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AUSTRALIA
PATENTS ACT 1990

WE ORTHO PHARMACEUTICAL CORPORATION

OF U.S. Rt. 202 Raritan, New Jersey, 08869-0602, U.S.A.

being the Applicant and Nominated Person request the grant of a patent for an invention entitled PROCESS FOR THE PREPARATION OF CERTAIN SUBSTITUTED BIPHENYL TETRAZOLES AND COMPOUNDS THEREOF which is described in the accompanying standard complete specification.

Convention priority is claimed from the following basic application:

BASIC APPLICANT	APPLICATION NUMBER	APPLICATION DATE	COUNTRY	COUNTRY CODE
WILLIAM V. MURRAY RONALD RUSSELL	786,666	1 NOVEMBER 1991	United States	US

WILLIAM V. MURRAY; RONALD RUSSELL is/are the actual inventor(s) of the invention.

The inventor(s) assigned ~~his~~/their entire rights in the invention to ORTHO PHARMACEUTICAL CORPORATION on NOVEMBER 1, 1991.

The basic application above was the first application made in a Convention country in respect of the invention the subject of this request.

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Attorney Code: GH

DATED this 21st day of October 1992

Signed Benjamin F. Lambert
(for and on behalf of Applicant)

Name: Benjamin F. Lambert

Title: Assistant Secretary

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(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 651014

(54) Title
PROCESS FOR THE PREPARATION OF CERTAIN SUBSTITUTED BIPHENYL TETRAZOLES AND COMPOUNDS THEREOF

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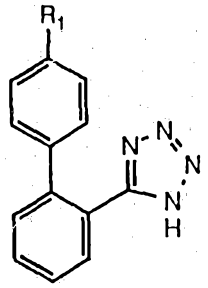
(56) Prior Art Documents
AU 71151/91 C07D 257/04 413/12
AU 90120/91 C07D 257/04 403/10

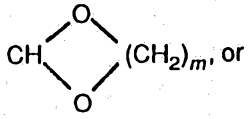
(57) Claim

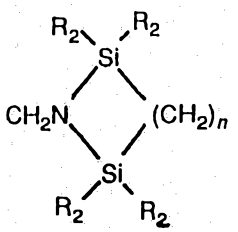
1. A process for the preparation of a compound of the formula I:



I

wherein R_1 is any of $CH(OR_2)_2$, CH_2OR_2, $CH_2N[Si(R_2)_3]_2$, $CH{=}C(R_2)_2$, $C{\equiv}CR_2$, C_1-C_4 alkyl,

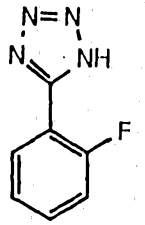




.../2

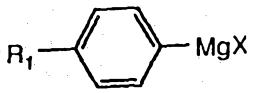
wherein R_2 is C_1-C_3 alkyl, n is 1-3 and m is 2-4,

comprising reacting a compound of the formula V:



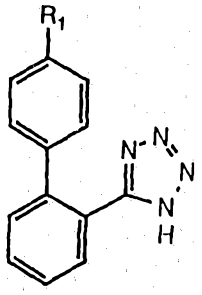
V

with a reagent of the formula:



wherein X is any of Cl, Br or 1, thereby producing the compound of formula I.

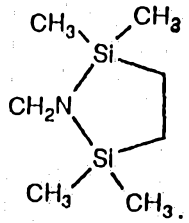
6. A compound of the formula I:



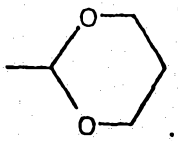
I

wherein R_1 is any of $CH(OR_2)_2$, CH_2OR_2, CH_2N $[Si(R_2)_3]_2$, $CH{-}C(R_2)_2$, $C{\equiv}CR_2$, C_2-C_4 alkyl.

8. The compound of claim 1, wherein R_1 is



9. The compound of claim 1, wherein R_1 is



P/00/011
Regulation 3.2

AUSTRALIA

Patents Act 1990

651014

ORIGINAL

COMPLETE SPECIFICATION

STANDARD PATENT

Invention Title: PROCESS FOR THE PREPARATION OF CERTAIN SUBSTITUTED BIPHENYL TETRAZOLES AND COMPOUNDS THEREOF

The following statement is a full description of this invention, including the best method of performing it known to us:

GH&CO REF: P04214-IN:VNV:RK

ORT-635

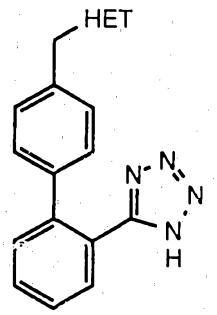
1A

PROCESS FOR THE PREPARATION OF CERTAIN SUBSTITUTED BIPHENYL TETRAZOLES AND COMPOUNDS THEREOF

BACKGROUND OF THE INVENTION

The renin-angiotensin system is one of the primary regulatory mechanisms for blood pressure in humans. Two drugs which act on the renin-angiotensin system are captopril and enalapril which are angiotensin converting enzyme (ACE) inhibitors. See Ondetti, M. et al., *Science* **1977**, *196*, 441; Ondetti, M. et al., *J. Med. Chem.* **1981**, *24*, 355 and Patchette, A. et al., *Nature*, **1980**, *288*, 280. A potentially more selective site for inhibition would be at the angiotensin II receptor as discussed by Duncia, J. et al., *J. Med. Chem.*, **1990**, *33*, 1312; Carini; D. et al., *J. Med. Chem.*, **1990**, *33*, 1330; Carini, D. and Duncia, J., Eur. Pat. Appl. 0253310 (Jan. 20, 1988); Johnson, A. et al., *Drug News and Perspectives*, **1990**, *3*, (6), 337; Chang, L., et al., European Patent Application No. 0412594A, (July 23, 1990); Naka, T., et al., JP 200963 (filed 7/27/90) and Roberts, D. et al., GB 18402 (filed 8/10/90).

Most of the compounds reported recently as angiotension II receptor antagonists have the (2'-tetrazol-5-yl)biphenyl-4-yl)methyl moiety attached to a heterocycle (HET) represented by the following formula II:

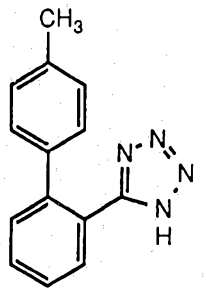


II

See Johnson, A., et al., *Drug News and Perspectives*, **1990**, *3*, (6), 337; Naka, T., et al., JP 200963 (filed 7/27/90); Roberts, D. et al., GB 18402 (filed

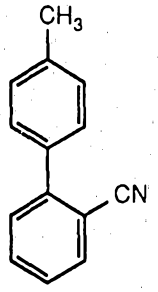
8/10/90); Chakravarty, P.K., et al., Eur. Pat. 0400974A (May 30, 1990); Oku, T., Setoi, H., Kayakiri, H., Inoue, I. and Kuroda, A., Eur. Pat. 0426021A (Oct., 26, 1990); Roberts, D. A., et al., Eur. Pat. 0425921A (May 18, 1990); Naka, T. and Nishikawa, K., Eur. Pat. 0425921A (Oct. 19, 1990) and Herold, P. and Bühlmayer, P., Eur. Pat. 0424317A (Oct. 10, 1990).

The preparation of compounds of the formula II starts with the intermediate 5-(4'-methyl[1,1'-biphenyl]-2-yl)-1*H*-tetrazole of the formula III:



III

which is prepared from the nitrile of the formula IV:



IV

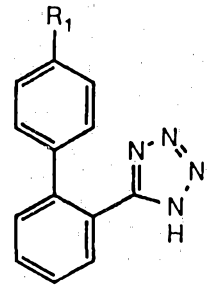
The conversion of the compound of formula IV to the compound of formula III is a process which requires the use of either highly toxic tin reagents (*e.g.* Bu_3SnN_3) or the production of triphenylphosphine oxide and acrylonitrile. See, Aldrich, P. E., et al., U. S. Pat. 4,870,186 (Nov. 23, 1988); Aldrich, P. E., et al., U. S. Pat. 4,874,867 (Nov. 23, 1988); Aldrich, P. E., et al., Eur. Pat. 0291969 (May 19, 1988); Chakravarty, P. K., et al., Eur. Pat. 0401030A (May 31, 1990); Duncia, J. V., Pierce, M. E. and Santella, J. B. III, *J. Org. Chem.*, **1991**, *56*, 2395;

George, E. F. and Riddell, W. D., U. S. Pat. 3,865,570 (Feb. 13, 1973) and Herbst, R. M. and Wilson, K. R., *J. Org. Chem.*, **1957**, *22*, 1142.

The preparation of certain biphenyl compounds has been reported when one reacts a Grignard reagent with a fluorobenzene which has a bis-oxazoline moiety. See, Cram, D. J., Katz, H. E. and Dicker, I.B., *J. Am. Chem. Soc.*, **1984**, *106*, 4987 and Meyers, A. I. and Williams, B. E., *Tetrahedron Lett.*, **1978**, 223. Such compounds are, however, quite different from the compounds of formula III and those of the present invention.

It is an object of the present invention to develop a process for the preparation of compounds of the type represented by formula III which avoid the use or generation of highly toxic materials.

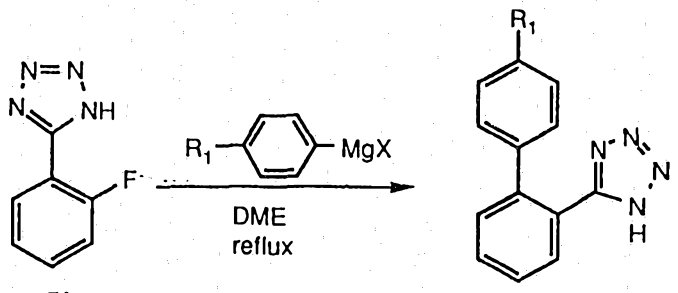
Accordingly, the present invention is directed to a process for the production of compounds of formula I:



I

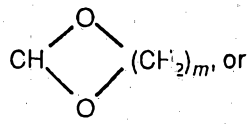
wherein R_1 is defined hereafter, generally comprising reacting 5-(2-fluorophenyl)-1*H*-tetrazole with a Grignard reagent to produce the desired compound of formula I. The process produces the desired compound in a yield of about 72-82% without the use or generation of highly toxic materials. The process of the present invention also produces certain novel compounds.

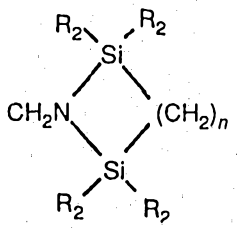
More particularly, the process of the present invention comprises producing certain biphenyl tetrazoles of formula I by the following reaction scheme:



V I

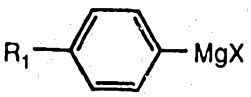
wherein R_1 is any of $CH(OR_2)_2$, CH_2OR_2, $CH_2N[Si(R_2)_3]_2$, $CH=C(R_2)_2$, $C\equiv CR_2$, C_1-C_4 alkyl,





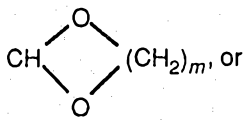
wherein R_2 is C_1-C_3 alkyl, n is 1-3, m is 2-4 and wherein X is Cl, Br or I.

In this process, a tetrazole of the formula V is treated with an excess of a Grignard reagent of the following formula:

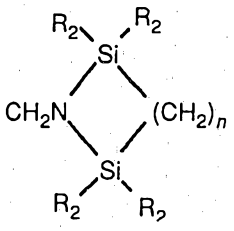


in a solvent such as diethylether, dimethoxyethane or dioxane and warmed to reflux, preferably for about 6 to 24 hours.

When R_1 is C_1-C_4 alkyl the Grignard reagent is either purchased from commercial sources (*e.g.* Aldrich Chemical Company, Inc.) or prepared by literature methods such as those described by DePuy, C. H. and R. A. Klein in *Organic Synthesis*, **Coll. Vol V**, Baumgarten, H. E., ed.; John Wiley and Sons: New York, 1973, pp 1058-1060 or Murray, W. V., Hadden, S. K. and Wachter, M. P., *J. Heterocycl. Chem.*, **1990**, *27*, 1933. The preparation of the protected aldehydes (see *e.g.*: *a*) Shauler, A. J. and Darley, P. A., *Chem. Rev.* **1967**, *67*, 427-440; b) Cole, J. E. et al., *J. Chem. Soc.*, **1962**, 244; and c) Dann, A. E. , et al., *J. Chem. Soc., Perkin Trans. I*, **1979**, 158] wherein R_1 is $CH(OR_2)_2$ and



the protected benzyl alcohols (see *e. g.* Stork, G. and Takahashi, T., *J. Amer. Chem. Soc*, **1977**, *99*, 1275 or Auerbach, J. and Weinreb, S. M., *J. Chem. Soc., Chem. Commun.*, **1974**, 298) wherein R_1 is CH_2OR_2, and the protected benzyl amines [see *e. g.* a) Pratt, J. R., Massey, W. D., Pinkerton, F. H. and Thames, S. F., *J. Org. Chem*; **1975**, *40*, 1090; b) Basha, F. Z. and DeBernardis, J. F., *Tetrahedron Lett.*, **1984**, *25*, 5271; and c) Diuric, S., Venit, J. and Magnus, P., *Tetrahedron Lett.*, **1981**, 1787] wherein R_1 is $CH_2N[Si(R_2)_3]_2$ and



may be effected by techniques well known in the art from commercially (*e. g.* Aldrich Chemical Company, Inc.) available 4-bromobenzaldehyde, 4-bromobenzyl alcohol and 4-bromobenzyl amine, respectively. The preparation of the 4-bromophenylacetylenes wherein R_1 is C≡CMe can be accomplished by the procedure of Hamer and Magee, *J. Chem. Soc.*, **1964**, 1847 and wherein R_1 is $CH=C(R_2)_2$ can be accomplished by the procedure of Mirviss, S. R., *J. Org. Chem.*, **1989**, *54*, 1948.

The halogen X of the Grignard is chlorine, bromine or iodine and is determined by the choice of starting material for the Grignard preparation (*i.e.* 4-chlorotoluene gives X = Cl ($R_1 = CH_3$), 4-bromotoluene gives X = Br ($R_1 = CH_3$).

The tetrazole of the formula V may be prepared by techniques well known in the art as described in Herbst, R.M. and Wilson, K.R., *J. Org. Chem.*, **1957**, 22, 1142. The preparation generally comprises reacting 2-fluorobenzonitrile with NaN_3 and glacial CH_3COOH in the presence of a solvent such as *n*-butanol.

In the process of the present invention, after warming to reflux, the final product is obtained by techniques known in the art, including extraction with a suitable agent such as CH_2Cl_2, filtration and either crystallization or purification by column chromatography. The process produces product in yields of from about 72 to 82%.

A particularly preferred process according to the present invention comprises the production of compounds of the formula I wherein R_1 is CH_3.

Certain of the compounds produced by the process of the present invention are novel compounds. These compounds are compounds of formula I wherein R_1 is any of $CH(OR_2)_2$, CH_2OR_2, $CH_2N[Si(R_2)_3]_2$, $CH{=}C(R_2)_2$, $C{\equiv}CR_2$, C_2-C_4 alkyl. Each of these compounds and the other known compounds represented by formula I may be employed in the preparation of angiotension II receptor antagonists which have the (2'-tetrazol-5-yl)biphenyl-4-yl)methyl moiety attached to a heterocycle as described in greater detail in the Background of the Invention.

The process of the present invention will now be illustrated by the following Example, which is not intended and should not be considered a limitation to the present invention.

EXAMPLE

Preparation of 5-(4'-methyl[1,1'-biphenyl]-2-yl)-1*H*-tetrazole

A 4-necked 3 l round-bottom flask was charged with 5-(2-fluorophenyl)-1*H*-tetrazole (32.8 g, 0.2 mol) and dry DME (1300 ml) under nitrogen. To this ice-cold solution was slowly added a 1 *M* solution of *p*-tolylmagnesium bromide in diethyl ether (600 ml, 0.6 mol). After the addition had been completed, the diethyl ether was removed by simple distillation and the resulting DME solution was warmed to reflux for 16 h under nitrogen. With ice-bath cooling, the reaction mixture was slowly quenched with 6*N* HCl (130 ml). The DME was removed under reduced pressure and the resulting aqueous residue was extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with 2*N* NaOH (3 x 100 ml) and these combined extracts were acidified to a pH of 1 with concentrated HCl. The acidic aqueous phase was extracted with CH_2Cl_2 and these combined extracts were washed with brine and dried (Na_2SO_4). Solvent removal under vacuum produced 46.2 g of tan material which was purified by crystallization from EtOAc/hexane (2/1, total volume = 250 ml). The compound of formula III was obtained (32.4 g, 68.6%) as a tan solid, mp 141-146°C [lit. mp 152-154°C (toluene); Chakravarty, P.K., et al., Eur. Pat. 0401030 (May 31, 1990)]. The filtrate was purified by silica gel filtration with CH_2Cl_2/MeOH/AcOH (97.5/2.70/0.05) and then crystallized from the above solvent mixture to produce another 4.54 g (9.6%) of the compound of formula III, mp 146-148°C. An analytical sample was prepared by recrystallization from toluene (2x) to afford a tan solid, mp 144-148°C.

Anal. Calc'd for $C_{14}H_{12}N_4$:	C, 71.17; H, 5.12; N, 23.71
Found:	C, 71.16; H, 5.10; N, 24.08

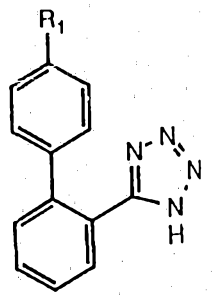
The 5-(2-fluorophenyl)-1*H*-tetrazole starting material was prepared as follows. A 3-necked 500 ml round-bottom flask was charged with 2-fluorobenzonitrile (48.4 g, 0.4 mol), *n*-butanol (160 ml), NaN_3 (34.3 g, 0.528 mol) and glacial acetic acid (31.7 g, 0.528 mol). The mixture was warmed to a mild reflux for 24 h under nitrogen behind a safety shield. After the mixture had cooled to room temperature, it was again charged with NaN_3 (34.3 g, 0.528 mol) and glacial acetic acid (31.7 g, 0.528 mol). The mixture was warmed to a mild reflux for an additional 24 h under nitrogen, cooled and then diluted with diethyl ether (320 ml). This organic mixture was extracted with 2*N* NaOH (4 x 100 ml) and the combined ice-cold basic extracts were carefully acidified to pH

1 with concentrated hydrochloric acid. The product was isolated as a light gray solid (45.2 g, 68.9%) after drying under vacuum at 60° C, mp 160.5–162° C [lit. mp 160–162° C; George, E. F. and Riddell, W. D., U. S. Pat. 3,865,570 (Feb. 13, 1973)]. There was obtained a second crop of product (1.0 g, 1.5%). A 1.0 g sample of this material was crystallized from water to produce a white solid, mp 162.5–163.5° C.

Anal. Calc'd for $C_7H_5FN_4$:	C, 51.22; H, 3.07; N, 34.13
Found:	C, 51.35; H, 3.02; N, 34.43

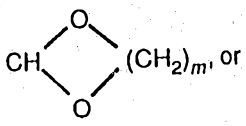
THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

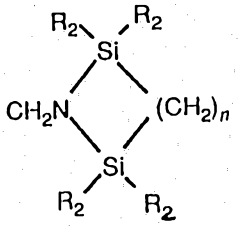
1. A process for the preparation of a compound of the formula I:



I

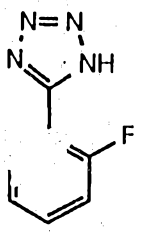
wherein R_1 is any of $CH(OR_2)_2$, CH_2OR_2, $CH_2N\ [Si(R_2)_3]_2$, $CH{=}C(R_2)_2)$, $C{\equiv}CR_2$, C_1-C_4 alkyl,





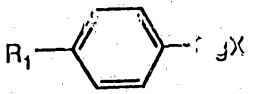
wherein R_2 is C_1-C_3 alkyl, n is 1-3 and m is 2-4,

comprising reacting a compound of the formula V:



V

with a reagent of the formula:



wherein X is any of Cl, Br or I, thereby producing the compound of formula I.

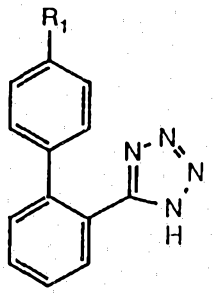
2. The process of claim 1, wherein the reaction is carried out in the presence of a solvent.

3. The process of claim 2, wherein the solvent is dimethoxyethane.

4. The process of claim 1, wherein the reaction is carried out by heating to reflux.

5. The process of claim 1, wherein R_1 is CH_3.

6. A compound of the formula I:

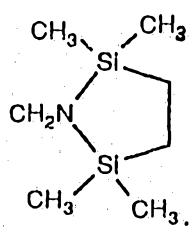


I

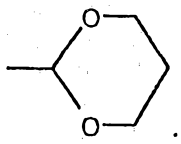
wherein R_1 is any of $CH(OR_2)_2$, CH_2OR_2, $CH_2N\,[Si(R_2)_3]_2$, $CH{=}C(R_2)_2$, $C{\equiv}CR_2$, C_2-C_4 alkyl.

7. The compound of claim 6, wherein R_1 is C_2-C_4 alkyl.

8. The compound of claim 1, wherein R_1 is



9. The compound of claim 1, wherein R_1 is



10. A process for the preparation of 5-(4'methyl [1,1'-biphenyl]-2-yl)-1H-tetrazole substantially as herein described with reference to the Example.

Dated this 11th day of May 1994

ORTHO PHARMACEUTICAL CORPORATION
By their Patent Attorneys
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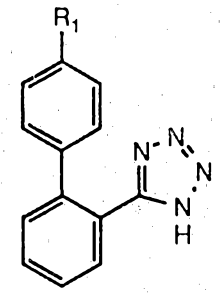
ABSTRACT OF THE DISCLOSURE

A process for producing a compound of formula I:



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comprising reacting 5-(2-fluorophenyl)-1*H*-tetrazole with a Grignard reagent to produce the desired product is disclosed. Novel compounds produced by this process for use as intermediates in making certain angiotension II antagonists are also disclosed.