633767

SPRUSON & FERGUSON

AUSTRALIA

PATENTS ACT 1990

PATENT REQUEST: STANDARD PATENT

I/We, the Applicant(s)/Nominated Person(s) specified below, request I/We be granted a patent for the invention disclosed in the accompanying standard complete specification.

[70,71] Applicant(s)/Nominated Person(s):

Pfizer Inc., of 235 East 42nd Street, New York, New York, 10017, UNITED STATES OF AMERICA

[54] Invention Title:

Thiophene Carboxylic Acid Intermediates

[72] Inventor(s):

Frederick Jacob Ehrgott, Carl Joseph Goddard and Gary Richard Schulte

[74] Address for service in Australia:

Spruson & Ferguson, Patent Attorneys
Level 33 St Martins Tower
31 Market Street
Sydney New South Wales Australia (Code **SF**)

Divisional Application Details

[62] Original Application No(s): 53626/90.
Person by whom made :Pfizer Inc.

DATED this TWENTY EIGHTH day of JANUARY 1992

Pfizer Inc.

By:

Registered Patent Attorney

IRN: 202430

INSTR CODE: 60031

S027058 28/01/92

5845/5

SPRUSON & FERGUSON
PC(Ph)7573AGCB
Div. 1

Australia

Patents Act 1990

NOTICE OF ENTITLEMENT

I, Allen J. Spiegel, Director of Foreign Patents
of Pfizer Inc., 235 East 42nd Street, New York,
New York 10017, United States of America

being authorised by the Applicant/Nominated Person in respect of an application entitled:

Thiophene Carboxylic Acid Intermediates

state the following:-

The Applicant/Nominated Person has entitlement from the actual inventors as follows:-

The Applicant/Nominated Person is the assignee of the actual inventors.

The Applicant/Nominated Person is the applicant/patentee of the original application/patent.

DATED this 10th day of February 1992

.....

ALLEN J. SPIEGEL
DIRECTOR OF FOREIGN PATENTS

IRN: 202430 INSTR CODE: 60031

ALB:9599D

AU9210510

(12) PATENT ABRIDGMENT (11) Document No. AU-B-10510/92
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 633767

(54) Title
THIOPHENE CARBOXYLIC ACID INTERMEDIATES

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(62) Related to Division(s) : 53626/90

(71) Applicant(s)
PFIZER INC.

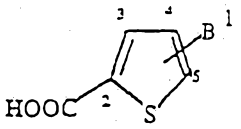
(72) Inventor(s)
FREDERICK JACOB EHRGOTT; CARL JOSEPH GODDARD; GARY RICHARD SCHULTE

(74) Attorney or Agent
SPRUSON & FERGUSON , GPO Box 3898, SYDNEY NSW 2001

(57) This invention relates to certain novel thiophene carboxylic acids useful as intermediates in the preparation of the 3-substituted-2-oxindole derivatives.

CLAIM

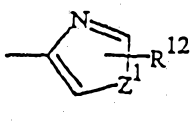
1. A compound of the formula

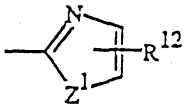


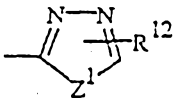
(I)

and the salts thereof

wherein B^1 is at the 4 position and is SOR^{16} or $COOCH_3$, or B^1 is at the 5 position and is SO_2NHCH_3, or B^1 is at the 4 or 5 position and is $CON(CH_3)_2$,







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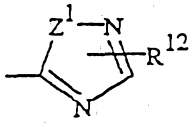
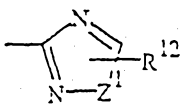


or



Z^1 is O or S; R^{12} is H, F, Cl, Br, CF_3 or (C_1-C_6)alkyl; and R^{16} is (C_1-C_4)alkyl.

2. A process of preparing a thiophene carboxylic acid derivative according to claim 1 which process is substantially as herein described with reference to any one of the Examples.

633767

S & F Ref: 202430

AUSTRALIA

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COMPLETE SPECIFICATION

FOR A STANDARD PATENT

ORIGINAL

Name and Address of Applicant: Pfizer Inc.
235 East 42nd Street
New York New York 10017
UNITED STATES OF AMERICA

Actual Inventor(s): Frederick Jacob Ehrgott, Carl Joseph Goddard and Gary Richard Schulte

Address for Service: Spruson & Ferguson, Patent Attorneys
Level 33 St Martins Tower, 31 Market Street
Sydney, New South Wales, 2000, Australia

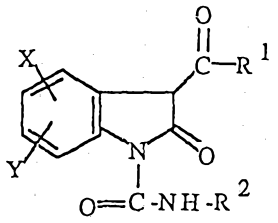
Invention Title: Thiophene Carboxylic Acid Intermediates

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

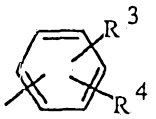
THIOPHENE CARBOXYLIC ACID INTERMEDIATES

This invention relates to certain novel thiophene carboxylic acids useful as intermediates in the preparation of the 3-substituted-2-oxindole derivatives.

U.S. 4,569,942 discloses certain 2-oxindole-1-carboxamides of the formula



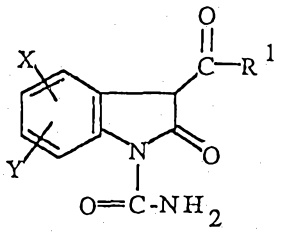
wherein inter alia, X is H, fluoro, chloro, bromo, (C_1-C_4)alkyl, (C_3-C_7)cycloalkyl, (C_1-C_4)alkoxy, (C_1-C_4)alkylthio, trifluoromethyl, (C_1-C_4)alkylsulfinyl, (C_1-C_4)-alkylsulfonyl, nitro, phenyl, (C_2-C_4)alkanoyl, benzoyl, thenoyl, (C_1-C_4)alkanamido, benzamido or N,N-dialkylsulfamoyl, having 1 to 3 carbons in each of said alkyls; Y is, H, fluoro, chloro, bromo, (C_1-C_4)alkyl, (C_3-C_7)cycloalkyl, (C_1-C_4)alkoxy, (C_1-C_4)-alkylthio and trifluoromethyl; R^1 is (C_1-C_6)alkyl, (C_3-C_7)cycloalkyl, (C_4-C_7)cyclo-alkenyl, phenyl, substituted phenyl, phenylalkyl having 1 to 3 carbons in said alkyl, (substituted phenyl)alkyl having 1 to 3 carbons in said alkyl, (substituted phenoxy)alkyl having 1 to 3 carbons in said alkyl, (thiophenoxy)alkyl having 1 to 3 carbons in said alkyl, naphthyl, bicyclo[2.2.1]heptan-2-yl, bicyclo[2.2.1]hept-5-en-2-yl or $-(CH_2)_n-Q-R^\circ$; n is zero, 1 or 2; Q is a divalent radical derived from furan, thiophene, pyrrole, pyrazole, imidazole, thiazole, isothiazole, oxazole, isoxazole, 1,2,3-thiadiazole, 1,3,4-thiadiazole, 1,2,5-thiadiazole, tetrahydrofuran, tetrahydrothiophene, tetrahydropyran, tetrahydrothiopyran, pyridine, pyrimidine, pyrazine, benzo[b]furan and benzo[b]thiophene; R°; is H or (C_1-C_3) alkyl; and R^2 is (C_1-C_6)alkyl, (C_3-C_7)cyclo-alkyl, benzyl, furyl, thienyl, pyridyl or



where R^3 and R^4 are each H, fluoro, chloro, (C_1-C_4)alkyl, (C_1-C_4)alkoxy or trifluoro-methyl.

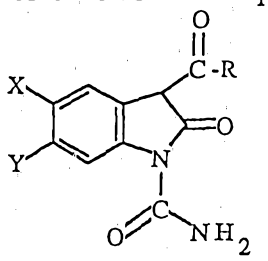
That patent also discloses that said 2-oxindole-1-carboxamides are inhibitors of cyclooxygenase and lipoxygenase, possess analgesic activity in mammals and are useful in treatment of pain and alleviation of symptoms of chronic diseases such as inflammation and pain associated with rheumatoid arthritis and osteoarthritis.

U.S. Patent 4,556,672 discloses certain 3-acyl substituted-2-oxindole-1-carboxamides of the formula



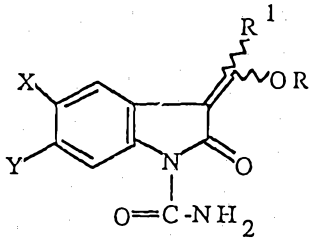
wherein X, Y and R^1 are as described above for the compounds of U.S. Patent 4,569,942. The compounds of U.S. 4,556,672 are disclosed as having the same activity as the compounds of U.S. Patent 4,569,942 discussed above.

U.S. Patent 4,861,794 discloses the use of compounds of the formula



and the pharmaceutically-acceptable base salts thereof wherein X is H, Cl or F, Y is H or Cl and R is benzyl or thienyl to inhibit biosynthesis of interleukin-1 (IL-1) and to treat IL-1 mediated disorders and dysfunctions.

PCT patent application Serial No. PCT/US88/03658, filed October 18, 1988, describes non-steroidal anti-inflammatory agents of the formula



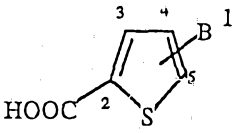
wherein each of X and Y is hydrogen, fluoro or chloro; R^1 is 2-thienyl or benzyl; and R is alkanoyl, cycloalkylcarbonyl, phenylalkanoyl, benzoyl and certain substituted benzoyl groups, thenoyl, omega-alkoxycarbonylalkanoyl, alkoxycarbonyl, phenoxycarbonyl, 1-alkoxycarbonyloxy, alkylsulfonyl, methylphenylsulfonyl and dialkyl phosphonate.

Interleukin-1 (IL-1) has been reported to stimulate bone resorption both in vitro and in vivo. Hayward, M. and Fiedler-Nagy, Ch., Agents and Actions, 22, 251-254 (1987). It is also reported therein that IL-1, inter alia, induces the production of prostaglandin E_2 (PGE_2). PGE_2 is a stimulator of bone resorption and has been implicated in bone loss. See Hayward, M.A. and Caggiano, T.J., Annual Reports in Medicinal Chemistry, 22, Sect. IV, Chapter 17, 169-178 (1987). Osteoporosis is defined as a debilitory loss of bone mineral which results in higher fracture rates. See Hayward, M.A. and Caggiano, T.J., supra, and references cited therein.

Interleukin-1 has been reported to be involved in the pathogenesis of many

diseases. See Dinarello, C.A., J. Clin. Immunol., 5, 287-297 (1985), the teachings of which are incorporated herein by reference. Further still, elevated levels of IL-1 like material have been found to be associated with psoriasis. Camp, R.D., et al., J. Immunol., 137, 3469-3474 (1986).

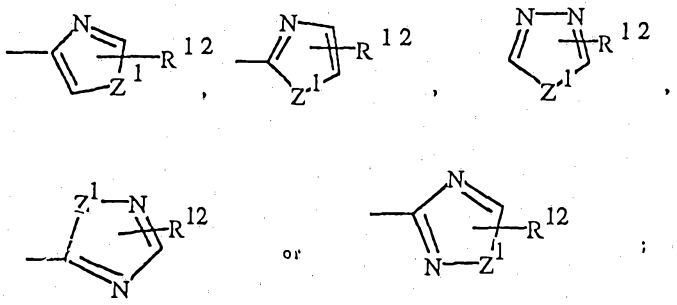
The present invention provides a compound of the formula



(I)

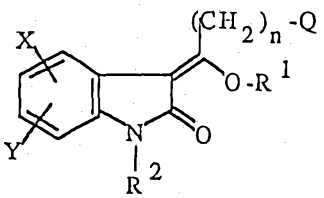
and the salts thereof

wherein B^1 is at the 4 position and is SOR^{16} or $COOCH_3$, or B^1 is at the 5 position and is SO_2NHCH_3 or B^1 is at the 4 or 5 position and is $CON(CH_3)_2$,



Z^1 is O or S; R^{12} is H, F, Cl, Br, CF_3 or $(C_1\text{-}C_6)$alkyl; and R^{16} is $(C_1\text{-}C_4)$alkyl.

The compounds of formula I are useful as intermediates in the preparation of certain compounds of formula II.



(II)

and the pharmaceutically acceptable salts thereof, wherein

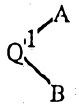
X is H, F, Cl, Br, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, NO_2, CF_3, CN, SH, $S(O)_mR^3$, OR^4, COR^4 or $CONR^4R^5$;

Y is H, F, Cl, Br, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, NO_2, CF_3, CN, SH, $S(O)_qR^{17}$, OR^{18} or $CONR^{18}R^{19}$;

R^1 is H, alkanoyl of two to ten carbon atoms, cycloalkylcarbonyl of five to seven carbon atoms, phenylalkanoyl of seven to ten carbon atoms, chlorobenzoyl, methoxybenzoyl, thenoyl, omega-alkoxycarbonylalkanoyl, said alkoxy having one to three carbon atoms and said alkanoyl having three to five carbon atoms, alkoxy carbonyl of two to ten carbon atoms, phenoxycarbonyl, 1-(acyloxy)alkyl wherein acyl has one to four carbon atoms and said alkyl has two to four carbon atoms, 1-(alkoxycarbonyloxy)alkyl wherein said alkoxy has two to five carbon atoms and said alkyl has one to four carbon atoms, alkyl of one to three carbon atoms, alkylsulfonyl of one to three carbon atoms, methylphenylsulfonyl or dialkylphosphonate wherein each of said alkyl is one to three carbon atoms;

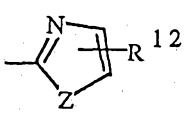
R^2 is COR^6, $CONR^7R^8$, $(C_1\text{-}C_6)$alkyl, $(C_3\text{-}C_8)$cycloalkyl, phenyl or mono- or disubstituted phenyl wherein the substituent or substituents are each Cl, F, Br, $(C_1\text{-}C_6)$alkyl, $(C_1\text{-}C_6)$alkoxy or CF_3;

Q is


or

;

A is H, F, Cl, Br, I, CF_3, OR^9, $S(O)_pR^{10}$, $COOR^{11}$, $CONR^9R^{11}$, CN, NO_2, COR^{10}, CH_2OR^{11}, $OCOR^{10}$, NR^9R^{11}, $N(R^9)COR^{11}$, $SO_2NR^9R^{11}$,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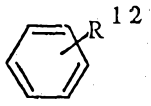
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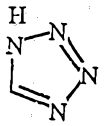
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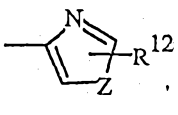
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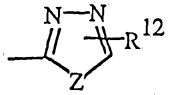
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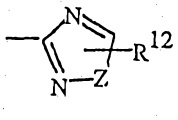

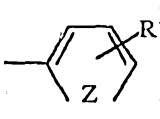
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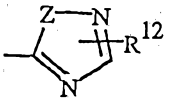
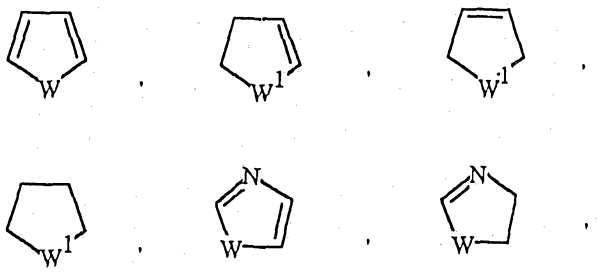

;

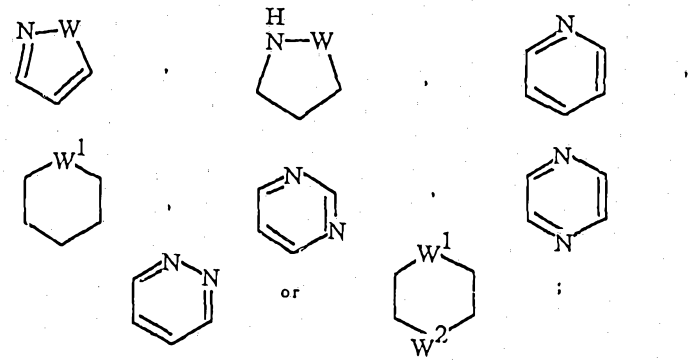
B is H, F, Cl, Br, I, CF_3, OR^{13}, $S(O)_tR^{14}$, $COOR^{15}$, $CONR^{13}R^{15}$, CN, NO_2, COR^{14}, CH_2OR^{15}, $OCOR^{14}$, $NR^{13}R^{15}$, $N(R^{13})COR^{15}$ or $SO_2NR^{13}R^{15}$;

provided that A and B cannot both be H; or A and B are taken together, bonded to the same ring carbon of Q^1 and equal oxo, or when A is not H, B is as defined above or $(C_1\text{-}C_4)$alkyl;

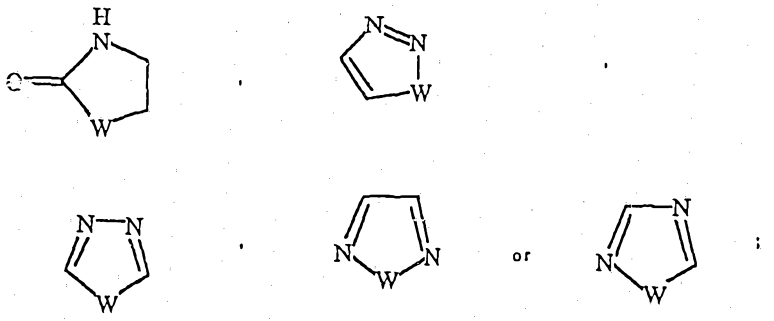
A^1 is F, Cl, Br, I, CF_3, OR^9, $S(O)_pR^{10}$, $COOR^{11}$, $CONR^9R^{11}$, CN, NO_2, COR^{10}, CH_2OR^{11}, $OCOR^{10}$, NR^9R^{11}, $N(R^9)COR^{11}$ or $SO_2NR^9R^{11}$;

Q^1 is





Q^2 is



m, n, p, q and t are each zero, one or two;

W and Z are each O, S or NR^{11};

W^1 and W^2 are each O, S, or NR^{10} provided that when one of W^1 or W^2 is O, S or NR^{10}, the other is O or S;

R^3, R^6, R^{10}, R^{14} and R^{17} are each $(C_1$-$C_6)$alkyl or phenyl; R^5, R^8, R^{11}, R^{15} and R^{19} are each H, $(C_1$-$C_6)$alkyl or phenyl; R^4, R^7, R^9, R^{13} and R^{18} are each H or $(C_1$-$C_6)$alkyl; and R^{12} is H, F, Cl, Br, CF_3 or $(C_1$-$C_6)$ alkyl.

The novel carboxylic acids of formula I are prepared according to known methods, or methods analogous to known methods. Such methods may include the preparation of the corresponding esters or nitriles of the respective carboxylic acids in which cases hydrolysis by known procedures yields the carboxylic acid of interest. For such methods, consult: Taylor, E.C., et al., J.O.C. 50:1002 (1985); Noto, R., et al., J. Chem. Soc. P.T. II, 689 (1987); Schick, J.W., et al., J. Am. Chem. Soc. 70:286 (1948); Carpenter, A.J., et al., Tetrahedron 41:3808 (1985); Gronowitz, S., et al., Arkiv. for Kemi. 21:265 (1963); Benkeser, R.A., et al., J.O.C. 38:3660 (1973); Corral, C., et al., Heterocycles 23:1431 (1985); Iriarte, J., et al., J. Het. Chem. 13:393 (1976); Reinecke, M.G., et al., Synthesis, 327 (1980); Lawesson, S.O., Arkiv. for Kemi. 11:317 (1957); Gronowitz, S., Arkiv. for Kemi. 8:87 (1955); Knight, D.W., et al., J. Chem. Soc. P.T.I., 791 (1983); Gronowitz, S., Arkiv. for Kemi. 12:239 (1958); Sice, J., J. Am. Chem. Soc. 75:3697 (1953); Bohlmann, F., et al., Chem. Ber. 106:497 (1973); Thames, S.F., et al., J. Het. Chem. 3:104 (1966); Arndt, F., et al., Chem. Ber. 94:1757 (1961); Cymerman-Craig, J., et al., J. Chem. Soc.:237 (1954); Lora-Tamayo, M., et al., Anales Real Soc. Espan. Fis. Quim. Ser. B 62:187 (1966); Nemec, N., et al., Coll. Czech. Chem. Comm. 39:3527 (1974); Janda, M., et al., Coll. Czech. Chem. Comm. 27:1191 (1962); Carpenter, A.J., et al., Tetrahedron Letters 26:1777 (1985); Satonaka, H., Bull. Chem. Soc. Japan 56:2463 (1983); Kinoshita, T., et al., Bull. Chem. Soc. Japan 48:1865 (1975); Schwertner, E., et al., CA 88:105790c (1978); Takaya, T., et al., Bull. Chem. Soc. Japan 41:2086 (1968); Kim, H., et al., J. Med. Chem. 29:1374 (1986); Dostert, P., et al., Eur. J. Med. Chem. - Chim. Ther. 17:437 (1982); Sato, N., et al., J. Heterocyclic Chem. 19:407 (1982); Ladruee, D., et al., Heterocycles 22:299 (1984); Leanza, W.J., et al., JACS 75:4086 (1953); Barlin, G.B., et al., Aust. J. Chem. 30:2319 (1977); Gregory, G.I., et al., JCS P.T.1:47 (1973); Moriarty, R.M., et al., JACS 89:5958 (1967); Ross, J.M., et al., JACS 86:2861 (1964); Goerdeler, J., et al., Chem. Ber. 99:1618 (1966); Demaree, P., et al., Can. J. Chem. 55:243 (1977); U.S. Patent 4,001,238; Kawazu, M. et al., J. Med. Chem. 15:914 (1972); Buckle, D.R., et al., JCS P.T.1:627 (1982); Naik, S.R., et al., JOC 38:4353 (1973); Okada, M., et al., Macromolecules 19:503 (1986); Ondetti, M.A., et al., CA 92:76268p (1980); Neth. Appl. 6,503,440, Sept. 20, 1965; Kenley, R.A., et al., CA101:90841f (1984); Schmidt, U., et al., CA 96:104572m (1982); Lukes, R. et al., Chem. listy 51:1510 (1957); Krowicki, K., et al., JOC 52:3493-

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The following Examples are illustrative of this invention and are not to be construed as limiting in any way the scope thereof.

EXAMPLE 1

4-Methylsulfinyl-2-thiophenecarboxylic acid

A stirred solution of 2.46 g (14.1 mmoles) of 4-methylthio-2-thiophenecarboxylic acid (prepared as described in Example 20 below) in 150 ml dichloromethane and 10 ml methanol was cooled to icebath temperature. A 120 ml dichloromethane solution of 2.82 g (13.9 mmoles) of m-chloroperoxybenzoic acid (technical grade, 80-85%) was slowly added to the cooled reaction solution. After 1 hour the reaction was essentially complete with a colorless precipitate forming. The precipitate was filtered and dried to give 1.18 g

(6.20 mmoles) of desired compound as a colorless solid, m.p. 188-190°C. The concentrated mother liquor was chromatographed (silica gel) to give an additional 0.83 g (4.36 mmoles) of desired 4-methylsulfinyl-2-thiophenecarboxylic acid, total yield 75% (10.56 mmoles).

Analysis: Calculated for $C_6H_6O_3S_2$: C, 37.88; H, 3.18%. Found: C, 37.89; H, 3.18%. EIMS (m/z): 190 (M^+, 45%) and 175 (M^+-CH_3). ^{1}HNMR (DMSO-d_6) delta, 13.4 (1H, exchangeable), 8.27 (1H, d, J=1.5Hz), 7.96 (1H, d, J=1.5Hz) and 2.86 (3H, s). ^{13}CNMR (DMSO-d_6) delta 162.1, 146.4, 137.2, 131.7, 128.9 and 42.2. ir(potassium bromide): 3420, 2550, 1705, 1245, 1015 cm^{-1}.

EXAMPLE 2

5-(N-Methylaminosulfonyl)-2-thiophenecarboxylic acid

Lithium diisopropylamide was prepared by slowly adding 17.5 ml (43.8 mmoles) of 2.5M n-butyllithium in hexane to a cooled (2-propanol/dry ice) tetrahydrofuran (200 ml) solution of diisopropylamine (7.0 ml, 50.0 mmoles) with the reaction temperature maintained below -60°C. After 5 minutes the reaction solution was warmed to room temperature for 30 minutes and then cooled to below -70°C again. A 100 ml tetrahydrofuran solution of 3.54 g (20.0 mmoles) of 2-(N-methylaminosulfonyl)-thiophene (prepared according to Slocum, D.W., et al., JOC 38, 4189 (1973)) was added slowly with the reaction temperature controlled below -70°C. After complete addition the reaction was stirred for 30 minutes and then ex ess carbon dioxide was bubbled through the solution. The solution was then warmed to 5°C and quenched with 50 ml of 1N sodium hydroxide. A 300 ml portion of diethyl ether was added to the aqueous tetrahydrofuran solution and the phases were separated in a separatory funnel. The organic layer was extracted with 50 ml of 1N sodium hydroxide. Both basic aqueous solutions were combined, washed with 50 ml of diethyl ether and acidified with concentrated hydrochloric acid. The acidic aqueous mixture was extracted with diethyl ether (2 x 100 ml). The ether solution was washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo to 3.38 g (15.3 mmoles) of desired thiophenecarboxylic acid as a colorless solid, m.p. 145-148°C. Total yield was 76%.

Analysis: Calculated for $C_6H_7NO_4S_2$: C, 32.57; H, 3.19; N, 6.33%. Found: C, 32.43; H, 3.08; N, 6.30%. EIMS (m/z): 221 (M^+, base), 191 (M^+-NHMe, 98%), 157 (unknown, 95%), 127 (unknown, 45%) and 115 (unknown, 73%). ^{1}HNMR (DMSO-d_6) delta, 7.92 (1H, exchangeable), 7.74 (1H, d, J=4.0Hz), 7.58 (1H, d, J=4.0Hz) and 2.51 (3H, d, J=5.2Hz); ir(potassium bromide): 3440 br, 3000 br, 1680, 1170 cm^{-1}.

EXAMPLE 3

5-Iodo-2-thiophenecarboxylic acid

The title compound has been described by Schick, J.W., et al., J. Am. Chem. Soc. 70:286 (1948), and was prepared according to the following procedure. A 25 ml (62.5 mmoles) volume of a 2.5M hexane solution of n-butyllithium was slowly added by

syringe to a cooled (dry ice/2-propanol) 100 ml tetrahydrofuran solution of 9.0 ml (64.2 mmoles) of diisopropylamine. The solution was maintained below -60°C during n-butyllithium addition. After addition, the cooling bath was removed and the solution allowed to reach room temperature (22°C), and then cooled again below -60°C. To the cooled reaction vessel, 3.2 g (25.0 mmol) of 2-thiophenecarboxylic acid dissolved in 100 ml of tetrahydrofuran was slowly added. Thirty minutes after complete addition of 2-thiophenecarboxylic acid, approximately 17.2 g (87.8 mmoles) of iodotrifluoromethane was condensed into the reaction. After 5 minutes the cooling bath was removed and the reaction warmed to 0°C and quenched with 50 ml of water. The basic aqueous solution was washed with 500 ml of diethyl ether. The ether solution was extracted with 50 ml of 1N sodium hydroxide and the two aqueous solutions were combined and washed with ether. The basic solution was acidified and extracted three times with 100 ml of diethyl ether. Drying of the organic solution with anhydrous magnesium sulfate followed by filtration and concentration gave a crude solid product. Partial purification was achieved by reprecipitation of the solid product from hot aqueous ethanol to give 3.79 g of slightly impure desired product as a mixture of dark red solid and yellow crystals. Recrystallization of the solid mixture gave 2.18 g (8.58 mmoles, 34% yield) of pure title compound as light yellow needles, m.p. 132-134°C (hexanes).

Analysis: Calculated for $C_5H_3IO_2S$: C, 23.64; H, 1.19%. Found: C, 23.86; H, 1.10%. EIMS (m/z): 254 (M^+, base), 237 (M^+-OH, 79%), 209 (M^+-CO_2H, 5%), 127 (M^+-I, 18%) and 82 (C_4H_2S, 36%); ^{1}HNMR ($CDCl_3$)delta, 7.50 (1H, d, J=3.9Hz) and 7.29 (1H, d, J=3.9Hz); ir ($CHCl_3$): 2977 br, 2565, 1679 and 1410 cm^{-1}.

EXAMPLE 4

5-[(N,N-Dimethylamino)carbonyl]-2-thiophenecarboxylic acid

A 2.39 g (13.04 mmoles) portion of the crude 5-[(N,N-dimethylamino)carbonyl]-2-thiophenecarboxaldehyde was added to a stirred suspension of silver oxide prepared by adding 2.29 g (57.13 mmoles) of sodium hydroxide 5.85 g (34.44 mmoles) of silver nitrate in 100 ml of water. After stirring at ambient temperature for fifteen minutes and filtration through a pad of diatomaceous earth the filtrate was acidified from pH 12 to pH 2 with concentrated hydrochloric acid and extracted with ethyl acetate. The extracts were dried (magnesium sulfate) and concentrated in vacuo to furnish a white solid (2.01 g, 77%). An analytical sample was obtained by trituration with warm ethyl acetate, m.p. 158-159°C.

Analysis: Calculated for $C_8H_9NO_3S$: C, 48.23; H, 4.55; N, 7.03%. Found: C, 48.30; H, 4.42; N, 6.79%. EIMS (m/z): 199 (M^+, 68%), 155 (M^+-$(CH_3)_2N$, base), 111 (M^+-$(CH_3)_2NCO$, 44%); ^{1}HNMR (DMSO-d_6) delta, 7.66 (1H, d, J=4.0Hz), 7.46 (1H, d, J=4.0Hz), 3.09 (6H, s);ir (potassium bromide): 3430, 1710, 1594, 1246 cm^{-1}.

EXAMPLE 5

4-[(N,N-Dimethylamino)carbonyl]-2-thiophenecarboxylic acid

A 1.12 g (6.11 mmoles) portion of the crude 4-[(N,N-dimethylamino)carbonyl]-2-thiophenecarboxaldehyde was added to a stirred suspension of silver oxide prepared by adding 1.08 g (26.90 mmoles) of sodium hydroxide to 2.74 g (16.14 mmoles) of silver nitrate in 40 ml of water. After stirring at ambient temperature for fifteen minutes the mixture was filtered through diatomaceous earth, acidified from pH 12 to pH 2 with concentrated hydrochloric acid and saturated with solid sodium chloride. After extraction with ethyl acetate (3 x 75 ml) the dried (magnesium sulfate) extracts were concentrated in vacuo to a pale yellow crystalline solid (1.10 g, 90%). An analytical sample was obtained by trituration with warm ethyl acetate, m.p. 112-114°C.

Analysis: Calculated for $C_8H_9NO_3S$: C, 48.23; H, 4.55; N, 7.03%. Found: C, 48.07; H, 4.58; N, 6.86%. EIMS (m/z): 199 (M^+, 26%), 181 (M^+-H_2O, 7%), 155 (M^+-$(CH_3)_2N$, base): ^{1}HNMR (DMSO-d_6) delta, 8.09 (1H, d, J=1.8Hz), 7.74 (1H, d, J=1.8Hz), 2.98 (6H, d, J=13.0Hz); ir (potassium bromide): 3388, 1706, 1594, 1250, 1186 cm^{-1}.

EXAMPLE 6

4-Methoxycarbonyl-2-thiophenecarboxylic acid

A stirred solution of methyl 2-formyl-4-thiophenecarboxylate (823 mg, 4.84 mmoles) in 50 ml of acetone was treated dropwise with Jones' reagent (5 ml). Once addition was complete the mixture was stirred at room temperature for 30 minutes, the excess oxidant was decomposed with isopropanol and the mixture filtered through diatomaceous earth. The acetone was removed in vacuo, the residue dissolved in ethyl acetate (30 ml) and the solution dried over magnesium sulfate. Concentration in vacuo furnished an off-white solid (880 mg, 98%). An analytical sample was obtained by trituration with a small amount of ethyl acetate, m.p. 141-143°C.

Analysis: Calculated for $C_7H_6O_4S$: C, 45.15; H, 3.25%. Found: C, 45.09; H, 3.14%. EIMS (m/z): 186 (M^+, 42%), 155 (M^+-CH_3O, base); ^{1}HNMR (DMSO-d_6) delta, 8.59 (1H, d, J=1.2Hz), 7.91 (1H, d, J=1.2Hz), 3.81 (3H, s); ir (potassium bromide): 3419, 1706, 1681 cm^{-1}.

EXAMPLE 7

Methyl 5-(5-Methyl-1,3,4-oxadiazol-2-yl)-2-thiophenecarboxylate

A stirred suspension of 5-methoxycarbonyl-2-thiophenecarboxylic acid hydrazide (548 mg, 2.74 mmoles) and ethyl acetimidate hydrochloride (372 mg, 3.01 mmoles) in 10 ml of pyridine was refluxed for four hours, cooled to room temperature and evaporated in vacuo. The residual oily solid was dissolved in ethyl acetate and washed with water, 1N hydrochloric acid and 5% sodium bicarbonate. The ethyl acetate was dried (magnesium sulfate) and evaporated in vacuo to a pale tan solid (242 mg, 39%), m.p. 142-145°C. This material was used directly without further purification. Exact Mass: 224.0253,

Calculated: 224.0256; EIMS (m/z): 224 (M^+, base), 193 (M^+ -CH_3O, 33%), 169 ($C_7H_5O_3S$, 83%); ^{1}HNMR (DMSO-d_6) delta, 7.88 (1H, d, J=3.9Hz), 7.80 (1H, d, J=3.9Hz), 3.87 (3H, s), 2.58 (3H, s); ir (potassium bromide): 1705, 1571, 1291, 1101, 751 cm^{-1}.

EXAMPLE 8

5-(5-Methyl-1,3,4-oxadiazol-2-yl)-2-thiophenecarboxylic acid

A mixture of methyl 5-(5-methyl-1,3,4-oxadiazol-2-yl)-2-thiophenecarboxylate (100 mg, 0.45 mmoles) in 3 ml of 2N sodium hydroxide was diluted with 1 ml of methanol and stirred at room temperature for 2 hours. The solution was filtered to remove some trace insolubles and acidified to pH 3 with concentrated hydrochloric acid. The precipitate was collected and air dried to furnish a pale yellow solid (67 mg, 71%), m.p. 281-284°C.

Analysis: Calculated for $C_8H_6N_2O_3S$: C, 45.70; H, 2.88; N, 13.33%. Found: C, 45.81; H, 2.81; N, 13.26%. EIMS (m/z): 210 (M^+, base), 193 (M^+ -OH, 3%), 168 (unknown, 8%), 155 ($C_6H_3O_3S$, 56%); ^{1}HNMR (DMSO-d_6) delta, 7.79 (1H, d, J=3.9Hz), 7.77 (1H, d, J=3.9Hz), 2.57 (3H, s); ir (potassium bromide): 3443, 1693, 1599, 1574, 1264, 744 cm^{-1}.

EXAMPLE 9

Methyl 4-(2-methylthiazol-4-yl)-2-thiophenecarboxylate monohydrobromide

A solution of methyl 4-bromoacetyl-2-thiophenecarboxylate (398 mg, 1.51 mmoles) and thioacetamide (125 mg, 1.66 mmoles) in 15 ml of acetone was refluxed for 2 hours. The mixture was cooled to room temperature, filtered and the residue dried in vacuo to yield a white solid (375 mg, 77%), m.p. 224-225°C.

Analysis: Calculated for $C_{10}H_9NO_2S_2$.HBr: C, 37.50; H, 3.15; N, 4.36%. Found: C, 37.53; H, 3.09; N, 4.28%. EIMS (m/z): 239 (M^+, base), 208 (M^+ -CH_3O, 65%), 198 (M^+ -C_2H_3N, 76%); ^{1}HNMR (DMSO-d_6) delta, 8.25 (1H, d, J=1.5Hz), 8.22 (1H, d, J=1.5Hz), 7.98 (1H, s), 5.98 (exchangeable), 3.82 (3H, s), 2.68 (3H, s); ir (potassium bromide): 3091, 1703, 1285 cm^{-1}.

EXAMPLE 10

4-(2-Methylthiazol-4-yl)-2-thiophenecarboxylic acid

A mixture of methyl 4-(2-methylthiazol-4-yl)-2-thiophenecarboxylate monohydrobromide, prepared according to Example 9, (3.20 g, 10.0 mmoles) in 50 ml of 2N sodium hydroxide was diluted with 15 ml of methanol and refluxed for 1 hour. The methanol was removed in vacuo and the residual aqueous solution was acidified to pH 3 with concentrated hydrochloric acid. The mixture was extracted with ethyl acetate (3 x 50 ml) and the dried (magnesium sulfate) extracts were concentrated to a white solid (2.12 g, 94%). An analytical sample was obtained by trituration with warm ethyl acetate, m.p. 195-197°C.

Analysis: Calculated for $C_9H_7NO_2S_2$; C, 47.98; H, 3.13; N, 6.22%. Found: C, 47.84; H, 3.01; N, 6.14%. EIMS (m/z): 225 (M^+, base), 208 (M^+ -OH, 1%), 184 (M^+ -C_2H_3N, 90%); ir (potassium bromide): 3103, 1676, 1284 cm^{-1}.

EXAMPLE 11

Methyl 5-(5-methyl-1,2,4-oxadiazol-3-yl)-2-thiophenecarboxylate

A stirred mixture of methyl 5-(N-hydroxy)carboximidamido-2-thiophenecarboxylate (734 mg, 3.67 mmoles) and acetic anhydride (1.12 g, 11.0 mmoles) in 25 ml of toluene was refluxed for 24 hours. The solvent was removed in vacuo and the residue triturated with a small portion of toluene to furnish an off-white solid (547 mg, 67%), m.p. 134-136°C. EIMS (m/z): 224 (M^+, 99%), 193 (M^+ -CH_3O, base), 183 (M^+ -C_2H_3N, 58%), 152 ($C_6H_2NO_2S$, 89%); ^{1}HNMR (DMSO-d_6) delta, 7.77 (1H, d, J=4.0Hz), 7.69 (1H, d, J=4.0Hz), 3.89 (3H), 2.64 (3H, s); ir (potassium bromide): 1720, 1597 and 887 cm^{-1}. This material was used directly without further purification.

EXAMPLE 12

5-(5-Methyl-1,2,4-oxadiazol-3-yl)-2-thiophenecarboxylic acid

A mixture of methyl 5-(5-methyl-1,2,4-oxadiazol-3-yl)-2-thiophenecarboxylate, prepared according to Example 11, (86 mg, 0.38 mmoles) in 3 ml of 2N sodium hydroxide was diluted with 1 ml of methanol and warmed to 60°C for 10 minutes. The solution was cooled to room temperature, diluted with 2 ml of water and acidified to pH 2 with concentrated hydrochloric acid. After standing for 30 minutes the fluffy crystalline solid which slowly separated was collected by filtration and dried in vacuo to furnish the title compound (45 mg, 56%), m.p. 218-220°C.

Analysis: Calculated for $C_8H_6N_2O_3S$: C, 45.70; H, 2.88; N, 13.33%. Found: C, 45.69; H, 2.81; N, 13.06%. EIMS (m/z): 210 (M^+, 89%), 169 (M^+ -C_2H_3N, base), 152 ($C_6H_2NO_2S$, 27%) ^{1}HNMR (DMSO-d_6) delta, 7.77 (2H, s), 2.65 (3H, s); ir (potassium bromide): 3429, 1668 and 889 cm^{-1}.

EXAMPLE 13

Methyl 5-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)-2-thiophenecarboxylate

A stirred mixture of methyl 5-(N-hydroxy)carboximidamido-2-thiophenecarboxylate (833 mg, 4.16 mmoles) and trifluoroacetic anhydride (2.62 g, 12.48 mmoles) in 25 ml of toluene was refluxed for one hour. The solvent was evaporated in vacuo, the residue triturated with a small portion of toluene and filtered to furnish a white crystalline solid (440 mg, 35%), m.p. 126-127°C. The product was used directly without further purification. Exact Mass: 277.9998; Calculated: 277.9974; EIMS (m/z): 278 (M^+, 67%), 247 (M^+ -CH_3O, base), 152 ($C_6H_2NO_2S$, 41%); ^{1}HNMR ($CDCl_3$) delta, 7.81 (2H, s), 3.91 (3H, s); ir (potassium bromide): 1712, 1255, 912 cm^{-1}.

EXAMPLE 14

5-(5-Trifluoromethyl-1,2,4-oxadiazol-3-yl)-2-thiophenecarboxylic acid

A mixture of methyl 5-(5-trifluoromethyl-1,2,4-oxadiazol-3-yl)-2-thiophene-

carboxylate, prepared according to Example 13, (100 mg, 0.36 mmoles) in 3 ml of 2N sodium hydroxide was diluted with 1 ml of methanol and warmed to 50°C for ten minutes. The solution was cooled to room temperature, diluted with 3 ml of water and acidified to pH 2 with concentrated hydrochloric acid. After standing for one hour the off-white crystalline solid (41 mg, 43%) was collected by filtration and dried in vacuo, m.p. 175-177°C.

Analysis: Calculated for $C_8H_3F_3N_2O_3S$: C, 36.37; H, 1.14; N, 10.61%. Found: 36.65; H, 1.18; N, 10.24%. EIMS (m/z): 264 (M^+, base), 247 (M^+ -OH, 43%), 169 (M^+ -C_2F_3N, 24%); ^{1}HNMR (DMSO-d_6) delta, 7.94 (1H, d, J=4.0Hz), 7.83 (1H, d, J=4.0Hz); ir (potassium bromide): 3430 br, 1661, 1208, 847 cm^{-1}.

EXAMPLE 15

Methyl 4-(thiazol-4-yl)-2-thiophenecarboxylate hydrobromide

A solution of methyl 4-(bromoacetyl)-2-thiophenecarboxylate (1.25 g, 4.75 mmoles) and thioformamide (436 mg, 7.13 mmoles) in 35 ml of acetone was refluxed for one hour. The mixture was cooled slightly and filtered to furnish a yellow solid (941 mg, 65%). The analytical sample was recrystallized from ethanol, m.p. 201-202°C.

Analysis: Calculated for $C_9H_7NO_2S_2$.HBr: C, 35.30; H, 2.63; N, 4.58%. Found: C, 35.31; H, 2.60; N, 4.48%. EIMS (m/z): 225 (M^+, base), 194 (M^+ -CH_3O, 92%), 167 ($C_8H_7O_2S$, 25%); ^{1}HNMR (DMSO-d_6) delta, 9.18 (1H, d, J=1.7Hz), 8.31 (1H, d, J=1.2Hz), 8.30 (1H, d, J=1.2Hz), 8.21 (1H, d, J=1.7Hz), 4.50 (1H, exchangeable), 3.85 (3H, s); ir (potassium bromide): 3054, 1711, 1272, 778 cm^{-1}.

EXAMPLE 16

4-(Thiazol-4-yl)-2-thiophenecarboxylic acid

A mixture of methyl 4-(thiazol-4-yl)-2-thiophenecarboxylate hydrobromide, prepared according to Example 15, (500 mg, 1.63 mmoles) in 8 ml of 2N sodium hydroxide was diluted with 1 ml of methanol and refluxed for thirty minutes. The methanol was removed in vacuo and the residual aqueous solution was acidified to pH 2 with concentrated hydrochloric acid. The mixture was extracted with ethyl acetate and the dried (magnesium sulfate) extracts were concentrated to a pale yellow solid (318 mg, 92%), m.p. 183-185°C.

Analysis: Calculated for $C_8H_5NO_2S_2$: C, 45.48; H, 2.39; N, 6.63%. Found: C, 45.42; H, 2.29; N, 6.46%. EIMS (m/z): 211 (M^+, base), 194 (M^+ -OH, 23%) and 184 ($C_7H_4O_2S_2$, 80%); ^{1}HNMR (DMSO-d_6)delta, 9.16 (1H, d, J=1.2Hz), 8.23 (2H, br s), 8.16 (1H, d, J=1.2Hz); ir (potassium bromide): 3440 br, 3110, 1691, 1285 cm^{-1}.

EXAMPLE 17

5-(N,N-Dimethylaminosulfonyl)-2-thiophenecarboxylic acid

Lithium diisopropylamide was prepared by slowly adding 10.5 ml (26.3 mmoles) of 2.5M n-butyllithium in hexanes to a cooled (2-propanol/dry ice) tetrahydrofuran (200 ml) solution of diisopropylamine (5.0 ml, 35.7 mmoles) with the reaction temperature

maintained below -60°C. After 5 minutes the reaction solution was warmed to room temperature for 30 minutes and then cooled to below -70°C again. A 100 ml tetrahydrofuran solution of 3.4 g (17.8 mmoles) of 2-(N,N-dimethylaminosulfonyl)thiophene (prepared according to Slocum, D.W., et al., JOC 38, 4189 (1973)) was added slowly with the reaction temperature controlled below -70°C. After complete addition the reaction was stirred for 30 minutes and then excess carbon dioxide was bubbled through the solution. The solution was then warmed to 0°C and quenched with 50 ml of 1N sodium hydroxide. A 300 ml portion of diethyl ether was added to the aqueous tetrahydrofuran solution and the phases were separated in a separatory funnel. The organic layer was extracted with 50 ml of 1N sodium hydroxide. Both basic aqueous solutions were combined, washed with 50 ml of diethyl ether and acidified with concentrated hydrochloric acid. The acidic aqueous mixture was extracted with diethyl ether (2 x 100 ml). The ether solution was washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo to 3.66 g (15.6 mmoles) of desired thiophenecarboxylic acid as a colorless solid, m.p. 184-186°C (lit. m.p.=170-172°C). Total yield was 87%.

EXAMPLE 18

Methyl 5-(3-methyl-1,2,4-oxadiazo-5-yl)-2-thiophenecarboxylate

A stirred suspension of 5-methoxycarbonyl-2-thiophenecarboxylic acid (1.50 g, 8.06 mmole) in 15 ml of thionyl chloride was refluxed for two hours. The solution was cooled to room temperature and concentrated in vacuo to an almost colorless oil which crystallized under vacuum. This solid was dissolved in 5 ml of chloroform and added dropwise at room temperature to a stirred mixture of acetamide oxime (prepared according to Eloy, et al., Helv. Chim. Acta., 45, 441 (1962)) (657 mg, 8.86 mmole) and triethylamine (897 mg, 1.24 ml, 8.86 mmole) in 30 ml of chloroform. Once addition was complete the solution was stirred at room temperature for one hour and washed with water (2 x 20 ml). The organic layer was dried (magnesium sulfate), evaporated and the residue triturated with toluene to furnish the intermediate O-(2-methoxycarbonyl-5-thenoyl)acetamide oxime, 1.55 g (80% yield), as a white solid, m.p. 150-152°C. ^{1}H-NMR (DMSO-d_6) delta, 8.03 (1H, d, J=3.9Hz), 7.83 (1H, d, J=3.9Hz), 6.54 (br s, exchangeable), 3.85 (3H, s) and 1.80 (3H, s). This material was used without additional purification.

A 1.43 g (5.90 mmole) portion of O-(2-methoxycarbonyl-5-thenoyl)acetamide oxime was suspended in 75 ml of toluene and warmed to reflux overnight. The solvent was removed in vacuo and the residue triturated with a small portion of toluene to furnish 1.10 g (83%) of the title compound as an off-white crystalline solid, m.p. 154-156°C. This material was used directly without further purification. Exact Mass: 224.0241, Calculated: 224.0256. EIMS (m/z): 224 (M^+, 98%) and 193 (M^+ -CH_3O, base; ^{1}H-NMR (DMSO-d_6) delta, 8.01 (1H, d, J=4.3Hz), 7.92 (1H, d, J=4.3Hz), 3.88 (3H, s) and 2.41 (3H, s).

EXAMPLE 19

5-(3-Methyl-1,2,4-oxadiazo-5-yl)-2-thiophenecarboxylic acid

A mixture of methyl 5-(3-methyl-1,2,4-oxadiazol-5-yl)-2-thiophenecarboxylate, prepared according to Example 18, (1.09 g, 4.86 mmole) in 35 ml of 2N sodium hydroxide was diluted with 5 ml of ethanol and warmed to 65°C for thirty minutes. The solution was cooled in an ice bath and acidified to pH 2 with concentrated hydrochloric acid. Filtration and drying furnished 870 mg (85% yield) of the title compound as an off-white solid. The analytical sample was recrystallized from methanol, m.p. 226-228°C.

Analysis: Calculated for $C_8H_6N_2O_3S$: C, 45.70; H, 2.88; N, 13.33%. Found: C, 45.57; H, 2.75; N, 13.37%. EIMS (m/z): 210 (M^+, base) and 153 ($M^+ - C_2H_3NO$, 99%); ^{1}H-NMR (DMSO-d_6) delta, 7.97 (1H, d, J=3.9Hz), 7.82 (1H, d, J=3.9Hz) and 2.40 (3H, s); ir (potassium bromide): 3112 (br), 1699, 1289, 1112 and 840 cm^{-1}.

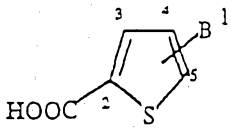
EXAMPLE 20

4-Methylthio-2-thiophenecarboxylic acid

Lithium diisopropylamide was prepared by slowly adding 31.0 ml (77.5 mmoles) 2.5M n-butyllithium in hexanes to a cooled (2-propanol/dry ice) tetrahydrofuran (200 ml) solution of diisopropylamine (11.0 ml, 78.5 mmoles) with the reaction temperature maintained below -60°C. After 15 minutes the reaction solution was warmed to room temperature for 30 minutes and then cooled to below -70°C again. A 100 ml tetrahydrofuran solution of 9.9 g (76.0 mmoles) of 3-methylthiothiophene (prepared according to Henrio, G., et al., Tetrahedron 33, 191 (1977)) was added slowly with the reaction temperature controlled below -70°C. After complete addition the reaction was stirred for 15 minutes and then excess carbon dioxide was bubbled through the solution. The solution was then warmed to 10°C and quenched with 100 ml of water. After stirring for a few minutes the reaction mixture was poured into a separatory funnel and extracted with a 500 ml portion of diethyl ether. The organic layer was extracted with 100 ml of 1N sodium hydroxide; both basic aqueous solutions were then combined, washed with 100 ml of diethyl ether and acidified with concentrated hydrochloric acid. The acidic aqueous mixture was then extracted with diethyl ether (2 x 250 ml). The ether solution was washed with brine, dried over magnesium sulfate, filtered and concentrated in vacuo to 11.75 g (67.4 mmoles) of yellow solid which NMR showed to be a 3:2 mixture of isomers (4- vs. 3-) of desired thiophenecarboxylic acid. This crude product was stirred in a 50 ml portion of diethyl ether for thirty minutes, then filtered, and the filtrate concentrated in vacuo to 8.68 g (49.8 mmoles) of solid which contained greater than 80% (estimated by NMR) of the desired 4-methylthio-2-thiophenecarboxylic acid. Recrystallization from chloroform afforded 4.11 g (23.6 mmoles) of pale yellow solid, m.p. 118-120°C (lit. m.p. 123-124°C), which was 95% 4-methylthio-2-thiophenecarboxylic acid (purity estimated by NMR). Total yield was 31%.

The claims defining the invention are as follows:

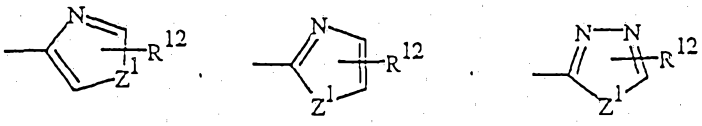
1. A compound of the formula

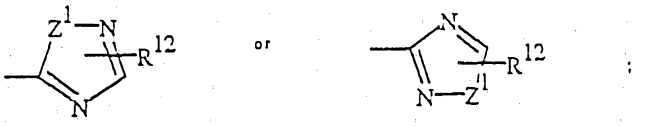


(I)

and the salts thereof

wherein B^1 is at the 4 position and is SOR^{16} or $COOCH_3$, or B^1 is at the 5 position and is SO_2NHCH_3, or B^1 is at the 4 or 5 position and is $CON(CH_3)_2$,





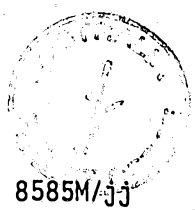
Z^1 is O or S; R^{12} is H, F, Cl, Br, CF_3 or (C_1-C_6)alkyl; and R^{16} is (C_1-C_4)alkyl.

2. A process of preparing a thiophene carboxylic acid derivative according to claim 1 which process is substantially as herein described with reference to any one of the Examples.

DATED this NINTH day of NOVEMBER 1992

Pfizer Inc.

Patent Attorneys for the Applicant
SPRUSON & FERGUSON

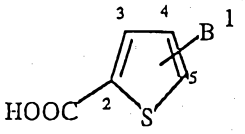


THIOPHENE CARBOXYLIC ACID INTERMEDIATES

Abstract

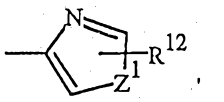
This invention relates to certain novel thiophene carboxylic acids useful as intermediates in the preparation of 3-substituted-2-oxindole derivatives.

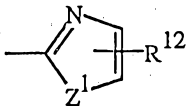
A compound of the formula

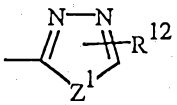


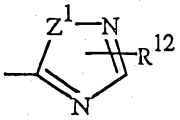
(I)

and the salts thereof wherein B^1 is at the 4 position and is SOR^{16} or $COOCH_3$, or B^1 is at the 5 position and is SO_2NHCH_3, or B^1 is at the 4 or 5 position and is $CON(CH_3)_2$,

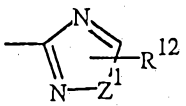








or



;

Z^1 is O or S; R^{12} is H, F, Cl, Br, CF_3 or $(C_1\text{-}C_6)$alkyl; and R^{16} is $(C_1\text{-}C_4)$alkyl.