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Novel and Efficient Synthesis of Tetrazolo[1,5-*b*]-1,2,5-oxadiazepines as Antibacterial Activities from Ethyl 1-aminotetrazole-5-carboxylate

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ABSTRACT. Ethyl 1-aminotetrazole-5-carboxylate **(1)** has been utilized to construct a variety of novel tetrazolo [1,5-*b*]-1,2,5-oxadiazepine derivatives which repesent a relatively little explored group with interesting antibacterial activities. The synthesized compounds were elucidated using IR, ^{1}H NMR and mass spectroscopic methods, besides elemental analyses.

Key words: Ethyl 1-aminotetrazole-5-carboxylate, Tetrazolo[1,5-*b*]-1,2,5-oxadiazepines, Antibacterial activities

INTRODUCTION

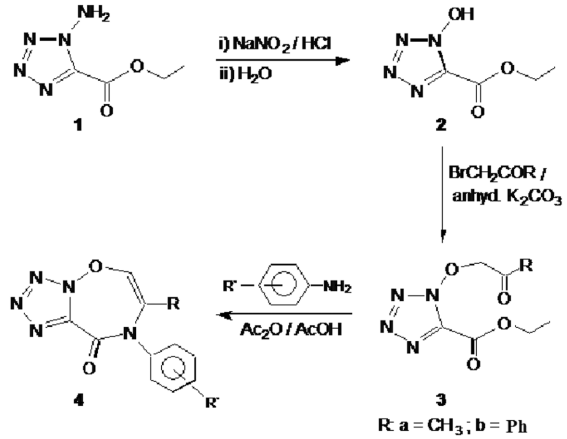
Tetrazoles and their derivatives have been described as useful building blocks for the assembly of different heteroyclic rings[1-7] because of their wide range of therapeutic and biological properties.[8,9] They have emerged as antibacterial, antiproliferation, anticancer, and anticonvulsant activities.[1-5,10-12] Numerous studies have been reported[13-24] on the synthesis of a variety of oxadiazepine derivatives covering a wide range of bioorganic, natural products, and medicinal chemistry. They are an important class of heterocyclic compounds that have pharmaceutical and biological activities[13,21-24] including antiherbicide, antimicrobial, antifungal, and anticancer. All these facts encouraged us to synthesize some new tetrazolo[1,5-*b*]-1,2,5-oxadiazepines in anticipation of expected interesting antibacterial activities.

RESULTS AND DISCUSSION

Chemsitry

The diazotization of ethyl 1-aminotetrazole-5-carboxylate[1] **(1)** in the presence of water resulted in the formation of ethyl 1-hydroxytetrazole-5-carboxylate **(2)**, which is used as a starting compound for bromoketone systems. Thus, condensation of **2** with bromoacetone and/or phenacylbromide in absolute ethanol in the presence of anhydrous potassium carbonate to provide acetonyloxy **3a** and 2-oxyacetophenone **3b**, respectively. The IR spectra of **3(a,b)** showed ester carbonyl (COOEt) bands in 1740, 1760 cm^{-1} and carbonyl ($COCH_3$(ph)) bands in 1712, 1720 cm^{-1} region. ^{1}H NMR spectra of **3a** and **3b** revealed four signals in the d 4.19, 4.23; 2.45, 2.40, 1.30, 1.33 and 2.35, 8.35-7.20 ppm which were attributed to be $\underline{CH_2}CH_3$, $\underline{CH_2}COCH_3$(Ph) $CH_2\underline{CH_3}$ and $CH_2CO\underline{CH_3}$(Ph), respectively. The El-MS spectra of **3a** and **3b** showed the molecular ion peaks at *m/z*: 214 (M^+) and 277 (M^++1) corresponding to $C_7H_{10}N_4O_4$ and $C_{12}H_{12}N_4O_4$, respectively.

7-Methyl(phenyl)-8-aryltetrazolo[1,5-*b*]-1,2,5-oxadiazepin-9-ones **4(a-l)** (*Scheme* 1) were obtained by condensation of **3(a,b)** with various 4-substituted anilines in the presence of acetic anhydride/acetic acid (*Table* 1). The IR spectra of **4(a-l)** showed bands at 1650-1985 cm^{-1} (*Table* 2) which were attributed to the amide (CON) stretching frequency and disappearance any COOEt or



***Scheme* 1.**

***Table* 1.** Physical and analytical data of **4(a-l)**

Compd. No.	M. P. (°C)	Yield (%)	Formiula (Mol. Mass)	Elemental Analysis Calcd/Found (%)		
				%C	%H	%N
4a	279-280	63	$C_{11}H_9N_5O_2$ (243)	54.32 54.72	3.70 3.92	28.81 29.22
4b	290-292	51	$C_{12}H_{11}N_5O_2$ (257)	56.03 55.92	4.28 4.42	27.24 26.92
4c	284-285	56	$C_{12}H_{11}N_5O_3$ (273)	52.75 53.11	4.03 3.92	25.64 25.82
4d	290-291	50	$C_{11}H_{10}N_6O_2$ (258)	51.16 50.92	3.88 4.21	32.56 32.67
4e	293-295	70	$C_{11}H_8ClN_5O_2$ (277.5)	47.57 47.22	2.88 3.21	25.23 24.94
4f	>300	75	$C_{11}H_8N_6O_4$ (288)	45.83 45.52	2.78 3.24	29.17 28.72
4g	258-260	73	$C_{16}H_{11}N_5O_2$ (305)	62.95 63.22	3.61 3.85	22.95 23.26
4h	265-267	61	$C_{17}H_{13}N_5O_2$ (319)	63.95 64.24	4.08 4.23	21.94 22.32
4i	280-282	67	$C_{17}H_{13}N_5O_3$ (335)	60.90 60.72	3.88 4.22	20.90 21.21
4j	289-291	61	$C_{16}H_{12}N_6O_2$ (320)	60.00 60.42	3.75 3.61	26.25 25.92
4k	>300	66	$C_{16}H_{10}ClN_5O_2$ (339.5)	56.55 56.24	2.95 3.22	20.62 20.41
4l	>300	72	$C_{16}H_{10}N_6O_4$ (350)	54.86 55.22	2.86 3.21	24.00 23.72

***Table* 2.** Spectral data of **4(a-l)**

Compd. No.	IR (ν, cm^{-1})	^1H NMR (DMSO-d_6)	Mass (*m*/*z*, %)
4a	1650(CON)	7.24-6.89 (m, 5H, ArH), 5.40 (s, 1H, CH of oxadiazepine ring), and 1.63 (s, 3H, CH_3)	243 (M^+, 40)
4b	1670(CON)	7.72-6.98 (m, 4H, ArH), 5.44 (s, 1H, CH of oxadiazepine ring), and 1.82, 1.61 (2s, 6H, $2CH_3$)	258 (M^++ 1, 60)
4c	1675 (CON)	7.77-6.90 (m, 4H, ArH), 5.44 (s, 1H, CH of oxadiazepine ring), and 3.28, 1.59 (2s, 6H, $2CH_3$)	274 (M^++1, 65)
4d	3480, 3300 (NH_2), and 1670 (CON)	7.78-6.92 (m, 4H, ArH), 5.33 (s, 1H, CH of oxadiazepine ring), 5.00 (s br, 2H, NH_2, D_2O-exchangeable), and 1.61(s, 3H, CH_3)	258 (M^+, 52)
4e	1673 (CON)	7.77-6.90 (m, 4H, ArH), 5.44 (s, 1H, CH of oxadiazepine ring), and 1.63(s, 3H, CH_3)	278 (M^+, 45)
4f	1680 (CON)	7.80-6.90 (m, 4H, ArH), 5.44 (s, 1H, CH of oxodiazepine ring), and 1.66 (s, 3H, CH_3)	289 (M^++1, 55)
4g	1674 (CON)	7.79-6.77 (m, 10H, ArH), and 5.40 (s, 1H, CH of oxadiazepine ring)	305 (M^+, 69)
4h	1680 (CON)	7.80-6.90 (m, 9H, ArH) and 5.39 (s, 1H, CH of oxadiazepine ring), and 1.87 (s, 3H, CH_3)	321 (M^++2, 60)
4i	1650 (CON)	7.82-6.77 (m, 9H, ArH) and 5.41 (s, 1H, CH of oxadiazepine ring), and 3.33 (s, 3H, CH_3)	336 (M^++1, 68)
4j	3450, 3350 (NH_2), and 1660 (CON)	7.88-6.82 (m, 9H, ArH), 5.42 (s, 1H, CH of oxadiazepine ring), and 5.10 (s br, 2H, NH_2, D_2O exchangeable)	321 (M^++ 1, 45)
4k	1674 (CON)	8.22-6.99 (m, 9H, ArH), and 5.41 (s, 1H, CH of oxadiazepine ring)	340 (M^+, 88)
4l	1985 (CON)	7.79-6.89 (m, 9H, ArH) and 5.39 (s, 1H, CH of oxadiazepine ring)	351(M^++ 1, 70)

$COCH_3$ (ph) absorption bands present in the spectra of the parent compounds **3(a**,**b)**. In the ^1H NMR spectra of **4(a-l)** not only revealed the absence of both the methylene proton (CH_2) and the ethyl protons but also the presence of the methine proton (CH) of oxadiazepine ring at d 5.44-5.39 besides aromatic protons at 8.22-6.99 ppm (*Table* 2). Moreover, the mass spectra of **4(a-l)** gave their correct parent ion peaks corresponding to their molecular formulas (*Table* 2).

Biological activities

Antibacterial activities of the aryl tetrazolo[1,5-*b*]-1,2,5-oxadiazepin-9-ones **4** listed in *Table* 3 were assessed against Gram-positive (*Staphylococus aureus and Bacillus sub-*

***Table* 3.** In vitro antibacterial activity of **4** and standards (MIC in μg/ml)

Compd. No	Gram-positive		Gram-negative	
	S.aureas	*B.subtilis*	*E.coli*	*K.peneumoniae*
4a	0.50	0.40	32	> 50
4b	0.21	0.023	0.13	> 50
4c	0.22	0.044	8	> 50
4f	0.45	0.49	37	> 60
4g	0.42	0.50	38	40
4h	0.39	0.44	25	> 60
4i	0.40	0.45	28	> 60
4l	0.41	0.35	26	24
Ciprofloxacin	0.43	0.03	0.14	0.03
Norfloxacin	1	0.06	0.49	0.14

tilis) and Gram-negative (*Escherichia coli and Klebsiella peneumoniae*) bacteria. Ciprofloxacin and Norfloxacin were used as antibacterial standarsds. The antibacterial activity against Gram-postive organisms had the most activity. However, all the compounds were nearly inactive against Gram-negative bacteria.

CONCLUSION

A successful preparation and characterization of new compounds substituted aryl tetrazolo[1,5-*b*]1,2,5-oxadiazepin-9-ones **4(a-l)** from condensation of acetonyloxy **3a** and oxyacetophenone **3b** tetrazoles with various 4-substituted anilines in the presence of acetic anhydride/acetic acid. The antibacterival activities of the prepared compounds were comparable to Ciprofloxacim and Norfloxacin and study showed that, against Gram-positive bacteria is in contrast to the good antibacterial activity of Ciprofloxacim aginst both Gram-positive and Gram-negative bacteria.

EXPERIMENTAL

General

Melting points were determined by using a Buchi-530 melting point apparatus and are uncorrected. Spectroscopic data were recorded on the following instruments. Infrared (IR) spectra (KBr, ν cm^{-1}) Perkin Elmer 1240 spectrophotomer, nuclear magnetic resonance (^{1}H NMR) spectra (chemical shift, e ppm) Varian Mercury (300 MHz) spectrometer using TMS as internal standard and electron impact Mass spectra (El-MS) GC-MS (QP/000EX) Shimadzu spectrometer (70 ev). Elemental analyses were performed by the Microanalysis Centre, Faculty of Science, Cairo University. The purity of the compounds was confirmed by Thin Layer Chromatography(TLC) on silica gel HF_{254} (Merck).

Ethyl 1-hydroxytetrazole-5-carboxylate (2)

To a cooled solution (-5 ºC) of **1** (1 g, 6 mmol) in concentrated hydrochloric acid (2N, 4 ml) was added portionwise sodium nitrite (0.4 g, 6 mmol). After stirring at room temperature for an hour, water (10 ml) was added to the mixture which was then heated under reflux for half hour. It was cooled at ambient temperature and neutralized with ammonium hydroxide solution. The precipitate was collected by filtration washed with water and purified by crystallization from aqueous ethanol to obtain **2** (0.7 g, 69% yield), m.p. 288-290 ºC; IR (KBr, ν cm^{-1}): 33340 (OH), 1750 (COOEt); ^{1}H NMR (*DMSO-d_6*, d/ppm): 12.30 (s, 1H, OH, D_2O exchangeable), 4,23 (q, 2H, $\underline{CH_2}CH_3$); 1.25 (t, 3H, $CH_2\underline{CH_3}$); El-MS: *m/z* (%): 159 (M^++1, 38); 158 (M^+, 79).

Anal. Calcd. for $C_4H_6N_4O_3$ (158): C, 30.38; H, 3.80; N, 35.44%; Found: C, 30.67; H,4.12; N, 35.90%.

Ethyl 1-acetonyloxytetrazole-5-carboxylate (3a)

To a solution of **2** (1 g, 6 mmol) in absolute ethanol (20 ml) was added bromoacetone (0.9 g, 6 mmol) in anhydrous potassium carbonate (2 g). The reaction mixture was refluxed for 3 hours and then left to cool 24 hours. The separated solid product was filtered and crystallized from aqueous ethanol to give **3a** (0.8 g, 57 % yield), m.p. 260-262 ºC; IR (KBr, ν cm^{-1}): 1740 (COOEt), 1712 ($COCH_3$); ^{1}H NMR (*DMSO-d_6*, d/ppm): 4.19 (q, 2H, $\underline{CH_2}CH_3$), 2.45 (s, 2H, $\underline{CH_2}COCH_3$), 2.35 (s, 3H, $CH_2CO\underline{CH_3}$), 1.30 (t, 3H, $CH_2\underline{CH_3}$); El-MS: *m/z* (%): 214 (M^+, 80).

Anal. Calcd. for $C_7H_{10}N_4O_4$ (214): C, 39.25; H, 4.67; N, 29.91%; Found: C, 39.70, H, 5.11; N, 30.23%.

Ethyl 1-(2-oxyacetophenone) tetrazole-5-carbolylate (3b)

To a solution of **2** (1 g, 6 mmol) in absolute ethanol (20 ml) was added phenacyl bromide (1.3 g, 6 mmol) and anhydrous potassium carbonate (2 g). The reaction mixture was heated under reflux for 3 hours and then left to cool overnight. The separated solid product was filtered and crystallized from aqueous ethanol to give **3b** (1.2 g, 67% yield), m.p. 238-240 ºC; IR (KBr, ν cm^{-1}): 1760 (COOEt), 1720 (COPh); ^{1}H NMR (*DMSO-d_6*, d/ppm: 8.35-7.20 (m, 5H, ArH), 4.23 (q, 2H, $\underline{CH_2}CH_3$), 2.40 (s, 2H, $\underline{CH_2}$COPh), 1.33 (t, 3H, $CH_2\underline{CH_3}$); El-MS: *m/z* (%): 277 (M^++1, 65).

Anal. Calcd. for $C_{17}H_{12}N_4O_4$ (276): C, 52.17; H, 4.35; N, 20.29%; Found: C, 51.96; H, 4.88; N, 20.72%.

General procedure for the preparation of 7-Methyl (phenyl)-8-aryltetrazolo[1,5-b]-1,2,5-oxadiazepin-9-ones 4(a-l)

A mixture of **3a** or **3b** (5 mmol) the appropriate 4-substituted aniline (5 mmol) and acetic anhydride (10 ml) in glacial acetic acid (15 ml) was refluxed for two hours. The solvent was evaporated under reduced presure and the residue was crystallized from ethanol. The physico-chemical and spectral data of **4(a-l)** are given in *Tables* 1 and 2, respectively.

Antibacterial assay

The in vitro antibacterial activity of the synthesized compounds against Gram-positive organisms (*S. aureas and B. subtilis*) and Gram-negative (*E. coli and K. peneumoniae*) organisms was done by conventional agar dilution methods[25] and compared with those of Ciprofloxacim and Norfloxacin. Twofold serial dilution of the compounds and reference drugs were used in Müller-Hinton Broth (oxoid) agar. Drugs were dissolved in dimethylsulfoxide (*DMSO*; 1 ml) and the solution was diluted with water (9 ml). Further progressive double dilution with melted Müller-Hinton Broth (oxoid) agar was performed to give the required concentrations. The Minimum Inhibitor Concentration (MIC) was the lowest concentration of the test compound, which yielded in no visible growth on the plate. To ensure that the solvent had no effect on bacterial growth, a control test was performed with test medium supplemented with *DMSO* at the same dilutions as prepared in the experiment.

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