Organic Process Research & Development

Highlights from the Patents

pubs.acs.org/OPRD

A Review of U.S. Patents in the Field of Organic Process Development Published During October and November 2011

SUMMARY

The current review contains 19 patents from an initial list of 343 that fitted the selection criteria, and although fewer than usual, several of the patents include quite extensive synthetic pathways. One of these describes a process for the production of substituted diarylamines that is claimed to be suitable for large-scale manufacture, but although the patent contains many examples there is no efficiency data. Another comprehensive patent covers the preparation of cyclopropylamides that are useful in treating allergic reactions and describes a reductive amination of a number of aldehyde bisulphite compounds. The compounds tolterodine and fesoterodine are used to treat bladder problems, and a patent provides an improved process and an extensive amount of chemistry for the synthesis of an intermediate for these materials. Another drug used to treat bladder problems is solifenacin, and a new process is described in which a key step uses a non-nucleophilic base to catalyse a condensation reaction. Another comprehensive patent describes the preparation of indolinone derivatives that are novel intermediates in the synthesis of antitumour drugs. Ranirestat is used to treat diabetes and can be resolved using cinchonidine, and because this compound is obtained in politically unstable regions an alternative process for making ranirestat has been developed. An improved synthesis is described for intermediates used to make the prostaglandins latanoprost and dinoprost. A patent for the preparation insecticide intermediates uses specially prepared solid KF for a fluorination reaction, and indications are that the reaction is dependent on particle size. Another fluorinated reaction is involved in the preparation of the anaesthetic sevoflurane from sevochlorane. Two patents cover the preparation of these compounds, and in the synthesis of sevochlorane the extremely volatile and carcinogenic bis-chloromethyl ether is formed, but this is not addressed in the patent. Enzymatic reduction of hydroxyimino acids is reported in the synthesis of the sweetener monatin and the amino acid tryptophan, but the process appears to give low yields. The production of isoxazoles from nitroaryls and an acetoacetate is reported to be more economical than other routes with more steps although little evidence is provided. A new process is disclosed for preparing the antiallergy drug levocetirizine, and this involves a number of novel intermediates. A process for the preparation of a very large number of amino-cyanobenzoic acid compounds is described. The process starts with optically pure reagents and gives high yields of products that are used to produce insecticides. Prazoles are a group of compounds used to treat gastric ulcers, and a patent describes a method of producing these compounds that avoids the production of a methylsulfone impurity that is difficult to remove. Anastrozole is used to treat breast cancer, and a regioisomer is often produced in the synthesis. A new process avoids producing the regioisomer and also identifies two new impurities and describes how they are removed. Cyclisation of nitriles with amines or ammonia is a method used to prepare a number of substituted 2-aminopyridines without using expensive reagents. A patent reports two polymorphs of the herbicide mesotrione, and a method is reported for producing the desired form without the need to use organic solvents by running the process semicontinuously or continuously. The coproduct in biodiesel production is glycerol, and a method is described for converting this to a propane fuel that does not look economically attractive. A number of the patents in this collection describe experiments carried out on a kilo or multikilo scale, thereby suggesting an advanced stage of development or even commercial operation. Several of the patents claim that the processes described are efficient and commercially viable yet provide no yield or purity data to support such claims. However, there is no legal or commercial significance in the choice of patents in this review. The advantages mentioned in this review are those claimed in the patent, unless this reviewer has personal knowledge of the subject.

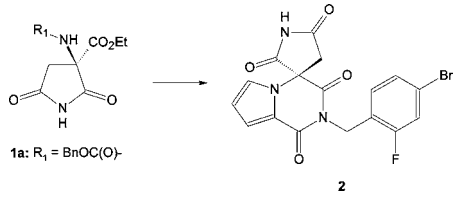
PATENT NO. U.S. 8,030,486

Assignee: Dainippon Sumitomo Pharma Co., and Katayama Seiyakusyo Co. Ltd., Osaka, Japan

Title or Subject: Process for Production of Succinic Acid Derivative and Its Use in the Production of Ranirestat

Ranirestat **2** is under trials for the treatment of complications in patients with diabetes. It is prepared from the optically pure enantiomer of the succinimide **1a** (Scheme 1) and this patent

Scheme 1



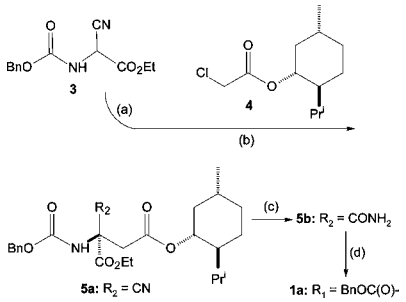
provides a process for preparing the intermediate **1a** and describes its use in the production of **2**.

An alternative process for preparing **2** from **1a** is said to require the use cinchonidine as a resolving agent in the preparation of **1a**. Cinchonidine is a natural occurring material, and the patent states that it is obtained in an area of political instability; thus, its future availability and price are questionable. Hence, it is claimed that an alternative method of resolving is required in the isolation of pure **1a**. The patent discloses that the novel compound **5b** is prepared and then converted to the desired enantiomer **1a**, and the route is shown in Scheme 2. In the first stage the cyanoacetate **3** is mixed with KI and K_2CO_3, then condensed with **4** to form **5a** that is isolated in 100% yield as an oil. The optical purity of the 2*R* derivative of **5a** is reported as 10.5% de. The nitrile **5a** is then converted to the

Published: February 10, 2012

dx.doi.org/10.1021/op300022v | *Org. Process Res. Dev.* 2012, 16, 376−388

Scheme 2.[a]

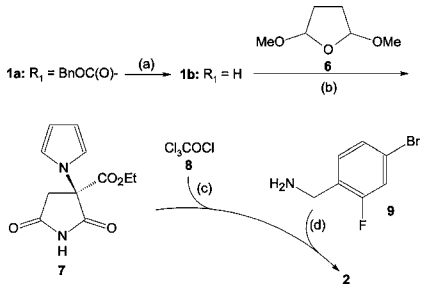


[a]Reagents and conditions: (a) (i) KI, K_2CO_3, Me_2CO, rt; (b) (i) <20 °C, 16 h; (ii) evaporate, add 3 M HCl, wash, dry; (c) (i) H_2O_2, Na_2CO_3, H_2O/Me_2CO, 40 °C, 4 h; (ii) cool to rt, add H_2O, filter, wash, dry; (iii) crystallise from Me_2CO; (d) (i) NaOEt, EtOH, −4 °C, 3.5 h; (ii) add concd HCl to pH 2; (iii) evaporate EtOH, add H_2O; (iv) extract in EtOAc, evaporate, crystallise from hexane.

amide **5b** by treatment with H_2O_2 in the presence of Na_2CO_3. The amide is obtained as a diastereomeric mixture in 88.4% yield and HPLC purity of 97.2% with optical purity of the 2*R* derivative of 12.2% de. Recrystallisation from Me_2CO gives the desired isomer **5b** in 38.6% yield and 98.8% de. The preparation of **1a** is carried out by treatment of **5b** with NaOEt and after workup the product is isolated in 86.6% yield with 99.4% ee.

The patent also describes the preparation of compounds **3** and **4** using literature methods. The process for the preparation of **2** from **1a** is described and is via the route shown in Scheme 3. Workup details are omitted, and only the main reaction

Scheme 3.[a]



[a]Reagents and conditions: (a) Pd/C, EtOH/H_2O, 40 °C, H_2, 33 h; (b) aq HOAc, 70 °C, 1.5 h; (ii) EtOAc, Pr^i_2O, Pr^i_2NH, <5 °C; (c) (i) H_2SO_4, EtOAc; (ii) **8**, EtOAc, reflux, 6 h; (d) (i) NMP, EtOAc, Pr^i_2NH; (ii) <5 °C, 18 h.

conditions are shown. The route begins with removal of the amine protective group from **1a** by catalytic hydrogenolysis using Pd/C. This produces **1b** (R_1 = H) that is isolated in 86.7% yield and 99.7% purity with ee of 100%. The amino group in **1b** is then converted to a pyrrolyl group by reaction with **6**, and **7** is obtained as a Pr^i_2NH salt in 88% yield. The salt is first treated with H_2SO_4 followed by **8**, and the resulting compound is not isolated but reacted with **9** to give **2** that is recrystallised from Pr^iOH and isolated in 58% yield. The purity is not reported.

The patent also describes the preparation of analogues of **4** and **5a** in which (+)-borneol or (+)-isopinocampheol is used to prepare the derivatives.

Advantages

The process is claimed to be cost-effective and suitable for operation on a commercial scale. In addition, it avoids the use of a resolving agent that may not always be available.

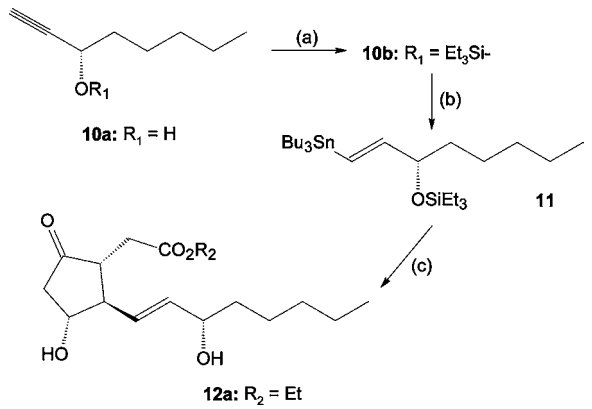
■ PATENT NO. U.S. 8,030,514

Assignee: Chirogate International Inc., Taipei, Taiwan

Title or Subject: Processes and Intermediates for the Preparation of Prostaglandins

The patent describes a process for preparing compounds that are intermediates in the synthesis of prostaglandins such as latanoprost and dinoprost. This patent is a divisional application of an earlier one from the same company that covers analogous intermediates and has been reviewed (*Org. Process Res. Dev.* **2010**, *14*, 459). The claims of the patent specifically cover crystalline forms of the esters such as **12a** where R is Et, Bn, and several other groups. An alternative method of making the lactone involves a 12-step linear synthesis that gives a low yield of the final product. Scheme 4 shows the preparation of

Scheme 4.[a]



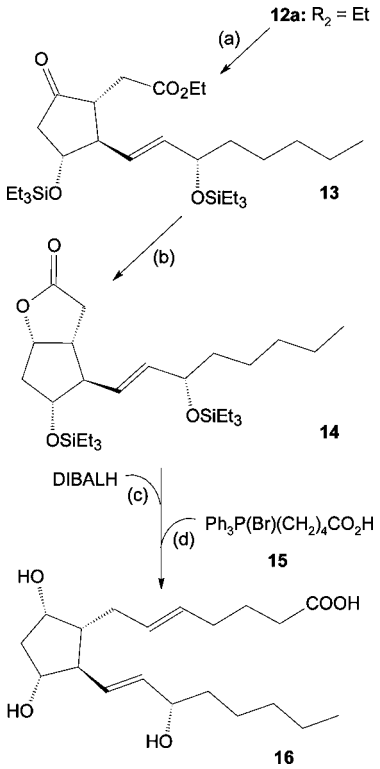
[a]Reagents and conditions: (a) (i) Et_3SiCl, imidazole, EtOAc, 5 °C, 0.5 h; (ii) filter off ppt at rt; (iii) wash, evaporate, distill; (b) (i) AIBN, Bu^n_3SnH, 130 °C, 2 h; (ii) cool to rt, distill.

12a that begins with the silylation of the OH group in **10a** using Et_3SiCl in the presence of imidazole, giving **10b**. This is obtained in 95% yield as an oil and then reacted with Bu^n_3SnH in the presence of AIBN to produce **11** that is recovered by vacuum distillation in 87% yield. **11** is then added to a mixture of CuCN and MeLi in THF to form **12a** (R_2 = Et) that is recovered in 89% yield. This is reported to contain a trace of the **15**-epimer that is removed after crystallisation of **12a** from Et_2O/hexane.

The ester **12a** is then used to prepare the lactone **14** that is an intermediate in the manufacture of dinoprost **16**; a drug used to induce labour in pregnant women. The main reactions and reagents for preparing **16** are shown in Scheme 5. The first stage is protection of the OH groups in **12a** by reaction with Et_3SiCl and imidazole to give **13** that is isolated in crude form in 93% yield. It is not mentioned whether **13** is purified before the next step where it is treated with $LiBHBu^s_3$ to produce **14** in 95% isolated yield. Again there is no mention if this is purified before the last step that begins with the reaction of **14** with DIBALH, producing the crude lactol of **14** as an oil. This is purified by extraction and washing and then is treated with the phosphonium salt **15** to form **16**. The crude product is isolated, but details of its yield and purification are not reported.

dx.doi.org/10.1021/op300022v | *Org. Process Res. Dev.* 2012, 16, 376−388

Scheme 5.[a]



[a]Reagents and conditions: (a) Et_3SiCl, imidazole, EtOAc, rt; (b) $LiBHBu^s_3$, THF, −70 °C, 2 h; (c) PhMe, −78 °C, 2 h; (d) Bu^tOK, THF, −10 °C, 18 h.

The contents of the patent appear to be virtually identical to the earlier one. The differences are primarily in the claims where the earlier patent focuses on intermediates to make latanoprost and the current one focuses on intermediates for making dinoprost.

Advantages

The process is claimed to give novel enantiomerically enriched intermediates that are useful in the preparation of prostaglandins.

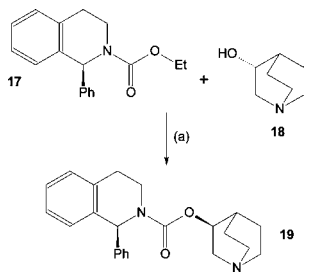
PATENT NO. U.S. 8,034,942

Assignee: Zentiva k s., Prague, Czech Republic

Title or Subject: Process for the Preparation of Solifenacin

This patent covers a new process for the preparation of solifenacin **19** that is used in treating an overactive bladder. The process involves a condensation reaction of **17** and **18** in the presence of a non-nucleophilic base and is shown in Scheme 6.

Scheme 6.[a]



[a]Reagents and conditions: (a) (i) Bu^tOK, PhMe, reflux, 3 h; (ii) add H_2O, rt, 20 min; (iii) separate, wash, evaporate; (iv) add HCl/MeOH; (v) evaporate.

Alternative processes are summarised and have problems such as low yields, use of large excess of reagents, or give high levels of impurities. The key finding in this process seems to be the use of a non-nucleophilic base to catalyse the condensation reaction, and several are investigated. The most suitable are said to be Bu^tOK, LDA, or DBU, and there are examples for all three. The claims of the patent cover the use of Bu^tOK and Bu^tONa, but there is no example using Bu^tONa. The reaction is carried out in refluxing PhMe, and the EtOH formed is removed as an azeotrope with PhMe. The product is recovered as the HCl salt in a yield of 68.8%. The reaction is followed by GC, and the patent reports the conversion and selectivity to R,R- and S,S-isomers compared to the desired S,R isomer. The conversion of the reactants is >97%, and degree of racemisation of both reactant and product is very low with levels of R,R- and S,S-isomers each <2%.

The patent states that the reaction requires only a small excess of **18** that is only slightly higher than the amount of base. However, there are certainly serious typographical mistakes in all of the examples since the mole ratio of **17** to **18** used is reported to be around 840:1. The amounts of **17** and **18** used are given in molar terms rather than weight, and they equate to using between 33 and 38 kilo of **17** per litre of PhMe. There is no excuse for such errors.

Advantages

The process gives good yields of product with high selectivity.

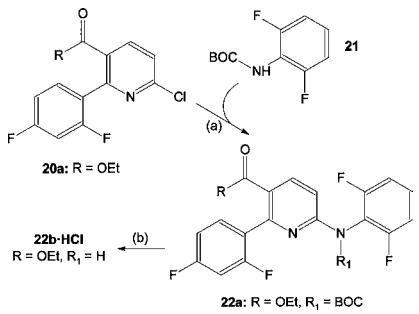
PATENT NO. U.S. 8,034,950

Assignee: Vertex Pharmaceuticals Inc., Cambridge, Massachusetts

Title or Subject: Processes for the Facile Synthesis of Diarylamines and Analogues Thereof

The amines covered by this patent are mitogen activated protein kinases and are under investigation for the treatment of autoimmune diseases and inflammatory processes. The patent states that there are few methods for making the desired diarylamines without significant byproduct formation. Common methods involve Pd-catalysed coupling reactions of aryl amines and aryl halides, but these can result in low yields when primary amines are used. Hence the use of primary amines in such processes is avoided, and this limits the use of the technique. The process disclosed in this patent overcomes this limitation by protecting primary amines that subsequently react as secondary amines and thereby give improved yields. An example of an amine produced by this method is **22a**, and its synthesis is shown in Scheme 7. After forming the protected

Scheme 7.[a]



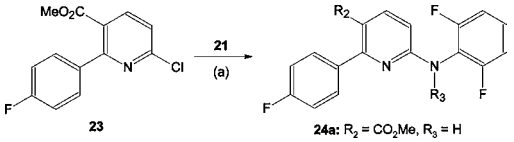
[a]Reagents and conditions: (a) (i) Cs_2CO_3, NMP, 65 °C, 36 h; (ii) cool 20 °C, add, H_2O; (iii) filter at 15 °C, dry, (b) (i) TFA, DCM, rt, 2 h; (ii) evaporate, dissolve in EtOAc; (iii) add aq $NaHCO_3$, brine wash, evaporate; (iv) dissolve in EtOAc, HCl/Et_2O, 1 h; (v) filter, dry.

dx.doi.org/10.1021/op300022v | Org. Process Res. Dev. 2012, 16, 376−388

amine **21**, it is added to a solution of **20a** containing a base such as Cs_2CO_3, and the reaction is followed by HPLC. After 18 h there is 85% conversion of **21**, and after a further 18 h the conversion reached 97%. The initial product is the BOC adduct **22a** (R = OEt, R_1 = BOC); this is isolated and then acidified with TFA to give the free amine that is recovered as an oil and then converted to the HCl salt **22b·HCl**. The crude salt is isolated in a yield of 70.5% that can be recrystallised, but the final purity is not reported.

The coupling reaction can also be carried out using a transition metal catalyst, and Scheme 8 shows the preparation

Scheme 8.[a]

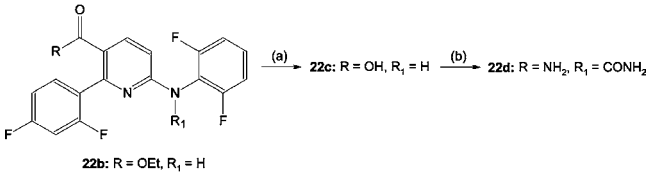


[a]Reagents and conditions: (a) (i) $Pd(OAc)_2$, *rac*-BINAP, K_3PO_4, PhMe, 100 °C, 16 h; (ii) cool rt, add EtOAc and 6 M HCl, filter; (iii) separate, brine wash, dry, evaporate; (iv) TFA, DCM, rt, 16 h; (v) evaporate, add EtOAc, add NaOH then 5% $NaHCO_3$ to pH 8−9; (vi) separate, wash, dry, evaporate; (vii) PhMe, azeotropic drying; (viii) Et_2O/HCl, heat filter, dry.

of **24a** from **21** and **23** using $Pd(OAc)_2$ and *rac*-BINAP. The BOC-protected product is isolated as an oil, treated with TFA, and following an extensive workup procedure, **24a** is isolated as a solid, but no yield or purity details are given.

The patent describes the saponification of the ester group in **22b** with NaOH followed by HCl to give the acid **22c** (R = OH, R_1 = H) as shown in Scheme 9. **22c** is then reacted

Scheme 9.[a]



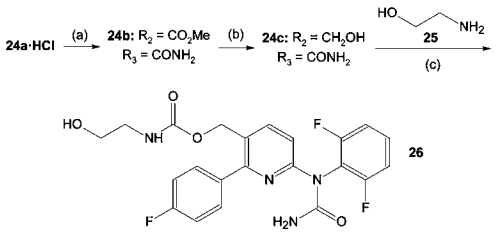
[a]Reagents and conditions: (a) (i) NaOH, THF; (ii) HCl; (b) (i) $ClC(O)OCCl_3$; (ii) NH_4OH.

with diphosgene giving the carbamoyl chloride intermediate that is not isolated and treated with NH_4OH to give the amide-urea compound **22d**. Although there are no examples for these steps, the claims of the patent specifically cover this route.

The patent does describe an example for the conversion of compound **24a** to **26** by the route shown in Scheme 10. In the first step the HCl salt of **24a** is converted to the urea **24b** by reaction with $COCl_2$, giving the carbamoyl chloride intermediate that is not isolated but treated with NH_4OH to give **24a**. The yield and purity are not reported, and the compound is treated with DIBALH to form the benzyl alcohol **24c** that is isolated in 80% yield. In the last step **24c** is treated with carbonyl diimidazole (CDI) followed by **25** to give **26**, but the final product yield and purity are not reported.

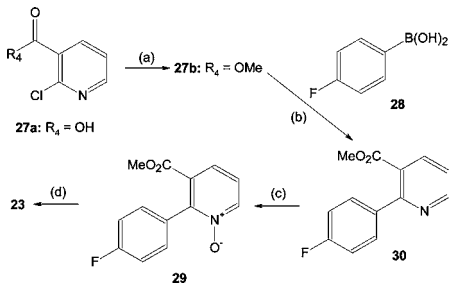
The patent describes the preparation of **23** by the route shown in Scheme 11. This begins with the esterification of **27a** forming **27b** that is isolated as an oil and then reacted with the boronic acid **28** to give **30**. The reaction takes place in the

Scheme 10.[a]



[a]Reagents and conditions: (a) (i) $COCl_2$, PhMe, 50 °C, 16 h; (ii) aq NH_4OH, −5 °C; (iii) filter, PhMe wash; (b) (i) DIBALH, THF, 20 °C, 0.5 h; (ii) 15% H_2SO_4, <10 °C, 0.25 h; (iii) MTBE, 50 °C, 1 h; (iv) cool, separate, concentrate; (v) MTBE, concentrate; (vi) cool <2 °C, 0.75 h; (vii) filter, PhMe wash, dry; (c) (i) CDI, THF, rt, 4 h; (ii) evaporate, add EtOAc; (iii) wash in NH_4Cl, brine; (iv) EtOAc, azeotropic drying; (v) PhMe, 40 °C; (vi) cool filter, PhMe wash.

Scheme 11.[a]



[a]Reagents and conditions: (a) (i) $SOCl_2$, DCM, 40 °C, 16 h; (ii) MeOH, 20 °C; (iii) evaporate, wash in 10% Na_2CO_3,; (iv) extract into EtOAc, dry, evaporate; (b) (i) $Pd(PPh_3)_4$, aq Na_2CO_3, EtOH, 78 °C, 16 h; (ii) cool, evaporate, add EtOAc; (iii) wash, dry, evaporate; (c) (i) urea/H_2O_2, HOAc, 75 °C; (ii) cool to rt, add to ice; (iii) 6 M NaOH to pH 7, 30 °C; (iv) EtOAc, solid $NaHCO_3$, to pH 8−9; (v) separate, wash in 5% $NaHCO_3$, dry, evaporate; (d) (i) $POCl_3$, DCE, 19 °C, (i) heat to 75 °C; (ii) cool to rt, concentrate; (iii) add to ice, extract in DCM, dry, evaporate.

presence of $Pd(PPh_3)_4$, and **30** is isolated as a solid and then oxidised to give the *N*-oxide **29**. The reaction is carried out using urea/H_2O_2 although other reagents are said to be suitable. In the final stage the *N*-oxide is halogenated using $POCl_3$ to give **23**. There are no details of product yield or purity for any steps in this reaction scheme.

Advantages

The process is claimed to be amenable to large-scale production and is said to give high yields of high purity product, but evidence to support this is not provided.

■ PATENT NO. U.S. 8,039,680

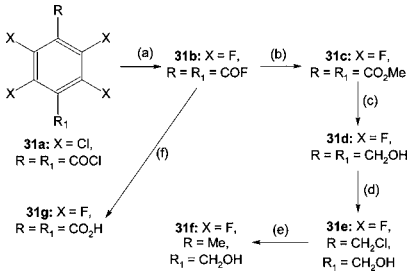
Assignee: Sumitomo Chemical Co. Ltd., Tokyo, Japan

Title or Subject: Process for Producing 4-Methyl-2,3,5,6-tetrafluorobenzyl Alcohol

The compound of interest in this patent, **31f**, is an intermediate in the production of insecticides. The process for producing **31f** has five steps and is outlined in Scheme 12. Alternative processes also have several steps, and the patent makes no claims regarding its advantages. The key fluorination step of **31a** is carried out using KF that is specially produced or is material that has been prepared by spray drying. This would suggest that the fluorination step is influenced by the particle

dx.doi.org/10.1021/op300022v | Org. Process Res. Dev. 2012, 16, 376−388

Scheme 12.[a]



[a]Reagents and conditions: (a) KF, sulpholane, 145 °C, 3.5 h; (b) (i) cool to 100 °C, add PhMe; (ii) cool to rt, add MeOH, 12 h; (c) (i) $NaBH_4$, DME, 50 °C, 8 h; (ii) 35% HCl, PhMe, 60 °C, 6 h; (d) 36% HCl, PhMe, 90 °C, 5 h; (e) Pd/C, Bu^nOH, H_2, 1 bar, 100 °C, 16 h; (f) H_2O, base, rt.

size of the KF although this is not mentioned in the patent. The method of preparation of KF is as follows:

a) Dissolve KF in MeOH at up to 50 parts MeOH by weight per part KF,
(b) Reflux the mixture, then add an aprotic solvent with bp higher than that of MeOH.
(c) Distill off MeOH and recover the suspension of KF for use in the fluorination step.

The patent claims state that step (b) is carried out in the presence of Me_2SO_2; because this is a solid with mp 108 °C an additional solvent is needed, and sulpholane is used in most of the examples. Scheme 12 outlines the reactions for preparing **31f** from **31a**, and space limitations mean that only the main reaction conditions are included. For most of the reaction steps there are at least two examples provided, and the reaction conditions in Scheme 12 are those that give the highest yield and purity. However, it is by no means clear whether these are the preferred conditions, and the interested reader is encouraged to consult the patent. The fluorination of **31a** is carried out using the above recovered mixture of KF. The initial product of this reaction is **31b**, and this can be isolated or hydrolysed to **31g**. In the synthesis of **31f**, **31b** is normally esterified in situ forming **31c**, and several examples are described for this fluorination/esterification step. PhMe is added for the esterification step so that the MeOH can be removed by azeotropic distillation, and N_2 gas is used to remove the HF formed. The ester **31c** is isolated in yields of up to 93% with purity up to 92%. There is no indication whether this is purified before the next step in which it is reduced using $NaBH_4$ to give **31d** in yields up to 95% and product purity as high as 95.1%. In the next step **31d** is chlorinated using HCl to give **31e** that is isolated in 93% yield and purity 98% containing 0.5% of the dichloromethyl compound. In the last step **31e** is catalytically hydrogenated over a Pd/C catalyst to produce **31f** that is isolated in 90% yield with purity of 98%.

Advantages

The patent provides a process for producing the desired intermediate, and the key may be the use of specially prepared KF as the fluorinating agent.

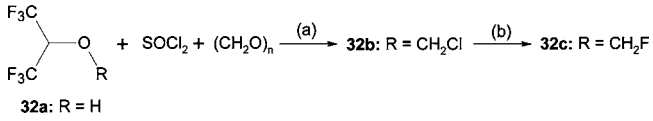
■ PATENT NOS. U.S. 8,039,678 AND U.S. 8,044,247

Assignee: Crystalia Produtos Quimicos Farmaceuticos Ltd.a., Itapira, Brazil

Title or Subject: Processes for the Preparation of Sevoflurane and Sevochlorane

Sevoflurane **32c** is used as an inhalation anaesthetic, and the first of these two patents covers a process to prepare sevochlorane **32b** that is an intermediate in the synthesis of **32c** while the synthesis of **32c** is covered by the second patent. Some of the processes used to prepare **32c** are summarised, and many have low selectivity or give poor yields. The synthesis of **32c** disclosed in these patents starts from the fluoroalcohol **32a**, and while there are other processes that also start from **32a**, these are said to give incomplete reactions or use highly toxic reagents. The first patent describes a novel synthesis of **32b** by the reaction of **1a** with HCHO and a chlorinating agent such as $SOCl_2$ in the presence of H_2SO_4. After neutralisation of the reaction mixture the conversion of **32b** to **32c** is carried out by using KF in the presence of KI that improves the rate and conversion. The formaldehyde is used as trioxane or as paraformaldehyde, and the reaction is outlined in Scheme 13.

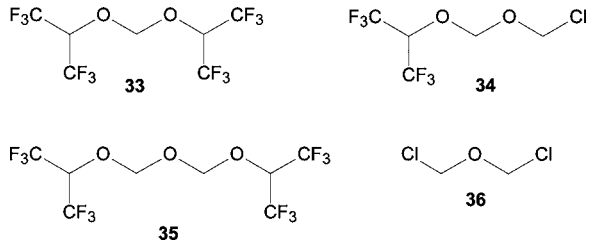
Scheme 13.[a]



[a]Reagents and conditions: (a) (i) H_2SO_4, <60 °C, 6 h; (ii) 10% aq Na_2CO_3 to pH 7, 0 °C; (iii) 10% aq NaOH, 1 h, separate; (b) KF, KI, solvent, reflux, 1.5 h, distill.

The purity of **32b** and reaction selectivity depends on the proportions of HCHO and $SOCl_2$ relative to **32a**, and these reagents are usually used in excess. The reaction is carried out by adding H_2SO_4 to the mixture of **32a**, $SOCl_2$, and HCHO, and this results in the formation of $ClSO_3H$. There are a number of byproducts that are formed in the reaction, and the main ones are shown below.

Byproducts



During the process **33**, **34**, and **35** are subsequently converted to **32b** by reaction with $ClSO_3H$. This finding is said to contradict alternative processes using **32a** as raw material where formation of these byproducts is said to reduce the chemical yield. The ether byproduct **36** is an extremely carcinogenic and volatile material that is readily formed when HCHO contacts $ClSO_3H$ or HCl, that is probably formed in the process. The effects of exposure to **36** may not be noticed for up to 20 years. The patent is critical of alternative processes that use toxic reagents, but there is no mention of these health problems in the patent. Although **36** is rapidly hydrolysed, its production is a serious health hazard. The maximum allowable airborne exposure limit is 1 ppb, and hence monitoring its concentration in and around the process would be essential because it is so volatile. Analysis of the crude reaction mixture from the production of **32b** showed levels of **36** up to 0.5%. The mixture is then neutralised with alkali, and **32b** is recovered in 80% yield. GC analysis showed the product to be 99.3% pure, containing 0.04% **32a**, 0.3% of **33**, and 0.4% of **34** and **35**. Treatment of

dx.doi.org/10.1021/op300022v | Org. Process Res. Dev. 2012, 16, 376−388

32b with KF is then carried out to form **32c**. A number of experiments show the effect of KI and solvent on the reaction. Addition of substoichiometric amounts KI reduces the reaction times and also reduces the quantity of KF that is needed. However, it is recommended to use excess KF to shift the reaction equilibrium to give **32c**. A number of different solvents were examined including sulpholane, DMF, glycols, and their ethers or esters and also mixtures of mono- and diglycerides (MDG) of medium chain length. The conversion of **32b** to **32c** in all cases was >97%; in one example using MDG as solvent with KF and KI, **32c** was recovered in 76% yield and purity >99% after fractional distillation.

Advantages

The process gives high yields but does produce an extremely hazardous byproduct that would not be tolerated in many establishments.

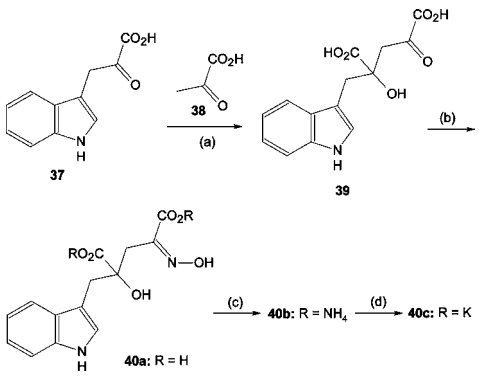
PATENT NO. U.S. 8,043,836

Assignee: Ajinomoto Co. Ltd., Tokyo, Japan

Title or Subject: Process for Producing Aminoacid Derivative from Hydroxyimino Acid

The patent describes a process for producing aminoacid derivatives and especially indole derivatives with two compounds being specifically mentioned. These are monatin **41**, a naturally occurring, highly intense sweetener, and the essential amino-acid, tryptophan, **43**. The process involves enzymatic reduction of an hydroxyimino acid. Although enzymatic reduction of hydoxyimines is known, the patent claims that enzymatic reduction of hydroxyimino acids is novel. Chemical methods are said to involve difficult isolation and extraction methods that are unsuitable for large-scale production of aminoacid derivatives. The first stage in the preparation of **41** is the formation of the oxime salt **40c** as shown in Scheme 14. In the first step the acid

Scheme 14.[a]

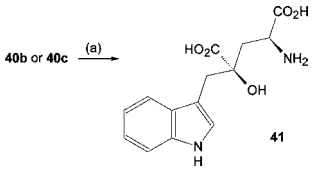


[a]Reagents and conditions: (a) (i) 1.6% aq NaOH, 35 °C; (ii) 30% NaOH to pH 11.1, 6.5 h; (b) (i) 30% aq NaOH to pH 7; (ii) 40% aq $H_2NOH{\cdot}HCl$, 5 °C, 17.5 h; (iii) concd HCl to pH 2, extract in EtOAc; (iv) concentrate, brine wash; (c) (i) 28% aq NH_4OH, Pr^iOH; (d) K^+ IER, H_2O.

37 is treated with dil. NaOH, and then **38** is added to produce the ketoglutaric acid **39**. This is not isolated, but the solution is kept at pH 7, and then $H_2NOH{\cdot}HCl$ is added to form the oxime **40a**. After extraction, the solution is concentrated and then treated with 28% NH_4OH to give **40b** as crystals in 40% yield based on **37**. This is converted to the K salt **40c** using a cation ion-exchange resin (IER), and the salt is isolated as an aqueous solution.

The solution of either **40b** or **40c** can be enzymatically reduced to give **41** as shown in Scheme 15, and four enzymes

Scheme 15.[a]

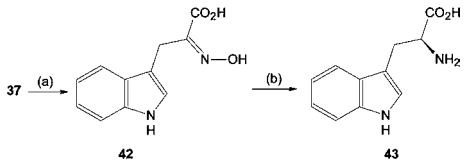


[a]Reagents and conditions: (a) enzyme, ACA, 30 °C, 24 h.

are covered in the patent. These are *Citrobacter freundii* (*CF*), *Escherichia intermedia* (*EI*), *Escherichia coli* (*EC*), and *Rhodococcus marionondscens* (*RM*), and the examples also indicate the effect of various auxiliary culture agents (ACA). The reactions were screened by using TLC analysis to show that **41** had been formed. HPLC analysis was then used to quantify the results. The data are reported showing the yield of **41** in millimoles produced from 50 mM of **40b** with the different enzymes: 3.2 (*CF*), 3.2 (*EI*), 2.1 (*EC*) and 1.2 (*RM*). Higher yields of **41** were obtained when using 50 mM of the K salt **40c**. Using *EI* the highest yield of **41** is 11.6 mM, and with *CF* the best yield is 11.3 mM.

The preparation of **43** from **37** via the oxime **42** is also described in the patent and outlined in Scheme 16. From 50 mM of **42** *EI* gave 2.0 mM of **43** and *CF* gave 2.2 mM.

Scheme 16.[a]



[a]Reagents and conditions: (a) (i) $H_2NOH{\cdot}HCl$, KOH, H_2O, rt, 16 h; (ii) add HCl to pH 2, rt; (iii) filter, dry; (b) enzyme, ACA, 30 °C, 24 h.

Advantages

The process does show that the amino acid derivatives can be produced by enzymatic reduction, but the yields are low.

PATENT NO. U.S. 8,044,214

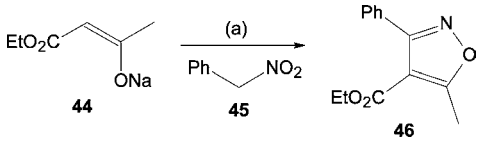
Assignee: Angus Chemical Co., Buffalo Grove, Illinois, United States, and Dow Global Technologies L.L.C., Midland, Michigan, United States

Title or Subject: Process for Preparing Isoxazole Compounds

Compounds such as **46** are intermediates in the production of a range of compounds. The patent states that they can be prepared from hydroximoyl halides via nitrile oxides, but the procedures have multiple steps and require potentially expensive reagents. The methods are therefore said to be commercially unattractive. The process disclosed in this patent involves the reaction of a nitroaryl compound with an acetoacetate in the presence of a base and an activating agent. Scheme 17 shows the reaction used to prepare **46** by reaction of **44** and **45** in the presence of the base Et_3N and $ClCO_2Et$ as activating agent. The reaction is carried out by dissolving $ClCO_2Et$ and **45** in THF; then this solution is added to **44** and Et_3N in

dx.doi.org/10.1021/op300022v | Org. Process Res. Dev. 2012, 16, 376−388

Scheme 17.[a]



[a]Reagents and conditions: (a) Et_3N, $ClCO_2Et$, THF, DMSO, rt, 1 h.

DMSO over 1 h. The product is shown to be present by HPLC and GC–MS, but it is not isolated, and the patent does not report any yield.

Advantages

The process does indeed produce the desired compound in fewer steps than alternatives. However, whether it is more economical is not known since there is no information on the selectivity of the reaction.

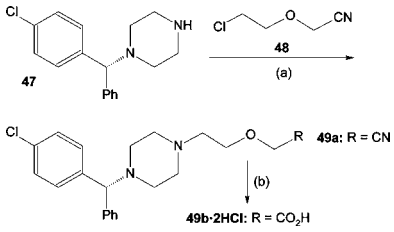
■ PATENT NO. U.S. 8,049,011

Assignee: KRKA Tovarna Zdravil D.D., Novo Mesto, Slovenia

Title or Subject: Process for the Preparation of Levocetirizine and Intermediates Thereof

Levocetirizine **49b** (R = CO_2H) is used to treat a range of allergic reactions and is available as the bis-HCl salt. A number of processes for the preparation of **49b** are mentioned, and improved methods giving high optical yields are said to be required. The process described in this patent starts from optically pure reagents and is shown in Scheme 18. In the first

Scheme 18.[a]

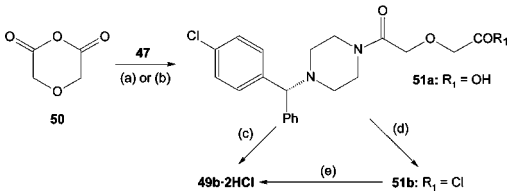


[a]Reagents and conditions: (a) (i) Na_2CO_3, KI, MeCN, 115 °C, 20 h; (ii) cool <90 °C, add active C, 20 min, filter; (iii) add dry HCl to pH 0.5, rt; (iii) filter, wash in EtOH, dry; (iv) MeOH, reflux, 20 min; (v) cool 0 °C, 1 h, filter, wash, dry; (b) (i) KOH, H_2O, MeOH, 76 °C, 24 h; (ii) cool to <45 °C, evaporate; (iii) add H_2O/DCM, <30 °C; (iv) 37% HCl to pH 4.2; (v) extract in DCM, dry, evaporate; (vi) dissolve in Me_2CO, add dry HCl to pH <1; (vii) reflux, 20 min; (viii) cool <35 °C, filter, wash, dry.

step the chiral piperazine **47** is condensed with **48** in the presence of a base to form **49a**. This is isolated as the bis-HCl salt in 95% yield with purity reported as 95 area% by HPLC. This is purified by refluxing in MeOH before being hydrolysed with KOH. The free amine is obtained as an oily residue and then treated with dry HCl gas to to form **49b·2HCl** that is isolated in 89% yield. A sample of the crude salt containing 0.17% of **47** was recrystallised from HOAc/Me_2CO and recovered in 77% yield and 99.9% purity (HPLC) with <0.005% of **47**. The examples report experiments carried out on half-kilo scale.

The patent also describes an alternative method of preparing **49b** using the glycolic anhydride **50** in place of **48**, and this is shown in Scheme 19. The reaction is carried out in DMSO

Scheme 19.[a]

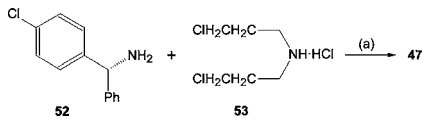


[a]Reagents and conditions: (a) (i) MeCN, reflux, 12 h; (ii) evaporate, add aq NaOH and DCM; (iii) separate, dry, evaporate; (b) (i) Bu^n_4NBr, DMSO, rt; (ii) add H_2O and Pr^iOAc, separate; (iii) add 2 M NaOH to pH 3.5; (iv) separate, evaporate; (c) (i) $NaBH_4$, dioxane, 10 °C; (ii) add HOAc, dioxane, reflux 2 h; (iii) cool rt, filter, evaporate; (iv) H_2O, pH 5, extract into DCM; (v) dry, evaporate; (vi) 36% HCl, Me_2CO, filter, dry; (d) $(COCl)_2$ THF, 0 °C, 0.5 h; (e) (i) $Me_2S{\cdot}BH_3$, (ii) add H_2O, 0.5 h; (iii) extract in EtOAc, adjust to pH 10, separate; (iv) add DCM and cond HCl to pH 4.2; (v) separate, H_2O wash, dry, evaporate; (vi) dissolve in Me_2CO, add dry HCl gas, to pH <1; (vii) reflux, 2 min; (viii) cool <35 °C, filter, wash, dry.

containing Bu^n_4NBr at rt or in refluxing MeCN and produces the oxo-acid **51a**. The latter method gives an oily product that can be used without further purification, whereas the product from the former method is isolated as a crystalline solid in 98.5% yield. There are two methods described in the patent for the conversion of **51a** to **49b**. In the first, the crude oil **51a** is reduced using $NaBH_4$, and after workup the bis-HCl is obtained by addition of 36% HCl. The alternative procedure was applied to the crystalline **51a** that was converted to the acyl chloride **51b** using $(COCl)_2$ before this was reduced to **49b** using the $Me_2S{\cdot}BH_3$ complex. The bis-HCl salt was then isolated by addition of dry HCl gas. In contrast to the examples for Scheme 18 these experiments are only carried out on gram scale.

The patent also describes the preparation of the starting material **47** from **52** as shown in Scheme 20. The reaction is

Scheme 20.[a]



[a]Reagents and conditions: (a) (i) $EtNPr^i_2$, reflux 3 h; (ii) cool to 60 °C, add Et_3N, reflux 5 h; (iii) evaporate, add H_2O, EtOAc; (iv) 30% NaOH to pH 11; (v) separate, extract in EtOAc, wash, add active C; (vi) filter, purify by ColC, evaporate; (vii) add active C, filter; (viii) cool <10 °C, 1 h, filter, dry

carried out by refluxing in $EtNPr^i_2$ and then adding Et_3N. After an extensive workup including two treatments with active C and purification by column chromatography (ColC), **47** is isolated with 98–99% purity, but the yield is not reported.

The patent also describes the preparation of a HOAc solvate of **49b·2HCl** and provides XRD, DSC, and FT-IR spectra for the solvate as well as for **49b·2HCl**, **49a**, and **51a**. The patent does not report the optical purity of the product, and it is expected that since the starting material **47** is optically pure then the product will be.

Advantages

The patent provides a new process for preparing the well-known drug via novel intermediates.

dx.doi.org/10.1021/op300022v | Org. Process Res. Dev. 2012, 16, 376–388

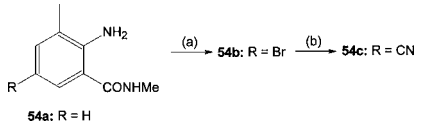
PATENT NO. U.S. 8,049,029

Assignee: E.I. Du Pont de Nemours and Co., Wilmington, Delaware, United States

Title or Subject: Process for Preparing 2-Amino-5-cyanobenzoic Acid Derivatives

The compounds covered by this patent, such as **54c**, are intermediates in the preparation of insecticides. The patent states that although there are patents covering the preparation of such compounds, improvements are required. This patent contains an extensive table of compounds that can be produced and probably covers all of the possible variations of substituents. The examples only cover the preparation of **54c** by the method shown in Scheme 21, and its use in the preparation of

Scheme 21.[a]

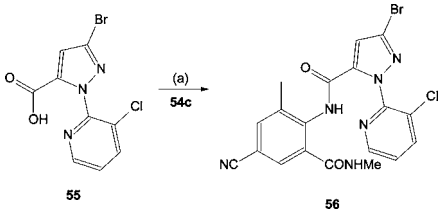


[a]Reagents and conditions: (a) (i) Br_2, aq NaOH, HOAc, 55 °C, 3 h; (ii) 45 °C, 16 h; (iii) wash in aq NaOH, 45 °C, 2.5 h; (iv) 10 °C, 1 h; (v) filter, MeOH wash, dry; (b) (i) NaCN, CuI, $(MeNHCH_2)_2$, xylenes, argon purge, rt, 20 min; (ii) reflux, 4.5 h; (iii) cool 25 °C, add H_2O, 0.5 h; (iv) filter, wash, dry.

56. The first stage is halogenation of **54a** by passing gaseous Br_2 into a solution of **54a** in HOAc containing aq NaOH. This produces **54b** that is isolated in 89.7% yield and 99.4 area % purity (HPLC) that is then converted to **54c** by reaction with NaCN in the presence of CuI and $(MeNHCH_2)_2$. The patent gives examples of this reaction being carried out in either xylenes, PhCl, or mesitylene as solvent. With the use of xylenes the product is isolated in 97% yield, but the purity is not reported.

The preparation of **54c** is also carried out using the chloro compound **54d** that is prepared by a procedure reported in WO 2006/62978. The cyano compound **54c** is used to prepare **56** as outlined in Scheme 22. The procedure used is reported in

Scheme 22.[a]



[a]Reagents and conditions: (a) (i) 3-picoline, MeCN, <20 °C; (ii) MsCl, <20 °C, 1 h; (iii) add H_2O, <20 °C; (iv) 45 °C, 0.5 h; (v) 20 °C, 1 h; (vi) filter, wash, dry.

WO 2006/62978 where the preparation of **55** is also described. The compounds **54c** and **55** are dissolved in MeCN in the presence of 3-picoline followed by MsCl. The product yield is 93.6% based on an assay of 91.6%.

The patent reports basic ^1H NMR data for **54c** and **56**.

Advantages

The patent provides a method of preparing the cyano compounds in high yield.

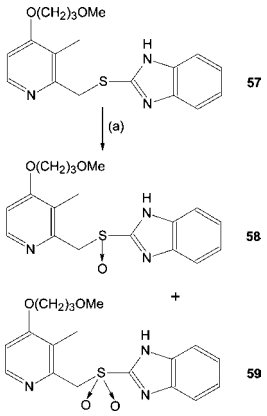
PATENT NO. U.S. 8,053,580

Assignee: Eisal R&D Management Co. Ltd., Tokyo, Japan

Title or Subject: Process for Manufacturing Amine Salts of Benzimidazole Derivative

The compounds covered by this patent are amine salts of **58** that are proton pump inhibitors and are used to treat gastric ulcers. An example is **58**, one of a group of molecules known as prazoles available as salts of alkali metals. Many prazoles are not available as amine salts, and it is the preparation of amine salts of **58** that is described in the patent. One problem common in the preparation of all prazoles is that the final step involves the oxidation of a thioether using *m*-CPBA that produces a sulphone impurity such as **59** that is difficult to remove. The single claim of the patent actually covers the Na salt of **58** and its preparation from amine salts. The current patent provides a method of synthesising **58** by oxidation of **57**, and this gives low levels of impurity **59** (Scheme 23). Similar impurity

Scheme 23.[a]



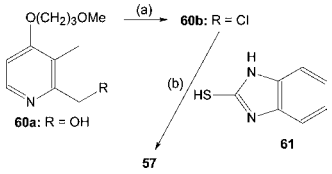
[a]Reagents and conditions: (a) (i) *m*-CPBA, DCM, −15 °C; (ii) 10% aq NaOH; (iii) separate, wash in DCM (× 2); (iii) add NH_4OAc, extract in DCM; (iv) wash, dry, concentrate; (v) add Et_2O, filter.

problems have been addressed in the synthesis of the well-known drug omeprazole and patents on the subject have been reviewed (*Org. Process Res. Dev.* **2008**, *12*, 146). Several examples are given in the patent for the preparation of **58**, and the yield varies from 23.9 to 55.4% with the product purity 99.1% or higher. The patent also gives details for preparing a number of amine salts of **58** from Pr^iNH_2, Bu^sNH_2 and cyclopentylamine. The preparation of the Pr^iNH_2 salt of **58** that contained 1.44% of **59** is carried out by heating **58** in MeCN at 55 °C. Crystallisation by addition of hexane and seeding gave the final product in 94.5% yield containing only 0.02% of **59**. The patent states that the unwanted impurity can be efficiently removed from amine salts. These can be converted to the more desirable Na salt by treatment with NaOH. An example describes the conversion of the Bu^sNH_2 salt to the Na salt that is isolated in 99.3% yield containing 0.02% of **59**.

The preparation of the thiol **57** is carried out as shown in Scheme 24 and starts with the chlorination of **60a** using $SOCl_2$ to give **60b**. The product is isolated in yields up to 99.2% and is then reacted with the thiol **61** in the presence of NaOH. The crude product is recovered in quantitative yield and recrystallised from a range of solvents including ethers, alcohols, MeCN, MTBE, or Me_2CO. The pure product is obtained in yields >95% and purity as high as 99.4%.

dx.doi.org/10.1021/op300022v | *Org. Process Res. Dev.* 2012, 16, 376−388

Scheme 24.[a]



[a]Reagents and conditions: (a) (i) $SOCl_2$, DCM, <25 °C; (ii) evaporate; (b) (i) NaOH, EtOH, 50 °C, 2 h; (ii) evaporate, add PhMe and H_2O; (iii) separate, wash in 10% aq NaOH, evaporate.

Advantages

The process provides an efficient method of removing the unwanted impurities from the particular prazole **58** that could have applications to other similar compounds.

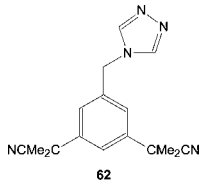
PATENT NO. U.S. 8,058,302

Assignee: Cadila Healthcare Limited, Ahmedabad, Gujarat, India

Title or Subject: Process for Preparing Anastrozole

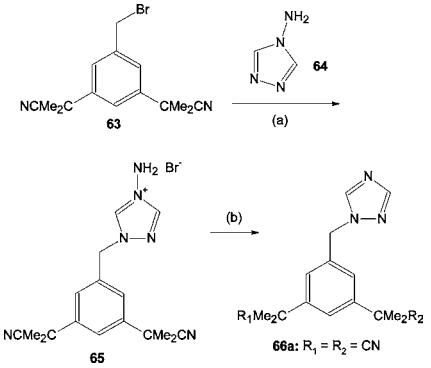
Anastrozole, **66a**, is useful in treating advanced breast cancer in postmenopausal women. The major disadvantage in the synthesis of **66a** by the original process disclosed in U.S. 4,935,437, is the formation of the regioisomer **62** that is an impurity and difficult to remove. The current patent actually shows the formula of **62** as being the same as **66a** which is not only initially confusing, but such errors should not be found in a legal document.

Impurity



An alternative route to **66a** is also reported in the original patent in which **64** reacts with **63**, forming the triazolium salt **65**. The conversion of **65** to **66a** is by diazotisation of **65** followed by a complex neutralisation, hydrolysis, and extraction procedure involving NH_4OH, concd HCl, PhMe, EtOAc, and cyclohexane. The synthetic route is outlined in Scheme 25, and for details of the workup the reader is referred to the patent.

Scheme 25.[a]



[a]Reagents and conditions: (a) See U.S. 4,935,437; (b) (i) concd HCl, $NaNO_2$; (ii) quench with urea/H_2O; (iii) see current patent for details.

This patent discloses that when using this route two new impurities have been identified; the amides **66b** (R_1 = CN, R_2 = $CONH_2$) and **66c** (R_1 = R_2 = $CONH_2$). They are formed by hydrolysis of the CN groups during the synthesis of **66a**. Using the method in Scheme 25 the crude **66a** is recovered as 98% pure by HPLC containing 0.36% of **66b** and 0.05% **66c**. These amide compounds were identified by NMR and MS, and both ^{13}C and ^{1}H NMR data are presented for them. The claims of the patent cover a process for the removal of these newly identified impurities that are present at levels of 0.02 to 1% in **66a**. They are removed by dissolving the crude solid in Pr^iOH at 45−50 °C cooling to <35 °C and adding cyclohexane. The purified **66a** is recovered in 69.7% yield and contains 0.09% of **66b** and no detectable **66c**.

Advantages

The process produces the desired drug molecule with extremely low levels of impurities.

PATENT NO. U.S. 8,058,484

Assignee: Syntroleum Corporation, Tulsa, Oklahoma, United States

Title or Subject: Flexible Glycerol Conversion Process

This patent describes a process for conversion of glycerol that has been recovered from the manufacture of biodiesel. The production of glycerol as a valuable byproduct drove the early development of biodiesel processes, but as more biodiesel was produced the price of glycerol fell dramatically. This fall in the price plus the high cost of recovering high-quality glycerol necessitated the development of alternative markets and uses for the glycerol in order to make biodiesel production economically attractive. The aim of this patent is to provide a process for converting glycerol into a propane-based synthetic fuel. The patent reports on the successful demonstration of a pilot plant to convert glycerol to propane synfuel by a catalytic hydrogenation/dehydration reaction. The process uses a Ni/W catalyst described as having a high macroporous texture, and this is held in a tubular trickle-bed reactor while the glycerol is passed over the catalysts. The reaction is carried out under H_2 at high pressure (>1000 bar) and 343 °C. The pilot plant uses 98% pure glycerol and 80 cm^3 of catalyst giving a 55% yield of propane. The major product in mass terms is H_2O which comprises 44.8% of the total product. The patent also reports on the effect of the metal content and surface texture of the catalyst. A finding that should not be surprising is that changing the metal content affects the conversion and yield as does the catalyst pore size. This patent does show that pure glycerol can be converted to propane by this method. However, glycerol produced in biodiesel processes is certainly not a clear colourless liquid, and this reviewer would expect it to have a detrimental effect on catalyst performance. Hence, the economics of converting glycerol to propane by such methods are unlikely to be attractive. Even if the glycerol is assumed to have zero cost, the reaction is an expensive way of converting 3 mol of H_2 to 3 mol of H_2O under extreme conditions and producing propane as a byproduct.

Advantages

The process produce propane from glycerol under extreme conditions and so does not have obvious advantages.

PATENT NO. U.S. 8,063,206

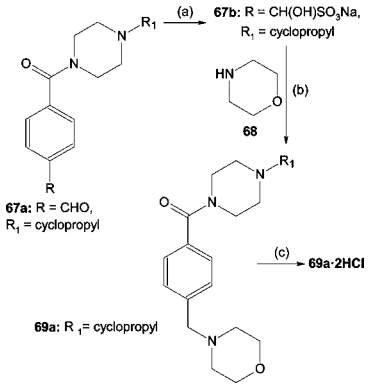
Assignee: Janssen Pharmaceutica NV, Beerse, Belgium

Title or Subject: Processes for the Preparation of Cyclopropylamide Derivatives

dx.doi.org/10.1021/op300022v | Org. Process Res. Dev. 2012, 16, 376−388

The compounds of interest in this patent are said to be useful in the treatment of allergies and a range of other ailments. The patent contains a substantial amount of detail and around 30 examples for the preparation of a number of compounds but the claims specifically cover the preparation of cyclopropyl derivative **69a** by the route outlined in Scheme 26. In the first step the aldehyde **67a** is converted to its bisulphite **67b** that is isolated but yield and purity are not reported. The next stage involves a reductive amination of **67b** with **68** in the presence of $NaBH(OAc)_3$ producing **69a**. This is obtained as a viscous yellow oil and converted to the salt **69a·HCl** as a solid but again no yield or purity data are provided. The preparation of the cyclobutyl analogue of **69a** is said to be made by the same process but there are no details. There are however a series of examples covering the preparation of the Pr^i analogue of **69a** and the various intermediates used in the synthesis.

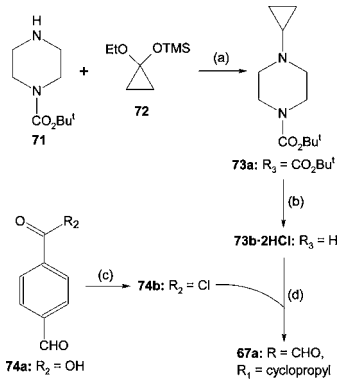
Scheme 26.[a]



[a]Reagents and conditions: (a) (i) $NaHSO_3$, H_2O, MeCN, 50 °C; (ii) cool to 5 °C, filter; (b) (i) DCE, rt, 5 min; (ii)add $NaBH(OAc)_3$ over 1 h, 10 °C; (iii) 10 °C, 2 h; (iv) 20 °C, 18 h; (v) add ice, 20 °C, 20 min; (vi) aq NaOH to pH 10, 10 min; (vii) separate, wash in 1 M NaOH, extract in DCM; (viii) evaporate.

The preparation of the intermediate **67a** is outlined in Scheme 27. The piperazine ester **71** is alkylated using the silane **72** in the presence of $NaBH_3CN$ and HOAc to give **73a** that is isolated as a solid. In the next step the protecting ester group is removed to give the HCl salt of **73b** that is also isolated as a solid but no yield or purity are reported for either **73a** or **73b**. In the next step **73b** is reacted with the benzoyl chloride **74b** to give the desired product **67a**. This is recovered as an oil but again no yield or purity details are reported. The preparation of **74b** is by chlorination of the acid **74a** and DMF/$SOCl_2$, and the product is isolated as a solution in PhMe that can be used directly. Examples are also given for preparing **74b** using DMF/$(COCl)_2$ or the Vilsmeier reagent $Me_2NCHCl^+Cl^-$ but since yield and purity details are given it is not known which method is preferred.

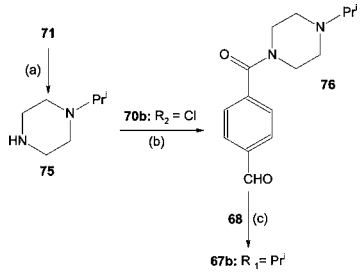
Scheme 27.[a]



[a]Reagents and conditions: (a) $NaBH_3CN$, HOAc, MeOH, 60 °C, 5 h; (ii) cool to rt, add, H_2O, 1 M NaOH, 0.25 h; (iii) concentrate, extract in DCM; (iii) wash, dry evaporate; (b) (i) HCl/dioxane, <40 °C, 10 min; (ii) 45 °C, 9 h; (iii) cool to rt, add hexane; (iv) cool 10 °C, filter, wash, dry; (c) (i) $SOCl_2$, PhMe, 60 °C, 2 h; (Iii) cool 5 °C; (d) (i) NaOH, H_2O, PhMe, <10 °C; (ii) rt, 16 h; (iii) 1 M NaOH to pH 10, separate; (iv) extract in PhMe, wash, dry, evaporate.

As mentioned above the patent also describes the preparation of the Pr^i compound **69b** (R_1 = Pr^i) using the same route as for **69a**. There is also an alternative synthesis of **69b** that is described and this is outlined in Scheme 28. This starts with the preparation of the Pr^i derivative **75** by alkylation of **71** in the presence of $NaBH(OAc)_3$ and HOAc. The product is recovered as a bis HCl salt and it is the free amine **75** that is used in the next step although the patent does not give details of how the salt is neutralised. The piperazine **75** is then reacted with **70b** in the presence of base to give **76**. The base is either aq $NaHCO_3$ or aq NaOH. No yield or purity details are given so it is not possible to compare the effectiveness of the two bases. Using $NaHCO_3$ the product is isolated as an oil whereas using NaOH the product is isolated as a solution in THF. Reaction of **76** with **68** in the presence of $NaBH(OAc)_3$ produces **67b** (R_1 = Pr^i) that is used without further treatment. The patent describes the preparation of various salts of **67b** including monosuccinate, monofumarate, bis-maleate, bis HBr and bis HCl salts from the appropriate acids but no yield details are given for any of them although the patent does provide elemental analysis.

Scheme 28.[a]



[a]Reagents and conditions: (a) (i) Me_2CO, $NaBH(OAc)_3$, HOAc, DCM, rt, 18 h; (ii) add 1 M NaOH, extract in DCM, dry, evaporate; (iii) HCl/dioxane, MeOH, rt, 18 h; (iv) evaporate, wash in Et_2O, dry; (b) (i) Et_3N, DCM, 0 °C, 1.5 h; (ii) rt, 2 h; (iii) filter, 0 °C; (iv) wash in H_2O, 0.5 M NaOH, brine, dry, evaporate; (v) add Et_2O, evaporate; (c) (i) THF, $NaBH(OAc)_3$, rt, 16 h; (ii) evaporate, add EtOAc, cool 0 °C; (iii) add 1 M NaOH, 0 °C, 0.5 h; (iv) separate, extract in DCM, wash, dry evaporate.

The patent provides a tabulation of a number of examples of the reductive amination of aldehyde bisulphite compounds with several amines. Bisulphites of the aromatic and cycloaliphatic aldehydes are included with the amines **68**, piperidine, pyrrolidine and $PhCH_2NHMe$ although details of yields and purities are not included.

Advantages

This interesting process is applicable to a very wide range of compounds although its efficiency and possible commercial

dx.doi.org/10.1021/op300022v | Org. Process Res. Dev. 2012, 16, 376−388

usefulness is not known. However, the frequent use of DCM as solvent is unacceptable in many places.

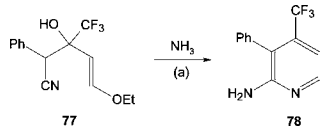
PATENT NO. U.S. 8,063,226

Assignee: Archimica GmbH, Frankfurt am Main, Germany

Title or Subject: Process for Preparing 2-Amino-4-(Haloalkyl)Pyridine Derivatives by Cyclisation of Nitriles and Nitrogen Compounds

Pyridine compounds are structural molecules in many chemical and pharmaceutical products. It is stated in the patent that methods for the preparation of 2-amino pyridines are not suitable for a commercial scale because of the need to use expensive reagents. This is especially the case when additional substituents are required. A particular example of a compound covered by this patent is **78** and it is prepared by a cyclisation reaction of the nitrile **77** that is heated with aq NH_3 in an autoclave. The reaction is shown in Scheme 29 using

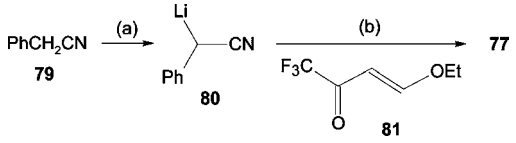
Scheme 29.[a]



[a]Reagents and conditions: (a) (i) H_2O, autoclave, 125 °C, 24 h; (ii) cool, extract in DCM, evaporate; (iii) recrystallise from cyclohexane.

crude **77**, prepared as shown in Scheme 30, and **78** is isolated after recrystallisation in 52% yield (purity not given).

Scheme 30.[a]

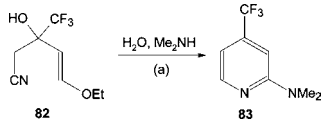


[a]Reagents and conditions: (a) BuLi, Pr^i_2NH, THF, −72 °C, 3 h; (b) (i) THF, −72 °C, 1 h; (ii) aq H_2SO_4, 0 °C; (iii) extract in PhMe, dry, evaporate.

The nitrile **77** is obtained by the one-pot process route outlined in Scheme 30 and begins with the lithiation of the nitrile **79** using LDA to form **80**. The solution of **80** is mixed with **81** to produce **77** that is recovered in 90% yield in crude form and used directly to produce **78**. The butenone **81** is prepared by a method reported in the literature (*Chem. Ber.* **1989**, *122*, 1179).

The patent also reports the use of **81** to prepare **82** from $LiCH_2CN$ and this is then used in the preparation of **83** by reaction with aq Me_2NH and the product is isolated in 62% yield as shown in Scheme 31.

Scheme 31.[a]



[a]Reagents and conditions: (a) see Scheme 29.

Advantages

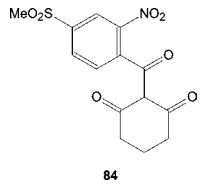
The process does not use expensive reagents and claimed to be technically simple to perform.

PATENT NO. U.S. 8,063,253

Assignee: Syngenta Crop Protection Inc., Greensboro, North Carolina, U.S.A.

Title or Subject: Process for the Crystallisation of Mesotrione

Mesotrione **84**, is a selective broad-leaf herbicide used to control weeds in grassed areas such as lawns, golf courses or sport fields. It is reported that two polymorphs of **84** have been discovered with the Form I being the thermodynamic polymorph and hence the desired form. The second is a metastable form, designated Form II, and has crystals that are noticeably smaller than crystals of Form I. Form II crystals are readily formed during crystallisation of **84** from aqueous solution and because the crystals are very fine it is difficult to recover them so that production time is increased and product is lost. Form II crystals can be avoided if organic solvents are used but this generates waste streams that can be difficult to treat. The patent describes a process for controlling the production of Form II crystals that also allows conversion to Form II to Form I crystals. The method involves a semicontinuous process which is said to maintain a higher level of Form I crystals than using a batch crystallisation process. In a batch crystallisation the level of Form II crystals can be reduced if a solvent such as MeCN is added but this is not required when a semicontinuous or continuous process is followed. A slurry of **84** crystals in aq NaOH is fed to a vessel which is maintained at pH of 2.5 to 4 by addition of HCl. A separate slurry of seed crystals of Form I is then added to the crystallisation vessel. A constant feed of crystals in aq NaOH is fed to the vessel until a maximum level is reached and then some crystal slurry is removed. More slurry is then added and the cycle repeated. In this way the recovered crystals were found to be Form I. A continuous process is also described.



Mesotrione

Advantages

The process gives the desired polymorphic form without the need to use organic solvents.

PATENT NO. U.S. 8,067,594

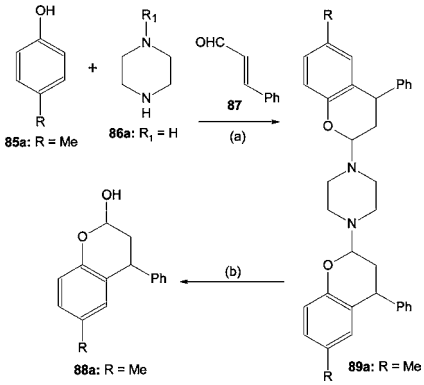
Assignee: Pfizer Inc., New York, New York, United States

Title or Subject: Process for the Production of Benzopyran-2-ol Derivatives

The patent describes a process for preparing **88a** (R = Me) that is an intermediate in the production of tolterodine **90a** and the fumarate salt fesoterodine **93·FA**. Both of these compounds are useful in treating bladder problems. A patent covering the synthesis of **90a** has been reviewed previously (*Org. Process Res. Dev.* **2009**, *13*, 11). Alternative methods of making **88a** are summarised, and the improvement claimed in the current patent is a one-pot synthesis starting from readily available *p*-cresol **85a**. The reaction is shown in Scheme 32 and is carried out by initially refluxing **85a**, **86a**, and **87** with removal of H_2O producing the novel intermediate **89a** (R = Me). This compound can be isolated and is the subject of one of the claims of the patent. No yield or purity data are provided, and

dx.doi.org/10.1021/op300022v | *Org. Process Res. Dev.* 2012, 16, 376−388

Scheme 32.[a]

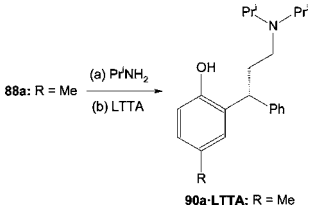


[a]Reagents and conditions: (a) (i) piperazine, PhMe, reflux, 0.5 h; (ii) reflux, 6 h; (iii) cool to 80 °C; (b) (i) add 0.67 M HCl; (ii) stir, 80 °C, 12 h; (iii) cool to rt, separate; (iv) wash in 1 M HCl then H_2O.

the only information is its mp of 241 °C and the report that ^1H and ^{13}C NMR confirm the structure. Subsequent reaction of **89a** with aq HCl produces **88a** that is isolated as a solution in PhMe.

The solution of **88a** in PhMe is used to prepare **90a** as shown in Scheme 33, and the first step is treatment of the PhMe

Scheme 33.[a]

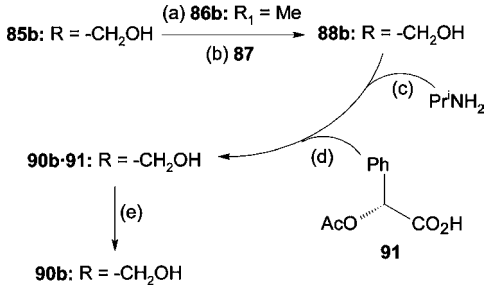


[a]Reagents and conditions: (a) (i) MeOH, Pr^iNH_2, rt; (ii) 10 wt % $Pd(OH)_2/C$, 6.21 bar H_2, 110 °C, 48 h; (iii) filter, distill off Pr^iNH_2 and MeOH, add PhMe; (b) (i) cool to 25 °C, add Me_2CO; (ii) LTTA, MeOH, 60 °C, 0.5 h; (iii) cool to rt, 12 h; (iv) filter, wash, dry.

solution of **88a** with MeOH and Pr^iNH_2. This mixture is then hydrogenated over $Pd(OH)_2/C$ catalyst to give **90a**. After removing the volatiles by distillation, the mixture is treated with *l*-tartaric acid (LTTA) and the salt **90a·LTTA** is finally isolated in 24% yield based on **85a** with achiral purity of 100% and 91.4% ee. The patent also describes the preparation of the racemic HCl salt of **90a**.

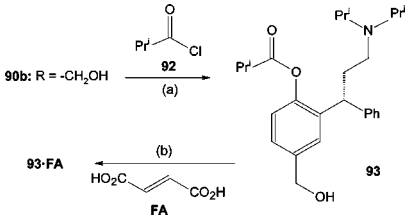
The patent reports the preparation of a number of related compounds to **90a** starting from analogues of **85a** and **86a**. An example is the fumarate salt of **93** that is prepared by the route shown in Schemes 34 and 35. The first stage is the preparation of **88b** (R = CH_2OH) by reaction of **85b** (R = CH_2OH) with **86b** (R_1 = Me) and **87**. This reaction is carried out on a kilo scale, and the product **88b** is recovered in 53.4% yield, then used directly in the next step. In this reaction **88b** undergoes reductive amination to give racemic **90b** (R = CH_2OH) in 89% yield that is isolated as a solution in *tert*-amyl alcohol (Am^tOH). The solution of racemic **90b** is resolved using **91**, and the pure *R*-enantiomer **90b** salt of **91** is obtained in 37.8% yield. Treatment of this salt with K_2CO_3 provides free **90b** that is isolated in 66.7% yield and 99% purity after crystallisation from PhMe.

Scheme 34.[a]



[a]Reagents and conditions: (a) and (b) see Scheme 32, (c) see step (a) in Scheme 33;(d) (i) Am^tOH, 70 °C, 1 h; (ii) seed, cool; (e) K_2CO_3, PhMe, 50 °C, 0.5 h.

Scheme 35.[a]

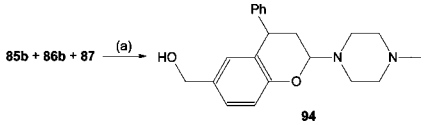


[a]Reagents and conditions: (a) and (b) see U.S. 6,858,650.

The next stages are shown in Scheme 35 and begin with the esterification of the phenol group in **90b** using **92** in the presence of Et_3N. This produces **93** that is treated with fumaric acid (FA) to give the salt **93·FA**. Details are not provided, and these reactions are carried using out a method described in U.S. 6,858,650.

Also described in the patent is the novel compound **94** that is obtained as a mixture of diastereoisomers and impurities as a dark oil from the reaction between **85b**, **86b**, and **87** (Scheme 36). ^1H NMR data are reported, but the purified

Scheme 36.[a]



[a]Reagents and conditions: (a) (i) reflux, 12 h; (ii) evaporate.

material is not isolated despite this compound being covered by one of the patent claims. The analogous novel compound from **85a**, **86b**, and **87** is also covered by the patent claims.

Advantages

The patent reports an improved process for preparing two useful drugs and also some novel intermediates.

■ PATENT NO. U.S. 8,067,617

Assignee: Boehringer Ingelheim International GmbH, Ingelheim am Rhein, Germany

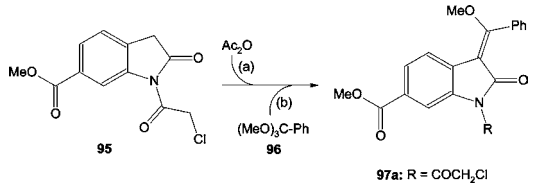
Title or Subject: Indolinone Derivatives and Process for Their Manufacture

The compounds covered by this patent, such as **97a** (R = $COCH_2Cl$), are novel intermediates for the preparation of drugs used to inhibit cell proliferation. The patent describes a process to prepare **97a** and also contains claims about the novel

dx.doi.org/10.1021/op300022v | Org. Process Res. Dev. 2012, 16, 376−388

compound itself. The process is shown in Scheme 37, and the reaction is carried out by refluxing a solution of **95** with Ac_2O

Scheme 37.[a]

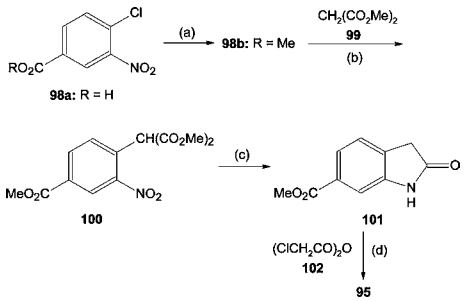


[a]Reagents and conditions: (a) PhMe, reflux 1 h; (b) (i) reflux 3 h; (ii) cool to 5 °C, stir 1 h; (iii) filter, wash in PhMe, wash in EtOAc, dry.

before adding **96** and distilling off volatile reaction products. After workup, **97a** is isolated as yellow crystals in yields up to 91.7%. The full elemental analysis indicates the product is of high purity, and ^1H and ^{13}C NMR data are provided.

The patent also describes the preparation of **95**, and this is outlined in Scheme 38. The method starts with esterification of

Scheme 38.[a]

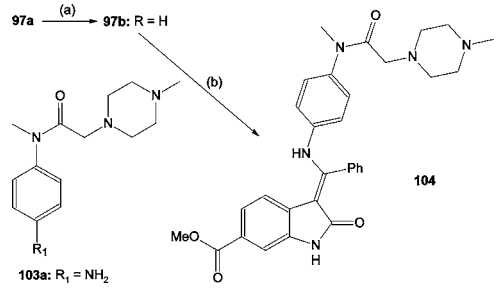


[a]Reagents and conditions: (a) (i) $SOCl_2$, MeOH, reflux 3 h; (ii) cool, centrifuge, dry; (b) (i) Na *tert*-amylate, NMP, 75 °C, 1.5 h; (ii) cool to 20 °C, add dil HCl to pH 1; (iii) stir, 5 °C, 1.5 h; (iv) centrifuge, dry; (c) (i) Pd/C, HOAc, H_2, 3 bar, 115 °C, 2 h; (ii) filter, add H_2O, 50 °C, (iii) cool 5 °C, centrifuge, dry; (d) (i) PhMe, reflux 3 h; (ii) cool to 80 °C, add Me-cyclohexane; (iii) cool to rt, filter, wash in MeOH, dry.

98a to form **98b** that is isolated in 88.8% yield with 99.8% purity (HPLC). The ester is then treated with **99** in the presence of the strong base Na *tert*-amylate to form **100** that is obtained in 95.4% yield and 99.9% purity (HPLC). This is then hydrogenated over a Pd/C catalyst to effect the cyclisation, and **101** is obtained in 87.2% yield and 99.8% purity (HPLC). In the last step **101** is reacted with **102** to produce **95** that is isolated in 93.5% yield. ^1H and ^{13}C NMR data plus full elemental analysis of the product are provided. The experiments describing the first three steps shown in Scheme 38 for the preparation of **101** are all carried out on a multikilo scale, thus indicating that this part of the process is suitable for commercial operation. Alternative published methods for preparing **101** are also referred to in the patent, but the current method claims to be better than these.

The patent also describes the use of **97a** in the preparation of **104** as shown in Scheme 39. First, **97a** is converted to **97b** (R = H) by treatment with base, and the product is recovered in 94.6% yield and then reacted with **103a** to give **104** that is isolated in 88.1% yield. Although the purity of **97b** and **104** are

Scheme 39.[a]

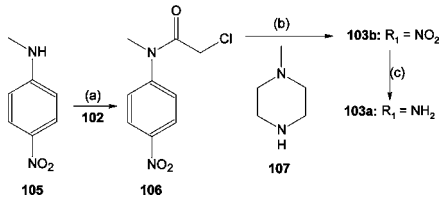


[a]Reagents and conditions: (a) (i) KOH, MeOH, 63 °C, 0.5 h; (ii) 0 °C, 2 h; (iii) filter, wash, dry; (b) (i) DMF, MeOH, reflux, 7 h; (ii) 0 °C, 2 h; (iii) filter, wash, dry.

not reported, there are full elemental analysis and NMR data for each compound.

The preparation of **103a** is also described in the patent and outlined in Scheme 40. The first stage is the reaction of **105**

Scheme 40.[a]



[a]Reagents and conditions: (a) (i) EtOAc, reflux, 1 h; (ii) cool to 60 °C, add Me-cyclohexane; (iii) 0 °C, 1 h; (iv) filter, wash, dry; (b) (i) PhMe, 55 °C, 2 h; (ii) cool to rt, H_2O wash; (c) (i) add Pr^iOH, Pd/C, H_2, 4 bar, 20 °C; (ii) filter, concentrate; (iii) add EtOAc/PhMe, heat to 80 °C; (iv) cool to 55 °C, seed; (v) cool to 0 °C, 3 h; (vi) filter, wash in PhMe, 0 °C, dry.

with **102** to give **106** that is recovered in 92.7% yield and then is condensed with **107** to form **103b**. This is not isolated from the reaction mixture that is washed with H_2O and then diluted with Pr^iOH. Then the mixture is subjected to hydrogenation with a Pd/C catalyst to give **103a** that is isolated in 88% yield. The purities of **103a** and **106** are not reported although full elemental analysis and NMR data are provided.

Advantages

The patent describes an efficient process that gives novel compound intermediates that are useful in the synthesis of antitumour drugs.

Keith Turner

Kappa Tau Consulting, 12 The Avenue, Fairfield, Stockton-on-Tees TS19 7EY, U.K.

AUTHOR INFORMATION

Corresponding Author

Telephone/fax: +44 (0)1642 653484. E-mail: keith@kappa-tau.co.uk.