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(12) # EUROPEAN PATENT SPECIFICATION

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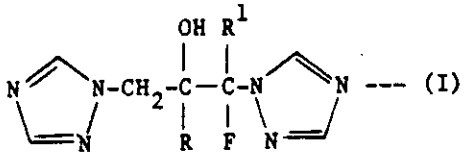
Description

This invention relates to novel bis-triazole derivatives which have antifungal activity and are useful in the treatment of fungal infections in animals, including humans, and as agricultural fungicides.

EP—A—44605 and EP—A—69442 disclose certain 1,3-bis(2,3,4-triazol-1-yl)-2-(optionally substituted phenyl)-propan-2-ol antifungal agents.

EP—A—149426, designating the Contracting States AT, BE, CH, DE, FR, IT, LI, LU and NL and claiming priority dates of 20th December, 1983 and 5th June, 1984, describes certain ketone intermediates of the formula (IV) as used herein. The method described for the preparation of these ketones differs from that of the present application. There is also a corresponding GB application, GB 2152045 A.

According to the invention, there are provided compounds of the formula:—



(I)

where R is phenyl optionally substituted by 1 to 3 substituents each independently selected from F, Cl, Br, I, CF_3, C_1—C_4 alkyl and C_1—C_4 alkoxy, or R is 5-chloro-pyrid-2-yl; and R^1 is H, CH_3 or F; and their pharmaceutically and agriculturally acceptable salts.

C_3 and C_4 alkyl and alkoxy groups can be straight or branched chain.

The invention also provides a pharmaceutical composition comprising a compound of the formula (I) or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

The invention further provides a compound of the formula (I) or a pharmaceutically acceptable salt thereof, for use in medicine, in particular for treating fungal infections in animals, including humans.

The invention yet further provides a plant or seed antifungal composition comprising a compound of the formula (I) or an agriculturally acceptable salt thereof, together with an agriculturally acceptable diluent or carrier.

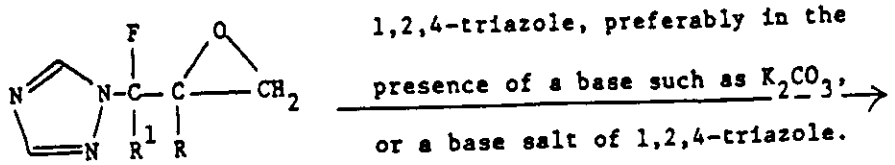
The invention yet further provides a method of treating a plant or seed having a fungal infection, which comprises treating said plant or seed, or the locus of said plant, with an antifungally effective amount of a compound of the formula (I) or with an agriculturally acceptable salt thereof.

When R is said optionally substituted phenyl group, it is preferably phenyl substituted by 1 to 3 substituents, more preferably 1 or 2 substituents, each independently selected from F, Cl, Br, I and CF_3. The preferred individual groups represented by R are 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-iodophenyl, 4-trifluoromethylphenyl, 2-chlorophenyl, 2,4-dichlorophenyl, 2,4-difluorophenyl, 2-chloro-4-fluorophenyl, 2-fluoro-4-chlorophenyl, 2,5-difluorophenyl, 2,4,6-trifluorophenyl and 4-bromo-2,5-difluorophenyl. The more preferred groups represented by R are 2,4-difluorophenyl, 2,4-dichlorophenyl, 4-fluorophenyl and 4-chlorophenyl. The most preferred group represented by R is 2,4-difluorophenyl.

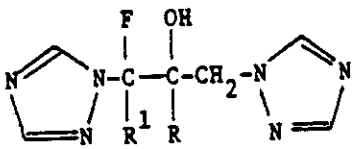
R^1 is preferably H or F.

In the most preferred compound, R is 2,4-difluorophenyl and R^1 is H.

The compounds of the formula (I) can be prepared in conventional manner according to the following reaction scheme:—



(II)

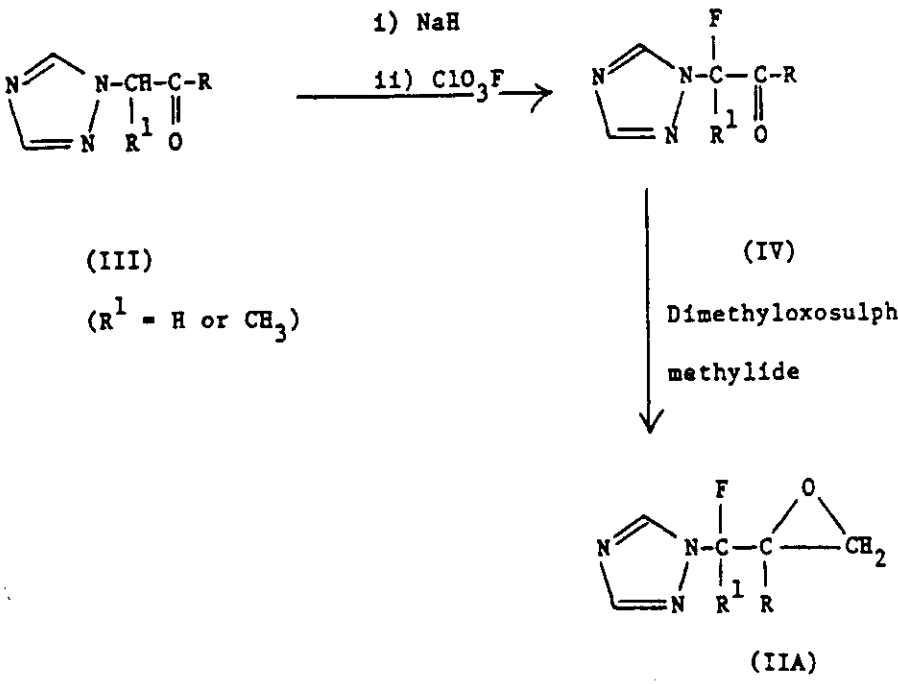


(I)

In a typical reaction, the epoxide (II), 1,2,4-triazole and anhydrous potassium carbonate are heated together at, say, 40—120°C, in a suitable solvent, e.g. anhydrous dimethylformamide, until the reaction is complete. The product (I) can then be isolated and purified in a conventional manner.

If a base salt of 1,2,4-triazole is used, this is preferably an alkali metal salt and, most preferably, the sodium or potassium salt.

The starting materials of the formula (II) in which R^1=H or CH_3 are obtainable conventionally, e.g.

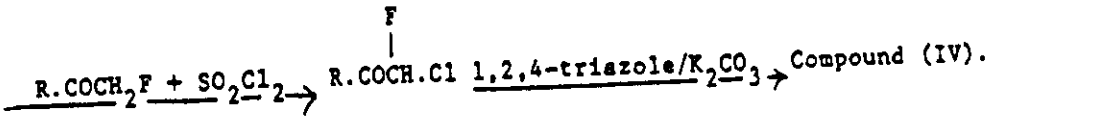


It is not essential to isolate and purify compound (IIA) and it can be converted *in situ* to the desired product.

Trimethylsulphoxonium iodide and sodium hydride in dimethylsulphoxide is generally used to generate dimethyloxosulphonium methylide *in situ*.

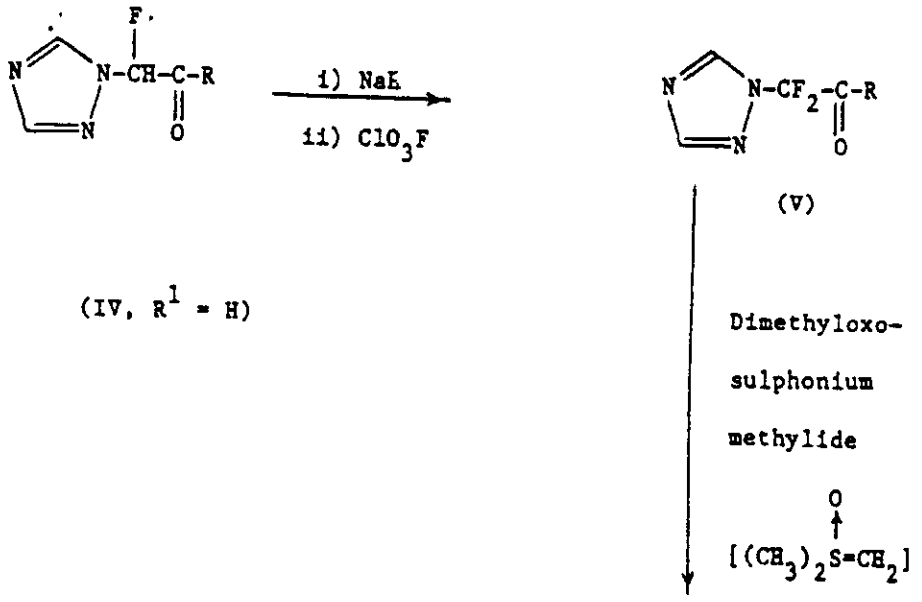
The ketones (III) are either known compounds (see e.g. European patent application publication no. 0044605 or U.K. patent application publication no. 2099818A) or can be prepared by methods analogous to those of the prior art.

An alternative route to the ketones (IV) (R^1 = H) is as follows:—

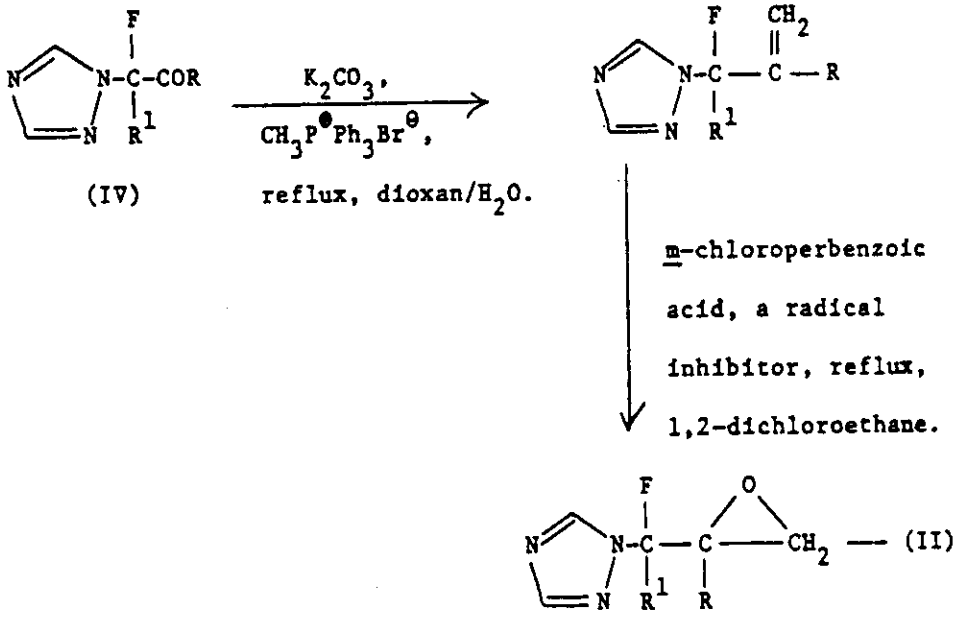


The compounds of the formula (I) contain at least one chiral centre, and the invention includes both resolved and unresolved forms. When R^1 is H or CH_3, the compounds exist in two diastereoisomeric pairs. A typical complete separation of such a compound of the formula (I) into its two diastereoisomeric pairs is described in Example 2, and a partial separation in Example 1(B).

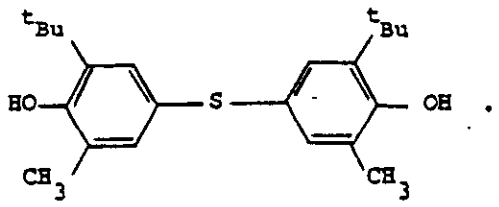
The starting materials of the formula (II) in which R^1 = F can be prepared as follows:—



Again it is not essential to isolate the intermediate (IIB).
Another route to the oxiranes (II) in which R^1 is H, CH_3 or F is as follows:—



The preferred free radical inhibitor is 3,3'-di-*t*-butyl-4,4'-dihydroxy-5,5'-dimethyl-diphenylsulphide, of the formula:—



Pharmaceutically acceptable acid addition salts of the compounds of the formula (I) are those formed from strong acids which form non-toxic acid addition salts, such as hydrochloric, hydrobromic, sulphuric, oxalic and methanesulphonic acids.

The salts may be obtained by conventional procedures, e.g. by mixing solutions containing approximately equimolar amounts of the free base and desired acid, and the required salt is collected by filtration, if insoluble, or by evaporation of the solvent.

The compounds of the formula (I) and their pharmaceutically acceptable salts are antifungal agents, useful in combating fungal infections in animals, including humans. For example they are useful in treating topical fungal infections in man caused by, among other organisms, species of *Candida, Trichophyton, Microsporum* or *Epidermophyton,* or in mucosal infections caused by *Candida albicans* (e.g. thrush and vaginal candidiasis). They can also be used in the treatment of systemic fungal infections caused by, for example, *Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus, Coccidioides, Paracoccidioides, Histoplasma* or *Blastomyces.*

The *in vitro* evaluation of the antifungal activity of the compounds can be performed by determining the minimum inhibitory concentration (m.i.c.) of the test compounds in a suitable medium at which growth of the particular micro-organism fails to occur. In practice, a series of agar plates, each having the test compound incorporated at a particular concentration is inoculated with a standard culture of, for example, *Candida albicans* and each plate is then incubated for 48 hours at 37°C. The plates are then examined for the presence or absence of growth of the fungus and the appropriate m.i.c. value is noted. Other micro-organisms used in such tests can include *Cryptococcus neoformans, Aspergillus fumigatus, Trichophyton* spp; *Microsporum* spp; *Epidermophyton floccosum, Coccidioides immitis* and *Torulopsis glabrata.*

The *in vivo* evaluation of the compounds can be carried out at a series of dose levels by intraperitoneal or intravenous injection or by oral administration, to mice which are inoculated with a strain of *Candida albicans.* Activity is based on the survival of a treated group of mice after the death of an untreated group of mice following 48 hours observation. The dose level at which the compound provides 50% protection against the lethal effect of the infection (PD_{50}) is noted.

For human use, the antifungal compounds of the formula (I) can be administered alone, but will generally be administered in admixture with a pharmaceutical carrier selected with regard to the intended route of administration and standard pharmaceutical practice. For example, they can be administered orally in the form of tablets containing such excipients as starch or lactose, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs or suspensions containing flavouring or colouring agents. They can be injected parenterally, for example, intravenously, intramuscularly or subcutaneously. For parenteral administration, they are best used in the form of a sterile aqueous solution which may contain other substances, for example, enough salts or glucose to make the solution isotonic with blood.

For oral and parenteral administration to human patients, the daily dosage level of the antifungal compounds of the formula (I) will be from 0.1 to 10 mg/kg (in divided doses) when administered by either the oral or parenteral route. Thus tablets or capsules of the compounds will contain from 5 mg to 0.5 g of active compound for administration singly or two or more at a time as appropriate. The physician in any event will determine the actual dosage which will be most suitable for an individual patient and it will vary with the age, weight and response of the particular patient. The above dosages are exemplary of the average case; there can, of course, be individual instances where higher or lower dosage ranges are merited, and such are within the scope of this invention.

Alternatively, the antifungal compounds of formula (I) can be administered in the form of a suppository or pessary, or they may be applied topically in the form of a lotions, solution, cream, ointment or dusting powder. For example, they can be incorporated into a cream consisting of an aqueous emulsion of polyethylene glycols or liquid paraffin; or they can be incorporated, at a concentration between 1 and 10%, into an ointment consisting of a white wax or white soft paraffin base together with such stabilizers and preservatives as may be required.

The compounds of the formula (I) and their salts also have activity against a variety of plant pathogenic fungi, including for example various rusts, mildews and moulds, and the compounds are thus useful for treating plants and seeds to eradicate or prevent such diseases.

The *in vitro* evaluation of the activity of the compounds against plant fungi can be determined by measuring their minimum inhibitory concentrations in the same way as previously described except that the plates are incubated at 30°C for 48 hours or longer before being examined for the presence or absence of growth.

Micro-organisms used in such tests include *Cochliobolus carbonum, Pyricularia oryzae, Glomerella cingulata, Penicillium digitatum, Botrytis cinerea* and *Rhizoctonia solani.*

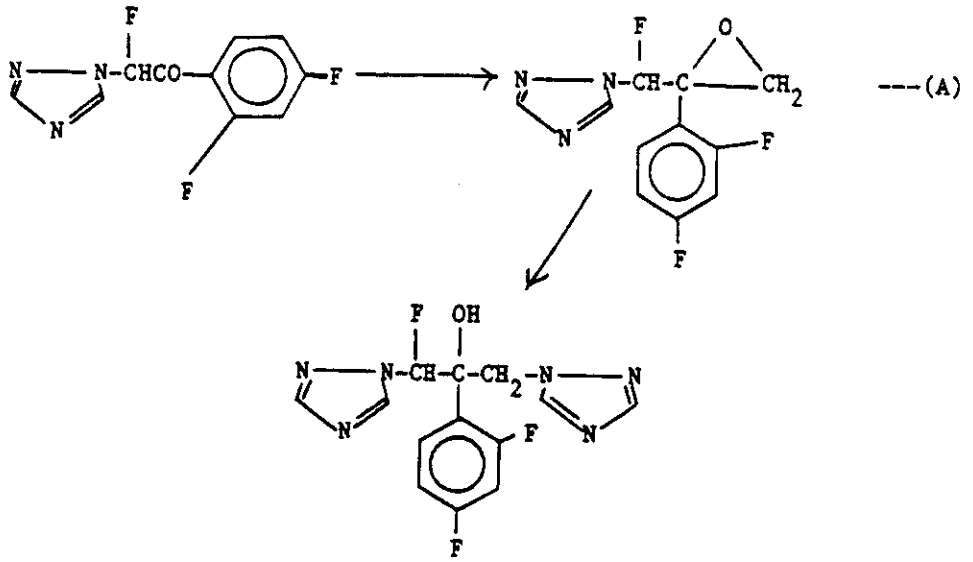
For agricultural and horticultural purposes the compounds and their agriculturally acceptable salts are preferably used in the form of a composition formulated as appropriate to the particular use and purpose desired. Thus the compounds may be applied in the form of dusting powders, or granules, seed dressings, aqueous solutions, dispersions or emulsions, dips, sprays, aerosols or smokes. Compositions may also be supplied in the form of dispersible powders, granules or grains, or concentrates for dilution prior to use. Such compositions may contain such conventional carriers, diluents or adjuvants as are known and acceptable in agriculture and horticulture and they are manufactured in accordance with conventional procedures. The compositions may also incorporate other active ingredients, for example, compounds having herbicidal or insecticidal activity or a further fungicide. The compounds and compositions can be applied in a number of ways, for example they can be applied directly to the plant foliage, stems, branches, seeds or roots or to the soil or other growing medium, and they may be used not only to eradicate disease, but also prophylactically to protect the plants or seeds from attack.

The following Examples illustrate the invention. All temperatures are in °C.

Example 1

Procedure (A)

1,3-Bis(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-1-fluoropropan-2-ol (mixture of two diastereomeric pairs)



A mixture of sodium hydride (21 mg. of a 60% dispersion in oil, 0.54 mM of sodium hydride) and trimethyl sulphoxonium iodide (143 mg; 0.65 mM) was stirred under dry nitrogen and anhydrous dimethyl sulphoxide (4 ml) was added. After forty minutes anhydrous tetrahydrofuran (4 ml) was added to the solution and the mixture was cooled to −40°. A solution of 2-(1H-1,2,4-triazol-1-yl)-2,2'4'-trifluoro-acetophenone (130 mg; 0.54 mM) in tetrahydrofuran (3 ml) was added and the temperature was allowed to rise slowly to room temperature. Water (10 ml) and ether (50 ml) were then added. The ethereal layer was separated, dried over magnesium sulphate and evaporated to yield the intermediate epoxide (A) as a gum. To this were added 1,2,4-triazole (112 mg; 1.62 mM), anhydrous potassium carbonate (223 mg; 1.62 mM) and anhydrous dimethylformamide (4 ml) and the mixture was stirred and heated at 70° for 2 hours. The mixture was cooled, water (50 ml) was added and the mixture was extracted with methylene chloride (2 × 50 ml). Co-evaporation of the combined methylene chloride extracts with xylene yielded a gum which contained the crude product as a mixture of 2 diastereomeric pairs. The gum was chromatographed on a column of silica eluting with a mixture of 4% (by volume) methanol in methylene chloride. Collection of the product-containing fractions followed by evaporation gave the title compound as a colourless solid (72 mg; 41%) which, after crystallisation from a mixture of ethyl acetate and cyclohexane, had a melting point of 142—145°. The compound was a mixture of two diastereoisomeric pairs in a ratio of approximately 4:1.

Analysis %:—

Found:	C, 48.3;	H, 3.5;	N, 25.6;
Required for $C_{13}H_{11}F_3N_6O$:	C, 48.2;	H, 3.4;	N, 25.9.

Procedure (B)

Partial resolution of the two diastereoisomeric pairs of 1,3-bis(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-1-fluoropropan-2-ol

A mixture of sodium hydride (406 mg. of a 60% dispersion in oil, 10.17 mM of sodium hydride) and trimethylsulphoxonium iodide (2.68 gm, 12.20 mM) was stirred under dry nitrogen and anhydrous dimethyl sulphoxide (40 ml.) was added. After 30 minutes anhydrous tetrahydrofuran (40 ml.) was added to the solution and the mixture cooled to −30°. A solution of 2-(1H-1,2,4-triazol-1-yl)-2,2',4'-trifluoroacetophenone (2.45 g; 10.17 mM) in tetrahydrofuran (30 ml.) was added and the temperature was allowed to rise slowly to 0°. Water (50 ml.) was added and the mixture was extracted with three aliquots (60 ml.) of ether. The combined ethereal layers were dried over $MgSO_4$ and evaporated to yield the intermediate epoxide (A) (1.89 g.) as a semi-crystalline solid. To this were added 1,2,4-triazole (3.51 g; 50.85 mM), anhydrous potassium carbonate (7.0 g; 50.85 mM) and anhyrous dimethylformamide (40 ml.) and the mixture was stirred and heated at 70° for 18 hours. The mixture was cooled, water (100 ml.) added and the mixture was extracted with methylene chloride (3 × 60 ml.). Co-evaporation of the combined methylene chloride extracts with xylene, after drying over $MgSO_4$, yielded a gum. This gum was chromatographed on a column of silica eluting with a mixture of 3% (by volume) methanol in methylene chloride followed by 4% methanol in methylene chloride. The two diastereoisomeric pairs were eluted pure in unresolved form. Collection and evaporation of the product-containing fractions gave the title compound as a colourless solid (1.1 g) (33%). High pressure liquid chromatography (HPLC) showed the product to be a mixture of two diastereomeric pairs in a ratio of approximately 4:1.

Crystallisation of this isomeric mixture from a mixture of ethyl acetate (20 ml) and hexane (30 ml) gave pure diastereoisomeric pair 1 as a colourless crystalline solid, (688 mg.), m.p. 149—150°.

Analysis %:—

Required for $C_{13}H_{11}F_3N_6O$:	C, 48.2;	H, 3.4;	N, 25.9;
Found:	C, 48.0;	H, 3.4;	N, 25.9.

Concentration of the crystallisation liquors gave a second crop of crystals (88 mg.), m.p. 117—123°. H.P.L.C. showed this to be a mixture of the two diastereomeric pairs in a ratio of approximately 1:5.

Analysis %:—

Required for $C_{13}H_{11}F_3N_6O$:	C, 48.2;	H, 3.4;	N, 25.9;
Found:	C, 48.0;	H, 3.5;	N, 26.0.

Evaporation of the final crystallisation liquors yielded a gum (170 mg), shown by H.P.L.C. to contain the two diastereomeric pairs in a ratio of approximately 1:1.

Example 2

Complete separation of the two diastereoisomeric pairs of 1,3-Bis(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-1-fluoropropan-1-ol

1,3-Bis(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-1-fluoropropan-1-ol (170 mg., as the approximately 1:1 mixture of the diastereomeric pairs from Example 1 Procedure (B) was dissolved in methylene chloride (1 ml) and then absorbed onto a column (2 × 30 cm) of Merck (Trademark) silica (230—400 mesh) prepared in a mixture of hexane/isopropanol/acetic acid (60/40/2). Elution with 500 ml. of the same solvent under moderate pressure (5 p.s.i., equivalent to 34.47 kPa) gave complete separation of the diastereoisomeric pairs. Evaporation of the solvent gave the isomers as colourless solids (ethyl acetate was successfully used as the eluent in a repeat of this procedure).

Diastereoisomeric pair 1 (eluted first): 80 mg. crystallisation from ethyl acetate/hexane gave a crystalline solid, m.p. 148—150°.

Analysis %:—

Required for $C_{13}H_{11}F_3N_6O$:	C, 48.2;	H, 3.4;	N, 25.9;
Found:	C, 48.0;	H, 3.4;	N, 25.9.

Diastereoisomeric pair 2: 70 mg. crystallisation from ethyl acetate/hexane gave a crystalline solid, m.p. 137—139°.

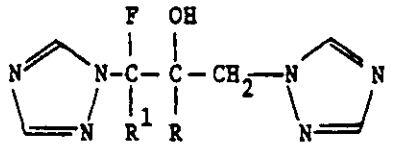
Analysis %:—

Required for $C_{13}H_{11}F_3N_6O$:	C, 48.2;	H, 3.4;	N, 25.9;
Found:	C, 48.4;	H, 3.5;	N, 25.7.

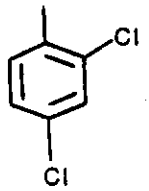
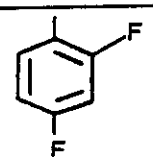
Examples 3—6

The following compounds were prepared similarly to the method of Example 1 Procedure (A) from appropriate starting materials, using, in the chromatography, methylene chloride containing, by volume,

2% isopropyl alcohol and 0.2% ammonia (S.G. 0.880), and crystallising the products from ethyl acetate/petroleum ether (b.p. 60—80°):—



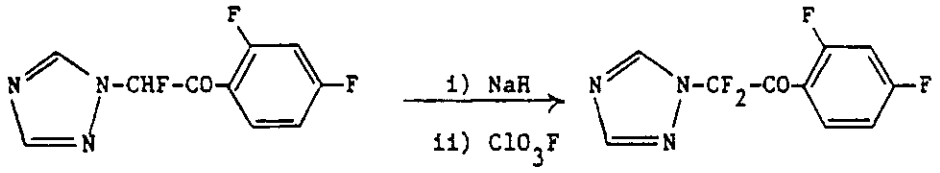
Example No.	R	R^1	m.p. (°C)	Analysis % (Theoretical in brackets) C	H	N
3		H	134—6	48.3	3.7	25.8
				(48.4	3.7	26.0)
4		H	74—6	50.6	4.1	26.7
				(50.9	3.9	27.4)

Example No.	R	R^1	m.p. (·C)	Analysis % (Theoretical in brackets) C	H	N
5		H	(a) 200—202	43.7	3.1	22.9
				(43.7	3.1	23.5)
			(b) 180—4	44.1	3.2	23.4
			(see below]	(43.7	3.1	23.5)
6		CH_3	138—145	49.2	3.8	24.6
				(49.6	3.9	24.8)

In Examples 3, 4 and 6, no separation of the diastereomers was achieved. In Example 5, the chromatography resulted in a partial separation. One pure diastereomer, called "(a)", was eluted first, and was crystallised from ethyl acetate/petroleum ether (b.p. 60—80°), m.p. 200—202°. After this, a mixture of the diastereomers in a ratio of about 1:1 was eluted, called "(b)", and was crystallised from ethyl acetate/petroleum ether (b.p. 60—80°), m.p. 180—184°.

Example 7

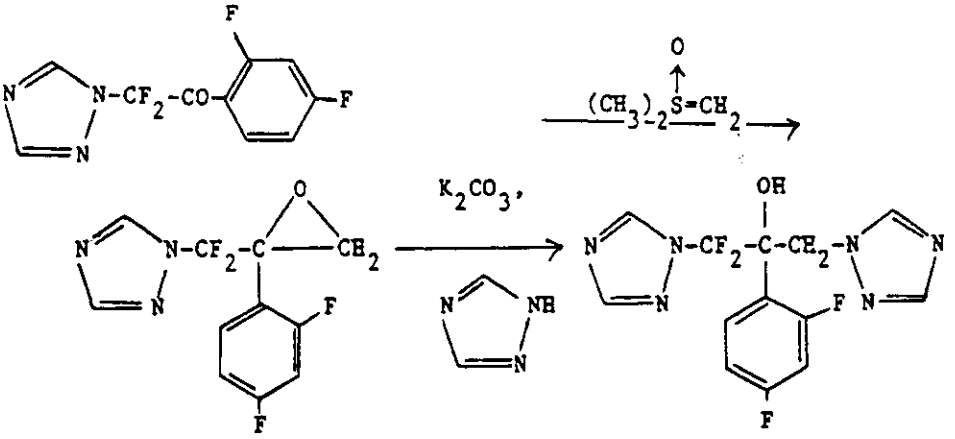
(i) 2-(1H-1,2,4-Triazol-1-yl)-2,2,2',4'-tetrafluoroacetophenone



2-(1H-1,2,4-Triazol-1-yl)-2,2',4'-trifluoroacetophenone (160 mg) was treated with ether-washed sodium hydride (25 mg) in dry tetrahydrofuran (5 ml) to give an orange solution. This solution was exposed to an atmosphere of perchloryl fluoride, when rapid uptake of this chemical occurred to give a pale yellow suspension. The tetrahydrofuran was removed under reduced pressure, the residue was partitioned between water (10 ml) and ethyl acetate (10 ml), the organic layer dried ($MgSO_4$) and evaporated to give the title compound as an oil, 127 mg.

N.m.r. ($CDCl_3$) δ = 6.95 (m), 2H; 8.0 (s), 1H; 8.2 (m), 1H; 8.69 (s), 1H.

(ii) 1,3-Bis(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-1,1-difluoropropan-2-ol



(B)

Procedure (a)

Dimethyloxosulphonium methylide was prepared from trimethylsulphoxonium iodide (0.44 g) and sodium hydride (0.12 g of a 50% suspension in oil) in dry dimethylsulphoxide (10 ml) at 50°. Dry tetrahydrofuran (10 ml) was added, and the mixture was cooled to −40°. Crude 2-(1H-1,2,4-triazol-1-yl)-2,2,2',4'-tetrafluoroacetophenone (0.52 g) was added in dry tetrahydrofuran (5 ml). The mixture was stirred at −40° for 10 minutes, then allowed to rise in temperature to −10° over 15 minutes, then poured onto ice (100 g), and extracted with ethyl acetate (2 × 50 ml). The combined ethyl acetate extracts were washed with brine (2 × 10 ml), dried ($MgSO_4$) and evaporated to give the oxirane (B) as an oil, 240 mg. This oil was heated in dimethylformamide (5 ml) at 50° for three hours with potassium carbonate (200 mg) and 1,2,4-triazole (200 mg). The reaction mixture was then allowed to cool, poured into water (30 ml), and extracted with ethyl acetate (3 × 15 ml). The combined organic extracts were washed with brine (2 × 5 ml), dried ($MgSO_4$) and evaporated to an oil, 235 mg.

Flash chromatography of this oil on silica, eluting with methylene chloride containing isopropanol (10% v/v) and 0.880 (S.G.) ammonium hydroxide (1% v/v), gave a material of Rf 0.3 (in the same solvent system), 53 mg, which solidified on trituration with ether. Crystallisation of this solid from cyclohexane/ethyl acetate gave colourless crystals of the title compound, m.p. 132—133°.

Analysis %:—

Required for $C_{13}H_{10}F_4N_6O$:	C, 45.7;	H, 2.9;	N, 24.6;
Found:	C, 45.6;	H, 3.0;	N, 24.3.

N.m.r. ($CDCl_3$) δ = 4.77 (d), 1H, J=14Hz; 5.39 (d), 1H, J=14Hz; 6.1 (6s), 1H; 6.75 (m), 2H; 7.44 (dd), 1H, J=14Hz, 7Hz; 7.73 (s), 1H; 7.82 (s), 1H; 7.10 (s), 1H; 8.32 (s), 1H.

m/e 343 (M + 1).

Procedure (b)

This is an alternative to route (a). In this route the oxirane (B) is not isolated.

Dimethyloxosulphonium methylide was prepared from trimethylsulphoxonium iodide (1.2 g) and sodium hydride (0.3 g of a 50% dispersion in oil) in dimethyl sulphoxide (20 ml). Dry tetrahydrofuran (30 ml) was then added and the mixture was cooled to −35°. 2 - (1H - 1,2,4 - Triazol - 1 - yl) - 2,2,2',4' - tetrafluoroacetophenone (1.3 g) was added in tetrahydrofuran (5 ml) and the mixture was stirred at −30° for 15 minutes, allowed to rise to −10° over 15 minutes, stirred for 30 minutes at −10°, and then allowed to rise to 10° over 15 minutes. At this stage 1,2,4-triazole (1.0 g) and anhydrous potassium carbonate (1.0 g) were added and the mixture was heated to 70° for 3 hours, then stirred overnight at room temperature. The reaction mixture was then poured into water (150 ml) and extracted with ethyl acetate (3 × 100 ml). The combined organic extracts were dried ($MgSO_4$), evaporated to an oil (1.6 g), and flash chromatographed on silica, eluting with methylene chloride/isopropanol/ammonia (0.880) (90:10:1 by volume) to give, on evaporation of the appropriate fractions, a crystalline solid, 447 mg. Re-crystallisation of this solid from cyclohexane/ethyl acetate gave colourless crystals, m.p. 132—133°, identical to the product of Procedure (a).

Example 8

1,3-Bis(1H-1,2,4-triazol-1-yl)-2-(2,4-dichlorophenyl)-1,1-difluoropropan-2-ol, m.p. 155—6°, was prepared similarly to the process of Example 7(b) from appropriate starting materials.

Analysis %:—

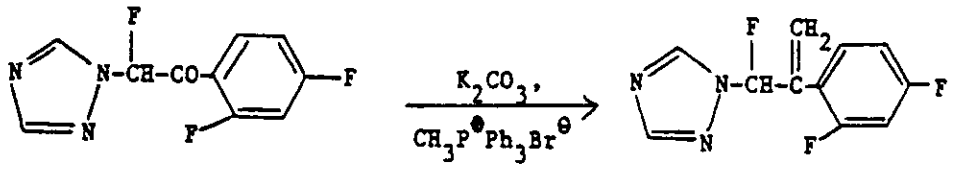
Found: C, 41.8; H, 2.7; N, 22.5;

Calculated for $C_{13}H_{10}Cl_2F_2N_6O$: C, 41.6; H, 2.7; N, 22.4.

The starting ketone, 2',4'-dichloro-2,2-difluoro-2-(1H-1,2,4-triazol-1-yl)acetophenone, was prepared similarly to Example 7 part (i). It was an oil. *N.m.r.* ($CDCl_3$): δ = 7.3 (m), 3H; 7.55 (s), 1H; 7.8 (s), 1H.

Example 9

(i) 2-(2,4-Difluorophenyl)-3-fluoro-3-(1H-1,2,4-triazol-1-yl)prop-1-ene



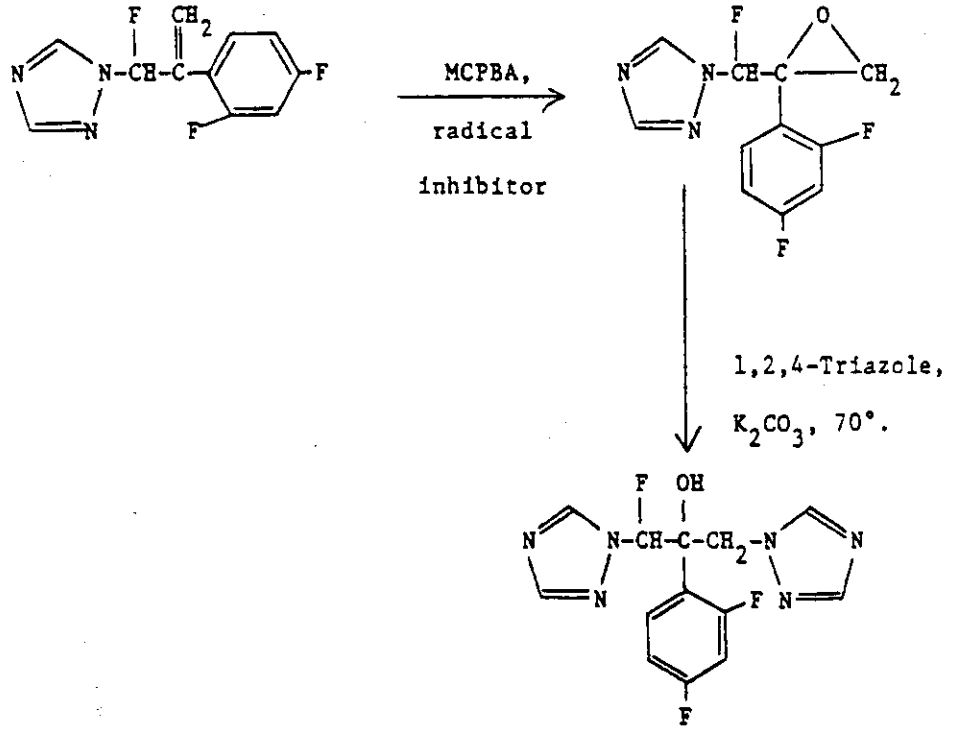
2-(1H-1,2,4-Triazol-1-yl)-2,2',4'-trifluoroacetophenone (10 g), anhydrous potassium carbonate (7.3 g), and methyltriphenylphosphonium bromide (15.5 g) were heated under reflux for 16 hours in 1,4-dioxan (250 ml), to which water (1.0 g) had been added.

A further amount of methyltriphenylphosphonium bromide (0.74 g) was then added, and heating was continued for a further 1 hour, when t.l.c. (silica, eluting with ether) showed that no starting material remained. The dioxan was then removed under reduced pressure, and the dark brown residue was triturated with ether (150 ml), when a precipitate of inorganic material and triphenylphosphine oxide formed. The ether solution was decanted from the precipitate, the precipitate was washed with ether (100 ml) and the washings were added to the decanted ether solution. The combined ether solutions were evaporated to a dark brown oil, 20.0 g.

This oil was chromatographed on silica (150 g), eluting with ether. The fractions containing product (as judged by t.l.c.) were combined and evaporated to yield the title compounds as an amber oil, 9.6 g.

N.m.r. ($CDCl_3$): δ = 5.78 (dd), 1H, J4Hz, 2Hz, 6.03 (d), 1H, J2Hz; 7.0, (m) 4H; 7.9 (s) 1H; 8.25 (s) 1H.

(ii) 1,3-Bis(1H-1,2,4-triazol-1-yl)-2-(2,4-difluorophenyl)-1-fluoropropan-2-ol



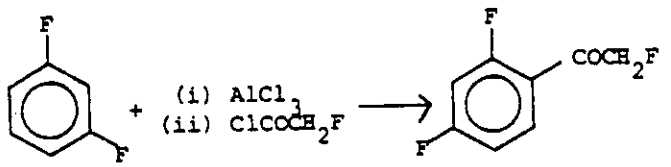
2-(2,4-Difluorophenyl)-3-fluoro-3-(1H-1,2,4-triazol-1-yl)prop-1-ene (5.0 g), *m*-chloroperbenzoic acid (10.8 g) (MCPBA) and a radical inhibitor, 3,3'-di-t-butyl-4,4'-dihydroxy-5,5'-dimethyldiphenylsulphide (0.11 g), were heated under reflux in 1,2-dichloroethane (75 ml) for 3 hours. The n.m.r. spectrum of an aliquot indicated that some starting material remained, so a further quantity of *m*-chloroperbenzoic acid (3.5 g) was added, and the reaction mixture was heated for a further 1 hour. After cooling and filtering to remove *m*-chlorobenzoic acid, the reaction mixture was diluted with methylene chloride (150 ml), washed with 10% sodium bisulphite solution (2 × 50 ml), and then with saturated sodium bicarbonate solution (2 × 100 ml). The organic layer was then washed with saturated sodium chloride solution (2 × 50 ml.), dried ($MgSO_4$), and evaporated to a yellow oil, 7.7 g.

The n.m.r. of this oil showed it to contain the epoxide as a mixture of two diastereomeric pairs in a ratio of 3:2, together with other organic residue. The total yield of epoxide was estimated to be about 50%. This crude reaction product was reacted with 1,2,4-triazole (7.5 g) and potassium carbonate (7.5 g) in dimethylformamide (100 ml) at 70° overnight. The reaction mixture was then cooled, diluted to 300 ml. with water, and extracted with ethyl acetate (3 × 100 ml.). The organic extract was washed with saturated sodium chloride solution (2 × 50 ml), dried ($MgSO_4$), and evaporated to a dark brown oil, 4.8 g. This oil was chromatographed on silica (200 g), eluting first with ethyl acetate, 1.5 litres, and then with ethyl acetate containing 5% isopropanol gradually increasing to 20% isopropanol (by volume). The later fractions contained the desired product as judged by t.l.c. and were evaporated to a white solid, 1.4 g., which was triturated with ether to give a white solid, 1.15 g., m.p. 138—140: This material was confirmed spectroscopically to be identical to the second diastereoisomeric pair isolated in Example 2.

The following Preparations illustrate the preparation of certain starting materials. All temperatures are in °C:—

Preparation 1

(i) *2,2',4'-Trifluoroacetophenone*



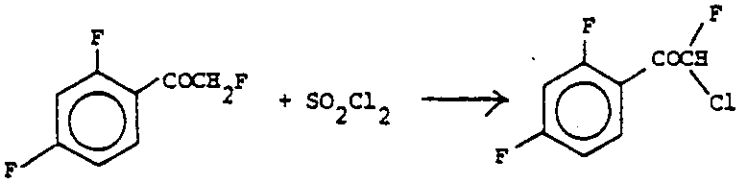
1,3-Difluòrobenzene (2.02 g; 17.7 mM) and anhydrous aluminium chloride (2.60 g; 19.47 mM) were stirred together under dry nitrogen at room temperature. A solution of fluoroacetyl chloride (1.71 g; 17.7 mM) in anhydrous methylene chloride (2 ml) was added over 30 minutes. The mixture was then warmed at

about 50°. for 3 hours. On cooling methylene chloride (40 ml) was added and the mixture was poured onto ice. The methylene chloride layer was separated, dried over magnesium sulphate and evaporated to give a white solid. This material was chromatographed on a column of silica eluting with a mixture of hexane/methylene chloride (65:35 by volume). The product-containing fractions were collected. The title compound crystallised on evaporation of these fractions and was dried in a vacuum desiccator to a colourless crystalline solid (1.12 g; 36% yield), melting point 57—8°.

Analysis %:—

Found:	C, 55.0;	H, 2.8;
Required for $C_8H_5F_3O$:	C, 55.2;	H, 2.9.

(ii) *2,2',4'-Trifluero-2-chloroacetophenone*



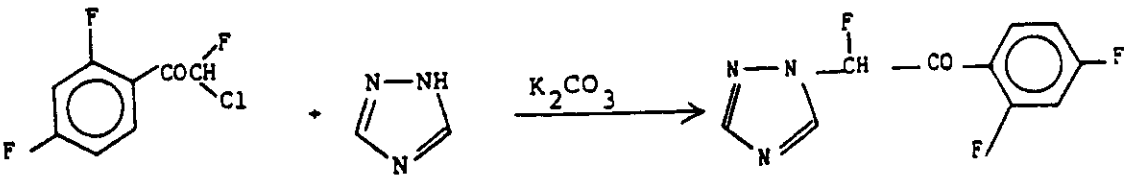
A solution of 2,2',4'-trifluoroacetophenone (1.60 g; 9.2 mM) in sulphuryl chloride (4 ml) was heated at 75° for 18 hours. The mixture was then cooled and iced-water (40 ml) was added. The product was extracted into ether (80 ml), which was washed with water and aqueous sodium bicarbonate solution, and then dried over magnesium sulphate. Evaporation yielded the desired product as a colourless, intensely lachrymatory liquid (2.0 g; 100%).

This liquid had N.M.R. and I.R. spectra consistent with the desired structure and was used directly in the next stage.

[*N.m.r.* ($CDCl_3$): δ = 8.05 (m, 1H); 6.95 (m, 2H); 6.87 (d, 1H, J=51)

I.R. (KBr), —C— at 1710 cm^{-1}.]

(iii) *2-(1H-1,2,4-Triazol-1-yl)-2,2',4'-trifluoroacetophenone*



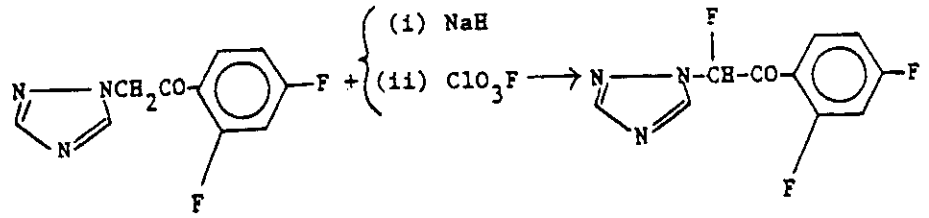
A mixture of 1,2,4-triazole (1.25 g; 18 mM) and anhydrous potassium carbonate (2.0 g; 14.5 mM) in anhydrous tetrahydrofuran (20 ml) was stirred at the reflux temperature. A solution of 2,2'4'-trifluoro-2-chloroacetophenone (1.5 g; 7.19 mM) in tetrahydrofuran (10 ml) was then added over a ten minute period. The mixtures was refluxed for 2 hours and then stood overnight at room temperature. Water (50 ml) was added and the mixture was extracted with methylene chloride (2 × 100 ml). The combined organic extracts were dried over magnesium sulphate and evaporated to yield a gum. Chromatography on a column of silica, eluting with a mixture of ethylacetate/hexane/diethylamine (ratio 70:30:3 by volume) yielded, after evaporation of appropriate fractions, the desired product as a gum, (130 mg; 7.5%). The n.m.r. was consistent with the desired structure.

The compound was characterised as the methanesulphonic acid salt, m.p. 158—160°, prepared by mixing a solution of the free base in ether/acetone with a solution of the acid in ether/acetone and collecting the precipitated salt.

Analysis %:—

Found:	C, 39.1;	H, 3.0;	N, 12.4;
Calculated for $C_{10}H_6F_3N_3O.CH_4O_3S$:	C, 39.2;	H, 3.0;	N, 12.5.

Preparation 2

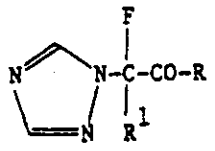


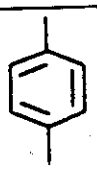
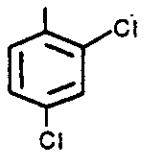
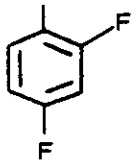
Sodium hydride (285 mg of a 50% dispersion in oil; 5.94 mM of sodium hydride) was washed with ether and dried under nitrogen. Anhydrous tetrahydrofuran was added (15 ml), followed by 2',4'-difluoro-2-(1H-1,2,4-triazol-1-yl)-acetophenone (1.115 g; 5 mM) (see U.K. patent application publication no. 2099818A) in portions over a 5 minute period. The resultant brown solution was stirred under an atmosphere of perchloryl fluoride until the theoretical amount had been absorbed. The pale yellow suspension was evaporated and partitioned between water (25 ml) and ethyl acetate (50 ml). The ethyl acetate phase was separated, washed with water, dried over magnesium sulphate and evaporated to give an oil which crystallised (1.21 g).

The product was confirmed by n.m.r. and t.l.c. to be the same as the product of Preparation 1 (iii), free base form, in about 80% purity.

Preparations 3—6

The following ketone intermediates were prepared similarly to the process of Preparation 2 from the appropriate acetophenone or propiophenone, sodium hydride and perchloryl fluoride:—



Preparation No.	R	R^1	m.p. (°C)	Analysis (%) (or n.m.r.) (Theoretical in brackets) C	H	N
3		H	98—100	*N.m.r.* ($CDCl_3$): δ = 7.2 (m), 2H; 7.3 (d), 1H, J 48Hz; 8.1 (m), 3H; 8.5 (s), 1H.		
4		H	137—8	50.3	3.0	17.5
				(50.2	2.9	17.6)
5		H	64—66	43.9	2.2	15.4
				(43.9	2.2	15.4)
6		CH_3	oil	*N.m.r.* ($CDCl_3$): δ = 2.25 (d), 3H, J 19Hz; 6.9 (m), 2H; 7.8 (m) 1H; 8.0 (s), 1H; 8.45 (s), 1H		

The starting acetophenones and propiophenone were prepared analogously to the procedure described in GB 2099818A for the preparation of 2',4'-difluoro-2-(1H-1,2,4-triazol-1-yl)acetophenone.

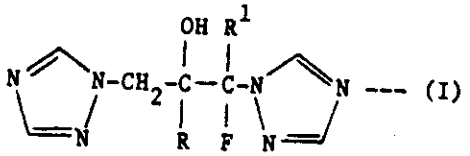
Activity Data

PD_{50} values (mg./kg.) in mice infected with *Candida albicans* obtained for the compounds of the Examples by the test procedure described in the text are as follows:—

Product of Example No.	PD_{50} (mg./kg.)
2 (diastereomeric pair 1)	0.29
2 (diastereomeric pair 2)	0.05
3	0.2
4	<1
5 (mixture of diastereomers)	0.13
5 (separated diastereomer)	0.49
6	0.32
7	0.06
8	0.2

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL

1. A triazole of the formula:—



--- (I)

where R is phenyl optionally substituted by 1 to 3 substituents each independently selected from F, Cl, Br, I, CF_3, C_1—C_4 alkyl and C_1—C_4 alkoxy, or R is 5-chloro-pyrid-2-yl; R^1 is H, CH_3 or F; or a pharmaceutically or agriculturally acceptable salt thereof.

2. A compound as claimed in claim 1, wherein R is phenyl substituted by one or two substituents each independently selected from F, Cl, Br, I and CF_3.

3. A compound as claimed in claim 2, wherein R is 2,4-difluorophenyl, 2,4-dichlorophenyl, 4-fluorophenyl or 4-chlorophenyl.

4. A compound as claimed in any one of the preceding claims, wherein R^1 is H or F.

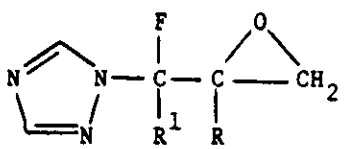
5. A compound or salt thereof as claimed in claim 1 wherein R is 2,4-difluorophenyl and R^1 is H.

6. A pharmaceutical composition comprising a compound of the formula (I) as claimed in any one of the preceding claims, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

7. A fungicidal composition for agricultural (including horticultural) use, comprising a compound of the formula (I) as claimed in any one of claims 1 to 5, or an agriculturally acceptable salt thereof, together with an agriculturally acceptable diluent or carrier.

8. A compound of the formula (I) as claimed in any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, for use in medicine, in particular for use in treating a fungal infection in a human being.

9. A process for preparing a compound of the formula (I) as claimed in claim 1, or a pharmaceutically or agriculturally acceptable salt thereof, characterised by reacting an oxirane of the formula:—



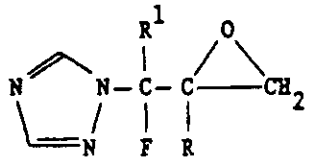
--- (II)

where R and R^1 are as defined in claim 1, with 1,2,4-triazole or a base salt thereof, followed by, optionally, conversion of the product of the formula (I) into a pharmaceutically or agriculturally acceptable salt and/or, where appropriate, separation of the product into its diastereomeric pairs.

10. A process as claimed in claim 9, characterised in that the oxirane (II) is reacted with 1,2,4-triazole in the presence of potassium carbonate.

11. A method of treating a plant or seed having a fungal infection, which comprises treating said plant or seed, or the locus of said plant, with an antifungally effective amount of a compound of the formula (I) as claimed in any one of claims 1 to 5, or with an agriculturally acceptable salt thereof.

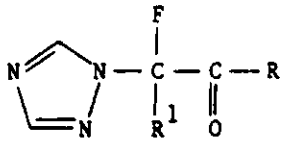
12. A compound of the formula:—



--- (II)

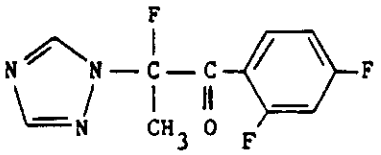
where R and R^1 are as defined in claim 1.

13. A compound of the formula:—

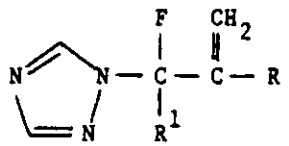


where R and R^1 are as defined in claim 1 with the proviso that when R^1 is CH_3, R is 5-chloropyrid-2-yl.

14. A compound of the formula:—



15. A compound of the formula:—

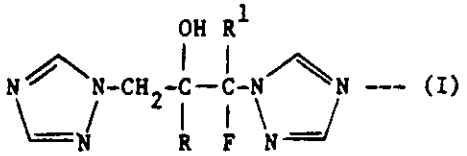


where R and R^1 are as defined in claim 1.

16. The use of a compound of the formula (I) as defined in claim 1, or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use as an antifungal agent.

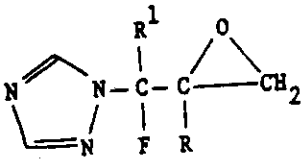
Claims for the Contracting State: AT

1. A process for preparing a triazole of the formula:—



--- (I)

where R is phenyl optionally substituted by 1 to 3 substituents each independently selected from F, Cl, Br, I, CF_3, C_1—C_4 alkyl and C_1—C_4 alkoxy, or R is 5-chloro-pyrid-2-yl; R^1 is H, CH_3 or F; or a pharmaceutically or agriculturally acceptable salt thereof, characterised by reacting an oxirane of the formula:—



--- (II)

where R and R^1 are as defined for formula (I), with 1,2,4-triazole or a base salt thereof, followed by, optionally, conversion of the products of the formula (I) into a pharmaceutically or agriculturally acceptable salt, and/or, where appropriate, separation of the product into its diastereomeric pairs.

2. A process according to claim 1, which is characterised by reacting the oxirane (II) with 1,2,4-triazole in the presence of a base.

3. A process according to claim 2, characterised in that the base is potassium carbonate.

4. A process according to claim 1, characterised in that the base is an alkali metal salt of 1,2,4-triazole.

5. A process according to claim 4, characterised in that the alkali metal salt is the sodium or potassium salt.

6. A process according to any one of the preceding claims, characterised in that it is carried out in an organic solvent at a temperature of from 40—120°C.

7. A process according to any one of the preceding claims, characterised in that R is a phenyl group substituted by 1 or 2 substituents each independently selected from F, Cl, Br, I and CF_3.

8. A process according to claim 7, characterised in that R is 2,4-difluorophenyl, 2,4-dichlorophenyl, 4-fluorophenyl or 4-chlorophenyl.

9. A process according to any one of the preceding claims, characterised in that R^1 is H or F.

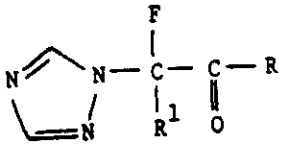
10. A process according to any one of the preceding claims, characterised in that R^1 is H and R is 2,4-difluorophenyl.

11. A process according to claim 10, characterised in that the product of the formula (I) is separated into its diastereomeric pairs by chromatography.

12. A composition for use as an agricultural or horticultural fungicide, comprising a compound of the formula (I) as defined in claim 1 or an agriculturally or horticulturally acceptable salt thereof, together with an agriculturally or horticulturally acceptable diluent or carrier.

13. A process for preparing a pharmaceutical composition, which comprises mixing a compound of the formula (I) as defined in claim 1, or a pharmaceutically acceptable salt thereof, with a pharmaceutically acceptable diluent or carrier.

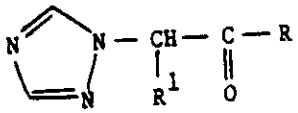
14. A process for preparing a compound of the formula (II) as defined in claim 1, characterised by reacting a compound of the formula:—



--- (A)

where R and R^1 are as defined in claim 1, with dimethyloxosulphonium methylide.

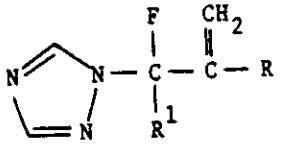
15. A process for preparing a compound of the formula (A) as defined in claim 14, characterised by reacting a compound of the formula:—



--- (B)

where R and R^1 are as defined in claim 1, with sodium hydride and then with perchloryl fluoride.

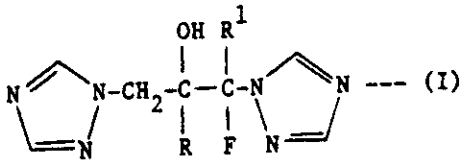
16. A process for preparing a compound of the formula (II) as defined in claim 1, characterised by reacting a compound of the formula:—



where R and R^1 are as defined in claim 1, with *m*-chloroperbenzoic acid in the presence of a radical inhibitor.

Claims for the Contracting State: SE

1. A triazole of the formula:—



--- (I)

where R is phenyl optionally substituted by 1 to 3 substituents each independently selected from F, Cl, Br, I, CF_3, C_1—C_4 alkyl and C_1—C_4 alkoxy, or R is 5-chloro-pyrid-2-yl; R^1 is H, CH_3 or F; or a pharmaceutically or agriculturally acceptable salt thereof.

2. A compound as claimed in claim 1, wherein R is phenyl substituted by one or two substituents each independently selected from F, Cl, Br, I and CF_3.

3. A compound as claimed in claim 2, wherein R is 2,4-difluorophenyl, 2,4-dichlorophenyl, 4-fluorophenyl or 4-chlorophenyl.

4. A compound as claimed in any one of the preceding claims, wherein R^1 is H or F.

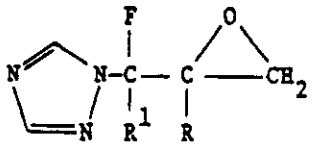
5. A compound or salt thereof as claimed in claim 1 wherein R is 2,4-difluorophenyl and R^1 is H.

6. A pharmaceutical composition comprising a compound of the formula (I) as claimed in any one of the preceding claims, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable diluent or carrier.

7. A fungicidal composition for agricultural (including horticultural) use, comprising a compound of the formula (I) as claimed in any one of claims 1 to 5, or an agriculturally acceptable salt thereof, together with an agriculturally acceptable diluent or carrier.

8. A compound of the formula (I) as claimed in any one of claims 1 to 5, or a pharmaceutically acceptable salt thereof, for use in medicine, in particular for use in treating a fungal infection in a human being.

9. A process for preparing a compound of the formula (I) as claimed in claim 1, or a pharmaceutically or agriculturally acceptable salt thereof, characterised by reacting an oxirane of the formula:—



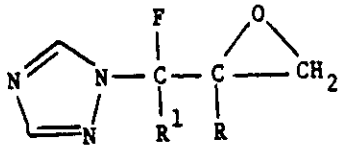
--- (II)

where R and R^1 are as defined in claim 1, with 1,2,4-triazole or a base salt thereof, followed by, optionally, conversion of the product of the formula (I) into a pharmaceutically or agriculturally acceptable salt and/or, where appropriate, separation of the product into its diastereomeric pairs.

10. A process as claimed in claim 9, characterised in that the oxirane (II) is reacted with 1,2,4-triazole in the presence of potassium carbonate.

11. A method of treating a plant or seed having a fungal infection, which comprises treating said plant or seed, or the locus of said plant, with an antifungally effective amount of a compound of the formula (I) as claimed in any one of claims 1 to 5, or with an agriculturally acceptable salt thereof.

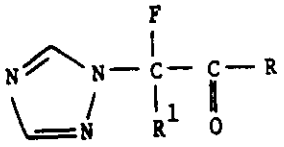
12. A compound of the formula:—



--- (II)

where R and R^1 are as defined in claim 1.

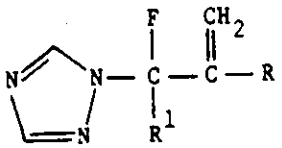
13. A compound of the formula:—



--- (A)

where R and R^1 are as defined in claim 1.

14. A compound of the formula:—

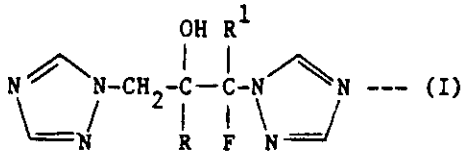


where R and R^1 are as defined in claim 1.

15. The use of a compound of the formula (I) as defined in claim 1, or of a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for use as an antifungal agent.

Patentansprüche für die Vertragsstaaten: BE CH DE FR GB IT LI LU NL

1. Triazol der Formel



--- (I)

worin R Phenyl, gegebenenfalls substituiert durch 1 bis 3 Substituenten, jeder unabhängig ausgewählt unter F, Cl, Br, I, CF_3, C_1—C_4-Alkyl und C_1—C_4-Alkoxy, oder R 5-Chlor-pyrid-2-yl, R^1 H, CH_3 oder F ist, oder ein pharmazeutisch oder landwirtschaftlich annehmbares Salz hiervon.

2. Verbindung gemäß Anspruch 1, worin R Phenyl, substituiert durch 1 oder 2 Substituenten, jeweils unabhängig ausgewählt aus F, Cl, Br, I und CF_3, ist.

3. Verbindung gemäß Anspruch 2, worin R 2,4-Difluorphenyl, 2,4-Dichlorphenyl, 4-Fluorphenyl oder 4-Chlorphenyl ist.

4. Verbindung gemäß irgendeinem der vorhergehenden Ansprüche, worin R^1 H oder F ist.

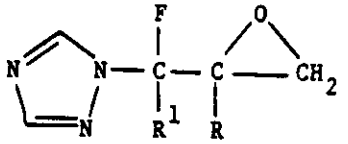
5. Verbindung oder ein Salz derselben gemäß Anspruch 1, worin R 2,4-Difluorphenyl und R^1 H ist.

6. Pharmazeutische Zusammensetzung, umfassend eine Verbindung der Formel (I) gemäß irgendeinem der vorhergehenden Ansprüche oder ein pharmazeutisch annehmbares Salz derselben, zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger.

7. Fungizide Zusammensetzung für landwirtschaftliche (einschließlich Gartenbau) Zwecke, umfassend eine Verbindung der Formel (I) gemäß irgendeinem der Ansprüche 1 bis 5 oder ein landwirtschaftlich annehmbares Salz derselben, zusammen mit einem landwirtschaftlich annehmbaren Verdünnungsmittel oder Träger.

8. Verbindung der Formel (I) gemäß irgendeinem der Ansprüche 1 bis 5 oder ein pharmazeutisch annehmbares Salz derselben zur Verwendung in der Medizin, insbesondere zur Verwendung bei der Behandlung einer Pilzinfektion beim Menschen.

9. Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß Anspruch 1 oder eines pharmazeutisch annehmbaren Salzes derselben, dadurch gekennzeichnet, daß ein Oxiran der Formel



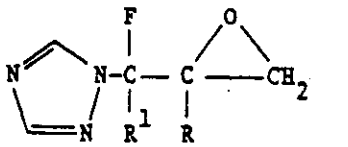
--- (II)

worin R und R^1 wie in Anspruch 1 definiert sind, mit 1,2,4,-Triazol oder einem Basensalz desselben umgesetzt wird, gegebenenfalls gefolgt von der Umwandlung des Produktes der Formel (I) in ein pharmazeutisch oder landwirtschaftlich annehmbares Salz und/oder, wo angemessen, Trennung des Produktes in seine diastereomeren Paare.

10. Verfahren gemäß Anspruch 9, dadurch gekennzeichnet, daß das Oxiran (II) mit 1,2,4-Triazol in Anwesenheit von Kaliumcarbonat umgesetzt wird.

11. Verfahren zur Behandlung einer Pflanze oder von Saatgut mit einer Pilzinfektion, das umfaßt das Behandeln der Pflanze oder des Saatgutes oder des Ortes der Pflanze mit einer zur Verhütung von Pilzbefall wirksamen Menge einer Verbindung der Formel (I) gemäß irgendeinem der Ansprüche 1 bis 5 oder mit einem landwirtschaftlich annehmbaren Salz derselben.

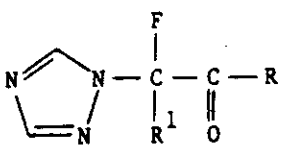
12. Verbindung der Formel



--- (II)

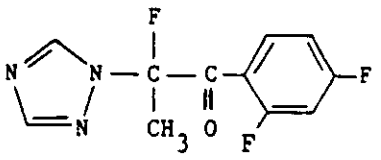
worin R und R^1 wie in Anspruch 1 definiert sind.

13. Verbindung der Formel

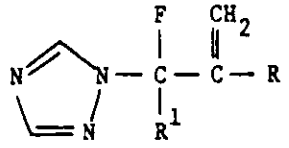


worin R und R^1 wie in Anspruch 1 definiert sind, mit der Bedingung, daß — wenn R^1 CH_3 ist — R 5-Chlorpyrid-2-yl ist.

14. Verbindung der Formel



15. Verbindung der Formel

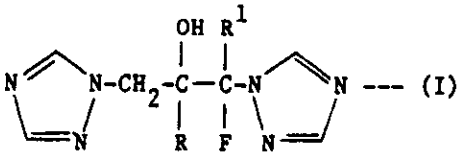


worin R und R^1 wie in Anspruch 1 definiert sind.

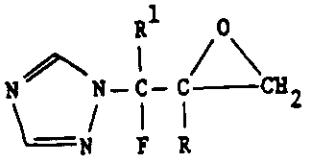
16. Verwendung einer Verbindung der Formel (I) gemäß Definition in Anspruch 1 oder eines pharmazeutisch annehmbaren Salzes derselben zur Herstellung eines Medikamentes zur Verwendung als pilzbefallverhütendes Mittel.

Patentansprüche für den Vertragsstaat: AT

1. Verfahren zur Herstellung eines Triazols der Formel



worin R Phenyl, gegebenenfalls substituiert durch 1 bis 3 Substituenten, jeder unabhängig ausgewählt unter F, Cl, Br, I, CF_3, C_1—C_4-Alkyl und C_1—C_4-Alkoxy, oder R 5-Chlor-pyrid-2-yl, R^1 H, CH_3 oder F ist, oder ein pharmazeutisch oder landwirtschaftlich annehmbares Salz hiervon, dadurch gekennzeichnet, daß ein Oxiran der Formel



--- (II)

worin R und R^1 wie für Formel (I) definiert sind, mit 1,2,4-Triazol oder einem Basensalz hiervon umgesetzt wird, worauf gegebenenfalls die Produkte der Formel (I) in ein pharmazeutisch oder landwirtschaftlich annehmbares Salz umgewandelt werden, und/oder, wo angebracht, das Produkt in seine diastereomeren Paare getrennt wird.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das Oxiran (II) mit 1,2,4-Triazol in Gegenwart einer Base umgesetzt wird.

3. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß die Base Kaliumcarbonat ist.

4. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das Basensalz ein Alkalimetallsalz von 1,2,4-Triazol ist.

5. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß das Alkalimetallsalz das Natrium- oder Kaliumsalz ist.

6. Verfahren nach irgendeinem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß es in einem organischen Lösungsmittel bei einer Temperatur von 40—120°C durchgeführt wird.

7. Verfahren nach irgendeinem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß R eine Phenylgruppe, substituiert durch 1 oder 2 Substituenten, jeder unabhängig ausgewählt unter F, Cl, Br, I und CF_3, ist.

8. Verfahren nach Anspruch 7, dadurch gekennzeichnet, daß R 2,4-Difluorphenyl, 2,4-Dichlorphenyl, 4-Fluorphenyl oder 4-Chlorphenyl ist.

9. Verfahren nach irgendeinem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß R^1 H oder F ist.

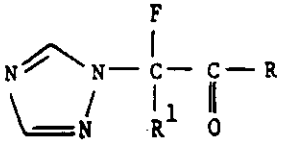
10. Verfahren nach irgendeinem der vorhergehenden Ansprüche, dadurch gekennzeichnet, daß R^1 H und R 2,4-Difluorphenyl ist.

11. Verfahren nach Anspruch 10, dadurch gekennzeichnet, daß das Produkt der Formel (I) chromatographisch in seine diastereomeren Paare getrennt wird.

12. Zusammensetzung zur Verwendung als land- oder gartenbauwirtschaftliches, den Pilzbefall verhütendes Mittel, umfassend eine Verbindung der Formel (I) gemäß Definition in Anspruch 1 oder ein land- oder gartenbauwirtschaftliches Salz derselben zusammen mit einem land- oder gartenbauwirtschaftlich annehmbaren Verdünnungsmittel oder Träger.

13. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, das umfaßt das Mischen einer Verbindung der Formel (I) gemäß Definition in Anspruch 1 oder eines pharmazeutisch annehmbaren Salzes derselben mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger.

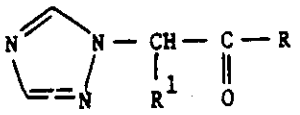
14. Verfahren zur Herstellung einer Verbindung der Formel (II) gemäß Definition in Anspruch 1, dadurch gekennzeichnet, daß eine Verbindung der Formel



--- (A)

worin R und R^1 wie in Anspruch 1 definiert sind, mit Dimethyloxosulfoniummethylid umgesetzt wird.

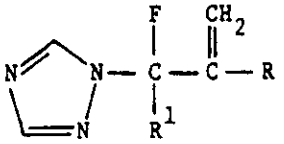
15. Verfahren zur Herstellung einer Verbindung der Formel (A) gemäß Definition in Anspruch 14, dadurch gekennzeichnet, daß eine Verbindung der Formel



--- (B)

worin R und R^1 wie in Anspruch 1 definiert sind, mit Natriumhydrid und dann mit Perchlorylfluorid umgesetzt wird.

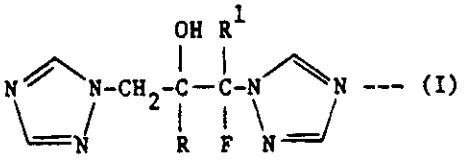
16. Verfahren zur Herstellung einer Verbindung der Formel (II) gemäß Definition in Anspruch 1, dadurch gekennzeichnet, daß eine Verbindung der Formel



worin R und R^1 wie in Anspruch 1 definiert sind, mit m-Chlorperbenzoesäure in Anwesenheit eines Radikal-Inhibitors umgesetzt wird.

Patentansprüche für den Vertragsstaat: SE

1. Triazol der Formel



--- (I)

worin R Phenyl, gegebenenfalls substituiert durch 1 bis 3 Substituenten, jeder unabhängig ausgewählt unter F, Cl, Br, I, CF_3, C_1—C_4-Alkyl und C_1—C_4-Alkoxy, oder R 5-Chlor-poyrid-2-yl, R^1 H, CH_3 oder F ist, oder ein pharmazeutisch oder landwirtschaftlich annehmbares Salz hiervon.

2. Verbindung gemäß Anspruch 1, worin R Phenyl, substituiert durch 1 oder 2 Substituenten, jeweils unabhängig ausgewählt aus F, Cl, Br, I und CF_3, ist.

3. Verbindung gemäß Anspruch 2, worin R 2,4-Difluorphenyl, 2,4-Dichlorphenyl, 4-Fluorphenyl oder 4-Chlorphenyl ist.

4. Verbindung gemäß irgendeinem der vorhergehenden Ansprüche, worin R^1 H oder F ist.

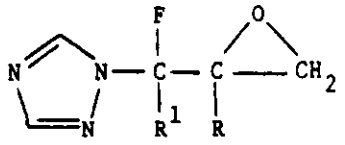
5. Verbindung oder ein Salz derselben gemäß Anspruch 1, worin R 2,4-Difluorphenyl und R^1 H ist.

6. Pharmazeutische Zusammensetzung, umfassend eine Verbindung der Formel (I) gemäß irgendeinem der vorhergehenden Ansprüche oder ein pharmazeutisch annehmbares Salz derselben, zusammen mit einem pharmazeutisch annehmbaren Verdünnungsmittel oder Träger.

7. Fungizide Zusammensetzung zur landwirtschaftlichen (einschließlich Gartenbau) Verwendung, umfassend eine Verbindung der Formel (I) gemäß irgendeinem der vorhergehenden Ansprüche 1 bis 5 oder ein landwirtschaftlich annehmbares Salz derselben, zusammen mit einem landwirtschaftlich annehmbaren Verdünnungsmittel oder Träger.

8. Verbindung der Formel (I) gemäß irgendeinem der Ansprüche 1 bis 5 oder ein pharmazeutisch annehmbares Salz derselben zur Verwendung in der Medizin, insbesondere zur Verwendung bei der Behandlung einer Pilzinfektion beim Menschen.

9. Verfahren zur Herstellung einer Verbindung der Formel (I) gemäß Anspruch 1 oder eines pharmazeutisch oder landwirtschaftlich annehmbaren Salzes derselben, dadurch gekennzeichnet, daß ein Oxiran der Formel



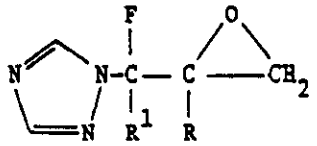
--- (II)

worin R und R^1 wie in Anspruch 1 definiert sind, mit 1,2,4,-Triazol oder einem Basensalz desselben umsetzt, gegebenenfalls gefolgt von der Umwandlung des Produktes der Formel (I) in ein pharmazeutisch oder landwirtschaftlich annehmbares Salz und/oder, wo angemessen, der Trennung des Produktes in seine diastereomeren Paare.

10. Verfahren gemäß Anspruch 9, dadurch gekennzeichnet, daß das Oxiran (II) mit 1,2,4-Triazol in Anwesenheit von Kaliumcarbonat umgesetzt wird.

11. Verfahren zur Behandlung einer Pflanze oder von Saatgut mit Pilzinfektion, das umfaßt das Behandeln der Pflanze oder des Saatgutes oder des Ortes der Pflanze mit einer zur Pilzbefall verhütung wirksamen Menge einer Verbindung der Formel (I) gemäß irgendeinem der Ansprüche 1 bis 5 oder mit einem landwirtschaftlich annehmbaren Salz derselben.

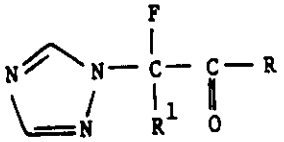
12. Verbindung der Formel



--- (II)

worin R und R^1 wie in Anspruch 1 definiert sind.

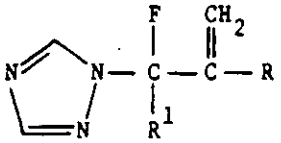
13. Verbindung der Formel



--- (A)

worin R und R^1 wie in Anspruch 1 definiert sind.

14. Verbindung der Formel

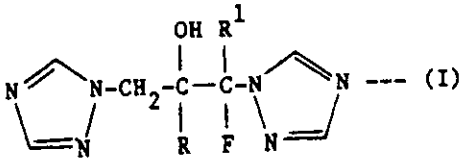


worin R und R^1 wie in Anspruch 1 definiert sind.

15. Verwendung einer Verbindung der Formel (I) gemäß Anspruch 1 oder eines pharmazeutisch annehmbaren Salzes derselben zur Herstellung eines Medikamentes zur Verwendung als ein pilzbefallverhütendes Mittel.

Revendications pour les Etats contractants: BE CH DE FR GB IT LI LU NL

1. Triazole de formule:



--- (I)

dans laquelle R est un groupe phényle, portant facultativement 1 à 3 substituants, chacun choisi indépendamment entre F, Cl, Br, I, CF_3, des groupes alkyle en C_1 à C_4 et alkoxy en C_1 à C_4, ou bien R est un groupe 5-chloropyrid-2-yle; R^1 représente H, CH_3 ou F; ou un de ses sels acceptables en pharmacie ou en agriculture.

2. Composé suivant la revendication 1, dans lequel R est un groupe phényle portant un ou deux substituants, chacun choisi indépendamment entre F, Cl, Br, I et CF_3.

3. Composé suivant la revendication 2, dans lequel R est le groupe 2,4-difluorophényle, 2,4-dichlorophényle, 4-fluorophényle ou 4-chlorophényle.

4. Composé suivant l'une quelconque des revendications précédentes, dans lequel R^1 représente H ou F.

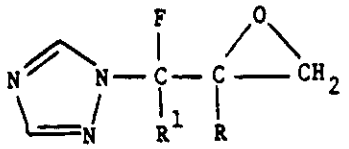
5. Composé ou un de ses sels suivant la revendication 1, dans lequel R est un groupe 2,4-difluorophényle et R^1 représente H.

6. Composition pharmaceutique comprenant un composé de formule (I) suivant l'une quelconque des revendications précédentes, ou un de ses sels pharmaceutiquement acceptables, associé à un diluant ou support pharmaceutiquement acceptable.

7. Composition fongicide destinée à être utilisée en agriculture (comprenant l'horticulture), contenant un composé de formule (I) suivant l'une quelconque des revendications 1 à 5, ou un de ses sels acceptables en agriculture, associé à un diluant ou support acceptable en agriculture.

8. Composé de formule (I) suivant l'une quelconque des revendications 1 à 5, ou un de sels pharmaceutiquement acceptables, destiné à être utilisé en médecine, en particulier pour l'utilisation dans le traitement d'une infection fongique chez l'homme.

9. Procédé de préparation d'un composé de formule (I) suivant la revendication 1, ou d'un de ses sels acceptables en pharmacie ou en agriculture, caractérisé en ce qu'il consiste à faire réagir un oxiranne de formule:



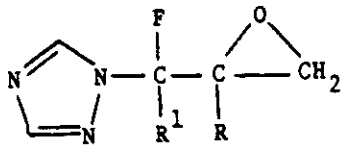
--- (II)

dans laquelle R et R^1 sont tels que définis dans la revendication 1, avec le 1,2,4-triazole ou un de ses sels formés avec une base, réaction suivie facultativement par la conversion du produit de formule (I) en un sel acceptable en pharmacie ou en agriculture et/ou, le cas échéant, la séparation du produit en ses paires de diastéréoisomères.

10. Procédé suivant la revendication 9, caractérisé en ce qu'on fait réagir l'oxiranne (II) avec le 1,2,4-triazole en présence de carbonate de potassium.

11. Procédé de traitement d'une plante ou de semences présentant une infection fongique, qui consiste à traiter ladite plante ou lesdites semences, ou le milieu de ladite plante, avec une quantité à effet antifongique d'un composé de formule (I) suivant l'une quelconque des revendications 1 à 5, ou avec un de ses sels acceptables en agriculture.

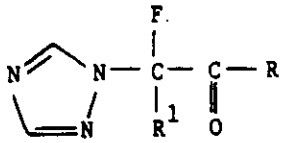
12. Composé de formule:



--- (II)

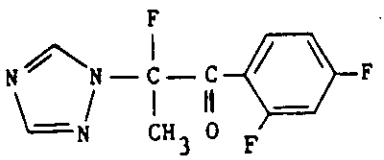
dans laquelle R et R^1 sont tels que définis dans la revendication 1.

13. Composé de formule:

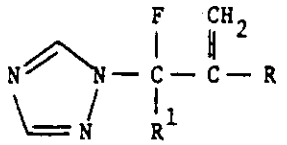


dans laquelle R et R^1 sont tels que définis dans la revendication 1, sous réserve que lorsque R^1 est un groupe CH_3, R soit le groupe 5-chloropyrid-2-yle.

14. Composé de formule:



15. Composé de formule:

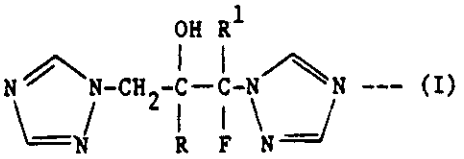


dans laquelle R et R^1 sont tels que définis dans la revendication 1.

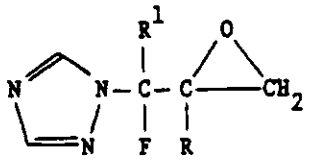
16. Utilisation d'un composé de formule (I) suivant la revendication 1, ou d'un de ses sels pharmaceutiquement acceptables, pour la production d'un médicament destiné à être utilisé comme agent antifongique.

Revendications pour l'Etat contractant: AT

1. Procédé de préparation d'un triazole de formule:



dans laquelle R est un groupe phényle, portant facultativement 1 à 3 substituants, chacun choisi indépendamment entre F, Cl, Br, I, CF_3, des groupes alkyle en C_1 à C_4 et alkoxy en C_1 à C_4, ou bien R est un groupe 5-chloropyrid-2-yle; R^1 représente H, CH_3 ou F; ou un de ses sels acceptables en pharmacie ou en agriculture, caractérisé en ce qu'il consiste à faire réagir un oxiranne de formule:



--- (II)

dans laquelle R et R^1 ont la définition répondant à la formule (I), avec le 1,2,4-triazole ou un de ses sels formés avec une base, réaction suivie facultativement par la conversion du produit de formule (I) en un sel acceptable en pharmacie ou en agriculture et/ou, le cas échéant, la séparation du produit en ses paires de diastéréo-isomères.

2. Procédé suivant la revendication 1, caractérisé en ce qu'on fait réagir l'oxiranne (II) avec le 1,2,4-triazole en présence d'une base.

3. Procédé suivant la revendication 2, caractérisé en ce que la base est le carbonate de potassium.

4. Procédé suivant la revendication 1, caractérisé en ce que le sel de base est un sel de métal alcalin du 1,2,4-triazole.

5. Procédé suivant la revendication 4, caractérisé en ce que le sel de métal alcalin est le sel de sodium ou de potassium.

6. Procédé suivant l'une quelconque des revendications précédentes, caractérisé en ce qu'il est mis en oeuvre dans un solvant organique à une température de 40 à 120°C.

7. Procédé suivant l'une quelconque des revendications précédentes, caractérisé en ce que R est un groupe phényle portant 1 ou 2 substituants, chacun choisi indépendamment entre F, Cl, Br, I et CF_3.

8. Procédé suivant la revendication 7, caractérisé en ce que R est le 2,4-difluorophényle, le 2,4-dichlorophényle, le 4-fluorophényle ou le 4-chlorophényle.

9. Procédé suivant l'une quelconque des revendications précédentes, caractérisé en ce que R^1 représente H ou F.

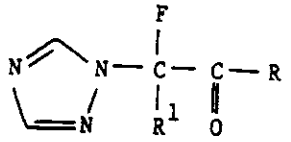
10. Procédé suivant l'une quelconque des revendications précédentes, caractérisé en ce que R^1 représente H et R représente le groupe 2,4-difluorophényle.

11. Procédé suivant la revendication 10, caractérisé en ce que le produit répondant à la formule (I) est séparé en ses paires de diastéréo-isomères par chromatographie.

12. Composition destinée à être utilisée comme fongicide en agriculture ou en horticulture, comprenant un composé de formule (I) suivant la revendication 1, ou un de ses sels acceptables en agriculture ou en horticulture, associé à un diluant ou support acceptable en agriculture ou en horticulture.

13. Procédé de préparation d'une composition pharmaceutique, qui consiste à mélanger un composé de formule (I) suivant la revendication 1, ou un de ses sels pharmaceutiquement acceptables, à un diluant ou support pharmaceutiquement acceptable.

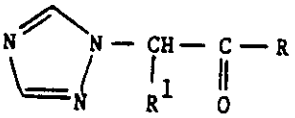
14. Procédé de préparation d'un composé de formule (II) suivant la revendication 1, caractérisé en ce qu'il consiste à faire réagir un composé de formule:



--- (A)

dans laquelle R et R^1 sont tels que définis dans la revendication 1, avec le méthylure de diméthyloxosulfonium.

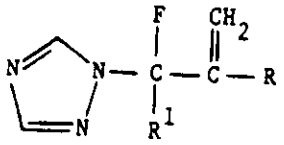
15. Procédé de préparation d'un composé de formule (A) suivant la revendication 14, caractérisé en ce qu'il consiste à faire réagir un composé de formule:



--- (B)

dans laquelle R et R^1 sont tels que définis dans la revendication 1, avec l'hydrure de sodium, puis avec le fluorure de perchloryle.

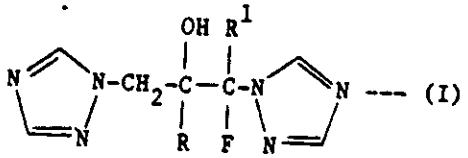
16. Procédé de préparation d'un composé de formule (II) suivant la revendication 1, caractérisé en ce qu'il consiste à faire réagir un composé de formule:



dans laquelle R et R^1 sont tels que définis dans la revendication 1, avec l'acide *m*-chloroperbonzoïque en présence d'un inhibiteur radicalaire.

Revendications pour l'Etat contractant: SE

1. Triazole de formule:



--- (I)

dans laquelle R est un groupe phényle, portant facultativement 1 à 3 substituants, chacun choisi indépendamment entre F, Cl, Br, I, CF_3, des groupes alkyle en C_1 à C_4 et alkoxy en C_1 à C_4, ou bien R est un groupe 5-chloropyrid-2-yle; R^1 représente H, CH_3 ou F; ou un de ses sels acceptables en pharmacie ou en agriculture.

2. Composé suivant la revendication 1, dans lequel R est un groupe phényle portant un ou deux substituants, chacun choisi indépendamment entre F, Cl, Br, I et CF_3.

3. Composé suivant la revendication 2, dans lequel R est le groupe 2,4-difluorophényle, 2,4-dichlorophényle, 4-fluorophényle ou 4-chlorophényle.

4. Composé suivant l'une quelconque des revendications précédentes, dans lequel R^1 représente H ou F.

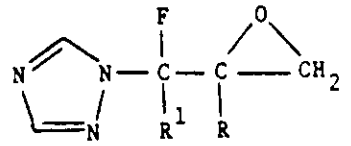
5. Composé ou un de ses sels suivant la revendication 1, dans lequel R est un groupe 2,4-difluorophényle et R^1 représente H.

6. Composition pharmaceutique comprenant un composé de formule (I) suivant l'une quelconque des revendications précédentes, ou un de ses sels pharmaceutiquement acceptables, associé à un diluant ou support pharmaceutiquement acceptable.

7. Composition fongicide destinée à être utilisée en agriculture (comprenant l'horticulture), contenant un composé de formule (I) suivant l'une quelconque des revendications 1 à 5, ou un de ses sels acceptables en agriculture, associé à un diluant ou support acceptable en agriculture.

8. Composé de formule (I) suivant l'une quelconque des revendications 1 à 5, ou un de ses sels pharmaceutiquement acceptables, destiné à être utilisé en médecine, en particulier pour l'utilisation dans le traitement d'une infection fongique chez l'homme.

9. Procédé de préparation d'un composé de formule (I) suivant la revendication 1, ou d'un de ses sels acceptables en pharmacie ou en agriculture, caractérisé en ce qu'il consiste à faire réagir un oxiranne de formule:



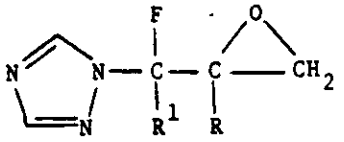
--- (II)

dans laquelle R et R^1 sont tels que définis dans la revendication 1, avec le 1,2,4-triazole ou un de ses sels formés avec une base, réaction suivie facultativement par la conversion du produit de formule (I) en un sel acceptable en pharmacie ou en agriculture et/ou, le cas échéant, la séparation du produit en ses paires de diastéréoisomères.

10. Procédé suivant la revendication 9, caractérisé en ce qu'on fait réagir l'oxiranne (II) avec le 1,2,4-triazole en présence de carbonate de potassium.

11. Procédé de traitement d'une plante ou de semences présentant une infection fongique, qui consiste à traiter ladite plante ou lesdites semences, ou le milieu de ladite plante, avec une quantité à effet antifongique d'un composé de formule (I) suivant l'une quelconque des revendications 1 à 5, ou avec un de ses sels acceptables en agriculture.

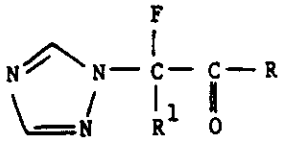
12. Composé de formule:



--- (II)

dans laquelle R et R^1 sont tels que définis dans la revendication 1.

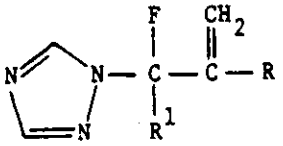
13. Composé de formule:



--- (A)

dans laquelle R et R^1 sont tels que définis dans la revendication 1.

14. Composé de formule:



dans laquelle R et R^1 sont tels que définis dans la revendication 1.

15. Utilisation d'un composé de formule (I) suivant la revendication 1, ou d'un de ses sels pharmaceutiquement acceptables, pour la production d'un médicament destiné à être utilisé comme agent antifongique.

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