Organic Process Research & Development

Highlights from the Patents

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A Review of U.S. Patents in the Field of Organic Process Development Published during January and February 2015

SUMMARY

The current review covers 16 patents from an original list containing 256 patents, and it is hoped that readers will find the wide range of topics to be of some interest. Patents are generally very selective in referring to previous work, and two patents on the synthesis of the mild antidepressant duloxetine provide good examples of this. Both patents ignore an earlier patent that uses the same starting reagent, which often contains a regioisomeric impurity that also takes part in the reaction, forming a byproduct that is difficult to remove. Reducing hazards and handling problems are often cited as reasons for developing processes. One patent refers to an earlier process involving a Friedel–Crafts reaction as having handling and disposal problems. The patent then describes the new process, which also involves a Friedel–Crafts reaction, and ignores the subsequent handling problems. The perception of what is a hazardous or difficult reagent to handle is invariably related to the experience of an individual or a company. One patent comments that using BuLi is hazardous because it is pyrophoric and then proceeds to describe a process that involves adding PhMe to a reaction mixture that is already at the boiling point of the solvent. A number of the patents in this collection describe experiments carried out on a kilo or multikilo scale, thus suggesting an advanced stage of development or even commercial operation. 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.

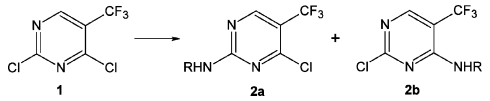
PATENT NO. U.S. 8,933,227

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

Title or Subject: Selective Synthesis of Functionalized Pyrimidines

The title compounds are said to be useful intermediates in the synthesis of pharmacologically active compounds. The patent is concerned with the selective nucleophilic substitution of pyrimidines such as **1** that can give the regioisomers **2a** and **2b**, where R is an aromatic group, as shown in Scheme 1. The

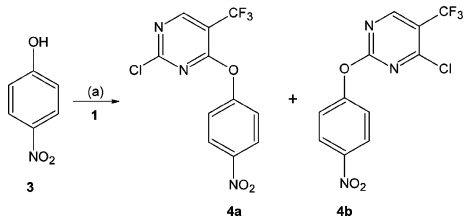
Scheme 1



desired isomer is compound **2a**, and the patent states that there are few reports of the selective synthesis of this type of compound from pyrimidines such as **1**. One example that uses $ZnCl_2$ is reported in WO 2005/023780, but using such Lewis acids is said to be inconvenient and not always feasible.

The objective of selectively forming a 2-amino-substituted pyrimidine from **1** has been achieved by a series of steps that begins by introducing a phenoxy group, containing an electron-withdrawing functional group, at the 4-position in **1**. Scheme 2

Scheme 2[a]

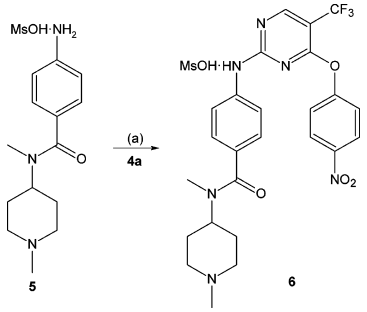


[a]Reagents and conditions: (a) (i) Bu^tOK, Pr^iOH, −15 °C, 0.5 h; (ii) rt, 16 h; (iii) reflux, add H_2O; (iv) cool to rt, 48 h; (v) filter, wash in H_2O/Pr^iOH, dry; (vi) recrystallize from $EtOH/H_2O$.

shows the method used to prepare **4a** by reaction of **1** with **3** in the presence of a strong base. This reaction forms a mixture of the desired isomer **4a** and **4b** with a selectivity of up to 87%. The desired isomer is isolated in 75% yield by recrystallization from $EtOH/H_2O$. The selective preparation of regioisomer **4b** by the reaction of **1** and **3** in the presence of *N*-methylmorpholine is also described in the patent, and the product is isolated in 90% yield after purification by column chromatography (ColC).

In the next step, compound **4a** is reacted with an amine, and Scheme 3 shows the preparation of **6** by reaction of **4a** with the MsOH salt of **5** in the presence of MsOH and Me_3SiCl as a water scavenger. The crude product is recovered as an oil and after purification is isolated in 62% yield as the MsOH salt. The patent also describes the preparation of analogues of **6** using other aromatic amines.

Scheme 3[a]



[a]Reagents and conditions: (a) (i) Me_3SiCl, MsOH, NMP, 60 °C, 39 h; (ii) add DCM/H_2O, separate; (iii) H_2O wash, wash in aq NaOH, brine wash; (iv) dry, evaporate.

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The patent states that the 4-nitrophenoxy group in **6** can be replaced by an amino, alkoxy, or thio substituent, but there are no specific examples.

Advantages. The process provides an indirect but more selective route to the desired regioisomers than alternative processes.

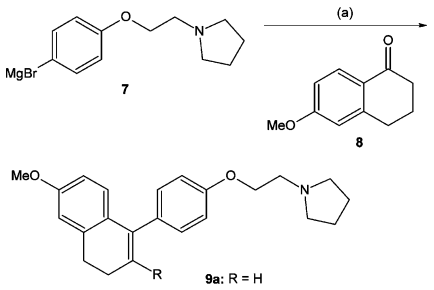
PATENT NO. U.S. 8,937,188

Assignee: Glenmark Generics Ltd., Mumbai, India

Title or Subject: Process for the Preparation of Lasofoxifene Tartrate

The title compound, **11**, is available as Fablyn for the treatment of osteoporosis in postmenopausal women. This patent describes a method for preparing **11** via a specific solid crystalline form of compound **9a** that is a key intermediate in the synthesis of **11**. The isolation of **11** as an oil is reported in U.S. Patent 5,948,809, whereas the current patent discloses the preparation of the compound as a crystalline solid, although the basis of the main claim of the patent is the preparation of a specific crystalline form of **9a**. The synthesis of **9a** is shown in Scheme 4 and involves the reaction of tetralone **8** with

Scheme 4[a]



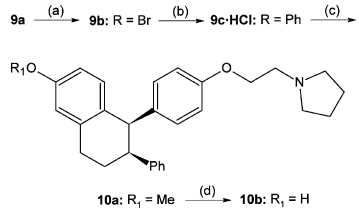
[a]Reagents and conditions: (a) (i) THF, rt, 16 h; (ii) add H_2O, filter; (iii) concentrate, add 2.5 M HCl to pH 2; (iv) wash in Pr^i_2O; (v) add 10% aq NaOH, extract in DCM; (vi) evaporate; (vii) add Pr^i_2O, rt, 5 h; (viii) filter.

Grignard **7**. The product is isolated as a light-brown solid in 59% yield. The purity is not reported, although ^{1}H NMR and FT-IR data are provided. X-ray diffraction (XRD) and differential scanning calorimetry (DSC) data for the compound are also provided.

As shown in Scheme 5, compound **9a** is then brominated using pyridinium bromide perbromide (PBPB) to form **9b**, which is recovered as an oil in 87.9% yield and 98% purity. Reaction of **9b** with $PhB(OH)_2$ in the presence of $Pd(PPh_3)_4$ and aq Na_2CO_3 gives a 95% yield of **9c**. This is converted to its HCl salt **9c·HCl**, which is isolated in 65.1% yield and 99% purity as a crystalline solid. This salt, known as nafoxidine hydrochloride, is hydrogenated using a Pd/C catalyst to produce the cis isomer **10a**, which is isolated in 49.9% yield and 95% purity. The reaction presumably forms a mixture of cis and trans isomers, but there is no mention of this in the patent. Treatment of **10a** with HBr gives **10b** in 82.7% yield and 95% purity.

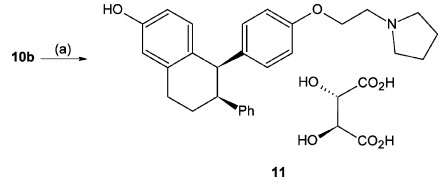
The formation of the tartrate salt **11** from **10b** and D-tartaric acid (DTTA) is shown in Scheme 6. The product is initially isolated with 95% purity, and after recrystallization from THF, THF/EtOH, MeOH, or EtOH/H_2O, it is recovered in up to 99.9% purity. XRD, DSC, thermogravimetric analysis (TGA),

Scheme 5[a]



[a]Reagents and conditions: (a) (i) PBPB, THF, rt, 60 h; (ii) concentrate, add H_2O + DCM, rt, 1 h; (iii) separate, wash in aq NaOH, brine wash, dry; (iv) concentrate. (b) (i) $PhB(OH)_2$, $Pd(PPh_3)_4$, aq Na_2CO_3, THF, reflux 18 h; (ii) separate, H_2O wash, brine wash, dry; (iii) concentrate; (iv) add DCM/EtOAc; (v) add HCl/Pr^i_2O, rt, 2 h; (vi) filter. (c) (i) Pd/C, EtOH/MeOH, H_2, 10 bar, 50 °C, 10 h; (ii) filter, evaporate. (d) (i) Aq HBr, reflux 5 h; (ii) rt, 16 h; (iii) add H_2O + DCM/MeOH; (iv) add aq $NaHCO_3$, rt; (v) separate, wash in DCM/MeOH; (vi) dry, concentrate.

Scheme 6[a]



[a]Reagents and conditions: (a) (i) DTTA, EtOH, H_2O, 50 °C; (ii) reflux 10 min; (iii) 25 °C, 20 h; (iv) filter, EtOH wash; (v) crystallize.

and IR traces for **11** are provided as well as a copy of a scanning electron microscopy (SEM) image.

Advantages. The process produces a crystalline product with high purity.

PATENT NO. U.S. 8,946,207

Assignee: Arena Pharmaceuticals Inc., San Diego, California, United States

Title or Subject: Process for Preparing 3-Benzazepines

The compounds of interest in this patent, such as **15**, are intermediates in the preparation of compounds for the treatment of obesity and central nervous disorders. The patent refers to several publications that describe routes to these compounds that typically involve the formation of an aryl compound containing an amine or amide chain that can cyclize to form the fused seven-membered ring of the benzazepine core of the molecule. Two routes to the desired compound are described, and the first is outlined in Scheme 7. This starts with the bromination of **12a** using PBr_3 to give **12b**, which is isolated in 95% yield as a clear oil with 96% purity. In the next step, **12b** is coupled with **13**, and **14a** is isolated as a colorless solid in 87% yield and 99% purity. Bromination of **14a** using $SOBr_2$ and a trace of DMF forms **14b**, which is recovered as a white powder in 63% yield and 97% purity. In the last step, **14b** is cyclized via an intramolecular Friedel–Crafts reaction by heating with $AlCl_3$, and crude **15** is recovered as a glutinous oil in quantitative yield. The *R* enantiomer of **15** is recovered as the L-tartaric acid (LTTA) salt by treatment with LTTA in *t*-BuOH. The salt is isolated in 53.3% yield with 98.7% ee. A microscale preparation of the HCl salt recovered the salt of ***R*-15** in 95% yield. The fate of the *S* enantiomer is not mentioned, although it is covered in the claims of the patent. The free

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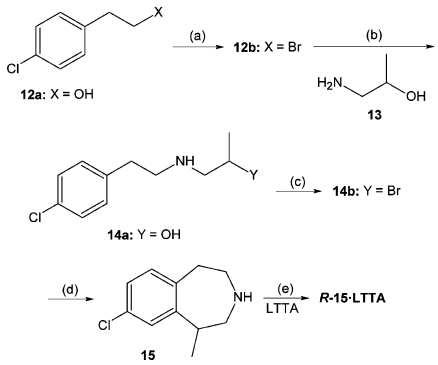
Scheme 7[a]

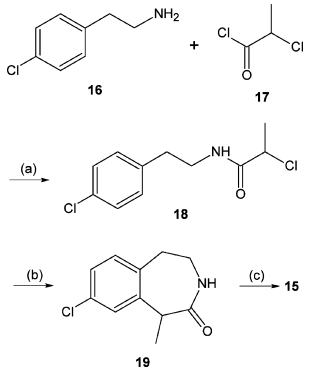


[a]Reagents and conditions: (a) (i) PBr_3, 0 °C; (ii) 95 °C, 2 h; (iii) add H_2O, 0 °C; (iv) extract in DCM, separate, dry, evaporate. (b) (i) 95 °C, 4 h; (ii) cool to rt, add H_2O; (iii) extract into MTBE, H_2O wash, evaporate. (c) (i) DMF, DCM, 0 °C; (ii) add $SOBr_2$; (iii) rt, 2 h; (iv) cool to 0 °C, filter, DCM wash, dry. (d) (i) $AlCl_3$, 1,2-$PhCl_2$, 140 °C, 12 h; (ii) cool to <30 °C; (iii) add to H_2O/30% aq NaOH/cyclohexane, <50 °C; (iv) separate, wash in HCl, H_2O wash; (v) add 30% aq NaOH; (vi) dry, evaporate. (e) (i) Aq LTTA, Bu^tOH, 20 °C, 16 h; (ii) filter, Me_2CO wash; (iii) Bu^tOH, reflux 1 h; (iv) cool <25 °C, 16 h; (v) filter, Me_2CO wash, dry.

amine **15** is obtained from the LTTA salt by treatment with aq NaOH.

An alternative synthesis of **15** is also described and is shown in Scheme 8. This involves a similar series of reactions as in the

Scheme 8[a]



[a]Reagents and conditions: (a) (i) Et_3N, MeCN, 0 °C, 20 min; (ii) 0 °C, 0.5 h; (iii) rt, 1 h; (iv) concentrate, add H_2O/EtOAc; (v) separate, brine wash (×2), dry, evaporate; (vi) add EtOAc/hexane, cool to 0 °C, filter. (b) (i) $AlCl_3$, 150 °C, 12 h; (ii) cool to rt, add MeOH; (iii) add 5% aq HCl + EtOAc; (iv) separate, dry, concentrate; (v) crystallize from hexane/EtOAc. (c) (i) BH_3·THF, rt, 10 h; (ii) add MeOH, evaporate; (iii) repeat step (ii).

first method and begins with the coupling of **16** and **17** in the presence of Et_3N to remove the HCl formed during the reaction. The reaction produces **18**, which is isolated in 85% yield and then heated with $AlCl_3$ to effect the cyclization and form **19**. The compound is recovered in 54% yield after recrystallization from hexane/EtOAc. Reduction of the amide is carried out using BH_3·THF with or without the addition of BF_3. Both methods give a 70% yield of **15**.

The patent describes the conversion of **18** to **14c** (Y = Cl), and this compound can be cyclized to give **15** by heating with $AlCl_3$. Compound **14c** can also be prepared by a procedure similar that used to prepare **14b** but with $SOCl_2$ in place of $SOBr_2$. ^1H NMR data are provided for all of the compounds shown in the schemes, and there are also ^{13}C NMR data for some of them.

Advantages. The process provides a route to the desired compounds but uses reagents that are difficult to handle such as PBr_3 and $SOBr_2$.

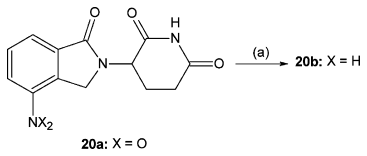
■ PATENT NO. U.S. 8,946,265

Assignee: Generics (UK) Ltd., Hertfordshire, United Kingdom

Title or Subject: Process for the Preparation of Lenalidomide

Although it is assigned to a UK-based company, the inventors named on this patent are all based in Maharashtra, India. The title compound, **20b**, is structurally similar to the notorious drug thalidomide and is under investigation in the treatment of various cancers. A patent covering an alternative synthesis has been reviewed recently (*Org. Process Res. Dev.* **2014**, *18*, 1270). A method for the synthesis of **20b** that is reported in the patents U.S. 5,635,517 and U.S. 6,281,230 is based on the hydrogenation of **20a** to **20b** as shown in Scheme 9. The yield for the reduction is only 36% using a Pd/C

Scheme 9[a]

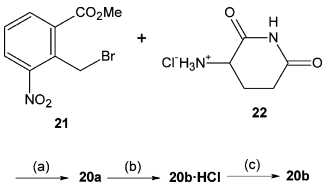


[a]Reagents and conditions: (a) Pd/C, H_2, dioxane.

catalyst, and the yield for the preparation of **20a** is only 55%. Hence, overall this is not an attractive route for commercial production. Other routes that are mentioned for preparing **20b** via **20a** are also described as uneconomical because they are hazardous, give low yields, and require large quantities of solvent in the hydrogenation step.

The route described in the current patent for preparing **20b** is outlined in Scheme 10, and like the earlier methods, it proceeds via the formation of **20a**, which is subsequently hydrogenated to give **20b**. The first step of the method is the coupling of **21** with HCl salt **22** to form **20a**. This reaction takes place in the presence of Et_3N in a mixed solvent system of

Scheme 10[a]



[a]Reagents and conditions: (a) (i) Et_3N, MeCNPr^iOH, 25−30 °C; (ii) 55 °C, 10 h; (iii) concentrate at 60 °C; (iv) H_2O, 60 °C, 1 h; (v) cool to <30 °C, filter; (vi) H_2O wash, 55 °C; (vii) cool to rt, filter; (viii) MeOH wash, 55 °C; (ix) cool to rt, filter; (x) dry, 55 °C. (b) (i) Pd/C, MeOH/MeCN, H_2, 1 atm, 35 °C, 1 h; (ii) add Pd/C, H_2, 1 atm, 35 °C, 1.5 h; (iii) filter, concentrate; (iv) add HCl/Pr^iOH, 50 °C; (v) cool to <10 °C, filter; (vi) MeOH wash, dry. (c) (i) Et_3N, MeOH, <10 °C; (ii) filter, MeOH, dry.

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around 1:1 MeCN/Pr^{i}OH. The product is isolated in 93% yield with 99.9 area % purity by HPLC. This is then hydrogenated using 5 wt % Pd/C catalyst. The product is initially isolated as the HCl salt, and upon treatment with Et_3N the free base is recovered in 78% yield with 99.5 area % purity. The material is further purified by reforming and decomposing the HCl salt, and the product is recovered in 93% yield and 99.9% purity.

Compound **20b** has been reported to exist in several forms, designated A to H in the patent U.S. 7,465,800, with form B being used in formulations of the drug. The present patent describes the preparation of form A, which is crystalline, anhydrous, and unsolvated and claimed to be the most thermodynamically stable anhydrous polymorphic form. The form A material is obtained from the solid prepared by the method shown in Scheme 10. The solid is stirred in a 1:1 EtOAc/MeOH mixture and then recovered by vacuum filtration and dried under vacuum. The patent provides XRD patterns and DSC and TGA traces for form A of the compound.

Advantages. The process provides a method of preparing the thermodynamically most stable polymorph of the drug molecule.

PATENT NO. U.S. 8,946,425

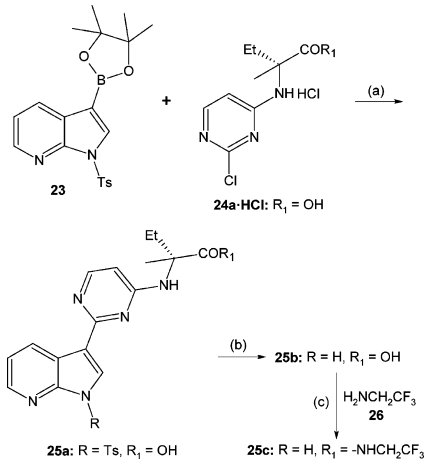
Assignee: Vertex Pharmaceuticals Inc., Boston, Massachusetts, United States

Title or Subject: Processes and Intermediates for Producing Azaindoles

The compounds of interest in this patent are described as kinase inhibitors, and a specific example is known as decernotinib (**25c**), which has been under phase III trials for the treatment of rheumatoid arthritis. The patent refers to the preparation of other kinase inhibitors in the patents WO 2005/095400 and WO 2007/084557 that are also assigned to Vertex. It is inferred that the processes in those two patents are not economical and therefore that an improved method of preparing the desired compounds is needed. The last stages of the synthesis of **25c** as described in the current patent are shown in Scheme 11. The workup for each of the reactions is quite lengthy, so only the main reagents are listed. The first step is the Pd-catalyzed cross-coupling of **23** (1.15 equiv) and the salt **24a·HCl** (1 equiv) to give **25a**. The catalyst contains a phosphine, and although the patent discusses a large number of phosphines, the example uses PPh_3. The reaction mixture also contains H_2O and a base. The reaction shows 86% conversion after 5 h, at which point additional portions of **24a·HCl** and catalyst are added, and after a further 12 h the conversion is 99.7%. The example in the patent is carried out on a kilo scale, but neither the yield nor the product purity are reported. In the next step, the Ts protection is removed from **25a** by treatment with KOH, and **25b** is recovered. This is also a kilo-scale reaction, producing 3.56 kg of **25b**, but the yield was not calculated. The product is reported as a mixture of the polymorphic forms B and E, although the relative amounts are not mentioned. XRD and DSC data plus ^{1}H NMR spectra for both forms are provided in the patent. In the final step, **25b** is reacted with amine **26** to form the amide **25c**, which is isolated in 94.8% yield and 98.6% purity and is identified as the polymorph form A. This reaction is carried out using the cyclic alkyltriphosphonate anhydride **27** (Scheme 12), also known as T3P, as a coupling reagent.

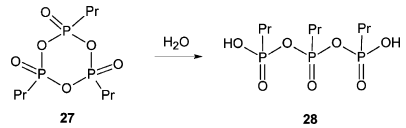
The use of the reagent T3P for the final reaction would seem to be a good choice because it is relatively cheap and has low toxicity. In addition, it is easily removed in the workup by washing with water, which converts it to the linear triphosphate **28** as shown in Scheme 12. Both of these compounds are very soluble in water and can be easily removed from the reaction mixture.

Scheme 11[a]



[a]Reagents and conditions: (a) (i) K_3PO_4, H_2O, MeCN, 30 °C, 0.5 h; (ii) add $Pd(OAc)_2/PPh_3$/MeCN, 65 °C; (iii) 75 °C, 5 h; (iv) add **24** + $Pd(OAc)_2/PPh_3$/MeCN, 75 °C, 12 h. (b) (i) KOH, H_2O, 75 °C, 5 h; (ii) add H_2O/Pr^{i}OAc, filter, separate; (iii) collect aqueous phase, add active C; (iv) add conc HCl to pH <1, 25 °C, 4 h; (v) filter, repeat active C treatment ×2; (vi) add 6 M NaOH to pH 4.5, 25 °C; (vii) cool <5 °C, 2 h; (viii) filter, H_2O wash, dry. (c) (i) Pr$^i_2$NEt, DCM, <30 °C; (ii) add trace H_2O, 30 °C, 0.5 h; (iii) cool to <5 °C, add T3P, 1 h; (iv) add **26**, 20 °C; (v) 25 °C, 5 h; (vi) add H_2O, 30 °C, 0.5 h; (vi) concentrate, add Pr^{i}OAc; (vii) add 6 M NaOH to pH 8, 35 °C; (viii) cool 10 °C, 1 h; (ix) filter, H_2O wash; (x) add MeOH + PL-BnSH MP-Resin, 25 °C, 12 h; (xi) filter, concentrate, <50 °C; (xii) rt, 60 h; (xiii) add H_2O, 45 °C; (xiv) remove MeOH, cool to 5 °C, 2 h; (xv) filter, H_2O wash, dry.

Scheme 12



The main claims of the patent actually cover the synthesis of compound **23**, which can be prepared by the two routes shown in Scheme 13. Both routes start from azaindole **29a** and proceed via compound **29d**, which can be prepared in two ways. One route to **29d** involves the formation of the tosylate **29b** followed by bromination using NBS, although there is no example describing this method. The example in the patent describes the kilo-scale preparation of **29d** via **29c**, which is formed by the reaction of **29a** with Br_2 and isolated in 89.6% yield with 99.1% purity. Compound **29d** is then formed by treatment of **29c** with portions of NaH followed by TsCl, and the product is isolated in 94% yield and 99.7% purity. Reaction of **29d** with B(OPr^i)$_3$ followed by BuLi forms the boronic acid **29e** in 69.4% isolated yield and 98.8% purity. In the final step, **29e** is reacted with diol **30** to give **23** in 80.8% yield and 99.7% purity.

The details of the preparation of compound **24a·HCl** are not actually described in the patent, and the method shown in

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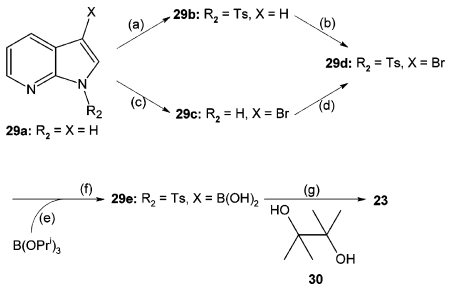
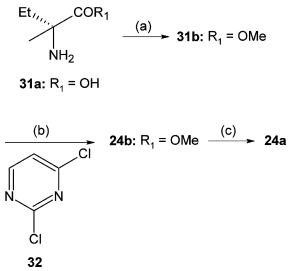
Scheme 13[a]



[a]Reagents and conditions: (a) and (b) No details. (c) (i) Br_2, DMF, <10 °C, 2.75 h; (ii) add 10% $NaHSO_3$, <15 °C; (iii) add aq $NaHCO_3$ to pH 8; (iv) filter, H_2O wash, wash in petroleum ether, dry. (d) NaH, THF, 10−15 °C, 1 h; (ii) TsCl, 10−20 °C, 4 h; (iii) <20 °C, 1.5 h; (iv) add H_2O, <20 °C; (v) add DCM + 3% HCl, <25 °C; (vi) separate, extract aqueous phase in DCM; (vii) combine organic phases, wash in 3% HCl, H_2O wash; (viii) filter, concentrate; (ix) add petroleum ether, filter; (x) wash in petroleum ether. (e) THF, rt. (f) (i) BuLi, −80 °C, 6−7 h; (ii) add H_2O, warm to 20 °C; (iii) concentrate, add H_2O + aq NaOH; (iv) filter, MTBE wash, add HCl to pH 4, 10−20 °C, 1 h; (v) centrifuge, H_2O wash, wash in petroleum ether, dry. (g) (i) DCM, <30 °C; (ii) filter, concentrate, <30 °C, 2 h; (iii) add Pr^iOH, reflux 0.5 h; (iv) cool to 35 °C: (v) cool to <10 °C, 2 h; (vi) filter, dry.

Scheme 14 is based on the preparation of racemic **24b**, for which there is an example. The patent also discusses the

Scheme 14[a]



[a]Reagents and conditions: (a) (i) MeOH, HCl/dioxane, 50 °C, 16 h; (ii) evaporate, rt. (b) (i) Et_3N, NMP, 80 °C, 18 h; (ii) add H_2O, extract in MTBE; (iii) H_2O wash, dry; (iv) evaporate. (c) (i) LiOH, H_2O, THF, reflux 18 h; (ii) cool to rt, add 1 M citric acid; (iii) wash in EtOAc (×3); (iv) filter, dry.

preparation of **24a·HCl** from D-isovaline (**31a**) and **32**, and the preferred method of preparing **24a·HCl** is not known. It is expected that it could be prepared by the route shown, which starts with esterification of the acid **31a** using HCl/dioxane. Reaction of the ester with **32** would then form **24b**, and hydrolysis using LiOH would produce **24a**. The racemic mixture of **24a** is used to prepare the racemic compounds **25a** to **25c** by the route shown in Scheme 11.

The patent describes the preparation of the ^{14}C-enriched analogue of **25c** as well as its ^{13}C,^{15}N-enriched analogue. The starting material for the former compound is ^{14}C-enriched urea, and that for the latter is ^{13}C,^{15}N-enriched uracil. Experimental details are described in the patent, and there are also details of the preparation of the deuterated analogue of **25c** in which five of the H atoms in the aromatic rings are replaced by deuterium atoms. This is carried out by treatment of **25c** with D_2O and a Pd/C catalyst.

Advantages. The process gives high yields of intermediates and the final product and is clearly suitable for large-scale production.

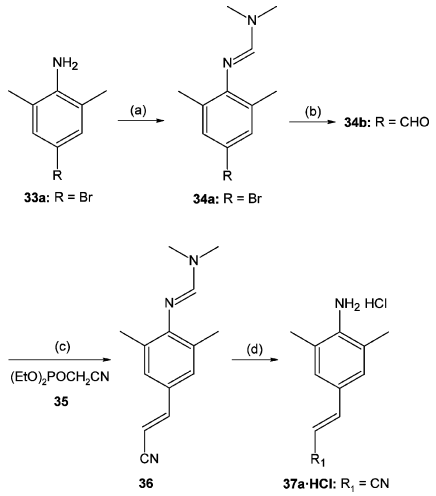
PATENT NO. U.S. 8,952,155

Assignee: Emcure Pharmaceuticals Limited, Pune, India

Title or Subject: Rilpivirine Process

The actual claims of this patent cover the synthesis of the *E* isomer of the HCl salt of **37a**, a key intermediate in the synthesis of the title compound, **42**, which is used as its HCl salt in the treatment of HIV. Alternative methods for the synthesis of **37a**, and hence **42**, are said to produce a material that can contain too high a proportion of the undesired *Z* isomer. Three methods of preparing **37a** are described in patent WO 2003/016306, and Scheme 15 shows one route that starts

Scheme 15[a]

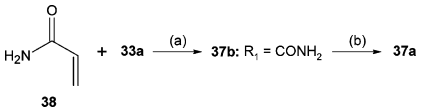


[a]Reagents and conditions: (a) No details. (b) BuLi, DMF. (c) No details. (d) $ZnCl_2$.

from **33a** in which the amine group is protected by conversion to **34a**, which is formylated using BuLi and DMF to give **34b**. The formyl derivative is then treated with phosphonate **35** to give **36**, which is treated with $ZnCl_2$ to remove the protective group, affording **37a**·HCl. The route is said to involve an elaborate synthetic sequence with a low yield in the formylation step, making it not viable for industrial production.

A second route to **37a** that is described in the same patent is shown in Scheme 16. This also starts from **33a**, which is reacted

Scheme 16[a]



[a]Reagents and conditions: (a) $Pd(OAc)_2$, (*o*-tolyl)$_3$P, $(H_2N)_2CHCH_3$. (b) $POCl_3$.

with acrylamide (**38**) in the presence of a Pd/phosphine catalyst to form amide **37b**. This is dehydrated using $POCl_3$, and **37a** is obtained in 67% yield.

The third route reported in WO 2003/016306, shown in Scheme 17, is a reaction between the iodo compound **33c** and acrylonitrile (**39**) in the presence of NaOAc and a Pd/C

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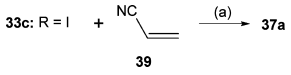
Scheme 17[a]



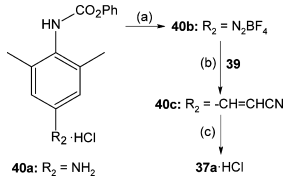
[a]Reagents and conditions: (a) NaOAc, Pd/C.

catalyst to give **37a** directly. Although the route avoids phosphine ligands, it requires a reaction time of 12 h at 130 °C, involves the use of multiple solvents, and gives only a moderate yield. In addition, the starting amine is not readily available on a commercial scale. The *E*/*Z* ratio of the final product is not reported in the above three routes, but the patent reports that when reproduced they gave values of 20–30% *Z* isomer.

Other routes to **37a** are also mentioned, and although some gave *E*/*Z* ratios as high as 90/10, they are also said to be unsuitable for commercial production. The drawbacks of the alternative routes include problems such as giving a high proportion of the *Z* isomer, using highly pyrophoric reagents such as BuLi or expensive and toxic phosphine ligands, or employing phase-transfer reagents such as Bu_4NBr in stoichiometric amounts. In addition, these routes require high temperatures of up to 150 °C. Therefore, an improved process for preparing **37a** and subsequently **42** is deemed to be necessary.

The route described in the current patent for the synthesis of **37a**·HCl is outlined in Scheme 18. It begins with diazotization

Scheme 18[a]



[a]Reagents and conditions: (a) (i) H_2O, HCl, $NaNO_2$, <15 °C; (ii) add aq $NaBF_4$, <15 °C; (iii) filter, dry. (b) (i) $Pd(OAc)_2$, MeOH, 30 °C; (ii) filter, concentrate. (c) (i) TFA, 30 °C; (ii) 45–60 °C; (iii) add H_2O + aq NH_3; (iv) extract in PhMe; (v) separate, concentrate; (vi) add Pr^iOH/Pr^i_2O, add HCl/Pr^iOH; (vii) filter, dry.

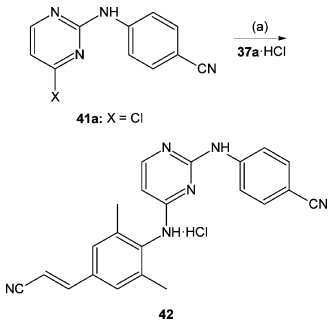
of **40a** to form the BF_4 salt **40b**, which is recovered in 91% yield as a dry solid that is reported to be stable. **40b** is then reacted with **39** in the presence of $Pd(OAc)_2$ to give **40c**, which is isolated in 97.8% yield and used directly in the next step, where it is treated with TFA followed by HCl to form **37a**·HCl, which is isolated in 80% yield based on **40b**. Interestingly, the patent does not disclose the *E*/*Z* ratio of the final product, although the claims state that the *Z* isomer is present at <0.5%. The patent does not mention reaction times for any of the reactions, but their completion is monitored by HPLC.

The synthesis of **42** is carried out by heating **37a**·HCl with **41**, as shown in Scheme 19. The HCl salt is isolated in 51.6% yield based on **41** and has <0.1% *Z* isomer.

The synthesis of **40a** is described in the patent and outlined in Scheme 20. The first step is the reaction of **43** with **44** to form **40d**, which is isolated in 88% yield. **40d** is then reduced to **40a** using $SnCl_2$ in MeOH, and the salt is isolated in 94% yield.

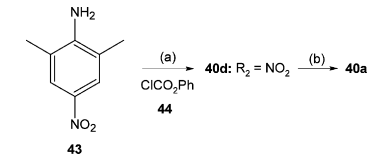
The patent also describes the preparation of the pyrimidine derivative **41a**, which is outlined in Scheme 21. This procedure starts with the coupling of alcohol **45** and aminonitrile **46** in the absence of any solvent to give **41b**. After the reaction is

Scheme 19[a]



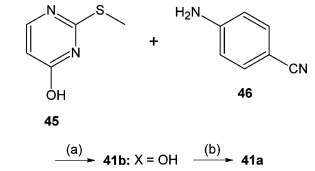
[a]Reagents and conditions: (a) (i) MeCN, 90 °C; (ii) cool to 40 °C, add aq Na_2CO_3 to pH 10; (iii) filter, <10 °C, dry; (iv) DMSO, 75 °C; (v) cool to <55 °C, add aq HCl; (vi) add H_2O, 45 °C; (vii) cool to <30 °C, filter, dry.

Scheme 20[a]



[a]Reagents and conditions: (a) (i) PhMe, 25 °C; (ii) reflux; (iii) filter at <15 °C, dry. (b) (i) $SnCl_2·2H_2O$, MeOH, 65 °C; (ii) add H_2O + 20% aq NaOH, 20 °C; (iii) extract in DCM, add aq HCl, <15 °C; (iv) filter, dry.

Scheme 21[a]



[a]Reagents and conditions: (a) (i) 125 °C; (ii) 185 °C; (iii) cool to 110 °C, add PhMe; (iv) cool to rt, filter, dry. (b) (i) PhMe, rt; (ii) add $POCl_3$, 50–70 °C; (iii) 70–75 °C; (iv) cool <20 °C, add H_2O + aq Na_2CO_3; (v) filter, < 20 °C, dry.

complete, PhMe is added to the reaction mixture at around 110 °C; since this is near the boiling point of PhMe, this step would seem to be somewhat hazardous, but this is not mentioned. The product is isolated as a solid and then chlorinated using $POCl_3$, affording **41a** in 83% isolated yield.

Advantages. The process gives a high *E*/*Z* ratio for the intermediate **37a**, which is then used to prepare the desired drug molecule with low levels of the undesired *Z* isomer.

■ PATENT NO. U.S. 8,957,204

Assignee: Lonza Ltd., Visp, Switzerland

Title or Subject: Process for the Synthesis of Cyclic Carbamates

The compounds of interest in this patent are described as intermediates in the synthesis of agrochemicals, pharmaceuticals, and compounds useful in materials science. The examples actually describe the use of propargyl alcohol **50** in the synthesis of **51**, which the patent calls DMP-266, also known as efavirenz, a drug used to treat HIV. A patent describing an alternative synthesis of **51** has recently been reviewed (*Org. Process Res. Dev.* **2014**, *18*, 1083). In the synthesis of

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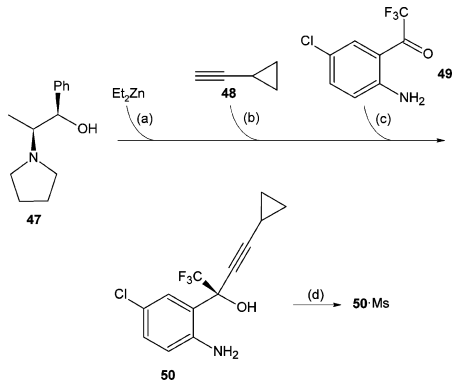
Org. Process Res. Dev. 2015, 19, 778–792

compounds such as **50**, large amounts of heavy-metal catalysts are often used. This makes it difficult, on an industrial scale, to achieve the low residual metal levels that are important in pharmaceutical products. An additional consideration is that intermediate **50** and the final product are both chiral molecules, so achieving high enantiomeric excess in their synthesis is very desirable. There is a literature report (*J. Org. Chem.* **2002**, *67*, 9449) that describes the synthesis of propargyl alcohols from acetylenes and aldehydes using equimolar amounts of Zn compounds, but this covers only racemic products. Large amounts of expensive Zn compounds are used to prepare chiral propargyl alcohols in processes disclosed in the patent WO 98/51676. The production of chiral propargyl alcohols is also disclosed in the patents WO 95/20389, WO 96/37457, WO 98/30453, and WO 98/30450. The objective of the current patent is to provide a process for preparing chiral propargyl alcohols with reduced amounts of catalysts and with high ee. Compound **50** is prepared by the route shown in Scheme 22,

Scheme 22[a]



[a]Reagents and conditions: (a) THF/PhMe, 17 °C, 0.5 h. (b) PhMe, 20 °C, 1 h. (c) (i) BuLi/PhMe, 20 °C, 3 h; (ii) 20 °C, 0.5 h; (iii) 30 °C, 6 h; (iv) 0 °C, 16 h; (v) add PhMe, 20 °C; (vi) add citric acid, 20 °C, 0.25 h; (vii) separate, H_2O wash, wash in aq $NaHCO_3$, H_2O wash; (viii) concentrate, add PhMe. (d) (i) Pr^iOH, add MsOH, 30 °C, 0.5 h; (ii) seed; (iii) 30 °C, 0.5 h; (iv) add MsOH at 30 °C over 1 h; (v) 30 °C, 0.5 h; (vi) cool to 5 °C over 1 h; (vii) 5 °C, 0.5 h; (viii) filter, wash in PhMe/Pr^iOH, 5 °C, dry.

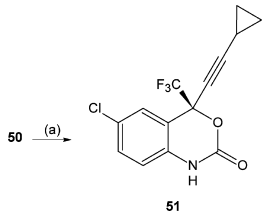
which starts by treatment of the chiral auxiliary **47** with an approximately equimolar amount of $ZnEt_2$ until all of the ethane has been released. The mixture is then treated with **48**, and additional ethane is released. A mixture of **49** and BuLi is then added, and the reaction is monitored by FTIR or calorimetric measurements. The quantity of **47** that is used is around 15−30% of the amount of **49**. After workup, compound **50** is isolated as a solution in PhMe with enantiomeric purity (ep) of 96−97%. This can be converted to the mesylate salt **50**·Ms, which is isolated in 86.5% yield with 99.9% purity and 99.7% ep.

The conversion of **50**·Ms to **51** is carried out by treatment with either diphosgene or triphosgene and Na_2CO_3, as shown in Scheme 23. In both cases the yields are as high as 94−95% with purities of up to 99.9% and ee of 99.6%.

The patent also describes the preparation of analogues of **50** and **51** in which the Cl group is replaced by Ph or Me.

Advantages. The process uses much less of the expensive alkylzinc compound and by using a chiral auxiliary produces an enantiomerically pure final product.

Scheme 23[a]



[a]Reagents and conditions: (a) (i) aq Na_2CO_3, EtOAc/heptanes, 15 °C, 5 min; (ii) separate; (iii) cool to 12 °C, add aq Na_2CO_3; (iv) add diphosgene, 12 °C, 1.5 h; (v) add heptanes, heat to 20 °C, 0.5 h; (vi) separate aqueous layer; (vii) distill EtOAc, add heptanes; (viii) heat to 55 °C, add seed; (ix) 55 °C, 0.25 h; (x) 50 °C, 2 h; (xi) cool to 25 °C over 2 h; (xii) cool to −10 °C over 2 h; (xiii) −13 °C, 1 h; (xiv) filter, wash in cold heptanes, 0 °C, dry.

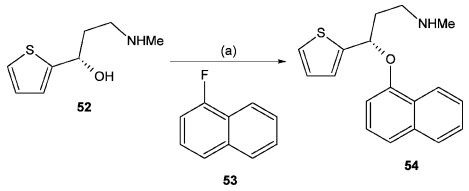
PATENT NO. U.S. 8,957,227

Assignee: SCI Pharmtech Inc., Taoyuan County, Taiwan

Title or Subject: Preparation of Duloxetine Hydrochloride Using Optically Active Methylhydroxylaminopropanol Compound as an Intermediate

This is the first of two patents covering processes for the preparation of intermediates used in the synthesis of duloxetine (**54**), a compound whose HCl salt is to treat mild depression. An early synthesis of **54** described in the patent U.S. 7,538,232 and shown in Scheme 24 is said to require a long workup

Scheme 24[a]



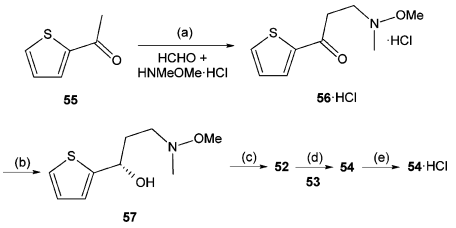
[a]Reagents and conditions: (a) KOH, DMSO, PhMe.

because of the mixed solvent system that is used. A similar method is also disclosed in the patent U.S. 8,362,279 and has been reviewed previously (*Org. Process Res. Dev.* **2013**, *17*, 736). This latter patent starts with resolution of the racemic dimethylamino analogue of **52**, and the *S* enantiomer is then used. The workup involves a subsequent demethylation step to obtain **54**, which is isolated as the HCl salt. No reference to this route is made in the current patent.

The synthesis of compound **52** is a key aspect of the current patent and is shown in Scheme 25. The route starts with the reaction of **55**, HCHO, and the HCl salt of HNMeOMe in an acidic solution of Pr^iOH. This gives **56**, which is isolated as the HCl salt in 75.9% yield. Asymmetric reduction of this salt using a chiral Ru phosphine catalyst produces alcohol **57** as an oily product in 95.8% purity and 95% ee. Hydrogenolysis using a Raney Ni catalyst forms **52**, which is isolated with 90.8% purity and 95% ee and then recrystallized from PhMe. The product is obtained with almost 100% ee, but the final yield is not reported. The preparation of **54** from **52** and **53** is carried out in DMSO in the presence of $KOBu^t$. The free base is initially recovered as an oil and then converted to the HCl salt by treatment with AcCl/Pr^iOH. The HCl salt is isolated in 82.6% yield with 98% purity and 99% ee and can be purified by charcoal treatment followed by crystallization from MeOH/

DOI: 10.1021/acs.oprd.5b00167
Org. Process Res. Dev. 2015, 19, 778−792

Scheme 25[a]

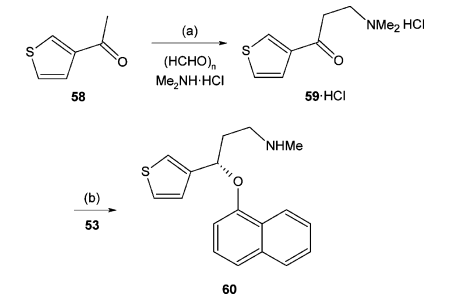


[a]Reagents and conditions: (a) (i) 32% HCl, Pr^{i}OH, 60 °C, 13 h; (ii) cool to rt, filter, wash in Pr^{i}OH, dry. (b) (i) $RuCl_2$[(*R*)-3,5-xylylBINAP]·[(2*R*)-DIAPEN], KOBu^t, MeOH, H_2, 20 °C, 12 h; (ii) concentrate. (c) (i) Raney Ni, MeOH, H_2, 50 °C, 12 h; (ii) filter, evaporate; (iii) crystallization. (d) (i) KOBu^t, DMSO, 60 °C, 8 h; (ii) cool to rt, extract in EtOAc; (iii) extract in H_2O; (iv) extract in dilute HCl; (v) add aq NaOH to pH 12; (vi) extract into EtOAc; (vii) concentrate. (e) (i) Me_2CO, 50 °C; (ii) add AcCl/Pr^{i}OH, 50 °C, pH <7.5; (iii) cool to <5 °C, filter.

Pr^{i}OH. The final product is isolated in 73% yield with 99% purity and 99.5% ee.

As mentioned above, this patent does not refer to U.S 8,362,279, which also describes a method for preparing **52** from **55**. In that case, HCHO and Me_2NH·HCl are used, and one problem discussed in that patent is that the starting material **55** contains the regioisomer **58** as an impurity. This reacts with the HCHO and Me_2NH·HCl to form **59**·HCl, as shown in Scheme 26. This compound subsequently reacts with **53**, and in the

Scheme 26[a]



[a]Reagents and conditions: (a) and (b) See Scheme 25.

following steps of the process compound **60** is formed and found as an impurity in **54**. It is highly likely that in the process described in the current patent, compound **58** would react with HCHO and the HCl salt of HNMeOMe to give the regioisomer of **56**, which would subsequently react with **53** to give **60** as an impurity in **54**. There is no mention of this possibility in the current patent, and if **58** is indeed present in the **55** that is used to make **52**, then this would have an impact on the purity of **54** produced by the currently described process.

Advantages. The process gives a higher yield of the desired product at lower cost than the alternatives.

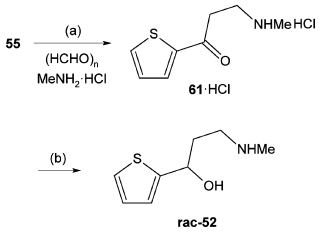
■ PATENT NO. U.S. 8,962,865

Assignee: Lonza AG, Basel, Switzerland

Title or Subject: Process for the Preparation of N-Monosubstituted *β*-Amino Alcohols

This is the second patent relating to duloxetine, although in this case the claims of the patent relate to a process for preparing the racemic alcohol *rac*-**52**. This could be used in the preparation of **54**, although there would need to be a resolution step at some stage in the synthesis in order to obtain **54** as the pure enantiomer. The synthesis of *rac*-**52** proceeds via ketone **61**, which is formed from **55** in a Mannich reaction, as shown in Scheme 27. This procedure is similar to the one for preparing

Scheme 27[a]

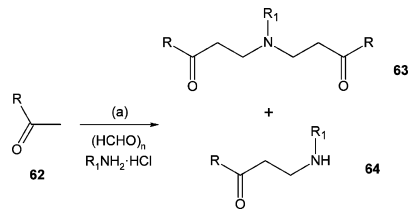


[a]Reagents and conditions: (a) (i) Conc HCl, EtOH, 2.5 bar, 110 °C, 9 h; (ii) evaporate, add EtOAc; (iii) filter, wash, dry. (b) (i) 50% aq NaOH, EtOH, 4 °C; (ii) add $NaBH_4$, 4 °C over 0.5 h; (iii) 4 °C, 4 h; (iv) add Me_2CO, 4 °C, 10 min; (v) add H_2O, concentrate; (vi) extract in MTBE, evaporate.

56 described in the previous Highlight and also the one for the dimethylamino analogue described in patent U.S. 8,362,279, although there is no reference to this patent. The preparation of *rac*-**52** is via **61**, which is obtained by treating **55** with HCHO and an amine salt in the presence of HCl. The ketone is recovered in yields of up to 71% and then converted to *rac*-**52** by reduction using $NaBH_4$. The alcohol is isolated in 84% yield as an orange oil that crystallizes after some time and can be used without further purification. The first step of this process involves the reaction of **55**, and as mentioned earlier, this can contain the regioisomer **58**, which would produce **59**·HCl as shown in Scheme 26; however, there is no reference to this in the current patent.

The patent points out that N-substituted *β*-amino ketone compounds, which are analogues of **61**, were first prepared in 1922 from methyl ketones such as **62**, amines, and HCHO. However, primary amines tended to favor the production of compounds such as **63**, as shown in Scheme 28, and recovery of

Scheme 28[a]



[a]Reagents and conditions: (a) HCl.

the desired product **64** was difficult. The current process is said to overcome these difficulties, and the use of $MeNH_2$·HCl is advantageous since the compound is a solid that is much easier and safer to handle than the amine itself.

The patent also describes the preparation of analogues of *rac*-**52** in which the methyl group in the amine is replaced by Et, Bu^i, or Bu^t. The claims of the patent cover these compounds and also cover the analogues of compounds **61** and **52** in which the thiophenyl group is replaced by a number of other groups such as furanyl, phenyl, benzofuranyl, and benzothienyl, although no examples are described for these. There is,

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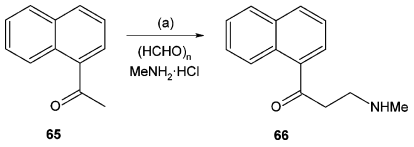
however, an example of the preparation of **66** from ketone **65** that gives the product in 42% yield (Scheme 29).

Scheme 29[a]



[a]Reagents and conditions: (a) See Scheme 27.

Advantages. The process does give good yields of the desired ketone, and using the HCl salt of $MeNH_2$ reduces the handling difficulties.

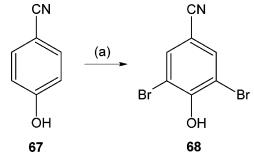
PATENT NO. U.S. 8,957,239

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

Title or Subject: Process for the Eco-Friendly Preparation of 3,5-Dibromo-4-hydroxybenzonitrile

The title compound, **68**, is a well-established herbicide, and there are several methods mentioned, going back to 1896, that describe its preparation. The current patent points out that these methods do not divulge how inorganic salts or mineral acids can be used and often rely on using liquid Br_2, which is a hazardous reagent on a large scale. Scheme 30 shows the preparation of **68** from **67** involving bromination using Br_2, and there are examples in the U.S. patents 3,349,111, 4,349,488, and 4,436,665 and French patent 1,375,311.

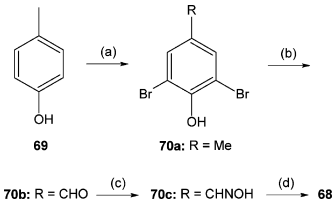
Scheme 30[a]



[a]Reagents and conditions: (a) Br_2, various solvents.

Other methods start from *p*-cresol (**69**), and Scheme 31 shows one such route that is reported in Indian patent 180,996.

Scheme 31[a]



[a]Reagents and conditions: (a)−(d) No specific details reported.

This starts with the bromination of **69** to give **70a**, which is oxidized to give aldehyde **70b**. Oxime **70c** is then formed, and dehydration of this affords **68**. Specific details of this route are not discussed in the current patent, as it is said to be uneconomical because of its multistep nature. Another route, which is described as hazardous, also starts from **69** and uses liquid Br_2 to form **70a**, which is converted to **68** using $EtNO_2$ and fused NaOAc.

The preparation of **68** from **67** that is disclosed in the current patent uses a mixture of bromide and bromate salts in a ratio of 2:1, respectively, as the brominating agent. The reaction occurs at rt and atmospheric pressure. After addition of the brominating mixture to **67**, concentrated HCl is added, and then the product is recovered and washed in H_2O. The yield is up to 99%, and the purity is >99%.

Advantages. The process is eco-friendly, has high yields, and gives high-purity product without requiring any catalysts.

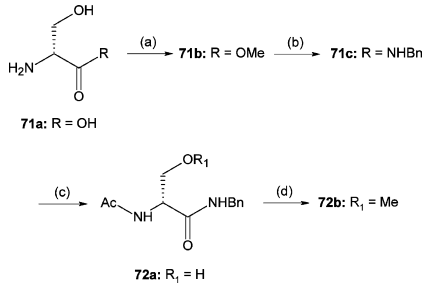
PATENT NO. U.S. 8,957,252

Assignee: Indoco Remedies Limited, Mumbai, India

Title or Subject: Process for the Preparation of Lacosamide and Some *N*-Benzyl-propanamide Intermediate Derivatives

Locasamide (**72b**) is an anticonvulsant drug used in the treatment of epilepsy. A number of methods are known for its preparation, and U.S. 5,773,475 reported three routes starting from D-serine (**71a**). The first route, shown in Scheme 32, begins with the esterification of **71a** to form **71b**, which is then treated with $BnNH_2$ to form **71c**. This is acetylated with Ac_2O to give **72a**, which is methylated using MeI and Ag_2O to form **72b**.

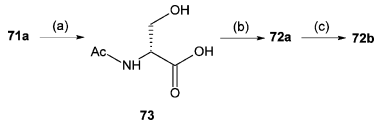
Scheme 32[a]



[a]Reagents and conditions: (a) No details. (b) $BnNH_2$. (c) Ac_2O, DCM. (d) MeI, Ag_2O, MeCN.

The second method from the patent, shown in Scheme 33, starts with acetylation to form **73**, which is converted to **72a** by a low-temperature reaction with $ClCO_2Bu^i$ in the presence of *N*-methylmorpholine (NMM) followed by $BnNH_2$. After purification by flash ColC, **72a** is alkylated with MeI and Ag_2O to give **72b**.

Scheme 33[a]



[a]Reagents and conditions: (a) No details. (b) (i) $ClCO_2Bu^i$, NMM, THF, −78 °C; (ii) $BnNH_2$. (c) MeI, Ag_2O, MeCN.

The third method for preparing **72b** in that patent, outlined in Scheme 34, begins with protection of the NH group in **71a** by reaction with BnOCOCl to form **74a**. This is alkylated using MeI and Ag_2O to form **74b**, which is purified by flash ColC and then hydrolyzed to give the acid **74c**. This is converted to **74d** by a low-temperature reaction with $ClCO_2Bu^i$ in the presence of NMM followed by $BnNH_2$. The NH protection in **74d** is then removed by hydrogenolysis using a Pd/C catalyst,

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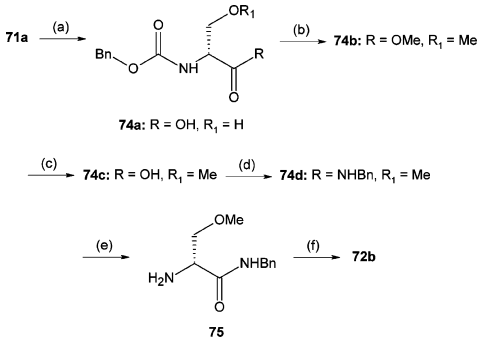
Scheme 34[a]



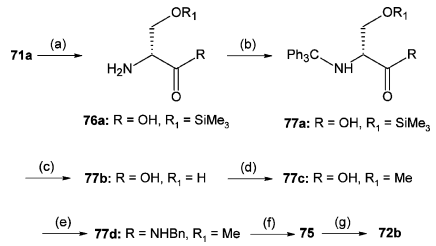
[a]Reagents and conditions: (a) BnOCOCl. (b) MeI, Ag_2O, MeCN. (c) Hydrolysis. (d) See Scheme 33, step (b). (e) Pd/C, H_2. (f) Ac_2O, pyridine.

producing **75**. Acetylation with Ac_2O gives crude **72b**, which is purified by flash ColC.

These three methods are said to be uneconomical for a number of reasons: they all have a methylation step using MeI and Ag_2O that is expensive; two require a low-temperature step, which again is expensive; and finally, chromatographic purification is needed for some intermediates. Overall, none of these routes is said to be commercially acceptable.

A number of other routes to **72b** have been reported, and Scheme 35 outlines the one reported in the patent U.S.

Scheme 35[a]

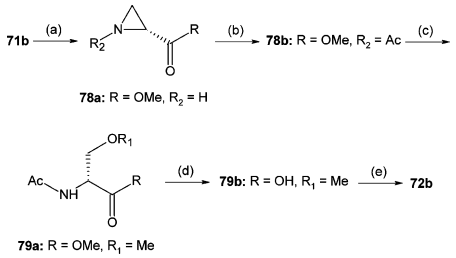


[a]Reagents and conditions: (a) Me_3SiCl. (b) Ph_3CCl. (c) No details. (d) MeI, NaH, imidazole. (e) (i) $ClCO_2Bu^i$, NMM; (ii) $BnNH_2$. (f) No details. (g) Ac_2O, DMAP.

8,093,426. This again starts from **71a**, which is reacted with Me_3SiCl to protect the OH group, forming **76a**. This is treated with Ph_3CCl to give **77a**. The silyl group is then removed, affording **77b**, which is methylated with MeI in the presence of NaH and imidazole to give **77c**. This is reacted with $ClCO_2Bu^i$ in the presence of NMM followed by $BnNH_2$ to give **77d**. The trityl group is removed to form **75**, and then acetylation with Ac_2O and DMAP forms **72b**. A route to **72b** that is similar to the one shown in Scheme 35 is reported in U.S. 7,884,134. This starts from the BOC-protected analogue of **77b**, which undergoes a series of reactions to produce **75** via analogues of **77c** and **77d**.

An intriguing route to **72b** from methyl ester **71b** was described previously (*Bioorg. Med. Chem.* **2008**, *16*, 8968). This route is outlined in Scheme 36 and starts with the reaction of **71b** with $(EtO)_2PPh_3$ to form aziridine **78a**. The reaction also produces the analogous ethyl ester, which is present at around 10% of the amount of the methyl ester. This mixture of esters is then treated with Ac_2O in the presence of Et_3N and DMAP to form **78b** along with the ethyl analogue. In the next step, the

Scheme 36[a]

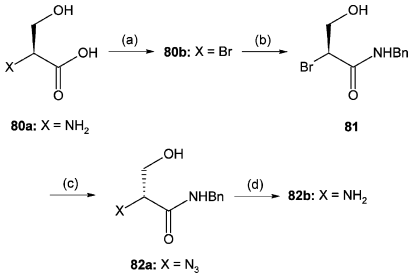


[a]Reagents and conditions: (a) $(EtO)_2PPh_3$. (b) Ac_2O, Et_3N, DMAP. (c) MeOH, $BF_3{\cdot}Et_2O$. (d) LiOH, H_2O. (e) $BnNH_2$, DMTMMC, THF.

aziridine ring is opened by treatment with MeOH and $BF_3{\cdot}Et_2O$ to give **79a** and the ethyl analogue. Both esters are then hydrolyzed using LiOH to give acid **79b**, which is reacted with $BnNH_2$ in the presence of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMMC) to give **72b**.

The routes shown in Schemes 34−36 all use **71a** or its derivatives to synthesize **72b**, and the high cost of the starting material is said to be a drawback in all of the alternative routes. Hence, the objective of the current patent is to provide a route that starts from cheaper, naturally occurring raw materials and does not use flash ColC for product purification. The synthesis of **72b** disclosed in the current patent starts from naturally occurring L-serine (**80a**), and the initial steps are shown in Scheme 37. The first step is bromination of **80a** using KBr and

Scheme 37[a]



[a]Reagents and conditions: (a) (i) KBr, HBr, H_2O, 30 °C; (ii) cool to −15 °C; (iii) add $NaNO_2$, N_2 sparge, −15 °C, 2.5 h; (iv) 0−10 °C, 4 h; (v) extract in EtOAc, dry, evaporate. (b) (i) $ClCO_2Bu^i$, EtOAc, 25 °C; (ii) cool to −12 °C, add NMM + $BnNH_2$ over 1 h; (iii) <0 °C, 0.5 h; (iv) 30 °C, 1 h; (v) concentrate, add Pr^i_2O; (vi) repeat step v; (vii) 30 °C, 0.5 h; (viii) add H_2O, 30 °C, 0.5 h; (ix) filter, wash in Pr^i_2O (×2), H_2O wash, dry. (c) (i) NaN_3, DMF, 55 °C, 5 h; (ii) cool to 25 °C, add H_2O + 5% $NaHCO_3$ to pH 9.5; (iii) extract in EtOAc, wash with aq NH_4Cl; (iv) evaporate. (d) (i) Pd/C, EtOAc, H_2 3.8 kg/m^2, 30 °C, 1 h; (ii) filter, concentrate; (iii) 5 °C, 2 h; (iv) filter, wash in EtOAc, dry.

HBr to give **80b**, which is recovered as a pale-yellow or green oil in 85.8% yield. This is then reacted with $ClCO_2Bu^i$, NMM, and $BnNH_2$ to form **81** in 66.4% isolated yield. Treatment of **81** with NaN_3 gives the azido compound **82a**, which is recovered as an oil in 99.6% yield. These two intermediates are both novel compounds that are covered by the claims of the patent, and ^1H and ^{13}C NMR data are provided. Hydrogenation of **82a** using Pd/C catalyst forms the amine. This is a key aspect of the process because it is in this step that the configuration is completely inverted and the desired stereochemistry is produced. The patent states that the product is

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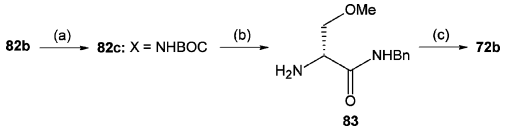
substantially free from the other enantiomer although no analytical data are provided. The conversion of **81** to **82b** can be carried out without isolation of **82a**, and this gives a 60.6% yield of **82b** based on **81**.

The final steps of the synthesis of **72b**, shown in Scheme 38, begin with protection of the NH_2 group in **82b** by reaction with

Scheme 38[a]



[a]Reagents and conditions: (a) (i) $(BOC)_2O$, EtOAc, 25 °C, 1 h; (ii) Et_3N, 25 °C, 1 h; (iii) concentrate, add cyclohexane; (iv) 25 °C, 1 h; (v) filter, cyclohexane wash, dry. (b) (i) Bu_4NBr, DCM, −10 °C; (ii) add aq NaOH, −10 °C; (iii) add $(MeO)_2SO_2$ at −10 °C over 1 h; (v) −10 °C, 4.5 h; (vi) add H_2O, 30 °C, 0.25 h; (vii) separate, add conc HCl, 30 °C, 2 h; (viii) add H_2O, 30 °C, 0.5 h; (ix) separate, extract in H_2O; (x) cool to <20 °C, add 50% aq NaOH to pH 13; (xi) extract in DCM, H_2O wash; (xii) add active C, 30 °C, 0.5 h; (xiii) filter, wash C in DCM; (xiv) concentrate. (c) (i) Et_3N, cyclohexane; (ii) add Ac_2O/EtOAc, 30 °C, 20 min; (iii) 40 °C, 4 h; (iv) cool to <5 °C over 1 h; (v) <5 °C, 1.5 h; (vi) filter, <5 °C; (vii) wash in EtOAc/cyclohexane; (viii) dissolve in Et_2O, 25 °C, 6 h; (ix) filter, wash in Et_2O, dry.

$(BOC)_2O$. This gives **82c** in 91.7% isolated yield, which is then converted to **72b** in a one-pot reaction. First, $(MeO)_2SO_2$ is added to an alkaline mixture of **83** in the presence of Bu_4NBr as a phase-transfer catalyst. After acidification and workup, the product is recovered as an oily mass in 90.7% yield. In the final step, acetylation of **83** with Ac_2O in the presence of Et_3N forms **72b**, which is isolated in 74.2% yield.

Advantages. The process uses a low-cost, naturally occurring starting material and produces the final product with high ee via novel intermediates.

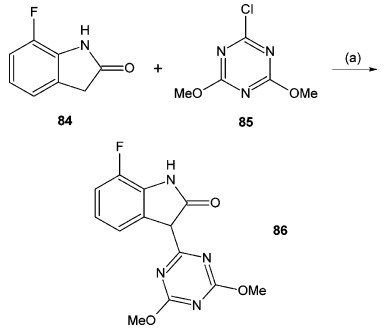
PATENT NO. U.S. 8,962,828

Assignee: Bayer Intellectual Property GmbH, Monheim, Germany

Title or Subject: Method for Producing Triazinyl-Substituted Oxindoles

The compounds of interest in this patent are intermediates in the synthesis of agrochemicals. The patent focuses on oxindoles that are substituted at the 3-position with triazinyl groups, and compound **86** is a specific example. The patent points out that the standard method for synthesizing 3-substituted oxindoles is to exchange an H atom at the 3-position with a suitable substituent, and several examples are mentioned. These include substituents such as pyridazines (*Org. Lett.* **2006**, *8*, 1447), quinazolines (*Tetrahedron Lett.* **1999**, *40*, 3881), and pyridines or pyridine *N*-oxides (U.S. Patent application 20090291982). The reactions take place in the presence of a strong base that deprotonates the oxindole at the 3-position. When bases such as NaH or LiH are used, the solvents must be extremely dry, and this can be difficult to control on a large scale. These bases also produce equimolar amounts of H_2 gas, and hence, it is suggested that they are not suitable for large-scale operations. A method for preparing a triazinyl-substituted oxindole using NaH is reported in U.S. Patent application 20090116388, but it gives the desired product in a yield of <7% and hence is not commercially acceptable. The patent discloses that it is possible to use relatively weak bases to prepare the desired compounds, and this is surprising in view of the low acidity of the H atoms at the 3-position in oxindoles. The key to the process is to use two relatively weak bases to deprotonate the H atom at the 3-position, and Scheme 39 outlines the synthesis of **86** by

Scheme 39[a]



[a]Reagents and conditions: (a) (i) KOH/K_2CO_3, H_2O/Me_2NAc, 0 °C; (ii) rt, 18 h; (iii) add PhMe + dil HCl to pH 3−4 + antifoam; (v) filter, H_2O wash (×3), heptane wash (×2), dry.

reaction of **84** and **85**. The patent describes five methods using different combinations of bases and solvents. The bases, solvents, and yields of **86** that are obtained from the various reactions are KOH/K_2CO_3, H_2O/Me_2NAc, 95%; KOH, Me_2CO, 81%; K_2CO_3, DMF, 80%; KOH, THF/H_2O, 91%; and NaOH, MeCN, 85%. When NaH in THF/DMF was used, the yield was only 39%. A previously reported procedure using Cs_2CO_3 in DMF (*Org. Lett.*, **2010**, *12*, 2306) gives **86** in only 22% yield, and several other products are obtained.

The patent also provides examples of the preparation of a number of compounds analogous to **86** using different oxindoles and/or triazines. These include oxindoles in which the F atom is replaced by H, Cl, or OMe, and the interested reader is encouraged to consult the patent. ^1H NMR data are provided for the various products that are prepared.

Advantages. The process gives high yields and uses bases that do not decompose in H_2O and do not produce H_2 during the reaction. They are therefore easier to handle and less expensive than stronger bases such as NaH.

PATENT NO. U.S. 8,962,851

Assignee: Cadila Healthcare Limited, Ahmedabad, India

Title or Subject: One-Pot Process for the Preparation of Benzimidazole Derivatives

This patent describes a process for the preparation of the *S* enantiomer of omeprazole, known as esomeprazole (**88**), a drug used to treat gastric ulcers. Specifically, the patent describes the preparation of the Mg salt of **88** by what is claimed to be a one-pot process. Patents describing the synthesis of omeprazole, the racemic compound, have been reviewed previously (*Org. Process Res. Dev.* **2008**, *12*, 146). A key step in the synthesis of **88** is the oxidation of the prochiral thioether group in **81** to the sulfoxide group in **82**, as shown in Scheme 40. Several methods for this reaction using a variety of oxidants have been reported. These include MeC(O)OOH (U.S. 6,229,021), *m*-CPBA (U.S. 6,603,009), a chiral transition-metal complex and a peroxide plus a base (U.S. 7,915,422), cumene hydroperoxide (CHP) and a chiral complex of Ti or V (WO 2003/089408), and perborate salts (WO 1999/47514). The patent states that there is no report of a one-pot procedure

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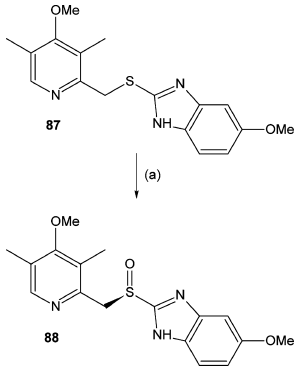
Scheme 40[a]

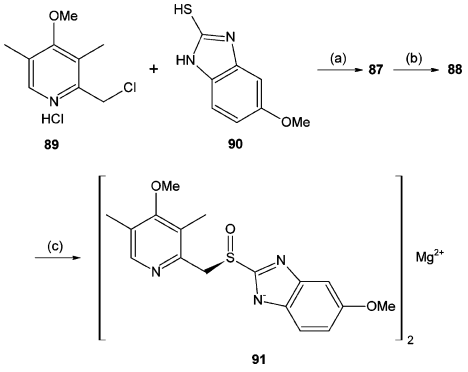


[a]Reagents and conditions: (a) Various oxidizing agents.

for the preparation of the Mg salt of **88**, and the objective of the process is to achieve this.

Scheme 41 shows the route used to prepare **88**. It starts with the reaction of **89** and **90** in the presence of aqueous NaOH to

Scheme 41[a]



[a]Reagents and conditions: (a) (i) Aq NaOH, MeOH, 25 °C, 0.75 h; (ii) add H_2O + HOAc; (iii) extract in PhMe; (iv) H_2O wash, azeotropic drying. (b) (i) Add D-(−)-$(CHOHCO_2Et)_2$, $Ti(OPr^i)_4$, 50 °C, 1 h; (ii) cool to 0 °C, add Pr^i_2NEt + CHP; (iii) 15 °C, 8.25 h; (iv) add aq NaOH + $Na_2S_2O_3$; (v) separate, collect aqueous layer; (vi) add DCM + HOAc to pH 6.5; (vii) separate, evaporate. (c) (i) $Mg(OMe)_2$, MeOH, 25 °C, 9 h; (ii) add trace H_2O; (iii) filter, charcoal treatment; (iv) evaporate, add Me_2CO; (v) 25 °C, 2 h; (vi) filter, wash in MeOH/Me_2CO, dry; (vii) recrystallize from MeOH/Me_2CO.

give **87**, which is actually recovered as a solution by extraction into PhMe. In the next stage, **87** is oxidized to **88** using a mixture of $Ti(OPr^i)_4$, CHP, and Pr^i_2NEt in the presence of D-(−)-diethyl tartrate. This product is recovered by extraction in DCM and isolated as a residue that is then converted to the Mg salt **91** by reaction with $Mg(OMe)_2$ in DCM. After purification, the salt is recovered as the dihydrate in 55.5% yield based on **90**. The process is described as a one-pot process, but this is clearly not the case. The intermediates **87** and **88** are actually isolated after extraction, so the route cannot realistically be described as a one-pot process. XRD and DSC scans of **91** are provided in the patent. The route is also said to be suitable for the preparation of dexlansoprazole, although no details are provided.

Advantages. The process does provide a route to esomprazole but cannot be described as a one-pot method as claimed.

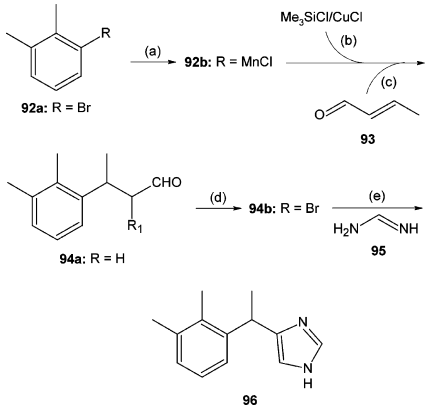
PATENT NO. U.S. 8,962,862

Assignee: Cambrex Karlskoga AB, Karlskoga, Sweden

Title or Subject: Process for Preparing 4-Substituted Imidazoles

This patent describes a process for preparing compound **96**, which is known as medetomidine. Its HCl salt is used as an analgesic for animals, and the compound is also useful as an antifoulant in marine paints. The majority of routes for its preparation involve the use of a reagent that already contains the imidazole ring. Examples are reported in the patents WO 2009/053709, EP 1,198,282, and GB 2,101,114. There are also routes in which the imidazole ring is formed during the synthesis, and these tend to have more steps and are potentially less efficient; an example is patent WO 2011/070069. The route described in the current patent is based on the formation of the imidazole ring during the synthesis and is shown in Scheme 42. It begins with the formation of the Grignard from

Scheme 42[a]



[a]Reagents and conditions: (a) (i) Mg, THF, <50 °C; (ii) 65 °C, 1 h; (iii) $MnCl_2$, −20 °C. (b) −20 °C. (c) (i) THF, −20 °C, 2 h; (ii) warm to rt, add heptane + H_2O; (iii) separate, add HCl/H_2O, rt, 2 h; (iv) separate, add BHT + $(EtO)_3N$; (v) evaporate, distill. (d) (i) 37% HCl, THF, 60 °C; (ii) add DBBA, <65 °C; (iii) 65 °C, 0.5 h; (iv) evaporate, add PhMe, distill THF/PhMe; (v) H_2O wash (×3), wash in aq $(EtO)_3N$, H_2O wash; (vi) add BHT + $(HOCH_2CH_2)_3N$; (vii) evaporate. (e) (i) 25% aq NH_3, EtOH, 120 °C, 2 h; (ii) evaporate, add H_2O + EtOAc; (iii) add Na_2CO_3 to pH 9−10; (iv) separate, extract in H_2O/HCl; (v) add Na_2CO_3 to pH 9−10; (vi) extract in EtOAc; (vii) separate, evaporate; (viii) add Me_2CO + 37% HCl; (ix) filter, dry; (x) charcoal, H_2O, 70 °C, 0.5 h; (xi) filter, add Me_2CO/H_2O; (xii) heat to 60 °C, add NaOH/H_2O, 1 h; (xiii) cool to 40 °C, seed; (xiv) cool to 0 °C, filter, H_2O wash, dry.

92a followed by the addition of $MnCl_2$ to form the intermediate **92b**, which is not isolated. The solution containing the Mn compound is then treated with Me_3SiCl and CuCl, followed by slow addition of **93**. This reaction forms aldehyde **94a** after an acidic workup, and this is recovered as a viscous oil by vacuum distillation in 48% yield. The aldehyde is a novel compound and is covered by one of the claims of the patent. It is recovered after stabilization by the addition of butylated hydroxytoluene (BHT) and $(HOCH_2CH_2)_3N$ and then brominated using 5,5-dibromobarbituric acid (DBBA) to form **94b**, which is isolated in 88% yield, and again BHT and

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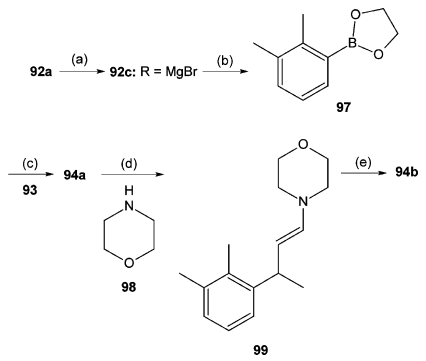
$(HOCH_2CH_2)_3N$ are added as antioxidants. This unusual brominating agent is the preferred reagent, although the more conventional reagent Br_2 in dioxane is used in a small-scale example. In the next step, the imidazole ring is formed by the reaction of **94b** with **95**, as the acetate, and a large excess of aqueous NH_3. The product is initially recovered as the HCl salt in 43% yield, and after treatment with NaOH, **96** is isolated in 89% yield.

The patent also describes a method for preparing **94a** from **92a** and crotyl alcohol using a Pd phosphine catalyst, but the yield is only 43%. Another route to **94a** involves the reaction of crotyl alcohol and the diazonium salt of 2,3-dimethylaniline using a Pd/phosphine catalyst. This is based on a previous report (*Synlett* **2009**, 973) and is not a selective reaction, giving several products.

The patent describes a second, longer route from **92a** to **94b** that also proceeds via **94a**, which is outlined in Scheme 43. This

Scheme 43[a]



[a]Reagents and conditions: (a) (i) Vitride, Mg, THF, rt; (ii) 50 °C, 2 h. (b) (i) $B(OMe)_3$, THF, < −20 °C; (ii) warm to 25 °C, evaporate; (iii) extract in hot $(HOCH_2)_2$; (iv) PhMe, 110 °C; (v) distill; (vi) add MeOH. (c) (i) $NaHCO_3$, THF, MeOH, H_2O, 20 °C; (ii) add $[Rh(MeCN)_2COD]BF_4$, exotherm; (iii) 40 °C, 8 h; (iv) add BHT + $(EtO)_3N$, evaporate, 60 °C; (v) add PhMe, 50 °C; (vi) H_2O wash, wash in $(EtO)_3N$; (vii) separate at 70 °C; (viii) evaporate. (d) (i) PhMe, reflux; (ii) distill. (e) (i) Br_2, EtOAc, −10 °C, 10 min; (ii) add H_2O, warm to 25 °C, add HCl to pH 4; (iii) separate, add $NaHCO_3$ + $Na_2S_2O_3$ + H_2O, 25 °C, 10 min; (iv) separate, H_2O wash; (v) add BHT + $(EtO)_3N$, evaporate.

proceeds via the Grignard **92c**, which is reacted with $B(OMe)_3$ to form **97**. This is isolated as a solution in MeOH after a complex workup involving extraction in hot $(HOCH_2)_2$ and azeotropic distillation of MeOH and PhMe. Full details are given in the patent but not reproduced here. The borate ester is mixed with **93** in the presence of a trace of $NaHCO_3$ and then $[Rh(MeCN)_2COD]BF_4$ is added, producing a slight exotherm. Before distillation to remove solvents, BHT and $(HOCH_2CH_2)_3N$ are added, and **94a** is recovered as a yellow oil in 69% yield with a GC purity of 96.4%. The aldehyde is then reacted with **98** to give enamine **99**. The crude product is recovered after distilling off the H_2O and solvents and then is brominated using Br_2 to give **94b** in an overall yield of 61% from **92a**.

The examples in the patent describe kilo-scale preparations of compound **96** via Scheme 42 and compound **94b** via Scheme 43, indicating the advanced stage of the development of the process.

Advantages. The process avoids the problem of using imidazole derivatives as starting materials and offers a novel method of preparing the desired compound via novel intermediates.

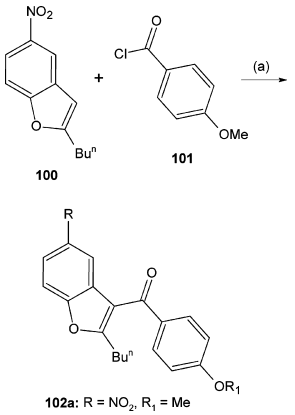
PATENT NO. U.S. 8,962,869

Assignee: Sanofi, Paris, France

Title or Subject: Process for Synthesizing Keto Benzofuran Derivatives

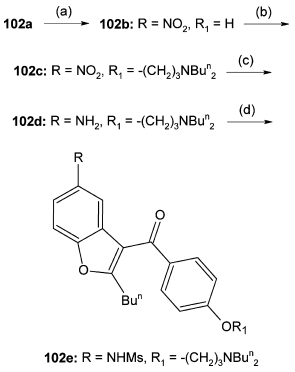
The patent describes a process for the preparation of dronedarone (**102e**), a drug used to treat cardiac arrhythmia. Two earlier patents from this company on an alternative synthesis of **102e** have been reviewed previously (*Org. Process Res. Dev.* **2014**, *18*, 850). This patent states that **102e** is currently synthesized by a route described in patent EP 471,609, also assigned to Sanofi, and this is outlined in Schemes 44 and 45. In this synthesis, intermediate **100** must be

Scheme 44[a]



[a]Reagents and conditions: (a) Friedel−Crafts reaction, no details.

Scheme 45[a]



[a]Reagents and conditions: (a)−(d) No specific details.

functionalized at the 3-position and transformed at the 5-position. Thus, alkylation of **100** is carried out with **101** in a Friedel−Crafts reaction to obtain **102a**, although precise details are not mentioned (Scheme 44).

In the next stage, shown in Scheme 45, the OMe group in **102a** is converted to OH in **102b**, which is transformed to give **102c**. The NO_2 group is then converted to the NHMs group by reduction to give **102d** followed by sulfonylation to form **102e**. The current patent states that implementation of this technically complex process has problems that reduce the yield. There are also safety aspects such as handling of H_2 and

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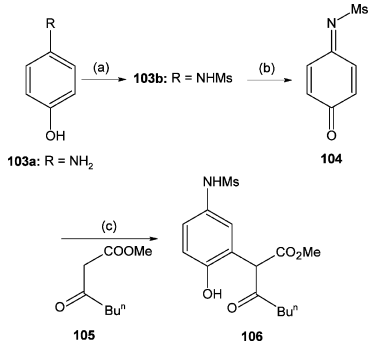
Friedel–Crafts salts such as those of Fe or Al, and hence, an improved route is required.

The latter stages of the synthesis of **102e** disclosed in the current patent use a benzofuran that is already suitably functionalized at the 2- and 5-positions. The first stage is shown in Scheme 46 and begins with sulfonylation of **103a** to

Scheme 46[a]

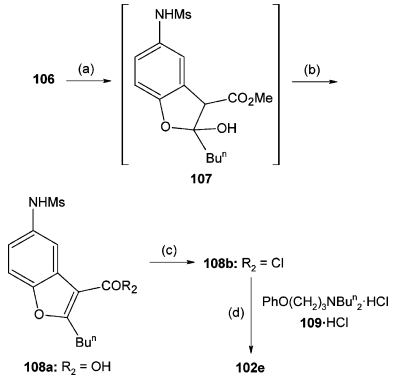


[a]Reagents and conditions: (a) (i) trace 37% HCl, MeOH; (ii) add MsCl at 20 °C over 10 min; (iii) 20 °C, 1 h; (iv) add $NaHCO_3$ to pH 5.5–6, 20 °C, 0.5 h; (iv) acidify with 36% HCl; (v) filter, concentrate; (vi) add 1 M HCl, concentrate; (vii) filter; (viii) extract mother liquors in EtOAc; (iv) concentrate. (b) (i) 85% MnO_2, HOAc, 25 °C, 1 h; (ii) filter; (iii) wash solids in HOAc; (iv) combine liquors, concentrate; (v) add DCM + H_2O; (vi) separate, concentrate; (vii) add EtOH, filter, dry. (c) (i) NaOMe, dioxane, 20 °C, 0.5 h; (ii) filter, add dioxane.

give **103b**, which is isolated in 87.2% yield. This is oxidized to **104** in 86% yield using $K_2Cr_2O_7$ or 91.5% yield using MnO_2/HOAc. The next step is the coupling of **104** and *β*-keto ester **105** in the presence of NaOMe. This produces **106**, which is recovered as a solution in Me_2CO that is used in the next stage outlined in Scheme 47.

In the next step, the solution of compound **106** in dioxane is treated with HCl, resulting in cyclization to form **107**, which is not isolated (Scheme 47). This compound loses H_2O, and after treatment with NaOH, the ester is hydrolyzed to form acid **108a**, which is isolated in 89.2% yield. The acid is then

Scheme 47[a]

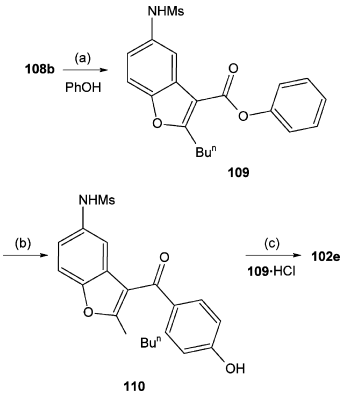


[a]Reagents and conditions: (a) (i) 36% HCl, dioxane, 50 °C, 1.5 h; (ii) concentrate. (b) (i) 10% NaOH, 25 °C, 21 h; (ii) add 36% HCl; (iii) filter. (c) (i) $SOCl_2$, 20 °C, 3 h; (ii) reflux 0.5 h; (iii) concentrate, add DCE. (d) (i) $AlCl_3$, DCE, <5 °C; (ii) 20–25 °C, 4 h; (iii) add to H_2O, <5 °C; (iv) H_2O wash (×3); (iv) concentrate, add DCE; (v) wash in 10% NaOH; (vi) ColC.

converted to the acyl chloride by treatment with $SOCl_2$, and **108b** is isolated as a solution in DCE. In the last stage, acyl chloride **108b** is reacted with **109**·HCl in a Friedel–Crafts reaction to form **110a**, which is isolated in 16.6% yield and 94.6% purity after ColC. No information about further purification is provided.

The patent also describes a route to **102e** involving a Fries rearrangement, and this is shown in Scheme 48. In this route,

Scheme 48[a]

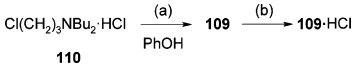


[a]Reagents and conditions: (a) (i) pyridine, DCM, 35 °C; (ii) add 36% HCl + H_2O, rt, 0.25 h; (iii) separate, H_2O wash, wash in 3% aq NaOH; (iv) H_2O wash, concentrate; (v) add cyclohexane, concentrate, filter. (b) (i) $AlCl_3$, PhCl, 95 °C, 17 h; (ii) cool to <25 °C, add DCM; (iii) add to H_2O, <35 °C; (iv) stir, 25 °C; (v) separate, H_2O wash (×2); (vi) add 30% NaOH to pH 12.5, 25 °C; (vii) separate, collect aqueous phase; (viii) add 36% HCl to pH <7; (ix) add DCM, separate; (x) concentrate, flash ColC. (c) No details provided.

108b is reacted with PhOH in the presence of pyridine to form **109**, which is isolated as an oily material with 84% purity. This undergoes a Fries rearrangement in PhCl to give **110**, which is recovered in 27.3% yield after flash ColC. The final step is the reaction of **110** with **109**·HCl to form **102e**, but experimental details of this reaction are not described.

The ammonium chloride **109**·HCl used in Scheme 47 to prepare **102e** is obtained from **110** and PhOH by the method shown in Scheme 49. The reaction takes place in aqueous

Scheme 49[a]



[a]Reagents and conditions: (a) (i) PhOH, NaOH, H_2O, reflux, 16 h; (ii) separate, H_2O wash; (iii) add MTBE, wash in 2% aq HCl; (iv) concentrate, add DCM, azeotropic distillation. (b) (i) 36% HCl, DCE, 20 °C, 1 h; (ii) azeotropic distillation, concentrate.

NaOH, and the initial product is the free base **109**, which is isolated as an oil in 91.4% yield. This is converted to the HCl salt by treatment with HCl in DCE, and the salt is isolated in quantitative yield.

Advantages. The process is convergent, does not require the isolation of intermediates, does not include a hydrogenation step, and uses readily available reagents. However, some of the steps give low yields, and handling Friedel–Crafts reagents is still necessary.

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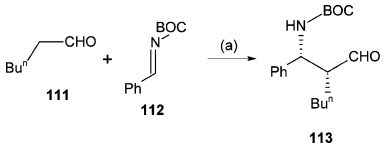
PATENT NO. U.S. 8,962,889

Assignee: Sumitomo Chemical Company Limited, Tokyo, Japan

Title or Subject: Process for Producing Optically Active β-Aminoaldehyde Compounds

This patent describes a process to produce β-amino aldehyde compounds that are said to be intermediates in the preparation of unspecified drugs used to treat diabetes or Alzheimer's disease. The patent refers to a method for the synthesis of β-aminoaldehydes such as **113** (*Angew. Chem. Int. Ed.* **2007**, *46*, 609). The synthesis is outlined in Scheme 50 and takes place in

Scheme 50[a]



[a]Reagents and conditions: (a) (*S*)-proline, MeCN, 0 °C, 8 h.

the presence of (*S*)-proline. The paper reports that there is no reaction when aliphatic imines are used, whereas the current patent describes a process in which aliphatic imines can be used to prepare β-amino aldehydes.

The reaction of aldehydes with aliphatic imines to prepare β-amino aldehydes is one aspect of the current patent. The β-amino aldehydes can also be prepared by the reaction of a sulfone with an aldehyde. The reactions are carried out in the presence of a chiral pyrrolidine-derived catalyst such as **114** (Figure 1), and this enables the formation of products with high enantioselectivity and diastereoselectivity.

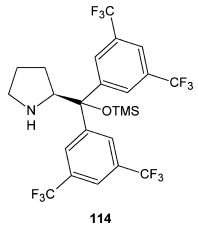
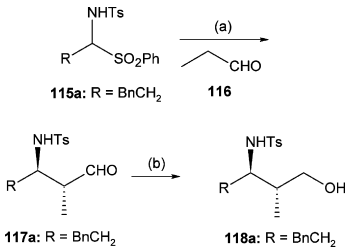


Figure 1.

The patent describes a number of compounds that are prepared by these methods, although specific experimental details are described for only two of them. For the rest of the compounds, the patent only reports data for their IR, HRMS, and ^{1}H and ^{13}C NMR spectra. Scheme 51 shows the route used to prepare compound **117a** by the reaction of **115a** and **116** in the presence of compound **114** and $NaHCO_3$. The yield, anti:syn ratio, and ee of the product vary with the reaction solvent. In 1,4-dioxane at a reaction temperature of 10 °C, the yield was 79% with an anti:syn ratio of 88:12 and 96% ee. At 0 °C in dioxane, the yield was 62%, the anti:syn ratio was 92:8, and the ee was 98.9%. In DCM at 0 °C, the yield was 38%, the ratio was 76:24, and the ee was 97%. Other solvents used were THF, H_2O, saturated brine, and DCM/saturated brine. In all cases, the ee was >94% with high anti:syn ratios, and the yields varied from 41% for H_2O at 0 °C to 76% for saturated brine at 10 °C. Aldehyde **117a** can then be reduced to alcohol **118a** using $NaBH_4$, although no specific details are provided.

Scheme 51[a]

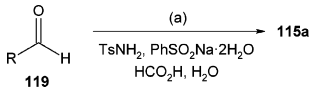


[a]Reagents and conditions: (a) (i) $NaHCO_3$, solvent, 10 °C, 20 h; (ii) add aq $NaHCO_3$, extract in $CHCl_3$; (iii) separate, dry, concentrate, ColC. (b) No details provided.

The process is also carried out on sulfone compounds analogous to **115a** in which R = Pr^i, Bu^i, Ph, Bn, BnO, or cyclohexyl. The yield, anti:syn ratio, and ee for the products of the reaction of these compounds with **116** are all provided in addition to the spectral data. The patent states that the reaction of an aldehyde and an imine can be carried out to give a β-amino aldehyde, although there are no experimental details. However, there are data for the preparation of products analogous to **117a** in which R = 4-MeOPh, 4-CF_3Ph, or 4-BrPh.

The patent describes a general method for the preparation of sulfone compounds such as **115a** that is shown in Scheme 52.

Scheme 52[a]



[a]Reagents and conditions: (a) (i) 23 °C, 12 h; (ii) filter, H_2O wash, hexane wash; (iii) add DCM, dry, evaporate; (iv) add hexane, filter, dry.

There are no specific examples for any of the compounds, although there are IR and NMR data for the various products that have been prepared. These include compounds formed from **119** in which R = Pr^i, Bu^i, Ph, Bn, BnO, or cyclohexyl.

Advantages. The process provides methods for producing a wide range of β-amino aldehydes with high enantioselectivity.

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