Formation of N-protected ~~bis-~~3,6-bis-(4-aminobutyl)-2,5-diketopiperazine Through a Cyclic α-*N*-Protected Active Amino Ester Intermediate

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This non-provisional patent application claims the benefit of U.S. provisional application No. 61/798,016 the content of which is hereby incorporated by reference as if recited herein in its entirety.

TECHNICAL FIELD

[0002] The present invention relates to compositions for delivering active agents, and particularly biologically active agents. Disclosed embodiments are in the field of chemical synthesis and more particularly are related to improved synthetic methods for the preparation of substituted diketopiperazines.

BACKGROUND

[0003] Drug delivery is a persistent problem in the administration of active agents to patients. Conventional means for delivering active agents are often severely limited by biological, chemical, and physical barriers. Typically, these barriers are imposed by the environment through which delivery occurs, the environment of the target for delivery, or the target itself.

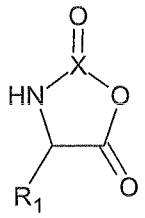
[0004] Biologically active agents are particularly vulnerable to such barriers. For example in the delivery to humans of pharmacological and therapeutic agents, barriers are imposed by the body. Examples of physical barriers are the skin and various organ membranes that must be traversed before reaching a target. Chemical barriers include, but are not limited to, pH variations, lipid bi-layers, and degrading enzymes.

[0005] These barriers are of particular significance in the design of oral delivery systems. Oral delivery of many biologically active agents would be the route of choice for administration to animals if not for biological, chemical, and physical barriers such as

cyclocondensation shown often requires high temperatures or harsh conditions to achieve full cyclization. Further, it is not compatible with each N-protecting group that might be necessary for further derivatization of the exo-cyclic nitrogens.

[0013] Some useful N-protecting groups include acetyl, trichloroacetyl, trifluoroacteyl and other amide forming protecting groups; carbamate protecting groups including benzyloxycarbonyl (Cbz) and t-butoxycarbonyl (BOC) among others.

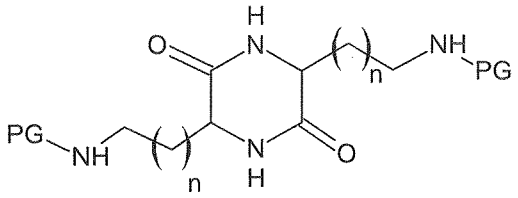
[0014] In an embodiment, a method for the synthesis of a 3,6-aminoalkyl-2,5-diketopiperazine is provided. The method comprises, adding a cyclic α-N protected active amino ester according to the formula below:



wherein R_1 is a N-protected amino C_1 to C_8 alkyl, and X is C, S or P, to a mixture of an amine catalyst in an organic solvent.

[0015] In an embodiment, a method for the synthesis of a 3,6-aminoalkyl-2,5-diketopiperazine is provided. The method comprises, adding a cyclic α-N protected active amino ester to a mixture of an amine catalyst in an organic solvent. In certain embodiments, the method provides 3,6-aminoalkyl-2,5-diketopiperazine in a yield of greater than 40 % (i.e., 40 to 100 %).

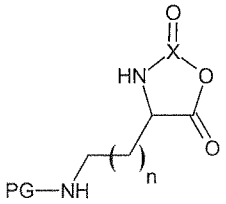
~~[0015a] In an embodiment, there is provided a method for the synthesis of a N-protected bis-3,6-aminoalkyl-2,5- diketopiperazine of Formula I,~~



~~Formula I~~

~~wherein PG is selected from CBz, Boc, trifluoroacetyl, and acetyl and wherein n is from 1 to 8;~~

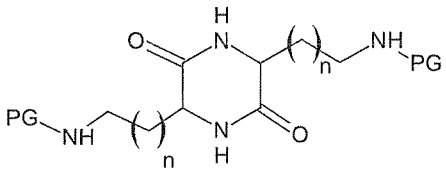
~~the method comprising: adding a cyclic α-N protected active amino ester according Formula II~~



~~Formula II~~

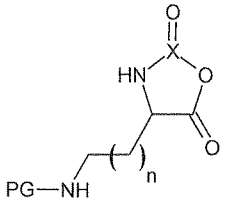
~~wherein PG is selected from CBz, Boc, trifluoroacetyl, and acetyl, wherein X is selected from C, S, and P, and wherein n is from 1 to 8; to a mixture of an amine catalyst in an organic solvent, the amine catalyst selected from the group comprising: aziridine and benzamidoxime.~~

[0015a] In an embodiment, there is provided a method for the synthesis of a N-protected 3,6-bis-aminoalkyl-2,5-diketopiperazine of Formula I,



Formula I

wherein PG is selected from CBz, Boc, trifluoroacetyl, and acetyl and wherein n is from 1 to 8; the method comprising: adding a cyclic α-N protected active amino ester according Formula II



Formula II

wherein PG is selected from CBz, Boc, trifluoroacetyl, and acetyl and wherein n is from 1 to 8; to a mixture of an amidoxine in an organic solvent.

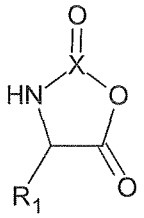
BRIEF DESCRIPTION OF THE DRAWINGS

[0016] Figure 1 is a reaction scheme showing an exemplary embodiment of a route for the formation of 3,6-aminoalkyl-2,5-diketopiperazine through a cyclic N-carboxy anhydride (NCA) intermediate.

[0017] Figure 2 is a bar graph showing results for a survey of several organic solvents.

[0040] Some useful N-protecting groups include acetyl, trichloroacetyl, trifluoroacetyl and other amide forming protecting groups; carbamate protecting groups including benzyloxycarbonyl (Cbz) and t-butoxycarbonyl (Boc) among others.

[0041] In an embodiment, a method for the synthesis of a 3,6-aminoalkyl-2,5-diketopiperazine is provided. The method comprises, adding a cyclic amino ester according to Compound 3.



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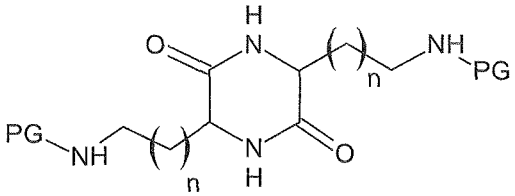
[0042] wherein R_1 is a N-protected amino C1 to C8 alkyl, and X is C, S or P, to a solution of an amine catalyst in an organic solvent.

[0043] In an embodiment a method for the synthesis of a ~~bis~~-N-protected 3,6-bis-aminoalkyl-2,5-diketopiperazine of formula I is provided.

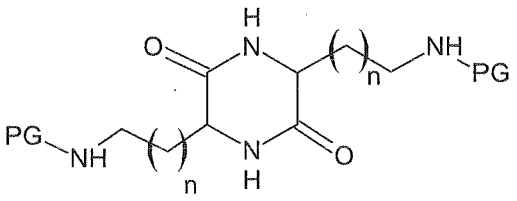


Formula I

[0044] The method comprises adding a N-protected cyclic alkyl amino acid according Formula II.

What is claimed is:

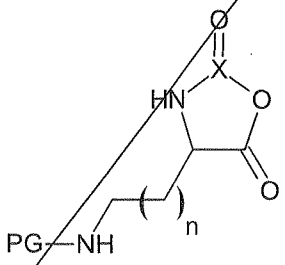
Claim 1. A method for the synthesis of a N-protected bis-3,6-aminoalkyl-2,5-diketopiperazine of Formula I,



Formula I

wherein PG is selected from CBz, Boc, trifluoroacetyl, and acetyl and wherein n is from 1 to 8;

the method comprising: adding a cyclic α-N protected active amino ester according Formula II



Formula II

wherein PG is selected from CBz, Boc, trifluoroacetyl, and acetyl, wherein X is selected from C, S, and P, and wherein n is from 1 to 8; to a mixture of an amine catalyst in an organic solvent, the amine catalyst selected from the group comprising: aziridine and benzamidoxime.

Claim 2. The method of claim 1, wherein PG is trifluoroacetyl.

Claim 3. The method of claim 1, wherein PG is acetyl.

Claim 4. The method of claim 1, wherein PG is Boc.

Claim 5. The method of claim 1, wherein n is 3.

Claim 6. The method of claim 1, wherein X is C and the amine catalyst is aziridine.

Claim 7. The method of claim 1, wherein X is C and the amine catalyst is an amidoxime.

Claim 8. The method of claim 1, wherein X is C and PG is trifluoroacetyl.

Claim 9. The method of claim 1, wherein the organic solvent is ethanol and the amine catalyst is aziridine.

Claim 10. The method of claim 1, wherein the organic solvent is THF and the amine catalyst is aziridine.

Claim 11. The method of claim 10, wherein the addition is at room temperature.

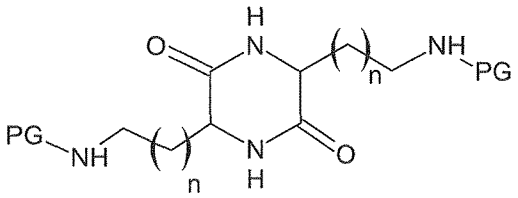
Claim 12. The method of claim 1, wherein the PG is removed prior to isolation of the diketopiperazine.

Claim 13. The method of claim 1, wherein PG is CBz.

Claim 14. The method of claim 13, wherein X is C, THF is the organic solvent and the cyclic α-N-protected active amino ester is added over 4 hours with heat.

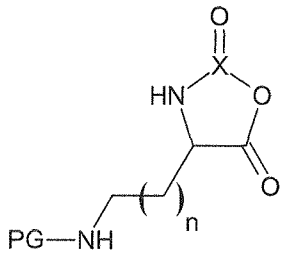
What is claimed is:

Claim 1. A method for the synthesis of a N-protected 3,6-bis-aminoalkyl-2,5-diketopiperazine of Formula I,



Formula I

wherein PG is selected from CBz, Boc, trifluoroacetyl, and acetyl and wherein n is from 1 to 8; the method comprising: adding a cyclic α-N protected active amino ester according Formula II



Formula II

wherein PG is selected from CBz, Boc, trifluoroacetyl, and acetyl and wherein n is from 1 to 8; to a mixture of an amidoxine in an organic solvent.

Claim 2. The method of claim 1, wherein PG is trifluoroacetyl.

Claim 3. The method of claim 1, wherein PG is acetyl.

Claim 4. The method of claim 1, wherein PG is Boc.

Claim 5. The method of claim 1, wherein n is 3.

Claim 6. The method of claim 1, wherein X is C.

Claim 7. The method of claim 1, wherein X is C and PG is trifluoroacetyl.

Claim 8. The method of claim 1, wherein the organic solvent is ethanol.

Claim 9. The method of claim 1, wherein the organic solvent is THF.

Claim 10. The method of claim 9, wherein the addition is at room temperature.

Claim 11. The method of claim 1, wherein the PG is removed prior to isolation of the diketopiperazine.

Claim 12. The method of claim 1, wherein PG is CBz.

Claim 13. The method of claim 12, wherein X is C, THF is the organic solvent and the cyclic α-N-protected active amino ester is added over 4 hours with heat.