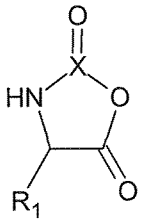
cyclocondensation shown often requires high temperatures or harsh conditions to achieve full cyclization. Further, it is not compatible with each N-protecting group that might be necessary for further derivatization of the exo-cyclic nitrogens.

[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.

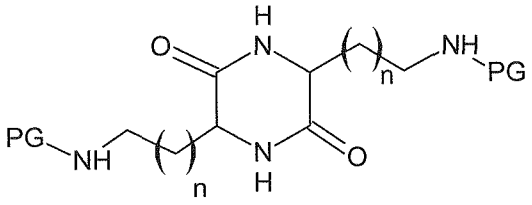
[0014] In an embodiment, a method for the synthesis of a 3,6-aminoalkyl-2,5-diketopiperazine is provided. The method comprises, adding a cyclic α-N protected active amino ester according to the formula below:



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.

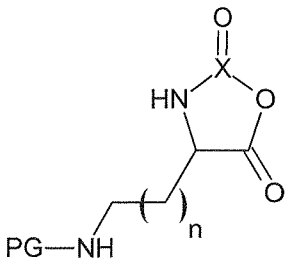
[0015] In an embodiment, a method for the synthesis of a 3,6-aminoalkyl-2,5-diketopiperazine is provided. The method comprises, adding a cyclic α-N protected active amino ester to a mixture of an amine catalyst in an organic solvent. In certain embodiments, the method provides 3,6-aminoalkyl-2,5-diketopiperazine 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 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, wherein X is C, and wherein n is from 1 to 8; to a mixture of an amidoxime in an organic solvent wherein the cyclic α-N protected active amino ester is added over a period of between 1 hour and 4 hours at a temperature of between 19° C and 75° C.

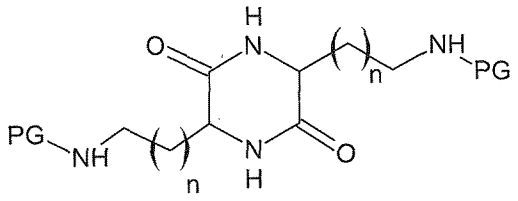
BRIEF DESCRIPTION OF THE DRAWINGS

[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.

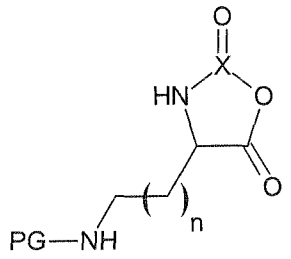
What is claimed is:

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, wherein X is C, and wherein n is from 1 to 8; to a mixture of an amidoxime in an organic solvent wherein the cyclic α-N protected active amino ester is added over a period of between 1 hour and 4 hours at a temperature of between 19° C and 75° C..

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 PG is trifluoroacetyl.

Claim 7. The method of claim 1, wherein the organic solvent is ethanol.

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

Claim 9. The method of claim 1, wherein the PG is removed prior to isolation of the diketopiperazine.

Claim 10. The method of claim 1, wherein PG is CBz.

Claim 11. The method of claim 12, wherein THF is the organic solvent and the cyclic α-N-protected active amino ester is added over 4 hours with heat.