Organic Process Research & Development **2002**, *6*, 346−356

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during December, 2001 to March, 2002

This review covers a selection of 21 patents from an initial list of 516 that fit our criteria. The selection covers a variety of subjects including what is claimed to be the first catalytic method for stereoselective addition of a keto-ester to nitroolefin producing nitromethyl compounds. The purification and recovery of reaction products from any reactions is always a problem. The metathesis of cycloalkenes to give cyclodienes is a high dilution process that gives a complex mixture, and one patent has described the recovery of the product dienes by adsorption on faujasites. In another purification problem the removal of carbonyl compounds from acetic acid and phenol using ion-exchange resins is described. A new process for the chlorination of ketones has been reported which uses phosgene and is catalysed by triphenylphosphine oxide. Examples of new polymorphs of old crystals continue to appear, and a three new forms of a depsipeptide used as an antiparasitic drug discovered over 10 year ago have been reported. In another patent two polymorphs of the antihypertension drug telmisartan have been discovered. A process for synthesising intermediates for vitamin D is described in which hydrogenation of an epoxide ring to an allylic alcohol is made stereoselective by the addition of fluoro alcohols. The importance of mixing is often overlooked, and one patent describes how to significantly improve a nitration reaction by the use of efficient mixing. As usual no attempt has been made to fully use IUPAC nomenclature, and the advantages are those claimed in the patent unless the reviewer has personal knowledge. Many of the patents give detailed spectroscopic data for new compounds, and some of them report synthesis on kilogram- and multikilogram scale. This may indicate the advanced commercial status of the technology although the legal position of any of the patents is not known. It may surprise many chemists that the use of chemical formulae in patents is not mandatory since if one designs a new machine a drawing has to be provided. It is not uncommon to see a chemical patent without a single structural formula, and this is the case with some in the current selection. Hence, when reading a patent in a field outside of one's own, this can make the patent and the chemistry in it very difficult to follow. Just imagine what it is like for the patent examiner who has to decide on the validity of a chemical patent.

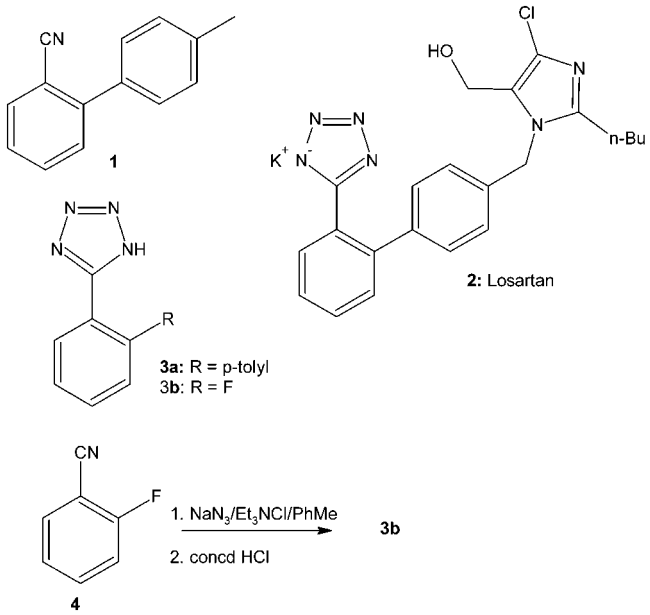
Patent No. U.S. 6,326,498

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

Title or Subject: Synthesis of 5-(2-Fluorophenyl)-1H-tetrazole

Tetrazole and its derivatives are used as intermediates in the preparation of a number of agrochemical and pharmaceutical intermediates. For example the tetrazolylation of **1** with tributyltin azide gives **3a** which is used to make losartan **2**. This is an angiotensin II receptor antagonist that is used to prevent the narrowing of blood vessels and to treat high blood pressure. This route from **1** to **3a** requires a rigorous purification step to remove the highly toxic tin compound and is not commercially attractive. An alternative method of producing **2** involves reacting **3b** (R = F) with the Grignard reagent *p*-tolylMgBr. This step is ineffective when R = Cl or Br, and hence for a viable route to **2** an efficient method of producing **3b** is required. This is what the patent aims to provide because it is claimed that there is only one other route to **3b.** This involves the use of sodium azide in acetic acid which is said to be impractical because of the production of hydrazoic acid.

The route to **3b** described here is shown below and starts from the 2-fluorobenzonitrile **4**. This is treated with NaN_3 for 8−10 h in refluxing toluene, and then **3b** is obtained in 75% yield by precipitation with concentrated HCl. The patent specifically claims this time period is needed for the synthesis to succeed.



Advantages

The method does not produce hydrazoic acid because acetic acid is not used and no byproducts are obtained.

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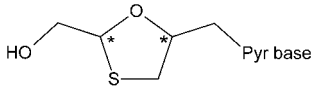
Patent No. U.S. 6,329,522

Assignee: Glaxo Group Limited, Greenford, U.K.

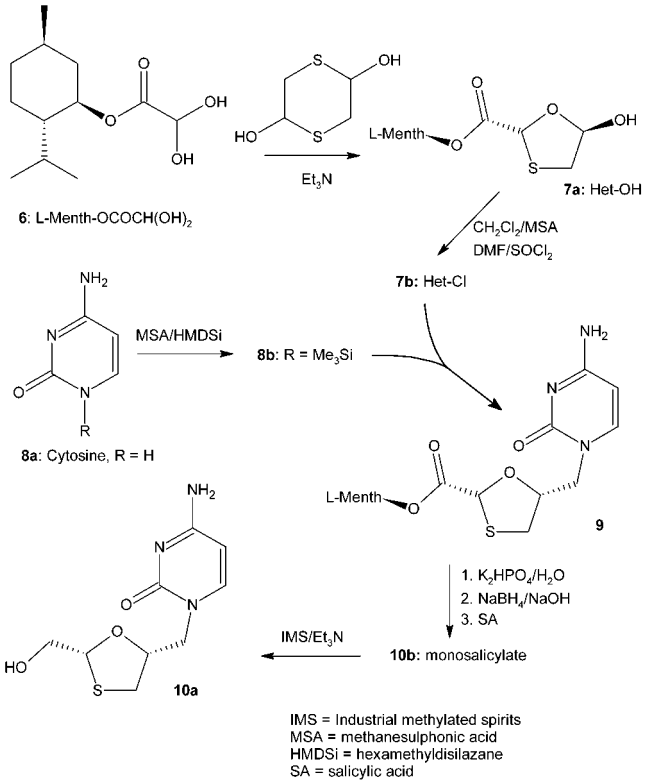
Title or Subject: Diastereoselective Synthesis of Nucleoside Analogues

This patent describes the synthesis of lamivudine **10a** which, under the name epivir, is used in the treatment of HIV and other viral infections. **10a** is one example of a group of nucleosides based on the structure of compound **5** that contains two chiral centres. It is generally only the *cis* isomers of such molecules that exhibit biological activity.



5: Pyr = pyrimidine

Routes to **5** therefore need to have a highly stereoselective step for maximum atom efficiency. The route to **10a** is shown below. The *l*-menthyl ester **6** is first selectively converted to the *trans*-oxathiolane alcohol **7a** by reaction with dithianediol in the presence of Et_3N. By using Et_3N this step is found to be stereoselective and allows preferential crystallisation of the *trans* isomer **7a**. The Et_3N interconverts the various *cis/trans* isomers of **7a** yet allows the *trans* form to crystallise from the mixture. The alcohol **7a** is treated with a Vilsmeier reagent and converted to the chloro compound **7b** that is not isolated from the mixture which is treated directly with the silylated cytosine **8b** to give **9**. The menthyl group is removed from **9**, and the lamivudine salicylate salt **10b** is isolated by crystallisation. The free lamivudine **10a** is obtained by treatment with Et_3N followed by recrystallisation.



An earlier route (WO 92/20669) to **10a** involves the reaction of **7a** with **8** to give **9** by using a Lewis acid such as trialkylsilyl compounds. This method is claimed to be unsuitable because the silyl compounds are unstable and hazardous to use. The present route overcomes these difficulties by selecting chlorine as a good leaving group in **7b** so that the reaction with **8b** efficiently produces compound **9**.

The patent gives ^1H NMR peak assignments for all isolated intermediates shown in the scheme above.

Advantages

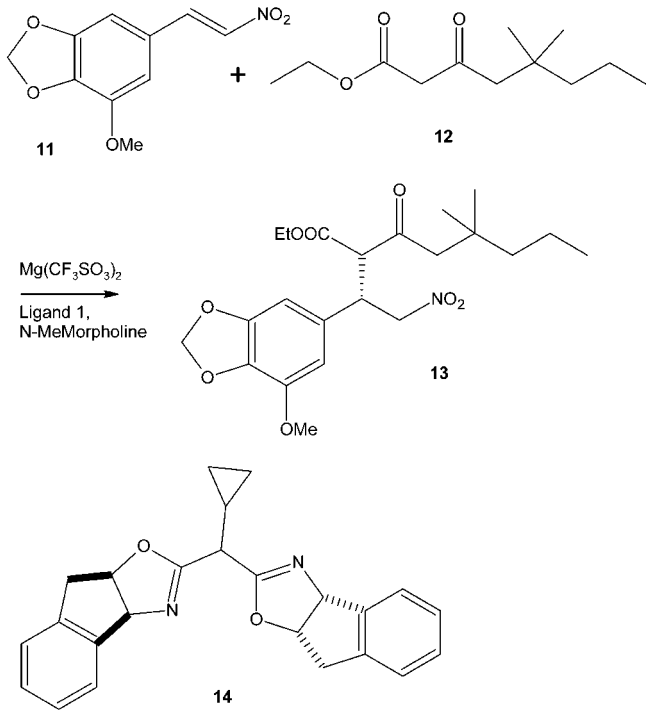
This route gives a highly stereoselective route to **10a** by the use of Et_3N as an agent that promotes interconversion of the various *cis/trans* isomers to give the key intermediate **7a**.

Patent No. U.S. 6,329,536

Assignee: Abbott Laboratories, Abbott Park, Illinois, U.S.A.

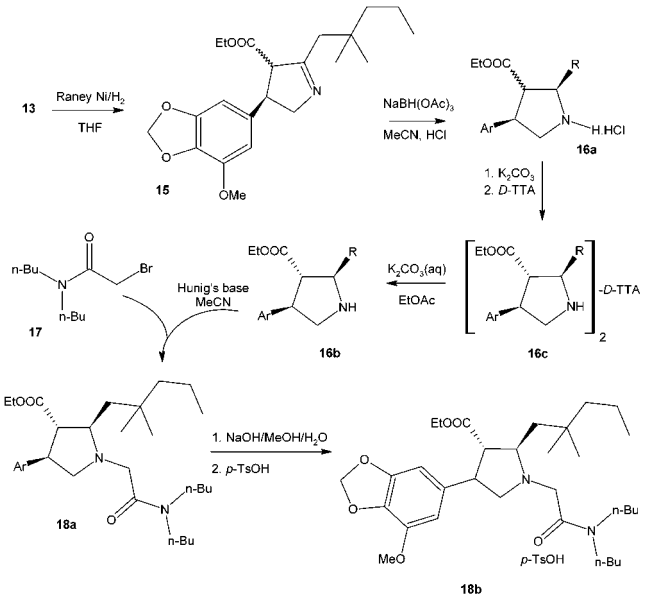
Title or Subject: Stereoselective Production of Nitromethyl Compounds by Addition of Nitroolefin to β-Dicarbonyl Compounds

This patent claims to describe the first catalytic method for producing the nitromethyl compound **13** by stereoselective addition of the keto-ester **12** with the nitrostyrene compound **11** (see scheme below). The compounds and intermediates formed by this route are useful endothelin antagonists. The catalyst used is a Mg-based complex formed from magnesium trifluoromethanesulphonate $Mg(TFMSA)_2$, a ligand such as **14** and a base such as *N*-ethylmorpholine. The reaction is carried out in chloroform at 35 °C over about 20 h, and this gives crude **13**. Although the reaction is presumably enantioselective, there is no indication as to value for the ee.

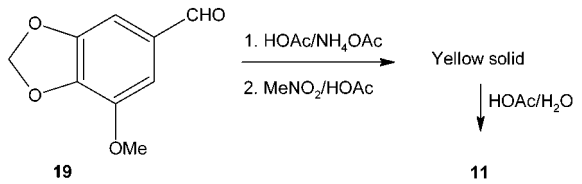


The nitroketone **13** is then converted to the pyrrolidine compound **18b** via the route shown in the scheme below.

The first step is reductive cyclisation using freshly prepared $NaBH(OAc)_3$ to give the air-sensitive imine **15** which is converted to the hydrochloride salt **16a**. The pyrrolidine **16a** was resolved by formation of the crystalline D-tartaric acid (D-TTA) salt **16c** and the free base **16b** was obtained in 70% yield by treatment of **16c** with K_2CO_3 in EtOAc. Reaction of **16b** with the bromo-amide **17** in the presence of Hunig's base gives **18a** and this was converted to the tosylate salt **18b**.



The patent gives details for the synthesis of the ligand **14** and also for the compounds **11** and **12**. The scheme below summarises the synthesis of the nitroolefin in 89% yield from the benzaldehyde **19**. ^1H NMR assignments are given for **19**.



Advantages

Addition reactions to substituted olefins can give two enantiomers, and this patent provides a highly enantioselective method of producing the nitroketone **13** by addition reaction of an olefin.

Patent No. U.S. 6,329,562

Assignee: Haarmann & Reimer GmbH, Holzminden, Germany

Title or Subject: Process for the Separation of Cycloalkadienes from Metathesis Reaction Mixtures

The 14- to 17-membered cycloalkadienes are valuable compounds that are used to prepare musk-type fragrances. Metathesis of cycloalkenes in low concentration in hydrocarbon solutions is a favoured method for synthesising the dienes, but recovering the pure dienes is difficult. Large volumes of solvent need to be removed, and vacuum fractional distillation is frequently used but can result in thermal degradation of the product. The process described here involves the use of zeolites to adsorb the dienes and hence remove them from the mixture. This takes place at about 65 °C, and the dienes are then recovered from the zeolite by displacement using ethylbenzene which is separated from the diene by distillation. Suitable zeolites are the faujasite X or Y types and the examples in the patent use a number of commercially available materials. A feature of the process is preferential adsorption of the *cis* and *trans* isomers of the dienes. For cyclohexadeca-1,9-diene the favoured order of adsorption is *cis,cis* > *cis,trans* > *trans,trans* so that the *trans,trans* isomer remains in solution. The zeolite requires activation before use, and this is carried out by heating at about 450 °C. The patent focuses on recovery of cyclohexadeca-1,9-diene which has been prepared from the reaction of cyclooctene with cycloheptene. This reaction also produces a range of cyclopolyenes and hence is a complex mixture to separate.

Advantages

This is an efficient method of recovering the pure materials and enables some degree of selective separation of isomers.

Patent No. U.S. 6,337,425

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Production of Chloroalkenes by Chlorination of Ketones Containing Acidic CH Protons Using Phosgene and Triphenylphosphine Oxide

The use of chlorinated olefins as chemical intermediates makes their synthesis an attractive goal. Methods described previously use the common chlorinating agents such as PCl_5, oxalyl chloride, or PPh_3Cl_2. The patent claims all these materials have problems such as being expensive or producing large quantities of wastes that are difficult to dispose of. The process described here uses phosgene with a catalytic amount of triphenylphosphine oxide (TPPO), and this is known to produce CO_2 and PPh_3Cl_2 which is the actual chlorinating agent. Most earlier reports of using this method use TPPO in excess, but there is a single report of chlorinating cyclopropylmethyl ketone using phosgene and a catalytic amounts of TPPO. Hence, this ketone is specifically excluded from the claims of the current patent.

The reaction predominantly gives the monochloroalkene, but dichloroalkanes are also formed. The patent is aimed at a fairly narrow range of ketones containing no substituents. The examples given in this patent cover the conversion of cyclohexanone to 1-chlorocyclohexene, the production of three isomeric chloroheptenes from hepta-2-one, and the chlorination of acetophenone to give 1-phenylvinyl chloride (79%) and 1,1-dichlorophenylethane (2%). The reaction is carried out by bubbling phosgene through the ketone containing the TPPO, and a solvent is not required if the ketone is a liquid. The by-product CO_2 is easily removed and product recovery made easier. The use of phosgene on a large scale is not difficult since phosgene generation units are available. However, the transport of phosgene is not

allowed in many countries and so small- and medium-scale processes may not be economical if a phosgene generator is not available.

Advantages

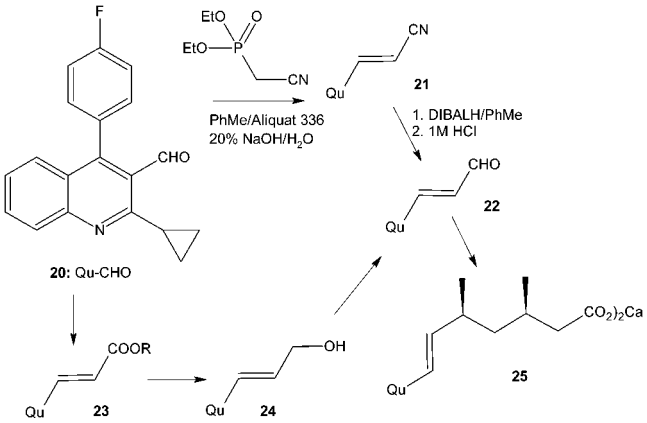
The process only produces gaseous wastes, and hence the recovery of products and disposal of waste products is not as much of a problem as it is when using other chlorinating agents.

Patent No. U.S. 6,335,449

Assignee: Nissan Chemical Industries Ltd., Tokyo, Japan

Title or Subject: Preparation of FluorophenylCyclopropylQuinoline Derivatives

The aldehyde **22** is a useful intermediate for the synthesis of **25** which is a cholesterol-reducing agent. The original route to **25** is disclosed in a 1991 patent (U.S. 5,011,930) and started from **20** which was converted to the unsaturated ester **23**. This was reduced to give **24** and **22** was obtained by oxidation of **24**. (No details are given for the steps from **20** to **23** to **24** to **22**). Although it was known that direct reduction of **23** to **22** would be more efficient, it is stated that this step could not be controlled. An improved route to **22** from **20** is described in this patent and proceeds via the intermediate nitrile **21** (scheme below).



The first step is production of the nitrile **21** in 88% yield by base-catalyzed reaction of **20** with diethylcyanomethylphosphonate in the presence of a phase transfer catalyst (PTC) which in this case was Aliquat 336 (tricaprylmethylammonium chloride). The nitrile **21** was then reduced using DIBALH in toluene, giving **22** in 93% yield.

Advantages

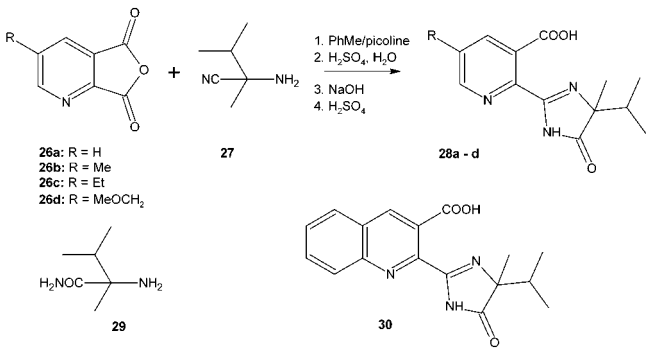
The new route gives a more efficient process for producing the desired intermediate, and the use of a PTC probably improves the overall reaction efficiency.

Patent No. U.S. 6,339,158

Assignee: American Cyanamid Co., Madison, New Jersey, U.S.A.

Title or Subject: Preparation of Chiral Imidazolinone Herbicides from (R)-2-Amino-2,3-dimethylbutyronitrile

Herbicides based on imidazolinone derivatives are potent, broad spectrum, and environmentally benign. These herbicides can be prepared by resolution of enantiomers of 2-amino-2,3-dimethylbutyramide **29**. These amides are formed by hydrolysis of the (*R*)-2-amino-2,3-dimethylbutyronitrile precursors and are unstable and difficult to isolate. Hence this patent describes a stereospecific process to prepare chiral nicotinic, quinolinic, or benzoic acid derivatives directly from (*R*)-2-amino-2,3-dimethylbutyronitrile **27** (see below).



This is a four-step process, and the first step is the reaction of the nitrile **27** with any of the anhydrides **26** in a water-free system consisting of toluene containing a tertiary amine such as picoline. In the next step the mixture is hydrolyzed in aqueous sulphuric acid, and this is then treated with NaOH. The aqueous phase is then acidified with sulphuric acid, and the product filtered off in high purity (>99%) and up to 95% of the *R* isomer. Examples are given for **28** in which R = H, Me, Et, and $MeOCH_2$ as well as the corresponding quinoline analogue **30**.

Advantages

The process allows the stereospecific synthesis of the desired herbicides without having to produce the relatively unstable amide **29**.

Patent No. U.S. 6,340,587

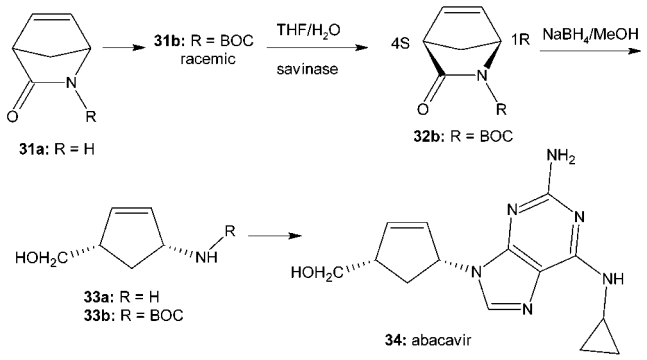
Assignee: SmithKline Beecham Corporation, Philadelphia, Pennsylvania, U.S.A.

Title or Subject: Preparation of Enantiomerically Enriched N-Derivatised Lactams Using Enzymes

The lactam **31a** (R = H) is an important intermediate in the synthesis of abacavir **34** which is used in the treatment of HIV and hepatitis B. A requirement in this route is the production of an enantiomerically pure cyclopentene ring such as in **33a**. One route to **33a** from cyclopentadiene and tosyl cyanide involves the use of lactamases that will allow separation of the enantiomers of **33a**.

The process described in this patent provides a high yield route to **32b** from racemic **31b** (scheme below). It was found that by forming the protected amine **31b** (R = BOC) the lactam bond is susceptible to hydrolysis by an acylase enzyme such as Savinase, whereas the unprotected compound **31a** is hydrolytically stable under the same conditions. Upon hydrolysis of **31b** only one enantiomer is hydrolyzed, and the other **32b** remains in solution and can be isolated by conventional extraction methods. If **32b** is then treated with $NaBH_4$ in MeOH, it can be converted to **33a** with high ee.

Thus, the desired enantiomerically pure precursor to **34** is obtained.



Advantages

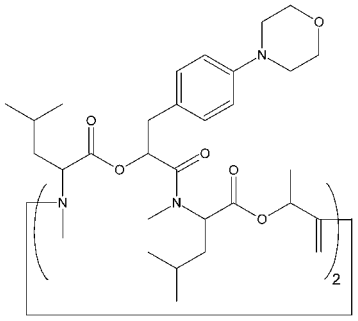
The route to give **33a** is claimed to give high yields and is cost-effective.

Patent No. U.S. 6,346,603

Assignee: Fujisawa Pharmaceutical Co. Ltd., Osaka, Japan

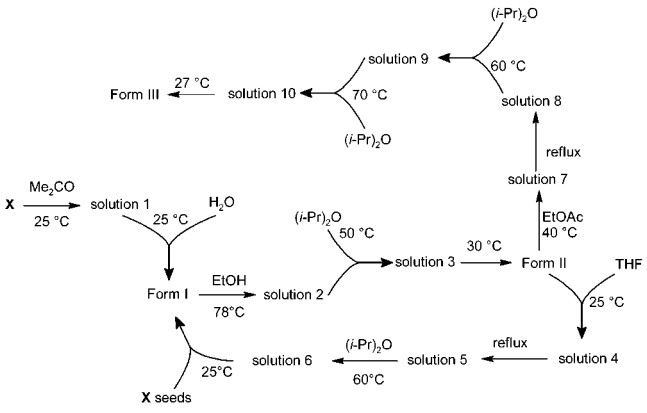
Title or Subject: Production of Pure Crystalline Forms of A Depsipeptide Derivative

Compound **35** has been known for about 10 years as having antiparasitic activity to animals and humans and was originally produced as an amorphous solid (WO 93/19053) in a nine-step synthesis. All intermediates and the final



35

product are difficult to crystallise, and their recovery is hampered by poor filtration and a tendency to stick together; hence, the synthetic route is claimed to be industrially unattractive. The patent describes three new crystalline forms of **35** designated as Forms I, II, and III, and full X-ray diffraction and IR data plus differential thermal analysis details are provided for each form. The production of the three forms is described in which form I can be converted to Form II, and this can be converted to Form III. The routes to these forms are shown below in which the original form of the crystal as synthesised is designated as X.



Advantages

The process gives good quality crystals of **35** that are easier to handle and to recover even when using the original synthetic route.

Patent No. U.S. 6,346,645

Assignee: UOP LLC, Des Plaines, Illinois, U.S.A.

Title or Subject: Adsorptive Removal of Carbonyl Compounds From Oxygen-Containing Organic Liquids

The patent is aimed at the large-scale production and purification of the bulk chemicals acetic acid and phenol. Acetic acid is manufactured by carbonylation of methanol using Rh/MeI catalysts and is purified by fractional distillation. The major impurities in acetic acid are acetone and acetaldehyde. Phenol is produced by oxidation of cumene, and problem impurities are mesityl oxide (MO) and hydroxyacetone (HA). Again fractional distillation is the main purification method, but nondistillation techniques are required to remove HA. The method described here uses an ion-exchange resin (IER) containing a tertiary amine functional group which adsorbs the carbonyl compounds by formation of a Schiff base that remains affixed to the IER. The IER can be regenerated by washing with a base to replace the amine functional groups. The resin used in the examples was AG 3-X4 resin (from Bio-Rad Laboratories, Richmond, CA). The experiments in the patent only describe treating synthetic mixtures of acetic acid and acetaldehyde, and there are no details for phenol purification. However, this patent has been included because the techniques used could equally well be applied to the purification of other organic chemicals.

Advantages

The impurities mentioned cannot be removed by distillation; hence, adsorption or chemical methods are required. This method has the advantage that the IER can be regenerated.

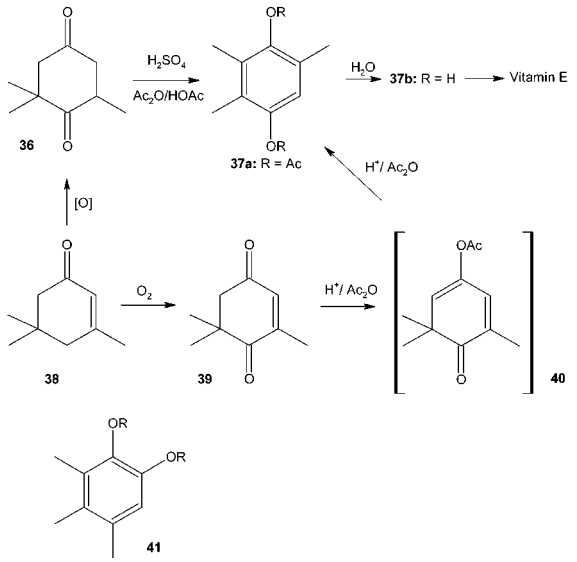
Patent No. U.S. 6,350,897

Assignee: Degussa AG, Hanau, Germany

Title or Subject: Process for Preparing Trimethylhydroquinone Diacetate and Trimethylhydroquinone

The subject of this patent is the production of the diacetate **37a** and its hydrolysis to quinone **37b** (R = H), a precursor to vitamin E. The scheme below shows the route to **37a** which is commonly prepared from **39** via a rearrangement of the enol ester **40**. The starting material **39** is relatively expensive, being prepared by oxygen oxidation of isophorone **38**. This patent provides an alternative route to **37b**, starting from **36** which is a more readily available material than **39**.

Several references to the synthesis of **36** are given, involving oxidation of **38** using oxidising reagents such as *m*-chlorobenzoic acid, *tert*-butylhydroperoxide, peracetic acid, or H_2O_2/formic acid. There are no experimental details in this patent for this reaction.



The process to convert **36** to **37a** takes place at about 100 °C using an acylating agent under oxidative conditions, and the examples describe the use of HOAc/Ac_2O in concentrated sulphuric acid. Higher temperatures tend to produce the byproduct **41.** Even at 100 °C there is about 5% of **41** and 94% of **37a** at 100% conversion of **36**. The patent also claims that solid superacids or Lewis acids can be used, but there are no examples of their use. Although the examples all cover the preparation of **37a**, the patent does discuss its hydrolysis and the production of the quinone **37b** without isolation of the diester **37a**. There are claims that acetic acid that is present during the production of **37a** acts as a phase promoter for hydrolysis of **37a**, but no examples are given.

Advantages

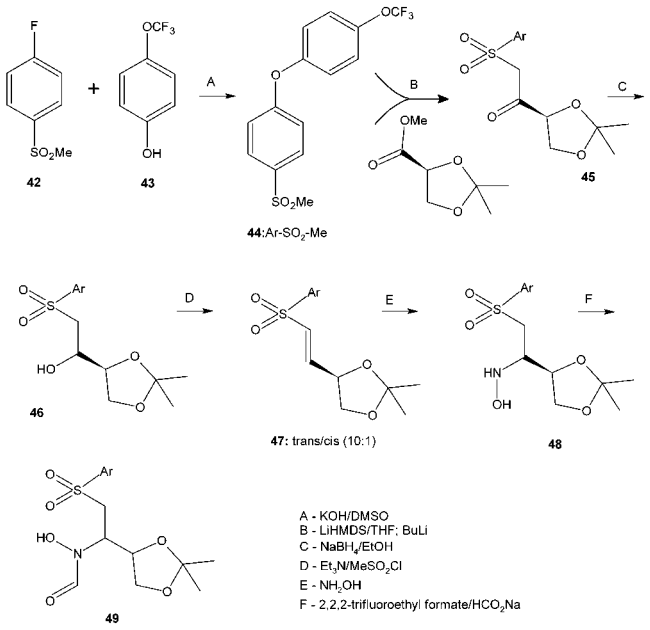
The process uses a more readily available intermediate for preparing the diester **37a** than alternative methods, and hence is more economically attractive.

Patent No. U.S. 6,350,902

Assignee: Abbott Laboratories, Abbott Park, Illinois, U.S.A.

Title or Subject: Production of N-Hydroxyformamides by Selective N-Formylation of N-Hydroxylamines Using 2,2,2-Trifluoroethyl Formate

This patent covers a number of hydroxyformamides but a specific claim is for the hydroxyformamide **49** which is made by the route shown below. Other routes for the formylation of hydroxylamines are said to have problems such as disproportionation to give oximes and formylated amines. The formylation of *N*-hydroxylamines described here uses 2,2,2-trifluoroethyl formate (TFEF), and this has not previously been reported. However, there is reference to the use of TFEF for the formylation of enolates.



The patent gives experimental details for the preparation of almost 6 kg of **49**, thus perhaps indicating the advanced commercial status of this process. The patent, however, does not indicate the applications or use of the formamide **49**. The first step in the synthesis is the production of the ether **44** in nearly 90% yield from the phenol **42** and the fluoro compound **41** by reaction in KOH/DMSO. After recovery of the crystalline product the methyl sulphonyl grouping **44** is then converted to the chiral dioxalone ketone **45** by treatment of **44** with LiHMDS followed by *n*-BuLi and (*R*)-methyl-*O*-isopropylidene glycerate (*R*-MIPG). The recrystallised ketone **45** is then reduced to the chiral alcohol **46** using $NaBH_4$/THF. The recovery of crystalline **46** was not necessary for the next step where the hydroxy group is removed after formation of the mesylate intermediate and a solution of **47** in methyl *tert*-butyl ether (MTBE) is recovered. A ratio of 10:1 *trans*/*cis* isomers of **47** is claimed in an example. The MTBE solution of **47** is then reacted with NH_2OH to give the hydroxyamine **48** in 64% yield as the *syn* product containing <1% *anti*. The final step is treatment of **48** with TFEF to give the hydroxyformamide **49** in 89% yield with an ee of >99.8%. This step is carried out in the presence of a buffer, and the patent does focus on this aspect. In particular if the hydroxylamine compounds such as **48** are acid-sensitive, then a buffer is preferred. Imidazole or sodium formate are the two materials preferred, but in the example given sodium formate is used.

Advantages

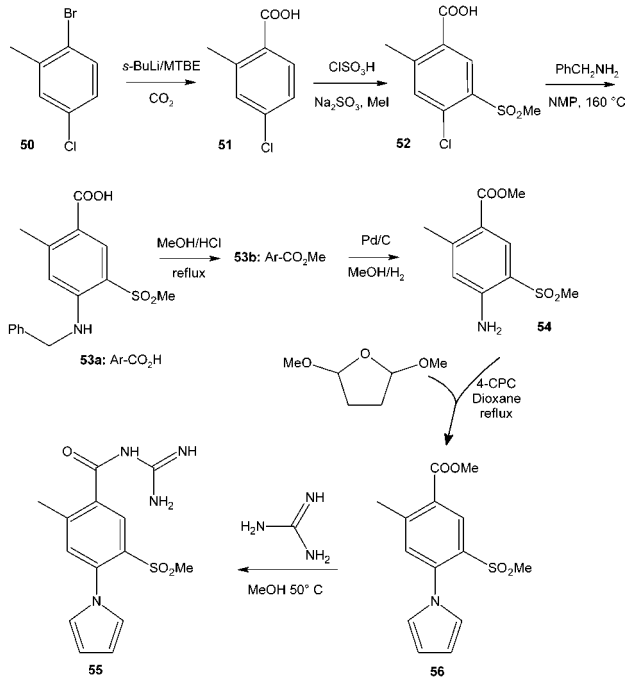
The route to **49** is claimed to involve novel chemistry that is carried out under mild conditions and minimises by-product formation.

Patent No. U.S. 6,350,904

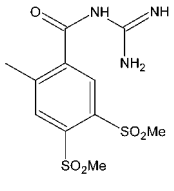
Assignee: Merck KgaA, Darmstadt, Germany

Title or Subject: Production of Ortho-Alkylated Benzoic Acid Derivatives

The ortho-alkylated benzoic acids (ortho-ABA) are generally useful chemical intermediates. Classical synthetic methods for ortho-ABA can involve multistep routes involving diazotisation of anilines followed by Sandmeyer reactions then nitrile hydrolysis. An alternative is ortho-metalation and then alkylation of benzoic acids. The synthesis of *p*-ABA can involve lithiation of aryl bromides followed by carboxylation. This is not a feasible method for *o*-ABA although the more reactive and more expensive aryl iodides can be used in this type of process. This patent enables the use of the relatively cheap aryl bromides to make *o*-ABA by a relatively simple process. The chloro compound **51** is used for the preparation of **55** (scheme below), and experimental details are given for all steps at a kilogram scale.



51 is obtained from the bromo compound **50** by reaction with CO_2 in the presence of *s*-BuLi in an ether such as MTBE. The acid **51** is then converted to the methylsulphonyl compound **52** by reaction with $ClSO_3H$ followed by Na_2SO_3 and MeI. The chlorine group in **52** is then converted to a benzylamino group with benzylamine in *N*-methylpyrrolidine to give the acid **53a** which is then converted to the methyl ester **53b**. The benzyl-protecting group is removed from **53b** by reduction giving the amine **54**. The pyrrole group is introduced, giving **56** by reaction of **54** with dimethoxy-THF in the presence of 4-chloropyridinium chloride (4-CPC)



in refluxing dioxane, and finally **55** is obtained by reaction of **56** with guanidine. Experimental details are also given for the preparation of the compound **57** from **51**.

Advantages

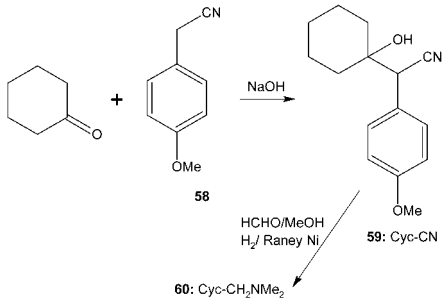
This process allows the cheaper aryl bromo compounds to be used to produce *o*-ABA on an industrial scale in preference to the more expensive aryl iodo compounds.

Patent No. U.S. 6,350,912

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

Title or Subject: One Pot Process For the Preparation of 2-(Dimethylamino-(4-methoxyphenyl)ethyl)cyclohexanol

The title compound **60** is commonly known as venlafaxine or effexor and is used as an antidepressant. The subject described in this patent is the catalytic hydrogenation of the nitrile **59** to give **60** (scheme below). The process is carried out in a mixture of protic solvent such as MeOH-containing formalin (HCHO) using Raney Ni. **59** is produced by condensation of cyclohexanone with the nitrile **58** using NaOH although no details are given for this condensation reaction. There are other methods reporting the synthesis of **60** that also involve an initial condensation of the nitrile **58** with cyclohexanone, but there are several further stages that are claimed to be hazardous and inconvenient in large-scale production. A method starting from anisole also involves several stages and is again said to be hazardous.



Advantages

The key advantage of this patent is that the conversion of the nitrile **59** to **60** takes place in a single step without the need to use hazardous materials.

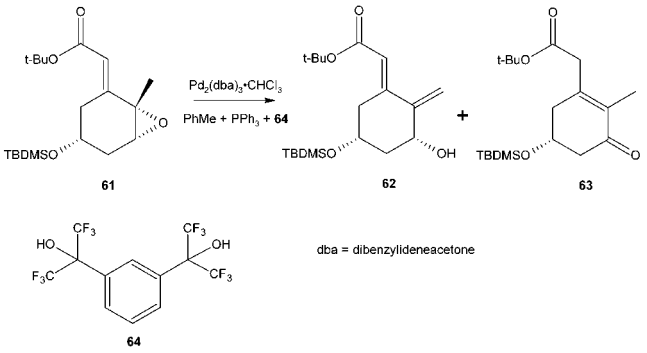
Patent No. U.S. 6,353,123

Assignee: Hoffmann-La—Roche Inc., Nutley, New Jersey, U.S.A.

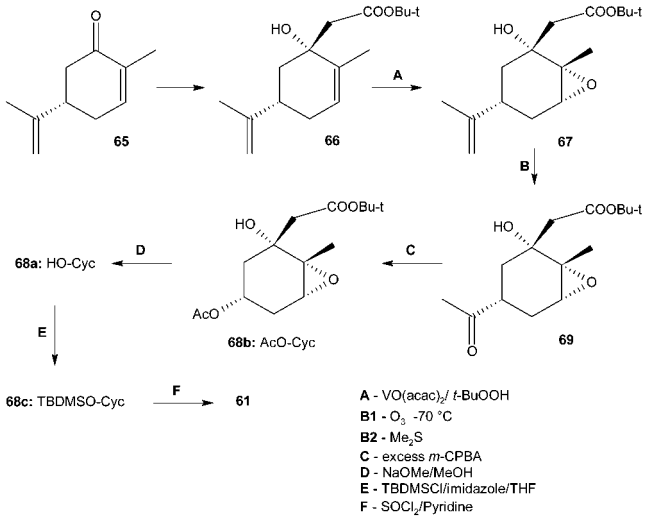
Title or Subject: Stereospecific Process For Intermediates Useful In The Production of Vitamin D Analogues

This patent describes methods for producing intermediates useful in the synthesis of the A-ring portion of vitamin D. A key feature covers a stereoselective method of hydrogenation of the epoxide **61** to give the allylic alcohol **62**. The scheme below shows that the configuration of the C atom containing the TBDMSO group is maintained and the OH group that is formed also has the same configuration if the

substituents are both *cis* as shown. The stereochemistry of the substituents on the cyclohexyl ring is discussed at length. The hydrogenation reaction is catalysed by Pd phosphine compounds, and it has been found that the selectivity to give **62** rather than **63** can be markedly improved by the addition of a fluorinated alcohol such as **64**. Without using **64** the ratio of **62** to **63** was 1:3, but when a catalytic amount of **64** was used the ratio of **62** to **63** increased to 10:1. It was found that using fluorinated alcohols with pK_a value <9 was very effective. It is suggested that this implies a divergent reaction pathway involving protonation of an intermediate compound of comparable basicity. Using other proton sources such as MeOH, phenol, or carboxylic acids gave no reaction or an incomplete reaction presumably due to destruction of the catalyst. The patent discusses this in some details with a range of fluoro alcohols.

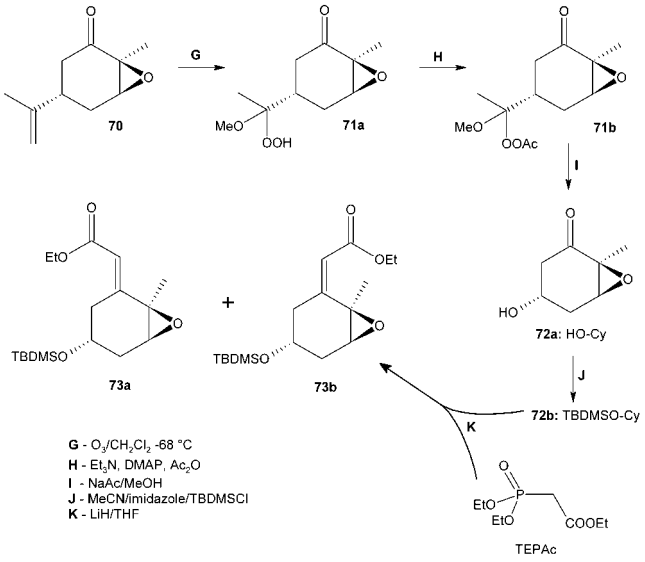


The patent also describes a method for the synthesis of the epoxide **61** starting with either (+)- or (−)-carvone **65** (see below). For the conversion of **65** to **66** a literature reference is given, but details are provided for the subsequent steps of the route. The production of the epoxide **67** form **66** by step A is highly regio- and stereospecific and is carried out using VO(acac)$_2$ and *t*-BuOOH with constant removal of water. Since **67** tends to be unstable, the reaction is quenched with NaHSO$_3$ before the ozonolysis reaction in step B which is carried out in two stages. In the first part of step B **67** is treated with ozonised air at −70 °C, and then Me$_2$S is added to form the ketone **69** by reduction of the ozonide. The oxidation of **69** to give the acetate **68b** is a



modified Baeyer−Villiger reaction using excess *m*-CPBA in the absence of a base. This is carried out in a mixture of hexane and EtOAc, and increased amounts of hexane increase the reaction rate at the expense of by-products. A ratio of 3:1 hexane/EtOAc was preferred. The acetate **68b** is hydrolyzed to give **68a** using MeOH/NaOMe, and the OH group was then protected using TBDMS chloride and imidazole to give **68c**. This silyl ether was then dehydrated to give **61** by the use of $SOCl_2$/pyridine.

A further disclosure in this patent is the synthesis of the *E* and *Z* isomers **73a** and **73b** which are the ethoxy *trans* analogues of **61**, and these are made by the route shown in the scheme below. The epoxide **70** can be made from **65**, but experimental details are not given. **70** is converted to the peroxyacetate **71b** via ozonolysis to give hydroperoxide **71a** which is not isolated. The peroxyacetate **71b** is obtained by acetylation of **71a** using Ac_2O in Et_3N and a catalytic amount of DMAP. The next stage is a Criegee rearrangement in NaOAc/MeOH giving the alcohol **72a**. A basic work-up is required to prevent acid-catalyzed solvolysis of **72a** that would give the dimethyl acetal. The Criegee rearrangement normally gives an acetate ester, but the acetate ester of **72a** has never been observed here, and this simplifies the recovery of the alcohol **72a**. For step J the solvent is changed to MeCN, the protected silyl ether **72b** is prepared, and this is subjected to a Wittig−Horner reaction by treatment with triethyl phosphonoacetate (TEPAc) and LiH in THF. The unsaturated ester product is a mixture of the *E* (**73a**) and *Z* (**73b**) isomers in a ratio of 8.5:1.



Advantages

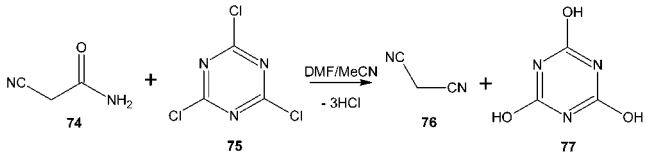
This patent covers a very large subject area related to vitamin D analogues and has produced novel compounds and unique process steps such as the use of fluoro alcohols to improve the selectivity of the catalytic hydrogenation of the epoxide. It is claimed that the methods disclosed provide an efficient route to the A-ring portion of vitamin D.

Patent No. U.S. 6,353,126

Assignee: Creanova Inc., Somerset, New Jersey, U.S.A.

Title or Subject: Process For Production of Malononitrile

Malononitrile **76** is a useful chemical intermediate that can be made by dehydration of **74** using PCl_5, but there are problems disposing of the waste products with this method of manufacture. The process described here is shown below and involves the dehydration of cyanoacetamide **74** using cyanuric chloride **75** in a polar solvent such as MeCN and in the presence of DMF as a catalyst. The reaction conditions



are mild (50−60 °C), and thus by-product formation is minimised. The reaction is exothermic and produces HCl gas so that efficient cooling and a suitable scrubbing system is required. Yields of up to 72% were obtained with purity of >98%. Experiments are described in which it is shown that there is an optimum concentration of DMF and that above this the yield of **76** declines. The patent discloses that the order of addition of the reactants is important and that the preferred order is

1. dissolve **74** in MeCN
2. add DMF to solution of **74** in MeCN
3. add **75** to solution
4. keep temperature at 50−60 °C
5. recover **76** from mixture.

Advantages

The key feature is improved selectivity and the avoidance of wastes that are common in processes using dehydration of **74**.

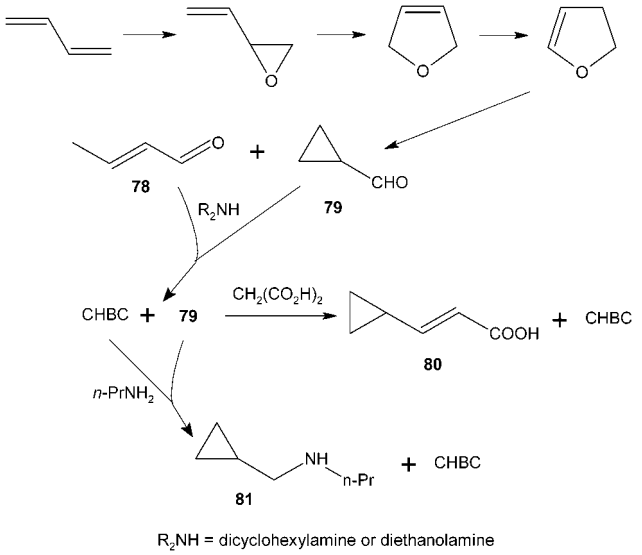
Patent No. U.S. 6,353,140

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

Title or Subject: Process For Purification of Cyclopropanecarboxaldehyde

The title compound **79** is a useful intermediate for introducing a cyclopropyl ring or for the synthesis of cyclopropylacetylene which is used in the manufacture of Du Pont's anti-HIV drug efavirenz. This patent covers a method of purifying **79** that has been made from 1,3-butadiene via the route shown below and contains crotonaldehyde **78** as an impurity. The separation of **79** from **78** by fractional distillation is almost impossible because there is only 4 °C difference in their boiling points; since they are both aldehydes, separation by derivative formation is also difficult.

The process is the base-catalyzed conversion of **78** to give higher-boiling compounds of crotonaldehyde (CHBC) formed by aldolisation or enamine alkylation reactions so that **79** can be recovered by distillation. Preferred bases are *sec*-amines such as dicyclohexylamine or diethanolamine which



are added to the mixture and refluxed under N_2 at around 100 °C. The water formed in the condensation reactions forms an azeotrope with **79** that boils at 68 °C and therefore is easily removed and the purified **79** is recovered by distillation.

A second aspect of this patent involves treating the mixture of CHBC and **79** with a compound to form a derivative of **79** without the compound reacting with the CHBC. Examples of the added compound are malonic acid or *n*-$PrNH_2$ which give the amine **80** of the acid **81** respectively as shown in the scheme above. This step may be carried out by simply adding the *n*-$PrNH_2$ to the mixture of **79** and CHBC obtained from the first step. The patent specifically claims the formation of **80** and **81**, but the significance of these compounds is not disclosed

Alternative methods of producing **79** also produce **78**, and therefore the purification process described here can also be applied these processes. None of the examples cover the purification of an impure reaction mixture of **79** that has been synthesised. All of the examples demonstrate the process using mixtures of **78** and **79** that have been prepared from pure components. It remains to be seen how a real reaction mixture would behave.

Advantages

The separation of **79** from **78** is indeed difficult, and the patent claims that this method is an improvement, but the evidence is not compelling.

Patent No. U.S. 6,353,142

Assignee: Bayer AG, Leverkusen, Germany

Title or Subject: Process For The Adiabatic Preparation of 3,4-Dichloronitrobenzene

This patent indicates how important mixing is in a chemical reaction which in this case is the nitration of 1,2-dichlorobenzene (DCB). A major problem for most chemists is how to maximise selectivity of the desired product at the highest rate, and yet very few chemists would consider mixing as a variable in optimising a process. The subject of this patent is extremely interesting, and although it is aimed

at a continuous production process it does discuss optimisation of the batch version of the process. Another point about the patent is that it discusses an adiabatic process, whereas chemists tend to focus on isothermal processes. This is particularly so when dealing with exothermic processes of which nitrations are a good example.

The process claims to be able to use less concentrated nitric acid (60−65%) and this is cheaper than the grade normally used. By using efficient mixing and this lower strength acid the process is claimed to give 25% fewer byproducts and high rates of reaction. The actual concentration of nitric acid is about 3%, and this is less than the 5% normally claimed to be used so that this improves the selectivity.

An example of a batch process is carried out in a heat-insulated beaker fitted with two turbine agitators which give very efficient rapid mixing. The beaker is charged at 30 °C with 87% H_2SO_4 and 65% HNO_3, and then this mixture is stirred, using a specific power input of 22 W/L. DCB was then added while stirring over a 3 s period at 30 °C. The reaction mixture was constantly stirred and allowed to increase in temperature to 67 °C over 170 s. The stirrer was then stopped and the mixture allowed to separate. The selectivity to the desired product 3,4-dichloronitrobenzene was 86.4% with 12.3% of the 2,3-isomer.

The examples for continuous operating units are at a rate of up to 15 kg/h, indicating that this process is operated at commercial scale.

Advantages

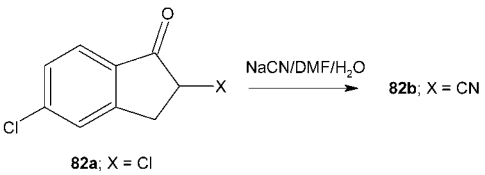
The process gives an improved product selectivity and at the same time a high rate of productivity when compared to those from conventional isothermal processes.

Patent No. U.S. 6,355,827

Assignee: Bayer AG, Leverkusen, Germany

Title or Subject: Process For Preparation of 2-Cyanoindan-1-ones

This patent describes an improved method of producing **82b** from **82a** by using a polar solvent such as DMF. The mixture should also contain water and one example uses around 5%. By using this method yields of 95% were achieved as opposed to 70% when methanol was used as the reaction solvent. Another feature of the reaction is that one of the claims states that it should be carried out at low pH (∼4.5) by addition of acid. However, in the single example in the patent the acid was added after reaction and only after the crude crystalline product had been obtained. The reaction was also applied to the preparation of the 6-chloro analogue of **82b**. No explanation was offered for this improved process. Apart from a change in solvent the process also uses less NaCN than the methanol-based method which requires a 10-fold excess and therefore involves a more hazardous and expensive work-up procedure.



82a; X = Cl

Advantages

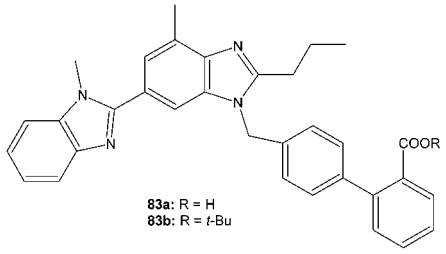
This process is a very much improved synthesis of the cyanoindanones when compared with that previously reported.

Patent No. U.S. 6,358,986

Assignee: Boehringer Ingelheim Pharma KG, Ingelheim, Germany

Title or Subject: Polymorphs of Telmisartan

Telmisartan **83a** can be used to treat hypertension and various cardiac problems and was previously not known to exist in polymorphic forms. In the synthesis of **83a** the final step is the saponification of the *tert*-butyl ester **83b**. The crystals of **83a** are long needles and are very difficult to handle so that drying is time-consuming and breakages are common so that a powder is formed. This powder has a great tendency to produce electrostatic charges, and these problems have prevented the scale-up of the manufacturing process.



83a: R = H
83b: R = *t*-Bu

This patent describes the formation of two polymorphs of **83a**. Form A is the name given to the form originally prepared, and form B is the polymorph obtained by the process described in the patent. Form B shows no tendency to electrostatic charging, is free flowing, and can be handled very easily.

Form B is obtained by dissolving crude **83a** in a mixture of formic acid, water, and a solvent which is either THF, EtOAc, or MEK. Activated charcoal is then added, and the solution is then heated to about 70 °C for 1 h. After removal of the charcoal by filtration more formic acid and solvent are added. The solvent is then removed by distillation while an equal volume of water is added to the solution. The solvent and water form an azeotrope so that both are removed in this manner. The solution is then cooled, and crystals of Form B of **83a** are formed by addition of ammonia solution. The solid obtained is initially 95−99% form B which exists as compact cubic to spherical crystals. However, Form B gradually reconverts to Form A although the actual conditions and rate are not disclosed. The patent does claim that only Form B is produced initially by this process, and even though some converts to Form A, the mixture of crystals is still much easier to handle than the pure Form A and the pharmaceutical activity is also acceptable.

Advantages

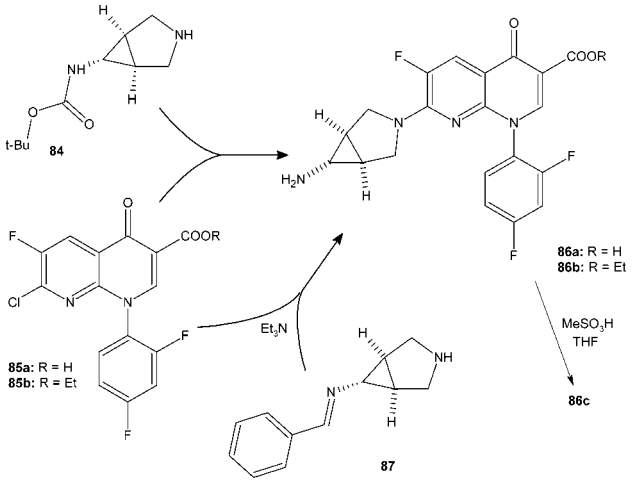
This process produces a crystalline form that is easier to handle and can improve the large-scale production of the compound.

Patent No. U.S. 6,359,137

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

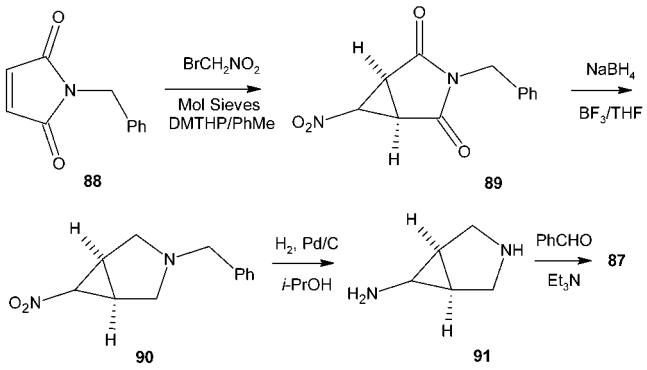
Title or Subject: Process For Preparing Trovafloxacin Acid Salts

Trovafloxacin **86a**, its ethyl ester **86b**, and the hydrochloride or methanesulphonate salt **86c** of the ethyl ester **86b** are useful as antibacterial agents. A previously reported synthesis of **86a** shown below involves the coupling of **84** with **85b** followed by hydrolysis using aqueous HCl. This is a reliable synthesis but produces equimolar amounts of isobutylene. This patent claims that since isobutylene is flammable and can damage the ozone layer a better route to **86a** is desirable. While these sentiments are admirable, it is unlikely to be the primary motivation for a new synthetic route.



The new route described here is similar and also starts from **85b** which in this cases is coupled with the benzylidene compound **87**. The reaction is carried out in Et_3N and can use **87** which has been synthesised by the route shown in the scheme below. In fact the patent provides an example of the synthesis of **86a** in which the coupling of **85b** and **87** is carried in the same reactor as that used for the final step in the scheme without isolation of **87**.

The scheme shows the synthetic route to **87** and involves the formation of the cyclopropyl imine compound **89** from the imide **88** and bromonitromethane (BNM) This reaction



was carried out in 1,2-dimethyl-1,4,5,6-tetrahydropyrimidine (DMTHP) and toluene in the presence of a large quantity of molecular sieves. In the example given in the patent 2 kg of molecular sieves were used in a solution containing 12 L of toluene containing 500 g of **88**, 830 g of BNM, and 600 g of DMTHP. No reason for using such a large amount of molecular sieves was given.

In the next stage the carbonyl groups in the imine **89** are reduced, giving **90** using $NaBH_4$ in the presence of BF_3·THF. Using Pd/C catalyst the nitro group in **90** is then hydrogenated to an amino group, and at the same time the *N*-benzyl group is removed, giving **91**. Reaction with benzaldehyde and Et_3N gives **87**. The reaction mixture can then be treated directly with the ethyl ester **85b** to give the ethyl ester **86b**. Treatment of **86b** with $MeSO_3H$ in THF gives the methanesulphonate salt ethyl ester **86c**. The patent also describes the production of the zwitterion form of **86a** by treatment of the salt **86c** with aqueous $NaHCO_3$ solution. The use of this form gives a higher wt % of active compound.

Advantages

The new route is claimed to be environmentally friendly and more efficient than the alternative.

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