

IMPROVEMENTS IN THE PREPARATION OF INTERMEDIATES LEADING TO [4-(5-AMINOMETHYL-2-
10 FLUORO-PHENYL)-PIPERIDIN-1-YL]-(4-BROMO-3-METHYL-5-PROPOXY-THIOPHEN-2-YL)-
METHANONE HYDROCHLORIDE

FIELD OF THE INVENTION

This invention is directed to improvements in the preparation of intermediates leading to [4-(5-
15 aminomethyl-2-fluoro-phenyl)-piperidin-1-yl]-(4-bromo-3-methyl-5-propoxy-thiophen-2-yl)-
methanone hydrochloride.

BACKGROUND OF THE INVENTION

Mast cell mediated inflammatory conditions, in particular asthma, are a growing public health concern.
20 Asthma is frequently characterized by progressive development of hyper-responsiveness of the trachea
and bronchi to both immunospecific allergens and generalized chemical or physical stimuli, which lead
to the onset of chronic inflammation. Leukocytes containing IgE receptors, notably mast cells and
basophils, are present in the epithelium and underlying smooth muscle tissues of bronchi. These
leukocytes initially become activated by the binding of specific inhaled antigens to the IgE receptors
25 and then release a number of chemical mediators. For example, degranulation of mast cells leads to the
release of proteoglycans, peroxidase, arylsulfatase B, chymase, and tryptase, which results in
bronchiole constriction.

Tryptase is stored in the mast cell secretory granules and is the major secretory protease of human mast
30 cells. Tryptase has been implicated in a variety of biological processes, including degradation of
vasodilating and bronchorelaxing neuropeptides (Caughey, et al., J. Pharmacol. Exp. Ther., 1988, 244,
pages 133-137; Franconi, et al., J. Pharmacol. Exp. Ther., 1988, 248, pages 947-951; and Tam, et al.,
Am. J. Respir. Cell Mol. Biol., 1990, 3, pages 27-32) and modulation of bronchial responsiveness to
histamine (Sekizawa, et al., J. Clin. Invest., 1989, 83, pages 175-179).

As a result, tryptase inhibitors may be useful as anti-inflammatory agents (K Rice, P.A. Sprengler, *Current Opinion in Drug Discovery and Development*, 1999, 2(5), pages 463-474) particularly in the treatment of chronic asthma (M.Q. Zhang, H. Timmerman, *Mediators Inflamm.*, 1997, 112, pages 311-317), and may also be useful in treating or preventing allergic rhinitis (S. J. Wilson et al, *Clin. Exp.*
5 *Allergy*, 1998, 28, pages 220-227), inflammatory bowel disease (S.C. Bischoff et al, *Histopathology*, 1996, 28, pages 1-13), psoriasis (A. Naukkarinen et al, *Arch. Dermatol. Res.*, 1993, 285, pages 341-346), conjunctivitis (A.A.Irani et al, *J. Allergy Clin. Immunol.*, 1990, 86, pages 34-40), atopic dermatitis (A. Jarvikallio et al, *Br. J. Dermatol.*, 1997, 136, pages 871-877), rheumatoid arthritis (L.C Tetlow et al, *Ann. Rheum. Dis.*, 1998, 54, pages 549-555), osteoarthritis (M.G. Buckley et al, *J.*
10 *Pathol.*, 1998, 186, pages 67-74), gouty arthritis, rheumatoid spondylitis, and diseases of joint cartilage destruction.

In addition, tryptase has been shown to be a potent mitogen for fibroblasts, suggesting its involvement in the pulmonary fibrosis in asthma and interstitial lung diseases (Ruoss et al., *J. Clin. Invest.*, 1991,
15 88, pages 493-499).

Therefore, tryptase inhibitors may be useful in treating or preventing fibrotic conditions (J.A. Cairns and A.E. Walls, *J. Clin. Invest.*, 1997, 99, pages 1313-1321) for example, fibrosis, scleroderma, pulmonary fibrosis, liver cirrhosis, myocardial fibrosis, neurofibromas and hypertrophic scars.

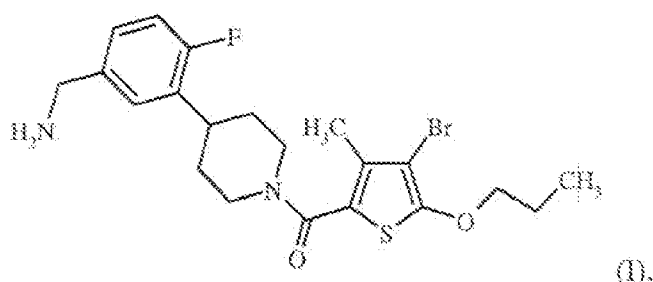
20 Additionally, tryptase inhibitors may be useful in treating or preventing myocardial infarction, stroke, angina and other consequences of atherosclerotic plaque rupture (M. Jeziorska et al, *J. Pathol.*, 1997, 182, pages 115-122).

25 Tryptase has also been discovered to activate prostromelysin that in turn activates collagenase, thereby initiating the destruction of cartilage and periodontal connective tissue, respectively.

Therefore, tryptase inhibitors could be useful in the treatment or prevention of arthritis, periodontal disease, diabetic retinopathy, and tumor growth (W.J. Beil et al, *Exp. Hematol.*, (1998) 26, pages 158-
30 169). Also, tryptase inhibitors may be useful in the treatment of anaphylaxis (L.B. Schwarz et al, *J. Clin. Invest.*, 1995, 96, pages 2702-2710), multiple sclerosis (M. Steinhoff et al, *Nat. Med. (N. Y.)*, 2000, 6(2), pages 151-158), peptic ulcers and syncytial viral infections.

The compound of formula I,

-3-



and its preparation for use in the treatment of disease states capable of being modulated by the inhibition of tryptase, are encompassed by U.S. Patent No. 6,977,263 and WO2005/097780. The compound of formula **I** is particularly useful for treating a patient suffering from conditions that can be ameliorated by the administration of an inhibitor of tryptase, e.g., mast cell mediated inflammatory conditions, inflammation, and diseases or disorders related to the degradation of vasodilating and bronchorelaxing neuropeptides.

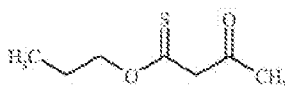
One method for preparing the compound of formula **I** disclosed in WO2005/097780 involves the preparation of the intermediate compound **13**, see Scheme II, in a three-step procedure in an overall approximate yield of 23%.

The present invention is directed to improvements in the method of preparing intermediate compound **13**. Additionally, the method is focused on improving safety and industrial hygiene advantages that would eliminate the need for using carbon disulfide and potassium hydride in the reaction. Furthermore, the method is focused such as to be more amenable for the manufacture of large-scale pharmaceutical amounts of the compound of formula **I**. The method would also eliminate three chromatographic separation steps and reduce the total reaction time of the three-step procedure.

SUMMARY OF THE INVENTION

The present invention is directed to improvements in the preparation of 3-oxo-1-propoxy-but-1-enylsulfanyl)-acetic acid methyl ester (compound of formula **13**) and 3-oxo-thiobutyric acid O-propyl ester (compound of formula **8**), which are useful intermediates for the preparation of the compound of formula **I**.

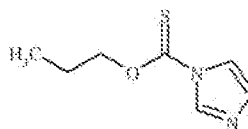
Furthermore, the present invention is directed to a method for preparing a compound of formula **8**



8,

comprising condensing the compound of formula **7**

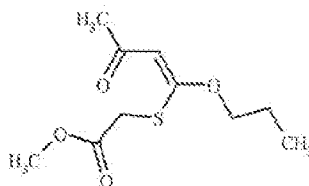
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7,

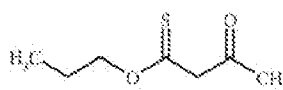
with acetone.

Furthermore, the present invention is directed to a method for preparing a compound of formula 13



13,

comprising alkylating a compound of formula 8



8,

using methyl bromoacetate.

Aspects, features and advantages of the present invention will be better understood from the following detailed descriptions, all of which are given by way of illustration only, and are not limitative of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The present invention will be better appreciated by reference to the following Detailed Description.

Definitions

As used above, and throughout the description of the invention including the appended claims, the following abbreviations and terms, unless otherwise indicated, are understood to have the following meanings:

"Compound(s) of the present invention", and equivalent expressions, are meant to embrace the intermediates of formulae 7, 8 and 13, which are useful intermediates for the preparation of the compound of formula I, as described herein. Reference to intermediates, whether or not they themselves are claimed, is meant to embrace the salts, and solvates, where the context so permits. For the sake of clarity, particular instances when the context so permits are sometimes indicated in the text,

but these instances are purely illustrative and they are not intended to exclude other instances when the context so permits.

"Treatment" or "treating" includes prophylactic therapy as well as treatment of an established condition.

"Patient" means a human or other mammal.

"Effective amount" is meant to describe an amount of a compound effective in producing the desired therapeutic effect.

Particular Embodiments

In a particular embodiment, the present invention is directed to the method for preparing a compound of formula 8 comprising condensing the compound of formula 7 with acetone, wherein the condensing is carried out in the presence of an aprotic organic solvent selected from an ethereal solvent and a hydrocarbon solvent.

In another particular embodiment, the present invention is directed to having an ethereal solvent selected from tetrahydrofuran, 2-methyltetrahydrofuran and tert-butyl methyl ether.

Another particular embodiment of that invention is wherein the hydrocarbon solvent selected from toluene and heptane.

Another particular embodiment of that invention is directed to condensing at a temperature from about 15° C to about 55° C.

Another particular embodiment of that invention is directed to condensing at a temperature from about 25° C to about 45° C.

Another particular embodiment of that invention is directed to condensing at a temperature of about 40° C.

Another particular embodiment of that invention is directed to condensing in the presence of an organic metal base.

Another particular embodiment of that invention is wherein the organic metal base is selected from an alkali metal amide base and an alkali metal hydride.

Another particular embodiment of that invention is wherein the alkali metal amide base is selected from lithium diisopropylamide, lithium dicyclohexylamide, lithium (bis)trimethylsilyl amide, sodium (bis)trimethylsilyl amide and potassium (bis)trimethylsilyl amide.

- 5 Another particular embodiment of that invention is wherein the alkali metal amide base is sodium (bis)trimethylsilyl amide.

Another particular embodiment of that invention is wherein the alkali metal hydride is selected from lithium hydride, sodium hydride and potassium hydride.

- 10 In another particular embodiment, the present invention is directed to the method for preparing a compound of formula 13 comprising alkylating a compound of formula 8 using methyl bromoacetate wherein the alkylating is carried out in the presence of an aprotic organic solvent, a mixture of aprotic organic solvents, or in the presence of a mixture containing a polar aprotic solvent and an ethereal solvent.
- 15

In another particular embodiment, the present invention is wherein the aprotic organic solvent is selected from a polar aprotic solvent and a chlorinated hydrocarbon solvent.

- 20 Another particular embodiment of that invention is wherein the polar aprotic solvent is selected from dimethylformamide, 1-methyl-2-pyrrolidone and dimethylsulfoxide.

Another particular embodiment of that invention is wherein the ethereal solvent is selected from tetrahydrofuran, 2-methyltetrahydrofuran and tert-butyl methyl ether.

- 25 In another particular embodiment, the present invention is directed to having dichloromethane as a chlorinated hydrocarbon solvent.

- Another particular embodiment of that invention is directed to alkylating at a temperature from about 0° C to about 50° C.
- 30

Another particular embodiment of that invention is directed to alkylating at a temperature from about 5° C to about 40° C.

- 35 Another particular embodiment of that invention is directed to alkylating at a temperature from about 8° C to about 35° C.

Another particular embodiment of that invention is directed to alkylating in the presence of an alkylamine base.

Another particular embodiment of that invention is wherein the alkylamine base is selected from triethylamine and diisopropylethylamine.

Another particular embodiment of that invention is wherein the alkylamine base is triethylamine.

Preparatory Details

The intermediate of formula **13** is prepared as described herein.

In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example, amino groups, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Greene and P.G.M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991. In particular, the compound of formula **1** may be prepared as shown in Schemes I-II, *infra*.

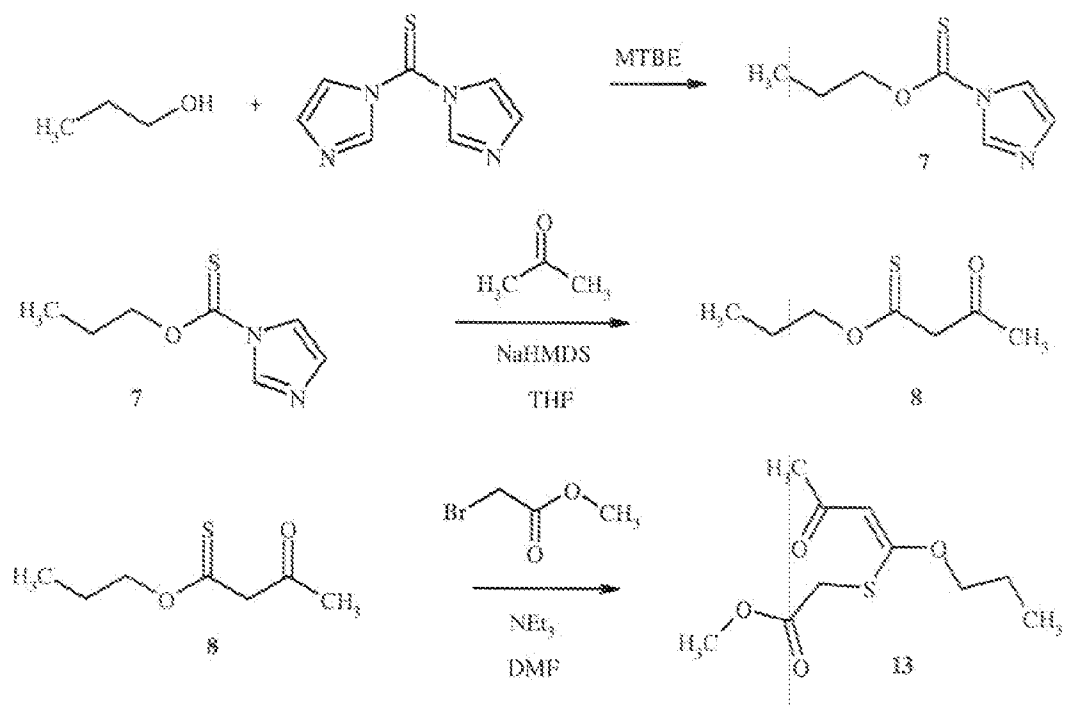
For example, the compound of the present invention is an achiral compound whose preparation is comprised of the stepwise procedures that culminate in the preparation of thiocarbamate **13**, as shown in Scheme I. Scheme II below then shows the stepwise procedures that result from reacting the thiocarbamate compound **13**, to culminate in the preparation of the compound of formula **1a**, which is the hydrochloride salt form of the compound of formula **1**, discussed *supra*. The preparations of the present inventions, the intermediates of the formulae **7**, **8** and **13**, are discussed in turn below.

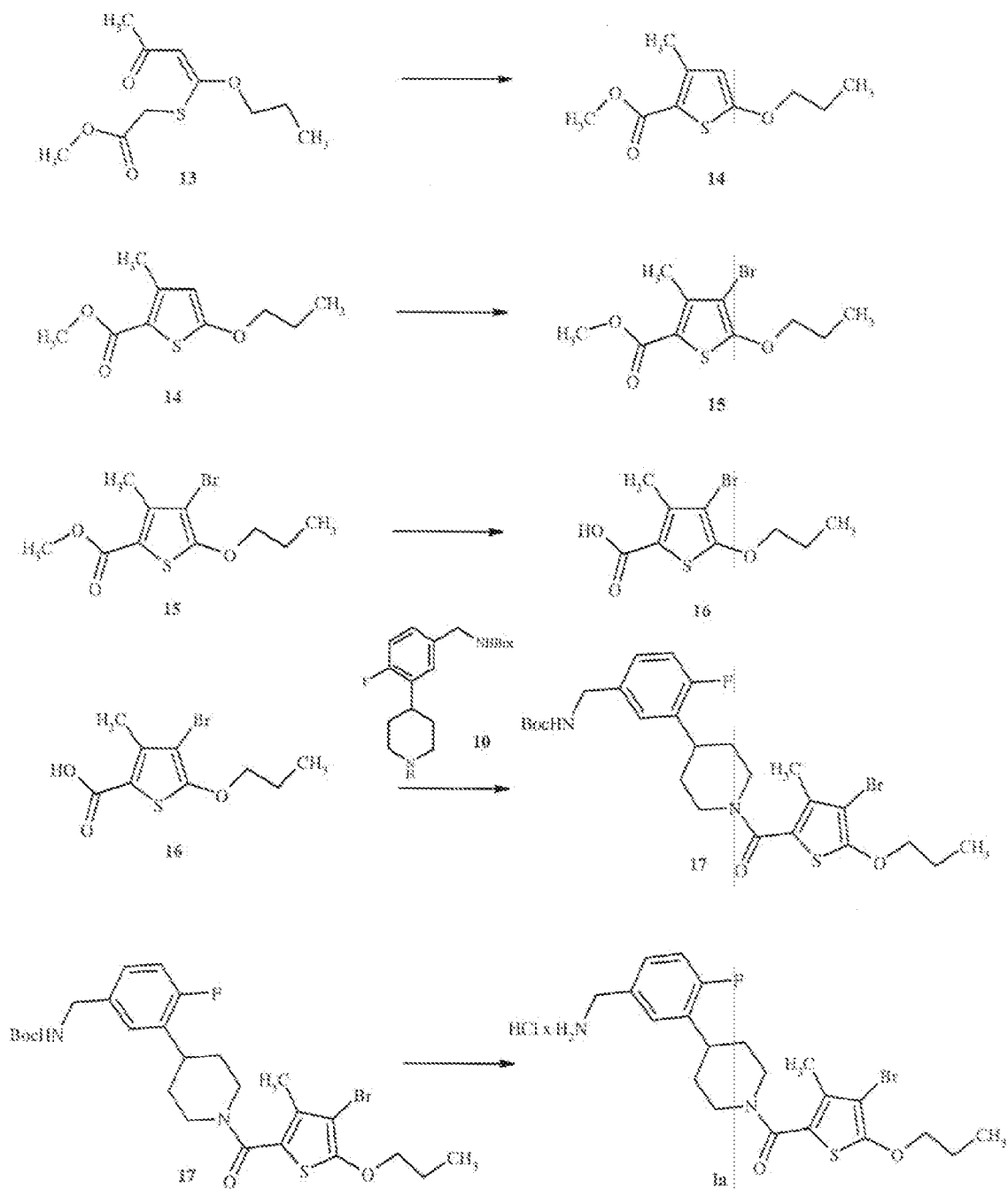
1,1'-thiocarbonyldiimidazole is converted to compound **7** by reacting 1-propanol in the presence of an ethereal solvent, aromatic hydrocarbon solvent or an ester solvent, such as methyl tert-butyl ester (MTBE), to yield thiocarbamate compound **7**.

Compound **7** is converted to compound **8** by condensing compound **7** with acetone in the presence of an ethereal solvent or aromatic hydrocarbon solvent, such as anhydrous tetrahydrofuran (THF) and adding the appropriate base to yield the keto-thioester product, i.e., the compound of formula **8**.

Compound **8** is converted to compound **9** by using an alkylating agent, such as methyl bromoacetate, in the presence of a chlorinated hydrocarbon solvent, polar aprotic solvent or a mixture of polar aprotic solvents, such as dimethylformamide (DMF), to yield the S-alkylated product, i.e., the compound intermediate of formula **13**.

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Scheme 1

Scheme II

- 5 The starting materials and intermediates may be prepared by the application or adaptation of known methods, for example methods as described in the Reference Examples or their obvious chemical equivalents.

The present invention is also directed to some intermediates in the above schemes and, as such, the
 10 processes described herein for their preparation constitute further features of the present invention.

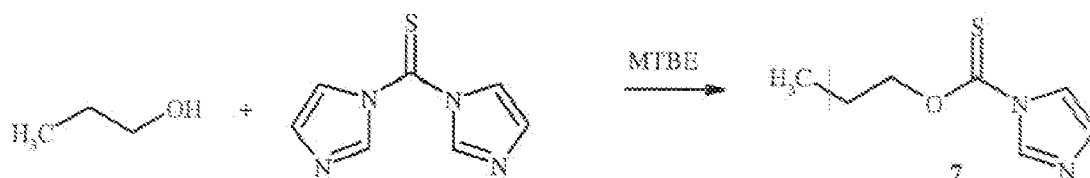
Examples

The present invention may be better understood by reference to the following non-limiting Examples, which are provided as exemplary of the invention. The following examples are presented in order to more fully illustrate particular embodiments of the invention. They should in no way be construed, however, as limiting the broad scope of the invention.

In the nuclear magnetic resonance spectra (NMR), reported *infra*, the chemical shifts are expressed in ppm relative to tetramethylsilane. Abbreviations have the following significances: br = broad, dd = double doublet, s = singlet; m = multiplet.

EXAMPLE 1

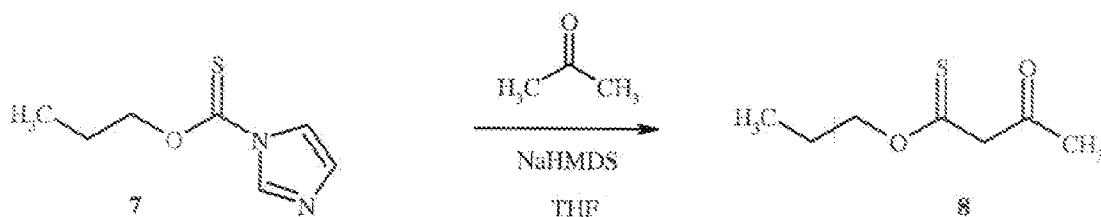
Preparation of Imidazole-1-carbothioic acid O-propyl ester



To the suspension of 1,1'-thiocarbonyldiimidazole (31.6 g, 177.3 mmol) methyl tert-butyl ether (MTBE, 95 mL) at 25°C is added 1-propanol (11.7 g, 14.6 mL, 195 mmol). Within 1 hour the reaction mixture reaches 28°C and becomes a clear solution. TLC analysis (SiO₂, EtOAc eluent, R_f of the product, 0.75; R_f of the starting material, 0.15) shows that the reaction is complete. The reaction mixture is partitioned between water (75 mL) and MTBE (25 mL). The organic phase is washed with water (75 mL), is saturated sodium bicarbonate solution (50 mL), brine (50 mL) and is concentrated on a rotary evaporator to an amber oil, compound **7** (28.5 g, 94% yield). Anal. Calculated for C₇H₉N₂OS: C, 49.39; H, 5.92; N, 16.46. Found: C, 49.47; H, 6.06; N, 16.50. HPLC purity: 98.4% by area at 225 nm (R_t = 2.5 min). MS (ES+) m/z 171 (M+H). ¹H NMR (300 MHz, CDCl₃) δ 8.33 (m, 1 H), 7.62 (m, 1 H), 7.02 (m, 1 H), 4.61 (t, 2H), 1.90 (m 2H), 1.06 (t, 3H). DSC: T_{onset} = 95°C, (579 kJ / kg). *Note: The material should be stored in refrigerator and used within 2 days. If prolonged storage is necessary it is recommended to keep it as a MTBE solution.*

EXAMPLE 2

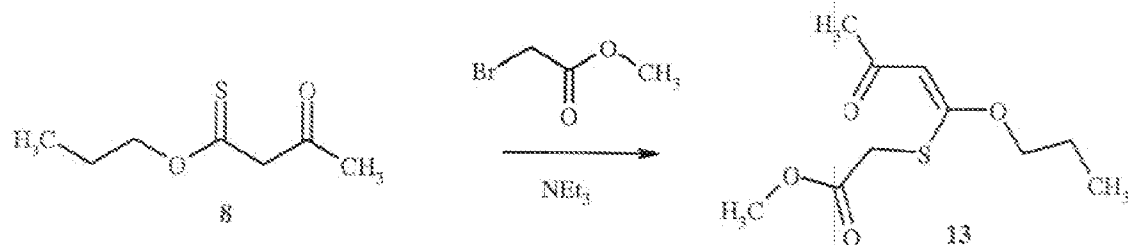
Preparation of 3-Oxo-thiobutyric acid O-propyl ester



To the solution of compound **7** (27.8 g, 163 mmol) and acetone (26.6 g, 457 mmol) in anhydrous THF (164 mL), is added dropwise a 2M solution of sodium (bis)trimethylsilyl amide in THF (163 mL, 326 mmol) over 25 minutes, between room temperature and 40°C. Following the end of addition, the reaction is completed as determined by TLC and HPLC analysis. TLC (SiO₂, EtOAc / heptane 1:2 eluent, R_f of the product, 0.70; and R_f of the starting material, 0.28). The reaction mixture is cooled to room temperature, then it is quenched with 200 mL of water. The phases are separated and the organic (top phase) is eliminated. The aqueous phase is cooled to 10°C and is acidified with aqueous 6N HCl solution to below pH 5, and it is extracted with MTBE (200 mL). The organic phase is washed with saturated sodium bicarbonate solution (50 mL), water (75 mL) and brine (50 mL). It is dried over sodium sulfate, then it is concentrated on rotary evaporator to an amber oil, compound **8** (18.3 g, 70% crude yield), as an enol-ketone mixture. MS (EI) m/z 160 (M⁺). ¹H NMR (300 MHz, CDCl₃, ketone / enol mixture approx 1:3) δ 13.6 (s, 1 H, enol O-H), 5.66 (s, 1 H, enol C-H), 4.42 (t, *J* = 6.6 Hz, 1 H, ketone O-CH₂), 4.35 (t, *J* = 6.7 Hz, 1H, enol O-CH₂), 3.90 (s, 1H, CS-CH₂-CO), 2.25 (s, 3H enol), 2.03 (s, 3H, ketone), 1.90-1.72 (m, 2H enol and ketone overlapping), 1.02-0.96 (t, 3H, enol and ketone overlapping).

EXAMPLE 3

Preparation of (3-Oxo-1-propoxy-but-1-enylsulfanyl)-acetic acid methyl ester



To a chilled (8°C) solution of keto-thioester **8** (17.0 g, 106 mmol) and methyl bromoacetate (22.7 g, 148 mmol) in DMF (125 mL), triethylamine (15.0 g, 148 mmol) is added portionwise. The resulting exotherm warms up the reaction mixture to 35°C and results in a thick suspension. TLC analysis 30 minutes following the end of addition shows the reaction to be complete. TLC (SiO₂, EtOAc / heptane 1:2 eluent, R_f of the product, 0.15; R_f of the starting material, 0.70). The reaction mixture is allowed to cool to room temperature over 1 hour, then it is partitioned between water (100 mL) and MTBE (150 mL). The aqueous phase is extracted with MTBE (3 x 100 mL). The combined organics are washed with water (100 mL), brine (75 mL) and then are concentrated on a rotary evaporator to 21.5 g of a yellow oil. The crude material is allowed to stand over-night at room temperature, after which it is turned into a mixture of crystalline solid and semi-solid material. It is then triturated with heptane (100 mL) for 3 hours, and then the solid is isolated by Buchner filtration. The filter cake is washed with heptane (10 mL), then it is dried for 3 hours under vacuum, affording compound **9** (16.6 g, 67%) as a yellow solid: mp = 54-57°C. Anal. Calcd for C₁₆H₁₈O₄S: C, 51.71; H, 6.94. Found: C, 51.68; H,

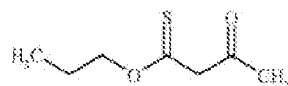
7.28. MS (ESI) m/z 233 (M+H). ^1H NMR (300 MHz, CDCl_3) δ 5.72 (s, 1 H), 3.92 (t, $J = 6.5$ Hz, 2H), 3.72 (s, 3H), 3.56 (s, 2H), 2.16 (s, 3H), 1.82-1.70 (m, 2H), 1.01 (t, $J = 7.5$ Hz). ^{13}C NMR (75 MHz, CDCl_3) δ 194.51, 170.42, 169.33, 98.15, 73.24, 52.19, 31.35, 30.14, 21.70, 10.22.

- 5 The present invention is not to be limited in scope by the specific embodiments describe herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and the accompanying figures. Such modifications are intended to fall within the scope of the appended claims.
- 10 Various publications are cited herein, the disclosures of which are incorporated by reference in their entireties.

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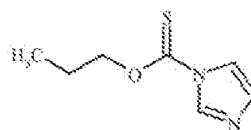
We Claim:

1. A method for preparing a compound of formula 8



8,

comprising condensing the compound of formula 7



7,

with acetone.

2. The method according to claim 1 wherein the condensing is carried out in the presence of an aprotic organic solvent.

3. The method according to claim 2 wherein the aprotic organic solvent is selected from an ethereal solvent and a hydrocarbon solvent.

4. The method according to claim 3 wherein the ethereal solvent is selected from tetrahydrofuran, 2-methyltetrahydrofuran and tert-butyl methyl ether.

5. The method according to claim 3 wherein the hydrocarbon solvent is selected from toluene and heptane.

6. The method according to claim 1 wherein the condensing is carried out at a temperature from about 15° C to about 55° C.

7. The method according to claim 6 wherein the condensing is carried out at a temperature from about 25° C to about 45° C.

8. The method according to claim 7 wherein the condensing is carried out at a temperature of about 40° C.

9. The method according to claim 1 wherein the condensing is carried out in the presence of an organic metal base.

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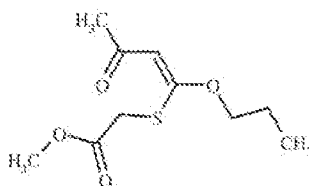
10. The method according to claim 9 wherein the base is selected from an alkali metal amide base and an alkali metal hydride.

11. The method according to claim 10 wherein the alkali metal amide base is selected from lithium diisopropylamide, lithium dicyclohexylamide, lithium (bis)trimethylsilyl amide, sodium (bis)trimethylsilyl amide and potassium (bis)trimethylsilyl amide.

12. The method according to claim 11 wherein the alkali metal amide base is sodium (bis)trimethylsilyl amide.

13. The method according to claim 10 wherein the alkali metal hydride is selected from lithium hydride, sodium hydride and potassium hydride.

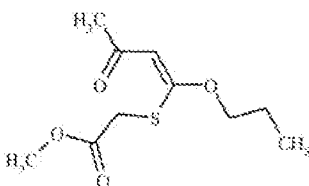
14. A method for preparing a compound of formula 13



13,

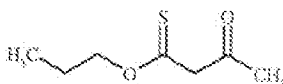
comprising alkylating the compound of formula 8 prepared according to the method of claim 1 using methyl bromoacetate.

15. A method for preparing a compound of formula 13



13,

comprising alkylating a compound of formula 8



8,

using methyl bromoacetate.

16. The method according to claim 14 or claim 15 further comprising alkylating in the presence of an aprotic organic solvent, a mixture of aprotic organic solvents, or in the presence of a mixture containing a polar aprotic solvent and an ethereal solvent.

17. The method according to claim 16 wherein the aprotic organic solvent is selected from a polar aprotic solvent and a chlorinated hydrocarbon solvent.

18. The method according to claim 17 wherein the polar aprotic solvent is selected from dimethylformamide, 1-methyl-2-pyrrolidone and dimethylsulfoxide.

19. The method according to claim 16 wherein the ethereal solvent is selected from tetrahydrofuran, 2-methyltetrahydrofuran and tert-butyl methyl ether.

20. The method according to claim 17 wherein the chlorinated hydrocarbon solvent is dichloromethane.

21. The method according to claim 14 or claim 15 wherein the alkylating is carried out at a temperature from about 0° C to about 50° C.

22. The method according to claim 21 wherein the alkylating is carried out at a temperature from about 5° C to about 40° C.

23. The method according to claim 22 wherein the alkylating is carried out at a temperature from about 8° C to about 35° C.

24. The method according to claim 14 or claim 15 wherein the alkylating is carried out in the presence of an alkylamine base.

25. The method according to claim 24 wherein the alkylamine base is selected from triethylamine and diisopropylethylamine.

26. The method according to claim 25 wherein the alkylamine base is triethylamine.