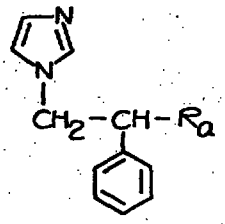
SPECIFICATION

1-Phenethylimidazole derivatives

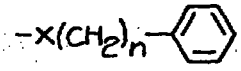
This invention relates to certain novel 1-phenethylimidazole derivatives and their antimicrobial acid addition salts, antimicrobial compositions containing the same, and methods of employing such derivatives, salts and compositions for inhibiting the growth of fungi and bacteria.

A large number of antifungal and antibacterial agents have been previously described which contain a 1-(β-aryl)ethyl-1H-imidazole moiety of the formula:

1



For example in U.S. 3,717,655 and E.F. Godefroi et al, J. Med. Chem. *12*, 784 (1969), compounds of formula *1* are disclosed in which R_a is:



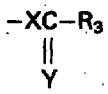
wherein X is 0 or NH.

In U.S. 3,991,201 and J. Heeres et al, J. Med. Chem. *20*, 1511 (1977), such compounds are disclosed in which R_a is $-(CH_2)_n-Ar$.

In J. Heeres et al, J. Med. Chem. *20*, 1516 (1977), such compounds are disclosed in which R_a is $-(CH_2)_nO-Ar$.

In U.S. 4,055,652 and 4,039,677, such compounds are disclosed in which R_a is $-SR_2$ wherein R_2 is H, benzyl, phenyl, etc.

In U.S. 4,039,677 and 4,038,409, such compounds are disclosed in which R_a is



wherein X and Y are O or S and R_3 is H, alkyl, cycloalkyl, phenalkyl, phenalkenyl, or $-XR_4$ wherein R_4 is alkyl, halophenyl, etc.

In U.S. 4,006,243, such compounds are disclosed in which R_a is H, alkyl or phenyl.

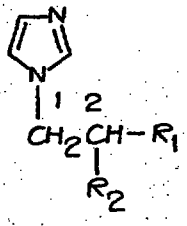
An entirely new class of compounds of formula *1* has now been discovered which have very good antifungal and antibacterial activity, namely those in which R_a is an optionally nuclearly substituted group of the formula:

A $-S-CH_2-S-CH_2-C_6H_5$

and the CH bonded phenyl ring is also optionally nuclearly substituted, and including the antimicrobial acid addition salts of such compounds.

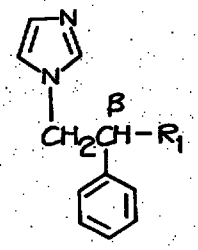
The products of the present invention are named as derivatives of 1-(ethyl)-1H-imidazole with the substituents R_1 and R_2 located at position 2 of the ethyl side chain, as in the following formula *2*:

2

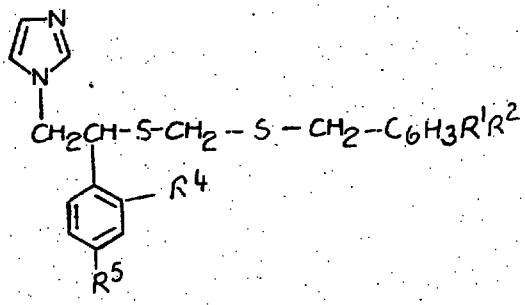


Alternatively, the products can be named as derivatives of 1-(phenethyl)-1H-imidazole where the substituent R_1 is attached β to the imidazole ring, as in the following formula *3*:

3



As indicated above, a primary feature of the present invention is the provision of novel compounds of formula *1* above in which R_a has the formula *A* above and the CH bonded phenyl ring is optionally nuclearly substituted, and including the antimicrobial, i.e. antifungal and antibacterial, acid addition salts of such compounds, actually compounds of the formula:

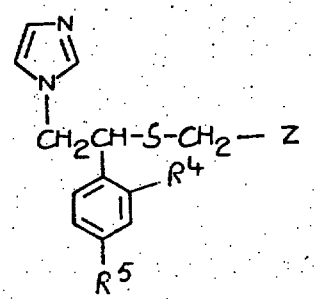


including the antimicrobial acid addition salts thereof, wherein:

R^1 and R^2 are independently hydrogen, halogen or C_1-C_6 alkyl, provided that R^1 and R^2, but not both of them, may be CH_3; and R^4 and R^5 are independently hydrogen or halogen.

The subject compounds of formula *4* above exhibit antifungal and antibacterial activity against animal and human pathogens as well as antifungal activity against fungi of primarily agricultural importance. Thus, the subject compounds are found to be useful antimicrobials, having not only pharmaceutical but also agricultural and industrial applications. Thus, a further feature of the present invention relates to methods of inhibiting the growth of fungi and bacteria by applying to a host object other than the human or animal body which contains, carries or is subject to attack by fungi or bacteria a fungicidally or bactericidally effective amount of a compound of this invention. A still further feature of the present invention relates to compositions for pharmaceutical, agricultural, and industrial use, which compositions comprise the subject compounds of formula *4* in combination with a suitable carrier.

Still another feature of this invention is the use, in a process for producing the compounds of formula *4* above, as further explained in respect of Scheme III below, of intermediates having the formula:



wherein Z is a member selected from the group consisting of SM, halo, COOalkyl, methanesulfonate and $-OSO_2-p-$tolyl, M is H or alkali metal, and R^4 and R^5 have the values defined above.

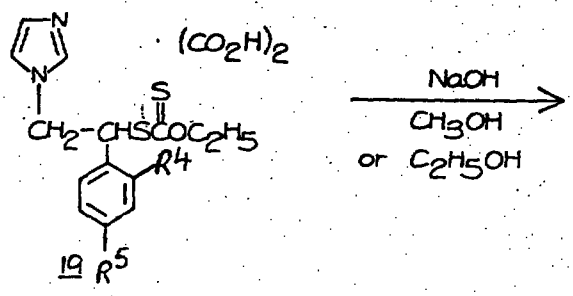
As employed herein and in the claims, "halogen" or "halo" refers to iodo, fluoro, bromo and most preferably chloro. The term "antimicrobial acid addition salts" refers to the crystalline salts of the subject compounds which possess the desired antimicrobial activity and which are neither biologically nor otherwise undesirable. Such salts are formed by contacting the subject compounds with inorganic acids such as hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric and phosphoric acids, and organic acids such as fumaric, oxalic, maleic, acetic, pyruvic, citric, tartaric, methanesulfonic, ethanesulfonic, p-toluenesulfonic, hydroxyethanesulfonic, sulfamic, malic, succinic, ascorbic, levulinic, propionic, glycolic, benzoic, mandelic, salicylic, lactic, p-aminosalicylic, 2-phenoxybenzoic, 2-acetoxybenzoic, 1,4-naphthalene disulfonic acids and the like.

The subject compounds of formula *4* are organic bases, the majority of which are viscous oils in the free base form. The free bases are usually purified by column chromatography on either silicic acid or alumina and may then be converted to their solid acid addition salts by contacting them with one of the above salt-forming acids, usually in a solvent such as water, ethanol, 1-propanol, ethyl acetate, acetonitrile or diethyl ether. Upon cooling or dilution with a less polar solvent the acid addition salts usually crystallize.

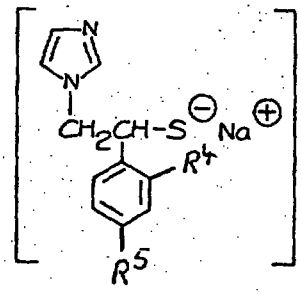
Such compounds of the formula *4* contain a chiral or asymmetric center, i.e. the carbon atom in the depicted CH link, and therefore may exist as enantiomers which may if desired be separated by known procedures such as by conventional resolution means employing optically active acids such as the optically active forms of camphor-10-sulfonic, α-bromocamphor-π-sulfonic, camphoric, menthoxyacetic, tartaric, malic, di-acetyltartaric, pyrrolidone-5-carboxylic acids and the like. It will be understood that this invention is inclusive of such optical isomers and the racemic mixtures thereof.

Products of this invention may be synthesized as shown in *Scheme I*, in which they are the products *22*.

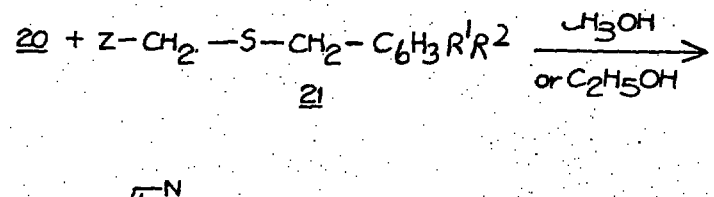
Scheme I

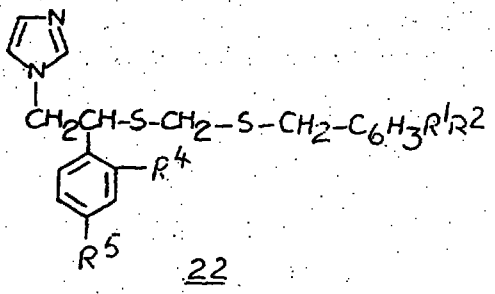


19



20





22

Z is a p-toluenesulfonate, chloro, bromo, iodo, methylsulfonate or other conventional leaving group.

U.S. 4,038,409 and 4,039,677 disclose the general methodology for the synthesis of the required xanthate salt *19* and for its hydrolysis to give thiol salt *20*, which is then utilized in the instant syntheses.

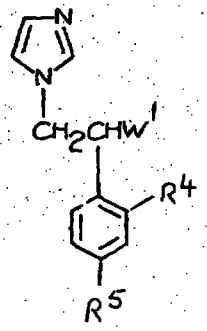
Thiol salt *20* is advantageously stockpiled as the solid xanthate *19* and is generated *in situ* as needed, under nitrogen to minimize oxidation. The alkylating species *21* are then introduced and the mixture stirred

at 25-80° for periods of 0.5-24 hours to afford the desired products *22*.

More generally, the compounds of formula *4* may be prepared, for example, by either:

Scheme II reacting a compound of the formula:

43



with an equimolar amount of a compound of the formula:

44 $W^2-CH_2-S-CH_2-C_6H_3R^1R^2$

wherein W^1 is either

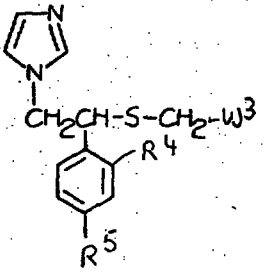
(a) SM, M being hydrogen or an alkali metal such as Na, K, or Li, or

(b) a leaving group such as Cl, Br, OSO_2p-tolyl or OSO_2CH_3, and

W^2 is the other of (a) or (b); *or*

Scheme III reacting a compound of the formula:

45



with an equimolar amount of a compound of the formula:

46 $W^4-CH_2-C_6H_3R^1R^2$

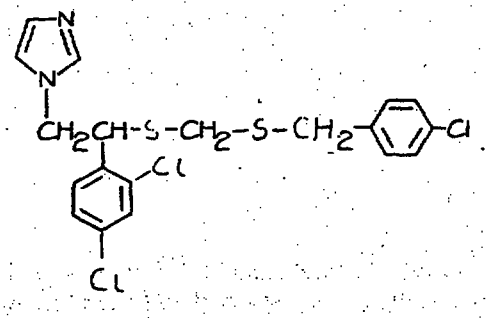
wherein W^3 is either

(c) SM, M being as defined in *Scheme II*, or

(d) a leaving group as defined in *Scheme II*, and W^4 is the other of (c) or (d),

R^1, R^2, R^4 and R^5 being as defined in formula *4*.

A particularly interesting compound of formula *4* which has been prepared is that having the following formula:-



As indicated in the Example given below, this compound may be treated with fumaric acid to give a product in the form of colorless crystals, the free base being a viscous brown oil.

The antifungal activity of compounds of general structure *4* is determinable by a broth dilution technique,

against several strains of the following human and animal pathogenic fungi: *Candida albicans, Candida tropicalis, Candida krusei, Trichophyton rubrum, Trichophyton mentagrophytes and Microsporum canis.*

Two-fold serial dilutions are made with Sabouraud's liquid medium from stock solutions of the test compounds, usually in dimethyl sulfoxide, N,N-dimethylformamide or water. The Minimum Inhibitory Concentrations (MIC's), which are considered to be the minimum concentrations of the test compounds in micrograms per milliliter which prevent grossly detectable growth of the test organisms, are then determined after inoculation of the medicated broths with the test organisms, and incubation at the appropriate temperature and for the appropriate time interval.

Candida species are incubated for 24 hours at 37°, and five days at 28° for the dermatophytes *Trichophyton rubrum, Trichophyton mentagrophytes* and *Microsporum canis.*

The following example is only illustrative of a certain preferred embodiment of the antimicrobial compounds of this invention, the structures of which as disclosed herein are supported by satisfactory infrared and proton magnetic resonance spectra. As employed herein and in the appended claims, all amounts and proportions are by weight unless otherwise indicated, temperatures are in °C, and melting and boiling points are uncorrected.

EXAMPLE

1-[2-(4-Chlorobenzylthiomethylthio)-2-(2,4-dichlorophenyl)ethyl]-1H-imidazole hydrogen fumarate

To a stirred solution of sodium hydroxide (2.02 g, 0.05 mole) in ethanol (180 ml) at 25° under a blanket of nitrogen, was added 1-[2-(2,4-dichlorophenyl)-2-(ethoxythiocarbonylthio)ethyl]-1H-imidazole hydrogen oxalate (4.51 g, 0.01 mole). After stirring at 25° for 0.75 hour a solution of 4-chlorobenzyl chloromethyl sulfide (2.07 g, 0.01 mole) in ethanol (2 ml) was added. The mixture was refluxed for twenty hours and concentrated to dryness. The residue was partitioned between diethyl ether and water. The ethereal layer was washed successively with H_2O, Na_2CO_3-H_2O, H_2O, brine and dried (Na_2SO_4). Removal of the ether left the free base (3.3 g) as a viscous brown oil. Treatment of a solution of the free base (3.3 g) in acetonitrile with fumaric acid (0.78 g) provided 2.5 g) of the title compound, mp 120-125°. Recrystallization from ethyl acetate gave colorless crystals, mp 121-123°, of the analytical sample.

Anal. Calc'd for $C_{19}H_{17}Cl_3N_2S_2.C_4H_4O_4$: C, 49.34; H, 3.78; Cl, 19.00; N, 5.00; S, 11.45.
Found: C,49.70; H, 3.90; Cl, 18.94; N, 5.24; S, 11.39

The antimicrobial compounds of this invention exhibit antifungal and antibacterial activity against a wide variety of human and animal pathogens in addition to those referred to above, and are accordingly useful not only in pharmaceutical applications but also in agricultural, industrial, household and other applications in which such activity is required. In general, antimicrobial compositions may contain such compounds in any concentrations, i.e. from about 0.1% to about 99.9% in a suitable or conventional carrier adapted for the intended use. For example, from about 10% to 90% concentrates may be supplied for dilution by the user to concentrations generally ranging from about 0.1% to 10%.

In pharmaceutical formulations compositions may be solid, semi-solid or liquid in form such as tablets, capsules, powders, suppositories, liquid solutions, suspensions, creams, lotions, gels, ointments and the like. Pharmaceutically acceptable non-toxic carriers, or excipients normally employed for solid formulations include tricalcium phosphate, calcium carbonate, kaolin, bentonite, talcum, gelatin, lactose, starch and the like; for semi-solid formulations there may be mentioned, for example, polyalkylene glycols, Vaseline (RTM), petrolatum and other cream bases; for liquid formulations there may be mentioned, for example, water, oils of vegetable origin and low boiling solvents such as isopropanol, hydrogenated naphthalenes and the like. The pharmaceutical compositions containing the compounds of the present invention may be subjected to conventional pharmaceutical expedients such as sterilization and can contain conventional pharmaceutical excipients such as preservatives, stabilizing agents, emulsifying agents, salts for the adjustment of osmotic pressure and buffers. The compositions may also contain other therapeutically active materials.

The pharmaceutical compositions of this invention typically comprise a pharmaceutically acceptable, non-toxic carrier in combination with one or more compounds represented by formula *4* in an amount effective for relief or prevention of the specific condition being treated. Since the active compounds of this invention exhibit anti-fungal and anti-bacterial activity over a wide range of concentration, the effective amount may vary. For example, in topical formulations the amount may be about 0.1% to about 10% of the total pharmaceutical formulation while in other formulations the amount may be about 5 to 95% or more. Preferably the pharmaceutical compositions of this invention are formulated in unit dosage form to facilitate administration (unit dosage being the amount of active ingredients administered on one occasion).

In pharmaceutical applications, the subject compounds and compositions may be administered to humans and animals by conventional methods, e.g. topically, orally, parenterally and the like. "Topical" administration includes intravaginal application while parenteral administration includes intramuscular as well as subcutaneous and intravenous injection. Intravenous injection of imidazole derivatives for certain systemic conditions has been demonstrated to be effective (see for example, Drugs *9*, 419-420 (1975), which describes the intravenous administration of Miconazole, i.e. 1-[2,4-dichloro-β-(2',4'-dichlorobenzyloxy)phenethyl]-imidazole nitrate, to patients with systemic candidiasis). Topical application is the preferred method of administration in pharmaceutical applications. For such treatment, an area having

an existing fungal or bacterial growth, or to be protected against attack by fungi or bacteria, may be treated with the subject compounds of formula 4 or compositions containing them by, for example, dusting, sprinkling, spraying, rinsing, brushing, dipping, smearing, coating, impregnating and the like.

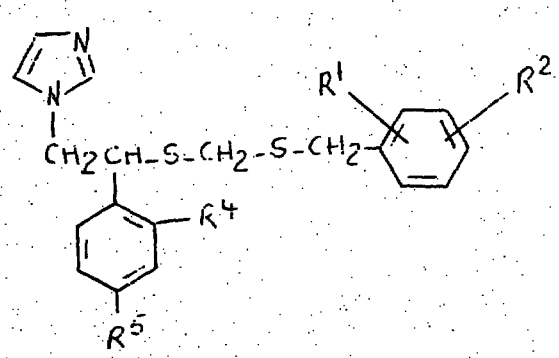
The exact regimen for pharmaceutical administration of the compounds and compositions disclosed herein will necessarily be dependent upon the needs of the individual subject being treated, the type of treatment, e.g., whether preventative or curative, the type or organism involved and, of course, the judgement of the attending practitioner. In general, for systemic (e.g., oral or parenteral) administration it is expedient to administer the active ingredient in amounts of between about 1 and 100 mg/kg body weight per day (preferably between about 5 and 50 mg/kg body weight per day) preferably distributed over several applications (e.g., in 3 individual doses) in order to achieve effective results. For localized (e.g., topical) administration, however, proportionately less of the active ingredient is required.

In agricultural applications, the subject compounds may be applied directly to plants (e.g., seeds, foliage) or to soil. For example, compounds of the present invention may be applied to seeds alone or in admixture with a powdered solid carrier. Typical powdered carriers are the various mineral silicates, e.g., mica, talc, pyrophyllite, and clays. The subject compounds may also be applied to the seeds in admixture with a conventional surface-active wetting agent with or without additional solid carrier. Surface-active wetting agents that can be used are any of the conventional anionic, non-ionic, amphoteric or cationic types. As a soil treatment for fungi and the like, the subject compounds can be applied as a dust in admixture with sand, soil or a powdered solid carrier such as mineral silicate with or without additional surface-active agent, or the subject compounds can be applied as an aqueous spray optionally containing a surface-active dispersing agent and a powdered solid carrier. As a foliage treatment, the subject compounds can be applied to growing plants as an aqueous spray whhich contains a surface-active dispersing agent with or without a powdered solid carrier and hydrocarbon solvents.

In industrial applications, the subject compounds may be used to control bacteria and fungi by contacting the pathogens with the compounds in any known manner. Materials capable of supporting bacteria and fungi may be protected by contacting, mixing or impregnating these materials with the subject compounds. In order to increase their effect, the subject compounds may be combined with other pesticidal control agents such as fungicides, bactericides, insecticides, miticides and the like. A particularly important industrial/agricultural use for the subject compounds of the present invention is as a food preservative against bacteria and fungi which cause deterioration and spoilage of foods.

CLAIMS

1. A compound of the formula:



including the antimicrobial acid addition salts thereof, wherein:

R^1 and R^2 are independently hydrogen, halogen or C_1-C_6 alkyl, provided that R^1 or R^2, but not both of them, may be CF_3; and R^4 and R^5 are independently hydrogen or halogen.

2. A compound of claim 1 wherein R^4 and R^5 are both chlorine.
3. A compound of claim 1 or 2 wherein R^1 is CF_3 or C_1-C_6 alkyl, and R^2 is H.
4. A compound of claim 1 or 2 wherein R^1 is chloro.
5. A compound of claim 4 wherein R^2 is chloro.
6. A compound of claim 4 wherein R^2 is H.
7. A compound of claim 1 or 2 wherein R^1 is F.
8. A compound of claim 1 or 2 wherein R^1 and R^2 are both hydrogen.
9. A compound in accordance with claim 2 wherein R^1 is 4-chloro, and R^2 is hydrogen.
10. A composition useful for inhibiting the growth of fungi or bacteria comprising an antifungally or antimicrobially effective amount of a compound as defined in any of claims 1 to 9 in admixture with a suitable carrier.
11. A composition of claim 10 for pharmaceutical use wherein the carrier is a pharmaceutically acceptable non-toxic carrier.
12. A composition of claim 11 for topical administration wherein said compound is present in an amount ranging from about 0.1 to about 10 weight percent.

an existing fungal or bacterial growth, or to be protected against attack by fungi or bacteria, may be treated with the subject compounds of formula *4* or compositions containing them by, for example, dusting, sprinkling, spraying, rinsing, brushing, dipping, smearing, coating, impregnating and the like.

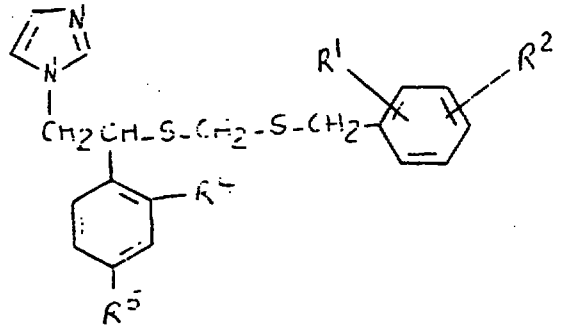
The exact regimen for pharmaceutical administration of the compounds and compositions disclosed herein will necessarily be dependent upon the needs of the individual subject being treated, the type of treatment, e.g., whether preventative or curative, the type or organism involved and, of course, the judgement of the attending practitioner. In general, for systemic (e.g., oral or parenteral) administration it is expedient to administer the active ingredient in amounts of between about 1 and 100 mg/kg body weight per day (preferably between about 5 and 50 mg/kg body weight per day) preferably distributed over several applications (e.g., in 3 individual doses) in order to achieve effective results. For localized (e.g., topical) administration, however, proportionately less of the active ingredient is required.

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CLAIMS

1. A compound of the formula:



including the antimicrobial acid addition salts thereof, wherein:

R^1 and R^2 are independently hydrogen, halogen or C_1-C_6 alkyl, provided that R^1 or R^2, but not both of them, may be CF_3; and R^4 and R^5 are independently hydrogen or halogen.

2. A compound of claim 1 wherein R^4 and R^5 are both chlorine.
3. A compound of claim 1 or 2 wherein R^1 is CF_3 or C_1-C_6 alkyl, and R^2 is H.
4. A compound of claim 1 or 2 wherein R^1 is chloro.
5. A compound of claim 4 wherein R^2 is chloro.
6. A compound of claim 4 wherein R^2 is H.
7. A compound of claim 1 or 2 wherein R^1 is F.
8. A compound of claim 1 or 2 wherein R^1 and R^2 are both hydrogen.
9. A compound in accordance with claim 2 wherein R^1 is 4-chloro, and R^2 is hydrogen.
10. A composition useful for inhibiting the growth of fungi or bacteria comprising an antifungally or antimicrobially effective amount of a compound as defined in any of claims 1 to 9 in admixture with a suitable carrier.
11. A composition of claim 10 for pharmaceutical use wherein the carrier is a pharmaceutically acceptable non-toxic carrier.
12. A composition of claim 11 for topical administration wherein said compound is present in an amount ranging from about 0.1 to about 10 weight percent.

13. A method of inhibiting the growth of fungi or bacteria comprising applying to a host object other than the human or animal body which contains, carries or is subject to attack by fungi or bacteria an antimicrobially effective amount of a compound as defined in claim 1.

14. The method of claim 13 applied topically.

15. A process for producing a compound of claim 1 comprising reacting a compound of Formula 45 with preferably an equimolar amount of a compound of Formula 46.

16. The process of claim 15, wherein W^3 in Formula 45 is selected from SM, halo, COOalkyl, methanesulfonate and OSO_2-p-tolyl, M being H or alkali metal.

17. A process for producing a compound of claim 1 comprising reacting a compound of Formula 43 with preferably an equimolar amount of a compound of Formula 44.

18. A compound as defined in claim 1 prepared by a procedure substantially as described in the foregoing Example.

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