

compared to the bis, tris, tetra or higher N-alkylated products.

The present invention concerns the reaction of an appropriate electrophile (E) with a free base polyazamacrocyclic (M) in a relatively non-polar, preferably relatively aprotic solvent. The ratio of E to M is about one E to about five M equivalents, preferably from about one E to about three M equivalents, more preferably from about one E to about two M equivalents, and most preferably from about one E to about one M equivalent.

The present process is very general and can produce selective mono-N-alkylation products with various polyazamacrocyclics and electrophilicities. A slight excess of polyazamacrocyclic is preferred to insure complete conversion of the electrophile; however, only small differences in isolated yield occur when larger excesses of the polyazamacrocyclic are used.

Accordingly, there is provided according to a broad form of the invention a process for preparing a mono-N-alkylated polyazamacrocyclic consisting essentially of reacting an electrophile with between about one and three equivalents of a polyazamacrocyclic in a solvent which will not promote a proton transfer and recovery of the thus prepared mono-N-alkylated polyazamacrocyclic; wherein the electrophile is represented by the formula RX wherein R is a C₁-C₄ alkyl; a C₁-C₄ alkyl which is substituted with a cyano, pyridinyl, CO₂R¹ or CON(R¹)₂ moiety where R¹ is H or C₁-C₄ alkyl; or an alkylaryl where the alkyl portion is C₁-C₄ and the aryl portion is a 5 or 6 member carbon ring or a 9 member ring containing carbon and one or more hetero atoms selected from sulfur, nitrogen or oxygen and X is chloro, bromo, iodo, acetate, trifluoroacetate, triflate, mesylate, diazo or brosylate; and wherein the polyazamacrocyclic contains at least two nitrogen atoms and at least one additional hetero atom selected from the group consisting of oxygen sulfur and nitrogen, and a methylene moiety, (-CH₂-)_n, where n is from 2-4, as a spacer between the hetero atoms such that the total carbon and hetero atoms in the polyazamacrocyclic is 12, 13 or 14.

The polyazamacrocyclics used in the present invention must contain at least two nitrogen atoms. However, the polyazamacrocyclics can also contain other hetero moieties such as oxygen atoms (polyoxazamacrocyclics) or sulfur atoms (polythioazamacrocyclics). Also included in the term polyazamacrocyclics are any symmetrical rings such as polyazamacrocyclic, azaoxamacrocyclic or bicyclopolyazamacrocyclic (i.e. bridged moieties or fused rings, but the mono-N-alkylation reaction occurs on the nitrogen atom of a saturated ring) which bears secondary amines capable of mono-N-alkylation. Preferably the secondary amines are all chemically equivalent. The macrocyclic preferably has a plane of symmetry and the

CLAIMS

1. A process for preparing a mono-N-alkylated polyazamacrocyclic consisting essentially of reacting an electrophile with between about one and three equivalents of a polyazamacrocyclic in a solvent which will not promote a proton transfer and recovery of the thus prepared mono-N-alkylated polyazamacrocyclic; wherein the electrophile is represented by the formula RX wherein R is a C_1-C_4 alkyl; a C_1-C_4 alkyl which is substituted with a cyano, pyridinyl, CO_2R^1 or $CON(R^1)_2$ moiety where R^1 is H or C_1-C_4 alkyl; or an alkylaryl where the alkyl portion is C_1-C_4 and the aryl portion is a 5 or 6 member carbon ring or a 9 member ring containing carbon and one or more hetero atoms selected from sulfur, nitrogen or oxygen and X is chloro, bromo, iodo, acetate, trifluoroacetate, triflate, mesylate, diazo or brosylate; and wherein the polyazamacrocyclic contains at least two nitrogen atoms and at least one additional hetero atom selected from the group consisting of oxygen sulfur and nitrogen, and a methylene moiety, $(-CH_2-)_n$, where n is from 2-4, as a spacer between the hetero atoms such that the total carbon and hetero atoms in the polyazamacrocyclic is 12, 13 or 14.
2. A process of claim 1 wherein the solvent is a non-polar, aprotic solvent; a polar, aprotic solvent; or a protic alcohol.
3. The process of claim 2 wherein the solvent is a non-polar, aprotic solvent.
4. The process of claim 3 wherein the solvent is carbon tetrachloride, toluene, benzene, cyclohexane or n-hexane.
5. The process of claim 2 wherein the solvent is a polar, aprotic solvent.
6. The process of claim 5 wherein the solvent is chloroform, methylene chloride, tetrahydrofuran, acetonitrile or 1,4-dioxane.
7. The process of claim 6 wherein the solvent is chloroform.
8. The process of claim 2 wherein the solvent is a protic alcohol.
9. The process of claim 8 wherein the solvent is n-butanol, t-butanol, isopropanol, or n-hexanol.
10. The process of claim 1 wherein the polyazamacrocyclic contains at least two nitrogen atoms and at least one additional hetero atom and a methylene moiety, $(-CH_2-)_n$, where n is from 2-4, as a spacer between the hetero atoms.
11. The process of claim 1 wherein the polyazamacrocyclic is symmetrical.
12. The process of claim 1 wherein the polyazamacrocyclic is 1,4,7,10-tetraazacyclododecane, 1,4,8,11-tetraazacyclotetradecane, or 1,7-diaza-4,10-dithiacyclododecane.
13. The process of claim 1 wherein the electrophile is d,l-2-bromo-4-N-phthalamidobutanoic acid isopropyl ester, d,l-2-bromo-4-(4-nitrophenyl) butanoic acid isopropyl ester, d,l-2-bromo-4-(4-nitrophenyl)butanoic acid methyl ester, 4-

nitrocinnamyl bromide, 4-nitrophenethyl bromide, 4-nitrobenzyl bromide, or benzyl bromide.

14. The process of claim 1 wherein R is an optically active α -haloacid ester.
15. The process of claim 14 wherein the resulting mono-N-alkylated polyazamacrocycle product has the opposite optical configuration from the optically active α -haloacid ester.
16. The process of claim 1 wherein the temperature is from about -78° to about 100° .
17. The process of claim 16 wherein the temperature is from about -25° to about 40° .
18. The process of claim 17 wherein the temperature is from about 0° to about 25° .
19. The process of claim 1 wherein between about one and about two equivalents of polyazamacrocycle are used relative to the electrophile.
20. The process of claim 1 wherein about one equivalent of polyazamacrocycle is used relative to the electrophile.
21. The process of claim 1 wherein the mono-N-alkylated polyazamacrocycle is obtained in a selectivity of at least 40%.
22. The process of claim 1 wherein the mono-N-alkylated polyazamacrocycle is obtained in a selectivity of from about 50 to about 98%.

PROCESS FOR PREPARING MONO-N-ALKYLATED POLYAZAMACROCYCLES

ABSTRACT

The invention relates to a novel process to prepare selectively mono-N-alkylated polyazamacrocycles which requires a electrophile with between one and five equivalents of a suitable macrocycle in a solvent which will not promote a proton transfer.