Highlights from the Patents

A Review of U.S. Patents in the Field of Organic Process Development Published during September and October 2004

Summary

The current selection of 21 patents was taken from an original list of 213, and it is hoped that readers will find something interesting and useful. Two patents in this crop are concerned with avoiding the problems caused by using HCl. One solves the problem of handling corrosive solutions in making sulphonics acids by using an alternative synthetic route. The second is concerned with imidoester synthesis and removes the need for handling gaseous HCl by using dioxane solutions of HCl. There is a report of a new crystalline form of neotame, the improved derivative of the well-known sweetener aspartame. An improved synthesis of vitamin E claims that removing the water formed in the process by azeotropic distillation actually reduces yield. By not removing water the yield increases by 4% and allows recycling of the catalyst. The synthesis of a range of sulphonic surfactants normally requires the use of anhydrous Na salts of phenylsulphonic acids, and methods used to dry the starting materials affect product quality. One patent shows how these problems can be overcome by using a special reaction solvent system. A process for the production of selenoamino acids is described as much safer because it avoids handling small pieces of Na metal. Since handling any selenium compound is hazardous, this seems an overstatement. A highly selective method of preparing chiral trifluorophenylethylamines is described that includes a new hydrogenolysis step of a sec-amine to remove the amine protective group. Cabergoline is used to treat Parkinsonism, and one patent reports the discovery of a second polymorph that can be obtained from the reaction mixture of the standard synthesis. Two patents from the same company describe structurally similar antibiotics. One of these is cefixime for animal use, while the other cefixime is for use in humans. The Na salt of cefixime is normally administered to animals, and a method of making this without going via the HCl salt is described which gives improved yields and higher purity. The synthesis of cefixime involves a hydrolysis of an amino ester, and it has been possible to perform this without protection of the amino group. Another patent on antibiotics describes an improved method of making quinolones without the need to remove byproducts from an early stage of the synthesis. Chiral β-amino alcohols are valuable reagents, and a new method of making them from α-amino acids is described. A new method for the synthesis of a range of pyrazines is described with experiments involving the preparation of 12 kg of product, suggesting an advanced stage of development. An improvement in the Pauson–Khand reaction for synthesis of cyclopentenones has been disclosed that involves the use of immobilised catalysts. This reduces the problems caused by using the volatile cobalt carbonyl catalysts. As usual there is no commercial or legal significance attached to any of the patents reviewed. It may be surmised that patents that include kilogram-scale experiments are at a more commercial stage than some of the others. The advantages stated are those claimed in the patent unless the author has personal knowledge. From the original short list of patents for inclusion in this review there were a few that had no chemical equations or formulae. This does not often present too much of a problem, given the easy access to the Internet. However, the names used for some of the reagents defied any logical naming method known to this reviewer and the usual search engines; hence, they were not included.

Patent No. U.S. 6,787,666
Assignee: Bayer Chemicals AG, Leverkusen, Germany
Title or Subject: Process for the Preparation of Isolated 3,4-Diaminobenzenesulphonic Acid

The patent describes a method of preparing the sulphonic acid 2 that is a useful intermediate particularly for UV absorbents in light-protection agents. The route to 2 is shown in Scheme 1 and is carried out by reacting 1 with anhydrous H$_2$SO$_4$ containing SO$_3$. One alternative method of preparing 2 involves the sulphonation of the HCl salt of 1, and a second method involves the reduction of 2-nitroaniline sulphinic acid with Sn/HCl. Both methods are claimed to be expensive because of the corrosive nature of HCl. The major hurdle to overcome in the present route is to limit the formation of the disulphonic acid. This is done by using SO$_3$ in stoichiometric amounts and by quenching the reaction with water or ice. The product is precipitated from the reaction mixture and is of high purity.

Scheme 1

Advantages

This process gives high-purity product without the use of expensive corrosion-resistant equipment.
**Patent No. U.S. 6,787,673**

**Assignee:** Sumitomo Chemical Company Limited, Osaka, Japan  
**Title or Subject:** Process for Producing 2-Bromocyclopentanone

Advantages

4 is a useful intermediate and can be prepared by bromination of 3 using Br2/CHCl3 or NBS. Such processes are said to be unsuitable for industrial scale production; hence, this patent provides an improvement involving a biphasic system of water and n-BuCl. The reaction is carried out at by adding Br2 to a mixture of 3 in water and n-BuCl at around 1 °C (Scheme 2). After 15 h more of the water and n-BuCl solution is added and the product recovered as an oily phase in n-BuCl. The patent specifically mentions that the new process does not produce the byproduct 6. In fact, the patent contains examples showing that 6 is formed as a byproduct when the reaction is carried out with excess 3 which is the normal procedure in the alternative processes. The patent also describes how to prepare 5 by treatment of the oily phase from the reaction mixture with LiBr in DMF in the presence of hydroquinone (HQ).

Scheme 2

**Advantages**

The process gives a higher quality product than alternative methods.

**Patent No. U.S. 6,790,470**

**Assignee:** Ajinomoto Co. Inc., Tokyo, Japan  
**Title or Subject:** Process for Producing a New Aspartame Derivative Crystal

This patent describes a procedure for the production of a new crystalline form of neotame, 8, the improved derivative of the well-known sweetener aspartame, 7. Since the original patents on 7 have expired, there has been much interest in alternative and more effective sweeteners, and 8 is one of these. The original form of 8, designated the A form, is claimed to have poor dissolution properties; this patent provides a new form of 8 with improved solubility that is designated form C. The normal A form has a water content of about 5%, and the C form is obtained by drying the A form at 50 °C in a vacuum until the water content is <0.8%. The new form was identified by X-ray diffraction (XRD) and was shown to dissolve more rapidly than the A form.

Aspartames

**Advantages**

This process gives higher yields of the product, and since the catalyst can be recycled, this reduces waste products.

**Patent No. U.S. 6,790,967**

**Assignee:** Sinon Corporation, Taichung, Taiwan  
**Title or Subject:** Process for Preparing 3,4-Dihydroxybenzonitrile

This patent discloses an improved process for making 13 that is a useful chemical starting material for preparing oxazolines, tetrazoles, benzamidines, and other intermediates. There are several routes for preparing 13; however, it is stated that these use expensive starting materials, give low yields, or are not generally suitable for commercial production. A route described in this patent starts from the aldehyde 11a that is converted to the nitrile 12a by reaction with H2NOH-HCl. The next stage (which is outlined in Scheme 4) is treatment of 12a with LiBr in DMF. The work up of the reaction mixture involves acidification, extraction with EtOAc, and cooling to obtain crystals of 13 in 67% yield and >99% purity.

**Advantages**

The procedure gives an improved, new, crystalline form of this sweetener with improved dissolution characteristics.
The dihydroxy compounds similar to 11a in which R₁ and R₂ are both H are not covered under the patent claims, and this point is specifically mentioned in the patent. Thus, the novel aspect of this patent is not clear, and the fact that similar processes have been known for many years tends to contradict the claimed advantages. Other examples in the patent start from the aldehydes 11b (R₁ = R₂ = Me) or 11c (R₁ = R₂ = Et) that give the nitriles 12b and 12c, and these are also converted to 13 by treatment with LiBr in DMF.

**Advantages**

This process claims to give a better yield than alternative methods and is suitable for large-scale commercial production.

**Patent No. U.S. 6,790,981**

**Assignee:** Clariant Finance (BVI) Ltd., Tortola, Virgin Islands

**Title or Subject:** Process for the Preparation of Acyl-oxybenzenesulfonates

Compounds such as 15 are used as surfactants or bleach activators, depending on the chain length of the acyl group. These compounds are usually prepared from phenylsulphonic acid derivatives such as the Na salt 14. All processes are said to require the use of anhydrous 14, whereas it is normally available commercially as the dihydrate that contains 15% water. Hence, before use in this reaction 14 must be dried; otherwise there is a significant loss in yield of 15. The method of drying 14 can have a detrimental effect on the process efficiency, and both under- or over-dried 14 causes problems. The objective of the process described in this patent is to use any grade of dried 14 that has water content <0.2%. The reaction shown in Scheme 5 is carried out by suspending the dried 14 in a hydrocarbon solvent containing a polyglycol ether (PGE). The solvent used in the examples is mixture of isoparaffins known as ISOPAR. An example of the PGE is diethyleneglycol dimethyl ether, and the acyl chlorides used are nonanoyl or lauroyl. The process is carried out continuously, and the water remaining in the 14 forms unspecified impurities that can be easily removed.

**Scheme 5**

**Advantages**

The process affords a convenient method of purification of this important drug.

**Patent No. U.S. 6,790,999**

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

**Title or Subject:** Process for the Production of 3-Buten-1-ol

21 is a useful chemical intermediate that may be made from propylene and formaldehyde or from various C4 precursors. This patent describes a route to 21 from 20 that is a frequently used starting material. Some of the previous routes from 20 to 21 are said to be inefficient or use dangerous or expensive chemicals. It is also noted that loss of yield of product is common by isomerisation to the 2-butene-1ol. The new route is shown in Scheme 7 is a catalytic transfer hydrogenation using formic acid and a Pd catalyst. The catalyst is used for several cycles, and one example equates to a catalyst turnover ratio of 37,500 mol. The process can be operated in batch, semi-continuous, or continuous modes. The reaction produces CO₂, and the products are collected as vapours from the reactor outlet, condensed, and purified by fractional distillation.

**Scheme 7**
Although THF is used in a batch experiment as a solvent, the patent does claim that the reaction byproducts are used as solvents when the reaction is operated in continuous mode. In this case the turnover ratio increased to 40,900.

Advantages

The process efficiently uses the expensive catalyst, and the distillation of the product prevents its isomerisation and subsequent yield losses.

Patent No. U.S. 6,794,537
Assignee: Sami Labs Limited, Bangalore, India
Title or Subject: Manufacturing Process for Se-Methyl-L-selenocysteine

Selenium is an essential element for human nutrition and is available from a variety of food sources. This patent describes a method of preparing the selenoamino acid 23 that is found in garlic and broccoli. Alternative methods of preparing 23 are known, and these usually start from amino acids and selenium derivatives. Scheme 8 shows the basic route to the preparation of 23 which starts from the ester salt 22a that is chlorinated using PCl₅ in CHCl₃ to give 22b. Treatment of 22b with MeSeNa that is formed from NaBH₄ and Me₂Se₂ gives the HCl salt of 23 by precipitation with concd HCl. The salt is then decomposed using Et₃N and 23 recovered in 99% purity.

Scheme 8

The patent also describes the use of hypophosphorous acid (H₃PO₂) to cleave the Se-Se bond in Me₂Se₂ and form MeSeNa. The conversion of the L-isomer of 23 to a racemic mixture can be carried out by heating 23 in HOAc and PhCHO.

Advantages

The process claims to be safer than alternatives because it does not involve handling dangerous materials. One of the alternative processes is said to be hazardous because it uses small pieces of sodium. This seems to be a trivial problem when compared to the difficulties of handling most selenium compounds.

Patent No. U.S. 6,797,842
Assignee: Central Glass Company Limited, Ube, Japan
Title or Subject: Process for Producing Pure Optically Active Trifluoromethylphenylethylamines

This is an extensive patent covering the production and purification of ethylamines such as 27. Such compounds are intermediates in the production of agrochemicals and pharmaceuticals. A variety of procedures is available for the synthesis of the compounds, but they are said to be incapable of producing optically active compounds efficiently and in high yield.

Scheme 9 shows a route to 27 described in the patent that begins with the dehydration and condensation of the ketone 24 with the chiral amine 25 to give the imine 26. In the next step asymmetric reduction of 26 using NaBH₄ or LiAlH₄ in MeOH, EtOH, i-ProH, or THF gives the amine 28. The ratio of S,S to R,S isomers was as high as 7.8 using NaBH₄ or as low as 2.1 when using LiAlH₄ in THF. The final step is hydrogenolysis of 28 to give 27 in 75% yield and ee of 76%. The stages leading up to the last one are said to allow the hydrogenolysis reaction to take place with reduced catalyst usage and at significantly reduced pressure. It is claimed that this step has not been reported previously and the high selectivity at the cleavage position is the key aspect of the patent.

Scheme 9

The patent describes a large number of experiments, and there are examples for the synthesis of monotrifluoro derivatives using the same procedure. The second aspect of the patent is the purification of the amine 28 by formation of salts of PTSA, mandelic or tartaric acids.

Advantages

The development of the hydrogenolysis of the sec-amine provides an efficient route to these amines that is an improvement over alternative processes.

Patent No. U.S. 6,800,635
Assignee: Pharmacia Italia S.p.A., Milan, Italy
Title or Subject: Crystalline Form II of Cabergoline

The subject of this patent 29 is a dopamine receptor agonist that was originally disclosed in 1985 and is available as Dostinex for the treatment of Parkinsonism. In some brief background research on 29 there were claims that it can be used in enhancing sexual activity. This aspect was not discussed in the current patent. Until now the drug has so far only been known as a single polymorph, and this patent describes a second form that is said to be the thermodynamically most stable form between -70 °C and +30 °C.
Cabergoline

The procedure is to take the crude oil from the conventional synthesis and dissolve it in a solvent such as MTBE, Et₂O, or MeOAc. An unspecified form of carbon and Na₂SO₄ are then added, and the mixture is stirred at room temperature. After filtration the solution is concentrated and cooled to -5 °C for up to 4 days. The crystals of Form II that are collected are characterised by XRD, DSC, IR, and NMR, and copies of the spectra are given in the patent. The patent also discloses that Form I can be converted to Form II if the two materials are suspended in hexane at 25 °C or Et₂O at -5 °C for about 12 h.

**Advantages**

The discovery of the new form of this drug can extend patent coverage.

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**Patent No. U.S. 6,800,755**

**Assignee:** Orchid Chemical and Pharmaceuticals Limited, Chennai, India

**Title or Subject:** Process for the Preparation of Cefixime

30b is a cephalosporin antibiotic that is more potent against Gram-negative bacteria and available as Suprax. The synthetic routes to give 30b initially produce the ester 30a, and this is hydrolysed to give the acid 30b; it is this difficult step that is the focus of this patent. In some processes the amino group is protected, in others it is not, but it is said that the final product from the alternative processes is obtained in low yield and is of poor quality containing coloured impurities. The conversion of 30a to 30b is carried out at 25 °C using NaHCO₃ in a biphasic mixture of EtOAc and aqueous NaHCO₃ (Scheme 10). After addition of NaOH and then neutralisation with HCl the product is extracted with Me₂CO and cooled to give crystals of the trihydrate form of 30b. The key aspect of the process is the use of a weak base to hydrolyse the ester and then the use of NaOH to improve the colour of the final product. The patent also specifically claims that Me₂CO should be used for the extraction step. It is also claimed that the product obtained by this process has enhanced solubility although no details are provided.

**Scheme 10**

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**Advantages**

The process gives a higher quality product without the need to use protective group methods.

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**Patent No. U.S. 6,800,756**

**Assignee:** Orchid Chemicals and Pharmaceuticals Limited, Tamilnadu, India

**Title or Subject:** Method of the Preparation of Ceftiofur Sodium Salts and Its Intermediates

The title compound 34c (R = H) has the same basic central molecular structure as the subject of the previous patent and is also an antibiotic. However, in this case it is used in the treatment of animals. Most of the synthetic routes to 34c give the HCl salt that is then converted to the Na salt 34b for veterinary use, but this patent discloses a direct route to 34b (Scheme 11). The procedure begins with the reaction of 31 with PCl₅ in DCM to give mixture A that is kept for an hour before being mixed with mixture B at -30 °C. This mixture contains the silylated form of the cephalosporin ester 32a formed from N₃,O-bis(trimethylsilyl)acetamide (BSA). The condensation reaction gives the novel compound 33a that is cyclised to give the novel thiazole 34a using thiourea and NaOAc in a water-miscible solvent. The Na salt is then obtained by treatment with TFA followed by anisole and sodium 2-ethylhexanoate in THF. Spectroscopic data are given for the new compounds.

**Scheme 11**

The patent also describes how to prepare the ester 32a from 32c (R = H) and p-MeOPhCH₂Cl. An alternative route to 32a is shown in Scheme 12 although there are no experimental details given in the patent. The first step is a base-catalyzed condensation of 35 with the thiol 36. In the second step the N-acetyl in 37 is removed by using, for example, PCl₃/pyridine at temperatures down to -40 °C.
Advantages

The process provides a method of making the required Na salt without the need to produce and isolate the HCl salt. This enables a better yield of higher purity product to be obtained on a commercial scale.

Patent No. U.S. 6,800,759
Assignee: Teva Pharmaceutical Industries Ltd., Petah Tiqva, Israel
Title or Subject: Racemisation and Enantiomer Separation of Clopidogrel

Clopidogrel 42 is used to treat atherosclerosis, and patents on the compound have previously been reviewed (Org. Process Res. Dev. 2004, 8, 823). The synthesis of 42 gives both enantiomers, and since only the S-form is active, it is desirable to remove and preferably recycle the inactive R-isomer. The basis of the current process is to prepare 42 by the route shown in Scheme 13.

Scheme 13

The route to 42 begins with the reaction of HCHO and the amine 38 to give the imine 39, but no experimental details are given. The imine is then cyclised to give the hydrochloride of 40 that, on reaction with 41, gives racemic 42. The product is recovered as the bisulphate salt by addition of H_2SO_4, and the free base is obtained by neutralisation with NaOH solution. Resolution was by formation of the S-enantiomer as the camphor sulphonate salt from DMF/PhMe. The R-enantiomer is then racemised using KOBu^+, and from the racemic mixture more S-isomer can be obtained. It is stated that the procedure can be carried out continuously.

Advantages

The process provides a simple procedure that may be used for obtaining an overall higher yield of this important drug.

Patent No. U.S. 6,800,764
Assignee: Wyeth, Madison, New Jersey, U.S.A
Title or Subject: Process for the Synthesis of Chirally Pure \( \beta \)-Amino Alcohols

This patent provides a novel process for preparing chirally pure S-enantiomers of amino alcohols such as 52. Also described are \( \alpha \)-amino acids that are intermediates in the synthesis of 52. The first part of the synthesis is shown in Scheme 14 and involves the preparation of the azide 46. The reaction starts with the preparation of the acid 44 by reaction of solid CO_2 with the Grignard reagent from 43. The acid is reacted with n-BuCOCl and Et_3N and converted to a mixed anhydride that is not isolated but converted to oxazolidinone 47 using 45. Treatment of 47 with the strong base (Me_3Si)_2NK forms the enolate anion of 47 that reacts with trisopropylbenzenesulphonyl azide to give 46.

Scheme 14

The second stage of the synthesis is shown in Scheme 15 and begins with the conversion of the azide 46 to the azido acid 48 by conventional treatment using LiOH. The azide group in 48 is then reduced to give the amino acid 49 using Pd/C catalyst in glacial HOAc. The amino acid 49 can be isolated or converted to the desired amino alcohol 52 by using LiBH_4/Me_3SiCl in 90% yield, but this can take up to 3 days for completion. The patent also describes that 50 gives 52 by reaction with the sulphonyl chloride 51 in the presence of a base such as Et_3N. A variety of pharmaceutical uses is indicated for 52.

Scheme 15

Advantages

This process gives a high yield of chirally pure amino acids and alcohols and these are valuable synthetic intermediates.
Pyrazine compounds such as 56 are useful in the treatment of central nervous system disorders, and this patent describes an improvement in a previously known synthesis of 57. A major problem with the earlier method is said to be that it gives poor yields because 53 is unstable in the basic conditions that exist towards the end of the reaction. The process disclosed in this patent overcomes this problem by changing the order of addition and reaction conditions while still using the same basic route shown in Scheme 16.

Scheme 16

The procedure is to add the acid salt 53 to a solution of KCN in MeOH and form the intermediate cyano salt 54. This is reacted immediately with the benzaldehyde 55 to form the intermediate 57 that is cyclised using LiOH in MeOH giving 56 in 91% yield. The single experiment in the patent describes the preparation of 12 kg of product, thus indicating the advanced stage of development of the work.

The improvement is believed to be due to the reduction in the acidity of the reaction mixture that prevents formation of acetals and hemiacetals of 55. The lower acidity is thought to be because of the reaction of the KCN with the acid salt 53 to give 54 that is less acidic.

Advantages
This procedure gives an improvement in yield of about 35% compared with the alternative method without changing the process costs.

Imidoesters are versatile intermediates and are typically prepared by a Pinner reaction using excess HCl gas. Hence, the patent describes a less hazardous process that uses solutions rather than gaseous HCl. The basic reaction is shown in Scheme 18 and involves treating an anhydrous mixture of a nitrile such as 63 or 65 with MeOH and a prepared solution of 4 M HCl in dioxane at 0 °C for up to 48 h. The excess HCl is then removed by bubbling N2 gas through the solution at 40 °C. The products 64 or 66 are

Advantages
This process converts byproducts into the desired product thereby substantially increasing the efficiency and overall yield of the reaction.
obtained by concentrating the solution, adding Et₂O to precipitate the solid, and then filtering. A range of other substrates is described, and HMR data are given for the products. Other alcohols are claimed in the patent, but no data are provided.

Scheme 18

Advantages

The process avoids the difficulties of handling gaseous HCl; by using a solution of known concentration the process is less wasteful and hence can claim to be environmentally friendly.

Patent No. U.S. 6,806,389
Assignee: AstraZeneca AB, Sodertalje, Sweden
Title or Subject: Immobilised Catalyst for Use in the Pauson–Khand Reaction

The production of cyclpentenones from an olefin and CO using a σ-alkynylcobaltcarbonyl catalyst is generally referred to as a Pauson–Khand reaction. A problem with the reaction is the volatility and toxicity of Co₂(CO)₈ from which the catalysts are usually made. The catalyst precursor is required in high purity, and commercial reagents are usually not of sufficiently high purity. Hence, the objective of this patent is to produce a nontoxic catalyst that can be easily prepared and recovered from the reaction mixture. Scheme 19 indicates the preparation of the supported catalyst 67c by treatment of Co₂(CO)₈ with a polystyrene-linked resin containing PPh₂ ligands. It is believed that the initial reaction gives the precursors 67a and 67b, and these form 67c. The structures of the precursors and final catalyst are merely suggestive, and the actual catalyst in the Pauson–Khand reaction is formed from 67c and the alkyne or alkene substrate.

Scheme 19

The catalyst 67c is not isolated and the mixture of the precursors is used to catalyse the conversion of 68 to 69 under CO in THF as shown in Scheme 20. It is suggested that by using a chiral ligand the product can be prepared with the desired that may be resolved or partially resolved. While this is likely there are no examples. The only example in the patent uses a ratio of 68 to precursors of 20:1 and no information on the reuse of the catalyst is given.

Scheme 20

Advantages

The use of immobilised catalysts does help product recovery in many catalytic reactions, but it is not clear in this patent how high the activity of the catalyst is.

Patent No. U.S. 6,809,221
Assignee: Teva Pharmaceutical Industries Ltd., Petah Tiqva, Israel
Title or Subject: Process for Making cis-Sertraline

Sertraline hydrochloride, 72c, is a widely used antidepressant available as Zoloft or Lustral. It was disclosed by Pfizer in 1985 and is currently of great interest because of the expiration of the original patents and the new routes to 72c that have previously been reviewed (Org. Process Res. Dev. 2004, 8, 553). The route to 72c in this patent starts with the formation of the Schiff base 71 from sertralone 70 by reaction with gaseous MeNH₂ in the presence of TiCl₄. The racemic sertaline free base 72a is then formed by hydrogenation of 71 using Pd/C at 1 atm pressure of H₂ and 40 °C. The recovery of the hydrochloride 72c is carried out via formation of the D-mandelic acid (D-MA) derivative 72b that is purified and then converted to 72c. The final product obtained was polymorphic Form V and contained 99% of the SS-enantiomer.

Scheme 21

The patent also describes the resolution of a racemic mixture of the hydrochloride 72c by formation of the D-MA
salt. A range of solvents was used with either 20% aqueous NaOH or 85% KOH powder being used to neutralise the HCl salt of 72c.

Advantages

The process provides an alternative method of making a generic form of a commonly used drug product.