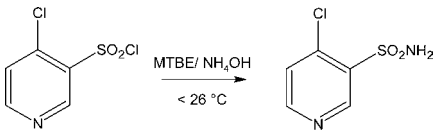
This is said to be a surprising finding and applicable to the commercial production of α-hydroxyacetals.

Patent No. U.S. 6,664,396

Assignee: Eastman Kodak Company, Rochester, New York, U.S.A.

Title or Subject: One Step Synthesis for Quinacridone Compounds

N,*N*′-Diarylquinacridones such as **52b** are used in the manufacture of light-emitting diodes. This patent describes a method of producing **52b** by arylation of an unsubstituted quinacridone such as **52a**. Alternative methods using this route are said to be unreported although the alkylation reaction is known. The process involves the Cu-catalysed arylation of **52a** with PhI in the presence of a base. The reaction scheme is shown below and is carried out by mixing **52a** with a mixture of Cu and CuI and then adding the PhI. This is then followed by addition of a base such as NaH and then 2,2,6,6-tetramethyl-3,5-heptanedione (TMHD) which acts as a ligand for the Cu. The yield of **52b** was up to 42%.



68 **69**

Another ligand that was used was 1,10-phenanthroline and $NaOBu^t$ was an alternative base. It is stated that solvents are not always required, although *N*-methylpyrrolidone was used. When a comparative experiment was carried out in which the ligand was omitted and K_2CO_3 was used as the base there was no reaction. However, this reaction was carried out at room temperature and hence the comparison is not entirely fair.

Advantages

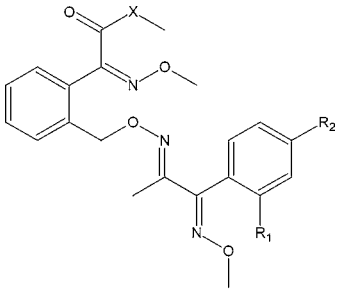
The route is novel and starts with readily available starting materials.

Patent No. U.S. 6,664,422

Assignee: Bayer AG, Leverkusen, Germany

Title or Subject: Process for the Preparation of Strobilurin Intermediates

This is the second patent from Bayer covering oximes, and it discloses a method of producing fungicides known as strobilurins. These compounds are highly active fungicides for use against plant infections. The original strobilurin is a naturally occurring material known as strobilurin A and is produced by the pine cone fungus. There are said to be only 30 synthetic versions of the compounds with the general formula **53** and not all combinations have been reported. Methods for their preparation are claimed to be suitable only for laboratory procedures although, since they are in commercial use, this hardly seems credible.

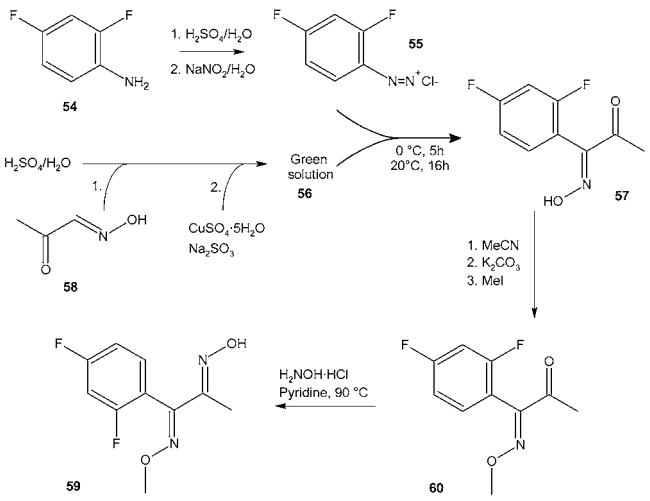


53

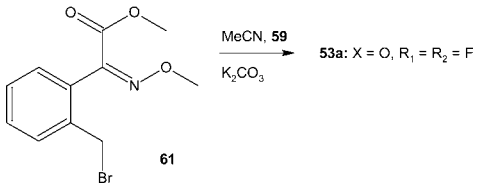
X = O or NH
R_1 = H, F or Cl
R_2 = R_1, Br, CN, Me, Et, OMe, OEt or CF_3

The patent claims relate to a process for the preparation of an oxime such as **59**. In the patent five of the formulae of intermediate oximes contain an O atom which has a valency of 4 and is due to the O atom being drawn instead of a C atom. This sort of error should not happen in a legal document.

In the production of **59**, by the scheme shown below, the first step is the formation the diazonium salt **55** from the aniline **54**. The diazonium salt **55** is then converted to the oxime **57** by treatment with the solution **56** that was formed from the anti-form of the oxime **58**. Methylation of **57** then gives the methoxyoxime **60** which is converted to the dioxime **59** by reaction with $H_2NOH{\cdot}HCl$. The examples refer to the production of a mixture of the *E,E* and *E,Z* isomer of **59**, and the mixture is used to make the required strobilurin products although it is stated that the *E,E* is the preferred isomer. No indication as to how to separate the isomers of **59** is given although a mixture containing 92% *E,E* can be obtained by treating the mixture with HCl at 63−65 °C for 2 h. The selectivity of the various steps is not specified apart from **60** being 80% of the oil obtained by methylation of **57**.



Examples are also given in the patent which describe the production of the strobilurin **53a** from **59** by reaction with the iminoester **61** as shown in the scheme below. In this reaction the mixture of isomers of **59** is used, and the ratio of *E,E,E* to *E,E,Z* in the product **53a** is 87:13.



Advantages

The process is said to be suitable for operation on a commercial scale.

Patent No. U.S. 6,670,472

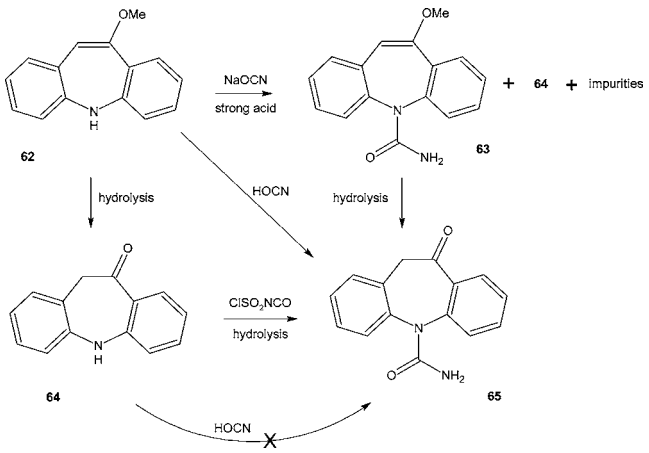
Assignee: Max India Limited, Karnataka, India

Title or Subject: Process for the Preparation of 10-Methoxycarbamazepine

The title compound **63** is used to prepare oxcarbazepine **65** which is an anti-convulsant drug used to treat various neural disorders. The patent describes an improved preparation of **63** and also a method of producing **65** by a biphasic hydrolysis of **63**.

The patent states that there is an alternative method of obtaining **63** from **62** by reaction with HOCN. This is produced in situ from NaOCN and a strong acid such as $ClCH_2CO_2H$. However, this reaction is not very selective and also produces **64** and various impurities, caused by many side reactions of **63** and **64**. The reason for the low yields is that there are two possible reactions of **62** with NaOCN and acids as shown below. In one reaction the enol−ether group in **62** is hydrolysed to give **64** which does not react with HOCN and therefore cannot form **65**. The other reaction of **62** is that of the NH group which does undergo a carboxamidation with HOCN and produces **65**. Hence, the reaction mixture contains several compounds from this complex series of reactions, and the subsequent recovery of the products is difficult and expensive. It is also possible to convert **62** to **65** via **64** by reaction of **64** with $ClSO_3NCO$. However, this reagent is not desirable because it is said to be very costly, toxic, and highly moisture sensitive. Thus, an improved method of converting **62** to **65** is claimed to be required. The process described in the patent is to generate HOCN by using a weak acid, and this avoids the hydrolysis of the enol−

ether in **62** so that the undesired side reactions are not observed.



The key finding of this work is said to be the reaction of **62** with HOCN which is generated in situ from NaNCO and a mild acid such as benzoic acid instead of a strong acid. The second aspect of this patent is the hydrolysis of **63** to give **65** which is carried out in a biphasic system using PhMe. The product **65** is not soluble in either phase and hence is more easily removed from the reaction mixture.

The key starting material **62** is prepared by a previously published, method but no details are given

Advantages

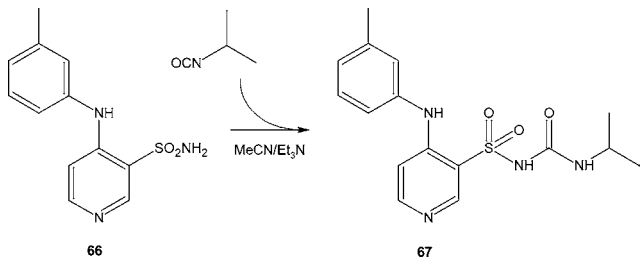
The process uses milder conditions and gives a higher yield than the alternative procedure.

Patent No. U.S. 6,670,478

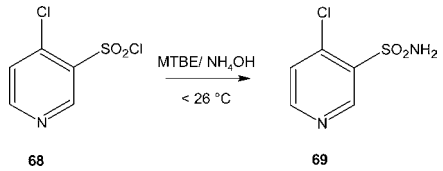
Assignee: Teva Pharmaceutical Industries Ltd., Petah Tiqva, Israel

Title or Subject: Process for Preparing Torsemide Intermediate

Torsemide **67** is a loop diuretic that is effective in the treatment of hypertension and edema associated with chronic renal failure. The subject of the claims of the patent is synthesis of **67** by the reaction of *i*-PrNCO with **66** in either MeCN or Me_2CO in the presence of Et_3N, and this is shown below. Previous routes to **67** using this reaction claim that solvents such as dioxane or CH_2Cl_2 are required. These are less attractive solvents, and the current method is said to give improved yields and a product of higher purity.



The patent also describes a synthesis of **69** from **68** by reaction with NH_4OH as shown in the scheme below. This is a known reaction and is usually carried out by the addition of **68** to a solution of NH_4OH so that the condensation of **68** with **69** is minimised. This procedure is said to require a large amount of NH_4OH and gives yields of <50% and the disposal of large volumes of basic waste solutions is an environmental problem. The improvement in the production of **69** described here is to add the base to a suspension of **68** in MTBE, and this increases the yield to >74% by reducing the amount of by-products. It is important that the temperature at this stage is maintained <26 °C.



The sulphonamide **69** can be converted to **66**, but no details of this are given in the patent.

Advantages

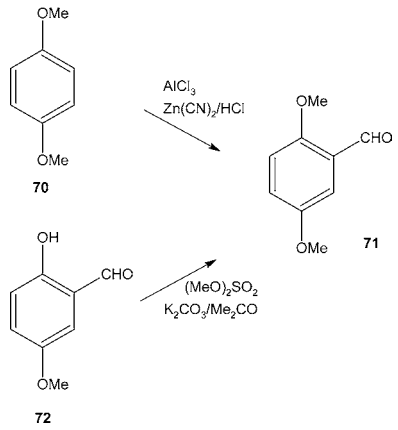
The new process is said to give improved yields of the intermediate **69** as well as a better method of producing **67**.

Patent No. U.S. 6,670,510

Assignee: Eastman Chemical Company, Kingsport, Tennessee, U.S.A.

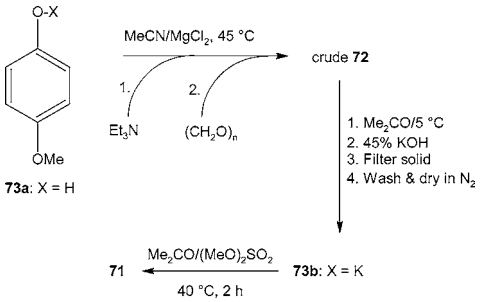
Title or Subject: Process for Preparing 2,5-Dimethoxybenzaldehyde

71 is an intermediate in the preparation of photographic developing agents and textile dyes. Several methods are available for its synthesis with the most commonly used being direct formylation of **70** or alkylation of **72** as shown below. The first method uses cyanides which are very toxic reagents, and this necessitates expensive equipment to contain the reaction mixture. The second method uses less dangerous reagents, but **72** requires expensive purification before being used. Hence, there is said to be a need for an improved method of preparing **71**.



The process disclosed in this patent is a development of the second method using **72**. However, the new route avoids the need to use purified **72** and starts with crude material instead. This is achieved by converting **72** to a metal salt by reaction with and alkali metal hydroxide in a polar solvent. The metal salt is then treated with the alkylating agent $(MeO)_2SO_2$ to give **71**. The scheme below shows a specific

example using KOH in Me_2CO. The process is carried out on the crude reaction product from a synthesis of **72** made by reaction of **73a** with paraformaldehyde in MeCN in the presence of Et_3N and $MgCl_2$. The crude product of this reaction is then dissolved in Me_2CO and converted to the K salt **73b** using concentrated KOH. Alkylation of **73b** with $(MeO)_2SO_2$ gave the desired **71** which after washing and drying was obtained in 88% yield at 100% purity by HPLC.



There are alternatives to the scheme in which the Na salt is produced or the solvent is a mixture of DMF/*n*-heptane or *i*-PrOH.

Advantages

The process avoids the need to use purified **72** and hence reduces the overall cost of making the desired product.

Keith Turner

Kappa Tau Consulting, 12 The Avenue, Fairfield, Stockton-on-Tees TS19 7EY, UK
E-mail: keith@kappa-tau.co.uk

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