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CHEMISTRY OF NOVEL BIPHENYL CYCLIC 3, 5 DISUBSTITUTED 1, 2, 4 - OXADIAZOLES DERIVATIVES- THEIR SYNTHESIS AND MICROBIAL EVALUATION

Vijay V Dabholkar*, Navnath Shinde, Abhishek karekar, Prem naik

Organic Research Laboratory, Department of Chemistry,
KC College, Churchgate, Mumbai-400 020.
E-mail: vijaydabholkar@gmail.com
navnath1983@gmail.com

Abstract:
2′-Cyano-4-bromomethyl biphenyl **(1)** was reacted with hydroxylamine hydrochloride in the presences of sodium carbonate to obtain **(2)** which on further treatment with 2 methyl, 4 amino pyridine yielded **(3),** compound **(2)** on condensation with L- valine methyl ester gave **(4)** which was then further cyclised with aliphatic bromo alkane to yield the respective cyclic 3,5 disubsutited 1,2,4 oxadiazoles.The structures of the synthesized compounds were confirmed by physico-chemical test and spectral techniques, representative samples evaluated for their antimicrobial activity against gram positive and gram negative bacteria.

Key words: Oxadiazole, Biphenyl compound, Dibromo alkane, L- valine methyl ester.

Introduction:

Oxadiazole are interesting heterocycles present in a variety of biological compounds such as coronary vasodilators, local anesthetics, anxiolytics [I] and diuretics [II]. These compounds can exhibit anti micotic properties [III] can act as anti-inflammatory agents [IV] and were tested on their antibacterial activity against Staphylococcus Aureus, Streptococcus Pneumonia Escherichia Coli, Pseudomonas Aeruginosa, and Micrococcus [V, VI]. Several methods were already described in the literature to synthesize 1 ,2,4-oxadiazoles [VII], also these were synthesized by condensation of amidoximes with carboxylic acids in the presence of a coupling reagent [VIII] as well as the cycloaddition of nitrile oxides to amidoximes in solution and on solid support [IX,X]. 1, 2, 4-Oxadiazole rings occur widely in biologically active synthetic compounds and are often used in drug discovery as hydrolysis-resisting bioisosteric replacements for ester or amide functionalities. [XI- XVII]

Experimental

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The progress of reaction was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as

visualizing agent. ^{1}H NMR spectra were recorded on Varian 300 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm). C, H, N estimation was recorded on Carlo Erba 1108 (CHN) Elemental Analyzer.

Synthesis of 3, 5 di (4-bromomethyl-biphenyl)-6', 6"-yl) 1, 2, 4–oxadiazole (2)

A solution of sodium carbonate (0.05 mol) in water (5 ml) was added to a mixture of 2′-cyano-4-bromomethyl biphenyl (0.05 moles) and hydroxylamine hydrochloride (0.05 moles) in ethylene glycol (15 ml). The resulting mixture was heated under reflux (T=195°C) for 30 hours with vigorous stirring. After cooling the reaction mixture was filtered to remove the sodium chloride formed during the reaction and 100 ml of water was added to dilute the solvent. Upon cooling colorless crystals separated out which was filtered & crystallized from ethanol to get pure (2).M.P. =115-120 °C, yield = 88 %

IR (cm-1): 1660(C=N), ^{1} HNMR (DMSO-d6, δ/ ppm): 4.32 (s, 4H, CH_2), 7.12-7.56 (m, 16H, Ar -H), ^{13}C NMR (DMSO-d6, δ/ ppm): 42.14 (Ar-CH_2), 121-135 (Ar-C), 156(C=N)

LCMS; m/z: 560; Anal.Calcd for $C_{28}H_{20}Br_2N_2O$ C, 60.02; H, 3.60; N, 5.00% Found: C, 60.54; H, 3.69, N, 5.05 %

Synthesis of 3, 5{4, 4'-2-aza-2-[2-methyl pyridine-4 yl] - propano} di (biphenyl-6', 6"-yl) -1, 2, 4 –Oxadiazole (3)

A mixture of compound **(2)** (1 mole), 2-methyl, 4-amine pyridine (2 mole), TEA (4 mole), & toluene was refluxed for 5-6 hr. Progress of reaction was monitored by TLC. Upon completion reaction mass was quenched in water. Organic layer was separated, concentrated to get pale yellow compound(3)

B.P=165°C, yield = 71%

IR (cm-1): 1666(C=N), ^{1}H NMR (DMSO-d6, δ/ ppm): 2.41(s, 3H, CH_3), 4.22 (s, 4H, CH_2), 7.12-8.31 (m, 19H, Ar -H), ^{13}C NMR (DMSO-d6, δ/ ppm): 21.42(CH_3),60.14 (Ar-CH_2), 122-141(Ar-C), 156(C=N) LCMS; m/z: 506; Anal.Calcd for $C_{34}H_{26}N_4O$ C,80.61; H, 5.16; N, 11.04% Found: C, 80.58; H, 5.66, N, 11.36 %

Synthesis of 3, 5 di [4-{2-aza, 3-carmethoxy, 4-methyl pentayl} biphenyl-6', 6"-yl]-1, 2, 4 – Oxadiazole (4)

A mixture of compound **(2)** (1 mole), L-valine methyl ester (2 mole), DMF, potassium carbonate (2.5 mole) & cuprous iodide (0.01 mole) was heated for 10 hr. (T=85^{0}C). The progress of reaction was monitored by TLC. Upon completion reaction mass was quenched in water. White solid was obtained by filtration (4)

M.P. =127-130°C, yield = 72 %

IR (cm-1): 1750 (C=O ester)^{1}H NMR (DMSO-d6, δ/ ppm):1.10(d,12H,CH_3),1.80 (m,2H ,CH)2.00(d, 2H, CH),3.60 (s, 6H,OCH_3),3.90(s,4H,Ar-CH_2),5.20 (bs,2H ,NH), 7.12-7.50 (m, 16H, Ar -H), ^{13}C NMR (DMSO-d6, δ/ ppm): 12.50(CH_3),17-20.0(CH),55.0(O-CH_3) ,58.14 (Ar-CH_2), 120-138 (Ar-C), 154(C=N) LCMS; m/z: 661; Anal.Calcd for $C_{40}H_{44}N_4O_5$ C,72.70; H, 6.71; N, 8.45% Found: C 72.80; H, 6.50, N, 8.36 %

Synthesis of (5-7)

A mixture of compound **(4)** (1 mole), dibromo alkane (n=2, 3, 4) (1 mole), acetonitrile, potassium carbonate (2.5 mole) & cuprous iodide (0.01 mole) was heated for 20 hr. (T=55^{0}C).

The progress of reaction was monitored by TLC. Upon completion reaction mass was quenched in water. White solid was obtained by filtration (5-7).

Spectral Data-3, 5[4, 4'-2, 6-diaza {2, 5 di (2-carbmethoxy-3methyl propyl) heptano}]-di (biphenyl-6', 6"-yl) -1, 2, 4 –Oxadiazole (5)

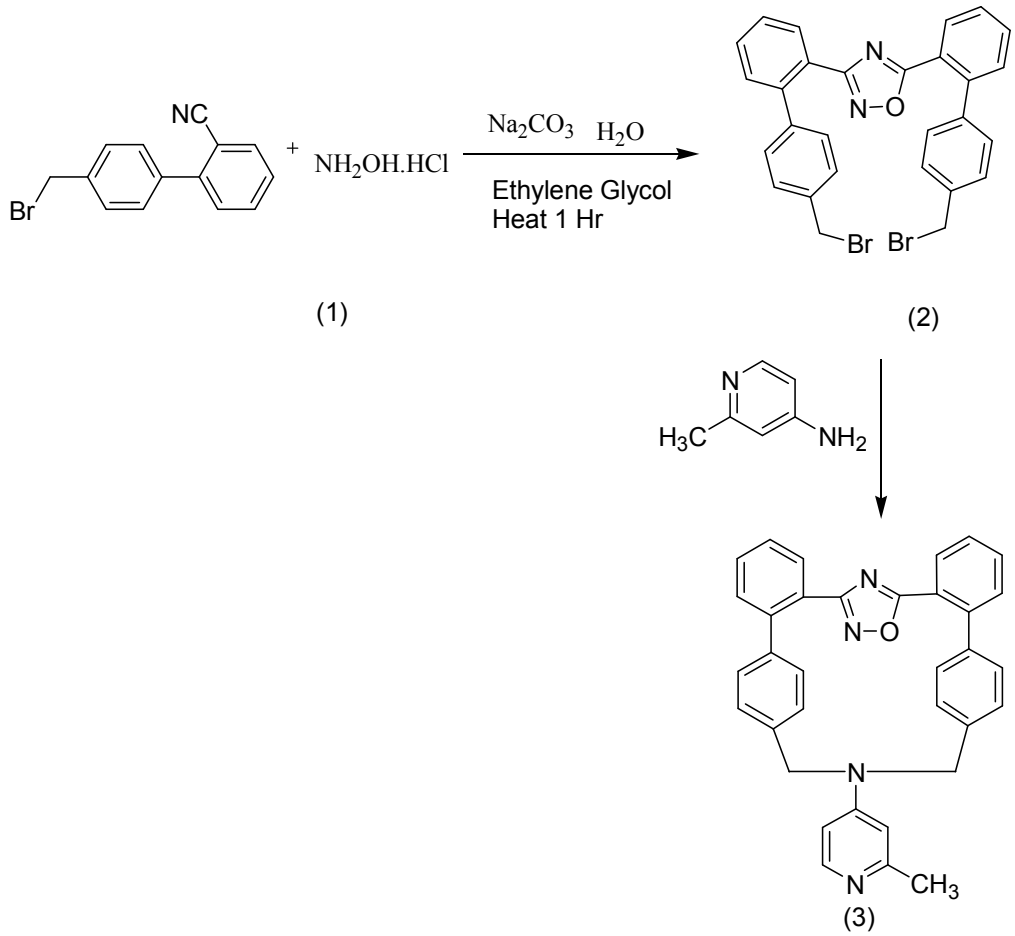
Yield: 65%; m.p. =150-155 °C: IR (cm-1): 1725(C=O ester), ^{1}H NMR (DMSO-d6, δ/ppm): 1.10(d,12H,CH_3),1.72 (m,2H ,CH),1.85 (d, 2H, CH), 2.0 (m,2H,CH2) ,2.50 (t,4H,N- CH_2),3.80 (s, 6H,OCH_3),4.15 (s,4H,Ar-CH_2),5.40 (bs,2H ,NH), 7.25-7.75 (m, 16H, Ar -H), ^{13}C NMR (DMSO-d6, δ/ppm): 11.50(CH_3),18.12(CH),25.25(CH_2),54.68(N-CH_2),58.0 (O-CH_3) ,60.25 (Ar-CH_2), 118-135 (Ar-C), 158(C=N) LCMS; m/z: 673; Anal.Calcd for $C_{41}H_{46}N_4O_5$ C, 72.70; H, 6.71; N, 8.45% Found: C 72.80; H, 6.50, N, 8.36 %

Spectral Data -3, 5[4, 4'-2,5-diaza{2,5 di (2-carbmethoxy-3methyl propyl) hexano }]-di (biphenyl-6', 6"-yl) -1, 2, 4 –Oxadiazole (6) Yield: 71%; m.p. =175-178 °C: IR(cm-1): 1725(C=O ester), ^{1}H NMR (DMSO-d6, δ/ppm):1.12(d,12H,CH_3),1.70 (m,2H ,CH),1.90 (d, 2H, CH),2.50 (t,4H CH_2),3.70 (s, 6H,OCH_3),4.02 (s,4H,Ar-CH_2),5.20 (bs,2H ,NH), 7.12-7.50 (m, 16H, Ar -H), ^{13}C NMR (DMSO-d6, δ/ppm): 12.50(CH_3),17-20.0(CH),48.68 (N-CH_2),55.0(O-CH_3) ,58.14 (Ar-CH_2), 120-138 (Ar-C), 154(C=N) LCMS; m/z: 661; Anal.Calcd for $C_{40}H_{44}N_4O_5$ C, 72.70; H, 6.71; N, 8.45% Found: C 72.80; H, 6.50, N, 8.36 %

Spectral Data for structure-3, 5[4, 4'-2, 7-diaza {2, 5 di (2-carbmethoxy-3methyl propyl) octane}] -di (biphenyl-6', 6"-yl) -1, 2, 4 –Oxadiazole (7)

Yield: 80%; m.p. =140-145 °C: IR (cm-1): 1730(C=O ester), ^{1}H NMR (DMSO-d6, δ/ ppm): 1.15(d,12H,CH_3),1.60 (m,2H ,CH),1.70 (d, 2H, CH), 2.1 (m,4H,CH2) ,2.60 (t,4H N-CH_2),3.67 (s, 6H,OCH_3),4.20 (s,4H,Ar-CH_2),5.25 (bs,2H ,NH), 7.15-7.75 (m, 16H, Ar -H), ^{13}C NMR (DMSO-d6, δ/ ppm):10.50(CH_3),19.25(CH),25.65(CH_2),55.12(N-CH_2),59.0 (O-CH_3) ,61.15 (Ar-CH_2), 120-135 (Ar-C), 155.68(C=N) LCMS; m/z: 685; Anal.Calcd for $C_{42}H_{48}N_4O_5$ C, 74.70; H, 7.71; N, 7.45% Found: C 74.80; H, 7.50, N, 7.36 %

Reaction Scheme :



Reaction Scheme :

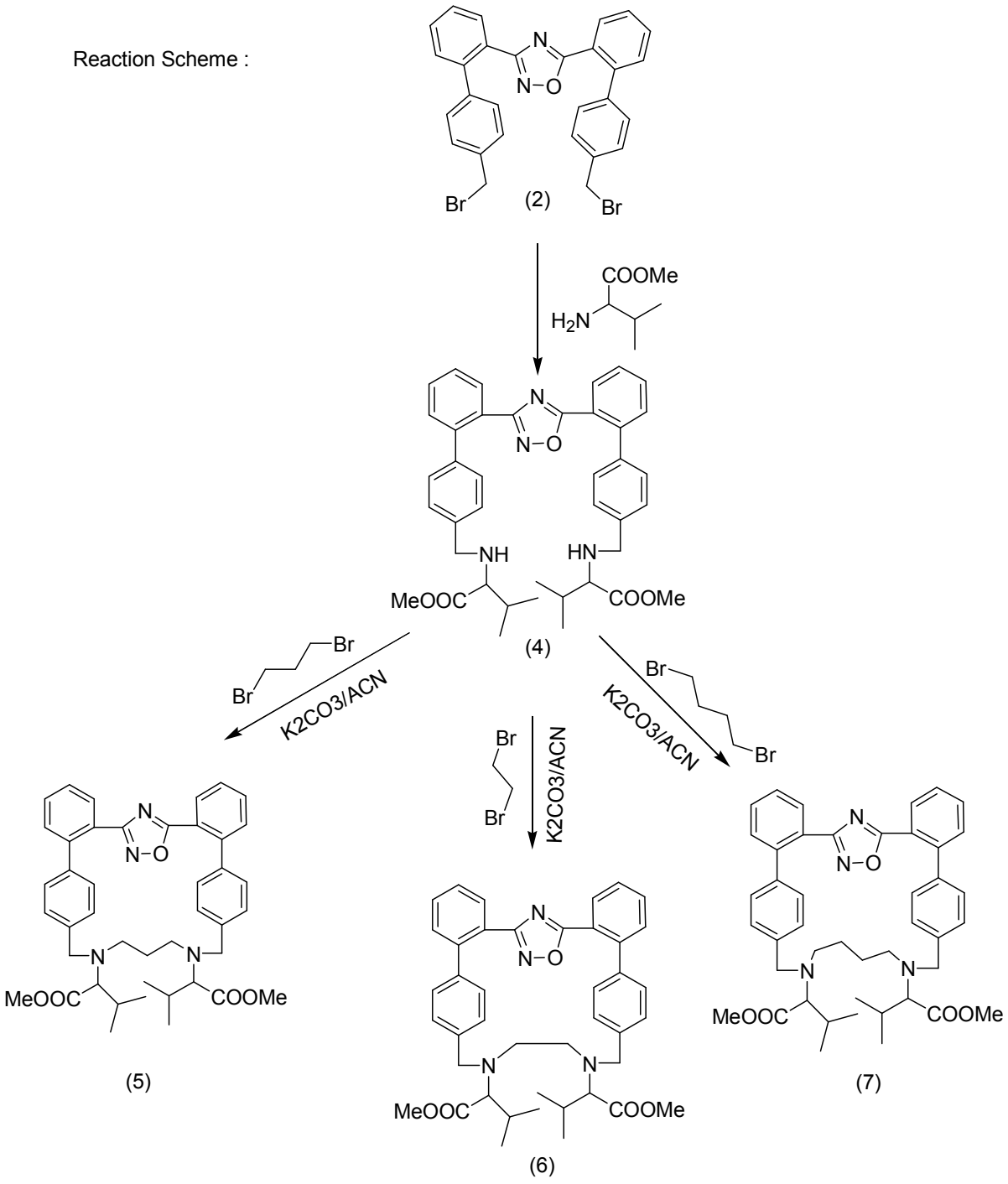


Table I. **Antimicrobial activities of some newly synthesized compounds.**

Compds	Inhibition Zone (mm)						
	Gram-negative		Gram-positive		Fungi		Yeast
	E.coli	*P.Putide*	*B.Subtilis*	*S.lactis*	*A.niger*	*P.Sp.*	*C.Albicans*
3	16	14	19	22	16	9	9
5	17	15	18	20	19	11	9
6	16	15	19	18	18	9	8
7	19	20	20	21	19	11	11
DMSO	0	0	0	0	0	0	0
Amphicilin®	23	21	20	22	23	15	15

E.coli. = Escherichia coli; P.Putide = Pseudomonas Putide; B. Subtilis = Bacillus Subtilis; S. lactis = Sterptococcuslactis; A. niger = Aspergillusniger; P. Sp. = PenicilliumSp; C. Albicans = candida Albicans.

The sensitivity of microorganisms to the tested compounds is identified in the following manner*;

Highly Sensitive = Inhibition zone: 15-21 mm

Moderately Sensitive = Inhibition zone: 9-15 mm

Slightly Sensitive = Inhibition zone: 5-8 mm

Not Sensitive = Inhibition zone: 0 mm

* Each result represents the average of triplicate readings.

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