

PATENT SPECIFICATION

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1267999

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780 791 79Y ML RV SN



009

(54) BENZIMIDAZOLES AND A PROCESS FOR THEIR PREPARATION

(71) We, ELI LILLY AND COMPANY, a Corporation organised and existing under the Laws of the State of Indiana, United States of America, of 307 East McCarty Street, City of Indianapolis, State of Indiana, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

Benzimidazoles are known to be useful in combating intestinal parasites of mammals and birds. Furthermore, 2-trifluoromethylbenzimidazoles have been found to be useful as herbicides, nematocides, molluscicides, and insecticides. (British patent 1,087,561; U.S. Patent 3,412,101; South African patent 65/5584; and Netherlands patent 67/13786 are exemplary.) The 2-trifluoromethyl derivatives most frequently employed as insecticides have been substituted in the benzene portion of the benzimidazole ring system with chlorine and nitro groups, with the most active compound being 2 - trifluoromethyl - 4,5,6,7 - tetrachlorobenzimidazole, 2 - trifluoromethyl - 5,6 - dichlorobenzimidazole, and phenyl 2 - trifluoromethyl - 4 - nitro - 6 - chloro - 1 - benzimidazolecarboxylate. In general these compounds have shown their greatest activity against insects of the order Lepidoptera, such as Southern armyworm, and of the order Diptera, such as house flies and mosquitoes. For example, 2 - trifluoromethyl - 4,5 - dichlorobenzimidazole gives a complete kill of Southern armyworm larvae at 250 ppm, but is without action against milkweed bugs, oriental roaches and boll weevils at that same concentration, and in fact, its activity against house flies is excellent only at 1000 ppm. The isomeric compound, 2 - trifluoromethyl - 5,6 - dichlorobenzimidazole, has the same excellent activity against Southern armyworm larvae, at 250 ppm, but no activity at the same level against milkweed bugs, house flies, oriental roach and boll weevil. In general, these chlorinated benzimidazoles do not approach, in absolute activity, the organic phosphate insecticides, nor do they have the same broad spectrum of action.

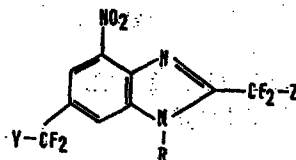
Two large classes of marketed insecticides which have been widely used and which have a reasonably broad spectrum against many orders of insects plus a low dosage range are the organic phosphates and the chlorinated hydrocarbons. Many of the most active of the organic phosphate insecticides are extremely toxic to humans and their toxicity by intradermal absorption is of the same order of magnitude as their toxicity by inhalation. Thus these very toxic compounds are extremely dangerous to handle, even when using a gas mask or oxygen mask. The safest of the phosphorus insecticides, Malathion (Registered Trade Mark), is still widely used, but its spectrum is not as broad as would be desirable and many species of insects or mites have become resistant to it over the years.

The deficiencies of the chlorinated hydrocarbons are of a different nature. Resistance is, of course, prevalent, but this problem is not as serious as might be expected because of the endless succession of new chlorinated hydrocarbons which have been produced. The chief drawback to the use of chlorinated hydrocarbons is their persistence in soil and water for many, many years, attributed chiefly to their metabolic

stability. This persistence has now begun to affect other forms of life, including birds and fish.

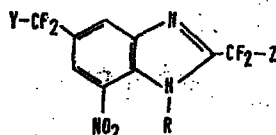
Thus, there is a need for compounds with both insecticide and acaricide activity, which have a broad spectrum, are safe to handle and are non-persistent.

The invention provides novel benzimidazoles of the formula:



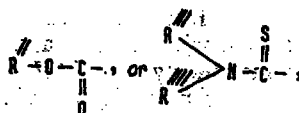
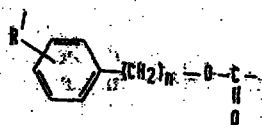
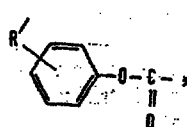
1(a)

and



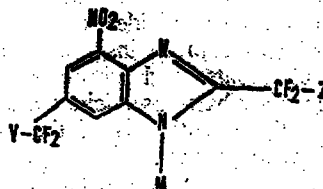
1(b)

wherein R is

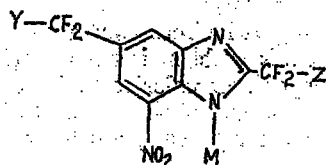


wherein R' is hydrogen, fluorine, chlorine, bromine, C₁-C₈ alkoxy, C₁-C₈ alkyl or nitro; and R'' is C₁-C₈ alkyl, halo-substituted C₁-C₈ alkyl, halo-substituted C₂-C₈ alkenyl, C₂-C₈ alkenyl or C₂-C₈ alkynyl; R''' and R'''' individually are hydrogen, C₁-C₈ alkyl or phenyl, or when taken together a pentamethylene or tetramethylene chain; and Y is F or H; Z is F, H, Cl, -CF₃ or -CF₂-CF₃; and halo is fluorine, chlorine, bromine and n is 1-3.

The novel benzimidazoles may be prepared by a process which comprises reacting an alkali metal salt of a benzimidazole of the formula:



and



wherein M is an alkali metal atom and Y and Z are as defined above, with a compound of the formula R—halo wherein R and halo are as defined above.

In the above process, the reaction is preferably carried out in the presence of an inert solvent.

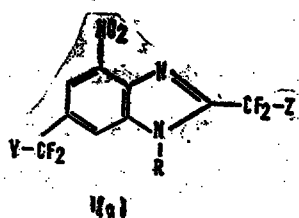
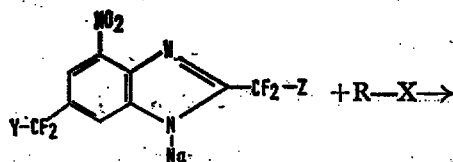
In the above formulae, it will be recognized that if R were hydrogen, the benzimidazole would exist in two tautomeric forms, one of which is named (when Y and Z are F) 2,6 - bis(trifluoromethyl) - 4 - nitrobenzimidazole and the other 2,5 - bis(trifluoromethyl) - 7 - nitrobenzimidazole. Both of these structures exist in equilibrium in any preparation of the pure compound. When the hydrogen on the benzimidazole nitrogen is replaced by phenylsulfonyl, carboxylate, thiocarboxamide or other radical comprehended within the term "R", as defined above, there is no longer the possibility for tautomerism and each preparation of the N-substituted derivative contains a mixture of two substances, one of which would be named, for example, using the same compound as above for illustrative purposes only, 2,6 - bis(trifluoromethyl) - 4 - nitro - 1 - phenylsulfonylbenzimidazole and the other would be 2,5 - bis(trifluoromethyl) - 7 - nitro - 1 - phenylsulfonylbenzimidazole. Only one of the two isomers may be readily isolatable. It should be understood that this invention includes within its scope both the 1 - substituted - 4 - nitro - 6 - fluoromethyl - 2 - fluoro - alkylbenzimidazoles and the 1 - substituted - 7 - nitro - 5 - fluoromethyl - 2 - fluoroalkylbenzimidazoles.

In the above formulas, "halo" can be chlorine, bromine, or fluorine. When R' is C₁—C₆ alkoxy, it can be for example methoxy, ethoxy, isopropoxy, *n*-propoxy, *sec*-butoxy, *n*-butoxy, isobutoxy, *n*-amyl, isoamyl or *sec*-amyl; and when R', R'', or R''' are C₁—C₆ alkyl, they can be for example, methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl, isobutyl, *sec*-butyl, *t*-amyl, *n*-amyl or *sec*-amyl. When R'' and R''' together form a pentamethylene or tetramethylene chain, the resulting group is piperidino or pyrrolidino. Groups illustrating the scope of R'' include those specified for C₁—C₆ alkyl above, as well as C₂—C₆ alkenyl groups including vinyl, 1-propenyl, isopropenyl, allyl, crotyl, methallyl and 2-pentenyl, and C₂—C₆ alkynyl groups including ethynyl, 1-propynyl, 1-butyne and 1-methyl-1-butyne. When R'' is halo-substituted C₂—C₆ alkenyl or halo-substituted C₁—C₆ alkyl, it can be any of the above groups used to illustrate the scope of the terms C₂—C₆ alkenyl or C₁—C₆ alkyl substituted with one or more halogens comprising chlorine, bromine, and fluorine. Typical groups illustrating the above terms include chloroalkyl, trifluoromethyl, chloromethyl, dichloromethyl, α -bromomethyl, 1,2 - dichloro - 2 - methylbutyl and 3 - bromo - 1 - pentenyl. When Y or Z are H or F, the resulting substituents are difluoromethyl and trifluoromethyl respectively. When Z is Cl, CF₃ or C₂F₅, the resulting 2-substituent is chlorodifluoromethyl, pentafluoroethyl or heptafluoropropyl.

Compounds represented by the Formulae I(a) or I(b) are conveniently prepared by reacting the sodium salt of the parent benzimidazole with the appropriate benzene-sulfonyl chloride or aryl or aliphatic chloroformate, or thiocarbonyl chloride.

The insecticidal compositions containing the compounds of this invention and their use as insecticides and acaricides are described and claimed in our copending application No. 22589/69 (Serial No. 1267998).

Novel compounds represented by Formulae I(a) and I(b) above are prepared by reacting the sodium salt of a 2 - fluoroalkyl - 6 - fluoromethyl - 4 - nitrobenzimidazole with a compound R—X according to the following equation:



wherein Y, Z, R, R', R'', R''', R'''' have the same meaning as above, and X is fluorine, chlorine, or bromine. (The preparation of the N-substituted derivatives of a 2 - fluoroalkyl - 6 - fluoromethyl - 4 - nitrobenzimidazole has been illustrated with respect to only the 6 - fluoromethyl - 4 - nitro isomer, but it will be understood from the previous discussion that the reaction also produces the 5 - fluoromethyl - 7 - nitro isomer, and that the sodium salt of the 2 - fluoroalkyl - 6 - fluoromethyl - 4 - nitrobenzimidazole is tautomeric and also includes the sodium salt of the 2 - fluoroalkyl - 5 - fluoromethyl - 7 - nitrobenzimidazole.)

Insecticidal compounds of this invention are prepared as follows:

Preparation of a Representative Starting Material

2,6-Bis(trifluoromethyl)-4-nitrobenzimidazole

The preparation of the above-identified representative starting material is disclosed and claimed in our copending application No. 57613/70 (Serial No. 1268000).

EXAMPLE I

2,6-Bis(trifluoromethyl)-4-nitro-1-phenylsulfonylbenzimidazole

A solution containing 6.4 g. of anhydrous sodium 2,6 - bis(trifluoromethyl) - 4 - nitrobenzimidazole was prepared in 50 ml. of anhydrous acetonitrile. Three and five tenths grams of benzenesulfonyl chloride and 20 ml. of anhydrous acetonitrile were added. Sodium chloride formed as a by-product in the reaction was separated by filtration and 2,6 - bis(trifluoromethyl - 4 - nitro - 1 - phenylsulfonylbenzimidazole thus prepared was isolated by evaporation of the solvent *in vacuo*. Recrystallization of the product from a benzene-pentane solvent mixture yielded 2,6 - bis(trifluoromethyl) - 4 - nitro - 1 - phenylsulfonylbenzimidazole melting at about 183—185°C. Nuclear magnetic resonance spectrum indicated that the desired product had been prepared and that there were no detectable quantities of impurities present.

EXAMPLE II

Phenyl 2,6-bis(trifluoromethyl)-4-nitro-1-benzimidazolecarboxylate and

Phenyl 2,5-bis(trifluoromethyl)-7-nitro-1-benzimidazolecarboxylate

The procedure of Example I was followed, except that phenyl chloroformate was used in place of benzenesulfonyl chloride. The product was isolated by the procedure of Example II and recrystallized from pentane to yield two fractions, the first melting at 83—92°C. and the second at 92—95°C. NMR spectrum indicated that the desired compounds had been prepared substantially free from impurities, although it was not possible to determine which fraction had a particular structure.

Other compounds prepared by the procedure of the above examples using the appropriate chloroformate or thiocarbonyl chloride in place of phenyl chloroformate include the following:

benzyl 2,6 - bis(trifluoromethyl) - 4 - nitro - 1 - benzimidazolecarboxylate, M.P.=109—113°C.

p-nitrophenyl 2,6 - bis(trifluoromethyl) - 4 - nitro - 1 - benzimidazole carboxylate, M.P.=60—80°C.

methyl 2,5 - bis(trifluoromethyl) - 7 - nitro - 1 - benzimidazole carboxylate, M.P.=93—98°C.

methyl 2,6 - bis(trifluoromethyl) - 4 - nitro - 1 - benzimidazole carboxylate, M.P.=93—98°C.

n - hexyl 2,6 - bis(trifluoromethyl) - 4 - nitro - 1 - benzimidazole carboxylate, M.P.=40—43°C.

ethyl 2,6 - bis(trifluoromethyl) - 4 - nitro - 1 - benzimidazole carboxylate, M.P.=78—84°C.

phenyl 2,6 - bis(trifluoromethyl) - 4 - nitro - 1 - benzimidazole carboxylate, M.P.=87—95°C.

isopropyl 2,6 - bis(trifluoromethyl) - 4 - nitro - 1 - benzimidazole carboxylate, M.P.=49—55°C.

allyl 2,6 - bis(trifluoromethyl) - 4 - nitro - 1 - benzimidazole carboxylate, M.P.=78—80°C.

N - ethyl - 2,6 - bis(trifluoromethyl) - 4 - nitro - benzimidazole - 1 - thio-carboxanilide, M.P.=96—104°C.

4 - nitro - 1 - piperidinothiocarbonyl - 2,6 - bis(trifluoromethyl)benzimidazole, M.P.=112—126°C.

1 - (N,N - di - *n* - propylthiocarboxamide) - 4 - nitro - 2,6 - bis(trifluoromethyl) benzimidazole, M.P.=118—127°C.

1 - (N,N - diethylthiocarboxamide) - 4 - nitro - 2,6 - bis(trifluoromethyl)-benzimidazole, M.P.=140—143°C.

1 - (N,N - dimethylthiocarboxamide - 4 - nitro - 2,6 - bis(trifluoromethyl)-benzimidazole, M.P.=105—114°C.

5 Most of the compounds coming within the scope of Formulae I(a) and I(b) above are phytotoxic at application rates considerably higher than those at which the compounds are insecticidally active, and many are effective herbicides for a wide variety of plants at application rates of 8 pounds per acre or higher. However, the extreme effectiveness of the insecticides represented by Formulae I(a) and I(b) provides a sufficient margin of safety to enable their use, either in the soil in the presence of growing or seedling crops, or by a one-time application to the foliage, as agricultural insecticides. 10

EXAMPLE III

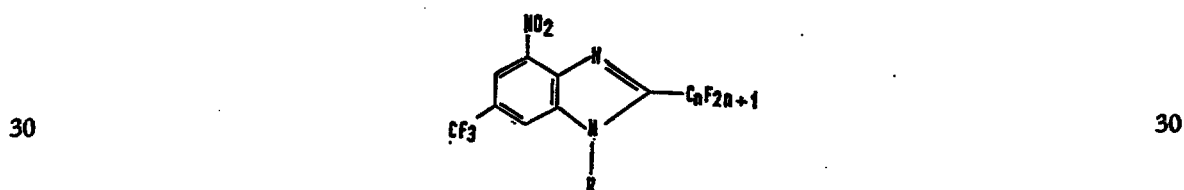
Preparation of Starting Material Salts

15 A mixture is prepared containing 6 g. of 2,6 - bis(trifluoromethyl) - 4 - nitrobenzimidazole, 1.1 g. of sodium methoxide and 100 ml. of methanol. The reaction mixture is shaken and filtered. Evaporation of the filtrate to dryness yields a mixture of the sodium salt of 2,6 - bis(trifluoromethyl) - 4 - nitrobenzimidazole and the sodium salt of 2,5 - bis(trifluoromethyl) - 7 - nitrobenzimidazole, melting at about 200°C. The compound is water soluble, but insoluble in acid. 20

Other alkali metal salts of 2,6 - bis(trifluoromethyl) - 4 - nitrobenzimidazole are prepared by substituting the appropriate metal alkoxide for sodium methoxide in the above preparation.

25 While the compounds of this invention resemble the organic phosphates in being toxic upon ingestion, they differ from the organic phosphates in having a low toxicity when applied to the skin. 25

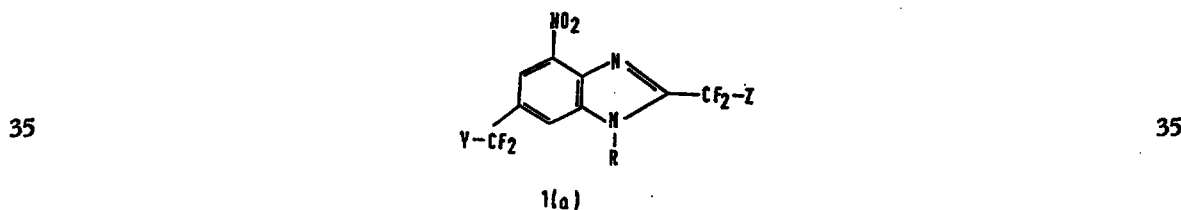
A group of highly active insecticides and arachnicides coming within the scope of Formulae I(a) and I(b) consists of the N-substituted derivatives of 2,6 - (5) - bis(trifluoromethyl) - 4(7) - benzimidazole as represented by the Formula:



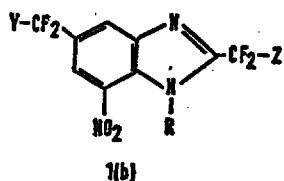
wherein R has the same meaning as hereinabove, and n is 1—3. The compounds of the above formula constitute a preferred feature of this invention.

WHAT WE CLAIM IS:—

1. A benzimidazole of the formulae:



and



1 - (N,N - diethylthiocarboxamide) - 4 - nitro - 2,6 - bis(trifluoromethyl)-benzimidazole, M.P.=140—143°C.

1 - (N,N - dimethylthiocarboxamide - 4 - nitro - 2,6 - bis(trifluoromethyl)-benzimidazole, M.P.=105—114°C.

Most of the compounds coming within the scope of Formulae I(a) and I(b) above are phytotoxic at application rates considerably higher than those at which the compounds are insecticidally active, and many are effective herbicides for a wide variety of plants at application rates of 8 pounds per acre or higher. However, the extreme effectiveness of the insecticides represented by Formulae I(a) and I(b) provides a sufficient margin of safety to enable their use, either in the soil in the presence of growing or seedling crops, or by a one-time application to the foliage, as agricultural insecticides.

EXAMPLE III

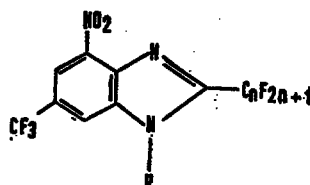
Preparation of Starting Material Salts

A mixture is prepared containing 6 g. of 2,6 - bis(trifluoromethyl) - 4 - nitrobenzimidazole, 1.1 g. of sodium methoxide and 100 ml. of methanol. The reaction mixture is shaken and filtered. Evaporation of the filtrate to dryness yields a mixture of the sodium salt of 2,6 - bis(trifluoromethyl) - 4 - nitrobenzimidazole and the sodium salt of 2,5 - bis(trifluoromethyl) - 7 - nitrobenzimidazole, melting at about 200°C. The compound is water soluble, but insoluble in acid.

Other alkali metal salts of 2,6 - bis(trifluoromethyl) - 4 - nitrobenzimidazole are prepared by substituting the appropriate metal alkoxide for sodium methoxide in the above preparation.

While the compounds of this invention resemble the organic phosphates in being toxic upon ingestion, they differ from the organic phosphates in having a low toxicity when applied to the skin.

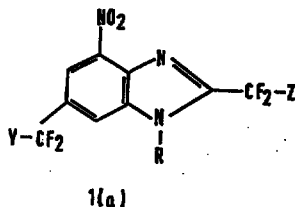
A group of highly active insecticides and arachnicides coming within the scope of Formulae I(a) and I(b) consists of the N-substituted derivatives of 2,6 - (5) - bis(trifluoromethyl) - 4(7) - benzimidazole as represented by the Formula:



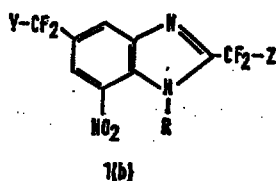
wherein R has the same meaning as hereinabove, and n is 1—3. The compounds of the above formula constitute a preferred feature of this invention.

WHAT WE CLAIM IS:—

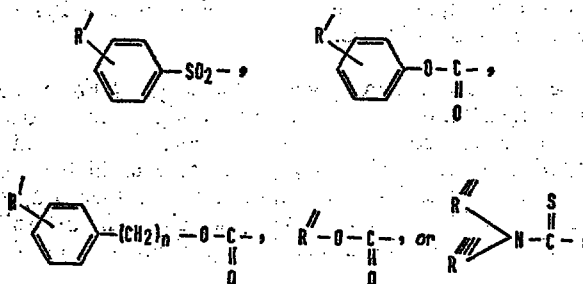
1. A benzimidazole of the formulae:



and

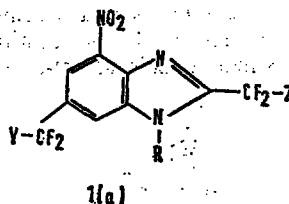


wherein R is

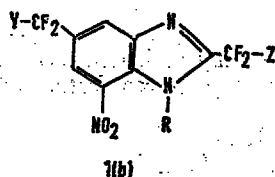


wherein R' is hydrogen, fluorine, chlorine, bromine, C₁-C₅ alkoxy, C₁-C₅ alkyl or nitro; and R'' is C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, halo-substituted C₂-C₅ alkenyl, C₂-C₅ alkynyl or C₂-C₅ alkenyl; R''' and R'''' individually are hydrogen, C₁-C₅ alkyl or phenyl, or when taken together a pentamethylene or tetramethylene chain; and Y is F or H; Z is F, H, Cl, -CF₃ or -CF₂-CF₃; and halo is fluorine, chlorine or bromine and n is 1-3.

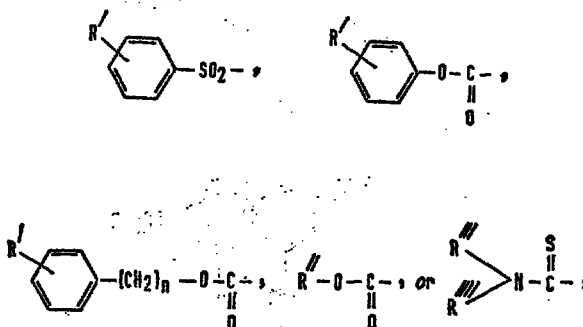
2. Allyl 2,6 - bis(trifluoromethyl) - 4 - nitro - 1 - benzimidazole - carboxylate.
3. 2,6 - bis(trifluoromethyl) - 4 - nitro - 1 - phenylsulfonylbenzimidazole.
4. Isopropyl 2,6 - bis(trifluoromethyl) - 4 - nitro - 1 - benzimidazolecarboxylate.
5. Ethyl 2,6 - bis (trifluoromethyl) - 4 - nitro - 1 - benzimidazolecarboxylate.
6. Benzyl 2,6 - bis (trifluoromethyl) - 4 - nitro - 1 - benzimidazolecarboxylate.
7. benzimidazole of the formulae



and

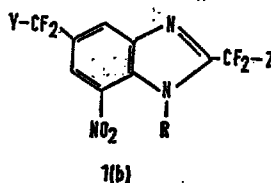
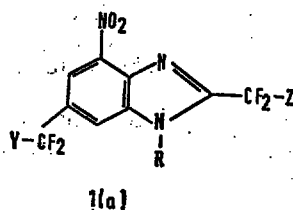


wherein R is

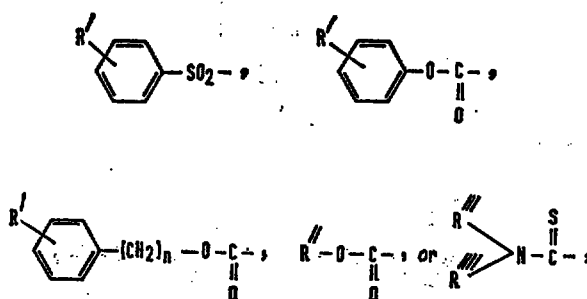


wherein R' is hydrogen, fluorine, chlorine, bromine, C₁-C₅ alkoxy, C₁-C₅ alkyl or nitro; and R'' is C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, halo-substituted C₂-C₅ alkenyl, C₂-C₅ alkynyl or C₂-C₅ alkenyl; R''' and R'''' individually are hydrogen, C₁-C₅ alkyl or phenyl, or when taken together a pentamethylene or tetramethylene chain; and Y is F or H; Z is F, H, Cl, -CF₃ or -CF₂-CF₃; halo is fluorine, chlorine or bromine and n is 1-3; substantially as hereinbefore described with particular reference to the examples.

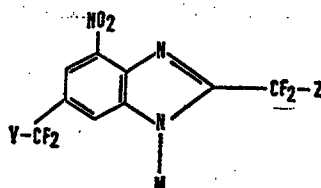
8. A process for preparing a benzimidazole compound of the formulae:



wherein R is

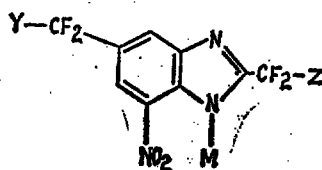


wherein R' is hydrogen, fluorine, chlorine, bromine, C₁-C₅ alkoxy, C₁-C₅ alkyl or nitro; and R'' is C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, halo-substituted C₂-C₅ alkenyl, C₂-C₅ alkynyl or C₂-C₅ alkenyl; R''' and R'''' individually are hydrogen, C₁-C₅ alkyl or phenyl, or when taken together a pentamethylene or tetramethylene chain; and Y is F or H; Z is F, H, Cl, -CF₃ or -CF₂-CF₃; halo is fluorine, chlorine or bromine and n is 1-3, which comprises reacting an alkali metal salt of a benzimidazole of the formulae



and





wherein M is an alkali metal atom and Y and Z are as defined above, with a compound of the formula R-halo wherein R and halo are as defined above.

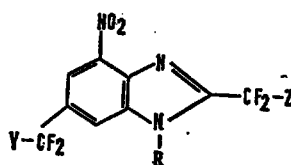
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9. The process of claim 8, wherein the reaction is carried out in the presence of an inert solvent.

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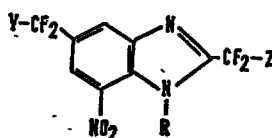
10. The process of claim 9, wherein the solvent is anhydrous acetonitrile.

11. A process for preparing a benzimidazole of the formulae:



1(a)

and

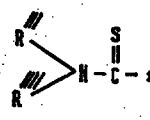
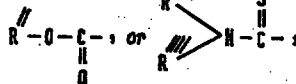
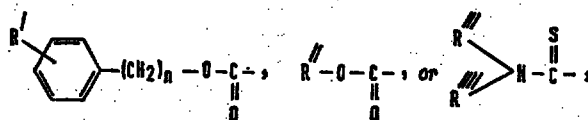
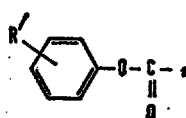
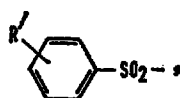


1(b)

10

10

wherein R is



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wherein R' is hydrogen, fluorine, chlorine, bromine, C₁-C₅ alkoxy, C₁-C₅ alkyl or nitro; and R'' is C₁-C₅ alkyl, halo-substituted C₁-C₅ alkyl, halo-substituted C₂-C₅ alkenyl, C₂-C₅ alkynyl or C₂-C₅ alkenyl; R''' and R'''' individually are

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hydrogen, C_1-C alkyl or phenyl, or when taken together a pentamethylene or tetramethylene chain; and Y is F or H; Z is F, H, Cl, $-CF_3$ or $-CF_2-CF_3$; and halo is fluorine, chlorine or bromine and n is 1-3; substantially as hereinbefore described with particular reference to the examples.

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