Organic Process Research & Development **2003**, *7*, 784−793

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during April to July 2003

Summary

I must first begin with a thank you and an apology for a basic mistake in the last patent review. The thank you goes to those readers who e-mailed to point out that gabapentin has a plane of symmetry and is a not a chiral molecule so that one cannot obtain racemic mixtures of it as I mentioned in the review. A correction was published in the last issue, but the damage was done and hence the apology. This was required because I clearly forgot to take my dose of gabapentin on the day I wrote the review of that patent and obviously suffered the consequences. Just to show that I have not been deterred, there is an attempt at a review of another patent on gabapentin this month. I am sure that if there are any mistakes in this or any other summary you will let me know. On a serious note, any comments on any of the reviews are welcome, especially if you have direct knowledge of the subject or are even one of the inventors. I am sure that the editor would be delighted to receive more detailed papers on many of the subjects covered by the patents that are reviewed, if you are free to publish the work.

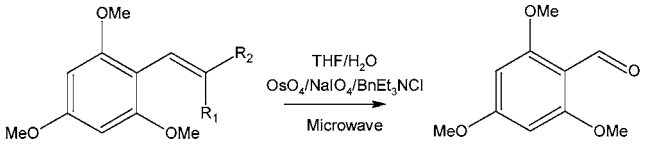
So to this month's collection which was culled from 631 patents that met the search criteria. The 22 patents included cover a wide range of topics which hopefully will generate interest among the readership. As already mentioned gabapentin is still of interest, and this time a purification method using membranes is described. Another unusual procedure that is described is the use of microwaves to activate a catalytic oxidation reaction to prepare aldehydes from olefins. The extraction of galanthamine from weeds rather than from protected plant species could be significant. There is only 0.03% of the important drug in the weeds compared to almost 10 times that in the normal sources. 1,3-Oxathiolane nucleosides receive attention as anti-HIV drugs, and two patents focus on these compounds. One provides new routes to these compounds, and the other provides a means of transforming unwanted isomers to the desired isomers. The importance of efficient mixing is demonstrated in a process to produce potassium monoethylmalonate where product yield and quality were reduced with poor mixing. Reuse of or recycling of by-products does increase atom yield, but this is not always possible, and two patents demonstrate this technique. One recovers iodine from alkylations using alkyl iodides and then converts the iodine back to the alkyl iodide. A second patent recycles by-product potassium salts in a synthesis of the flecainide and converts them to reactants. Another patent on flecainide uses NaH in DMF which is well-known to be hazardous on a large scale. Interest in statins continues with one patent reporting experiments on a 6000-L scale, thus indicating the advanced commercial status of the process, and several other patents report pilot-plant test work. As usual there is no legal or commercial significance in the choice, and advantages claimed are those claimed or alluded to in the patent unless this reviewer has personal knowledge.

Patent No. U.S. 6,544,390

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

Title or Subject: Microwave-Assisted Preparation of Aromatic Aldehydes from Phenylpropenes

Aromatic aldehydes are used as intermediates for a variety of syntheses including flavours, perfumes, and pharmaceuticals. Many of the aldehydes are obtained from natural sources such as flowers plants, and some can be synthesised by Vilsmeier Haack reactions of methoxybenzenes using $POCl_3$ at low temperatures. Such processes have significant waste disposal and handling problems and are said to give low yields. This patent describes a method of preparing compounds such as **2** by oxidation of the propene **1a** or **1b** using $OsO_4/NaIO_4$ as shown in the scheme below. The reaction mixture may also contain an acidic ion-exchange resin (IER) such as Amberlite IRA-410 or a quaternary ammonium salt as cocatalyst.



1a: R_1 = H, R_2 = Me
1b: R_1 = Me, R_2 = H

2

The reaction is carried out at ambient temperature under irradiation by microwaves in the frequency range 2−2.8 GHz. A key aspect of the process is the capability to make use of the toxic *cis*-propene **1b** as well as the nontoxic *trans*-isomer **1a**. The starting material can be either pure **1a** or **1b** or is a mixture of **1a** and **1b** which is available from calamus oil. Asian sources of this material have a higher proportion of toxic **1b** than does the oil from European or American sources. Thus, the Asian oils are cheaper, and this process allows them to be used in this synthesis. The conversion of **1b** to **2** with irradiation was the same (84%) as the conversion of **1a** to **2** without irradiation. The process was also applied to the preparation of other aldehydes such as 3,4-dimethoxybenzaldehyde and 4-methoxybenzaldehyde.

Advantages

The patent claims a number of advantages, but the chief one is related to the ability to use the cheaper calamus oils that contain the toxic *cis*-isomer.

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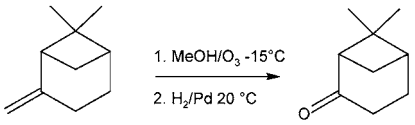
Patent No. 6,545,186

Assignee: DSM Fine Chemicals Austria Nfg GmbH & Co. KG, Linz, Austria

Title or Subject: Purification of Ketones Obtained by Ozonolysis and Reduction of Terpenes

Like the first patent this one is aimed at the fragrance and pharmaceutical industries and covers the preparation and purification of nopinone **4** from β-pinene **3**. This conversion of **3** to **4** shown below can be accomplished either by catalytic oxidation or ozonolysis, and both methods can produce many side reactions, making purification of **4** difficult.



3 **4**

Formation of peroxides is a particular problem, making vacuum distillation a hazardous procedure. This patent provides a safe method of recovering the ketone by means of vacuum steam distillation. This is carried out immediately following the reduction step by treating the reaction solution and proceeds as follows:

1. Adjust pH to 6 with dilute H_2SO_4.
2. Concentrate by evaporation.
3. Mix with water and white oil.
4. Steam distill to recover crude **4** overhead.

The residue contained all of the peroxides dissolved in the white oil, and the ketone **4** was extracted from the distillate with methyl *tert*-butyl ether (MTBE) and then purified by vacuum distillation. A yield of 79% was claimed. Steam distillation is a particularly effective method of distilling nonvolatile or thermally unstable mixtures, although productivity is reduced since most of the distillate is in fact water.

Advantages

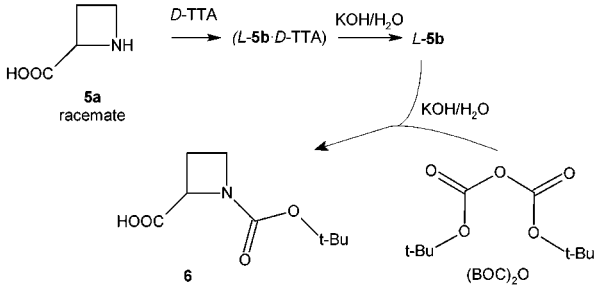
This method provides a safe process for purifying a potentially explosive reaction mixture.

Patent No. U.S. 6,548,680

Assignee: AstraZeneca AB, Sodertalje, Sweden

Title or Subject: Production of N-Protected Azetidine-2-carboxylic Acids

The title compounds such as **5a** are intermediates in the production of antithrombotic agents, and methods for their resolution and synthesis have been reviewed previously (*Org. Process Res. Dev.* **2001**, *5*, 100). This patent describes a process for protecting the azetidine with the acid-stable *tert*-butoxycarbonyl group. The procedure, shown in the scheme below, is to react a tartrate salt of **5a** with di-*tert*-butyl dicarbonate, $(BOC)_2O$ in basic solution to displace the tartrate group and form the protected compound **6**. The tartrate salt **5b** is obtained in a resolution reaction using D-tartaric acid (D-TTA). Hence, the whole process is used to produce enantiomerically pure and protected **6** which can be used in subsequent synthetic steps.



Advantages

This provides a convenient method of protecting the N atom using a well-known reagent without the need to isolate the free amino acid.

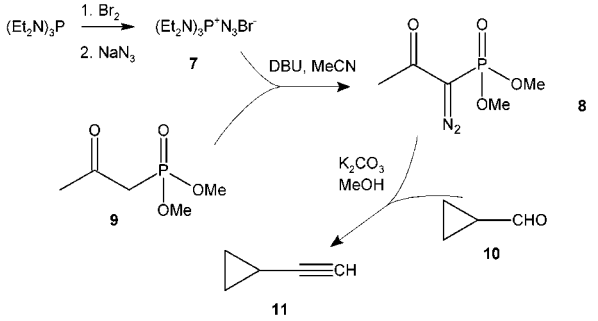
Patent No. U.S. 6,552,239

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

Title or Subject: Synthesis of Cyclopropylacetylene by a One-Pot Process

The title compound **11** is a key intermediate in the synthesis of the anti-AIDS drug, efavirenz, and other patents on its synthesis have been reviewed (*Org. Process Res. Dev.* **2002**, *6*, 346 and **2000**, *4*, 246). This patent claims that the alternative methods of synthesising **11** suffer from low yield and have impurities in the final product. The method disclosed here is a one-pot synthesis starting from the ketophosphonate **9** which is converted to the azide **8** which reacts with the aldehyde **10** to form **11** as shown below. The azide **8** is formed from **9**, using the phosphonium salt **7** as the diazo transfer agent. The synthesis of **7** is another one-pot process and is produced from HMPA by reaction with Br_2 in MeCN at about −15 °C. Alternative methods exist for synthesising **8**, but these give low yield and are not compatible with the one-pot strategy for synthesis of **11**.

The procedure is to dissolve **8** and **9** in an aprotic solvent such as MeCN and age the solution for about 1 h. The DBU is then added followed by **10** in a protic solvent such as $MeOH/K_2CO_3$, and the mixture is stirred at room temperature overnight. Extraction with *n*-octane and distillation gave 95% yield of **11**. The yield of **11** was shown to be dependent on the aprotic solvent and on the ratio of aprotic to protic solvents and reagents. A better yield was obtained using MeCN/MeOH (95%) than when using DMF/MeOH (74%). In addition the type and ratio of the bases used in the final



step was examined, and it was found that K_2CO_3 was better than Et_3N which did not produce any **11**.

Advantages

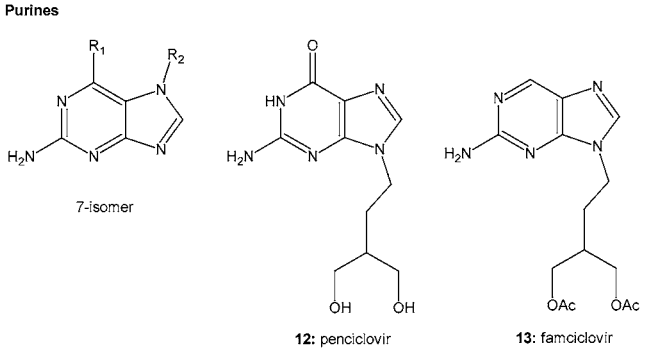
This process improves overall yield of **11** by carrying out the steps using readily available reagents without the necessity of isolating intermediates.

Patent No. U.S. 6,555,685

Assignee: Novartis International Pharmaceutical Ltd., Hamilton, Bermuda

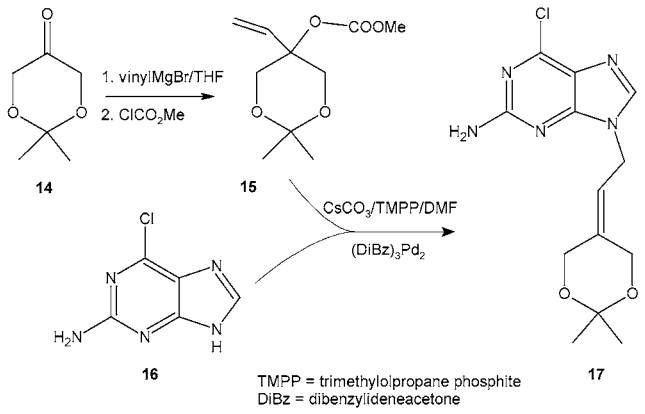
Title or Subject: Process for the Production of Purine Derivatives

The compounds disclosed in this patent are intermediates in synthesising drugs such as penciclovir **12** and famciclovir **13** that are used against infectious viral diseases including herpes, hepatitis, and AIDS. When making purine compounds such as those shown below, a mixture of the 7- and 9-isomers is formed with the unwanted 7-isomer being the more thermodynamically favoured.



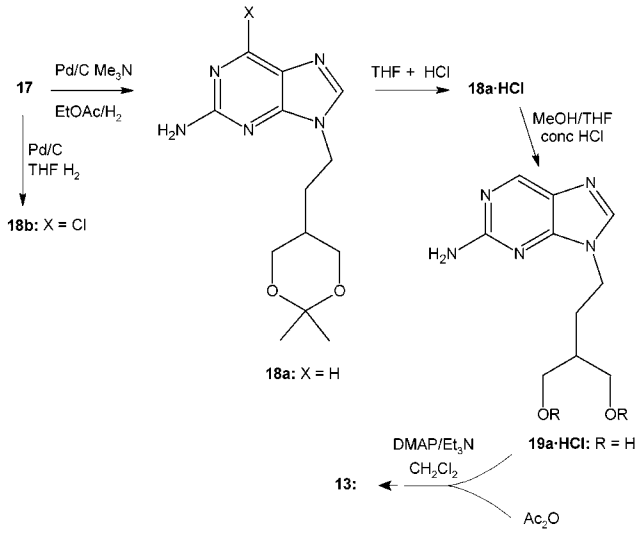
Hence, attempts to make the 9-isomer also produce the 7-isomer often at up to 35%. One route which has been reviewed (*Org. Process Res. Dev.* **2000**, *4*, 450) overcame the problem by blocking the 7-position before a critical substitution step was carried out.

The approach here is to react the purine **16** with a dioxane derivative **15** containing a carbonate-leaving group to give the 9-isomer **17**. The preparation of the dioxane **15** is carried out by reaction of **14** with vinylMgBr and $ClCO_2Me$, and this introduces the carbonate group in **15**. The novel step in the patent is the reaction of **15** with **16** which gives a surprisingly high selectivity to **17** over the undesirable



7-isomer. This step, shown below, is carried out in DMF under argon using a Pd catalyst with a phosphite ligand such as TMPP and in the presence $CsCO_3$ as a basic cocatalyst.

The reduction of **17** can be controlled to remove only the vinyl group, giving **18b** if the reaction is performed in the absence of a base. However, if a base such as Et_3N is used, then the chloro group can also be removed to give **18a** as shown below. The hydrochloride **18a**·HCl is formed by treating **18a** with concentrated HCl, and this is converted to the hydrochloride **19a**·HCl which produces famciclovir **13** by reaction with Ac_2O. The patent claims cover the production of penciclovir **12**, but no experimental details are given for this.



Advantages

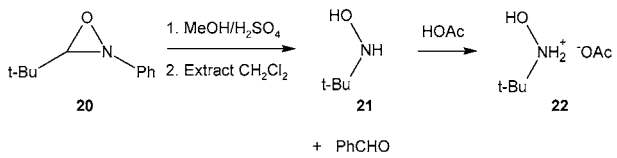
This process gives high selectivity to give the desired 9-isomer, thus simplifying the purification of the desired product.

Patent No. U.S. 6,559,340

Assignee: Bayer AG, Leverkusen, Germany

Title or Subject: Preparation of N-Susbtituted Hydroxylamines from Oxaziridines

The *N*-hydroxylamines such as **21** are useful synthetic intermediates but do suffer from not being stable when stored, whereas the salts such as **22** are more stable. There are known methods of synthesis of **22** by hydrolysis of **20**, but these are said to be relatively low yield, and there are difficulties in the removal of the aldehyde that is formed on hydrolysis. This patent provides an improved route from **20** to **21** which is shown below. After acid hydrolysis of **20** extraction with CH_2Cl_2 removed 95% of the benzaldehyde. Adjustment to pH 9 and treatment with HOAc gave crude **22** which was purified by crystallisation by addition of cyclohexane and cooling. The overall yield was 70%. A



possible impurity in the product is *tert*-butylphenylnitrone which can be formed from the benzaldehyde and **21** when distilling off the CH_2Cl_2, and GC analysis of the product showed 0.3 area % of the nitrone. Presumably, this level is acceptable, but no mention is made of this fact in the patent.

Advantages

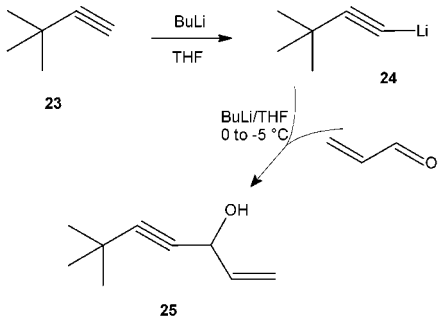
This process improves a known procedure and gives a higher yield of the product by using an improved extraction process to remove the aldehyde from the hydrolysis mixture.

Patent No. U.S. 6,570,044

Assignee: Chemagis Ltd., Tel Aviv, Israel

Title or Subject: Process for the Preparation of 6,6-Dimethylhept-1-en-4-yn-3-ol

The subject of the patent, **25**, is used to produce the antifungal drug, terbinafine. There are said to be two significant synthetic routes to terbinafine that both use **25**, and this patent provides a process to prepare **25** that is said to be capable of being performed on a large scale. Alternative routes to **25** involve the use of BuLi to generate *tert*-butylacetylide **24** from **23** at −40 °C, and **24** is condensed with acrolein also at temperatures below −40 °C. Such low temperatures require expensive refrigeration equipment and reaction vessels, and the objective of the inventors was to avoid the use of temperatures below −40 °C and hence reduce costs. The process disclosed here uses the same reagents, but the reactions are carried at around 0 °C. Alternatively, the patent describes the use of Grignard type reagent for the formation of *tert*-butylacetylide or even metallic Li. Both reagents are used at 0 °C and give reasonable yields, compared to using BuLi at <−40 °C.



Advantages

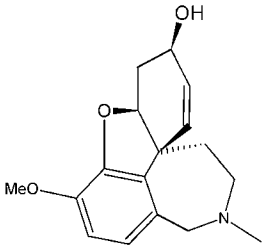
This ability to operate at temperatures above −40 °C is a significant improvement for any reaction. It appears that the yields are comparable; thus, overall the process is more attractive.

Patent No. U.S. 6,573,376

Assignee: LTS Lohmann Therapie-Systeme AG, Neuwied, Germany

Title or Subject: Process for the Isolation of Galanthamine

Galanthamine **26** and related compounds are of great interest in the treatment of Alzheimer's disease, as well as alcohol and nictotine dependence, and patents on this compound have previously been reviewed (*Org. Process Res. Dev.* **2001**, *5*, 350). **26** can be extracted from the bulbs of a number of plants such as daffodils and snowdrops. There are also synthetic routes available, but because the molecule has three chiral centres, these routes are by necessity long and complicated. Some of the plant species which contain up to 0.3% of **26** are protected, and hence alternatives are desirable. Processes which have been used to extract **26** from plants often use chlorinated solvents, and hence this is also discouraged. Hence, this patent describes a method of extracting **26**, using non-chlorinated solvents, from plants which are not protected and which are, in fact, said to be weeds. The plants used are of the amaryllidaceae genus including narcissi or crinum species, and even though they only contain 0.03% **26**, the process developed is said to be attractive.



26: (-)-galanthamine

The process involves the following steps and is carried out using air-dried bulbs of *Narcissus pseudonarcissus* which can be agriculturally cultivated:

1. Mix the comminuted bulbs with Na_2CO_3 at about 4 wt %.
2. Add petroleum ether (80/110) and leave 24 h.
3. Renew solvent twice, collect, and evaporate to dryness under vacuum.
4. Mix extracts with 2% H_2SO_4 an adjust pH to 4 using aqueous ammonia.
5. Extract five times with Et_2O and evaporate extract to give yellow oil.
6. Recrystallise from hot *i*-PrOH to give pure **26**.

From 100 kg of dried bulbs 10 g of **26** purified was obtained. The patent shows the HPLC of **26** obtained by this method and also a HPLC trace of **26** obtained by an alternative patented method using dichloroethane. The material obtained by the alternative method shows at least four contaminants, whereas this method gives a trace with only the peak from **26**. No comment is made about the relative attenuation or magnification of the two traces.

Advantages

This process uses nontoxic solvents to extract a valuable material from nonprotected plant species, and hence is of interest as a commercial process.

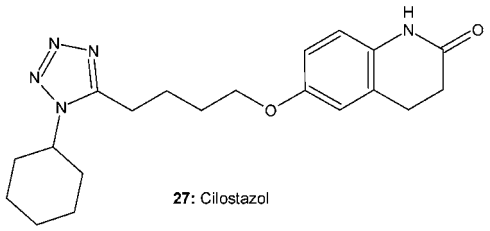
Patent No. U.S. 6,573,382

Assignee: Grayson Walker Stowell and Robert R. Whittle

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

The title compound is commonly known as cilostazol **27** and is claimed to be useful in the treatment of erectile

dysfunction. The current patent is analogous to an earlier one from these two inventors which was reviewed last year (*Org. Process Res. Dev.* **2002**, *6*, 749). Both patents describe two new polymorphs of **27** named B and C with the former patent covering form C, whereas the claims of the current one cover form B. The experimental work describes methods to produce either form. The production of B and C and the conversion of the original form A of **27** is based on a controlled melting and cooling technique which has been described previously. The original form A is not particularly soluble, whereas both forms B and C are stable and soluble in water and therefore more suitable for preparing pharmaceutical formulations.



27: Cilostazol

Advantages

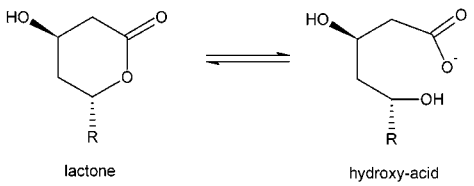
Producing new polymorphs of drugs whose patents have expired can extend the protection of the drug, and Stowell and Whittle have a number of patents covering polymorphs of several drugs.

Patent No. U.S. 6,573,392

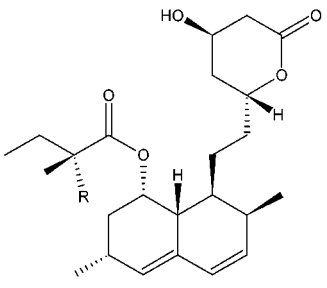
Assignee: Biocon India Limited, Bangalore, India

Title or Subject: Process for the Manufacture of Simvastatin from Lovastatin

There is a great deal of interest in statins for the treatment of cardiovascular diseases, and another patent is reviewed later. Patents on the subject have been reviewed previously (*Org. Process Res. Dev.* **2003**, *7*, 459). Simvastatin **28b** is reported to be twice as potent as lovastatin **28a** which is sold by Merck under the name Mevacor, and hence the synthesis of **28b** is a major goal. The recovery of statins is difficult because they exist as an equilibrium mixture of the hydroxy-acid and lactone shown below; hence, protecting the reactive carboxylic group is usually necessary, and this patent does this by conversion to an amide.

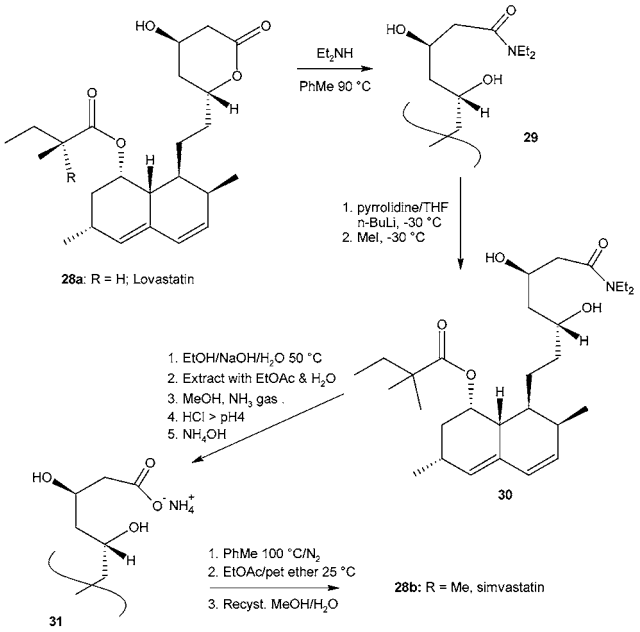


lactone hydroxy-acid



28a: R = H; Lovastatin
28b: R = Me; simvastatin

The process is shown below and is carried out in four steps. The first step is production of the amide **29** by reaction of **28a** with Et_2NH in PhMe. The amide **29** is then converted to the methylated compound **30** by initial treatment with Li pyrollidide amide followed by MeI at −30 °C. The next stage is production of the ammonium salt **31** by a multistep procedure. The pure ammonium salt **31** is then converted to the free acid and cyclised to give simvastatin **28b**.



The preferred amine in step 1 is Et_2NH, but experiments are also described using pyrrolidone or piperidine, and these are covered by separate claims in the patent.

Advantages

The process is able to use less metal amide and gives fewer side reactions than similar processes.

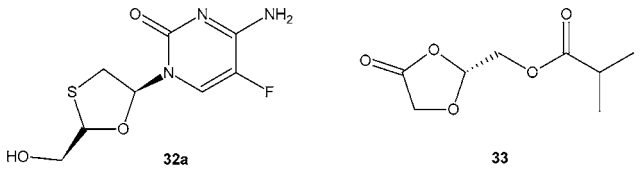
Patent No. U.S. 6,576,776

Assignee: Triangle Pharmaceuticals Inc., Durham, North Carolina, U.S.A.

Title or Subject: Method of Manufacture of 1,3-Oxathiolane Nucleosides

The title compounds such as **32a** and their 1,3-dioxolane analogues are used to treat HIV and other viral infections, and patents on these compounds have been reviewed previously (*Org. Process Res. Dev.* **2002**, *6*, 346). This and the next patent cover improvements in the synthesis of these important materials. The current patent provides new routes, whereas the next patent is aimed primarily at the recovery

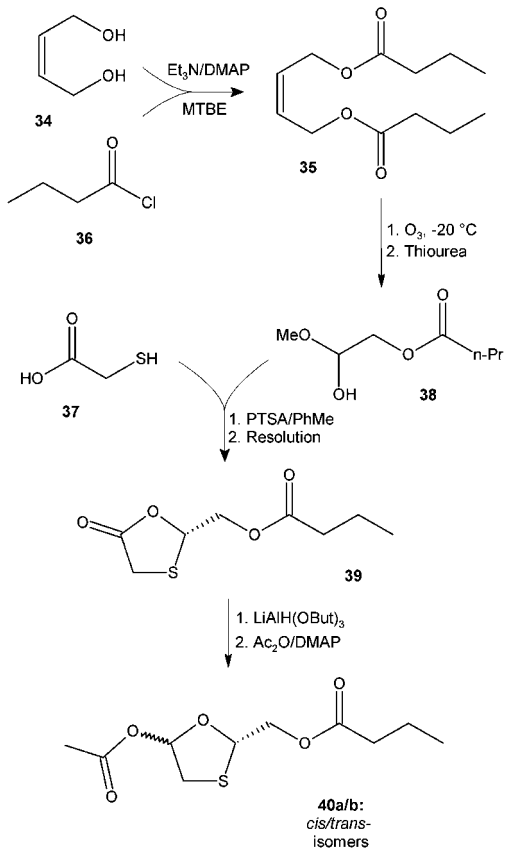
Nucleosides



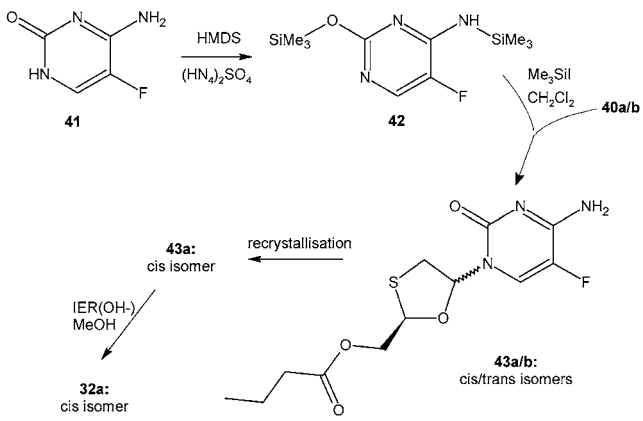
32a **33**

of the desired isomer. This patent describes experiments for producing **32a** by a multistep route; however, the claims actually cover the formation of the 1,3-dioxalone compound **33** although there are no detailed experiments for the synthesis of **33**.

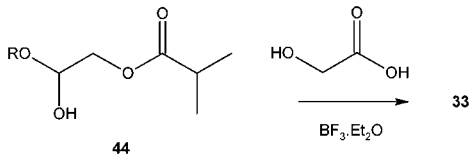
This patent provides quite an extensive review of previous work and claims that there are three key aspects of any route to these important materials. The first aspect is the need to produce the 1,3-oxathiolane ring (1,3-OR) that contains the desired substituent groups for subsequent reactions. The next aspect is the need to provide a method of condensing the 1,3-OR with a protected base. The final aspect is that the reaction must be stereoselective and must produce the single desired isomer from the four possible optical isomers. The route to **32a** has two sections, and the first, shown below, is to produce the 1,- OR **39**. This sequence begins with the formation of the diester **35** by reaction of the diol **34** with **36** catalysed by DMAP. In the next step **35** is cleaved using ozone at −20 °C to produce the hemi-acetal **38**. This reaction is quenched using thiourea rather than the more usual dimethyl sulphide since this reagent was found to give **38** in higher purity. Cyclisation of **38** with **37** then forms the 1,3-OR, but this step produces two enantiomers; after an unspecified resolution step the desired enantiomer **39** is obtained. This step does not give a racemic mixture but produces an excess **39** which, after recovery, can then be converted to the acetoxy compound **40a/b** which is a mixture of isomers.



The other section of the synthesis is shown below and begins with the formation of the protected base **42** by silylation. The silylated base **42** is then condensed with **40a/b** using a Lewis acid such as Me_3SiI. This reaction forms a mixture of two isomers, and the desired isomer **43a** is obtained by a crystallisation. In the next step the butyrate group was removed by treatment with a strong basic IER in MeOH to give the desired nucleoside **32a**.



The patent provides a process scheme with several alternative routes to the desired compounds, but experiments are not described for many of them. An interesting feature of this patent is the fact that the claims relate to **33** and not **32a**, and there are no details for preparing **33**. The only reference to the synthesis of **33** is that it can be prepared by reaction of an acetal with glycolic acid using a Lewis acid. This is analogous to formation of **39** from **37** and **38** and is shown below.



Advantages

The objective of the patent is to provide a method of making the nucleosides that can be operated on a manufacturing scale. Some of the experiments involve the use of large-scale equipment (72 L), and hence the process seems to have advantages that allow its scale up.

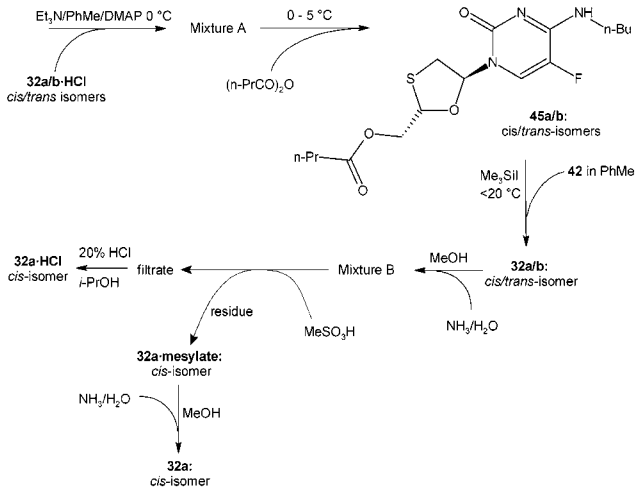
Patent No. U.S. 6,600,044

Assignee: Brantford Chemicals Inc., Brantford, Canada

Title or Subject: Process for Recovery of cis-1,3-Oxathiolane Nucleosides from Their Undesired trans-Isomers

This patent again provides a review of the methods used to synthesise the nucleosides including procedures for converting general nucleosides from the *trans*- to the *cis*-form in a process termed anomerisation and *trans*-glycosylation. The patent claims that this technique has not been applied to the conversion of *trans*-1,3-oxathiolane nucleosides and hence discloses such a process to obtain the desired isomers. The procedure is shown below and begins with the conversion of the *cis*/*trans* mixture of the HCl salts of **32a/b**. These are added to a mixture of Et_3N/DMAP in PhMe to

give Mixture A which is then treated with butyric dianhydride to give the butyrylamino butyrate **45a/b** as the mixed isomers. When this mixture is treated with the base **42** and Me_3SiI is added, the salt free mixture of **32a/b** is formed, and treating this mixture with aqueous NH_3 gives mixture B. After treatment of B with $MeSO_3H$ and filtration, the filtrate, on acidification, produces the pure HCl salt of the *cis*-isomer **32a**·HCl. The *cis* salt of **32a**·mesylate is obtained from the residue, and this can be converted to the free amine **32a** by treatment with aqueous NH_3.



Advantages

The process is able to convert the undesired *trans*-isomer to the desired *cis*-, and hence it improves the overall yield.

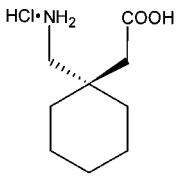
Patent No. U.S. 6,576,790

Assignee: Bioindustria Laboratorio Italiano Medicinali S.p.A., Novi Ligure, Italy

Title or Subject: Process for Preparation of Gabapentin and Purification Using Membranes

Gabapentin **46** is used as the hydrochloride salt **46·HCl** to treat cerebral diseases such as epilepsy, and several patents on this compound were summarised in the last review (*Org. Process Res. Dev.* **2003**, 7, 459). Many processes for preparing **46** use basic IER to obtain the free amino acid, but the current patent employs membranes for a diafiltration process used to separate ionic salts from the **46·HCl**. Membranes are finding increasing uses in purifying organic compounds, and this has generally been possible because of developments in the production of membrane materials.

Gabapentin



46•HCl

The diafiltration process uses a membrane that retains organic compounds having molecular weight >150 and allows permeation of inorganic monovalent ions. The membrane used in the experiments was ACN2540HS manufactured by Permeare S.r.l (Italy), and the process described by the patent is carried out as follows:

1. Dissolve **46·HCl** in water, adjusting the pH to the isoelectric point for **46** (7.14) using NaOH.
2. Pass aqueous solution through the selective membrane at 14 bar pressure to give an aqueous permeate containing chloride ions and a permeate free of ionic species.
3. Concentrate retentate by increasing pressure to 22 bar.
4. Evaporate retentate solution under vacuum at <35 °C.
5. Add *i*-PrOH to precipitate **46** and recrystallise from MeOH.

The procedure was carried to obtain >3 kg of **46**, thus indicating the advanced stage of the process.

Advantages

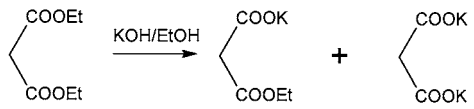
This process makes the best use of membranes which are ideal for concentrating solutions especially when ionic species need to be removed.

Patent No. U.S. 6,580,004

Assignee: Degussa AG, Duesseldorf, Germany

Title or Subject: Process for Preparing Potassium Monoethylmalonate

The title compound **48** is used to prepare pharmaceuticals with the quinolone structure and is required in high purity with minimum levels of the dipotassium salt **49**. Controlled saponification of diethyl malonate **47** in ethanol is a method commonly employed. One problem encountered in removing **49** from reaction mixtures is related to the fact that the process is carried out in high dilution; another difficulty is slow filtration of the product.



47 **48** **49**

There are a number of important features of the process. The first is that the KOH solution is added to the diester **47** which is present in molar excess of >1.5. Effective mixing of the KOH throughout the mixture is also important. It would appear that without this the reaction is mass-transfer limited, and product yield depends on having efficient mixing. Although there are no specific claims to this effect, the importance of mixing is stressed in the patent. The claims of the patent also cover recycling of mother liquor to improve process efficiency.

Advantages

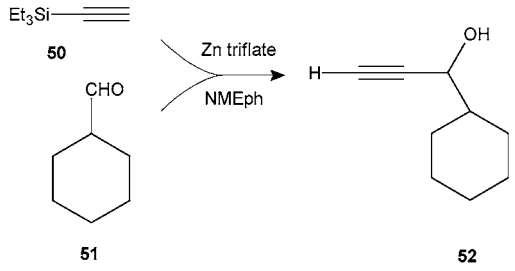
The process claims to improve overall yields and also makes the filtration of the product faster than the alternative procedures.

Patent No. U.S. 6,586,644

Assignee: Erick M. Carreira, Zurich Switzerland and Sumika Fine Chemicals Company Limited, Osaka, Japan

Title or Subject: Process for Producing Optically Active Propargyl Alcohols

Propargyl alcohols such as **52** are useful intermediates and are often prepared from stoichiometric amounts of metal acetylides and aldehydes or ketones. This patent describes a method of making **52** from an acetylene **50** and aldehyde **51** using zinc triflate as a catalyst. The zinc triflate used is preferably that which ahs been dried at 100−140 °C and is used at about 20 mol % of the aldehyde. The reaction is carried out in the presence of an optically active amino alcohol such as *N*-methylephedrine (N-MEph), and the chirality of the amine dictates the course of the reaction so that using (+)-N-MEph gives the (*R*)-**52**. A feature of the procedure is that no solvent is required although it is claimed that toluene can be used, and this simplifies the recovery of the product.



Advantages

The process gives a high yield of product using catalytic quantities of the metal salt and without a solvent. Hence, wastes are reduced, and product purification is simplified.

Patent No. U.S. 6,586,648

Assignee: Tanaka Kikinzoku Kogyo K. K., Tokyo, Japan

Title or Subject: Process and Apparatus for Producing Metallocenes

Metallocene chemistry has expanded enormously over the past 5 years particularly driven by olefin polymerisation processes. Metallocenes are also seen as source of metal films in chemical vapour deposition (CVD) since they are volatile and have high vapour pressures. This patent describes a method of producing pure cyclopentadiene (Cp) and alkyl-Cp which can be used to produce Ru(Alkyl-Cp) complexes. Cp and its derivatives are fairly reactive and often exist as dimeric species at room temperature. Hence, the normal procedure is to distill the dimer to decompose it to the monomer, and this is used fairly quickly in subsequent reactions. There is often little attempt made to purify the monomer so that by-products are still present in the reaction system. Such by-products are often present in the metallocene used in CVD processes, and their presence is undesirable when highly pure metal films are required. Hence, this patent describes a technique for obtaining pure Cp which can then be used to produce pure metallocenes.

The process is basically a two-stage fractional distillation in which high-boiling impurities are removed in the first stage and volatile impurities in the second. Hence, any suitable fractionation column can be used, and the methyl, ethyl, and unsubstituted Cp derivatives were all obtained with purity of >99.5%. These were then used to prepare Ru metallocenes.

Advantages

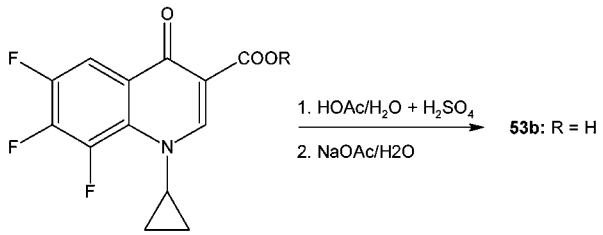
Producing metal films by CVD requires high-purity materials, and this method provides highly pure raw materials in a simple procedure. However, it is difficult to see how the process described here is anything other than good practice.

Patent No. U.S. 6,590,101

Assignee: Bayer AG, Leverkusen, Germany

Title or Subject: Process for Preparation of Fluoroquinolonecarboxylic Acids

The compounds such as **53b** are useful intermediates and are often prepared by hydrolysis of the ester in HOAc in the presence of excess sulphuric acid. This causes large amounts of wastes and difficulties in purification of the final product. This patent describes a hydrolysis method that significantly reduces the amount of sulphuric acid that is required. This is achieved by extending the time that the process is heated and also by distilling off any volatile materials that are formed. It was found that reducing the heating time or not removing distillate significantly reduced product yield. A previous process had been able to reduce heating time, but this required increased amounts of H_2SO_4. The process shown below is carried out by adding the H_2SO_4 to **53a** which is dissolved in aqueous HOAc. The amount of H_2SO_4 used is around 3 g per mol of ester which can be 10% of that previously recommended.



Advantages

This procedure produces a higher-purity product with less waste disposal problems than alternative methods.

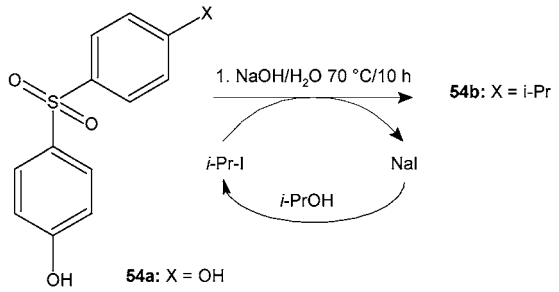
Patent No. U.S. 6,590,126

Assignee: Nippon Soda Co. Ltd., Tokyo, Japan

Title or Subject: Industrial Process for Producing Diphenyl Sulphone Compounds

Diphenyl sulphones such as **54b** are used as leuco dyes in producing thermally sensitive papers. Currently, known methods of synthesis involve the reaction of alkyl bromides with the dihydroxy compound 5**4a**, and it is stated that the alkyl iodide would be preferred, but they are not generally available at a reasonable cost. The patent overcomes this limitation by recovering the iodine and then using it in the

production of alkyl iodide. Thus, there is no loss of iodide and a reduction in the overall cost of raw materials. The route is shown below. The patent describes methods for recovering the iodine in the vapour form and then using this to produce *i*-PrI. This is carried out by reacting I_2 with *i*-PrOH in the presence of red P and then steam distilling the *i*-PrI. A recovery of 98% of the iodine and *i*-PrI was claimed.



Advantages

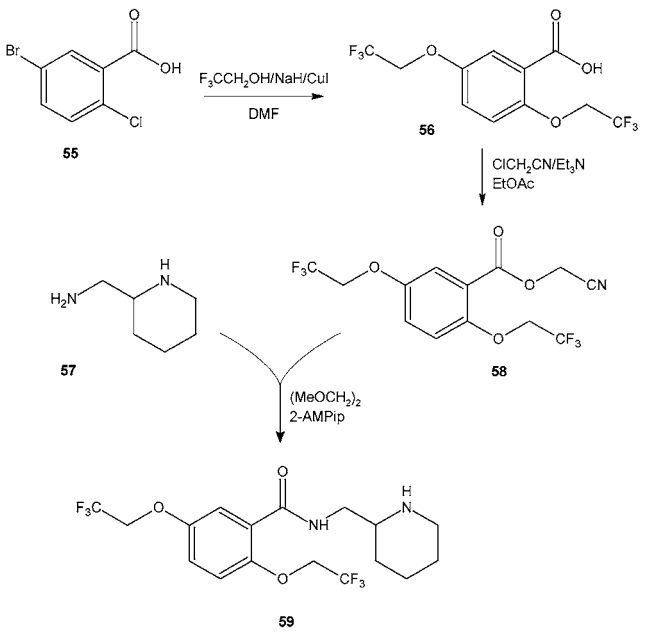
By using the alkyl iodide this process allows a more efficient alkylation reaction to be carried out and reuses the expensive starting materials.

Patent No. U.S. 6,593,486

Assignee: Par Pharmaceutical Inc., Spring Valley, New York, U.S.A.

Title or Subject: Process for Making Cyanomethyl Ester Precursors of Flecainide

This patent and the next one describe methods for producing flecainide **59** which belongs to the group of medicines known as antiarrhythmics and is used to correct irregular heartbeats to a normal rhythm. The two patents approach the synthesis from quite different directions. Previously known syntheses of **59** have a number of disadvantages such as using unstable reactants or requiring the use of materials that are not readily available. This new route to **59** is shown below and begins with the fluoroethoxy



compound **56** which is formed by a copper-catalysed coupling reaction in DMF between the halobenzoic acid **55** and trifluoroethanol in the presence of the strong base NaH which is added as a suspension in mineral oil.

The next step is formation of the cyano compound **58** by reaction of **56** with $ClCH_2CN$ in the presence of Et_3N. The reaction of **58** with the piperidine **57** in the presence of 2(aminomethyl)piperidine (2-AMPip) then gives the desired flecainide **59**. The key step in the process is the finding that the cyano methyl group in compound **58** increases the reactivity and selectivity in the reaction with the amine **57** to give high yield of **59**.

Advantages

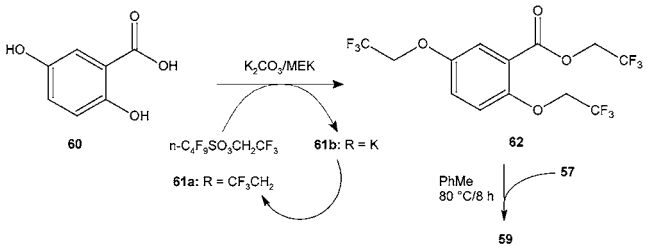
This process produces a key intermediate that enables a more selective route to the desired compound. However, the patent does not mention the dangers of the large-scale use of NaH in DMF, which are well-known.

Patent No. U.S. 6,599,922

Assignee: A. M. S.A Anonima Materie Sintetiche e Affini S.p.A., Milan, Italy

Title or Subject: Process for Preparation of Flecainide

This patent approaches the synthesis of **59** by introducing the CF_3CH_2 groups by reaction of **60** with the sulphonate **61a** to form **62**. The process efficiency is then improved by converting the by-product K salt **61b** back to **61a** although the details of this conversion are not provided. The acid **61c** (R = H) is readily obtained from **61b**, and a procedure is described for producing **61a** from the fluoride **61d** (R = F), but no details are given of how **61d** may be produced from **61c**.



Advantages

This process uses readily available reagents and improves overall process efficiency by recycling by-products. It would be interesting to combine the improvements of this process with that of the previous patent.

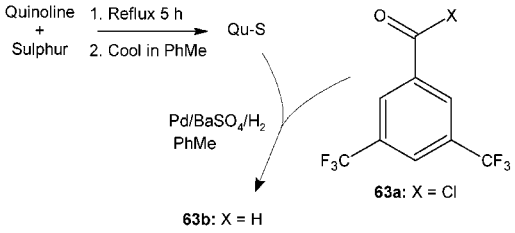
Patent No. U.S. 6,596,906

Assignee: Bayer AG, Leverkusen, Germany

Title or Subject: Process For Preparing Fluoromethylbenzaldehydes

The title compounds such as **63b** are important intermediates and can be prepared by a number of methods. Reduction of benzoyl chlorides is practised but can result in over-hydrogenation and formation of the benzene derivative. Oxidation of alcohols is also known as is the reaction of halobenzenes with organometallics. These and other processes are said to suffer from many drawbacks and poor

yields. The process disclosed in this patent is the catalytic reduction of benzoyl chlorides, such as **63a**, using Pd supported on $BaSO_4$ and in the presence of a quinoline−sulphur complex (Qu−S). The Qu−S is said to be a catalyst moderator, and it presumably prevents the over-reduction of the aldehyde to the benzene. A comparison of the yield of **63b** prepared using this process (86%) does not appear to give a great improvement over a method using Raney Ni (82.5%) The current method took 12 h, the alternative was complete in 7.5 h, but the new process was carried out at atmospheric pressure compared to 30 bar for the alternative. A higher pressure may give shorter reaction times. Examples are also given for preparing other aldehydes such as 4-trifluoromethylbenzaldehyde and 3-bromo-4-trifluoromethylbenzaldehyde.



Advantages

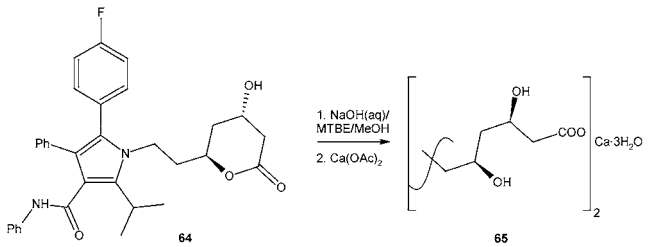
The inhibited catalyst used in the process prevents over-reduction and maintains a high yield of the aldehyde.

Patent No. U.S. 6,600,051

Assignee: Warner-Lambert Company, Morris Plains, New Jersey, U.S.A.

Title or Subject: Factory-Scale Process for Producing Atorvastatin Trihydrate Hemi-calcium Salt

The great interest in statins for treating cardiovcascular disorders continues, and this patent describes a method of producing commercial quantities of **65**. The single example in the patent describes a process carried out in a 6000-L reactor. Several patents on statins have been reviewed (*Org. Process Res. Dev.* **2003**, *7*, 459), and this one is aimed at producing crystalline material with a consistent size range. However, there is no information on the actual particle size distribution required. The process shown below starts from the lactone **64** which is dissolved in MTBE and MeOH, and then aqueous NaOH is added. After heating for 45 min at 57 °C the organic layer is discarded and the aqueous layer extracted with MTBE. The next step is to add extra MTBE and heat the mixture. It is this addition of more MTBE which is said to ensure consistent size range of crystals. The explanation given is that the extra MTBE compensates for increased solubility after heating and ensures a saturated crystallisation matrix. Hence, the MTBE is acting as an antisolvent. $Ca(OAc)_2$ is then added to the hot mixture followed by addition of a slurry mixture of seed crystals of **65** in aqueous MeOH. The seed mixture is made up in a rocking autoclave and added to the reaction by pressurisation of the rocking autoclave in less than 5 min. This precise procedure forms part of the claims in the patent and appears to be vital, but it may also be difficult to control; hence, this may not be sufficiently robust a process so that there may be the potential for maloperation, leading to poor product.



Advantages

The precise procedure for producing the crystals gives consistent product which is a distinct advantage in a large-scale manufacturing process.

Keith Turner

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