Organic Process Research & Development **2001**, *5*, 557–567

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during April to June, 2001

Summary

This review covers 23 U.S. Patents from an initial list of 513 that fit our original criteria. In this collection there is a wide selection of subjects including novel synthetic routes and processes, as well as purification or recovery methods. The use of UV irradiation to initiate reactions is well known and requires a UV source. One patent describes a method of causing materials to emit UV light by irradiating them with microwaves. The irradiated materials are contained within the reaction of interest, and hence, the UV is available inside the reaction mixture. A novel diazotisation reaction is disclosed which can be carried out in the presence of unprotected hydroxyl groups in purine derivatives. The method relies on a specific combination of solvents and may have application elsewhere. A range of thermally stable, supported Sn transesterification catalysts is described that is used in reactions without using solvents, and high conversions are possible. They are used by simply mixing the catalyst together with esters and alcohol and heating to melt the mixture. The one-step conversion of pyranose epoxides to azides using sodium azide is described with claims that the reaction is more widely applicable. One patent provides a method of recovery of fluorination catalysts, and another gives new route to the antiulcer drug omeprazole. The synthesis of the antidepressant sertaline by catalytic hydrogenation of cyclohexylidenamines is described which noted that careful activation of the catalyst improved the process. This is an important point when using hydrogenation catalysts and is often overlooked but should not be ignored. As usual, no commercial significance should be attached to the patents chosen, although some do have examples involving multikilogram experiments. This would often indicate more than laboratory curiosity. No attempt has been made to comply with IUPAC nomenclature, and usually the names used in the patent are those that have been used here. Any advantages described are those claimed in the patent unless this author has specific knowledge.

Patent No. U.S. 6,210,538

Assignee: Gunter Knapp, Graz, Austria
Title or Subject: Generation of UV Rays For Performing Chemical Reactions by Initial Irradiation with Microwaves

This patent describes a method of producing specific wavelength UV bands within a vessel containing a mixture of chemicals to effect a reaction. The UV rays are produced by microwave irradiation of noble gases, methane, CO_2, or a range of metals which then emit UV radiation. The basic system is shown in Figure 1 and consists of an inner vessel

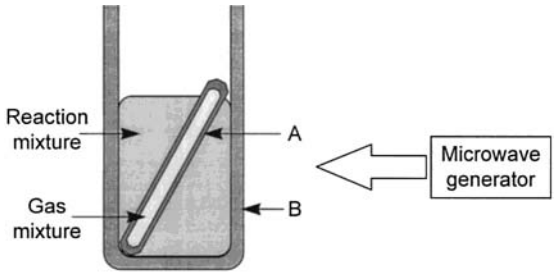

Figure 1. **Method of producing UV rays by irradiation with microwaves.**

A, permeable to UV and microwaves, containing the gas or metal. This vessel is surrounded by the desired chemical reactants which are inside a vessel B that is permeable to microwaves but impermeable to UV. The contents of A are excited upon irradiation with microwaves and emit UV which is then absorbed by the reaction medium.

There are no examples of reactions to which this method has been applied, but it is an intriguing concept. Previous references to this concept are given in the patent, but in the earlier cases the UV emitter surrounds the entire reaction vessel rather than by the method described here.

Advantages

The main advantage claimed is that by having the UV emitter within the reaction mixture the size of the equipment is significantly reduced. The small size and method described also provides the capability of using higher temperatures and elevated pressures that were not possible using the earlier secondary UV emission techniques.

Patent No. U.S. 6,210,956

Assignee: Eastman Kodak Company, Tennessee, U.S.A.
Title or Subject: Preparation of High Purity Enantiomers of Monoesters of cis-1,3-Cyclohexanedicarboxylic Acid

The title compounds **1b** and **1c** can be used to prepare chiral pharmaceutical intermediates or polyester modifiers. In the process described the *cis* diester **1a** is selectively hydrolysed with a lipase to give the monoester **1b** or **1c**, depending on the choice of enzyme. **1a** is preferably produced by esterification of the *cis* anhydride **2** which is obtained from a mixture of the *cis*/*trans* diacid **1d** ($R_1 = R_2 = H$) as shown in Scheme 1. The enzymes used for the

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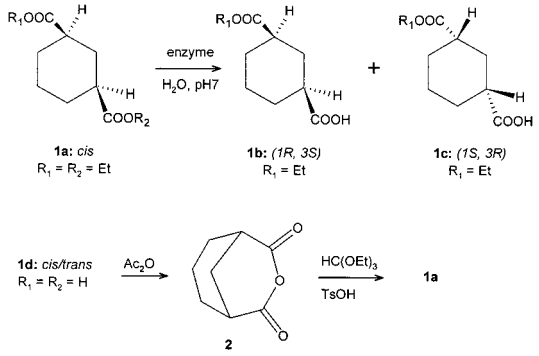
hydrolysis were either *Pseudomonas* or *Candida* species and >90% ee of **1b** or **1c** was obtainable.

Scheme 1



Advantages

Alternative methods only synthesise one enantiomer or involve resolution and hence only achieve a 50% yield. This method can start from a *cis/trans* mixture of the diacid **1d** and produce either enantiomer of the monoesters in high yields.

Patent No. 6,215,023

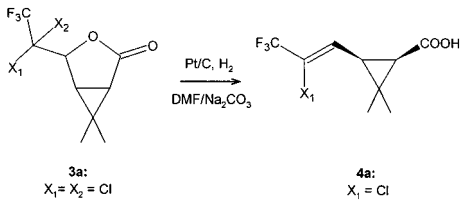
Assignee: Cheminova Agro A/S, Harboør, Denmark

Title or Subject: Preparation of Cyclopropane Carboxylic Acids

Esters of the acids **4a** are used as insecticides and are generally known as pyrethroids. These materials have low mammalian toxicity and hence are of great interest. It is known that high insecticidal activity is achieved when the 1*R*, *cis* geometry is used; hence, synthetic routes to **4a** attempt to optimise the yield of this configuration.

The general method of producing **4a** is by reduction of the lactone **3a** which already has the desired configuration. This has been carried out previously using metallic Zn in a stoichiometric reaction, but the patent describes a catalytic process using sodium formate or hydrogen in the presence of Pt/C. The reaction takes place in DMF between 20 and 50 °C and at only slightly increased pressure of hydrogen. It is claimed that this method gives high yields of the desired *Z*-isomer especially at lower temperatures. In addition the new process does not form by-products **3b** (X_1 = Cl, X_2 = H) or **4b** (X_1 = H) which are difficult to remove when purifying **3a** (Scheme 2).

Scheme 2



Advantages

The present process uses mild conditions, thus favouring high selectivity. It is claimed that it is more economical than using metallic Zn. The use of catalysts that can be reused is an improvement because the Zn-based process also has disposal problems to be considered.

Patent No. U.S. 6,215,032

Assignee: Albermarle Corporation, Richmond, VA, U.S.A.

Title or Subject: Recovery of Aminophosphonium Catalysts from Halogen-Exchange Reactions in Aromatics

The title compounds such as $(Et_2N)_4PBr$ **5** are used as effective catalysts in the preparation of fluoroaromatics. Although they are effective catalysts, they are also relatively expensive, and their recovery is desirable. However, the formation of heavy by-products during fluorination complicates the possible recovery of active **5** from the reaction mixture and limits their use. This patent describes a method to recover catalytically active material from reaction mixtures, thus making the use of catalysts such as **5** more attractive in aromatic fluorination reactions. The stepwise process involves leaching and solvent extraction from the reaction mixture containing **5**.

In the production of chlorofluorobenzenes from hexachlorobenzene using KF in nitrobenzene, **5** was used as catalyst. Following the completion of the reaction the following steps are involved to recover active **5**:

1. Separate solids and liquids from reaction by centrifugation.
2. The solution was collected and concentrated by evaporation to give an oil.
3. The oil was then extracted with dilute HCl and the aqueous extract collected.
4. The aqueous solution was extracted with CH_2Cl_2 and the organic fraction collected.
5. The CH_2Cl_2 fraction was then extracted with nitrobenzene, and the resulting nitrobenzene solution of **5** was used in subsequent fluorination reactions.

Advantages

The main claim of this patent is that it is possible to recover **5** from the fluorination. The ability to undertake the fluorination in nitrobenzene simplifies the overall fluorination process and catalyst recovery and is an improvement on noncatalytic methods.

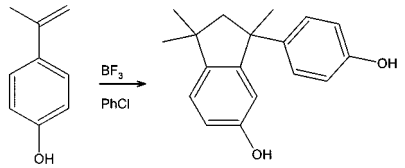
Patent No. U.S. 6,225,512

Assignee: Bayer AG, Leverkusen, Germany

Title or Subject: Production and purification of 3-(4-hydroxyphenyl)-1,1,3-trimethylindan-5-ol

The bisphenol compound **7** is use in the production of high-performance polycarbonate plastics. The production of **7** described here is based on the acid-catalysed isomerisation of isopropenylphenol **6** or its dimers or oligomers (Scheme 3). The specific isomer of **6** that is used is not specified nor are the structures of the so-called dimers and oligomers. The process is carried out in refluxing chlorobenzene using BF_3 catalyst and pure product was obtained by recrystallisation from aqueous acetic acid. The yield of **7** is >60%, and one example describes a kilogram-scale experiment (Scheme 3).

Scheme 3



6 7

Advantages

Other processes to make **7** from **6** use a variety of acids and date from up to 50 years ago. They are said to give low yields and are not suitable for industrial production. The current method gives good yields of high-purity material.

Patent No. U.S. 6,229,042

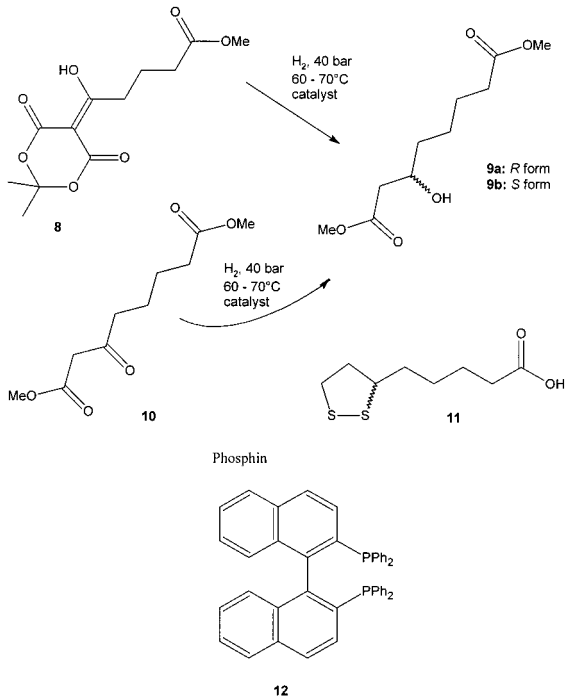
Assignee: ASTA Medica AG, Germany

Title or Subject: Preparation of Enantiomerically Pure 3-Hydroxyoctanedioic Acid Diesters by Asymmetric Catalytic Hydrogenation

The *S*-form of the title compounds such as **9b** are known and used in the synthesis of α-lipoic acid **11.** The *R*- and *S*-forms of **11** have different medicinal properties; hence, a method to make each is desirable. The *R*-form **9a** can also be used to make **11**; however, it is a novel compound, and this patent provides a means of making both **9a** and **9b** by asymmetric hydrogenation of the ketone **8**, which is preferred, or of the ketoester **10**. Other methods of preparing **11** include resolution of its salts or an epoxidation of expensive allylic alcohols. A method involving the asymmetric reduction of **9** using Baker's yeast is only applicable to the isobutyl ester and only has low space−time yield.

Hence, this patent describes an improved process for the hydrogenation step that can be carried out with either one of two catalyst systems (Scheme 4). The first uses Ru complexes containing chiral phosphines such as **12**, and the second uses Raney Ni with either enantiomer of tartaric acid, TTA. The patent contains a wide selection of suitable chiral phosphine ligands which seems to be the favoured catalyst system over the Raney Ni/TTA. By appropriate choice of the ligand or co-catalyst the either **9a** or **9b** can be obtained in ee of up to 98% (Scheme 4).

Scheme 4



Advantages

The ability to prepare either enantiomer of **9** provides high yield economic routes to **11** from a readily available ketone such as **8**.

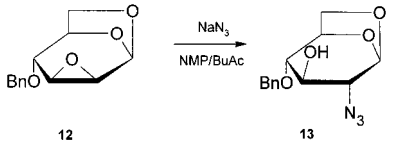
Patent No. U.S. 6,232,451

Assignee: Akzo Nobel N.V., Arnhem, The Netherlands

Title or Subject: Preparation of a Pyranose Azide Derivative from an Epoxide

Although the actual patent title mentions organic azides, it is actually aimed at the conversion of epoxy pyranose compounds such as **13** to the azide **14** by reaction with sodium azide at 100−120°C (Scheme 5). The azido compounds can be used to prepare a glycosaminoglycan that has antithrombotic properties. It is claimed that other methods used to introduce an azide group into carbohydrates involve several steps or involve the handling of explosive ammonium azide or hydrazoic acid. The use of these chemicals means that special materials of construction for the equipment are needed.

Scheme 5



12 13

NMP = N-methylpyrrolidone

This process is claimed to provide a simple method of producing an azidopyranose compound from readily available epoxy derivatives. The patent claims cover conversion of several epoxides to azides, but the only example is for producing over 10 kg of **14**, and ^{1}H NMR peak assignments are given.

Advantages

This appears to be a relatively simple one-step process for the synthesis of an azide that is otherwise difficult to prepare.

Patent No. U.S. 6,232,473

Assignee: Kuraray Co. Ltd., Kurashiki, Japan

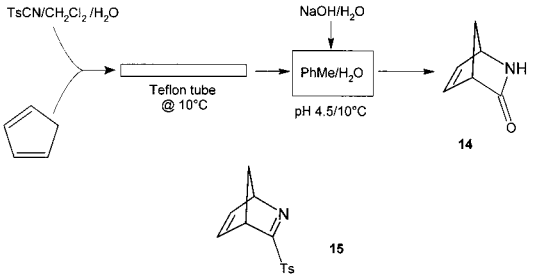
Title or Subject: Process for Producing 2-Azabicyclo[2.2.1]hept-5-en-3-one

This patent describes the synthesis of the title compound **15** which is an intermediate in the preparation of carbocyclic nucleosides that are useful medicines, including anti-HIV agents. There are a number of method of synthesising **15** from cyclopentadiene and sulphonyl cyanides such as TsCN, and all are said to have problems. One problem is that the methods proceed via the production of 3-sulphonyl-2-

azabicyclo[2.2.1]hepta-2,5-diene **16** which is unstable and can decompose violently. Other problems include using up to 35× excess of TsCN and difficulty controlling the exothermic reaction in one of the intermediate synthetic steps. Waste disposal is another problem of the methods which overall are not satisfactory from an industrial point.

The process here is improved by being carried out on a continuous basis so that the amount of **16** is kept to an absolute minimum Scheme 6. The process is carried out by pumping the two reactants through a tube that is kept at about 10 °C. The mixture then flows into a flask containing toluene and water that is kept at a pH of about 4.5 by addition of 25% NaOH solution. After all reactants are used, the pH is increased to 7.5, and **15** was recovered from the solution. The yield by HPLC was about 95%.

Scheme 6



Although continuous processes are not popular in the synthesis of fine chemicals, this process shows clearly the advantages that can be gained by operating in this manner. Higher yields are often achieved by limiting by-product formation as a result of reducing the inventory of intermediates that have alternative reaction paths to those desired.

Advantages

The process is able to decrease the hazards associated with this synthetic route, and it improves yields by limiting the inventory of the intermediate **16** and using it almost as rapidly as it is produced.

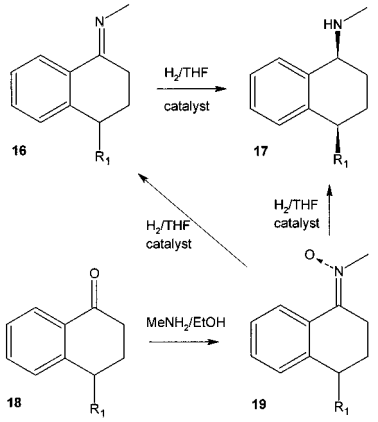
Patent No. U.S. 6,232,501

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

Title or Subject: Production of Sertraline by cis-Selective Catalytic Hydrogenation of Cyclohexylidenamines

Sertraline **18** is an antidepressant that is sold as the hydrochloride under the name Lustral and Zoloft. A patent assigned to Pfizer in 1985 (U.S. 4,536,518) describes the preparation of **18** by Pd-catalysed hydrogenation of the imine **17** (Scheme 7). There are four enantiomers of **18** with two *cis* and two *trans* pairs, and the objective of the hydrogenation step is to maximise the yield of the *cis* pairs over the *trans* pairs. The Pd catalyst is reported to give a 70/30 mixture, and later patents using Raney Ni catalysts give a *cis/trans* ratio of 8. The current patent describes further improvements using Cu-based catalysts where yields of >95% of *cis* isomers are claimed. The catalysts used are commercially available copper chromite or Cu/Zn/Al types.

Scheme 7



R_1 = 3,4-dichlorophenyl

The examples in the patent compare the activity of pre-activated and non-activated catalysts and show that there is a slight improvement with pre-activated catalyst. Previous personal experience of this reviewer has shown that the activity of copper catalysts can be dramatically improved by carefully controlled activation procedures.

The *cis* enantiomers that are obtained in the hydrogenation are subsequently separated by conventional methods to obtain optically pure **18**. A variation of the route to **18** is the conversion of the ketone **19** to the imine **17** via the nitrone **20** and then hydrogenation to give **18**. If optically pure **17, 19** or **20** is used, and then the single enantiomer **18** can be obtained.

Advantages

The improved yield of the *cis* isomers compared with that of the previous processes greatly improves the economics of the method and reduces losses.

Patent No. U.S. 6,235,198

Assignee: Elf Aquitaine Exploration, Courbevoie, France

Title or Subject: Process for Purification of DMSO

DMSO can contain traces of metals such as Na and Fe that require removal before use in several applications. This is the second patent from Elf on purification of DMSO using ion-exchange resins (IER). Both patents were filed on the same date, and the first using a sulphonic IER has been reviewed (*Org. Process Res. Dev.* **2000**, *4*, 246). This patent describes treating anhydrous DMSO with a chelating IER containing aminophosphonic groups and a sulphonic IER.

Advantages

Presumably the use of the chelating IER can remove multiple charged ions, whereas using only the sulphonic IER removes single charged Na ions.

Patent No. U.S. 6,235,911

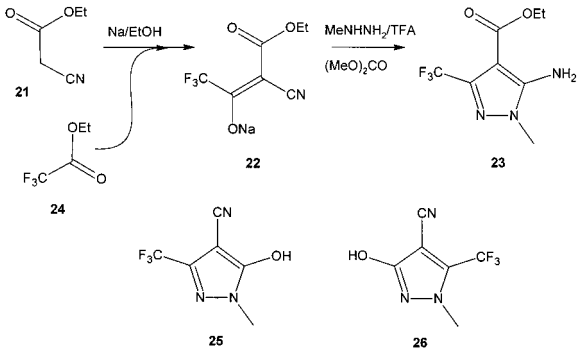
Assignee: Mitsui Chemicals Inc., Chiba-ken, Japan

Title or Subject: Process for Preparing 5-Amino-pyrazole-4-Carboxylates

The trifluoromethylpyrazole **23** is a novel compound and is claimed to be an intermediate in the synthesis of various

agrochemicals and medicines. Similar pyrazoles without the CF_3 substituent have been prepared, but **23** has not been reported. It is suggested in the patent that the reason for this is the difficulty of preparing **22** which is the precursor to **23**. The patent describes a method of producing **23** and also **22** which is obtained by condensing ethyl cyanoacetate **21** with ethyl trifluoroacetate **24** (Scheme 8). A factor in synthesising **23** is to avoid the production of large amounts **25** and **26** which necessitates a complex recovery procedure to obtain **23** in a pure state. The alternative synthetic methods to analogues of **23** tend to produce similar compounds, and hence their production needs to be minimised. The patent describes a route to **23** by condensation of methylhydrazine as the sulphate salt with the sodium salt **22**. The reaction takes place in the presence of an acid such as TFA and a dehydrating agent such as 3Å molecular sieves; without these materials the yield of **23** falls by 50%.

Scheme 8



Advantages

The synthetic route starts with readily available raw materials and reduces the yields of unwanted by-products, and the small amounts that are formed are easy to remove.

Patent No. U.S. 6,245,911

Assignee: Eisai Co. Ltd, Tokyo, Japan

Title or Subject: Process for Producing Polymorphic Crystals of Donepezil

Donepezil **27** is used as its hydrochloride salt **27**·HCl in the treatment of senile dementia, and earlier this year a patent describing four polymorphs of the salt was reviewed (*Org. Process Res. Dev.* **2001**, *5*, 100). The current patent describes the production and characterisation of three polymorphs of the parent compound.

The three polymorphs are obtained by crystallisation from different solvents with or without seeding. Types A and B are obtained by crystallisation from methanol-denatured ethanol. At below 10 ˚C over a 20 h period Type A is obtained. Over a longer period of time Type B was obtained. Alternative methods of obtaining Types A and B were developed using seeding. However, the slight differences in the methods used for Types A and B would seem to make it difficult to ensure only the desired polymorph is obtained.

The production of Type C is much more involved, and most examples in the patent are devoted to this polymorph. A number of methods are described involving a range of solvents. Methods involving cooling and reheating of solutions and then further cooling are all described as well as the use of seeding. It is difficult to determine which is the preferred method from the patent, and the process cannot be described as robust and capable of scale up. This is perhaps a good example of crystallisation being described as a black art.

The patent contains copies of X-ray diffraction patterns, differential scanning calorimetry traces, and IR spectra for all three polymorphs. The crystals of the three polymorphs are non-sticky and hence easily handled, with type C being preferred.

Advantages

The patent describes polymorphs that were previously unknown, and hence provides important data on a drug candidate.

Patent No. U.S. 6,245,913

Assignee: Wockhardt Europe Limited, Dublin, Ireland

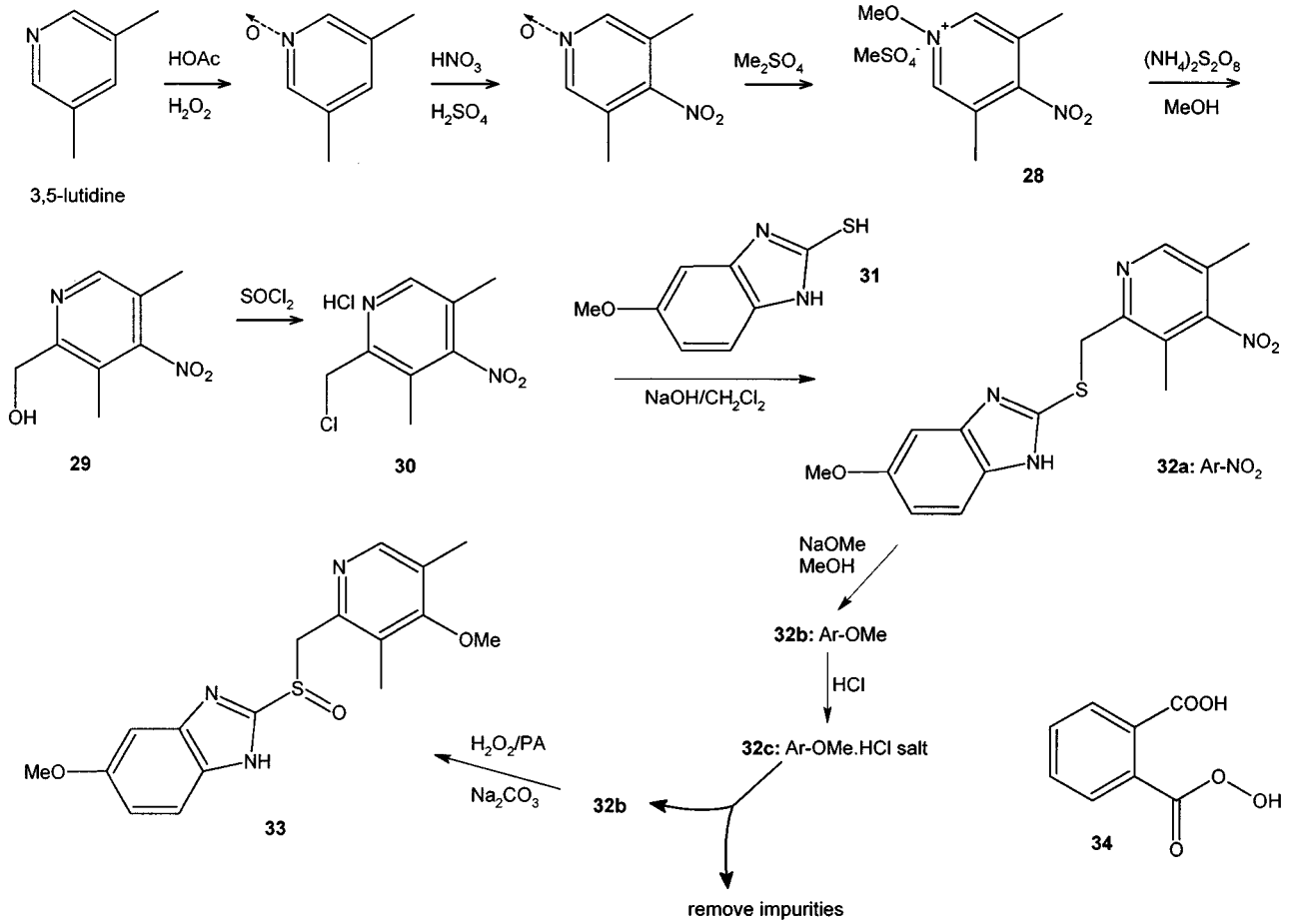
Title or Subject: Production of Omeprazole from 3,5-Lutidine by a Multi-Step Synthesis

Omeprazole **33** is available as the antiulcer drug Losec or Prilosec. A key step in the synthesis of **33** is the last stage that involves oxidation of the thioether **32b**, and a recent patent from Merck focusing on this step has been reviewed (*Org. Process Res. Dev.* **2001**, *5*, 350). The current patent describes a multistep route to **33** involving a novel oxidation process for converting **32b** to **33** via **32c**, the hydrochloride salt of **32b**. The patent provides experimental details for a multistep synthesis of **33** from 3,5-lutidine. This is shown in Scheme 9 and involves conversion of 3,5-lutidine to its nitro *N*-oxide and then to the dimethyl sulphate adduct **28**. Treatment of **28** with ammonium persulphate and methanol gives the hydroxymethyl compound **29** which is then converted to the hydrochloride salt **30.** Reaction of **30** with the benzimidazole **31** gives the nitro-thioether **32a** that is converted to the methoxy-thioether **32b** and then to the hydrochloride salt **32c**.

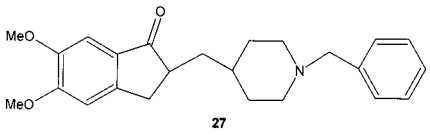
The key step in this patent is the production of the salt **32c.** This salt is obtainable in a pure crystalline form, whereas **32b** is difficult to crystallise and hence cannot easily be obtained pure. The impurities formed when **32b** is produced are easily removed from **32c**, and hence they are prevented from undergoing side reactions during the subsequent oxidation step and causing further purification problems to **33**.

As in the Merck patent the difficulties of oxidising **32b** to **33** are stressed, and the solution presented here is to convert **32b** to its hydrochloride salt **32c** which is purified and reconverted to **32b** which is recovered as a solution in CH_2Cl_2. Phthalic anhydride (PA) is then added to the solution of **32b** and the mixture added to aqueous Na_2CO_3. The two-phase mixture is then treated with H_2O_2 at about 0 ˚C and **33** was obtained in 86% yield. The use of the two-phase system means that impurities remain in the aqueous phase while **33** stays in the organic phase.

Scheme 9



It is postulated in the patent that the active oxidising agent in conversion of **32b** to **33** is the sodium salt of monoperoxy phthalic acid **34** which is formed in situ. It is suggested that the steric bulk of **34** enables selective oxidation of the thioether **32b** to **33** without over-oxidation.



Advantages

This process overcomes the problems of handling the impure thioether in a key reaction step that is known to produce impurities and make isolation of **33** more difficult. Other solutions to this problem involve handling toxic oxidising agents, whereas the reagents employed here are relatively benign.

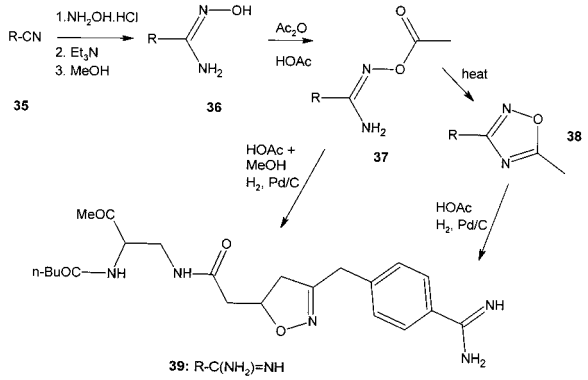
Patent No. U.S. 6,245,914

Assignee: DuPont Pharmaceutical Company, Wilmington, DE, U.S.A.

Title or Subject: Efficient Method of Conversion of Nitriles to Amidines and Amidine Salts

The amidines such as **39** are used to prepare drugs to treat thromboembolic disorders, and this patent is a division of an earlier one from DuPont that has been reviewed (*Org. Process Res. Dev.* **2000**, *4*, 68). The claims in this patent specifically cover the various intermediates **35**, **36**, **37**, and **38** that are produced during the synthesis of **39**, whereas the earlier patent covers the overall process itself which is outlined in Scheme 10.

Scheme 10



Advantages

The advantages are those claimed in the earlier patent for the route from the nitrile **35** to **39**, involving the novel hydrogenation of **37** to **39.** A previous route from **35** to **39** involves the Pinner reaction using HCl gas which causes handling problems on a commercial scale.

Patent No. U.S. 6,245,936

Assignee: Rhodia Chimie, Boulogne Billian Court, Cedex, France

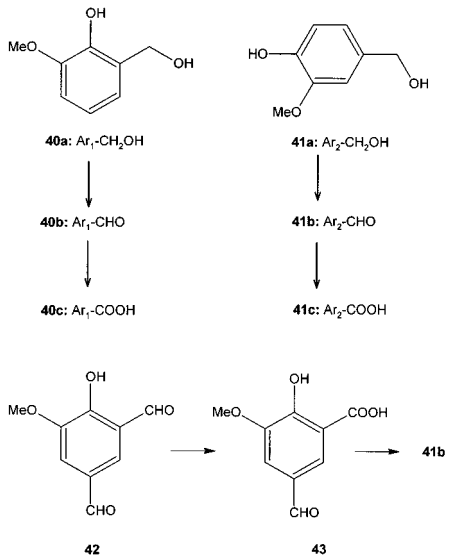
Title or Subject: Selective Preparation of Vanillin and 4-Hydroxybenzaldehydes and 2-Hydroxybenzoic Acids

This patent covers the preparation of hydroxybenzaldehydes and benzoic acids but specifically mentions *p*-vanillin **41b** which is used as a fragrance and flavour. An alternative method of producing **41b** is to start with **42** which is converted to the carboxy aldehyde **43** and then to **41b** by decarboxylation. This process involves the selective catalytic oxidation of *o*- and *p*-hydroxymethyl-phenols (HM-phenols) to hydroxybenzaldehyde or -benzoic acid. The catalyst system is Pt or Pd on C in aqueous Na_2CO_3 containing Bi_2O_3 as an activator, and air is the oxidant.

The main oxidation product of the HM group depends on its position in relation to the OH group. For example in the oxidation of the HM-guaiacols **40a** and **41a** the *o*-HM group in **40a** is almost completely oxidised to the carboxy group and gives 93% selectivity to **40c** and 7% to **40b**. In contrast the *p*-HM group in **41a** is oxidised to a formyl group and gives 89% selectivity of **41b** and 11% of the acid **41c** (Scheme 11).

The selectivity to oxidation of the *o*-isomer was also shown when oxidising an equimolar mixture of **40b** and **41b**. The *o*-isomer **40b** was completely converted to the acid **41c**, but only 20% of the *p*-isomer **41b** was oxidised to the acid **41c**. The aldehyde and acids may be separated from the mixture by pH-controlled extraction.

Scheme 11



Advantages

The ability to selectively oxidise the HM-phenols means that in producing vanillin it is possible to start with a mixture of relatively cheap raw materials compared to those required for other processes.

Patent No. U.S. 6,245,939

Assignee: E. I. Du Pont de Nemours and Company, Wilmington, DE, U.S.A.

Title or Subject: Process for Producing Highly Pure Aromatic Carboxylic Acids

Many aromatic acids are produced in oxidation processes, and this patent is specifically aimed at terephthalic and isophthalic acids which are both manufactured on a large scale by catalytic oxidation of alkyl aromatics. This process results in high levels of impurities that require removal before the acids can be used in polycondensation reactions to make polyester fibres. Very high-purity acid (99.99%) is required to avoid problems both in the polymerisation step and the properties of the final polymer.

The crude acid is often a lumpy solid that is not very water soluble, and the normal purification process involves production of an aqueous slurry and catalytic hydrogenation at about 280 °C. The acid is recovered by crystallisation from the aqueous solution. The main difficulties are in handling the lumps and the low solubility of the acids in the water even at elevated temperatures; hence, the equipment used is prone to damage.

The process described here is to control the density of the slurry sent to the hydrogenation step by on-line density measurement. The density measurement is then converted to a feedback signal that is sent to a metering device controlling the addition of more solid to the mixing vessel. In this way the slurry is of a consistent composition, and large lumps are prevented from passing on to the hydrogenation process.

The development of the on-line measurement of physical properties can provide numerous opportunities of controlling and monitoring chemical processes. As long as the measurement is more rapid than the response required, then any technique can be used for control purposes. As well as optimising the chemistry, process development staff should be aware of other areas where process improvements can be undertaken.

Advantages

This method does overcome the handling problems that are associated with purifying terephthalic acid and is likely to provide improvements in the operation of this part of the process.

Patent No. U.S. 6,245,944

Assignee: BASF AG., Ludwigshafen, Germany

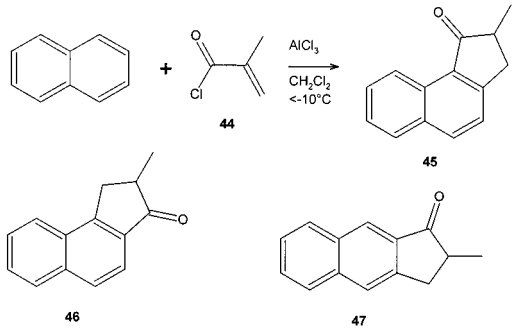
Title or Subject: Regioselective Synthesis of Benzindanones

The indanone **45** can be converted to an indene that is used to synthesise Zr metallocene complexes that are extremely efficient olefin polymerisation catalysts. Methods of making indanones are generally multistep and hence have the potential for low yield. This patent describes a Friedel–Crafts (FC) reaction between naphthalene and methacrolyl

chloride **44** which is highly regioselective and produces only the desired isomer. Other reports of FC reactions to make indanones produce large amounts of waste and give low yields because of the production of the undesirable isomers **46** and **47**.

Scheme 12 shows the reaction to make **45** which is carried in CH_2Cl_2 and uses $AlCl_3$ as a conventional FC catalyst.

Scheme 12



Advantages

This is a straightforward reaction using readily available raw materials and hence is a major improvement over other methods of making the indanones.

Patent No. U.S. 6,248,892

Assignee: Clariant GmbH, Frankfurt, Germany

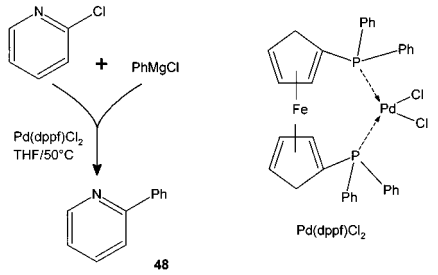
Title or Subject: Preparation of 2-, 3-, or 4-Arylpyridines

Arylpyridines are used in the production of agrochemicals and are often made on a laboratory scale by a Pd-catalysed cross-coupling reaction between iodoaromatics and aryl Grignard reagents. It is claimed that this coupling method has not been successfully applied on an industrial scale. One reason is that catalyst levels of >1% are needed, and on a commercial scale it is essential that the Pd catalyst can recovered and reused to reduce the overall costs.

This patent claims to provide a viable process using this coupling reaction by using a homogeneous Pd catalyst containing ferrocenylphosphine ligands. The synthesis of 2-phenylpyridine **48** in 98% yield is accomplished by coupling of 2-chloropyridine with phenylMgCl in THF using $Pd(dppf)Cl_2$ (Scheme 13). Similar arylpyridines were also made in >95% yields and at selectivity by GC of >98%. It is recommended that the Grignard reagent is metered into the reaction mixture, and this limits the formation of by-products resulting from dimerisation of the Grignard.

The patent does not discuss the fate of the Pd catalyst, nor does it mention if it can be reused. However, since the catalyst is only used at a 0.03 mol % concentration, the overall catalyst cost in the process is not going to be large. Presumably, the residue would be recovered and returned for precious metal recovery in the usual manner.

Scheme 13



Advantages

This process uses very efficient and selective catalysts, enabling a useful laboratory synthetic route to be applied on a commercial scale.

Patent No. U.S. 6,248,899

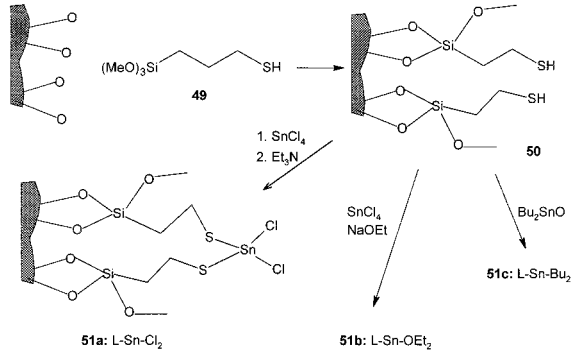
Assignee: Ciba Specialty Chemicals Corporation, Tarrytown, NY, U.S.A.

Title or Subject: Silica Supported Transesterification Organotin Catalysts

There are many types of transesterification (TE) catalysts, and organotin compounds are well known. A problem with the use of these and all homogeneous catalysts is the separation of the products from the catalysts. This patent describes immobilised organotin sulphur catalysts that are fixed to a silica support via a short alkyl chain. Thus, after the reaction the catalysts can be easily separated from the reaction mixture.

The main focus of the patent therefore is the synthesis of the catalysts and examples of their use in TE reactions. Scheme 14 show the route used to prepare the catalysts **51a, 51b**, and **51c** whose idealised structures are shown. The first step in making the catalyst is to react the thiol **49** with the silica gel support to produce the anchored thiol moiety **50**. The Sn is then attached to this by reaction with the thiol group with a Sn compound giving the final supported catalysts such as **51a**, **51b**, or **51c**. Several other similar catalysts are described which have variable ratios of S/Sn from about 2 to 11.

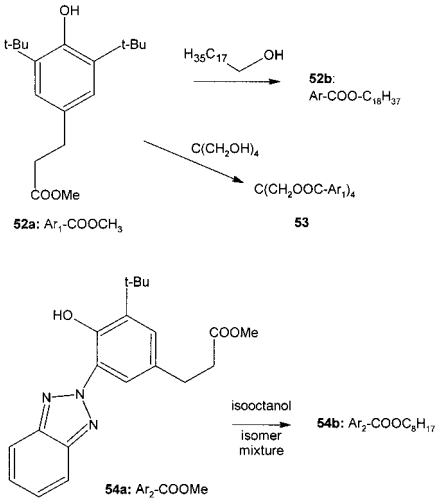
Scheme 14



These catalysts were used in TE reactions to prepare esters of long-chain fatty alcohols **52b** and **53** or the ester **54b** (Scheme 15). All of these esters are antioxidants and used in lubricants and hydraulic fluids. The reactions were carried out without solvent by melting the reactants containing the

catalysts. This allows higher temperatures than may normally be used because the catalysts are stable and conversions approaching 100% are possible. After the reaction the catalyst is filtered off and can be reused.

Scheme 15



Advantages

The advantages of using heterogeneous catalysts are well known and the catalysts described here are thermally stable so that high temperatures can be used. The ability to perform the reactions without solvents also facilitates the overall process.

Patent No. U.S. 6,248,924

Assignee: BASF AG, Ludwigshafen, Germany

Title or Subject: Supported Ru Catalysts for the Hydrogenation of Organic Compounds and Polymers

The subject of this patent is the production of supported Ru catalysts. It is stated in the patent that these catalysts can be used for a whole range of reactions on organic compounds including dehydrogenation, hydrogenolysis, and dehalogenation, but they are mainly used as hydrogenation catalysts. They are suitable for producing cyclohexyl alcohols or amines by hydrogenation of the aromatic ring in phenols or anilines. The product alcohols have uses as chemical intermediates for perfumes and medicines, and the amines are used in producing anticorrosive agents and plant protection chemicals. Hydrogenation of aliphatic ketones and aldehydes to alcohols is another use for the catalysts as well as the hydrogenation of nitrile groups in polymers to produce polymers containing amino groups. These polymers may then be used in cross-linking reactions and have application in the paper industry, detergents, and cosmetics.

Although the patent claims that the catalysts can contain other metals, the only example given is the preparation of one containing 0.05% Ru supported on alumina. This is used in a wide variety of reactions. A key feature of the catalyst is that it contains up to 50% macropores, and the remainder are mesopores.

Advantages

This patent claims that the catalysts do not cause over-hydrogenation of the functional groups on aromatics which is certainly a problem with many catalysts. The activity of these catalysts is said to be higher than Rh catalysts, and hence a lesser quantity of them is required; since Ru is much cheaper than Rh, this is especially useful.

Patent No. U.S. 6,251,642

Assignee: Samsung Fine Chemicals Co. Ltd., Korea

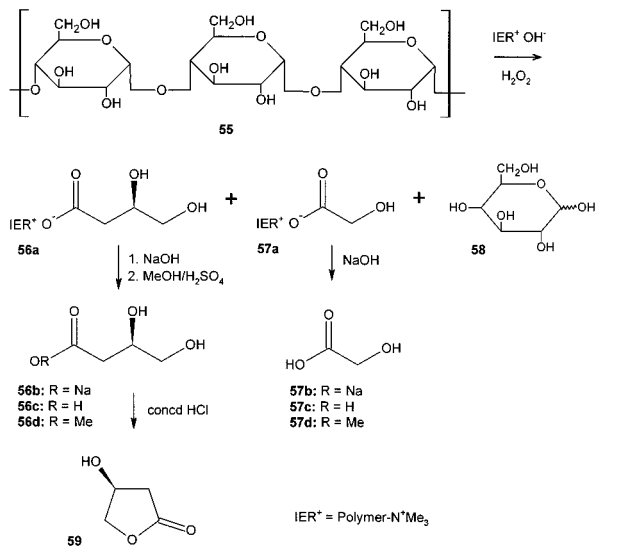
Title or Subject: Preparation of Optically Pure (S)-3-Hydroxy-γ-butyrolactone from Polysaccharides

The tile compound **59** is an intermediate in the preparation of various chiral drug compounds, and a similar patent from this company was reviewed earlier this year (*Org. Process Res. Dev.* **2001**, *5*, 100). Both patents describe a commercial process to produce **59** from high-molecular weight polysaccharides which previously had not been possible. The process comprises the following steps :

1. preparation of a (1,4)-linked oligosaccharide **55** from amylopectin,
2. oxidation of **55** using basic H_2O_2 to give acid **56c** (R = H),
3. esterification of **56c** to afford ester **56d** (R = Me), and
4. acid-catalysed cyclisation of **56d** to give desired lactone **59**.

The difference between the two patents is that in the first patent the oxidation in step 2 was carried out in the presence of NaOH, whereas in this patent the reaction is carried out using basic IER. The oxidation reaction is shown in Scheme 16, and this produces the IER absorbed acids **56a** and **57a**. The other product of the oxidation is the glucose **58** which remains in the solution. By washing the IER with alkali the Na salts of the acids are formed **56b** and **57b** (R = Na), and the patent does not indicate that they were separated. Hence, it is presumed that both the ester **56d** and **57d** were produced when, in the next stage, the sodium salts were treated with $MeOH/H_2SO_4$. In the final step the lactone **59** was obtained from the ester **57d** by cyclisation using concentrated HCl or methanesulphonic acid. Experiments were carried out on kilogram scale, and yields of >50% of **59** based on amylopectin were obtained.

Scheme 16



Advantages

The process uses readily available chiral raw materials, and employing IER improves the by-product removal and product purification. The yields are said to be double those achievable when disaccharides are used.

Patent No. U.S. 6,252,061

Assignee: Reliable Biopharmaceutical Inc., St. Louis, MO, U.S.A.

Title or Subject: Process for Production of 2-Halo-6-aminopurines

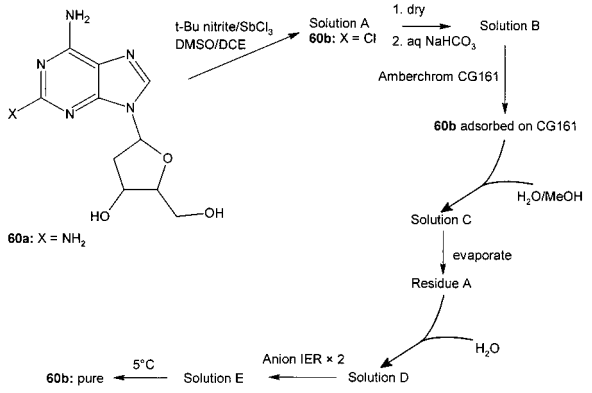
Derivatives of the title compounds such as **60b** are antileukemic agents, and this patent provides a method of synthesising this and related compounds. Several methods exist for preparing such compounds, but they are usually multistep and result in low yields. Some of the multistep routes also start with expensive raw materials and thus cannot be said to be viable for commercial-scale production. A common feature of these routes is the necessity of nucleoside hydroxyl protection and deprotection reactions. The present patent describes a route that does not require such protection, and an increase in yield is obtained.

60b is obtained from the 2-amino purine **60a** which is subjected to a diazotisation of the 2-amino group using *tert*-butyl nitrite and $SbCl_3$ at room temperature (Scheme 17). This is an unusual diazotisation of a 2-amino-purine because it proceeds in high yield without the need for protection of the nucleoside. This reaction must be conducted using a combination of the polar aprotic solvent (DMSO) and the nonpolar aprotic solvent (dichloroethane, DCE). If the reaction is carried out using either solvent alone, then the diazotisation does not proceed.

The product of the diazotisation reaction is Solution A, and this is then evaporated to dryness and the residue neutralised to obtain crude **60b** as Solution B. This is then immediately applied to a polystyrene−divinylbenzene cross-linked polymeric resin column to prevent product degradation. It is vital that Solution B is applied to the resin shortly after the neutralisation because even storage at 0°C will degrade the product.

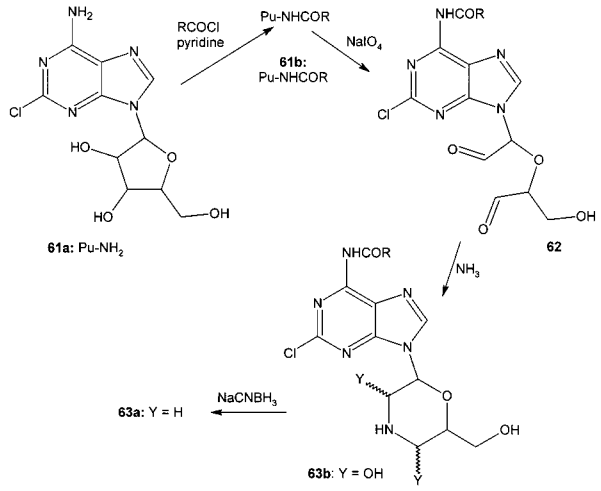
The **60b** adsorbed on CG161 is then worked up as shown in Scheme 17, and finally 99% pure **60b** is obtained in 27% yield by crystallisation.

Scheme 17



The patent also describes a method for the synthesis of the novel morpholino purine derivatives **63a** from the hydroxy purine compound **61a** by a route shown in scheme 18. The 4-amino group in **61a** is first protected, and then the ribose sugar ring in **61b** cleaved with periodate to give a dialdehyde **62**. The morpholino ring is then formed by reaction of **62** with ammonia to give **63b** which on reduction with cyanoborohydride gives **63a**. Although the reaction scheme is shown in the patent no experimental details are given and **63a** is presumably the subject of another patent.

Scheme 18



Advantages

The key aspect of this patent is undoubtedly the capability to carry out a diazotisation reaction without protecting the OH groups. It would be interesting to know if the method used is applicable to other diazotisation reactions.

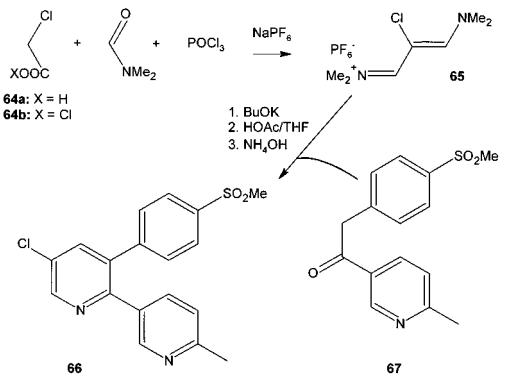
Patent No. U.S. 6,252,116

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

Title or Subject: Preparation of Iminium Salts: Useful Intermediates in the Synthesis of Arylpyridine COX-2 Inhibitors

The synthesis of COX-2 inhibitors is a very active area because of their use in pain inhibition and reduction of inflammation. Merck is very active in this area, and other patents from the company have been reviewed (*Org. Process Res. Dev.* **2000**, *4*, 246 and 450). This patent is, in a fact, a division of an earlier patents that covers the whole process, and the subject of the current patent is the iminium salt **65**

Scheme 19



which is used in the route to the arylpyridines **66**. The salt **65** can be made in a Vilsmeier reaction between DMF/$POCl_3$ and either choroacetic acid **64a** or chloroacetyl chloride **64b**. The reaction is carried out in the presence of $NaPF_6$ so that the hexafluorophosphate form of the salt is obtained. The aryl pyridine **66** is then obtained by reaction of the salt **65** with the ketone **67** whose synthesis is also described in the patent. One example describes the production of >2 kg of **65**, possibly indicating the advanced commercial stage of the process.

Advantages

The process is carried out at moderate temperatures and results in high yields with the minimum number of process steps.

Keith Turner

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