SYNTHESIS AND ANTIBACTERIAL ACTIVITIES OF 1,3-BIS[3-N-ACETYL-2-ARYL-1,3,4-OXADIAZOLINE-5-YL]BENZENES

De-Jiang Li*, Fei-Jun Dan[a], He-Qing Fu[b]
College of Chemistry and Life Science, China Three Gorges University, Yichang 443002, P. R. China[a] and Research Institute of Chemical Engineering, South China University of Technology, Guangzhou 510640, P. R. China[b]
e-mail: lideiiang999@yahoo.com.cn

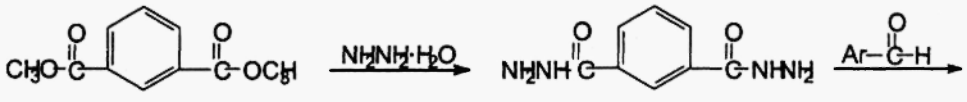
Abstract: Dimethyl isophthalate (**1**) was reacted with 80% hydrazine hydrate in refluxing ethanol for 16 h to give isophthalic dihydrazide (**2**). Condensation of **2** with aromatic aldehydes afforded corresponding hydrazones **3a-3i.** Cyclization of **3a-3i** with acetic anhydride in refluxing for 4-5 h afforded 1,3-Bis[3-N-acetyl-2-aryl-1,3,4-oxadiazoline-5-yl]benzenes (**4a-4i**). The structures of 4a-4i 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

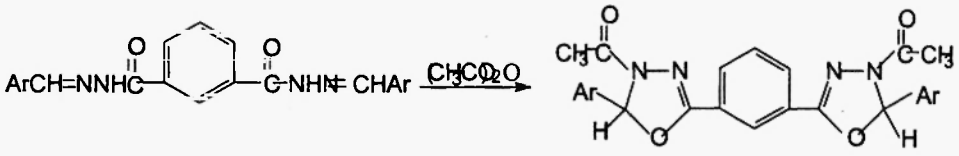
1,3,4-Oxadiazoline derivatives are found to possess significant biological activities such as antifungal (1), insecticidal (2), CNS depressant (3-5), anticonvulsant effects and growth accelerator for plant. They are highly important heterocycles, and have been used in research and development of agrochemicals 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-3i** 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 isophthalate (**1**) was reacted with 80% hydrazine hydrate in refluxing ethanol for 16 h to give isophthalic dihydrazide (**2**). Condensation of **2** with aromatic aldehydes afforded corresponding hydrazones **3a-3i.** Cyclization of **3a-3i** with acetic anhydride in refluxing for 4-5 h gave the title compounds **4a-4i** (Table-1). Thin layer chromatography was employed to follow the progress of the above reactions.



1 **2a ~ 2i**



3a ~ 3i 4a ~ 4i

Scheme-1

The structures of all compounds **4a-4i** were established on the basis of elemental analysis and spectral data. The IR spectral data of compounds **4a-4i** showed bands at 1669-1685 cm^{-1}, 1629-1638 cm^{-1}, 1231-1245 cm^{-1}, and 1075-1091 cm^{-1} due to C=O, N=C, N-N=C and C-O-C, respectively. The ^1H NMR spectra of **4a-4i** exhibited multiple signals in the δ 7.11-8.49 range accounting for hydrogen of aryl group, 2.30-2.38 range accounting for the 6 hydrogens of $-2COCH_3$. With compound **4a** as an example, it exhibited multiple signals in the δ 7.50-7.41, 7.94-7.52, 8.53 ~ 8.15 ranges accounting for 14 hydrogens of two oxadiazoline rings and phenyl groups.The EI-MS for compounds **4a-4i** exhibited molecular ion peaks. For example, **4a** showed strong molecular ion peak M^+, M+2 with m/z 522, 524 and 11%, 6% relative abundance, respectively.

Table-1 : Preparation of 1,3-Bis[3-N-acetyl-2-aryl-1,3,4-oxadiazoline-5-yl]benzenes (**4a-4i**) from hydrazones **3a-3i**

Entry	Ar	Condition	Yield (%)[a]	m.p. (°C)
4a	4-Cl-Ph	150-155°C/4.5 h	75	190-192
4b	2-Cl-Ph	150-155°C/5.0 h	70	177-179
4c	2,4-Cl_2-Ph	1150-155°C/4.0 h	67	201-203
4d	4-CH_3-Ph	150-155°C/5.0 h	80	201-203
4e	4-OCH_3-Ph	150-155°C/4.5 h	79	194-196
4f	4-OH-Ph	150-155°C/5.0 h	65	178-180
4g	Ph	150-155°C/4.0h	80	193-195
4h	4-NO_2-Ph	150-155°C/4.5 h	70	198-199
4i	3-NO_2-Ph	150-155°C/5.0 h	72	188-190

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

Compounds **4a-4i** 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-2 : The Antibacterial Activities of Compounds **4a-4i**

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

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 isophthalate(**1**), isophthalic 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 4.0-4.5 hours at 150-155°C, 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-4i.**

4a: White powder, IR (KBr, cm^{-1}): 1675, 1638, 1231, 1090; ^1H NMR (CF_3COOD, 400 MHz): 2.32 (6H, $2COCH_3$), 7.4-7.50 (m, 5H, 2-H, Ar-H), 7.52-7.94 (m, 5H, Ar-H), 8.15 ~ 8.53 (m, 4H, Ar-H); MS (m/z): 524 (6), 522 (M^+, 11), 480 (11), 438 (19), 327 (14), 285 (100), 42 (37). Anal. Calcd For $C_{26}H_{20}N_4O_4Cl_2$: C, 59.67; H, 3.85; N, 10.71. Found: C, 59.79; H, 3.72; N, 10.60.

4b: White powder, IR (KBr, cm^{-1}): 1684, 1633, 1238, 1087; ^1H NMR (CF_3COOD, 400 MHz): 2.34 (6H, $2COCH_3$), 7.34-7.42 (m, 4H, 2-H, Ar-H), 7.49-7.51 (m, 3H, Ar-H),

7.53-7.84 (m, 4H, Ar-H), 8.14-8.43 (m, 3H, Ar-H); MS (m/z): 524 (4), 522 (M^+, 9), 480 (15), 438 (10), 327 (10), 285 (100), 42 (40). Anal. Calcd For $C_{26}H_{20}N_4O_4Cl_2$: C, 59.67; H, 3.85; N, 10.71. Found: C, 59.50; H, 3.94; N, 10.71.

4c: White powder, IR (KBr, cm^{-1}): 1691, 1640, 1244, 1080; ^1H NMR (CF_3COOD, 400 MHz): 2.31 (6H, $2COCH_3$), 7.47-7.52 (m, 5H, 2-H, Ar-H), 7.56-7.71 (m, 4H, Ar-H), 8.10-8.28 (m, 3H, Ar - H); MS (m/z): 592 (3), 590 (M^+, 4), 548 (6), 319 (42), 317 (5), 283 (100), 42 (25). Anal. Calcd For $C_{26}H_{18}N_4O_4Cl_4$: C, 52.73; H, 3.06; N, 9.46. Found: C, 52.84; H, 3.15; N, 9.29.

4d: White powder, IR (KBr, cm^{-1}): 1673, 1645, 1240, 1075; ^1H NMR (CF_3COOD, 400 MHz): 2.32 (6H, $2COCH_3$), 2.44 (s, 6H, $2CH_3$), 7.41-7.53 (m, 5H, 2-H, Ar-H), 7.57-7.89 (m, 5H, Ar-H), 8.01-8.06 (m, 4H, Ar-H); MS (m/z): 482 (M^+, 6), 440 (12), 265 (100), 117 (30), 42 (26). Anal. Calcd For $C_{28}H_{26}N_4O_4$: C, 69.97; H, 5.43; N, 11.61. Found: C, 69.78; H, 5.50; N, 11.56.

4e: White powder, IR (KBr, cm^{-1}): 1682, 1641, 1237, 1083; ^1H NMR (CF_3COOD, 400 MHz): 2.38 (6H, $2COCH_3$), 3.93 (s, 6H, $2OCH_3$), 7.02-7.26 (m, 4H, 2-H, Ar-H), 7.53-7.96 (m, 5H, Ar-H), 8.32-8.48 (m, 5H, Ar-H); MS (m/z): 514 (M^+, 49), 473 (26), 430 (18), 281 (62), 133 (100), 42 (24). 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}): 1690, 1628, 1243, 1078; ^1H NMR (CF_3COOD, 400 MHz): 2.35 (6H, $2COCH_3$), 7.11-7.28 (m, 5H, 2-H, Ar-H), 7.47-7.82 (m, 5H, Ar-H), 8.03-8.15 (m, 4H, Ar-H), 9.93 (s, 2H, 2OH); MS (m/z): 486 (M^+, 5), 444(14), 402 (30), 266 (100) , 42 (31). Anal. Calcd For $C_{26}H_{22}N_4O_6$: C, 64.19; H, 4.56; N, 11.52. Found: C, 64.33; H, 4.48; N, 11.45.

4g: White powder, IR (KBr, cm^{-1}): 1689, 1633, 1240, 1082; ^1H NMR (CF_3COOD, 400 MHz): 2.33 (6H, $2COCH_3$), 7.61-7.65 (m, 5H, 2-H, Ar-H), 7.73-7.81 (m, 4H, Ar-H), 8.01-8.03 (m, 5H, Ar-H), 8.19-8.22 (m, 2H, Ar-H); MS (m/z): 454 (M^+, 5), 412 (5), 368 (11), 267 (38), 251 (100), 42 (27). Anal. Calcd For $C_{26}H_{22}N_4O_4$: C, 68.71; H, 4.88; N, 12.33. Found: C, 68.56; H, 4.72; N, 12.49.

4h: Yellow powder, IR (KBr, cm^{-1}): 1669, 1641, 1245, 1087; ^1H NMR (CF_3COOD, 400 MHz): 2.30 (6H, $2COCH_3$), 7.30-7.57 (m, 5H, 2-H, Ar-H), 7.69-7.91 (m, 5H, Ar-H), 8.21-8.43 (m, 4H, Ar-H); MS (m/z): 544 (M^+, 3), 502 (10), 460 (25), 296 (87), 147(100), 42 (18). Anal. Calcd For $C_{26}H_{20}N_6O_8$: C, 57.35; H, 3.70; N, 15.43. Found: C, 57.51; H, 3.76; N, 15.33.

4i: Yellow powder, IR (KBr, cm^{-1}): 1670, 1629, 1241, 1091; ^1H NMR (CF_3COOD, 400 MHz): 2.34 (6H, $2COCH_3$), 7.48-7.69 (m, 5H, 2-H, Ar-H), 7.75-8.07 (m, 4H, Ar-H), 8.35-8.49 (m, 5H, Ar-H); MS (m/z): 544 (M^+, 5), 502 (21), 460 (10), 296 (100), 147 (36), 42 (30). Anal. Calcd For $C_{26}H_{20}N_6O_8$: C, 57.35; H, 3.70; N, 15.43. Found: C, 57.26; H, 3.65; N, 15.58.

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