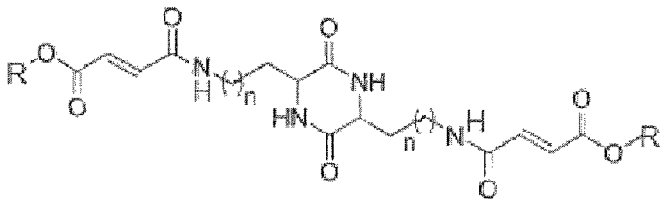
anhydride of MEF and another acid and reacting the mixed anhydride with an alcohol to produce the activated ester of MEF; and wherein the mixed anhydride is trifluoroacetyl-ethyl-fumarate.

[0021a] In one aspect, there is provided a method of preparing a diketopiperazine of Formula I (R=H or ethyl, n=3):



Formula I

comprising:

generating an aminoalkyldiketopiperazine;

providing an activated derivative of monoethyl fumarate;

reacting the aminoalkyl-diketopiperazine with the activated monoethyl fumarate derivative; wherein the activated derivative is a mixed anhydride, the mixed anhydride resulting from the reaction of monoethyl fumarate and a reagent selected from the group comprising: diphenylphosphoryl azide, pivaloyl chloride, chlorosulfonyl isocyanate, and trifluoroacetic anhydride;

and wherein the activated derivative of monoethyl fumarate is reacted with the aminoalkyldiketopiperazine in situ without purification.

[0021b] In one aspect, there is provided a method of preparing a diketopiperazine of Formula I

comprising: in a first reaction mixture, mixing monoethyl fumarate and a proton scavenger in an appropriate solvent;

adding an electrophile selected from the group: diphenylphosphoryl azide, pivaloyl chloride, chlorosulfonyl isocyanate, trifluoroacetic anhydride, and monoethyl fumaroyl chloride and

using this mixture in the synthesis of the diketopiperazine of Formula I without purification.

BRIEF DESCRIPTION OF THE DRAWINGS

[0022] A better understanding of the exemplary embodiments of the invention will be had when reference is made to the accompanying drawings, wherein identical parts are identified with identical reference numerals, and wherein:

[0023] FIGURE 1 is a scheme showing the synthesis of a substituted 3,6-aminoalkyl-2,5-diketopiperazine using an embodiment described herein.

[0024] FIGURE 2 shows results from experiments for a series of acetone/water mixtures that were explored to determine the optimum ratio for the reaction embodied in Part A.

[0025] FIGURE 3 is a graph showing the effects of the p-nitrophenol (p-NP) reactant concentration on quality of compound of the Formula 4 obtained.

[0026] FIGURE 4 is a graph showing the effects of pH control of Part A [same as above] reaction versus no pH control during the reaction.

[0027] FIGURE 5 shows the results from experiments comparing quality of product produced from Part B with reaction temperature at ambient versus elevated temperatures to 50°C.

[0028] FIGURE 6 a graph displaying the results obtained when varying the acetone/water ratios for the TFA deprotection of the diketopiperazine intermediate.

[0029] FIGURE 7 a graph depicting data on the characteristics of compound of the Formula 4 when the reaction concentration is varied during the TFA deprotection step.

[0030] FIGURE 8 is a graph depicting results comparing the charge of ethyl-4-nitrophenylfumarate on quality of compound of the Formula 4 obtained by a reaction embodiment disclosed herewith.

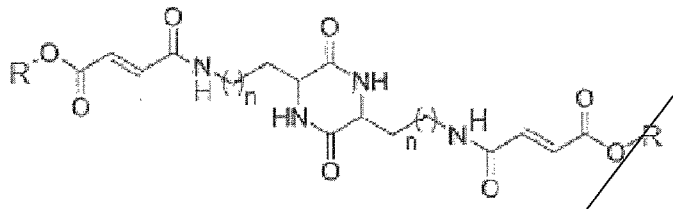
[0031] FIGURE 9 is a graph depicting results obtained using either crude or recrystallized TFA-DKP when forming the compound of Formula 4.

[0032] FIGURE 10 is a graph comparing the compound of the Formula 4 overall quality obtained using a conventional method versus employing the *in situ* methodology described herein.

[0033] FIGURE 11 is a chemical scheme showing an embodiment of a synthesis for a substituted aminoalkyl-diketopiperazine.

What is clamed is:

Claim 1. A method of preparing a diketopiperazine of Formulal (R=H or ethyl, n=3): comprising:



Formula I

generating an aminoalkyldiketopiperazine;

providing an activated derivative of monoethyl fumarate;

reacting the aminoalkyl-diketopiperazine with the activated monoethyl fumarate derivative; wherein the activated derivative is a mixed anhydride, the mixed anhydride resulting from the reaction of monoethyl fumarate and a reagent selected from the group comprising: diphenylphosphoryl azide, pivaloyl chloride, chlorosulfonyl isocyanate, and trifluoroacetic anhydride

and wherein the activated derivative of monoethyl fumarate is reacted with the aminoalkyldiketopiperazine in situ without purification.

Claim 2. The method of claim 1, further comprising the step of removing a protecting group from the aminoalkyl-diketopiperazine prior to reaction with the activated monoethyl fumarate.

Claim 3. The method of claim 1, wherein the activated derivative is a mixed anhydride generated by reacting monoethyl fumaroyl chloride with pivalic acid

Claim 4. The method of claim 1, further comprising saponification of the ethyl esters of the diketopiperazine of Formula 1.

Claim 5. The method of claim 1, further comprising isolation of the activated derivative of monoethyl fumarate before reacting with the aminoalkyldiketopiperazine.

Claim 6. A method for the synthesis of an activated 4-nitrophenyl ester of mono-ethyl fumarate comprising:

in a first reaction mixture, providing a reactive electrophilic derivative of monoethyl fumaric acid;

in a second reaction mixture, generating the salt of 4-nitrophenol by reacting with an appropriate base chosen from the group comprising: organic and inorganic metallic bases; and

combining the mixtures without purification..

Claim 7. The method of claim 6, wherein the base is an inorganic metallic base.

Claim 8. The method of claim 6, wherein the base is sodium hydroxide.

Claim 9. The method of claim 6, wherein the reactive electrophilic derivative is monoethyl fumaroyl chloride.

Claim 10. The method of claim 6, wherein the reactive electrophilic derivative is monoethyl fumaroyl mixed anhydride.

Claim 11. A method of preparing a diketopiperazine of Formula I comprising:

in a first reaction mixture, mixing monoethyl fumarate and a proton scavenger in an appropriate solvent;

adding an electrophile and

using this mixture in the synthesis of the diketopiperazine of Formula I without purification.

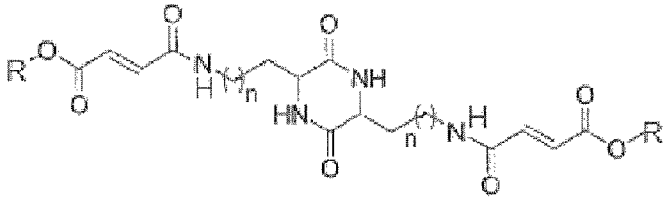
Claim 12. The method of claim 11 wherein the electrophile is chosen from the group: diphenylphophoryl azide, pivaloyl chloride, chlorosulfonyl isocyanate, trifluoroacetic anhydride, and monoethyl fumaroyl chloride.

Claim 13. The method of claim 11wherein the proton scavenger is an organic amine.

Claim 14. The method of claim 11wherein the solvent is a polar organic solvent.

What is clamed is:

1. A method of preparing a diketopiperazine of Formula I (R=H or ethyl, n=3):



Formula I

comprising:

generating an aminoalkyldiketopiperazine;

providing an activated derivative of monoethyl fumarate;

reacting the aminoalkyl-diketopiperazine with the activated monoethyl fumarate derivative; wherein the activated derivative is a mixed anhydride, the mixed anhydride resulting from the reaction of monoethyl fumarate and a reagent selected from the group comprising: diphenylphosphoryl azide, pivaloyl chloride, chlorosulfonyl isocyanate, and trifluoroacetic anhydride;

and wherein the activated derivative of monoethyl fumarate is reacted with the aminoalkyldiketopiperazine in situ without purification.

2. The method of claim 1, further comprising the step of removing a protecting group from the aminoalkyl-diketopiperazine prior to reaction with the activated monoethyl fumarate.

3. The method of claim 1, further comprising saponification of the ethyl esters of the diketopiperazine of Formula 1.

4. The method of claim 1, further comprising isolation of the activated derivative of monoethyl fumarate before reacting with the aminoalkyldiketopiperazine.

5. A method of preparing a diketopiperazine of Formula I

comprising: in a first reaction mixture, mixing monoethyl fumarate and a proton scavenger in an appropriate solvent;

adding an electrophile selected from the group:
diphenylphosphoryl azide, pivaloyl chloride, chlorosulfonyl isocyanate, trifluoroacetic anhydride, and monoethyl fumaroyl chloride and

using this mixture in the synthesis of the diketopiperazine of Formula I without purification.

6. The method of claim 5, wherein the proton scavenger is an organic amine.

7. The method of claim 5, wherein the solvent is a polar organic solvent.