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Synthesis and Antimicrobial Activity of Ethyl-2-chloro-4-substituted 6-(4-Methoxybenzoyl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylates

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Ethyl-2-chloro-6-(4-methoxybenzoyl)-4*H*-thieno[2,3-*b*]pyrrole-5-carboxylate (**3**) has been prepared by refluxing a mixture of 2-chlorothieno[2,3-*b*]pyrrole-5-carboxylate, 4-methoxy benzoylchloride and $TiCl_4$ in dichloromethane. Ethyl-2-chloro-4-substituted 6-(4-methoxybenzoyl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylates (**4a-e**) were synthesized in good yields by treating **3** with ethyl chloroformate at cold conditions in presence of 60 % sodium hydride in DMF. All the compounds synthesized were characterized on the basis of their IR, ^{1}H NMR and mass spectral data and screened for their antimicrobial activity.

Key Words: Thienopyrrole, Methoxybenzoylchloride, Titanium tetrachloride, Antimicrobial activity.

INTRODUCTION

Thienopyrroles are pharmaceutically important compounds because they are isosteric with indole. Furthermore, the development of the synthesis of electroconducting polymers based on heteroaromatic monomers has stimulated a search for the efficient synthesis of thienopyrrole derivatives[1]. The synthesis of thienopyrroles, analogs of amino acid tryptophan is of particular interest because of the possibility that the greater chemical reactivity of the thienopyrrole nucleus, as compared to the indole nucleus, might greatly alter the biochemical function of a peptide containing a unit of the new amino acid in a position normally occupied by a tryptophan residue[2]. Thieno [3,2-*b*]pyrroles are a novel class of allosteric inhibitors of HCV NS5B RNA-dependent RNA polymerase which show potent affinity for the NS5B enzyme. Introduction of a polar substituent in the position N1 led to a compound that efficiently blocks subgenomic HCV RNA replication in HUH-7 cells[3]. Thiophene[3,2-*b*]pyrrole derivatives are potential antiinflammatory agents[4] and exhibit neurochemical effects[5]. Thienopyrroles are potential bioisosteres of N,N-dimethyltryptamine, therefore hallucinogen-like activity was evaluated[6] for some thienopyrroles. Thieno[2,3-*b*]pyrrole derivatives also act as antagonists of gonadotropin releasing hormone (GnRH)[7].

Furthermore thiophene with its six π-electron aromaticity is electronically and sterically similar to benzene. Perusal of literature indicates that synthesis and biological evaluation of thienopyrroles have been a topic of special interest to organic and medicinal chemists. In continuation of our earlier work on biodynamic heterocycles and to explore their biological activities, herein the synthesis and antimicrobial activity of a few thienopyrroles are reported.

EXPERIMENTAL

Melting points were taken in open capillary tubes in sulphuric acid bath and are uncorrected. FT-IR spectra were recorded on Perkin-Elmer spectrophotometer. ^{1}H NMR spectra were recorded on Varian Gemini 200 MHz spectrophotometer with TMS as internal standard. EI-Mass spectra were obtained on VG Micromass 7070 H instrument.

Microbial activity: All the compounds were tested for their antibacterial activity by filter paper disc method against the bacteria *Staphylococus aureus* and *Esherichia coli* at 1, 10, 100 and 500 ppm concentrations using streptomycin as a standard drug at the same concentrations for comparison. All the compounds showed promising antibacterial activity at all concentrations against both *Staphylococus aureus* and *Esherichia coli*.

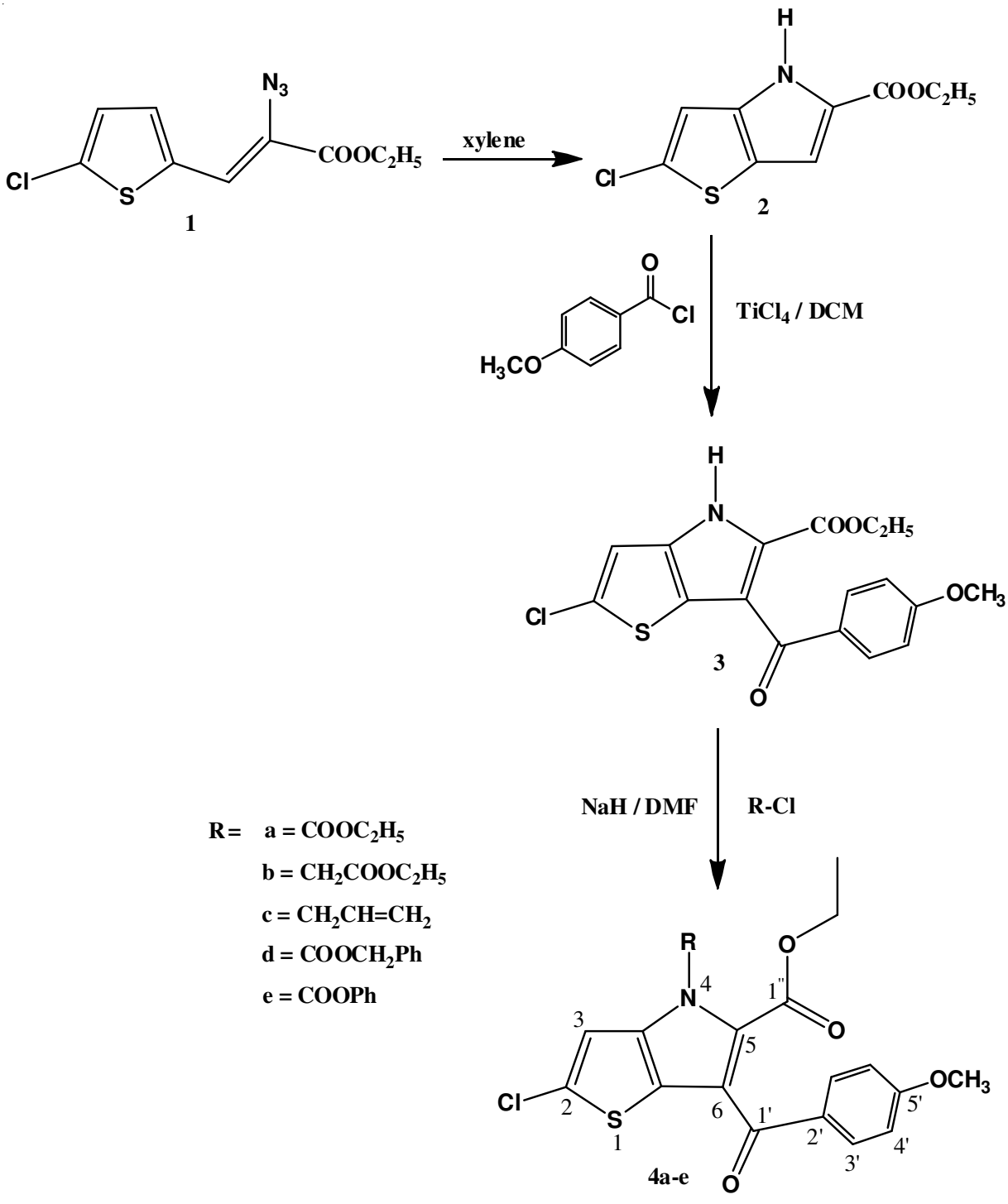
Synthesis of ethyl-2-chloro-6-(5-methyl-2-thienyl-carbonyl)-4*H*-thieno[3,2-*b*]pyrrole-5-carboxylate (3): A mixture of ethyl-2-chlorothieno[3,2-*b*]pyrrole-5-carboxylate (**2**) (0.01 mol), 4-methoxy benzoylchloride (0.01 mol), titanium tetrachloride (0.5 mL) and dichloromethane (30 mL) was refluxed on water bath for 15 h. Progress of the reaction was monitored with the help of TLC. At the end, reaction mass was cooled, washed with 5 % sodium bicarbonate solution followed by brine and dried over sodium sulphate. Solvent

was removed under reduced pressure and the residue was recrystallized from cyclohexane to yield **3**. m.p. 129 ºC.

General procedure for the synthesis of ethyl-2-chloro-4-substituted 6-(4-methoxybenzoyl)-4*H*-thieno[2,3-*b*]pyrrole-4,5-dicarboxylate (4a-e): To a stirred solution of sodium hydride (60 %) (0.13 mol) in dry N,N-dimethylformamide (10 mL) under N_2 atmosphere was added to a solution of ethyl-2-chloro-6-(4-methoxybenzoyl)thieno [3,2-*b*]pyrrole-5-carboxylates (0.1 mol) in dry N,N-dimethyl formamide (8 mL). Then alkyl or acyl reagent was added slowly. After stirring for 2 h at room temperature the reaction mixture was quenched by the addition of cold water and extracted with diethyl ether. The ethereal layer was dried over sodium sulphate, filtered, evaporated and the residue obtained was recrystallized from alcohol (**Scheme-I**). The physical data of synthesized compounds (**4a-e**) are given in Table-1.

Spectral data

Ethyl-2-chloro-6-(4-methoxybenzoyl)-4*H*-thieno[3,2-*b*]-pyrrole-5-carboxylate (3): IR (KBr, ν_{max}, cm^{-1}): 3350 (NH stretching), 1700 (ester carbonyl) and 1640 (aroyl carbonyl); ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, $C_{3''}$-CH_3), 3.82 (s, 3H, C_5-OCH_3),



Scheme-I

TABLE-1
PHYSICAL DATA OF SYNTHESIZED COMPOUNDS **4a-e**

Compound	R	m.p. (ºC)	Yield (%)
4a	$COOC_2H_5$	163	85
4b	$CH_2COOC_2H_5$	193	80
4c	$CH_2CH=CH_2$	148	78
4d	$COOCH_2Ph$	172	81
4e	COOPh	187	77

All the compounds gave satisfactory elemental analysis.

3.97 (q, 2H, $C_{2''}$-CH_2), 6.90 (d, 2H, Ar-H), 7.0 (s, 1H, C_3-H), 7.80 (d, 2H, Ar-H), 12.45 (bs, 1H, N-H); MS: m/z = 363 (M^+) (77 %).

Diethyl-2-chloro-6-(4-methoxybenzoyl)-4*H*-thieno[2,3-*b*]-pyrrole-4,5-dicarboxylate (4a): IR (KBr, ν_{max}, cm^{-1}): 1763 ($C_{1''}$ carbonyl), 1731 ($C_{1'''}$ carbonyl), 1600 ($C_{1'}$ carbonyl); ^1H NMR ($CDCl_3$) δ 1.20 (t, 3H, $C_{3'''}$-CH_3), 1.60 (t, 3H, $C_{3'''}$-CH_3), 3.90 (s, 3H, $C_{5'}$-OCH_3), 4.15 (q, 2H, $C_{2''}$-CH_2), 4.50 (q, 2H, $C_{2'''}$-CH_2), 7.01 (d, 2H, Ar-H), 7.30 (s, 1H, C_3-H), 7.90 (d, 2H, Ar-H); MS: m/z = 435 (M^+).

Ethyl-2-(2-chloro-5-ethyloxycarbonyl-6-(4-methoxy-benzoyl)-4*H*-thieno[2,3-*b*]pyrrole-4-yl)acetate (4b): IR (KBr, ν_{max}, cm^{-1}): 1751 ($C_{1''}$ carbonyl), 1689 ($C_{1'''}$ carbonyl), 1621 ($C_{1'}$ carbonyl); ^1H NMR ($CDCl_3$) δ 0.90 (t, 3H, $C_{3'''}$-CH_3), 1.35 (t, 3H, $C_{3'''}$-CH_3), 3.82 (m, 3H, $C_{5'}$-OCH_3), 3.90 (q, 2H, $C_{2''}$-CH_2), 4.25 (q, 2H, $C_{2'''}$-CH_2), 5.20 (s, 2H, N-CH_2), 6.81 (s, 1H, C_3-H), 7.89 (d, 2H, Ar-H), 6.90 (d, 2H, Ar-H); MS: m/z = 449 (M^+).

Ethyl-2-chloro-4-allyl-6-(4-methoxybenzoyl)-4*H*-thieno[2,3-*b*]pyrrole-5-carboxylate (4c): IR (KBr, ν_{max}, cm^{-1}): 1706 ($C_{1'''}$ carbonyl), 1600 ($C_{1'}$ carbonyl); ^1H NMR ($CDCl_3$) δ 0.92 (t, 3H, $C_{3'''}$-CH_3), 3.85 (m, 3H, $C_{5'}$-OCH_3), 3.90 (m, 2H, $C_{2''}$-CH_2), 5.10-5.40 (dd, 4H, $C_{1'''}$-CH_2 and $C_{3'''}$-CH_2), 6.0 (m, 1H, $C_{2''}$-CH), 6.80 (s, 1H, C_3-H), 7.80 (d, 2H, Ar-H), 6.90 (d, 2H, Ar-H); MS: m/z = 403 (M^+).

5-Ethyl-2-chloro-4-benzyl-6-(4-methoxybenzoyl)-4*H*-thieno[2,3-*b*]pyrrole-4,5-dicarboxylate (4d): IR (KBr, ν_{max}, cm^{-1}): 1702 ($C_{1'''}$ carbonyl), 1600 ($C_{1'}$ carbonyl); ^1H NMR ($CDCl_3$) δ 0.80 (t, 3H, $C_{3''}$-CH_3), 3.90 (s, 3H, $C_{5'}$-CH_3), 3.80 (q, 2H, $C_{2''}$-CH_2), 5.60 (s, 2H, benzyl-CH_2), 6.71 (s, 1H, C_3-H), 7.20 (m, 5H, Ar-H), 7.80 (d, 2H, Ar-H), 6.80 (d, 2H, Ar-H); MS: m/z = 497 (M^+).

5-Ethyl-2-chloro-4-phenyl-6-(4-methoxybenzoyl)-4*H*-thieno[2,3-*b*]pyrrole-4,5-dicarboxylate (4e): IR (KBr, ν_{max}, cm^{-1}): 1784 ($C_{1'''}$ carbonyl), 1627 ($C_{1'}$ carbonyl); ^1H NMR ($CDCl_3$) δ 1.10 (t, 3H, $C_{3''}$-CH_3), 3.80 (s, 3H, $C_{5'}$-OCH_3), 4.10 (q, 2H, $C_{2''}$-CH_2), 7.29 (s, 1H, C_3-H), 7.31 (m, 5H, Ar-H), 7.80 (d, 2H, Ar-H), 6.90 (d, 2H, Ar-H); MS: m/z = 483 (M^+).

RESULTS AND DISCUSSION

Ethyl-2-chloro-6-(4-methoxybenzoyl)-4*H*-thieno[2,3-*b*]pyrrole-5-carboxylate (**3**) has been prepared by refluxing a mixture of 2-chlorothieno[2,3-*b*]pyrrole-5-carboxylate, 4-methoxy benzoylchloride and $TiCl_4$ in dichloromethane. Compound **3** was characterised by analytical and spectral data[8]. IR (KBr) spectrum of **3** showed strong bands at 3350, 1700 and 1640 cm^{-1} were assigned to N-H, ester carbonyl and keto carbonyl stretchings, respectively. ^1H NMR spectrum exhibited a triplet at d 0.90 integrating for three protons was assigned to methyl protons of ester group. A quartet at δ 3.97 integrating for two protons was assigned to CH_2 protons of ester group. The spectrum also exhibited a singlet at δ 3.82 integrating for three protons were assigned to $C_{5'}$-OCH_3 and a singlet at δ 7.0 integrating for one proton was assigned to C_3-H proton. Two doublets appeared at δ 6.90 and δ 7.80 integrating for two protons each were assigned to aromatic protons. A broad singlet at δ 12.5 integrating for one proton was assigned to N-H proton. Molecular ion peak of **3** was observed at m/z = 363 (77 %) in mass spectrum.

Diethyl-2-chloro-6-(4-methoxybenzoyl)-4*H*-thieno[2,3-*b*]pyrrole-4,5-dicarboxylate (**4a**) was synthesized by treating **3** with ethyl chloroformate at cold conditions in the presence of 60 % sodium hydride in DMF. The IR (KBr) spectrum of **4a** showed strong absorption at 1763, 1731 and 1600 cm^{-1} were assigned to ester, amide and keto carbonyl stretching, respectively. ^1H NMR spectrum of **4a** exhibited two triplets at δ 1.20 and δ 1.60 integrating for three protons each were assigned to methyl protons of ester and amide, respectively. Two quartets at δ 4.15 and δ 4.50 integrating for two protons each were assigned to methylene protons of ester and amide, respectively. The spectrum also exhibited a singlet at δ 7.30 integrating for one proton was assigned to C_3-H proton. A singlet at δ 3.90 integrating for three protons was assigned to $C_{5'}$-OCH_3 protons. Two doublets at δ 7.0 and δ 7.90 integrating for two protons each were assigned to aromatic protons. Mass spectrum of **4a** showed molecular ion peak at m/z = 435 (100 %).

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