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Synthesis of nitrogen-containing dispiroheterocycles using nitrilimines (II)

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Abstract: A series of 1,2,4,9,10,12-hexaazadispiro[4.2.4.2]tetradeca-2,10-dienes **5a**–**j** was synthesized by the reaction of 1,4-cyclohexanedione dioxime (**3**) with appropriate nitrilimines (**2**). The microanalysis and spectral data of the synthesized compounds are in full agreement with their molecular structure. The microbial features of some of the synthesized compounds were studied by a known method.

Keywords: Dispiroheterocycles; 1,4-cyclohexanedione oxime; nitrilimines; cycloaddition.

INTRODUCTION

Recently, a versatile and efficient one-pot synthesis of octaazadispiroheterocyclic compounds was described in which 1,4-cyclohexanedione methyl hydrazone and nitrilimines, generated *in situ* from the corresponding hydrazonoyl halides by the action of a suitable base, were utilized.[1] As part of our continuing interest in the construction of spiroheterocyclic systems by means of the nitrilimine 1,3-dipolar cycloaddition methodology,[2–5] the reaction of *C*-substituted-*N*--arylnitrilimines (**2**) with 1,4-cyclohexanedione dioxime (**3**) in an attempt to synthesize the hitherto unknown hexaazadispiroheterocyclic compounds **5a**–**j** is reported herein, with the aim of investigating their biological activities.

RESULTS AND DISCUSSION

The hydrazonoyl halides **1a**–**j** were prepared by a modified literature procedure[6–14] and the nitrilimines **2** were generated *in situ* from **1** by reaction with triethylamine (Et_3N). The non-isolatable nitrilimines **2** reacted readily with 1,4--cyclohexanedione dioxime **3** affording the corresponding 1,2,4,9,10,12-hexaaza-

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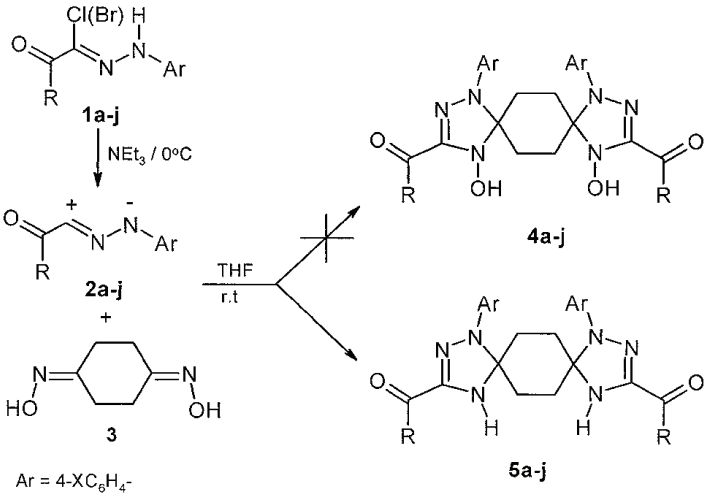
dispiro[4.2.4.2]tetradeca-2,10-dienes **5a**–**j** (Scheme 1). The formation of compounds **5a**–**j** is assumed to involve the primary cycloadducts **4**, which tautomerize to amine oxide-type intermediates that are deoxygenated by triethylamine to NH triazoles **5a**–**j**. It is worth mentioning that the nitrile oxides generated *in situ* from the respective hydroxamoyl chlorides with triethylamine as the base react with oximes to give 4-hydroxy-4,5-dihydro-1,2,4-oxadiazoles.[15]



Entry	a	b	c	d	e	f	g	h	i	j
R	Me	Me	MeO	Ph	PhNH	PhNH	PhNH	2-$C_{10}H_7$	2-C_4H_3O	2-C_4H_3S
X	H	Cl	Cl	Cl	Cl	Br	Me	Cl	Cl	Cl

Scheme 1. Synthetic pathway for the preparation of compounds **5a–j.**

Characterization data for the synthesized compounds

*3,11-Diacetyl-1,9-diphenyl-1,2,4,9,10,12-hexaazadispiro[4.2.4.2]tetradeca--2,10-diene (**5a**)*. Yield: 47 %; m.p. 180–182 °C. Anal. Calcd. for $C_{24}H_{26}N_6O_2$ (FW 430.51): C, 66.96; H, 6.09; N, 19.52 %. Found: C, 67.18; H, 5.90; N, 19.40 %. IR (KBr, cm^{-1}): 3385 (NH), 1678 (C=O), 1622 (C=N), 630 (C–Cl). ^{1}H-NMR (DMSO-d_6, δ / ppm): 7.42–7.12 (10H, *m*, aromatic), 5.74 (2H, *s*, 2 NH, D_2O exchangeable), 2.48 (6H, *s*, 2 CH_3), 2.17–2.03 (8H, *m*, 4 CH_2). ^{13}C-NMR (DMSO--d_6, δ / ppm): 189.65 (C=O), 147.95 (C=N), 141.46–120.18 (C=C Ar), 87.45 (spiro carbons), 35.07, 34.83 (2 CH_2), 26.45 (CH_3); MS (*m/z*): 430 ($M^{+\bullet}$).

*3,11-Diacetyl-1,9-bis(4-chlorophenyl)-1,2,4,9,10,12-hexaazadispiro[4.2.4.2]-tetradeca-2,10-diene (**5b**)*. Yield: 45 %; m.p. 186–188 °C. Anal. Calcd. for $C_{24}H_{24}Cl_2N_6O_2$ (FW 499.40): C, 57.72; H, 4.84; N, 16.83 %. Found: C, 57.88; H, 4.74; N, 16.71 %. IR (KBr, cm^{-1}): 3385 (NH), 1676 (C=O), 1620 (C=N), 631

(C–Cl). ^{1}H-NMR (DMSO-d_6, δ / ppm): 7.48–7.14 (8H, *m*, aromatic), 5.74 (2H, *s*, 2 NH, D_2O exchangeable), 2.47 (6H, *s*, 2 CH_3), 2.16–2.01 (8H, *m*, 4 CH_2). ^{13}C-NMR (DMSO-d_6, δ / ppm): 189.71 (C=O), 147.96 (C=N), 141.94–121.10 (C=C Ar), 87.22 (spiro carbons), 35.10, 34.86 (2 CH_2), 26.48 (CH_3). MS (*m/z*): 498/500 (M^+, chlorine isotopes).

*1,9-Bis(4-chlorophenyl)-3,11-bis(methoxycarbonyl)-1,2,4,9,10,12-hexaaza-dispiro[4.2.4.2]tetradeca-2,10-diene (**5c**)*. Yield: 50 %; m.p. 173–175 °C. Anal. Calcd. for $C_{24}H_{24}Cl_2N_6O_4$ (FW 531.40): C, 54.25; H, 4.55; N, 15.81 %. Found: C, 54.46; H, 4.41; N, 15.95 %. IR (KBr, cm^{-1}): 3380 (NH), 1720 (C=O), 1625 (C=N), 628 (C–Cl). ^{1}H-NMR (DMSO-d_6, δ / ppm): 7.57–7.20 (8H, *m*, aromatic), 5.74 (2H, *s*, 2 NH, D_2O exchangeable), 3.74 (6H, *s*, 2 OCH_3), 2.18-2.04 (8H, *m*, 4 CH_2). ^{13}C-NMR (DMSO-d_6, δ / ppm): 156.69 (O–C=O), 147.90 (C=N), 141.90–121.16 (C=C Ar), 88.95 (spiro carbons), 54.22 (OCH_3), 35.56, 34.72 (2 CH_2). MS (*m/z*): 530/532 (M^+, chlorine isotopes).

*3,11-Dibenzoyl-1,9-bis(4-chlorophenyl)-1,2,4,9,10,12-hexaazadispiro[4.2.4.2]-tetradeca-2,10-diene (**5d**)*. Yield: 52 %; m.p. 179–181 °C. Anal. Calcd. for $C_{34}H_{28}Cl_2N_6O_2$ (FW 623.55): C, 65.49; H, 4.53; N, 13.48 %. Found: C, 65.30; H, 4.70; N, 13.65 %. IR (KBr, cm^{-1}): 3365 (NH), 1665 (C=O), 1618 (C=N), 620 (C–Cl). ^{1}H-NMR (DMSO-d_6, δ / ppm): 8.46–7.26 (18H, *m*, aromatic), 5.74 (2H, *s*, 2 NH, D_2O exchangeable), 2.00–1.95 (8H, *m*, 4 CH_2). ^{13}C-NMR (DMSO-d_6, δ / ppm): 184.86 (C=O), 148.10 (C=N), 142.15–121.19 (C=C Ar), 91.50 (spiro carbons), 35.54, 34.76 (2 CH_2). MS (*m/z*): 622/624 (M^+, chlorine isotopes).

*1,9-Bis(4-chlorophenyl)-3,11-bis(phenylaminocarbonyl)-1,2,4,9,10,12-hexa-azadispiro[4.2.4.2]-tetradeca-2,10-diene (**5e**)*. Yield: 47 %; m.p. 196–198 °C. Anal. Calcd. for $C_{34}H_{30}Cl_2N_8O_2$ (FW 653.58): C, 62.48; H, 4.63; N, 17.14 %. Found: C, 62.30; H, 4.72; N, 17.02 %. IR (KBr, cm^{-1}): 3375, 3248 (NH), 1655 (C=O), 1615 (C=N), 622 (C–Cl). ^{1}H-NMR (DMSO-d_6, δ / ppm): 8.90 (2H, *s*, 2 PhNH), 7.76–7.03 (18H, *m*, aromatic), 5.68 (2H, *s*, 2 NH, D_2O exchangeable), 2.13–2.06 (8H, *m*, 4 CH_2). ^{13}C-NMR (DMSO-d_6, δ / ppm): 159.36 (C=O), 147.86 (C=N), 141.43–121.10 (C=C Ar), 89.52 (spiro carbons), 35.50, 34.90 (2 CH_2); MS (*m/z*): 652/654 (M^+, chlorine isotopes).

*1,9-Bis(4-bromophenyl)-3,11-bis(phenylaminocarbonyl)-1,2,4,9,10,12-hexa-azadispiro[4.2.4.2]-tetradeca-2,12-diene (**5f**)*. Yield: 45 %; m.p. 201–203 °C. Anal. Calcd. for $C_{34}H_{30}Br_2N_8O_2$ (FW 742.48): C, 55.00; H, 4.07; N, 15.09 %. Found: C, 55.22; H, 3.95; N, 14.90 %. IR (KBr, cm^{-1}): 3380, 3257 (NH), 1654 (C=O), 1612 (C=N), 631 (C–Br). ^{1}H-NMR (DMSO-d_6, δ / ppm): 8.87 (2H, *s*, 2 PhNH), 7.78–7.15 (18H, *m*, aromatic), 5.67 (2H, *s*, 2 NH, D_2O exchangeable), 2.11–2.05 (8H, *m*, 4 CH_2). ^{13}C-NMR (DMSO-d_6, δ / ppm): 159.40 (C=O), 147.84 (C=N), 141.62–116.50 (C=C Ar), 89.60 (spiro carbons), 35.26, 34.90 (2 CH_2). MS (*m/z*): 742/744 (M^+, bromine isotopes).

*1,9-Bis(4-methylphenyl)-3,11-bis(phenylaminocarbonyl)-1,2,4,9,10,12-hexaazadispiro[4.2.4.2]-tetradeca-2,12-diene (**5g**)*. Yield: 48 %; m.p. 191–193 °C. Anal. Calcd. for $C_{36}H_{36}N_8O_2$ (FW 612.74): C, 70.57; H, 5.92; N, 18.29 %. Found: C, 70.45; H, 4.79; N, 18.42 %. IR (KBr, cm^{-1}): 3380, 3260 (NH), 1655 (C=O), 1612 (C=N). ^{1}H-NMR (DMSO-d_6, δ / ppm): 8.89 (2H, *s*, 2 PhNH), 7.80––7.13 (18H, *m*, aromatic), 5.67 (2H, *s*, 2 NH, D_2O exchangeable), 2.26 (6H, *s*, $2CH_3$), 2.10–2.04 (8H, *m*, 4 CH_2). ^{13}C-NMR (DMSO-d_6, δ / ppm): 159.24 (C=O), 147.90 (C=N), 141.55–119.94 (C=C Ar), 89.65 (spiro carbons), 35.50, 34.96 (2 CH_2), 23.40 (CH_3); MS (*m/z*): 612 (M^+).

*1,9-Bis(4-chlorophenyl)-3,11-di-2-naphthoyl-1,2,4,9,10,12-hexaazadispiro-[4.2.4.2]tetradeca-2,10-diene (**5h**)*. Yield: 54 %; m.p. 216–218 °C. Anal. Calcd. for $C_{42}H_{32}Cl_2N_6O_2$ (FW 723.67): C, 69.71; H, 4.46; N, 11.61 %. Found: C, 69.50; H, 4.35; N, 11.70 %. IR (KBr, cm^{-1}): 3365 (NH), 1650 (C=O), 1605 (C=N), 630 (C–Cl). ^{1}H-NMR (DMSO-d_6, δ / ppm): 8.45–7.22 (22H, *m*, aromatic), 5.74 (2H, *s*, 2 NH, D_2O exchangeable), 2.10–2.03 (8H, *m*, 4 CH_2). ^{13}C--NMR (DMSO-d_6, δ / ppm): 184.56 (C=O), 148.32 (C=N), 142.12–120.86 (C=C Ar), 91.63 (spiro carbons), 35.30, 34.75 (2 CH_2); MS (*m/z*): 722/724 (M^+, chlorine isotopes).

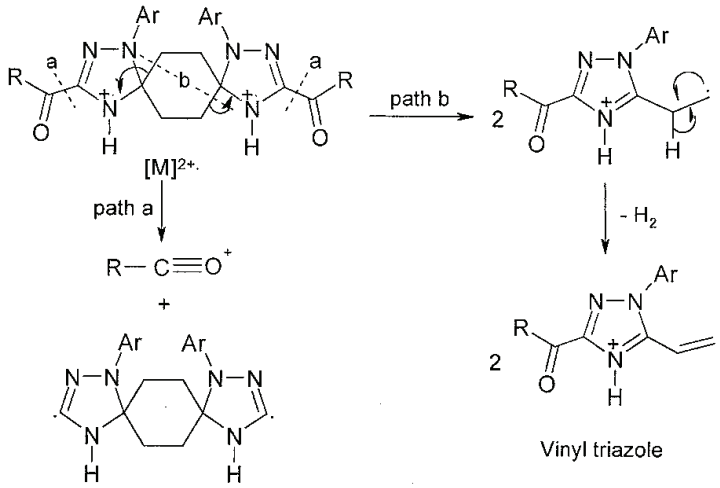
*1,9-Bis(4-chlorophenyl)-3,11-di-2-furoyl-1,2,4,9,10,12-hexaazadispiro-[4.2.4.2]tetradeca-2,10-diene (**5i**)*. Yield: 48 %; m.p. 194–196 °C. Anal. Calcd. for $C_{30}H_{24}Cl_2N_6O_4$ (FW 603.47): C, 59.71; H, 4.01; N, 13.93 %. Found: C, 59.85; H, 3.90; N, 13.85 %. IR (KBr, cm^{-1}) 3370 (NH), 1665 (C=O), 1615 (C=N), 627 (C–Cl). ^{1}H-NMR (DMSO-d_6, δ / ppm): 7.80–7.16 (14H, *m*, aromatic), 5.64 (2H, *s*, 2 NH, D_2O exchangeable), 2.16–2.10 (8H, *m*, 4 CH_2). ^{13}C--NMR (DMSO-d_6, δ / ppm): 174.56 (C=O), 148.25 (C=N), 143.20–121.58 (C=C Ar), 94.85 (spiro carbons), 35.41, 34.83 (2 CH_2). MS (*m/z*): 602/604 (M^+, chlorine isotopes).

*1,9-Bis(4-chlorophenyl)-3,11-di-2-thenoyl-1,2,4,9,10,12-hexaazadispiro-[4.2.4.2]tetradeca-2,10-diene (**5j**)*. Yield: 50 %; m.p. 180–182 °C. Anal. Calcd. for $C_{30}H_{24}Cl_2N_6O_2S_2$ (FW 635.60): C, 56.69; H, 3.81; N, 13.22 %. Found: C, 56.80; H, 3.65; N, 13.06 %. IR (KBr, cm^{-1}): 3375 (NH), 1660 (C=O), 1610 (C=N), 628 (C–Cl). ^{1}H-NMR (DMSO-d_6, δ / ppm): 7.84–7.12 (14H, *m*, aromatic), 5.65 (2H, *s*, 2 NH, D_2O exchangeable), 2.15–2.06 (8H, *m*, 4 CH_2). ^{13}C--NMR (DMSO-d_6, δ / ppm): 175.82 (C=O), 148.30 (C=N), 143.73–121.68 (C=C Ar), 94.64 (spiro carbons), 35.35, 34.66 (2 CH_2); MS (*m/z*): 634/636 (M^+, chlorine isotopes).

Spectral data analysis

Compounds **5a**–**j** gave satisfactory analyses for the proposed structures which are confirmed on the bases of their spectroscopic data. The electron impact (EI) mass spectra displayed the correct molecular ions (M^+) in accordance with the suggested structures. The base peak in all these compounds was that of the con-

jugated vinyl triazole cation (Scheme 2). This fragmentation pattern is well known for cycloalkanones.[16]



Scheme 2. The main fragmentation of compounds **5a**–**j**.

The IR spectra for **5a**–**j** showed absorption bands in the region 3380–3360 cm^{-1} and 1680–1650 cm^{-1}, assignable to NH and carbonyl group signals, respectively. Their ^{1}H-NMR spectra revealed, besides aromatic protons at 8.5–7.1 ppm, a D_2O exchangeable singlet signal in the region 5.7–5.6 ppm, assignable to the triazole ring NH proton. The ^{13}C-NMR spectra showed all the signals expected for the proposed structures and, in particular, the C5 and C8 signals (spiro carbons) were found at about 95–85 ppm. This is similar to reported values for spiro carbons flanked by two nitrogen atoms in five-membered heterocycles,[3–5] which provides strong evidence in support of the structures **5a**–**j**. The signal at about 148 ppm was attributed to the C=N of the triazole ring. The ^{15}N-NMR spectra of similar triazoles, such as 3-acetyl-5,5-dimethyl-1-phenyl-4,5-dihydro-1,2,4-triazole, which displayed a doublet for NH at 284.26 ppm relative to nitromethane ($^1J_{N–H}$ = 85 Hz, $^3J_{N–CH_3}$ = 2.5 Hz) were reported to support the suggested structure of the reaction products.[17] Further work on the structures of the synthesized compounds is ongoing.

Antimicrobial activity

The obtained antimicrobial activity data is reported in Table I as the average of three experiments. The results showed that all the tested compounds exhibited a marked degree of activity against bacteria and fungi compared with well-known antibacterial and antifungal substances, such as tetracycline and fluconazole. According to NCCLS (2004), zones of inhibition for tetracycline and fluconazole < 14 mm were considered resistant, between 15 and 18 mm as weakly

sensitive and > 19 mm sensitive. In addition, the results showed the degree of inhibition varied between the tested compounds.

TABLE I. Antimicrobial screening results of the tested compounds (zone of inhibition in mm)

Compound	Bacteria					Fungi	
	Enterococcus sp.	*E. coli*	*S. aureus*	*Klebsiella.* sp.	*Proteus* sp.	*C. albicans*	*A. niger*
5a	14	19	11	10	0	11	10
5c	14	18	12	0	0	13	8
5d	17	13	12	17	14	15	14
5f	12	15	10	8	0	12	12
5h	9	9	14	19	0	13	0
5j	15	12	10	15	11	14	10
DMF	–	–	–	–	–	–	–

EXPERIMENTAL

All melting points were determined on an A. Krüss Melting Point Meter equipped with a thermometer and are uncorrected. The IR spectra were measured as potassium bromide pellets using a Satellite 3000 Mid infrared spectrophotometer. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Bruker AM 300 MHz spectrometer at room temperature in DMSO-d_6 solution using tetramethylsilane (TMS) as the internal reference. Chemical shifts were recorded as δ values in ppm downfield from the internal TMS. Electron impact (EI) mass spectra were run on a Shimadzu GCMS-QP1000 EX spectrometer at 70 eV. Elemental analyses were performed at Cairo University, Egypt. The hydrazonoyl halides **1a**–**j**[6-14] and 1,4-cyclohexanedione dioxime **3**[18] were prepared according to literature procedures. Tetrahydrofuran (THF) and triethylamine were purchased from Avocado Research Chemicals, England, and used without further purification.

*General procedure for the reaction of nitrilimines **2** with 1,4-cyclohexanedione dioxime (**3**)*

Triethylamine (0.05 mol, 7 mL) in tetrahydrofuran (10 mL) was added dropwise to stirred mixture of oxime **3** (0.025 mol) and the appropriate hydrazonoyl halides **1a**–**j** (0.05 mol) in tetrahydrofuran (70 mL) at –5–0 °C. The reaction temperature was allowed to rise slowly to room temperature and stirring was continued over night. The precipitated salts were filtered off and the solvent was then evaporated. The residue was washed with water (100 mL) and in few cases the gummy products were triturated with ethanol (10 mL). The crude solid product was collected and recrystallized from ethanol to give the desired compounds.

Antimicrobial activity testing

Six of the newly synthesized compounds were screened *in vitro* for their antimicrobial activity against a variety of bacterial strains, such as *Enterococcus* sp., *Escherichia coli*, *Staphylococcus aureus*, *Klebsiella* sp. and *Proteus* sp., and fungi, such as *Aspergillus niger*, *Candida albicans*, employing the nutrient agar disc diffusion method[29-21] at a concentration of 10 mg mL^{-1} in dimethylformamide (DMF) and disc diameter of 6.5 mm by measuring the average diameter of the inhibition zone in mm.

CONCLUSIONS

Several new 1,2,4,9,10,12-hexaazadispiro[4.2.4.2]tetradeca-2,10-dienes were synthesized and characterized, and some of them proved to have potent antibac-

terial and antifungal activity. The results confirm that the antimicrobial activity is strongly dependent on the nature of the substituents at C3 and C11 of the triazole rings.

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ИЗВОД

СИНТЕЗА АЗОТОВИХ ДИСПИРОХЕТЕРОЦИКЛА УПОТРЕБОМ НИТРИЛИМИНА (II)

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Синтетисана је серија 1,2,4,9,10,12-хексаазадиспиро[4.2.4.2]тетрадека-2,10-диена **5a–j** реакцијом 1,4-циклохексадион-диоксима (**3**) и одговарајућих нитрилимина (**2**). Резултати микроанализе и спектрални подаци у складу су са претпостављеном структуром једињења. Испитане су микробиолошке активности једињења.

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