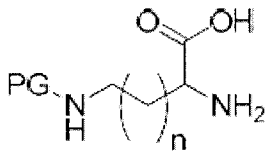
method that can accommodate a number of diverse N-protecting groups and produce good yield of N-protected diketopiperazine is desired.

[0012] Some useful protecting groups include trifluoroacteyl, acetyl and other amide forming protecting groups; carbamate protecting groups including benzyloxycarbonyl (Cbz) and t-butoxycarbonyl (BOC).

[0012a] In one embodiment, there is provided a method for the synthesis of 3,6-bis-[N-protected aminoalkyl]-2,5-diketopiperazine comprising:



Formula I

heating a mixture of an amino acid of general formula I in the presence of a catalyst in an organic solvent;

wherein the catalyst is selected from the group consisting of: sulfuric acid, phosphoric acid, p-toluenesulfonic acid, 1-propylphosphonic acid cyclic anhydride, tributyl phosphate, phenyl phosphonic acid and phosphorous pentoxide; and

wherein the solvent is selected from the group consisting of: dimethylacetamide, N-methyl-2-pyrrolidone, diglyme, ethyl glyme, proglyme, ethyldiglyme, m-cresol, p-cresol, o-cresol, xylenes, ethylene glycol and phenol.

[0012b] In one embodiment, there is provided a method for the synthesis of 3,6-bis-[N-protected aminobutyl]-2,5-diketopiperazine comprising:

heating a mixture of a N-protected lysine in the presence of a catalyst in an organic solvent, to a temperature of between 110° and 175°C for between 0.25 and 5 hours;

wherein the catalyst is selected from the group consisting of: sulfuric acid, phosphoric acid and phosphorous pentoxide,

the concentration of catalyst from about 5% to about 50% that of the lysine; and

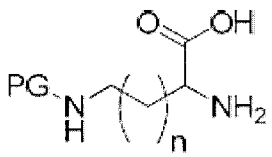
the solvent is selected from the group consisting of: dimethylacetamide, N-methyl-2-pyrrolidone, diglyme, ethyl glyme, proglyme, ethyldiglyme, m-cresol, p-cresol, o-cresol, xylenes, ethylene glycol and phenol.

[0012b] In one embodiment, there is provided a method for the synthesis of 3,6-bis-4-(N-trifluoroacetyl)aminobutyl-2,5-diketopiperazine comprising:

heating a mixture of ε-trifluoroacetyl-L-lysine in the presence of phosphorous pentoxide in N-methyl-2-pyrrolidone, to a temperature of between 150° and 175°C for between 0.25 and 5 hours, the concentration of phosphorous pentoxide is from about 10% to about 40% that of the lysine; and

quenching the mixture with a second solvent.

[0013] In an embodiment, 3,6-bis-4-(N-trifluoroacetyl)aminobutyl-2,5-diketopiperazine is formed by heating ε-trifluoroacetyl-L-lysine in a water miscible solvent such as N-methyl-2-pyrrolidone (NMP) in the presence of a catalyst chosen from the group comprising phosphoric acid, sulfuric acid and phosphorous pentoxide to a temperature of about 150-175°C. The diketopiperazine is isolated by quenching with water and filtering the resulting solid.



Formula I

[0014] Disclosed embodiments describe methods for the synthesis of 3,6-bis-[N-protected aminoalkyl]-2,5-diketopiperazine comprising heating a mixture of an amino acid of general formula I in the presence of a catalyst in an organic solvent; wherein the catalyst is selected from the group comprising sulfuric acid, phosphoric acid, p-toluenesulfonic acid, 1-propylphosphonic acid cyclic anhydride, tributyl phosphate, phenyl phosphonic acid and phosphorous pentoxide among others; and wherein the solvent is selected from the group comprising: dimethylacetamide, N-methyl-2-