Organic Process Research & Development **2003**, *7*, 135–147

Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during August to November 2002

Summary

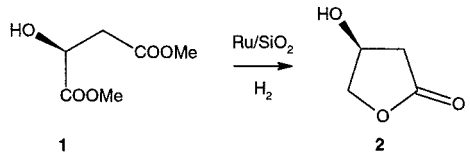
The search for this review produced 760 patents, and of these, 23 have been selected as being of interest to readers and have been summarised. There is continued interest in the use of simulated moving bed chromatography (SBMC) in the separation of enantiomers with two patents from UOP. The use of supercritical fluids (SCF) as reaction solvents continues to develop, and a patent from the University of California combines SCF and phase-transfer catalysis to improve catalyst and product recovery using homogeneous Rh catalysts for a number of reactions. Workers at the University at Cambridge also investigated this area by focusing on several Pd-catalysed reactions and found improved solubility and reactivity for various ligand systems in SCF CO_2. There are two patents that focus on the hydrolysis of amides with one providing an unusual method for obtaining amines by direct hydrolysis and also eliminating waste production in the reaction. The second one is aimed at methionine precursors and shows the importance of considering the reactor design in improving reaction selectivity and uses two types of reactor in series to carry out the two-stage hydrolysis of nitriles via amides to acids. Waste disposal is a major concern in the chemical process industries, and a method of safe disposal of spent acid catalysts is described which is not too different from what is probably standard operating practice. An improved method for direct fluorination of β-dicarbonyls is described that relies on using oxygen as a radical scavenger to reduce by-products. A comprehensive patent describing improvements in the synthesis of tetrapyrroles for large-scale production is only very briefly reviewed since it has 149 claims. A method of overcoming the thermodynamic equilibrium limitations in *E*/*Z* mixtures of pentol isomers is disclosed in which Br radicals are used to achieve production of larger quantities of the less favoured *E* isomer. Polymorphs continue to attract patent interest, and a new form of formoterol has been described that enables higher purity of the previously known forms to be achieved. There are several patents that describe experiments involving the manufacture of multikilogram quantities of materials, and in one case 330 kg of product is produced. However, a number of other patents contain no experimental data whatsoever. It can probably be inferred that the processes describing multikilogram batches have been in commercial operation at least once. Apart from this inference there is no legal or commercial significance in the choice of patents for this review and as usual any advantages are those claimed in the patent unless this reviewer has prior knowledge.

Patent No. U.S. 6,429,319

Assignee: SK Corporation, Seoul, Korea

Title or Subject: Continuous Process for the Production of Optically Pure (S)-β-Hydroxy-γ-butyrolactone

The title compound **2** is an intermediate in the preparation of various chiral drug compounds as well as agrochemicals, seasonings, and flavourings. The synthesis of **2** from oligosaccharides has previously been reviewed (*Org. Process Res. Dev.* **2001**, *5*, 100 and 557). Continuous processes are not often favoured in the synthesis of fine chemicals, but this patent describes an efficient continuous route to **2** via the catalytic hydrogenation of substituted carboxylic acid esters such as dimethyl (*S*)-malate **1** (see below).



1 **2**

The process uses a fixed bed of catalyst containing about 3% Ru supported on silica. The reaction is carried out by pumping a 30% solution of the ester **1** in water through a tubular trickle bed reactor containing the catalyst. The reaction takes place in the liquid phase at about 145 °C and a pressure of 165 bar or higher. The solution is fed to the reactor at a space velocity of about 0.5 h^{-1}. The conversion of **1** to **2** is around 92% with a selectivity of >74%. It is also possible to start from L-malic acid which is dissolved in MeOH, and the ester is formed by passing the solution through a tubular reactor packed with a solid acid catalyst such as a cationic ion-exchange resin (IER). The ester **2** is formed in 99% conversion and at a selectivity to **2** of 99%. This solution can be mixed with water and hydrogenated to give **2**. Some experiments involve extended running times of up to 500 h, and it is claimed that the catalyst shows no loss in activity. The ester **2** is recovered from the reaction product by extraction with EtOAc followed by vacuum distillation. The use of a fixed bed of catalyst means that the need for a separation step to remove and recover the catalyst is unnecessary.

Advantages

Other methods available for this hydrogenation are noncatalytic and use $NaBH_4$-based catalysts in batch processes. As such, these methods produce wastes that are environmentally difficult to dispose of. This process claims to alleviate these problems and to give **2** in high productivity in an economic manner. A key feature of this process is that

10.1021/op0340154 CCC: $25.00
Published on Web 02/07/2003

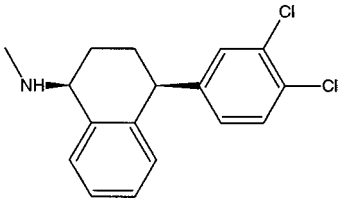
by running continuously the overall efficiency is much improved and the process is more economic than batch processes.

Patent No. U.S. 6,452,054

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

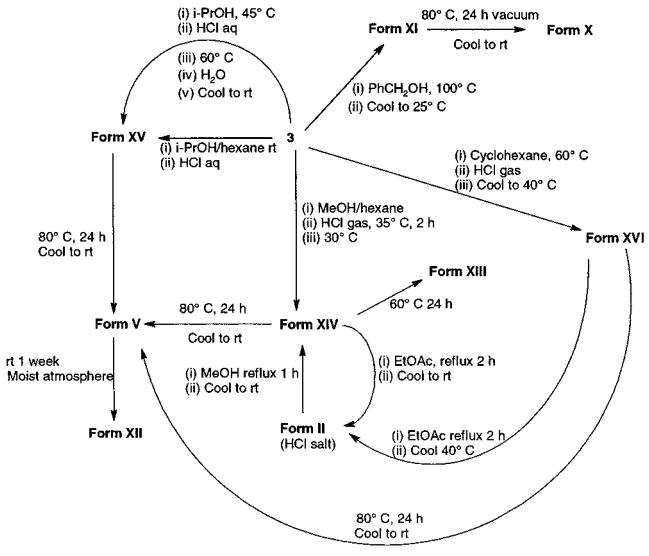
Title or Subject: Processes for Preparing Novel Polymorphs of Sertraline Hydrochloride

Sertraline **3** is an antidepressant that is sold as the hydrochloride under the name Lustral and Zoloft. The expiration of the original patents has produced a flurry of interest in this compound from a number of generic drug manufacturers. The original patent assigned to Pfizer in 1985 (U.S. Patent 4,536,518) describes one main polymorph (Form II) and a later Pfizer patent (U.S. Patent 5,248,699) describes four more polymorphs (Forms I, III, IV, and V) of **3**.



3

The current patent describes details of how to produce six novel polymorphs (Forms XI, XII, XIII, XIV, XV, and XIV). A further five polymorphs (Forms VI, VII, VIII, IX, and X) are described in a co-pending application (now U.S. Patent 6,495,721) that had not been published at the time of the current search. The new polymorphs are distinguished by X-ray diffraction (XRD) and IR spectroscopy, and copies of both IR and XRD spectra for the new polymorphs are provided. The patent describes methods of obtaining the novel polymorphs XI−XVI and also of the various interconversions of a number of polymorphs. Several of these are summarised in the scheme below. The patent also describes a number of formulations of the new polymorphs for use in treating various disorders.



Advantages

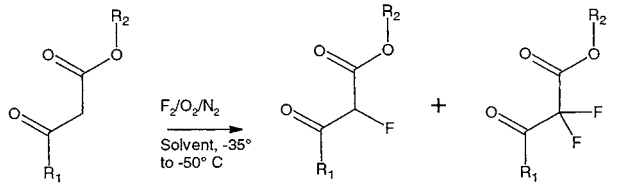
The patent claims that some of the new polymorphs have improved physical properties, making them more suitable for formulating various medicines than previously known polymorphs.

Patent No. U.S. 6,455,728

Assignee: Air Products and Chemicals Inc., Allentown, Pennsylvania, U.S.A.

Title or Subject: Process for the Preparation of Fluorinated β-Dicarbonyl Compounds by Direct Fluorination in the Presence of Oxygen

Fluorinated β-dicarbonyl compounds such as **5a, 5b**, and **5c** are extremely useful intermediates in the synthesis of pharmaceuticals. A problem when preparing such compounds by direct fluorination is that it is common for impurities such as **6a**, **6b**, and **6c** to be obtained in substantial amounts (>10%). Fluorination technology in acid conditions does exist for the preparation of fluoro dicarbonyl compounds, but it is said to be reasonably selective only when the enol form of the diketone or ketoester is stabilised under the reaction conditions. Furthermore, fluorination of perfluoroalkyl compounds such as **4c** is said to be effective only in nonpolar solvents, and even then 30% by-products such as **6c** are produced. The process disclosed here adds oxygen gas to the fluorination mixture, and the patent claims that this surprisingly reduces the formation of such by-products. In addition it was found that in some cases a solvent was not required for the reaction so that the recovery of the products from the reaction mixture is simplified.



4a: R_1 = Et, R_2 = Me
4b: R_1 = Me, R_2 = Et
4c: R_1 = CF_3, R_2 = Et

5a: R_1 = Et, R_2 = Me
5b: R_1 = Me, R_2 = Et
5c: R_1 = CF_3, R_2 = Et

6a: R_1 = Et, R_2 = Me
6b: R_1 = Me, R_2 = Et
6c: R_1 = CF_3, R_2 = Et

When the substrate is a diketone such as **4a** or **4b**, the process is carried out by sparging a solution of the substrate in an acidic solvent such as HF, TFA, or HCO_2H with a mixture of F_2 and O_2/N_2. Various ratios of the three gases are used apart from normal air. If the substrate is a fluorinated compound such as **4c**, then $CFCl_3$ is the preferred solvent. Experiments are described with **4c** without any solvent in which the use of O_2 can reduce the amounts of by-product **6c** from 80% down to 5%.

Advantages

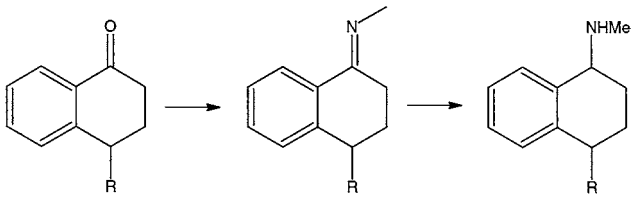
The process clearly improves the overall atom efficiency and simplifies the purification of the desired products.

Patent No. U.S. 6,455,736

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

Title or Subject: Preparation of Sertraline and its Analogues in High Enantiomeric Purity by Simulated Moving Bed Chromatography

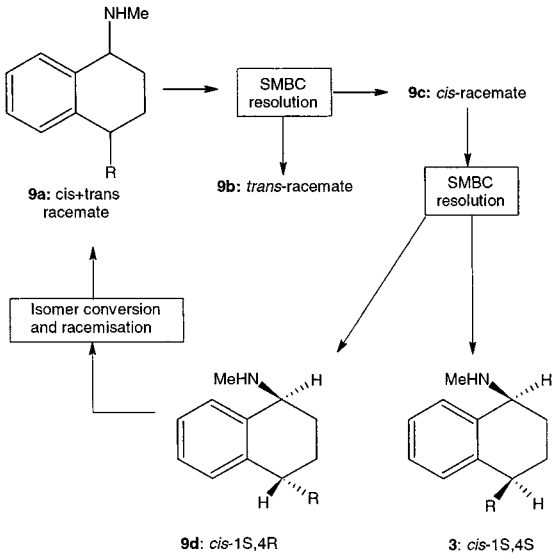
UOP was the first company to commercialise SMBC for separating xylene isomers. Many hundreds of thousands of tonnes of pure *p*-xylene are obtained annually from such mixtures using SMBC technology. Many companies including UOP are now very active in using the technique for separation of enantiomers and this is the subject of both this and the next patent. As mentioned earlier sertraline **3** is currently of great interest, and this patent describes the use of SMBC to obtain **3** in high enantiomeric purity. The separation using SMBC is coupled with a racemisation step of the undesired enantiomer to improve the overall yield of the process. The use of SMBC to obtain enantiomerically pure precursors to **3** containing an amine protecting group has already been described by UOP, and this was reviewed recently (*Org. Process Res. Dev.* **2002**, *6*, 749). This patent focuses on an alternative approach, involving the recovery of the *cis* isomer of the amine **9c** from the *cis* and *trans* racemate **9a**. The patent does not give any specific experimental details, but the process relates to the production and separation of the racemic amine **9a**. This is formed from the tetralone **7** by reduction of the imine **8** as shown below and the claims of the patent specifically relate to production of **3**.



7 **8** **9a:** cis+trans racemate

R = 3,4dichlorophenyl

The desired compound **3** is obtained by using two stage SMBC. In the first stage, shown below, either a chiral or nonchiral adsorbent is used to separate the *cis* and *trans* racemate isomers **9b** and **9c** from the racemate mixture **9a**. The *cis* racemate **9c** is then resolved into the *cis* enantiomeric pairs **9d** and **3** using SMBC with a chiral adsorbent. The undesired *cis*-1*S*,4*R* enantiomer **9d** is recycled via an isomeric conversion and racemisation step to give racemate **9a** but no specific details are given. On the face of it the only loss to the process is the *trans* racemate **9d**, but it is anticipated that this can be readily converted to **9a** although details are not included in the patent. The flow scheme shown in the patent is actually incorrect since it claims that **9c** is resolved to give two additional intermediate enantiomers, and one of these is then further resolved to give **3** and **9d**. This is clearly impossible since it would require a further chiral centre in the molecule **9a**. The absence of experimental details does not help in trying to determine what is being claimed and certainly leaves the patent open to criticism.



R = 3,4dichlorophenyl

Advantages

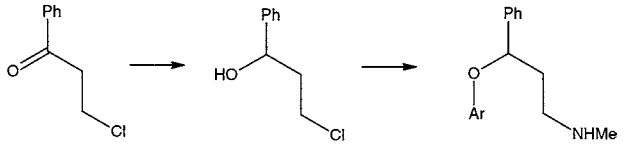
The use of SMBC avoids the use of expensive chiral resolving agents, and it is claimed that product quality control is better since SMBC is a continuous separation process. If the *trans* isomer **9b** can be recycled, then the route should also have a high atom yield.

Patent No. U.S. 6,458,955

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

Title or Subject: Use of Simulated Moving Bed Chromatography for Preparation of Enantiomers of Oxetines

This second patent from UOP uses again SMBC for enantiomer separation, and the actual title of the patent is very general and relates to pharmaceutical enantiomers. The patent does specifically mention oxetines which are a class of serotonin-uptake inhibitors. The most well-known is fluoxetine which is available as Prozac for use as an antidepressant. The general route to oxetines such as **12** is shown in the scheme below, and this contains three key elements.



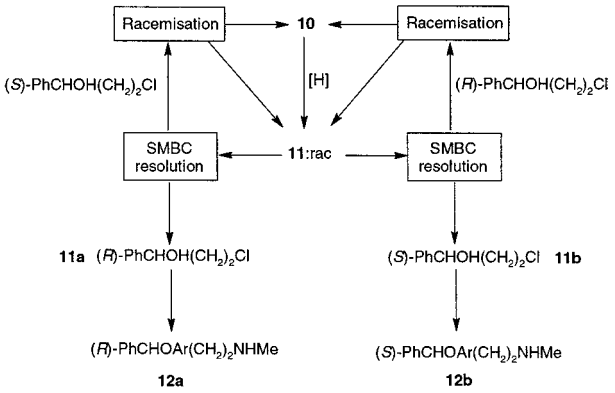
10 **11:** racemate **12**

Ar = 4-CF_3Ph, 2-MePh or 2-EtOPh

The first aspect is reduction of the carbonyl group in **10** to the chiral benzylic alcohol **11**. The next is arylation of the OH group, and the final element is formation of the methylamino group to give **12**. No experimental details are provided for the resolution steps nor for the various reactions steps, and hence there is no indication of efficiency and productivity. Reference is made to the literature for suitable reaction conditions for all of the conversions.

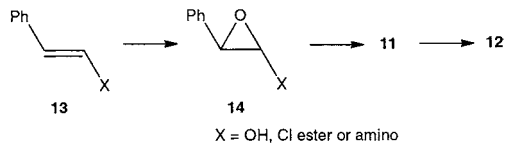
The patent describes the use of SMBC using a chiral adsorbent coupled with an appropriate racemisation step to

obtain the desired enantiomer of **11** and therefore **12**. The resolution and racemisation procedure for production of **12** is shown below.



This scheme shows that either the *R* or *S* isomer of the benzylic alcohol **11a** or **11b** can be obtained and converted to the appropriate oxetine **12a** or **12b**. The undesired enantiomeric alcohol is racemised by any suitable method and then recycled either directly to give the racemic **11** or oxidised to give the ketone **10**.

The patent also mentions an alternative route to oxetines that also involves a SMBC resolution and a racemisation step. This route involves the epoxidation of the cinnamyl compounds **13** and is summarised in the scheme below. The SMBC resolution is applied to the epoxide **14** as well as to the alcohol **11**.



The patent is devoid of experimental information, and hence the efficiency of the procedure is not given. However, it is known that SMBC is an extremely efficient technique for separating enantiomers.

Advantages

As with the previous patent the use of SMBC avoids the use of expensive chiral resolving agents, and by coupling this with racemisation the overall process is likely to be highly efficient.

Patent No. U.S. 6,458,963

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

Title or Subject: Preparation of Eprosartan Using Regioselective Protection of 2,4-Disubstituted Imidazole Intermediates

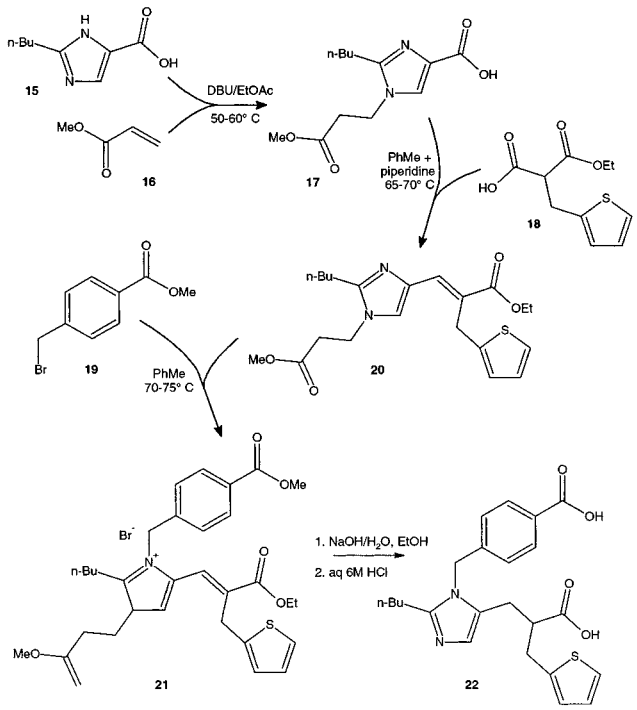
Eprosartan **22** is used in the treatment of congestive heart failure and renal failure, and this patent describes a three-stage process to **22** that is suitable for large-scale production and involves the following steps:

(1) production of the ester-protected imidazole **17** from **15** by regioselective protection of the least hindered N atom in **15** with methyl acrylate **16** using DBU,

(2) reaction between **17** and the monoester of the dioic acid 18 to give **20**, and

(3) formation of quaternary salt **21** by reaction of **20** with benzoate **19** and then basic workup and acidification.

The first two stages are carried out without purification of the intermediates **17** and **20**. The overall route is shown in the scheme below. An alternative approach is to carry out stages 1 and 2 in the reverse order.



The patent describes one experiment to produce 330 kg of **22**, thereby indicating the advanced commercial status of the process.

Advantages

The original patent describing the synthesis of dates back to 1993, and the new patent is said to be a great improvement and particularly suitable for large-scale operation although the specific reasons are not mentioned.

Patent No. U.S. 6,485,985

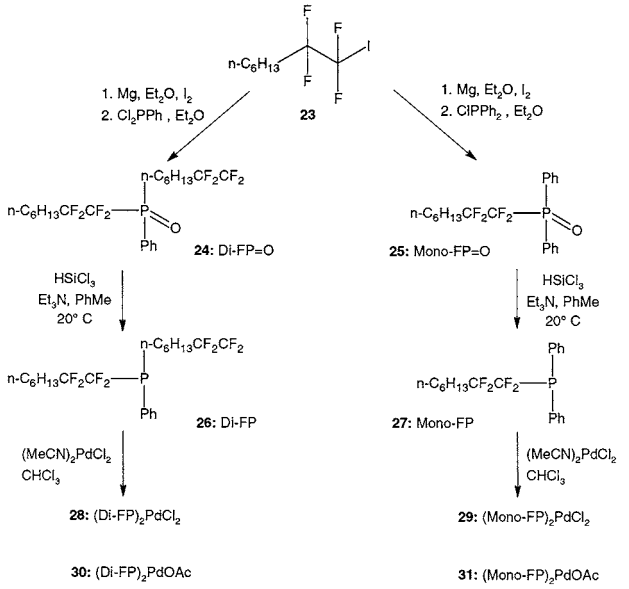
Assignee: Cambridge University Technical Services Ltd., Cambridge, United Kingdom

Title or Subject: Use of Compressed CO_2 in Chemical Reactions

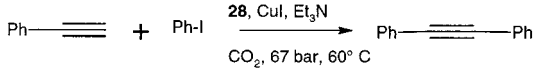
There are two major aspects of this patent that involve the use of supercritical (SC) CO_2 as a solvent which is an active area of research. The first finding is that Pd complexes have a dramatically increased solubility in SC CO_2 when they contain perfluorinated alkylphosphine ligands bound to the Pd. This enables homogeneous metal-catalysed reactions to take place in nonpolar solvents without the CO_2 participating in the reaction. For examples, the patent mentions the method is applicable to such useful Pd-catalysed reactions as the Heck, Stille, Sonogashira, and Suzuki reactions. In particular the use in the Heck reaction is noteworthy because

it is generally recommended that polar solvents are used. The second aspect of the patent is related to the formation of cross-linked polymers from multifunctional monomers in SC CO_2. Examples are given for a selection of monomers such as divinylbenzene, styrene, plus the dimethylacrylate **37** and trimethylacrylate **38**.

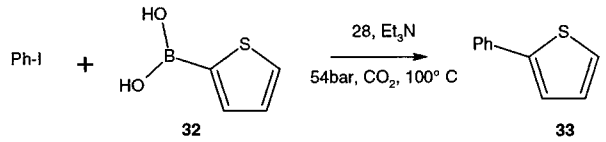
The compounds **28** and **29** are examples of the type of dichloro Pd complexes used as a catalyst in various reactions, and their synthesis is shown in the scheme below. The corresponding acetate compounds **30** and **31** were also prepared although no experimental details are given.



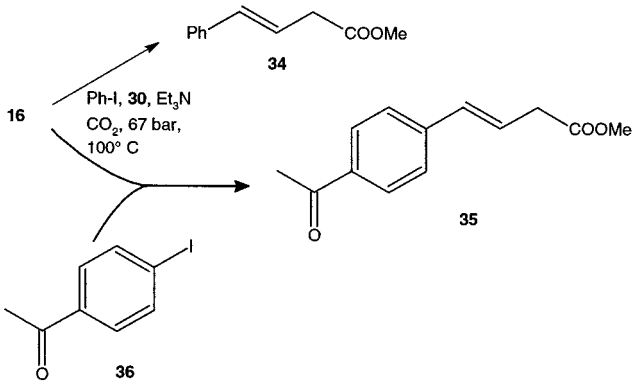
The catalyst **28** was used in an example of a Sonogashira reaction to produce diphenylacetylene from iodobenzene and phenylacetylene as shown below. The pressure shown is that before the reaction was heated.



28 was also used in an example of a Suzuki reaction to give the thiophene **33** from iodobenzene and the boronic acid **32** as in the equation below. Again the pressure is that recorded before heating the mixture.

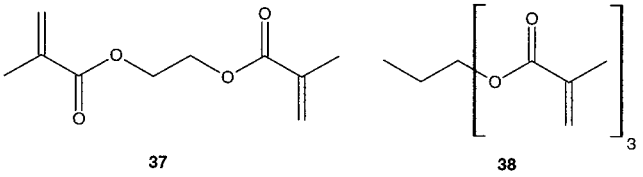


There are several examples of the Heck reaction in the patent with a range of alkenes and aryl iodides. In these examples the acetate catalyst **30** was used. The best yield of 97% was obtained in the production of **34** by the reaction of iodobenzene with methyl acrylate **16**, whereas formation of the ketoester **35** from **16** and **36** gave a yield of 72%. These reactions are shown in the scheme below, and again the pressures are those before heating.



All of the coupling reactions took place in stainless steel cells and took upwards of 40 h for completion. The experiments were only carried out on a small scale with maximum quantities of substrates below 500 mg and generally below 100 mg.

The second part of the patent is related to copolymerisation in SC CO_2 to produce free-flowing discreet microspheres. Such copolymers are said to be capable of incorporating other molecules, and these materials can be used for a wide variety of applications. Such uses are molecular imprinting, solid-phase synthesis, combinatorial chemistry, and medical diagnostics; however, the patent is very vague on this area with no claims related to the copolymers, and such claims may the subject of another patent. There are several examples of experiments to produce such copolymers which are all carried out using an initiator such as AIBN that does not require heating.



Advantages

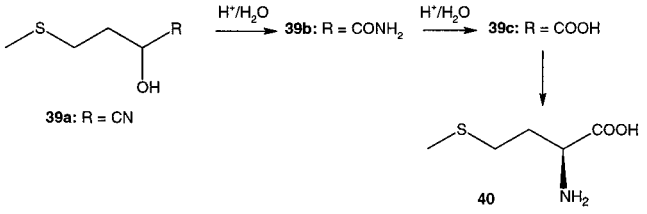
The use of SC CO_2 as solvent means that at the end of the reaction the solvent is removed as a gas by depressurisation of the system. However, the extensive reaction times needed for the coupling reactions mean that it is not yet attractive to carry out such reactions in this manner for the simple examples given. It remains to be seen if more synthetically useful examples can be developed.

Patent No. U.S. 6,458,997

Assignee: Novus International Inc., St. Louis, Missouri, U.S.A.

Title or Subject: Continuous Hydrolysis Process for Preparing 2-Hydroxy-4-methylthiobutanoic Acid

The title compound **39c** is an analogue of the essential amino acid methionine **40** and is suitable for use as a supply of **40** in nutritional uses as a poultry feed supplement. The synthesis of **39c** is normally by hydrolysis of the nitrile **39b**, and many processes are operated batchwise. The hydrolysis proceeds in two steps via the amide **39b** which may be isolated if desired but is often not. The process is shown below.



Reference to prior work indicates that reaction times for both steps can reach 6 h, and coupled with extensive turnaround time the overall productivity is limited; as is normal with batch processes, the quality can vary between batches. This patent attempts to alleviate such difficulties and describes a continuous process for producing **39c** in a two-stage process by aqueous hydrolysis of **39a** using sulphuric acid. The first stage, which basically produces the amide **39b**, is carried out in a continuous stirred tank reactor (CSTR), and the second stage giving **39c** uses a simple tubular or plug flow reactor (PFR).

The reason for using the two types of reactors is the first stage is much more exothermic than the second and heat removal is much more efficient from the CSTR than from the PFR. In the second stage the PFR, when operated properly, prevents back-mixing of products and reactants, thereby reducing side reactions. This significantly reduces the possibility of formation of and precipitation of ammonium bisulphate (ABS) by reaction of the sulphuric acid with the NH_3 liberated in hydrolysis of the amide. It is interesting to compare this patent with one from Rohm and Haas (U.S. 6,476,270) reviewed later that focuses on the hydrolysis of an amide to an amine using ABS as the hydrolysis catalyst.

The patent contains extensive experimental details covering the process and the various reaction parameters such as residence time, acid/nitrile ratio, and temperature. The work was carried out on bench-scale reactors operating at around 1.5 g/min and in a large-scale plant at up to 50 kg/h. Hence, it can be inferred that a version of this process is probably being used commercially to produce **39c**.

Advantages

The continuous hydrolysis gives high productivity and product quality with good control of the reaction while keeping capital and maintenance costs low. It is also claimed that emissions of vapours are much lower than those from batch processes. A further advantage claimed is the ability to use concentrated sulphuric acid because of the improved heat removal capabilities when running continuously.

Patent No. U.S. 6,462,192

Assignee: Miravant Pharmaceuticals Inc., Santa Barbara, California, U.S.A.

Title or Subject: Processes for Large Scale Production of Tetrapyrroles

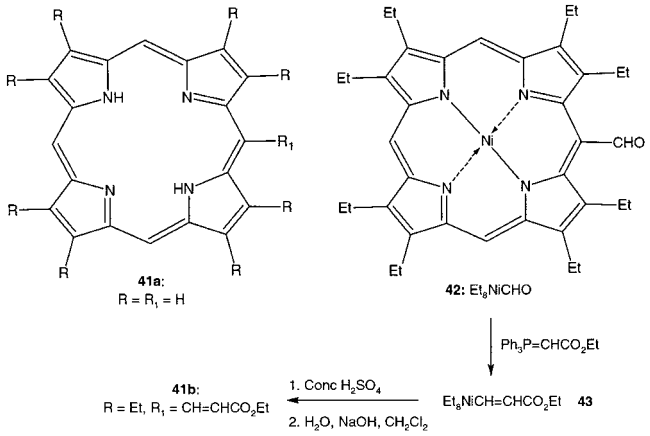
Tetrapyrroles are useful for the production of photosensitisers used in photodynamic therapy or as the building blocks for several compounds based on the parent molecule porphyrin **41a**. This patent is extremely comprehensive and has 149 claims relating to a number of different types and reactions of porphyrins. Hence, this short summary can only convey but a fraction of what is covered. The patent discloses methods that are amenable to the large-scale production, reaction, and isolation of several types of tetrapyrrole compound, and some specific types of claim are listed here:

(1) isolation and formylation of metalated tetrapyrrolic compounds such as nickel (II) meso-formyl octaethylporphyrin **42**,

(2) production and isolation of mono- or diacrylates such as nickel (II) meso-acrylate octaethylporphyrin **43** by reacting a Wittig reagent with **42**, and

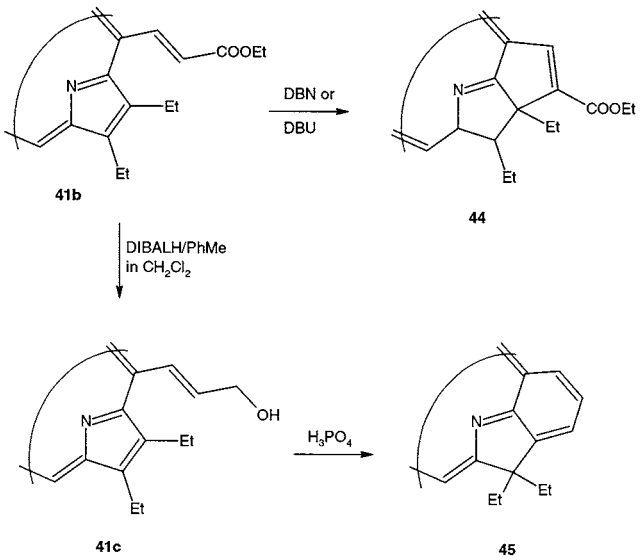
(3) demetalation of metallo−tetrapyrrolic compounds such as **42** using sulphuric acid to remove the metal from the ring and isolation of the product **41b**.

The above transformations are summarised in the scheme below.

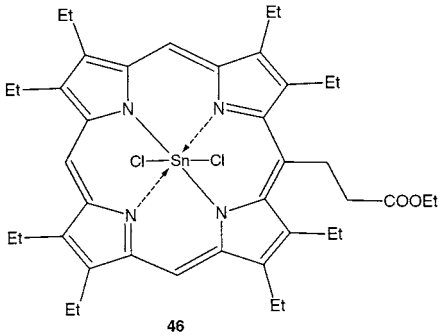


A further reaction covered is the cyclisation of the demetalated products **41b** using bases such as DBN or DBU to give the purpurin **44** which is isolated by solvent-extraction methods.

Reduction of the ester group in **41b** using DIBALH in CH_2Cl_2 gives the 2-hydroxymethylvinyl compound **41c**, and this is cyclised with H_3PO_4 to give the benzochlorin **45** as shown below.



The final section of the patent covers the formation and recrystallisation of tin(IV) tetrapyrrolic complexes such as **46** from the corresponding nonmetalated compounds and a tin salt in the presence of oxygen.



46

Examples are given for production of such tin compounds that are analogues of **41a**, **41b**, **44**, or **45**. The patent states that there is growing interest in the incorporation of tin into tetrapyrrolic compounds. There are studies underway into the use of such compounds as heme oxygenase inhibitors and a variety of other medical applications and phototherapeutic uses. The purification of the tin compounds is said to very difficult with the use of chromatographic methods; hence, specific recrystallisation techniques have been developed and are the subject of claims in the patent.

Advantages

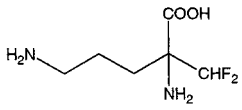
Many of the transformations are novel and are said to be suitable for large-scale synthesis, and several of the examples use in excess of 200 g of substrate.

Patent No. U.S. 6,462,229

Assignee: Lonza Ltd, Visp, Switzerland

Title or Subject: Resolution of α-Difluoromethylornithine Using Di-p-toluoyltartaric Acid

The racemate of **47** is an active inhibitor of ornithine decarboxylase, but it is desirable to use the (−) form which has the greater activity. This patent uses the commercially available (−)-*O*,*O*′-di-*p*-toluoyl-L-tartaric acid (DPTTA) as a resolving agent to obtain the desired *R*-(−)-form of **47**. The formation of the 1:1 salt between DPTTA and **47** is carried out by boiling in aqueous MeCN, and the salt is precipitated on cooling and is recovered. The 1:1 salt is then treated with aqueous HCl to obtain the monohydrate hydrochloride salt of **47**·HCl. The analogous salt of the *S*-(+) form can also be recovered from the mother liquor of the resolution step.



47

Advantages

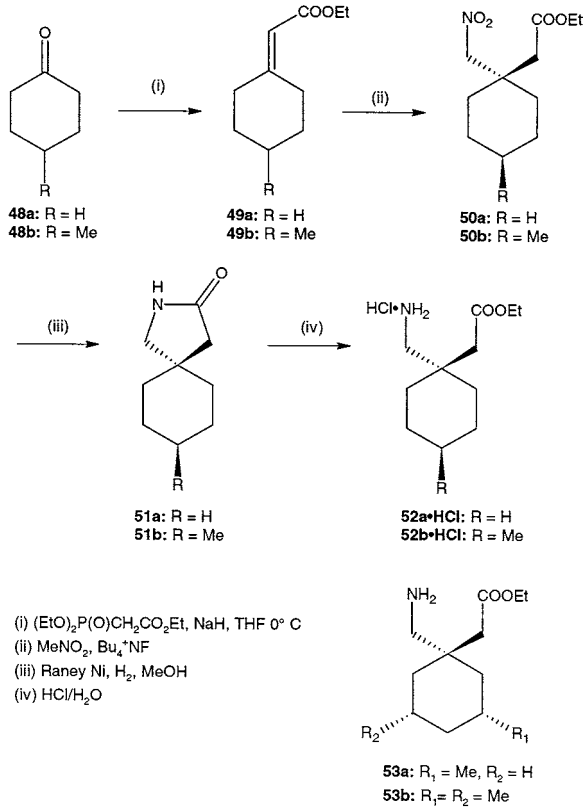
This process is claimed to be more efficient and gives higher yield of **47** which has a higher optical purity than previous resolution techniques that use, for example, (+)-camphor-10-sulphonic acid.

Patent No. U.S. 6,465,689

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

Title or Subject: Stereoselective Preparation of Gabapentin Analogues

Gabapentin **52a** is useful in the treatment of epilepsy and is normally used as the hydrochloride salt **52a·HCl**. This patent provides a stereoselective route to the hydrochloride salts and free forms of the compounds **52a**, **52b** and **53a** or **53b**. The synthetic route developed is shown below and involves four steps.



The first step is conversion of the cyclohexanone **48** to the α,β-unsaturated ester **49** using triethylphosphonoacetate in the presence of a base such as NaH in THF at around 0 °C. **49** was then extracted with Et_2O after acidification with HCl and partially purified by flash chromatography. The nitro-ester compound **50** was prepared from **49** by reaction with $MeNO_2$ in refluxing THF using a base such as Bu_4NF. The third step is catalytic hydrogenation using Raney Ni to give the lactam **51**, and finally hydrolysis of **51** using HCl gave **52** as the hydrochloride. Treatment of the hydrochloride with a basic ion-exchange resin (IER) produces the free form of the gabapentin. The same procedure can be used to prepare analogues **53a** and **53b** from the corresponding cyclohexanone.

The key step in this route seems to be the formation of the nitroester **50** with a high stereoselectivity. The reason for the efficiency of this step is not discussed.

Advantages

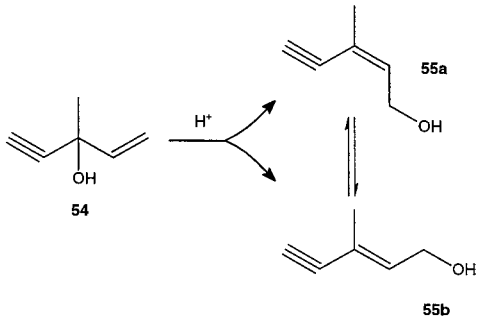
The synthetic route to these compounds in the patent gives control of the stereochemistry, and no resolution is required at the end of the synthesis.

Patent No. U.S. 6,465,698

Assignee: Roche Vitamins Inc., Parsippany, New Jersey, U.S.A.

Title or Subject: Catalytic Isomerisation of Z-pentol to E-Pentol

The two isomeric pentols **55a** and **55b** are both useful intermediates in their own right, and the thermodynamic equilibrium mixture of the pentols contains 85% *Z* and 15% *E*. The *Z*-isomer **55a** is used in synthesising vitamin A, while the *E*-isomer **55b** is useful in the synthesis of carotenoids such as astaxanthin and zeaxanthin. The equilibrium mixture can be formed by acid-catalysed allylic rearrangement of **54** as shown in the scheme below. Although the isomers can be separated by fractional distillation, it is claimed that there is a need for an economical method of producing a mixture with a higher proportion of the *E*-isomer. The subsequent separation of such a mixture would then be economically viable.



This patent discloses that bromine radicals catalyse the *Z*-to-*E* isomerisation and these Br radicals are generated in an aqueous solution at a pH of 0.5−1. The Br radicals originate from NaBr or KBr and Mn^{2+} salts such as bromide, acetate, or sulphate and in the presence of oxygen or an oxidant such as H_2O_2 or peroxodisulphates. The low pH is attained by adding acids such as HOAc, H_2SO_4, or HBr to the mixture. The catalyst mixture is a simple redox system, and the oxygen or oxidant is used to regenerate the Mn^{3+} ions which catalyse the formation of the Br radicals because the Mn^{2+} ions cannot perform this function. The reaction is carried by mixing the pentols with the aqueous solution and then heating to about 50 °C. The patent claims that the pentols may be dissolved in a water-immiscible solvent although there are no examples of this. A wide range of organic solvents is claimed to be suitable, such as hexane, toluene, CH_2Cl_2, alcohols, or ethers.

Advantages

The adjustment of the thermodynamic mixture allows the production of mixtures containing a higher concentration of the *E*-isomer which can then be economically separated.

Patent No. U.S. 6,469,202

Assignee: Nippon Shokubai Co. Ltd., Hyogo, Japan

Title or Subject: Method for Disposal of Used Acidic Ion-Exchange Resin Catalysts

The disposal of any waste is now an integral aspect of any process development programme. This patent is specifically aimed at disposal of an acid IER that has been used in the production of esters of acrylic or methacrylic acids. The disposal of the spent IER catalysts can pose an environmental and health hazard, and the patent claims that this can cause spiritual displeasure to the operator who has to discharge the catalyst from the reactor. The spent IER often has an offensive odour and usually contains a volatile flammable solvent The process that is described involves washing the spent IER with the alcohol used in the esterification reaction and then with water. The washings are collected and distilled so that they may be reused in the esterification process.

This patent seems to cover what should be normal operating practice when using and disposing of spent catalysts in any form. The validity of this patent is not being questioned, but if it is held to be valid then it could create difficulties for others wishing to use this procedure.

Advantages

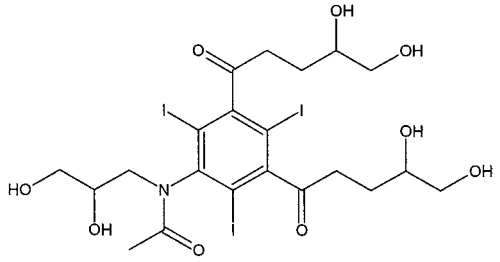
The process improves the health and safety problems associated with the discharge of spent IER.

Patent No. U.S. 6,469,208

Assignee: Hovione Inter Ltd., Switzerland

Title or Subject: Process for the Preparation of Crystalline and Solvent Free Iohexol

Iohexol **56** is used as an X-ray contrast media that is injected into the patient to enhance the X-ray image of internal organs. **56** is an example of a nonionic X-ray material, and smaller quantities are required than ionic types that were previously used. Hence, its use is safer for the patient, but at the same time any impurities need to be minimised. The purification of **56** is difficult because the primary impurities are O-alkylated materials (OAM) that have solubility similar to that of **56**, thus making its purification by recrystallisation more difficult. In addition, residual solvent levels should be kept to an absolute minimum, and chromatographic methods are said to be unsuitable uneconomically for the large-scale production of **56**. Other methods used to purify **56** often produce amorphous material via a spray-drying or freeze-drying technique, whereas pharmaceutical materials are usually preferred as crystals. The strategy employed here is to remove OAM by a chemical treatment and then to recrystallise **56**.



56

The procedure is to prepare a concentrated solution of **56** in water and then to add EtOH and seed with crystals of **56**. The crystals are then recovered by filtration and dried and are of increased purity with <100 ppm of EtOH. The levels of OAM are found to be reduced by up to 40%.

Advantages

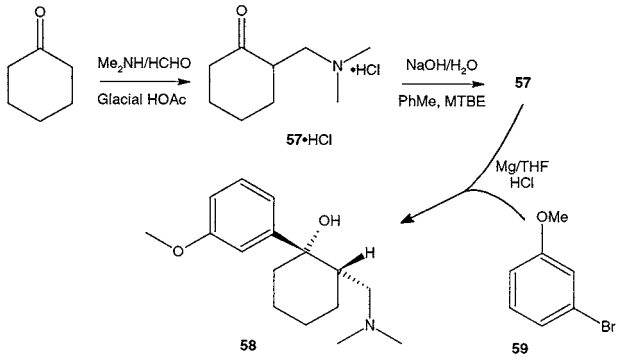
This procedure provides a suitable method that can be carried out on a large scale without the need for expensive equipment.

Patent No. U.S. 6,469,213

Assignee: Russinsky Limited, Cork, Ireland

Title or Subject: Process for the Preparation of Tramadol and its Salts

The *cis* racemate tramadol **58** is used in the form of the hydrated hydrochloride salt **58**·HCl as an analgesic that does not have many of the side effects of opioids. Other methods for the synthesis of **58** also produce relatively high amounts of the *trans* racemate and the separation of the isomers is difficult. The route developed is shown below and consists of three synthetic steps plus two further purification and isolation steps.



The first step is the formation of the Mannich hydrochloride of **57** from cyclohexanone and Me_2NH and paraformaldehyde in glacial HOAc. The next step is liberation of the Mannich base **57** using aqueous NaOH in PhMe and methyl-*tert*-buyl ether (MTBE). Treatment of **57** with the Grignard of bromoanisole **59** then produces the crude hydrate of **58**. Purification is carried out by extracting with EtOAc; recrystallisation and then acidification with HCl give the salt **58**·HCl. The final product contained <0.03% of the *trans* isomer. The one example describes the production of 17 kg of **59**, suggesting that this is a process in full commercial operation.

Advantages

The process gives the desired isomer in high yield with very low levels of *trans* impurity.

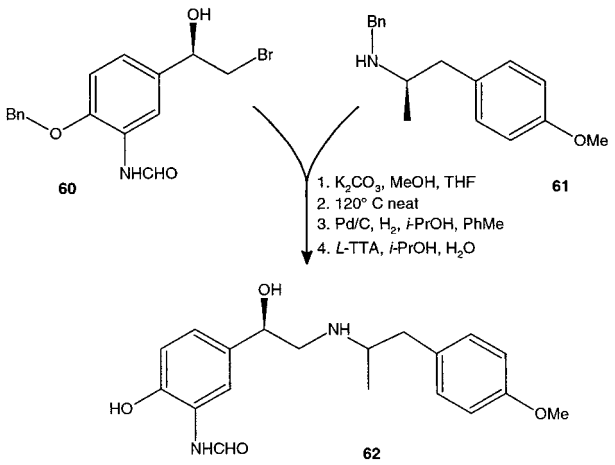
Patent No. U.S. 6,472,563

Assignee: Sepracor Inc., Marlborough, Massachusetts, U.S.A.

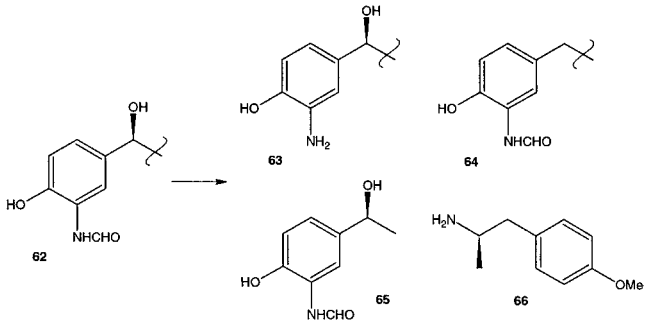
Title or Subject: Process for the Preparation of a Stable Polymorph of Formoterol Tartrate

The title compound **62** is a β_2-selective adrenoceptor that has a long-lasting bronchodilating effect when it is inhaled. **62** has two chiral centres, and a total of four isomers are possible. At present **62** is only available as a racemic diastereomer (*R*,*R*) plus (*S*,*S*) in a 1:1 ratio. The generic name formoterol refers to this mixture, and the (*R*,*R*) form is over 1000 times more potent than the (*S*,*S*) isomer. The drug is normally available as the dihydrate of the fumarate salt although a recent patent (U.S. Patent 6,268,533) claims that the L-tartrate salt is much more useful since it is easier to handle and nonhygroscopic and the patent discloses two polymorphs A and B of the L-tartrate salt. A third polymorphic form designated C of **62** is described in the current patent, and comprehensive IR, DSC, and X-ray diffraction (XRD) data are provided for this new form.

The patent states that there is only one practical and economic synthesis for **62**, and this, from U.S. Patent 6,268,533, is shown below. This produces the kinetically favoured polymorph, Form B, although Form A is the most stable form and is marketed as the active drug.



The synthesis of **62** by the original process always contains at least 0.5% of four chemical impurities, **63**−**66**, that cannot be removed, and these are shown below. It is suggested that **63** is formed by hydrolysis of the formamide group **62**, while **64** is formed by hydrogenolysis; compounds **65** and **66** are produced from the starting compounds **60** and **61**. It has not previously been possible to reduce **63** to <0.2% by crystallisation methods, and the solution to the impurity problem is the subject of this patent and is based on the formation of the new polymorph, Form C.



The procedure for producing pure Form A by intermediate production of Form C is as follows:

(1) A solution of crude **62** in *i*-PrOH/PhMe was mixed with an aqueous solution of L-tartaric acid (L-TTA) and stirred at room temperature for 2 h to form a slurry of Form B of the L-TTA salt of **62**.

(2) Warm the mixture at 45−50 °C for up to 3 h to reduce the level of **64** to <0.15%.

(3) Cool mixture to 22 °C to obtain crude Form C crystals.

(4) Mix crystals with water and *i*-PrOH and heat to 50−55 °C to give a solution.

(5) Seed the solution with Form A crystals of L-TTA salt of **62**.

(6) Dilute solution with *i*-PrOH and cool to 40−45 °C.

(7) After 30 min cool solution to 0 °C, stir 2 h, and then filter off Form A crystals of **62** as the L-TTA salt.

The final product was found to have <0.12% of compound **63**, 0.05% of **64**, and undetectable amounts of either **65** or **66**.

The purification method is based on the higher solubility of Forms B and C in *i*-PrOH compared to Form A plus the fact that Form C can be produced in higher purity than Form B. By seeding with the most stable form A the overall process gives a much improved method for synthesis of pure **62**.

Advantages

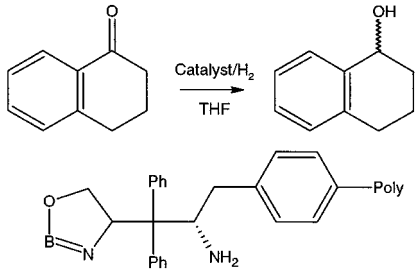
This is a much improved process for producing pure product yet still uses the same synthetic route that was previously developed.

Patent No. U.S. 6,472,571

Assignee: Degussa-Huls AG, Frankfurt am Main, Germany

Title or Subject: Process for the Production of Organic Compounds in a Membrane Reactor

The title and subject matter of this patent are extremely wide-ranging, and yet the only example relates to reduction of tetralone to tetralol (see below). The patent is very similar to an earlier one from Degussa-Huls that has been previously reviewed (*Org. Process Res. Dev.* **2001**, *5*, 350−360). The procedure is to carry out a reaction using a homogeneous catalysts containing a large polymeric ligand with a high molecular weight. The solution of substrate and catalysts is pumped through a tubular membrane reactor. To allow the use of higher temperatures and pressures an inorganic membrane of silica or a metal oxide is preferred to an organic membrane. The catalysts are soluble in the reaction medium although the high-molecular weight ligand means that the catalyst molecule is physically too large to pass through a membrane. Hence, the catalyst can be separated from the reaction products by size exclusion using a suitably sized membrane. The specific catalyst mentioned contains an oxazaborolidine ligand that is bonded to a polystyrene polymer. The catalyst described here could be similar to **67** which was the catalyst used in the earlier patent. The example claims that that reduction of tetralone proceeds at 100% conversion with around 95% ee but does not say which enantiomer is obtained.



67

Advantages

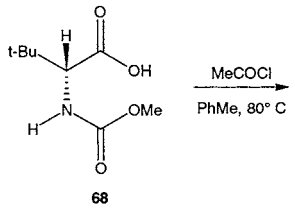
This is an interesting method of separating homogeneous catalysts from reaction mixtures and overcomes the biggest problem when using such catalysts.

Patent No. U.S. 6,476,231

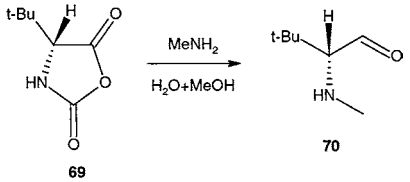
Assignee: DSM N.V., Heerlen, Netherlands

Title or Subject: Process for the Preparation of N-Carboxy-tert-leucine Anhydride

The subject of this patent is the cyclisation of the L-*N*-carboxy amino acid **68** to the L-anhydride **69** without the use of thionyl chloride or phosgene. The problems associated with using such useful but potentially dangerous materials are the motivation behind this patent. The method used to effect the cyclisation is to heat **68** with acetyl chloride in toluene at about 80 °C (see below).



68



69 70

69 can be used to prepare substituted amino acid amides such as **70**, and this can be done by treating **69** with aqueous $MeNH_2$ in MeOH. Alternatively, **70** can be obtained without isolation of the anhydride after the reaction of **68** with acetyl chloride.

Advantages

The use of acetyl chloride presents fewer operating problems than the use of either phosgene or thionyl chloride.

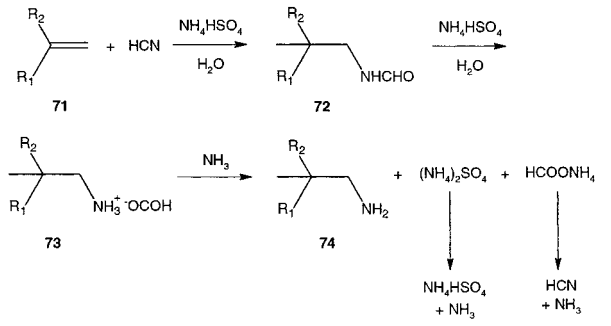
Patent No. U.S. 6,476,270

Assignee: Rohm and Haas Company, Philadelphia, Pennsylvania, U.S.A.

Title or Subject: Waste-Free Process for Manufacture of Amides and Amines from Carbonium Ion Precursors and Nitriles

This is the second patent in this selection that focuses on the hydrolysis of amides, but in this case the product is unusually an amine and not an acid. See the review above of U.S. 6,458,997 from Novus International. In the current patent the overall process is the conversion of a HCN to an amine **74** via hydrolysis of the intermediate amide **72**. The conventional procedure for converting an amide to an amine is via reduction. An objective in this process is to avoid using strong acid catalysts such as sulphuric acid in the reaction between the HCN and alkene **71** and also to avoid formation of wastes. Although the patent claims nitriles, it does actually focus on only one, and this is HCN.

The first step is the addition of HCN to a carbonium ion precursor which in this case is an alkene **71**. This is carried out in water at >130 °C in the presence of ABS. The amide **72** is then hydrolysed to form the amine salt **73** which, when treated with NH_3, decomposes to give the amine **74**, ammonium formate (AF), and ammonium sulphate (AS). **74** can then be extracted from the mixture with a suitable water-immiscible solvent.



Normally AF and AS are wastes, but the patent describes a method of recovering and recycling both salts. The two ammonium salts are produced in aqueous solution, and so the first stage of recovery is to distill the solution. This results in decomposition of AS to give ABS and NH_3 which are both recovered and reused. The AF is dehydrated by contacting it with activated alumina in the presence of NH_3 > 300 °C to produce HCN which again can be reused. Thus, overall there are no waste products formed in the process.

The patent does not provide any specific examples, and the claims cover the use of HCN rather than an organic nitrile.

Advantages

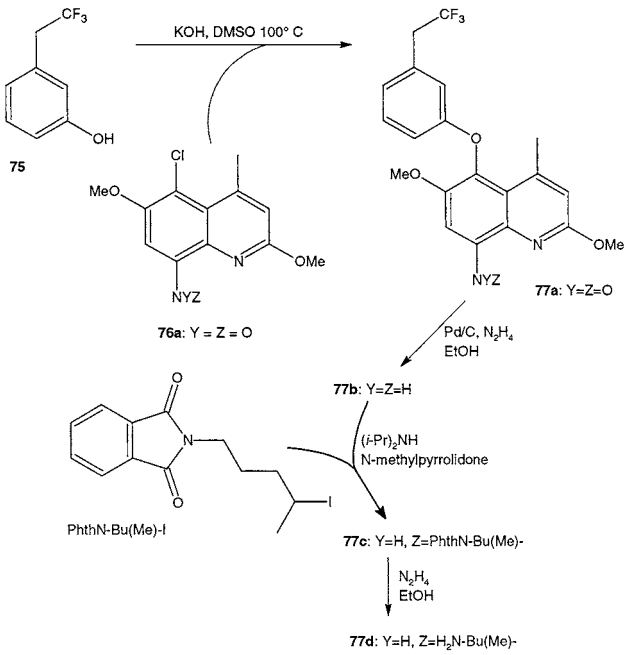
This patent describes a very unusual hydrolysis and for the specific case of HCN the process is extremely efficient. Extending the reaction to organic nitriles could be a significant reaction with wide potential uses.

Patent No. U.S. 6,479,660

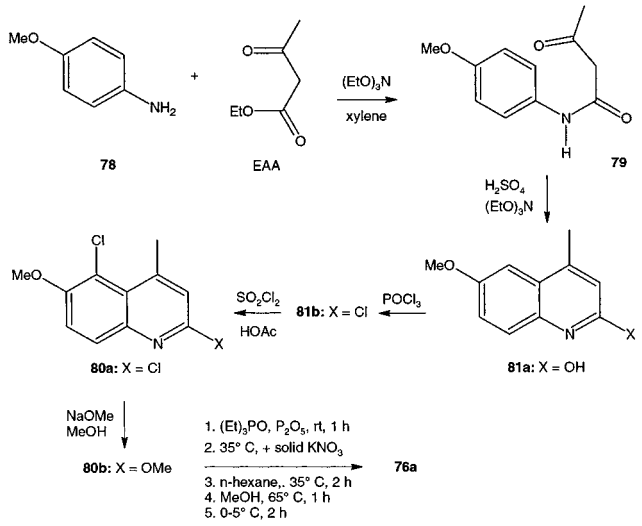
Assignee: SmithKline Beecham, Brentford, United Kingdom and Philadelphia, Pennsylvania, U.S.A.

Title or Subject: Process for the Preparation of Substituted Quinolines Useful Anti-malarial Drugs

The patent describes a route to **77a** which is used to produce the amino compound **77b**, an intermediate in the synthesis of antimalarial drugs such as **77d**. The final step in the synthesis of **77a** is the reaction between the phenol **75** and the chloronitroquinoline **76a** in DMSO at 100 °C containing a strong base such as KOH. **77b** is formed by reduction of **77a** using hydrazine hydrate (HH) and Pd/C catalyst. Compounds similar to **77a** have been previously prepared by multistage syntheses which are said to give a low yield and use reagents that are not suitable for use in large-scale production. The conversion of **77b** to **77d** proceeds via formation of **77c** that contains the phthalimide group to protect the amine function. The final removal of the protecting phthalimide group is carried out using HH (see below).



The patent also provides details of the synthesis of **76a** which is used in preparing **77a**, and the route used is shown below. The first step is condensation of *p*-anisidine **78** with ethyl acetoacetate (EAA) to give **79** which is cyclised using H_2SO_4 in triethanolamine (TEA), giving the hydroxyquinoline **81a** which is chlorinated to give **81b** using $POCl_3$. The 5-chloro compound **80a** is formed by reaction of **81b** with SO_2Cl_2 and then converted to the dimethoxyquinoline **80b** using NaOMe. The nitration of **80b** to **76a** is a five-step, one-pot procedure that proceeds in 65% yield.



The patent gives experimental details for all steps shown in the two schemes, and NMR assignments are given for all compounds. Many of the experiments reported are carried out at kilogram scale, and hence, scale-up procedures have been established.

Advantages

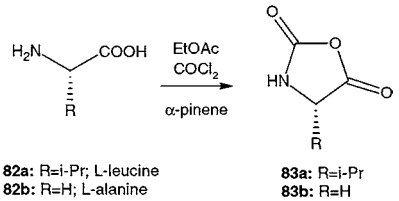
The patent appears to have succeeded in producing a synthetic route capable of being operated at a reasonable scale and, hence, seems to offer improvements over previous processes.

Patent No. U.S. 6,479,665

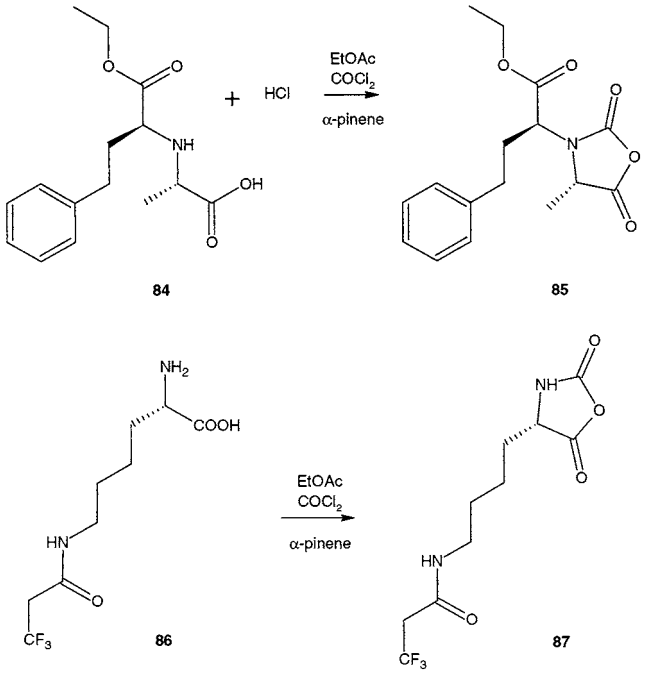
Assignee: Isochem, Paris Cedex, France

Title or Subject: Preparation of N-Carboxyanhydrides

N-carboxyanhydrides such as **83a** and **83b** contain an activated acid group and are thus useful in reactions with nucleophilic reagents. They are used to form peptides by reaction of the acid group with amines and can easily form esters with alcohols. Such compounds are often synthesised by the reaction of an amino acid with $COCl_2$ and in the presence of hydrochloric acid. It is said that a large amount of HCl is required, and this gives rise to side reactions that form chlorinated by-products. This patent describes an improved method based on this route for the synthesis of **83a**, **83b**, and several similar compounds. The reaction is carried out in a specially chosen solvent that does not react with HCl, and an unsaturated compound is added to react with any HCl present in the mixture and prevent chlorination reactions. Esters are the preferred solvent, EtOAc is used in the examples, and α-pinene is added as a HCl scavenger. The production of **83a** from L-leucine **82a**, and **83b** from L-alanine **82b**, shown below, are examples of the process.



Other examples are given using derivatives of L-lysine, L-alanine, and glutamic acid esters including **84** which give **85**, and **86** which forms **87**, and these routes are shown below.



Advantages

The selectivity of the original synthetic route is improved by adding a HCl scavenger so that the overall process efficiency and product quality are improved.

Patent No. U.S. 6,479,708

Assignee: The Regents of the University of California, Los Alamos, New Mexico, U.S.A.

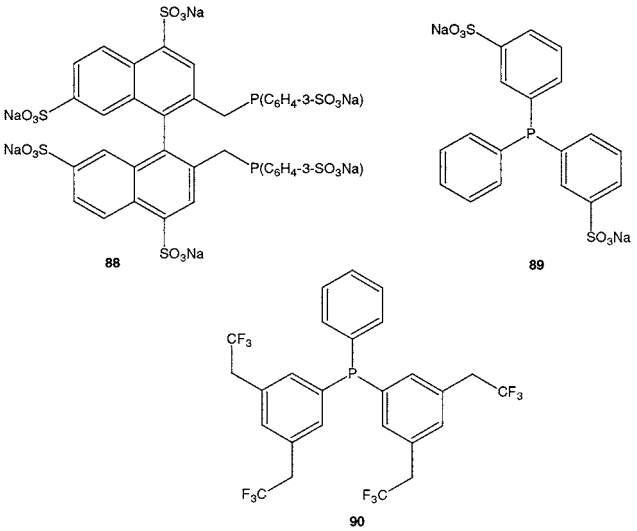
Title or Subject: Catalysis of Organic Reactions in Biphasic Water and Supercritical Carbon Dioxide Micellar Systems

The work described here is an attempt to improve catalyst and product separation in homogeneous catalytic reactions. The patent describes the use of a biphasic system of water and SC CO_2 containing surfactants. This mixture allows separation of catalyst and product by enabling the products to move from one phase to the other while the catalyst remains in the other phase. The reaction catalyst can be chosen to be soluble in either phase.

This patent therefore has the advantages of using SC fluids and phase-transfer catalysis (PTC) to improve reaction rate and selectivity as well as product recovery. The addition of a surfactant produces a microemulsion of one phase in the other, reduces surface tension, and increases the surface area available between the two phases. This reduces the resistance to mass transfer and hence improves reaction rate.

The patent claims the technique is suitable for many if not all catalytic reactions and provides examples covering both water-soluble and non-water-soluble catalysts. The water solubility of the catalysts is dictated by the ligands used on the catalyst. Sulphonated or ionic phosphines such as **88** and

89 are used to impart water solubility, whereas fluorinated phosphines such as **90** impart solubility in the nonaqueous phase.



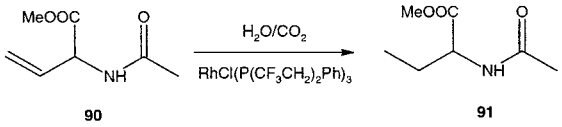
Examples given in the patent using water-soluble catalysts are as follows:

(1) Rh-catalysed hydroformylation of 1-decene to give 1-decanal,

(2) Rh-catalysed hydrogenation of styrene to give PhEt or 1-decene to give decane, and

(3) oxidation of 2-octanol to 1-octanal by H_2O_2 catalysed by Na_2WO_4.

An example using Rh catalysts soluble in SC CO_2 is the hydrogenation reaction shown below.



Advantages

This method does improve separation and recovery in homogeneous reactions, and if it can be applied to other catalysts apart from Rh, it may have wide ranging application.

Patent No. U.S. 6,482,438

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

Title or Subject: Apparatus for Preparing Crystalline Particles of Substances Used in Inhalation Therapy

The production of uniform particles with specific crystal size distribution (CSD) is very important in the production of many pharmaceutical formulations as well as for other applications. The control of CSD in precipitation reactions is difficult, and milling or micronisation is often employed to produce the correct CSD. However, there are many examples where milled crystals do not have the same physical properties as precipitated particles of the same size. Hence, the production of suitably sized crystals in a consistent manner is critical to the performance and application of many solid materials. This patent describes an apparatus that enables the control of CSD by precipitation under the influence of ultrasound. The use of ultrasound to enhance reactions and other processes is increasing and has been under development for many years.

The process is shown in Figure 1 and is carried out by

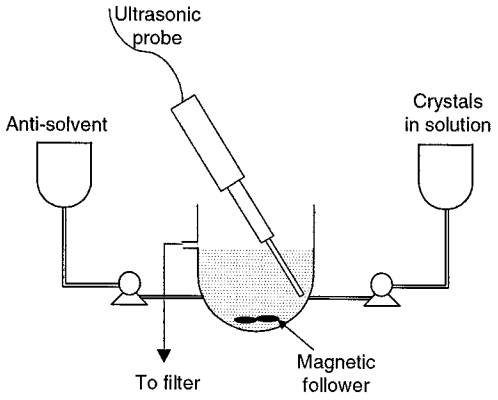


Figure 1. **Method of controlling crystal size distribution using ultrasound.**

pumping a solution of the compound to be crystallised into the bottom of a mixing chamber or reactor containing an ultrasonic probe. At the same time an antisolvent is pumped into the opposite side of the reactor, and the crystals are removed from the top of the reactor by the flowing liquids. The crystals are filtered off and collected. The method of mixing in the patent is by the use of a magnetic follower; however, in practice this is not likely to be suitable. An alternative and more efficient method of agitation would be preferred because it is well known that mixing also affects the CSD in precipitation reactions.

The patent gives examples of producing particles of the drug compounds fluticasone propionate and salmeterol xinafoate which are used in inhalation therapies.

Advantages

The process gives better control over particle size than conventional precipitation methods and can be used in a continuous operating process and is scaled-up relatively easily.

Keith Turner*

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

OP0340154