Process for Preparing MKC-442

This application claims priority to U.S. provisional application no. 60/128,925, filed on April 13, 1999.

This application is in the area of synthetic pharmaceutical chemistry, and in particular, includes an efficient method for preparing 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil, which is also known as MKC-442.

In 1983, the etiological cause of Acquired Immune Deficiency Syndrome (AIDS) was determined to be the human immunodeficiency virus (HIV). It is currently believed that a key factor in whether a person infected with HIV develops AIDS is the amount of HIV in the body at a given time (i.e., "the viral load"). Researchers have focused on halting HIV replication and reducing viral load by blocking one or both of two key enzymes required for viral replication, reverse transcriptase and protease.

The first enzyme, reverse transcriptase, is active early in the replication cycle of HIV and allows the virus, which is made of RNA, to produce DNA necessary for continued replication. This enzyme can be inhibited by two general classes of drugs defined by their structure as well as their mechanism of action. The first general class, nucleoside analogue reverse transcriptase inhibitors such as 3'-azido-3'-deoxythymidine (AZT), 2',3'-dideoxyinosine (ddI), 2',3'-dideoxycytidine (ddC), and (-)-cis-2-hydroxymethyl-5-(cytosin-1-yl)-1,3-oxathiolane (3TC), bear a strong chemical resemblance to the natural building blocks (nucleosides) of DNA and interfere with the function of the enzyme by displacing the natural nucleosides used by the enzyme. The second general class, non-nucleoside reverse transcriptase inhibitors, such as MKC-442 and nevirapine, is composed of an extremely diverse group of chemicals that act by binding to the enzyme and modifying it so that it functions less efficiently.

Since 1985, a number of nucleoside reverse transcriptase inhibitors, including AZT, ddI, ddC, 3TC, 2',3'-dideoxy-2',3'-didehydrothymidine (D4T), and cis-2-hydroxymethyl-5-(5-fluorocytosin-1-yl)-1,3-oxathiolane (FTC), have been proven to be effective against HIV. After cellular phosphorylation to the 5'-triphosphate by cellular kinases, these synthetic nucleosides are also incorporated into a growing strand of viral DNA, causing chain termination due to the absence of the 3'-hydroxyl group.

MKC-442 functions as a non-nucleoside reverse transcriptase inhibitor. MKC-442 is considered an allosteric inhibitor because it appears to exert its activity by binding to an "allosteric position", i.e., one other than the binding site, of the enzyme. Preclinical tests suggest that MKC-442 may possess characteristics that address several of the therapeutic challenges of HIV. When tested in cell culture assay systems against wild-type (drug-sensitive) and several mutant strains of HIV known to be resistant to established non-nucleoside reverse transcriptase inhibitors, MKC-442 retained much of its ability to inhibit HIV replication. In these studies, MKC-442 displayed greater potency than nevirapine against wild-type and mutant strains of HIV. Preclinical studies of MKC-442 in two drug combinations with AZT or with ddI and in three drug combinations with AZT and saquinavir have demonstrated synergistic inhibition of HIV replication.

Studies in animals suggest a favorable safety and pharmacokinetic profile for MKC-442. Animal pharmacokinetic analyses showed good oral bioavailability and excellent penetration into the central nervous system, a significant site of HIV replication that is poorly penetrated by many currently marketed anti-HIV drugs. In rats, for example, the concentration of MKC-442 in the brain was 100% of that seen in the plasma.

A Phase I study evaluated the pharmacokinetics and tolerance of single escalating doses of MKC-442 in HIV-infected volunteers. The compound was generally well tolerated, with only a few participants experiencing minor adverse effects at the higher dose levels. In the groups receiving higher doses, concentrations of the drug in the plasma reached levels much higher than the levels required to suppress 90% of the virus in culture.

Preliminary data from a Phase I/II double-blind, placebo controlled trial designed to evaluate the safety and efficacy of repeated multiple oral doses of MKC-442 in HIV-infected patients has now also been evaluated. A total of 49 patients were treated with MKC-442 for up to two months. Doses ranging from 100 mg to 1000 mg twice a day were given to groups of six to eight patients at each dosage level. At the highest doses tested (750 mg and 1000 mg twice a day), the viral load was reduced by an average of 96% in all patients after one week. This reduction was mostly sustained at two weeks whereafter it was followed by a gradual increase in viral load toward baseline levels. A single point mutation at position 13 of the reverse transcriptase that may be associated with resistance was found in the virus obtained from some patients. In over 308 patient-weeks of drug exposure, MKC-442 was well tolerated.

MKC-442 is described, for example, in U.S. Patent No. 5,461,060, which is incorporated herein by reference in its entirety.

U.S. Patent No. 5,604,209, issued on February 18, 1997 to Ubasawa et al., and assigned to Mitsubishi Chemical Corporation, discloses that certain 6-benzyl-1-ethoxymethyl-5-substituted uracil derivatives, including MKC-442, and certain 2',3'-dideoxyribonucleosides, including 2',3'-dideoxyinosine (ddI), 3'-azido-3'-deoxythymidine (AZT), AZT triphosphate, and 2',3'-dideoxycytidine (ddC), exhibit a synergistic effect against HIV.

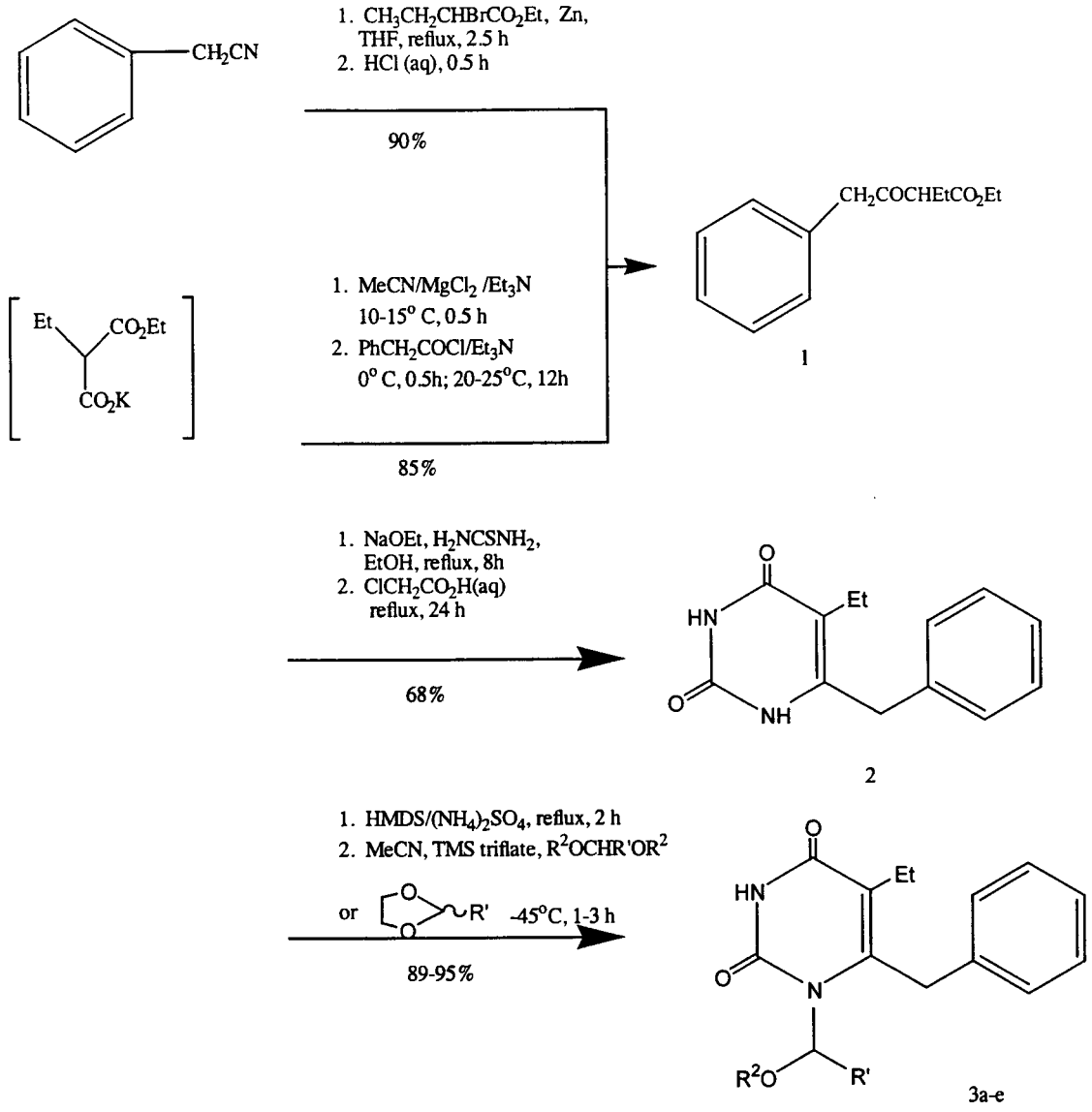
Because of the pharmaceutical activity of MKC-442 alone and in combination with other antiviral agents, there is growing interest in efficient methods for its manufacture.

Since MKC-442 is a 5,6-substituted uracil derivative that has an alkoxyalkyl group in the 1 position (see Figure 1), methods for its synthesis must include steps to add these three 1,5,6-substituents. Typical synthetic routes to MKC-442 have included condensation of the alkoxyalkyl moiety with a 5-substituted thiouracil, followed by desulfurization of the thiouracil, lithiation at the 6-position, reaction with benzaldehyde, subsequent acetylation and eventual reduction of the hydroxy group using hydrogenolysis to yield MKC-442 . Rosowsky, et al., *J. Med Chem.*, 1981, 24, 1177; Tanaka, et al., *J. Med. Chem.* 1992, 35, 4713. See also Baba, et al., Nucleosides and Nucleotides, 14(3-5), 575-583 (1995). Baba et al. noted that it is well known that glycosidation of 6-substituted uracils almost invariably results in the formation of N-3-glycosylated products due to steric hindrance by the substituents, and for that reason the 6-substituent should be introduced after the acyclic portion has been introduced.

Danel, et al. reported a synthesis of 5,6-disubstituted acyluridine derivatives that includes inserting the ethoxymethyl moiety of the molecule at the N-1 position in the last step of the synthesis (*J. Med. Chem.*, 1996, 39, 2427-2431; *Synthesis*, August 1995, 934-936). Danel, et al. first reacts an arylacetonitrile with a 2-bromoester in a Reformatsky reaction to form an ethyl-2-alkyl-4-aryl-3-oxobutyrate (see Scheme 1), i.e., a β-keto ester. The β-keto ester is then condensed with thiourea in the presence of sodium ethoxide to form a 2-thiouracil which is refluxed with chloroacetic acid in aqueous acetic acid overnight to give 6-benzyl-5-ethyluracil. Silylation of the uracil is required prior to condensation with an alkylating agent of choice. While reasonable for small scale, the Danel method has substantial drawbacks for the manufacturing scale preparation of MKC-442, as it requires a

large excess of Zn and the use of sodium metal to generate the base *in situ,* which is a serious safety concern. Also, a 20-fold excess of the ethoxide was specified in the article, which is not reasonable for industrial scale-up. Further, the Danel method required the use of fifteen equivalents of thiourea, which prevents a clean crystallization of the thiouracil derivative. Further, the thiouracil intermediate was not at all soluble in the chloroacetic acid solution used, and when the material was heated to reflux, a sticky mass formed and coated the agitator and flask walls. Finally, when the desulfurization reaction was homogenized using either alcohols or tetrahydrofuran, the thiouracil was converted to an undetermined impurity. On scale up of the Danel method, the yield of MKC-442 dropped dramatically, providing only 25-50% product having only 90% purity.

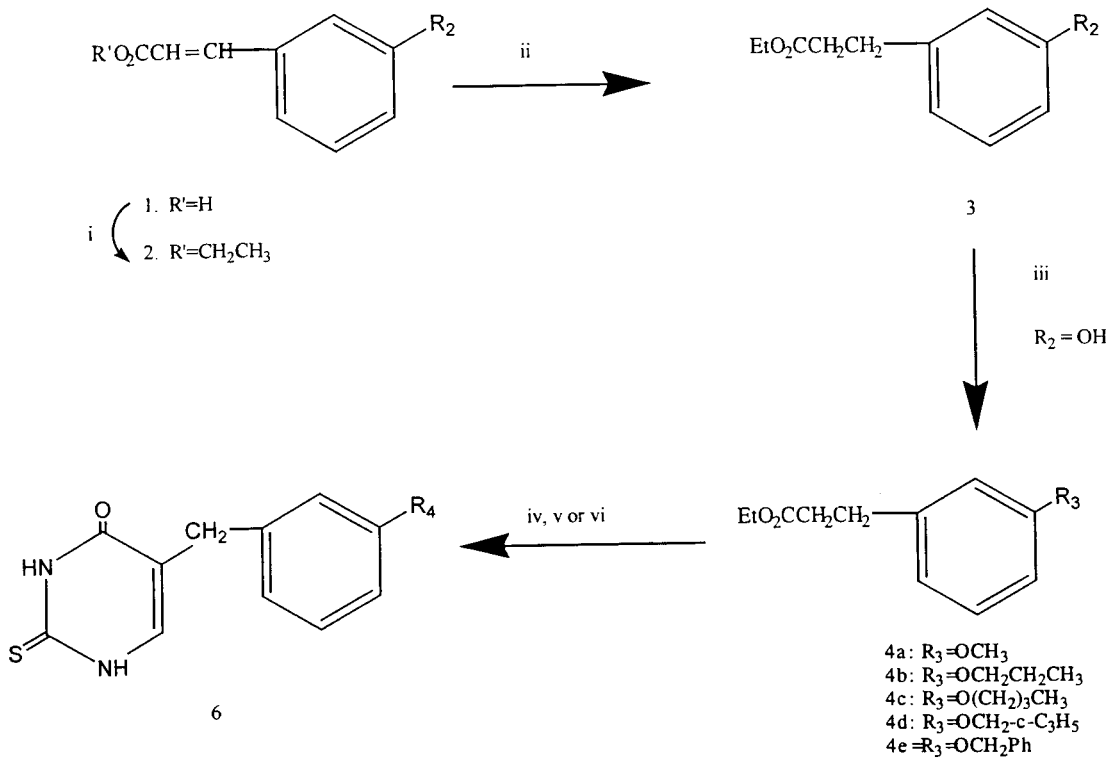
Scheme 1



	R'	R^2
3a	H	Et
3b	Me	Me
3c	Me	Et
3d	H	CH_2CH_2OH
3e	Me	CH_2CH_2OH

Orr and Musso in 1996 reported the synthesis of a 5-substituted uracil derivative (not a 5,6-disubstituted uracil) by the reaction of ethyl phenylpropanoate with thiourea. They reported that, while the conventional literature precedent involves the use of sodium metal as the base in the preparation of the 2-thiouracil from thiourea, it can cause problems in the synthesis and result in a low yield. Synthetic Communications, 26(1), 179-189 (1996). Orr et al. compared the preparations of 2-thiouracil through the reactions of ethyl phenyl propanoate with (i) sodium, ethylformate, diethyl ether, and then thiourea and ethanol with reflux; (ii) lithium diisopropylamide, tetrahydrofuran, ethyl formate, low temperature, then thiourea and ethanol in reflux; (iii) potassium tert-butoxide in tetrahydrofuran, ethyl formate, diethyl ether at ambient temperature, then thiourea and 2-propanol at reflux. Orr et al. reported that the use of lithium diisopropylamide or potassium tert-butoxide instead of sodium metal in the preparation of 5-benzyl-2-thiouracil improves the yield of reaction, and that substituting 2-propanol for ethanol as the solvent for condensing the enolate with thiourea results in improved yields. Using ethyl orthoformate, the Orr reaction cannot be used to provide a 5,6-disubstituted uracil, but at best, a 5-substituted uracil or a 5,5-dihydrouracil (see Scheme 2).

Scheme 2



[a] Reagents: (i) EtOH, Et_2O, HCl, reflux; (ii) EtOH, H_2, PtO_2; (iii) Me_2CO, R_3Br, K_2CO_3; (iv) Na, HCO_2Et, Et_2O then thiourea, EtOH, reflux; (v) LDA, THF, HCO_2Et, -60° - -78° then thiourea, EtOH, reflux; (vi) tert-BuOK in THF, HCO_2Et, Et_2O, ambient temperature; then thiourea, 2-PrOH, reflux.

Baba et al. reported a method to produce MKC-442 by reacting a silylated 5-isopropyl-2-thiouracil with carcinogenic $CH_3CH_2OCH_2Cl$ (KI/CH_2Cl_2) to yield the N-1-ethoxymethyl product (Nucleosides and Nucleotides, 14(3-5), 575-583 (1995)). Lithiation with lithium diisopropylamide (LDA) resulted in a 6-substituted product. Oxidative hydrolysis of the 6-substituted product followed by conventional hydrogenolysis led to MKC-442.

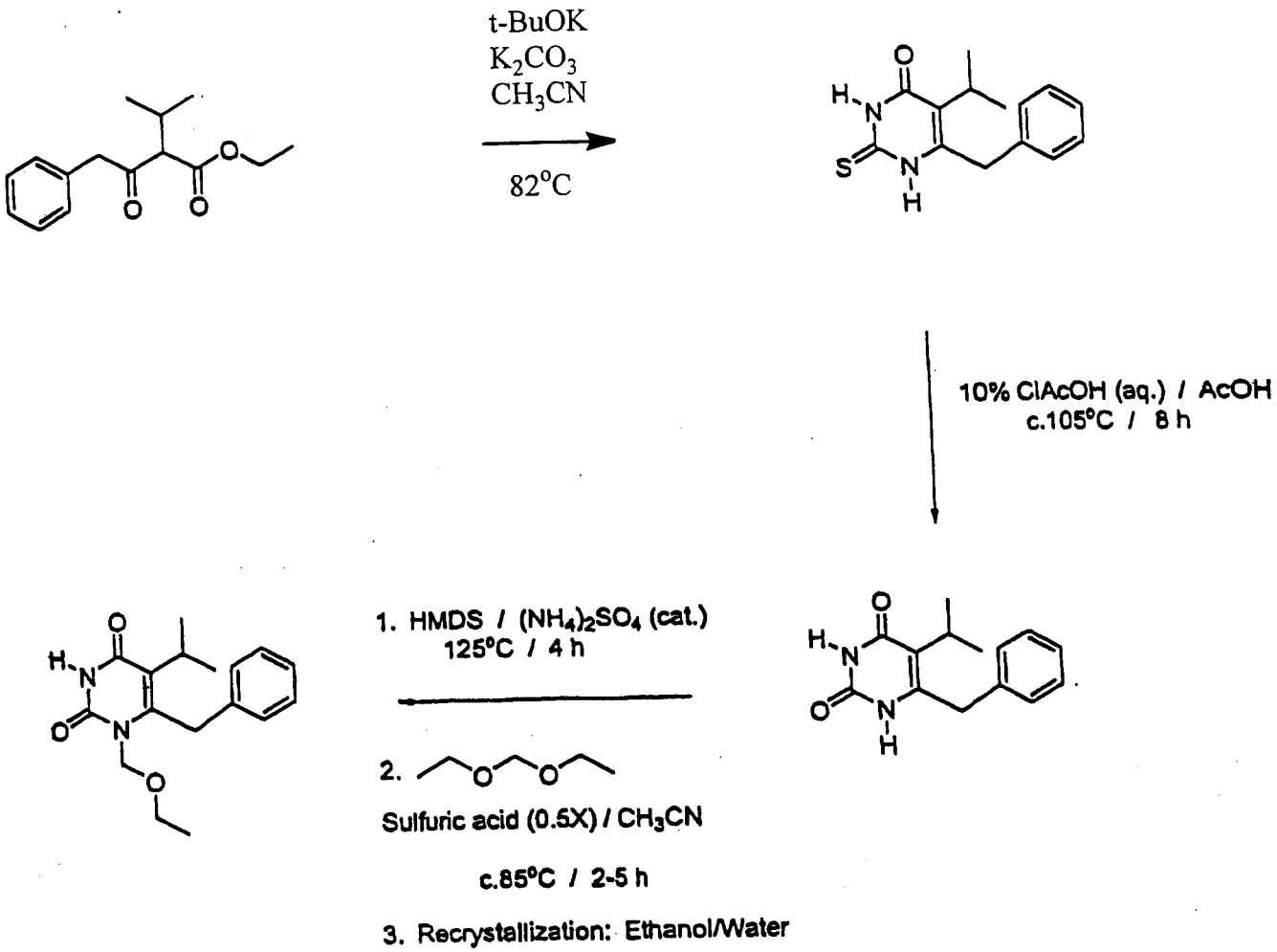
In light of the fact that MKC-442 is useful in the treatment of HIV-infected patients, there is a need to develop cost effective and scalable methods for manufacturing pure MKC-442 in large quantity, high purity, and high yield. It is therefore an object of the present invention to provide an improved synthetic process for preparing 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (MKC-442) in high yield and greater purity.

Summary of the Invention

It has been discovered that a 5,6-disubstituted uracil can be produced in good yield by the reaction of an appropriate β-keto ester with thiourea in the presence of potassium t-butoxide. When the β-keto ester is ethyl-2-isopropyl-3-oxo-4-phenyl-butyrate, the resulting product is 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil, also known as MKC-442.

Therefore, in one embodiment, a method for producing a 5,6-disubstituted uracil is provided that includes the use of two bases simultaneously to effectively synthesize the 5,6-disubstituted uracil in high yield from a β-keto ester. Preferred bases include potassium carbonate and potassium t-butoxide as the co-bases in acetonitrile. This embodiment is depicted in Scheme 3.

Scheme 3


t-BuOK
K_2CO_3
CH_3CN
82°C
10% ClAcOH (aq.) / AcOH
c.105°C / 8 h
1. HMDS / $(NH_4)_2SO_4$ (cat.)
125°C / 4 h
2.
Sulfuric acid (0.5X) / CH_3CN
c.85°C / 2-5 h
3. Recrystallization: Ethanol/Water

As a nonlimiting example for the synthesis of MKC-442, an isopropyl β-keto ester such as ethyl-2-isopropyl-3-oxo-4-phenyl-butyrate can be synthesized using any known method, including from benzyl cyanide and ethyl-2-bromo-3,3-dimethyl-propionate with activated zinc in a Reformatsky reaction. The β-keto ester is then reacted with a two-base system, including but not limited to potassium carbonate and potassium t-butoxide, in a solvent, for example acetonitrile.

The process provides several advantages over the prior art. First, the reaction is a single-step process that proceeds to form a product in greater than 80% yield . Additionally, the two-base system results in products of greater purity. For example, the use of potassium carbonate and potassium t-butoxide in acetonitrile results in a product having a purity of 90-95%.

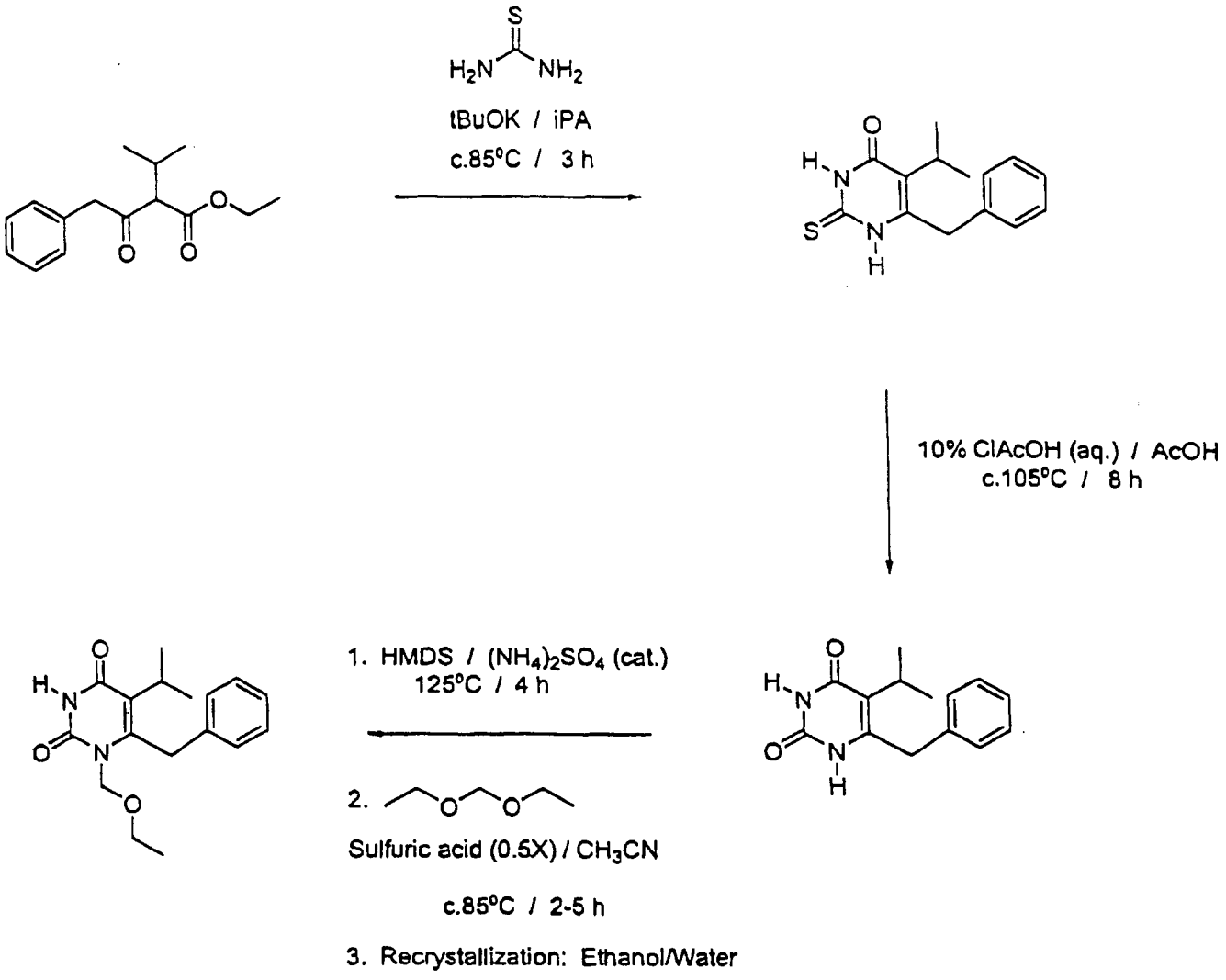
In synthesizing the substituted thiouracil ring, bases of high pK_b alone destroy the starting β-keto ester and have higher levels of impurities. As a result, use of bases with high pK_b alone leads to products of lower yield. Bases of lower pK_bs tend to have longer reaction times and tend to contain residual starting material. It is therefore beneficial to use a two-base system to counteract these tendencies.

Bases useful in the two-base system of the present invention include, but are not limited to potassium carbonate, potassium t-butoxide, sodium carbonate, di-isopropyl amine, triethyl amine, 2,6-dimethyl pyridine, sodium acetate, potassium acetate, ammonia, potassium ethoxide, and potassium cyanide. The bases are used in combination with a solvent.

Solvents useful in the two-base system of the present invention include, but are not limited to acetonitrile, butyronitrile, isobutyronitrile, chloroacetonitrile and other alkyl nitrile solvents, isopropyl alcohol, methanol, ethanol, propanol, butanol, and other alcohol solvents.

In another embodiment of the present invention, a method for producing a 5,6-disubstituted uracil is provided that includes reacting a β-keto ester with thiourea in the presence of potassium t-butoxide, preferably in iso-propyl alcohol. This embodiment of this reaction is depicted in Scheme 4.

Scheme 4


tBuOK / iPA
c.85°C / 3 h
10% ClAcOH (aq.) / AcOH
c.105°C / 8 h
1. HMDS / $(NH_4)_2SO_4$ (cat.)
125°C / 4 h
2.
Sulfuric acid (0.5X) / CH_3CN
c.85°C / 2-5 h
3. Recrystallization: Ethanol/Water

As a nonlimiting example for the synthesis of MKC-442, an isopropyl β-ketoester such as ethyl-2-isopropyl-3-oxo-4-phenyl-butyrate can be synthesized using any known method, including from benzyl cyanide and ethyl-2-bromo-3,3-dimethyl-propionate with activated zinc in a Reformatsky reaction, and then the ethyl-2-isopropyl-3-oxo-4-phenyl-butyrate is condensed with thiourea in the presence of potassium t-butoxide in process step (A) of the present invention to form a benzyl isopropyl thiouracil, which is desulfurized in process step (B), and then the benzyl isopropyl uracil is alkoxyalkylated in process step (C) to form MKC-442. The improved process of the present invention provides several unexpected advantages over the prior art while producing MKC-442 in greater yield and purity.

The process provides several advantages over the prior art. The substitution of t-BuOK for NaOEt in the cyclocondensation reaction of step (A) affords a dramatically purer product. The increased yields gained with t-BuOK have precedent in the literature, however the increased purity of the product obtained is heretofore unknown and unexpected. Additionally, the substitution of t-BuOK for NaOEt afforded a tractable, crude thiouracil, making the workup both manageable and scalable. It is also surprising that this reaction of step (A) occurs with a sub-stoichiometric amount of t-BuOK. Finally, the use of diethoxy methane in the presence of an acid catalyst such as sulfuric acid of step (C), rather than the very toxic TMS triflate or chloromethyl ether used in the prior art, offers a cost advantage as well as a safety benefit.

The slow and controlled evolution of hydrogen sulfide in the desulfurization reaction of step (B) is also unexpected. A rapid and uncontrollable gas evolution would prevent scale up and commercialization of the process.

The alkylation reaction of step (C) has two unexpected aspects associated with it. First, it is surprising that this reaction proceeds so efficiently in the presence of sub-stoichiometric amounts of sulfuric acid. Secondly, it is extremely convenient that the removal of HMDS is not necessary. The alkylation proceeds in an efficient fashion with sub-stoichiometric amounts of sulfuric acid, even in the presence of HMDS.

Detailed Description of the Invention

An improved process for preparing 5,6-disubstituted uracils is provided. This improved process offers several advantages over the prior art. Most significantly, the process

of the present invention produces MKC-442 in higher yields, without sacrificing purity of the product. In fact, the process can yield a product having 95% or greater purity.

The invention includes at least the following embodiments:

A first process for preparing a 5,6-disubstituted uracil, preferably MKC-442, via the reaction of a β-keto ester with thiourea in a two-base system. The process includes the use of two bases simultaneously to effectively synthesize the 5,6-disubstituted uracil. The process includes reacting a β-keto ester with thiourea in the presence of a two-base system and a solvent at temperatures ranging from 80-85 ° C.

The one-step process of this first process of the present invention comprises reacting a 2,4-disubstituted-3-oxo-butyrate, preferably ethyl-2-isopropyl-3-oxo-4-phenylbutyrate, with thiourea in a two-base system and a solvent. Preferred bases for the two-base system include, but are not limited to, potassium t-butoxide and potassium carbonate. A preferred solvent for the reaction includes, but is not limited to, acetonitrile. The reaction proceeds at a temperature from 80 °C to 85 °C. A preferred reaction temperature is about 85 °C.

As used herein, the term "two-base system" refers to the use of two bases simultaneously in the presence of a solvent. Nonlimiting examples of bases included in the two-base system are potassium carbonate, potassium t-butoxide, sodium carbonate, di-isopropyl amine, triethyl amine, 2,6-dimethyl pyridine, sodium acetate, potassium acetate, ammonia, potassium ethoxide, and potassium cyanide. The bases are used in combination with a solvent.

Solvents useful in the two-base system of the present invention include, but are not limited to acetonitrile, butyronitrile, isobutyronitrile, chloroacetonitrile and other alkyl nitrile solvents, isopropyl alcohol, methanol, ethanol, propanol, butanol, and other alcohol solvents.

A second process for preparing a 5,6-disubstituted uracil, preferably MKC-442, that includes:

(i) a step (A) that includes the preparation of a 5,6-disubstituted thiouracil via the reaction of a 2,4-disubstituted-3-oxo-butyrate ester with thiourea in the presence of potassium t-butoxide in an organic solvent, wherein the intermediate is a 5,6-disubstituted-2-thio-uracil;

(ii) the process of step (A) wherein the solvent is an alcohol, preferably isopropyl alcohol;

(iii) the process of step (A) wherein molar ratio of thiourea to 2,4-disubstituted-3-keto-butyrate is not greater than approximately 10% excess, and more preferably no more than 5% excess;

(iv) the process of step (A) wherein the reaction is quenched with water and acetic acid;

(v) a step (B) that includes the process of step (A) further including desulfurizing the 5,6-disubstituted-2-thiouracil to a 5,6-disubstituted-uracil, preferably using 10% chloroacetic acid (aq) in acetic acid;

(vi) the process of step (B) further including isolating the thiouracil prior to desulfurization;

(vii) the process of step (B) wherein the acetic acid is between approximately 25 and 40% of the total solvent volume used, and preferably, approximately 35%;

(viii) the process of step (B) wherein the reaction is heated to between 85° C and 105° C to form a solution;

(ix) a step (C) that includes the silylation of the 5,6-disubstituted uracil of step (v) with any suitable reagent according to known methods;

(x) the process of step (C) wherein the reagent is a silylating agent such as hexamethyldisilizane;

(xi) the process of step (x) wherein the hexamethyldisilizane is reacted in the presence of a catalytic amount of ammonium sulfate;

(xii) reacting the product of step C with an alkylating or alkoxyalkylating agent, for example, diethoxymethane;

(xiii) the process of step (xii) wherein the reaction is accomplished in sulfuric acid or methanesulfonic acid;

(xiv) the process of step (xiii), wherein sub-stoichiometric equivalent amounts of sulfuric acid are used, and preferably, between 0.25 and 0.5 equivalent amounts; and

(xv) the process of step (xiv), wherein the reaction is run in refluxing acetonitrile (or other alkyl nitriles), preferably for 2-5 hours.

The two-stage process of the second process of the present invention comprises steps (A) and (B) in Stage I. Step (A) comprises cyclizing isopropyl-β-ketoester with thiourea and potassium tert-butoxide in isopropyl alcohol at reflux to produce benzyl isopropyl thiouracil. The benzyl thiouracil is then desulfurized under reflux in step (B) to produce benzyl

isopropyl uracil (BIU) using chloroacetic solution, 10% ClAcOH (aq), AcOH. The reaction work up involves a quench with water and acetic acid, then filtration of a crystalline solid in 70-80% yield.

The Stage I process differs from Danel's process (J. Med. Chem. 1996, 39,2427-2431) by eliminating the use of sodium metal, used by Danel to generate the base *in situ*. Elimination of the sodium resolved a serious safety concerns during scale up. Danel also specified a 20-fold excess of the ethoxide while only a 5%-20% excess is required by the process of the present invention. Additionally, the Danel process produces a thiouracil intermediate which, when heated to reflux, forms a sticky mass which coats the agitator and flask walls. In contrast, using discretely isolated thiouracil produced by the process of step (A) of the present invention, conversion and purity are increased. The addition of acetic acid to the reaction in step (B) (approximately 35% of the total solvent volume) accomplished two tasks: it allowed for the formation of a solution when heated to 95°C; it served as a recrystallization cosolvent when the reaction was scaled. The process of the present invention eliminates the sticky mass formed by the Danel process, making the improved process scalable to production sized equipment. In addition, the BIU was recovered in approximately 90% yield of >98% pure material.

In Stage II of the process of the present invention, BIU is silylated with 1,1,1,3,3,3-hexamethyldisilazane (HMDS) in the presence of a catalytic amount of ammonium sulfate, followed by alkylation with diethoxymethane in acetonitrile containing sulfuric acid. This process is referred to herein as step (C). Optionally, one can also use methanesulfonic acid as the acid catalyst. The conditions were optimized to employ sub-stoichiometric amounts (0.25 - 0.5 equivalents) of concentrated sulfuric acid at reflux in acetonitrile for 2-5 hours in order to effect alkylation. Typical reaction profiles showed MKC-442 at 90-95% yields possessing <3% BIU as an impurity.

The two-stage process of the present invention provides several improvements over the prior art processes. First, the substitution of t-BuOK for NaOEt in the cyclocondensation reaction of step (A) affords a dramatically purer product. The increased yields gained with t-BuOK has literature precedence, but in this case, the increased purity of the product obtained was unexpected. Moreover, the substitution of t-BuOK for the NaOEt unexpectedly afforded a tractable, crude thiouracil, making the workup both manageable and scalable. With the

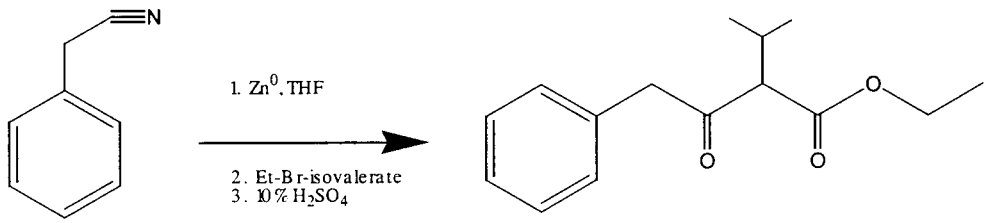
NaOEt, an intractable, sticky mass was obtained, making scale-up difficult. Also, it is surprising that this reaction occurs with a sub-stoichiometric amount of t-BuOK.

Another advantage to the process of the present invention is the slow and controlled evolution of hydrogen sulfide in the desulfurization reaction of step (B). A rapid and difficult-to-control gas evolution would have severely limited the scalability of the process.

Finally, the alkylation reaction of step (C) has several unexpected aspects associated with it. First, it is surprising that this reaction proceeds so efficiently in the presence of sub-stoichiometric amounts of sulfuric acid. Second, it is unexpected and quite convenient that the removal of the HMDS is unnecessary. The alkylation proceeds in an efficient fashion, with sub-stoichiometric amounts of sulfuric acid, even in the presence of HMDS. Finally, the use of diethoxymethane as an alkylating agent offers a significant advantage over the prior art processes which employ trimethylsilyl triflate or chloromethyl ether. Not only is the diethoxymethane less expensive, it is also a significantly less toxic reagent, making its use safer than the reagents of the prior art.

Example 1

Stage I: Synthesis of the i-propyl β-ketoester



A 12 liter reaction flask fitted with a mechanical stirrer and twin condensers was purged with argon and charged with -100 mesh zinc metal (301 g, 4.6 mol) and 5000 ml tetrahydrofuran (THF). A catalytic amount of iodine (3.0 g) was added and the suspension was stirred until the color faded. The activated zinc suspension was then treated with benzyl cyanide (179 g, 1.53 mol) and the mix was heated to 60°C.

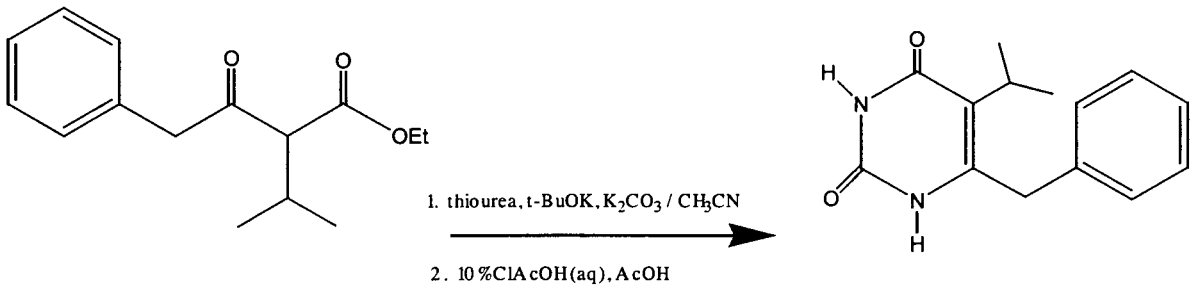
The reaction was then treated with ethyl 2-bromoisovalerate (481 g, 2.30 mol). Approximately 50 g of the bromo ester were added, and the reaction was allowed to initiate,

raising the batch temperature to 69°C after five minutes. The remaining ester was then added over 35 minutes, so that a minimal reflux was maintained. Following the addition, the reaction was left to stir at 65°C for one hour.

An in-process sample was obtained and quenched with 1.8 M sulfuric acid. Gas chromatography showed 90% isopropyl β-ketoester, and 1% benzyl cyanide. The batch was then cooled to 35°C and 4L THF were removed by evaporation under reduced pressure. The reaction was then diluted with 3L EtOAc and was carefully quenched with 2.0L 1.8M H_2SO_4(aq). After one hour, the layers were separated. The organics were then washed with 1L saturated $NaHCO_3$ and 500 ml brine. The aqueous layers were then back extracted with 250 ml EtOAc each. The organics were combined and concentrated to an oil. 341 g 90% yield, 90% AUC (area under the curve) by gas chromatography. The material is typically used as is, however it can be distilled at 5 mm Hg, 110-120°C to give 240 g 96% (AUC) by gas chromatography.

Example 2

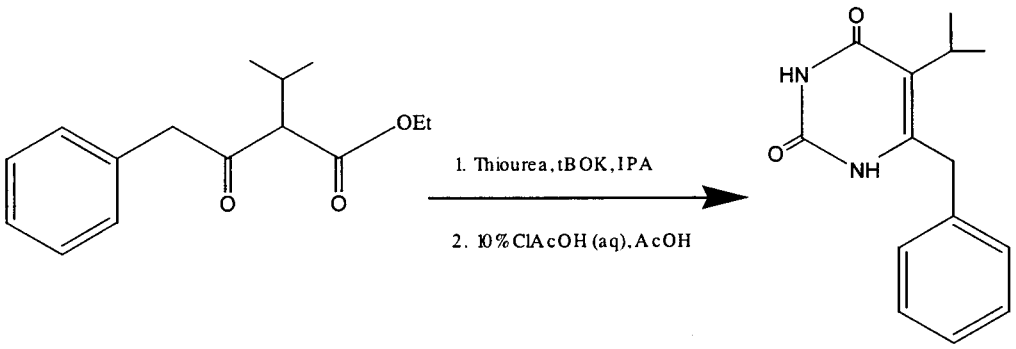
Synthesis of Isopropyl Benzyl Uracil Using a Two-Base System



A 1000 mL round bottom flask fitted with a mechanical stirrer and condensor was charged with isopropyl – β -ketoester (74.0g, 289 mmol), thiourea (45.6g, 599 mmoL), and acetonitrile (500 mL). The reaction mixture was then charged with potassium t-butoxide (37.0g, 330 mmoL), potassium carbonate (61.9g, 448 mmoL), and heated to 82°C. After 3 hours, the mix was cooled to c. 40°C and quenched with water (300 mL). The volume of the entire mixture was reduced by half, the pH was adjusted to c. 3 (via HCl), and the precipitated solids were collected via filtration. The solids were dried at 45°C for 18 h

affording 62.7g (81%) of a white solid having a purity of 95% (AUC).

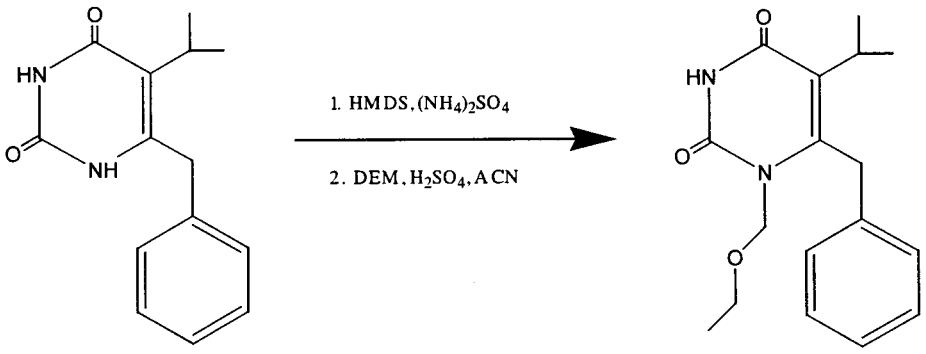
Synthesis of Isopropyl Benzyl Uracil



A 3000 ml 4 neck round bottom flask fitted with a mechanical stirrer and condenser was charged with iso-propyl beta ketoester (259 g, 1.04 mol), thiourea (83 g, 1.1 mol) and 1150 ml isopropanol. The reaction was then treated with potassium t-butoxide (140 g, 1.25 mol) added in 20 g portions, and the mix was heated to 85°C. After 2 hours, the mix was cooled to 60°C and quenched with water (600 ml). The 2-propanol was removed by evaporation under reduced pressure and the remaining solution was cooled to 30°C and further diluted with 600 ml water and 450 ml acetic acid (pH=4). The solids were collected by vacuum filtration and were washed with 2 x 250 ml water. Dried to leave 200 g, >99.5% AUC by HPLC, 78% yield.

166 g of the thiouracil were resuspended in a solution containing water (450 ml), glacial acetic acid (200 ml), and chloracetic acid (250 g). The heterogeneous reaction was heated at 95°C. After about one hour, a solution formed, and after one additional hour, a white solid precipitated. The reaction was heated for six more hours then was cooled to room temperature and the product was collected by vacuum filtration. The product, a white crystalline solid, was washed with water (2 x 150 ml) and dried in a vacuum oven (60°C, 5 mm Hg) overnight. The product was isolated in a 70% overall yield from the ketoester and had a 99.5% AUC purity by HPLC.

Stage 2: Alkylation of Isopropyl Benzyl Uracil, Synthesis of MKC-442



A 1L 3 neck round bottom flask was charged with 6-benzyl-5-i-propyl uracil (BIU) (50 g, 0.20 mol), ammonium sulfate (0.5 g, catalytic) and 1,1,1,3,3,3-hexamethyldisilazane (258 g, 1.6 mol). The slurry was heated to reflux (125-130°C) under argon for four hours. The resulting solution was concentrated to a thick oil (about 125 ml) under reduced pressure (85°C, 30 mm Hg). The oil was resuspended in 350 ml acetonitrile. Sulfuric acid (4.9 g, 0.05 mol) followed by diethoxymethane (36 g, 0.30 mol) were added at 80°C. A precipitate formed after the H_2SO_4 was added, but a solution reformed after about 30 minutes. The solution was stirred for 5 hours. An additional portion of H_2SO_4 was added (2.5 g, 0.025 mol) and the mix was heated for an additional 2.5 hours.

After 10 hours, HPLC showed <3% remaining starting material and >90% MKC-442. The reaction was quenched with 175 ml 0.5 N KOH at 50-60°C (pH=10-11) and the acetonitrile was removed by evaporation under reduced pressure (65-70°C, 30 m Hg). The remaining slurry was diluted with 175 ml ethyl acetate and the layers were split. The aqueous layer was washed with ethyl acetate (50 ml) and the organic fractions combined. The organic fractions were concentrated to a volume of about 75 ml, then were chased with 75 ml ethanol to a volume of about 75 ml. The crude MKC-442 was then taken up in an additional 100 ml EtOH at 85°C and was diluted with 60 ml H_2O, cooled to ambient and crystallized. After 2 hours, the crude material was filtered and washed with 25 ml 25% EtOH in water. 52 g, 94% HPLC AUC.

The material was then taken up in 115 ml EtOH at 85°C, diluted with 50 ml H_2O, and the product was left to cool to ambient temperature and crystallize. The product was filtered and washed twice with 25 ml 25% EtOH in water to leave 45 g, 99.8% AUC, with 0.10% (AUC) BIU.

This invention has been described with reference to its preferred embodiments. Variations and modifications of the invention, will be obvious to those skilled in the art from the foregoing detailed description of the invention. It is intended that all of these variations and modifications be included within the scope of this invention.

We claim:

1. A process for preparing 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (MKC-442) comprising

(i) preparing a 5,6-disubstituted thiouracil by reacting a 2,4-disubstituted-3-oxo-butyrate ester with thiourea in a two-base system in the presence of a solvent;

(ii) desulfurizing the 5,6-disubstituted-2-thiouracil in chloracetic acid (aq) in acetic acid to form a 5,6-disubstituted-uracil;

(iii) silylating the 5,6-disubstituted uracil with a suitable reagent according to known methods;

(iv) reacting the product of step (iii) with an alkylating or alkoxyalkylating agent to form 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (MKC-442).

2. The process of claim 1, wherein the two-base system comprises potassium t-butoxide and potassium carbonate.

3. The process of claim 1, wherein the solvent is acetonitrile.

4. The process of claim 1, wherein the reaction is conducted at a temperature between 80-85 ° C.

5. The process of claim 1, wherein the two-base system comprises potassium t-butoxide and potassium carbonate, the solvent is acetonitrile and the reaction is conducted at a temperature between 80-85 ° C.

6. A process for preparing 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (MKC-442) comprising

(i) preparing a 5,6-disubstituted thiouracil by reacting a 2,4-disubstituted-3-oxo-butyrate ester with thiourea in the presence of potassium t-butoxide in an organic solvent, to form a 5,6-disubstituted-2-thio-uracil intermediate;

(ii) desulfurizing the 5,6-disubstituted-2-thiouracil in chloracetic acid (aq) in acetic acid to form a 5,6-disubstituted-uracil;

(iii) silylating the 5,6-disubstituted uracil with a suitable reagent according to known methods;

(iv) reacting the product of step (iii) with an alkylating or alkoxyalkylating agent to form 6-benzyl-1-(ethoxymethyl)-5-isopropyluracil (MKC-442).

7. The process of claim 6, wherein in step (i), the solvent is an alcohol.

8. The process of claim 7, wherein the alcohol is isopropyl alcohol.

9. The process of claim 6, wherein the molar ratio of thiourea to 2,4-disubstituted-3-keto-butyrate is not greater than approximately 10% excess.

10. The process of claim 9, wherein the molar ration of thiourea to 2,4-disubstituted-3-keto-butyrate is no more than 5% excess.

11. The process of claim 6, wherein the reaction of step (ii) is quenched with water and acetic acid.

12. The process of claim 11, wherein the reaction of step (ii) is quenched with water and 10% chloroacetic acid (aq) in acetic acid.

13. The process of claim 6, wherein the thiouracil formed in step (i) is isolated prior to desulfurization.

14. The process of claim 6, wherein in step (ii) the acetic acid is between approximately 25 and 40% of the total solvent volume used

15. The process of claim 14, wherein in step (ii) the acetic acid is approximately 35%.

16. The process of claim 6, wherein in step (ii) the reaction is heated to between 85° C and 105° C to form a solution.

17. The process of claim 6, wherein in step (iii) the reagent is a silylating agent.

18. The process of claim 17, wherein the silylating agent is hexamethyldisilizane.

19. The process of claim 18, wherein the hexamethyldisilizane is reacted in the presence of a catalytic amount of ammonium sulfate.

20. The process of claim 6, wherein in step (iv) the alkoxyalkylating agent is diethoxymethane.

21. The process of claim 20, wherein the reaction is accomplished in sulfuric acid or methanesulfonic acid.

22. The process of claim 21, wherein sub-stoichiometric equivalent amounts of sulfuric acid are used.

23. The process of claim 22, wherein the amount of sulfuric acid is between 0.25 and 0.5 equivalent amounts.

24. The process of claim 23, wherein the reaction is run in refluxing acetonitrile for 2-5 hours.