A FACILE SYNTHESES OF ETHYL 5-SUBSTITUTED ALLYLOXY 11*H*-BENZO[e]THIENO[2',3':4,5]PYRROLO[1,2-*a*][1,4]DIAZEPINE-2-CARBOXYLATES

P. Satish Goud, P. Mallikarjun Goud and D. Ashok*
Department of Chemistry, P.G. College of Science, Saifabad,
Osmania University, Hyderabad-7

Abstract : A new class of thienobenzodiazepine derivatives have been synthesized for the first time using an inexpensive and readily available reagents. These compounds were found to exhibit potential antibacterial activity.

Introduction

Several substituted 1,4-benzodiazepines and their alkyl derivatives have acquired pharmacological importance as potential tranquelizing, CNS depressant, antiinflamatory, anticonvulsant, antispasmodic, muscle relaxtant, hypnotics and sedative agents [1]. It is well known that a number of indolo[1,4]diazepine derivatives exhibit potent antibacterial activity [2-4]. Many examples in the literature, where various electron donating or withdrawing substituents on the benzene ring system are required to enhance the activity. Due to the biological significance of benzodiazepine derivatives, we have planned to synthesis 1,4-diazepine derivatives, which have a thiophene moiety in place of benzene moiety in the indolo[1,4]diazepine ring system. Since thiophene behaves as a electron rich aromatic system, it may be superior to substituted benzene in certain cases.

The necessity of developing a new thienopyrrolo[1,4]diazepine derivatives is due to electron rich property as well as the slightly smaller steric volume of thiophene (6π-electron hetero aromatic system) as compared to benzene may play an important role in fitting the necessary biological receptor sites [5]. At the same time the presence of hetero atom or the low resonance energy in thiophene may alter its metabolite fate, thus the thiophene derivatives may have less toxic effects / or a better therapeutic profile [5]. Moreover literature survey revealed that the synthesis and antibacterial activity of the title compounds have not been reported so far. In order to know the effct of thieophene moiety on physiological activity, we have taken up the synthesis of some new ethyl 5-oxo-6,11-

dihydro-5*H*-benzo[e]thieno[2',3':4,5]pyrrolo[1,2-a][1,4]diazepine-2-carboxylate and its O-allyl derivatives.

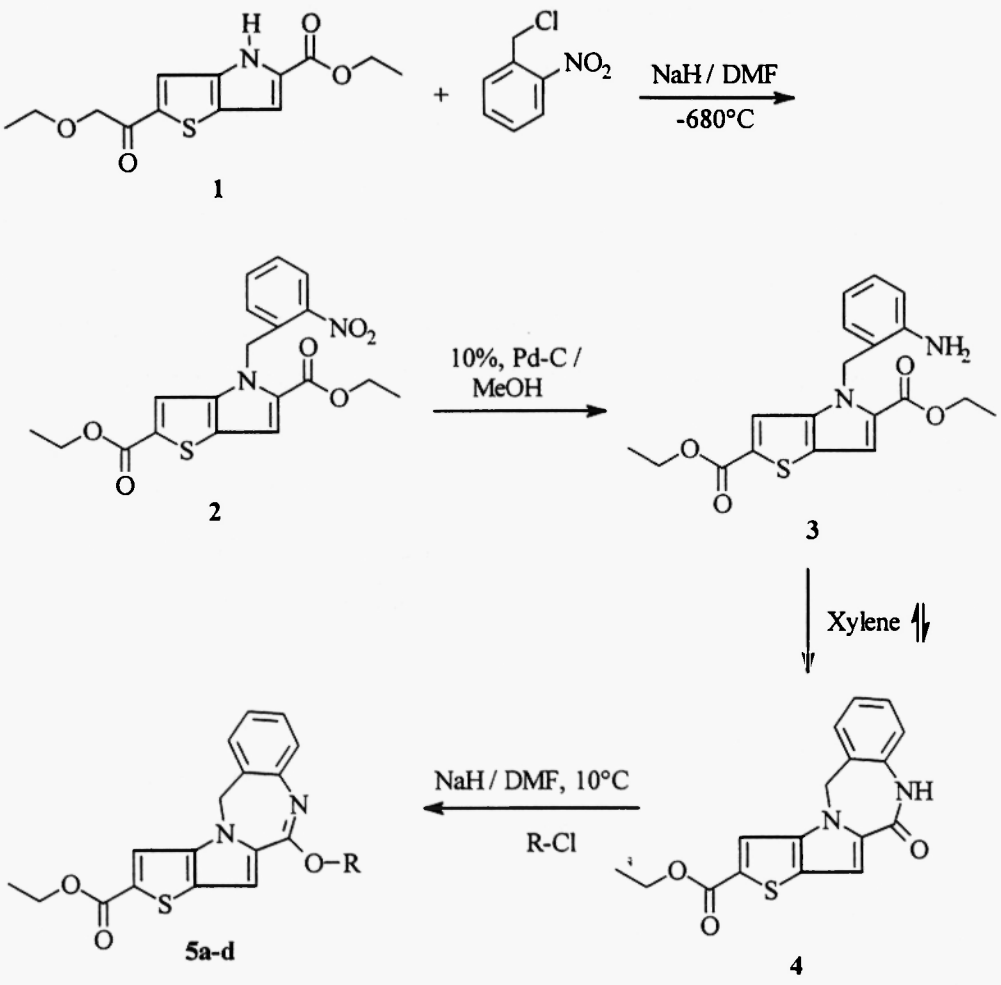
Results and Discussions

The key starting material 2,5-dicarbethoxy thieno[3,2-b]pyrrole (**1**) has been prepared from 5-methyl-2-thienoic acid [6]. The reaction of 2,5-dicarbethoxy thieno[3,2-b] pyrrole (**1**) with o-nitrobenzyl chloride in the presence of sodiumhydride in dimethyl formamide at -68°C gave diethyl-4-(2'-nitro benzyl)-4*H*-thieno[3,2-b] pyrrole-2,5-dicarboxylate (**2**), which was characterized by ^{1}H NMR, IR, UV spectral analysis. The reaction of compound **2** with 10% Pd-C in methanol at 60 psi gave diethyl-4-(2'-amino benzyl)-4*H*-thieno[3,2-b]pyrrole-2,5-dicarboxylate (**3**). The cyclization of compound **3** in refluxing xylene in the presence of catalytic amount of 2-hydroxypyridine [4] afforded ethyl 5-oxo-6,11-dihydro-5*H*-benzo[e]thieno[2',3';4,5]pyrrolo[1,2-a][1,4]diazepine-2-carboxylate. The raction of compound **4** with different alkyl halides in the presence of sodiumhydride in N,N'-dimethyl formamide at 0°C under nitrogen atmosphere gave the corresponding ethyl 5-[substitutedallyloxy-11*H*-benzo[e]thieno[2',3':4,5]pyrrolo[1,2-a][1,4]diazepine-2-carboxylates (**5a-d**) in good yield.

All the compounds **4** and **5a-d** were tested for their antibacterial activity by filter paper disc method against the bacteria *Staphylococcus aureus* and *Escherichia coli* at 1, 10, 100 and 500 ppm concentrations using Streptomycin as a standard drug at the same concentrations for comparision. From the above compounds **5**a was showed highest antibacterial activity only at 10 µg/disc concentration against *Staphylococus aureus*.

Experimental Section

Melting points were taken in open capillary tubes in sulfuric acid bath and are incorrected. FT-IR spectra were obtained on Perkin-Elmer spectrophotometer. UV spectra were obtained on Hilachi U-3410 spectrometer. ^{1}H NMR spectra were taken in $CDCl_3$ on varian Gemini 200 MHz spectrometer with TMS as internal standard (Chemical shifts in δ, ppm). EI Mass spectra were obtained on V.G. Micromass 7070H instrument, column chromatography was carried out using Acme silica gel (200 mesh).



1

2

3

4

5a-d

5a, R = CH_2-CH=CH_2

5b, R = CH_2CH=CH-CH_3

5c, R = $CH_2C(CH_3)$=CH2

5d, R = CH_2CH=CH-Ph

Scheme

Diethyl-4-(2'-nitro benzyl)-4*H*-thieno[3,2-b]pyrrole-2,5-dicarboxylate (2). To a stirred solution of sodium hydride (5.35 g) in dry N,N'-dimethylformamide (30 ml) was added a solution of 2,5-dicarbethoxythieno[3,2-b]pyrrole (**1**, 5.0 g) in N,N'-dimethylformamide at 0°C and stirred at room temperature for over night. The resulting reaction mass was cooled to -65°C, and a solution of 2-nitro benzylchloride (3g) in N,N'-dimethylformamide (15 ml) was added slowly and the reaction mixture was stirred at room temperature for 8 hours. After completion of the reaction, as indicated by TLC, the reaction mass was poured into ice cold water and filtered off. The solid was washed with excess of water and crystallized from alcohol to afford compound **2**, in 80% yield (6 g). m.p. : 172°C; IR (KBr) : 1708 cm^{-1} (carbonyl), 1518, 1344 cm^{-1} (-NO_2); UV λ_{max}^{MeOH} nm (log ε) : 202 (3.86), 255 (3.56) and 315 (4.04); ^1H NMR (200 MHz, $CDCl_3$) : δ 1.3 (6H, t, C_2,C_5-OCH_2-$C\underline{H}_3$), 4.2 (4H, q, C_2,C_5-$OC\underline{H}_2$), 6.1 (2H, s, benzylic), 6.4 (1H, m, phenyl), 7.3 (1H, s, C_6-H), 7.45 (2H, m, phenyl), 7.6 (1H, s, C_3-H), 8.2 (1H, m, phenyl).

Diethyl -4-(2'-amino benzyl)-4*H*-thieno[3,2-b]pyrrole-2,5-dicarboxyalte (3) : A mixture of diethyl-4-(2'-nitro benzyl)4*H*-thieno[3,2-b]pyrrole-2,5-dicarboxylate (**2**, 3.0 g), 10% Pd/C (200 mg) in methanol was hydrogenated under 60 psi of hydrogen pressure at room temperature for 1.5 h. The catalyst was removed by filteration, the filterate was concentrated *in vacuo* and the resulting product was crystallized from alcohol to afford compound **3** in 70% yeild (2.4 g). m.p. : 191°C; IR (KBr) : 3296 cm^{-1} (NH), 1712, 1687 cm-1 (ester carbonyls); U.V. λ_{max}^{MeOH} nm (log ε) 221 (3.28), 255 (2.43) and 316 (4.26). ^1H NMR (200 MHz, $CDCl_3$ + DMSO), δ 1.25 (6H, t, C_2,C_5-OCH_2-$C\underline{H}_3$), 4.2 (4H, q, C_2,C_5-$OC\underline{H}_2$,CH_3), 6.0 (2H, s, benzylic), 6.4 (1H, d, phenyl), 7.1 (2H, m, phenyl), 7.5 (1H, s, C_6-H), 7.7 (1H, m, phenyl), 7.8 (1H, s, C_3-H); EIMS : m/z 372 (M^+).

Ethyl 5-oxo-6,11-dihydro-5*H*-benzo[e]thieno[2',3':4,5]pyrrolo [1,2-*a*] [1,4]diazepine-2-carboxylate (4). A mixture of diethyl-4-(2'-amino benzyl)-4*H*-thieno[3,2-b]pyrrolo-2,5-dicarboxylate (**3**) (2.0 g) and 2-hydroxypyridine (200 mg) in dry xylene (30 ml) was refluxed for 8.0 hr with continuous removal of water by using dean-stark apparatus. Cooled the reaction mass filtered the precipitated solid and crystallized from isopropanol to afford compound **4** in 80% yield (1.4 g). m.p. 203°C; IR (KBr) : 3435 cm^{-1} (-NH). 1694 cm^{-1} (ester carbonyl) 1624 cm^{-1} (amide carbonyl); UV λ_{max}^{MeOH} nm (log ε) : 201 (3.77), 224 (3.39) and 325 (3.79); ^1H NMR (200 MHz, $CDCl_3$ + DMSO) : δ 1.4 (3H, t, C_2-OCH_2-$C\underline{H}_3$),

4.35 (2H, q, C_2-OC<u>H</u>$_2$-CH_3), 5.4 (2H, s, C_{11}-CH_2), 7.12 (2H, m, **phenyl** & C_4-H), 7.3 (**2**H, m, phenyl), 7.5 (1H, m, phenyl), 8.1 (1H, s, C_1-H); EIMS : m/z (M^+) 326.

Ethyl 5-(substitutedallyloxy)-11*H*-benzo[e]thieno[2',3':4,5] pyrrolo[1,2-a][1,4] diazepine-2-carboxylates (5a-d)

General procedure : To a solution of sodium hydride (98%) (0.012 mole) in dry N,N'-dimethyl formamide (10 ml) at 0°C was added a solution of ethyl-5-oxo-6,11-dihydro-5*H*-benzo[e]thieno[2',3':4,5]pyrrolo[1,2-a][1,4] diazepine -2-carboxylate (**4**), (0.01 mole) in N,N'-dimethylformamide (5 ml) over a period of 10 min., by maintaining the temperature below 10°C under N_2 atmosphere. Slowly warmed the reaction mass to room temperature and stirred for 1 hour. The reaction mass was cooled to 10°C and 0.01 mole of substituted allylchloride was added and stirred for 1.5 hour at room temperature. After completion of the reaction, the reaction mass was poured into ice cold water (50 ml) and extracted twice with ether (25 x 2). The combined organic layers were dried over Na_2SO_4, concentrated *in vacuo* and purified by column chromotography over silica gel (200 mesh, chloroform-pet.ether, 8:2) to afford the title product which was further recrystalized from methyl cyclohexane to yield (**5a-d**) (75-85%) pure product.

Ethyl 5-(allyloxy)-11*H*-benzo[e]thieno[2',3':5,4]pyrrolo[1,2-a][1,4]diazepine-2-carboxylate (5a) : ^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.5 (3H, t, C_2-OCH_2-C<u>H</u>$_3$), 4.4 (2H, q, C_2-OC<u>H</u>$_2$-CH_3), 4.7 (2H, d, $C_{1'}$-CH_2), 5.2 (4H, m, $C_{3'}$-CH_2,C_{11}-CH_2), 6.0 (1H, m, $C_{2'}$-CH), 7.1 (1H, s, C_4-H), 7.2-7.4 (4H, m, phenyl) 7.7 (1H, s, C_1-H); Anal. Calcd. for $C_{20}H_{18}N_2O_3S$: C, 65.57; H, 11.91; N, 7.65. Found : C,65.58; H, 11.93; N, 7.67.

Ethyl 5-[(E)-2-butenyloxy]-11*H*-benzo[e]thieno[2',3':5,4]pyrrolo[1,2-a][1,4]diazepine-2-carboxylate (5b) : ^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.5 (3H, t, C_2-OCH_2-C<u>H</u>$_3$), 1.7 (3H, d, $C_{4'}$-CH_3), 4.3 (2H, q, C_2-O-C<u>H</u>$_2$-CH_3), 4.6 (2H, d, $C_{1'}$-CH_2), 5.1 (2H, s, C_{11}-CH_2), 5.5-5.7 (2H, m, $C_{2'}$,$C_{3'}$-H), 7.0 (1H, s, C_4-H), 7.3 (4H, m, phenyl), 7.7 (1H, s, C_1-H); Anal. Calcd. for $C_{20}H_{20}N_2O_3S$: C, 66.31; H, 5.26; N, 7.36; Found : C, 66.32; H, 5.28; N, 7.37.

Ethyl 5-(2-methylalyloxy)-11*H*-benzo[e]thieno[2',3':5,4]pyrrolo[1,2-a][1,4]diazepine-2-carboxylate (5c) : ^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.5 (3H, t, C_2-OCH_2-C<u>H</u>$_3$), 1.8 (3H, s, $C_{4'}$-CH_3), 4.4 (2H, q, C_2-O-C<u>H</u>$_2$-CH_3), 4.7 (2H, s, $C_{1'}$-CH_2), 4.9 (2H, s, $C_{3'}$-CH_2), 5.2 (2H, s, C_{11}-CH_2), 7.1 (1H, s, C_4-H), 7.4 (4H, m, phenyl), 7.75 (1H, s, C_1-H); Anal. calcd. for $C_{21}H_{20}N_2O_3S$: C, 66.31; H, 5.26; N, 7.36. Found : C, 66.32; H, 5.28; N, 7.38.

Ethyl 5-[3-phenyl-(E)-2-propenyloxy]-11*H*-benzo[e]thieno[2',3':5,4]pyrrolo[1,2-*a*][1,4]diazepine-2-carboxylate (5d) : ^{1}H NMR (200 MHz, $CDCl_3$) : δ 1.4 (3H, t, C_2-O-CH_2-CH_3), 4.35 (2H, q, C_2-O-CH_2-CH_3), 4.75 (2H, d, $C_{1'}$-CH_2), 5.2 (2H, s, C_{11}-CH_2), 6.5 (2H, m, C_2,$C_{3'}$-CH), 7.1 (1H, s, C_4-H), 7.2-7.5 (9H, m, phenyl), 7.7 (1H, s, C_1-H). Anal. Calcd for $C_{20}H_{22}N_2O_3S$: C, 70.58; H, 11.97; N, 6.33. Found C, 70.59; N, 11.98; N, 6.38.

Acknowledgments : D. Ashok and PSG thank to the principal of the P.G. College of Science Saifabad, O.U., Hyderabad for his encouragement and fruitful suggestions.

References

1. Vida, J.A. Medicinal Chemistry, Part-III, M.W. Wolf, and A. Burger, Eds., John Wiely & Sons, New York, 1981, 787 and references cited therein.
2. Hughes, G.K.; Francis Lions, McKean, J.G.; Murray, A.J.; Callaman, V.; Freeman, D.H.; Ralph, C.S.; Rassack, R.; Dombroski, J.; Finch, F.; Andrews, R. and Laurence, R.C. *J. Proc. Roy. Soc.*, **71**, 475 (1938).
3. Hiremath, S.P.; Muruthyunjayswamy, B.H.M. and Purohit, M.G. *Indian J. Chem.*, **16B**, 789 (1978).
4. Chih, Y. Ho, William, E.; Hageman, and Francis, J. Persico. *J. Med. Chem.*, **29**, 1118 (1986).
5. Erlenmeyer, H. *Bull. Soc. Chim. Biol (Paris)*, **30**, 792 (1948).
6. Walter W. Gale, Alan, N. Scott. and Snyder, H.R. *J. Org. Chem.*, **29**, 2160 (1964).

Received on January 10, 2001