Synthesis and Antibacterial Activities of Bis-1,3,4-oxadiazoline derivatives

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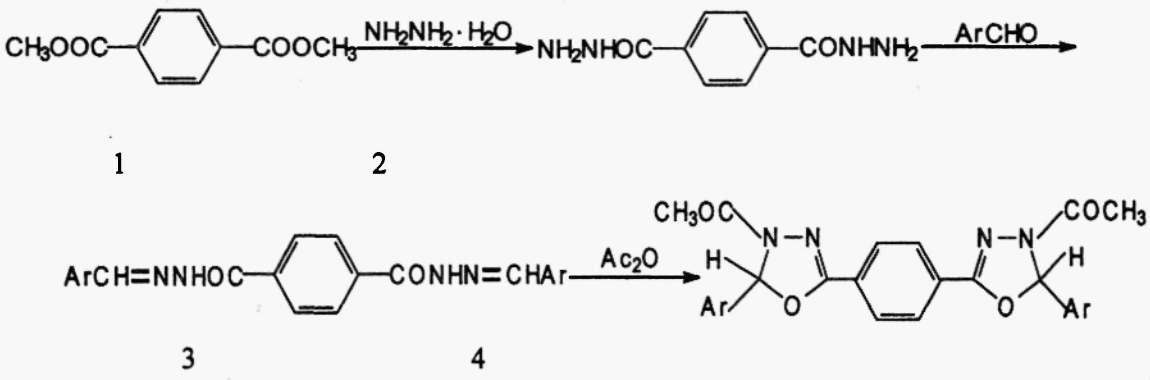
Abstract: Dimethyl terephthalate (1) was reacted with 80% hydrazine hydrate in refluxing methanol for 12 h to afford terephthalate dihydrazide (2). Condensation of 2 with aromatic aldehydes afforded corresponding hydrazones 3a-3j. Cyclization of 3a-3j with acetic anhydride in refluxing for 4-5 h afforded bis-1,3,4-oxadiazoline derivatives(4a-4j). The structures of 4a-4j were characterized by elementary analyses, IR, ^{1}H NMR, and MS spectroscopy. The preliminary antibacterial tests showed that most of them were effective against S.aureus.

Introduction

Oxadiazoline derivatives are found to possess significant biological activities such as antifungal (1), insecticidal (2), CNS depressant (3-5), anticonvulsant effects and growth accelerator for plant. They are highly important heterocyclic compounds, and have been used in research and development of agrochemicals and pharmaceutical chemistry. Most of those compounds only contain one 1,3,4-oxadiazoline unit in one molecule. As part of our current studies on the synthesis of the biologically active 1, 3, 4-oxadiazoline derivatives, we now report an efficient synthesis the compounds combining two 1,3,4-oxadiazoline rings in one framwork by cyclization of corresponding hydrazones 3a-3j with acetic anhydride, respectively. The synthesis, characterization and the results of antibacterial activities screening studies of the newly synthesized compounds are presented in this paper.

Result and discussion

The synthetic route is depicted in Scheme-1. Dimethyl terephthalate (1) was reacted with 80% hydrazine hydrate in refluxing methanol for 12 h to give terephthalic dihydrazide (2). Condensation of 2 with aromatic aldehydes afforded corresponding hydrazones 3a-3j. Cyclization of 3a-3j with acetic anhydride in refluxing for 4-5 h gave the title compounds 4a-4j (Table-1). Thin layer chromatography was employed to follow the progress of the above reactions.



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Scheme-1

The structures of all compounds 4a-4j were established on the basis of elemental analysis and spectral data. The IR spectral data of compounds 4a-4j showed bands at 1720-1687 cm^{-1}, 1626-1640 cm^{-1}, 1275-1244 cm^{-1}, and 1075-1087 cm^{-1} due to C=O, N=C, N-N=C and C-O-C, respectively. The ^1H NMR spectra of 4a-4j exhibited multiple signals in the δ 6.90-8.23 range accounting for hydrogen of aryl group, 2.35-2.40 range accounting for the 6 hydrogens of $-2COCH_3$. With compound 4a as an example, it exhibited multiple signals in the δ 7.81-7.68, 7.50-7.41, 7.32-7.20 ranges accounting for 12 hydrogens of phenyl groups, δ 6.98 accounting for two hydrogens on oxadiazoline rings, δ 2.37 accounting for 6 hydrogens of $2COCH_3$. The EI-MS for compounds 4a-4j exhibited molecular ion peaks. For example, 4a showed strong molecular ion peak M^+, M+2, M+4 with m/z 522, 524, 526 and 3%, 1% , 2% relative abundance, respectively.

Compounds 4a-4j were screened for their antibacterial activities against E. coli, S. aureus, and B. subtilis employing the cup-plate method at the concentration of 100 μg/mL in the nutrient agar. The preliminary results indicated that most of compounds express significant antibacterial activity. The results of such studies are given in Table-2.

Table-1: Preparation of bis-1,3,4-oxadiazoline derivatives (4a-4j) from hydrazones 3a-3j

Entry	Ar	Condition	Yield (%)[a]	m.p. (□)
4a	4-Cl-Ph	150-155□/4.0 h	68	132-134
4b	2-Cl-Ph	150-155□/4.5 h	60	125-126
4c	2,4-Cl_2-Ph	150-155□/4.0 h	58	122-123
4d	4-CH_3-Ph	150-155□/5.0 h	75	120-122
4e	4-OCH_3-Ph	150-155□/4.5 h	71	119-120
4f	4-OH-Ph	150-155□/5.0 h	55	140-141
4g	4-$N(CH_3)_2$Ph	150-155□/4.0h	81	135-137
4h	4-NO_2-Ph	150-155□/4.0 h	67	165-167
4i	3-NO_2-Ph	150-155□/4.0 h	69	154-156
4j	Ph	150-155□/4.0h	78	170-172

[a]Yields of 4a-4j based on 3a-3j, respectively.

Table-2: The Antibacterial Activities of Compounds 4a-4j

Compd.	S.aureus	E.coli	B.subtilis
4a	+ + +	+	+ +
4b	+ + +	+ +	+
4c	+ +	+ +	+
4d	+ +	+	-
4e	+ +	-	-
4f	+ +	-	-
4g	+ +	-	-
4h	+ + +	+ +	-
4i	+ + +	+ +	+
4j	+ +	-	-

Zone diameter of growth inhibition: <10 mm (-), 10 ~ 12 mm (+), 13 ~ 15 mm (+ +), 16 ~ 20 mm (+ + +); Diameter of the cup=8 mm.

Experimental

Melting points were determined on an X_4 melting point apparatus and were uncorrected. The IR spectra were recorded on a Nicolet Nexus 470 FT-IR spectrophotometer using KBr discs in the range 4000-400 cm^{-1}. ^1H NMR spectra were recorded on a Varian Mercury-Plus 400 NMR spectrometer in CF_3COOD solution using TMS as an internal reference. MS spectra were recorded on a Finnigan Trace GC-MS spectrometer. Elemental Analyses were taken on a Perkin-Elemer-2400-C H N Elemental Analysis Instrument.

Compound Dimethyl terephthalate (1), terephthalic dihydrazide(2) and hydrazones (3a-3i) were prepared from aromatic carboxylic acids by four steps according to the literature (6-7).

General preparation of 4 A mixture of compound 3 (1.0 mmol) and excessive acetic anhydride (13 mL) was refluxed for 4-5 hours at 150-155□, the excessive acetic anhydride was distilled off and the residue was poured into crushed ice, stirred for 2-3 h. The separated solid was filtered, washed with water, ethanol, then dried. The crude material was recrystallized from a mixture of ethanol and pyridine to give the pure products 4a-4j.

4a: White powder, IR (KBr, cm^{-1}): 1715, 1630, 1264, 1061; ^1H NMR (CF_3COOD, 400 MHz): 7.81-7.68 (m, 4H, Ar-H), 7.50-7.41 (m, 4H, Ar-H), 7.32-7.20 (m, 4H, Ar-H), 6.98 (s, 2H, 2-H), 2.37 (s, 6H, CH_3); MS (m/z, %): 526 (2), 524 (1), 522 (M^+, 3), 480 (4), 438 (5), 327 (16), 285 (9), 42 (100). Anal. Calcd For $C_{26}H_{20}N_4O_4Cl_2$: C, 59.67; H, 3.85; N, 10.71. Found: C, 59.74; H, 3.77; N, 10.65.

4b: White powder, IR (KBr, cm^{-1}): 1708, 1633, 1275, 1082; ^1H NMR (CF_3COOD, 400 MHz): 7.79-7.63 (m, 5H, Ar-H), 7.52-7.43 (m, 4H, Ar-H), 7.28-7.10 (m, 5H, 2-H, Ar-H), 2.36 (s, 6H, CH_3); MS (m/z, %): 524 (2), 522 (M^+, 3), 48 (7), 438 (5), 285 (12), 42 (100). Anal. Calcd For $C_{26}H_{20}N_4O_4Cl_2$: C, 59.67; H, 3.85; N, 10.71. Found: C, 59.53; H, 33.81; N, 10.82.

4c: White powder, IR (KBr, cm^{-1}): 1691, 1640, 1244, 1080; ^1H NMR (CF_3COOD, 400 MHz): 7.79-7.63 (m, 3H, Ar-H), 7.52-7.43 (m, 4H, Ar-H), 7.28-7.10 (m, 5H, 2-H, Ar-H), 2.37 (s, 6H, CH_3); MS (m/z, %): 592 (2), 590 (M^+, 3), 548 (3), 319 (68), 317 (9), 283 (100), 42 (43). Anal. Calcd For $C_{26}H_{18}N_4O_4Cl_4$: C, 52.73; H, 3.06; N, 9.46. Found: C, 52.89; H, 3.14; N, 9.32.

4d: White powder, IR (KBr, cm^{-1}):1714, 1626, 1263, 1074; ^1H NMR (CF_3COOD, 400 MHz): 73-7.61 (m, 4H, Ar - H), 7.32-7.29 (m, 4H, Ar-H), 7.22-7.11 (m, 4H, Ar-H), 6.95 (s,2H, 2 - H), 2.44 (s, 6H, $2CH_3$), 2.38 (6H, $2COCH_3$); MS (m/z, %): 482 (M^+, 12), 440 (21), 396 (6), 265 (100), 263 (73), 147 (26), 117 (10), 102 (84), 42 (89). Anal. Calcd For$C_{28}H_{26}N_4O_4$:C,69.97; H, 5.43; N, 11.61.Found:C, 69.81; H, 5.50; N, 11.61.

4e: White powder, IR (KBr, cm^{-1}): 1687, 1629, 1261, 1081; ^1H NMR (CF_3COOD, 400 MHz): 7.81-7.59 (m, 4H, Ar-H), 7.34-7.18 (m, 4H, Ar-H), 7.09-7.01 (m, 4H, Ar-H), 6.91 (s, 2H, 2-H), 3.75 (s, 6H, $2OCH_3$), 2.39 (6H, $2COCH_3$); MS (m/z): 514 (M^+, 7), 472 (11), 468 (21), 281 (100), 279 (45), 147 (21), 102 (76), 42 (91). Anal. Calcd For $C_{28}H_{26}N_4O_6$: C, 65.32; H, 5.09; N, 10.89. Found: C, 65.49; H, 5.11; N, 10.72.

4f: White powder, IR (KBr, cm^{-1}): 1702, 1631, 1273, 1082; ^1H NMR (CF_3COOD, 400 MHz): 9.96 (s, 2H, 2OH); 7.87-7.56 (m, 4H, Ar-H), 7.31-7.17 (m, 5H, Ar-H), 7.09-7.01 (m, 5H, 2-H, Ar-H), 2.40 (6H, $2COCH_3$); MS (m/z): 486 (M^+, 3), 444 (21), 402 (15), 267 (87), 265 (19), 147 (29), 102 (73), 42 (100). Anal. Calcd For $C_{26}H_{22}N_4O_6$: C, 64.19; H, 4.56; N, 11.52. Found: C, 64.33; H, 4.49; N, 11.47.

4g: White powder, IR (KBr, cm^{-1}): 1714, 1629, 1260, 1084; ^1H NMR (CF_3COOD, 400 MHz): 7.74-7.67 (m, 4H, Ar-H), 7.45-7.23 (m, 5H, Ar-H), 6.79-6.74 (m, 5H, 2-H, Ar-H), 2.91 (s, 12H, $2N(CH_3)_2$), 2.38 (6H, $2COCH_3$); MS (m/z): 540 (M^+, 3), 49 (14), 456 (9), 32 4(100), 322 (63), 147 (32), 102 (41), 42 (46). Anal. Calcd For $C_{30}H_{32}N_6O_4$: C, 66.65; H, 5.97; N, 15.55. Found: C, 66.52; H, 5.90; N, 15.41.

4h: Yellow powder, IR (KBr, cm^{-1}): 1697, 1630,1271, 1087; ^1H NMR (CF_3COOD, 400 MHz): 7.86-8.23 (m, 4H, Ar-H), 7.76-7.43 (m, 4H, Ar-H), 7.26-7.13 (m, 4H, Ar-H), 7.10 (s, 2H, 2 - H), 2.36 (6H, $2COCH_3$); MS (m/z): 544 (M^+, 4), 502 (12), 460 (17), 296 (87), 147(51), 102 (17), 42 (100). Anal. Calcd For $C_{26}H_{20}N_6O_8$: C, 57.35; H, 3.70; N, 15.43. Found: C, 57.49; H, 3.81; N, 15.32.

4i: Pale Yellow powder, IR (KBr, cm^{-1}): 1720, 1634, 1263, 1082; ^1H NMR (CF_3COOD, 400 MHz): 7.89-7.80 (m, 3H, Ar-H), 7.69-7.53 (m, 4H, Ar-H), 7.31-7.20 (m, 5H, Ar-H), 7.08 (s, 2H, 2 - H), 2.38 (6H, $2COCH_3$); MS (m/z): 544 (M^+, 8), 502 (21), 460 (10), 296 (100), 147 (33), 102 (21), 42 (76). Anal. Calcd For $C_{26}H_{20}N_6O_8$: C, 57.35; H, 3.70; N, 15.43. Found: C, 57.21; H, 3.62; N, 15.57.

4j: White powder, IR (KBr, cm^{-1}): 1711, 1631, 1257, 1078; ^1H NMR (CF_3COOD, 400 MHz): 8.19-8.16 (m, 4H, Ar-H), 8.06-8.02 (m, 4H, Ar-H), 7.79-7.70 (m, 5H, Ar-H), 7.66-7.63 (m, 2H, 2-H, Ar-H), 2.35 (6H, $2COCH_3$), MS (m/z): 454 (M^+, 4), 412 (3), 368 (7), 267 (38), 251 (100), 42 (12). Anal. Calcd For $C_{26}H_{22}N_4O_4$: C, 68.71; H, 4.88; N, 12.33. Found: C, 68.60; H, 4.95; N, 12.47.

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