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PROCESS FOR PRODUCING 2-CARBALKOXY-AMINOBENZIMIDAZOLES

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ABSTRACT OF THE DISCLOSURE

A process for selectively acylating 2-aminobenzimidazoles in the 2-position, by heating the reaction product of 2-aminobenzimidazole and an alkyl haloformate in the presence of a suitable non-hydroxylic solvent. The resulting 2-carboalkoxyaminobenzimidazoles are generally known compounds, which have anthelmintic activity.

This invention relates to a process for preparing carbalkoxyaminobenzimidazoles. In particular, this invention relates to a chemical process for the preparation of 2-carbalkoxyaminobenzimidazoles having a high degree of anthelmintic activity.

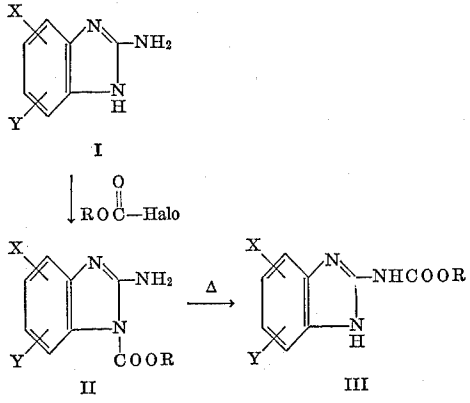
The high incidence of helminth infections throughout many areas of the world motivates the search for an effective, nontoxic, inexpensive, and readily obtainable anthelmintic. 2 - carbalkoxyaminobenzimidazoles have been found to possess considerable activity against pinworm, hookworm, and whipworm infections and offer considerable promise in fulfilling the above-mentioned criteria for an anthelmintic agent.

Prior methods of preparation of 2-carbalkoxyaminobenzimidazoles include condensation of o-phenylenediamine with the reaction product of S-methylthiourea and an alkyl chloroformate.

The present process is advantageous in relation to the prior art processes due to its ease of execution and lack of evolution of odiferous mercaptans. It also avoids the problem of the preparation of an undesired isomeric compound, often encountered in the direct reaction of 2-aminobenzimidazole with an alkyl chloroformate. Further, it requires the use of only one molecular equivalent of acylating agent.

The present process provides a convenient and relatively inexpensive method for the preparation of the anthelmintic 2-carbalkoxyaminobenzimidazoles.

The process of the invention is represented graphically as follows:



In the above process, acylation of a ring-substituted, or unsubstituted, 2-aminobenzimidazole with an alkyl haloformate under cold conditions, give the 1-carbalkoxy derivative of the starting compound. By heating this reaction product from 5 minutes to two days at 50°–100° C., in the presence of a suitable nonhydroxylic solvent, preferably pyridine, the 1-substituted compound is converted to its 2-carbalkoxyamino isomer. Other useful solvents are dimethyl formamide and acetonitrile.

The 2-aminobenzimidazole reactant can have any of a number of conventional substituents, preferably one or two, on the benzene ring (represented by X and Y in the Formula I above) which are inert to the condensation reaction, such as alkyl straight or branched containing from one to nine carbon atoms, alkaryl preferably benzyl, aryl preferably phenyl, dialkylamino, halo preferably chloro, alkoxy straight or branched containing from one to nine carbon atotms, trifluoromethyl, alkylthio, cyano, carbalkoxy, the alkyl moieties not specifically defined having from one to four carbons.

The resulting 2-carbalkoxyaminobenzimidazoles bear these substituents at the corresponding position of the benzene ring. The nature of the novel reaction is such that it is generally applicable to 2-aminobenzimidazoles, regardless of the substituents which may appear on the benzene ring.

The alkyl haloformate can be a chloroformate or a bromoformate, the chloroformate being preferred for reasons of availability and cost. The side alkyl group R can have from one to about twelve carbon atoms, therein, the choice of alkyl group being dependent upon the particular alkyl ester product desired. The term alkyl is also intended to refer to cycloalkyl groups of 3 to 6 carbon atoms, and alkylcycloalkyl groups of 4 to 6 carbon atoms.

The starting materials of Formula I above are either known or are prepared by methods known to the art.

The compounds of Formula I where X is 5-alkl, -aryl or -aralkyl and Y is hydrogen may be prepared starting with the appropriate para-substituted aniline, which is first acetylated with acetic anhydride to protect the amino group, forming p-substituted acetanilide. The anilide is nitrated in the presence of acetic or sulfuric acid to form 2-nitro-4-alkylanilide, e.g., which is reduced with tin chloride to give 2-amino-4-alkylanilide. Hydrolysis liberates the amino group to give 4-alkyl substituted o-phenylenediamine. Treatment of the latter with bromocyanogen forms the 5-alkyl substituted 2-aminobenzimidazole. Similarly, are the aryl or aralkyl substituted congeners prepared.

The compounds of Formula I wherein both of X and Y are lower alkyl may be prepared starting with the appropriate dialkyl benzene. For example, ortho-xylene is nitrated in the presence of acetic acid to form the 4-nitro-1,2-dimethyl benzene. This intermediate is reduced with tin chloride to give the corresponding 4-amino compound, followed by nitration in mineral acid medium with amyl nitrate to give a 5-nitro-4-amino-1,2-dimethyl benzene. This latter intermediate is again reduced with tin chloride to yield a 4,5-dimethyl o-phenylenediamine. The diamine intermediate is converted by the afore-discussed bromocyanogenation to the appropriate dimethyl substituted 2-aminobenzimidazole.

The compounds of Formula I in which X is dialkylamino and Y is hydrogen, can be prepared starting with a dialkylaminobenzene, and following the above-described sequence of steps to yield the dialkylamino substituted 2-aminobenzimidazole.

The compounds of Formula I wherein X is halo and Y is hydrogen, are prepared starting with a p-haloaniline, such as p-chloroaniline. The halo compound is first acetylated with acetic anhydride to protect the amino group forming p-chloroacetanilide. The anilide is nitrated in the presence of acetic or sulfuric acid to form 2-nitro-4-chloroacetanilide, which is reduced catalytically, such as with tin chloride, to give the corresponding

2-amino-4-chloroacetanilide. This amino compound is hydrolyzed to produce 4-chloro-o-phenylenediamine. The diamine is converted to the corresponding 5-chloro-2-amino-benzimidazole by the afore-discussed bromocyanogenation.

The compounds of Formula I wherein X and Y are Y is hydrogen are prepared starting with 4-hydroxyacetanilide. The anilide is treated with the appropriate alkyl bromide and an alkali metal hydroxide, to yield the corresponding o-dialkoxybenzene. The substituted procedure of Buu-Hoi et al., J. Chem. Soc., 1955, 1573. The substituted compound is nitrated with red fuming nitric acid, while suspended in glacial acetic acid and acetic anhydride at about 0° C. The resulting o-nitro-p-alkoxyacetanilide is collected, and is recrystallized from methanol. This disubstituted acetanilide is then deacylated by refluxing with an alkali metal hydroxide in ethanol, with the disubstituted aniline being recovered from acidified water. The disubstituted aniline is then hydrogenated at 50–80 p.s.i. in benzene, with removal of the solvent by distillation, yielding the corresponding diamine. This diamine intermediate is converted by either of the afore discussed bromocyanogenation to the appropriate lower alkoxy substituted 2-aminobenzimidazole.

The compounds of Formula I wherein X and Y are alkoxy are prepared starting with o-dihydroxybenzene. The benzene is treated with the appropriate alkyl bromide, and an alkali metal hydroxide in ethanol, to yield the corresponding o-dialkoxybenzene. The substituted compound is nitrated with nitric acid while suspended in acetic acid, to yield 1,2-dialkoxy-4,5-dinitrobenzene (J. Proc. Roy. Soc., N. S. Wales, 71, 103–11 (1938)), followed by hydrogenation to give the corresponding substituted diamine. The diamine is converted, as previously described, to a 4,5 - dialkoxy-substituted - 2-aminobenzimidazole.

All of the foregoing classes of substituted 2-aminobenzimidazole are then subjected to the process of the present invention.

The prior art discloses a process for the direct acylation of 2-aminobenzimidazole with alkylchloroformate allegedly to give 2-carbalkoxyaminobenzimidazole (M. Ridi and S. Checchi, Ann. Chim, Rome), 28–38 (1954). I have demonstrated that following the teaching of Ridi et al, the only product isolable, under normal conditions, is a 1-carbalkoxyaminobenzimidazole. Consequently, when selective 2-acylation is sought, the prior art process is inoperative. Only the here disclosed reaction conditions gives the preferred 2-isomer.

The following examples are intended to illustrate the process of the invention, but are not to be considered as limiting the scope thereof. Certain variations in the conditions and reactants of the present process may be made which are obvious to one skilled in the art of organic chemistry, but to the extent that they are within the spirit of the invention, they are within the scope thereof.

EXAMPLE 1

Attempted preparation of 2-carboethoxyaminobenzimidazole

The procedure reported by Ridi et al., Chemical Abstracts, vol. 49: 4658–59 (1955), was followed to determine what product was the result of the teaching.

To a cooled solution (0° C.) of 3 g. of 2-aminobenzimidazole (Eastman Chemicals Company), in 25 ml. of water is added slowly 2.4 g. of ethylchloroformate. Eight ml. of 10% sodium hydroxide were added concurrently, the resulting mixture having a basic pH when all reactants were added. The mixture was stirred for about 30 minutes with cooling. The pH was then adjusted to 7.5 with 3 N HCl, precipitating a solid, which was collected, washed with 25 ml. of 95% ethanol, and air dried on a porous plate.

The mother liquor was refrigerated and a second crop was precipitated therefrom, collected, and washed with water, both crops yielding a total of 2.574 g. of product. The product had an M.P. of 195° C. after which it resolidified. It then failed to remelt below 300° C.

The collected material was submitted for an infra-red spectrum which was compared with the spectrum for an authentic sample of 1-carboethoxyaminobenzimidazole. The spectra were identical. Additional samples were submitted for thin layer chromatography and compared with a chromatogram for an authentic sample of 2-carboethoxyaminobenzimidazole. This chromatogram indicated that only a trace of the 2-isomer was present.

It was concluded, therefore, that the prior art method yielded substantially only 1-carboalkoxyaminobenzimidazole.

EXAMPLE 2

Preparation of 2-carboethoxyaminobenzimidazole

To a cooled solution (0° C.) of 5 g. of 2-aminobenzimidazole in 30 ml. of dry pyridine is slowly added 4.06 g. of ethyl chloroformate, with a solid suspension forming during the addition. The mixture is stirred for about 10 minutes with cooling. Upon the addition of about 2 volumes of water, a white solid precipitates, which is collected, washed with cold water, and oven dried.

The structure of this product is confirmed by elemental analysis and spectral data as being 1-carboethoxyaminobenzimidazole.

1-carboethoxybenzimidazole (4 g.) is dispersed in 40 ml. of dry pyridine and is refluxed for 2 hours. Upon the addition of 3 volumes of water, a solid precipitates, which is collected, washed liberally with water, and air dried on a porous plate.

The crude product is suspended in 50 ml. of 50% aqueous ethanol, then 10% aqueous sodium hydroxide is added until strongly basic. The insoluble material is removed by filtration, and the filtrate is neutralized with 3 N hydrochloric acid to a pH of about 7.5. A white solid precipitate is collected, washed and desiccated, M.P. 326° C. (d.).

The structure of the product is confirmed by elemental analysis and spectral data as 2-carboethoxyaminobenzimidazole.

EXAMPLE 3

Preparation of 5-n-butyl-2-carbomethoxyaminobenzimidazole

The available intermediate p,n-butylaniline is treated with acetic anhydride in hexane solution, yielding 4-n-butylacetanilide. The acetanilide is nitrated with fuming nitric acid in the presence of acetic anhydride and glacial acetic acid to produce 4-n-butyl-2-nitroacetanilide. The preceding 2-nitro compound is refluxed in 12 N hydrochloric acid to deacetylate the amino group. The resulting 2-nitroaniline derivative is reduced with stannous chloride in 6 N hydrochloric acid to yield 4-n-butyl-o-phenylenediamine. The dihydrochloride salt of the above substituted phenylenediamine is treated in a water solution with bromocyanogen to yield 5-n-butyl-2-aminobenzimidazole.

To a cooled solution of 3 g. of 5-n-butyl-2-aminobenzimidazole in 18 ml. of dry pyridine, is slowly added 1.49 g. of methyl chloroformate, while stirring. The mixture is stirred for about 10 minutes with cooling, then refluxed for about 15 minutes, and finally immediately recooled. Upon addition of one volume of water (18 ml.), a white solid precipitates, which is collected, washed with cold water, and is oven dried.

The crude product is then suspended in 50% aqueous ethanol, with 3 N hydrochloric acid being added until the pH is acid, and stirred for several minutes. The insoluble material is filtered off, and the filtrate is basified to pH 7.5 by the addition of 10% sodium hydroxide aqueous solution, which precipitates a white solid product.

The product is collected, washed with 50% aqueous ethanol, desiccated over P_2O_5, and is oven dried, M.P. 218–222° C. (d.).

The structure is confirmed by elemental analysis and spectral data.

EXAMPLE 4

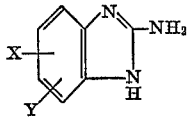
When the following substituted 2-aminobenzimidazoles are substituted for the 5-n-butyl-2-aminobenzimidazole in the procedure of Example 3, the corresponding listed products are obtained.

Starting material	Product
5-chloro-2-aminobenzimidazole	5-chloro-2-carbomethoxyaminobenzimidazole.
5-ethoxy-2-aminobenzimidazole	5-ethoxy-2-carbomethoxyaminobenzimidazole.
5-methoxy-2-aminobenzimidazole	5-methoxy-2-carbomethoxyaminobenzimidazole.
5-propoxy-2-aminobenzimidazole	5-propoxy-2-carbomethoxyaminobenzimidazole.
5-isopropoxy-2-aminobenzimidazole	5-isopropoxy-2-carbomethoxyaminobenzimidazole.
5-butoxy-2-aminobenzimidzaole	5-butoxy-2-carbomethoxyaminobenzimidazole.
5-amyloxy-2-aminobenzimidazole	5-amyloxy-2-carbomethoxyaminobenzimidazole.
5,6-dibutoxy-2-aminobenzimidazole	5,6-dibutoxy-2-carbomethoxyaminobenzimidazole.
5-methyl-2-aminobenzimidazole	5-methyl-2-carbomethoxyaminobenzimidazole.
5-n-propyl-2-aminobenzimidazole	5-n-propyl-2-carbomethoxyaminobenzimidazole.
5-n-amyl-2-aminobenzimidazole	5-n-amyl-2-carbomethoxyaminobenzimidazole.
5-n-hexyl-2-aminobenzimidazole	5-n-hexyl-2-carbomethoxyaminobenzimidazole.
5,6-dimethyl-2-aminobenzimidazole	5,6-dimethyl-2-carbomethoxyamino-benzimidazole.
5-carbomethoxy-2-aminobenzimidazole.	5-carbomethoxy-2-carbomethoxyamino-benzimidazole.
5-dimethylamino-2-aminobenzimidazole.	5-dimethylamino-2-carbomethoxyaminobenzimidazole.

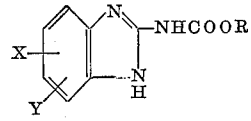
I claim:

1. A process for preparing a 2-carboalkoxyaminobenzimidazole comprising treating a 2-aminobenzimidazole with an alkyl haloformate to form a 1-carbalkoxy-2-aminobenzimidazole, and then heating the 1-carbalkoxy compound in a non-hydroxylic solvent selected from one of pyridine, dimethyl formamide, and acetonitrile sufficiently long in the temperature range of 50° to 100° C. to form the corresponding 2-carbalkoxyaminobenzimidazole.

2. A process for preparing a 2-carboalkoxyaminobenzimidazole which comprises treating a 2-aminobenzimidazole of the formula:



where X and Y are hydrogen, alkyl straight or branched from one to nine carbon atoms, phenyl, benzyl, chloro, bromo, alkoxy straight or branched from one to nine carbon atoms, alkylthio, dialkylamino, carbalkoxy, trifluoromethyl, or cyano, the alkyl moieties having from one to four carbon atoms, with Hal-COOR, where Hal is halo and R is alkyl from one to six carbon atoms or cycloalkyl from three to twelve carbon atoms, to form a 1-carbalkoxy-2-aminobenzimidazole, and then heating the 1-carbalkoxy compound in a non-hydroxylic solvent selected from one of pyridine, dimethyl formamide, and acetonitrile sufficiently long in a temperature range of 50° to 100° C. to form a 2-carbalkoxyaminobenzimidazole of the formula:



where X, Y, and R are as defined above.

3. A process according to claim **1**, in which the solvent is pyridine.

4. A process according to claim **1**, in which the heating is carried out in the range of from 50° to 100° C., and from 5 minutes to two days.

5. A process according to claim **2**, wherein X is alkyl and Y is hydrogen.

6. A process according to claim **2**, wherein X is alkoxy and Y is hydrogen.

7. A process according to claim **2**, wherein X is chloro and Y is hydrogen.

8. A process according to claim **2**, wherein both X and Y are alkyl.

9. A process according to claim **2**, wherein both X and Y are alkoxy.

10. A process according to claim **2**, wherein X is n-butyl and Y is hydrogen.

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