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Synthesis, Antifungal and Antibacterial Activity of Substituted 4,5-Dicarbomethoxy-1,3-dithioles

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ABSTRACT

The title compounds are prepared from the reaction of 4,5-dicarbomethoxy-1,3-dithiolyltributylphosphonium tetraflouroborate and aromatic aldehydes in the presence of triethylamine. Antifungal and antibacterial effects of the final compounds are reported.

Key Words: Substituted 4,5-dicarbomethoxy-1,3-dithioles, 1,3-Dithiole, Antifungal, Antibacterial.

INTRODUCTION

Recently compounds that act as π-electron donors have received considerable attention in the context of the preparation of organic conductors (1-4). In particular, the modification of 1,3-Dithiole derivatives have been popular because they are structural components of many organic superconductors (5-7). Because one of the important property of an antibiotic should be a good π-electron and considering biological importance of imidazole, nitroimidazole, quinoline, indole, thiophen and furan (8,9), it was decided to attach these two groups and prepare new substituted 4,5-dicarbomethoxy-1,3-di-thioles as possible effective drugs against tropical diseases.

MATERIALS AND METHODS

Melting points were taken on a Kofler hot stage apparatus and are uncorrected. The UV spectra were recorded on Perkin-Elmer 550 SE spectrophotometer. The IR spectra were obtained using a Nicolet FT-IR Magna 550. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Burker FT-80 spectrometer and chemical shifts (δ) are in ppm relative to internal TMS.The mass spectra were run on a Finigan Model MAT MS-311 spectrometer at 70 eV. All compounds gave satisfactory C, H, N analysis within ±0.4% of theoretical values.

2-(1-Methyl-2-imidazolylmethylidene)-4,5-dicarbomethoxy-1,3-dithiole (6a).

To a stirred solution of 4,5-dicarbo-methoxy-1,3-dithiolyltributylphosphonium tetrafluoroborate (1g,1.9 mmoles) under nitrogen gas and 1-methyl-2-imidazole carboxaldehyde (0.209 g, 1.9 mmoles) (10) in tetrahydrofuran at room temperature, triethylamine (1 ml) was added. The solution became orange. The mixture was stirred for 15 minutes. The solvent was evaporated and the residue was crystallized from n-hexane to give 0.42 g (71%) of 6a, mp 148-150°C.

^{1}H-NMR ($CDCl_3$): δ 7.20 (s, 1H, imidazole), 6.8 (s,1H, H_5-imidazole),6.35 (s, 1H, -CH=) and 3.85 ppm (s, 6H, OCH_3).

^{13}C NMR ($CDCl_3$): δ159.8 (C=O), 144 (C_2-imidazole),136 (C_2-dithiole), 133 (C_4 and C_5 -dithiole), 128.35 (C_4-imidazole), 119.9 (C_5-imidazole), 53 and 54 (OCH_3), 98 (-H=), and 32 ppm (CH_3N).

MS: m/z (%) 312 (M^+, 10), 297 (11), 285 (24), 232 (10), 219 (100), 170 (58), 106 (18), 92 (99), 78 (62).

IR (film): ν_{max} 3100 (C-H imidazole), 1749 (C=O), 1697 (C=O),and 1602 cm^{-1} (C=C aromatic).

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UV(Ethanol): λ_{max} 330 nm (log ε = 4.25).

Compounds 6b to 6k were prepared similarly, the physical and spectral data are as the following:

2-(1-Methyl-5-nitro-2-imidazolyl-methylidene)-4,5-dicarbomethoxy-1,3-dithiole (6b).

Yield: 75%, mp: 110-111°C.

^{1}H-NMR ($CDCl_3$): δ 8.15(s, 1H, H_4-imidazole), 6.35 (s, 1H, -CH=), 3.90 (s, 3H, $COOCH_3$), 3.85 (s, 3H, $COOCH_3$), and 3.80 ppm (s, 3H, NCH_3).

MS: m/z (%) 357 (M^+,100), 341 (5), 327 (51), 299 (30), 270 (72), 257 (11), 243 (26), 219 (44), 137 (13), 96 (38), 90 (17). 85 (27), 69 (41), 59 (55), 46 (28).

IR (film): ν_{max} 3120 (C_4-H imidazole), 1750 (C=O),1698 (C=O), 1653 (C=C aromatic), 1540 (NO_2), 1440 (C=C aromatic), and 1330 cm^{-1}(NO_2).

UV (Ethanol): λ_{max} 305.4 nm (logε=5.69).

2 - (2 - Quinolylmethylidene) -4,5-dicarbomethoxy-1,3-dithiole (6c):

Yield: 80%, mp: 150-152°C

^{1}H-NMR ($CDCl_3$):δ 7.70 (m,6H, quinoline), 6.67 (s, 1H, -CH=), 3.93 (s, 3H, $COOCH_3$) and 3.67 ppm (s, 3H, $COOCH_3$).

MS: m/z (%) 359 (M^+, 11), 299 (10), 218 (15), 189 (100), 105 (15), 92 (98), 78 (65).

IR (film): ν_{max} 3150 (C-H quinoline), 1750 (C=O), 1696 (C=O),and 1645 cm^{-1}(C=C aromatic).

UV (Ethanol): λ_{max} 396 (logε=4.01), 335.5 (logε=3.36), 321.5 (logε=3.48), 295 (logε = 3.78) and 226 nm (logε=4.27).

2 - (3 - Indolylmethylidene) -4, 5 - dicarbomethoxy-1,3-dithiole (6d):

Yield: 66%, mp: 101-104°C

^{1}H-NMR ($CDCl_3$): δ 8.27 (m, 1H, H_2-indole),7.3 (m,4H, Indole),6.51(s,1H,-CH=), 3.84 (s, 3H, $COOCH_3$) and 3.78 ppm (s, 3H, $COOCH_3$).

^{13}C-NMR(CDCl3): δ 159.51 (C=O), 137.19 (C_4 and C_5-dithiole), 136.61 (C_8 and C_9-indole) , 131.51 (C_2 - dithiole), 123.96 (C_2-indole) , 122.57 (C_6-indole), 121.54 (C_4-indole), 112 (-CH=) and 53.59 ppm (OCH_3).

MS: m/z (%) 347 (M^+, 100), 173 (75), 172 (32), 129 (53), 116 (21), 59 (97).

IR (film): ν_{max} 3413 (N-H indole), 3125 (C-H indole), 1754 (C=O), 1705 (C=O), 1661 (C=C aromatic) and 1441 cm^{-1}(C=C aromatic).

UV (Ethanol): λ_{max} 296.4 (logε=3.47),and 242.6 nm (logε=3.64).

2 - (2 -Thienylmethylidene) -4, 5-dicarbomethoxy-1,3-dithiole (6e):

Yield: 78%, mp: 74-76°C

^{1}H - NMR ($CDCl_3$) : δ 7.29 (d , 1H, H_5-thiophen, J=5.2 Hz), 7.04 (t, 1H, H_4-thiophen, J=4Hz), 6.90 (d, 1H, H_3-thiophen, J=4 Hz), 6.66 (s, 1H,-CH=), 3.86 (s, 3H, $COOCH_3$) and 3.85 ppm (s, 3H, $COOCH_3$).

MS: m/z (%) 314 (M^+, 100), 283 (15), 256 (10), 219 (15), 140 (55), 59 (10).

IR (film): ν_{max} 3110 (C-H thiophen), 1770 (C=O), 1741 (C=O),and 1688 cm^{-1} (C=C). V (Ethanol): λ_{max} 328.4 (logε=4.88),and 240.2 nm (logε=4.23).

2 - (2 - Furylmethylidene) - 4, 5-dicarbomethoxy-1,3-dithiole (6f):

Yield: 62%, mp: 72-73°C

^{1}H-NMR ($CDCl_3$): δ 7.44 (d, 1H, H_5-furan, J=2.4 Hz), 6.43 (q, 1H, H_4-furan, J=3.2, 2.4 Hz), 6.33 (s, 1H, -CH=), 6.14 (d, 1H, H_3-furan, J=3.2 Hz), 3.86 (s, 3H, $COOCH_3$) and 3.85 ppm (s, 3H, $COOCH_3$).

^{13}C-NMR ($CDCl_3$): δ 159.7 (C=O), 153 (C_2-furyl), 141.57 (C_5-furyl), 111.64 (C_4-furyl), 106 (C_6-furyl), 103.64 (-CH=) and 53.16 ppm (OCH_3).

MS: m/z (%) 298 (M^+, 100), 240 (12),179 (10).

IR (film): ν_{max} 3160 (C-H furan), 2946 (C-H methoxy), 1758 (C=O), 1715 (C=O), 1650 (C=C), 1430 (C=C aromatic), 880 and 730 cm^{-1}(C-H furan).

UV (Ethanol): λ_{max} 326.8 (logε=4.19), and 239 nm (logε=4.29).

2-(5-Chloro-2-nitrobenzylidene)-4,5-dicarbomethoxy-1,3-dithiole (6g):

Yield: 73%, mp: 100-102°C

^{1}H-NMR ($CDCl_3$): δ 7.92 (ABq, 2H, H_3 and H_4-phenyl), 7.41 (m, 1H, H_6-phenyl), 6.21 (s, 1H, -CH=), 3.87 (s, 3H, $COOCH_3$) and 3.84 ppm (s, 3H, $COOCH_3$).

MS: m/z (%) 389 (M^+, 3), 387 (M^+, 9), 247 (10), 219 (3), 157 (19), 155 (57), 127 (34), 125 (100), 111 (43), 90 (67), 75 (59), 59(98).

IR (film): ν_{max} 3120 (C-H phenyl), 1771 (C=O), 1741(C=O), 1602 (C=C aromatic), 1507 (NO_2), 1430 (C=C aromatic), 906 and 818 cm^{-1}(C-H phenyl).

UV (Ethanol): λ_{max} 205.8 nm (logε=4.15).

2-(5-Fluoro-2-nitrobenzylidene)-4,5-dicarbomethoxy-1,3-dithiole (6h):

Yield: 74%, mp: 135-138°C

^{1}H-NMR ($CDCl_3$): δ 8.15 (m, 2H, H_3 and H_4-phenyl), 7.45 (d, 1H, H_6-phenyl), 7.15 (s, 1H, -CH=), 3.87 (s, 3H, $COOCH_3$) and 3.84 ppm (s, 3H, $COOCH_3$).

^{13}C-NMR(CDCl3): δ 166.22 (C_5-phenyl) ,159.22 and 159.54 (C=O), 143(C_2-phenyl), 139 (C_2-dithiole), 134.78 (C_1-phenyl), 132.5 (C_4 and C_5-dithiole), 128.2 (C_3-phenyl), 114.6 (C_6-phenyl), 114.2 (C_4-phenyl), 113 (C_6-phenyl), 108(-CH=), 53.27 and 53.41 ppm (OCH_3).

MS: m/z (%) 371 (M^+, 26), 354 (21), 340 (12), 313 (10), 247 (30), 219 (39), 185 (18), 165 (12), 153 (13), 137 (41), 110 (28), 109 (100), 76 (25), 59 (60).

IR (film) : ν_{max} 3110(C-H phenyl), 3030(C-H phenyl), 2966(C-H methoxy), 1756 (C=O), 1719 (C=O), 1590 (C=C aromatic), 1520 (NO_2),1430 (C=C aromatic) and 1350 cm^{-1} (NO_2).

UV (Ethanol): λ_{max} 210 nm (logε=4.02).

2-(2,4-Dichlorobenzylidene)-4,5-dicarbomethoxy-1,3-dithiole (6i):

Yield: 79%, mp: 117-119°C

^{1}H-NMR ($CDCl_3$):δ 7.40 (m, 1H, H_3-phenyl), 7.30 (m, 2H, H_5 and H_6-phenyl) ,6.64 (s, 1H, -CH=), 3.87 (s, 3H, $COOCH_3$) and 3.84 ppm (s, 3H, $COOCH_3$).

MS: m/z (%) 380 (M^+, 14), 379 (M^+, 15), 378 (M^+, 88), 376 (M^+, 100), 345 (10), 257 (12), 202 (20), 59(10).

IR (film): ν_{max} 3120 (C-H phenyl), 1772 (C=O), 1745 (C=O), 1650 (C=C), 1430 cm^{-1} (C=C aromatic).

UV (Ethanol): λ_{max} 337.5 nm (logε=3.37).

2-(3 - Fluorobenzylidene) - 4 , 5 - dicarbomethoxy-1,3-dithiole (6j):

Yield: 69%, mp: 83-85°C

^{1}H-NMR ($CDCl_3$): δ 7.32 (td, 1H, H_2-phenyl, J_t=8, J_d=6 Hz), 6.99 (qd, 1H, H_3-phenyl, J_q=0.8, J_d=8 Hz), 6.91 (m, 2H,H_5 and H_6-phenyl),6.4(s,1H,-CH=),3.85 (s,3H, $COOCH_3$), and 3.84 ppm (s ,3H,$COOCH_3$).

^{13}C-NMR($CDCl_3$):δ 164.2 (C_3-phenyl), 159.5(C=O), 140.5 (C_2-dithiole), 132.2(C_4 and C_5-dithiole) ,129.7 (C_5-phenyl), 122.5 (C_6-phenyl), 114.1 (C_2-phenyl), 113.7 (C_4-phenyl), 113.2 (-CH=) and 53 ppm (OCH_3).

MS: m/z (%) 326 (M^+, 100), 295 (15), 167 (12), 207 (15) ,183 (10), 152 (25), 107 (21), 59 (10).

IR(film):ν_{max} 3070 (C-H phenyl), 3010 (C-H phenyl), 1749 (C=O), 1698 (C=O), 1597 (C=C aromatic), 891, 771 and 684 cm^{-1}(C-H phenyl).

UV(Ethanol): λ_{max} 326.8 (logε=4.19), 239.4 nm (logε=4.29).

2- (2, 4-Dimethoxybenzylidene) -4, 5-dicarbomethoxy-1,3-dithiole (6k):

Yield :69%, mp: 83-85°C

^{1}H-NMR($CDCl_3$):δ 7.15(d,1H, H_6-phenyl, J=8.16 Hz), 6.50 (m, 2H, H_3 and H_5-phenyl), 4.52 (s, 1H, -CH=), 3.90 (s, 1H, $COOCH_3$), 3.87 (s, 1H, $COOCH_3$), 3.84 (s, 1H, OCH_3) and 3.80 ppm (s, 1H, OCH_3).

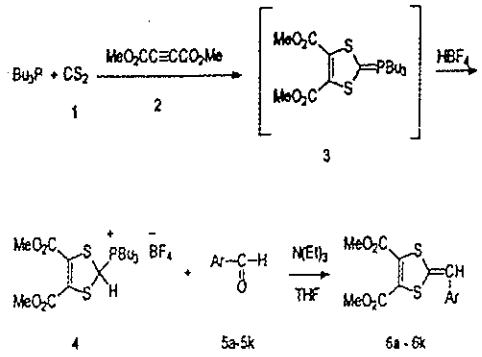
MS: m/z (%) 368 (M^+,80),353 (15),310 (10), 232 (65),194 (21), 151 (24),136 (17),58 (26).

IR(film):ν_{max}3115(C-H phenyl),1771(C=O) 1741(C=O) , 1617 (C=C aromatic) and 1287 cm^{-1}(=C-O-C-).

UV (Ethanol): λ_{max} 330.8 nm (4.09).

Antibacterial and Antifungal assay:

All compounds were tested against Bacillus subtilis (ATCC 6633), Staphylococcus aureus (ATCC 6538), Escherichia coli (endemic), Klebsiela pneumonia (ATCC 10031), Pseu-domonas aeruginosa (ATCC 27853), Sta-phylococcus epidermidis (ATCC 12228), Candida albicans (10231) and Aspergillus niger (ATCC 16404).



Scheme 1. a=1-methyl-2-imidazolyl; b=1-methyl-5-nitro-2-imidazolyl; c= 2-quinolyl; d= 3-indolyl; e=2-thienyl; f=2-furyl; g= 5-chloro-2-nitrophenyl; h= 5-fluoro-2-nitrophenyl; i= 2,4-dichlorophenyl; j= 3-fluorophenyl; k= 2,4-dimethoxyphenyl.

For antibacterial assay compounds 6a to 6k were dissolved in acetone. They were diluted to 1 mg/ml concentration. To standard paper disk of 6 mm diameter the latter solution was added until the desired amount of compound was absorbed by the disk. The disks were placed on inoculated assay medium surface. Miconazole and Gentamycin were used for comparison (Table 1).

RESULTS AND DISCUSSION

Several methods exist for the preparation of 1,3-dithiole derivatives (11). However we developed a new method for the preparation of the titled compounds according to Scheme 1 (12). The reaction of carbon disulfide (1) with dimethyl acetylenedicarboxylate (2) in the presence of tributylphosphine and fluoroboric acid etherate at -65°C afforded 4,5-dicarbomethoxy-1 ,3 - dithiolyl tributylphosphonium tetrafluoroborate (4). The reaction of aromatic aldehyde 5 with compound 4 in the presence of triethylamine at room temperature under nitrogen gave the dithiafulvene 6 in moderate to good yield. The antibacterial and antifungal activities of compound were determined. Compounds 6g and 6h were active against S. aureus and E. coli (see Table 1).

Table 1: Antibacterial and antifungal activities of compounds 6g & 6h.

Microorganism	Compund No.	Concentration (µg/disk)	Average zone (mm)
S.Aureus	6g	30	13
		60	16
		90	19
	6h	30	11
		60	13
		90	16
	gentamycin	10	18
E.coli	6g	90	8
	6h	90	9
	gentamycin	10	17

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