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SYNTHESIS OF NITROGEN- CONTAINING DISPIRO-HETEROCYCLES (III) USING NITRILIMINES

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ABSTRACT

A number of new substituted 1,2,4,9,10,12-hexaazadispiro-[4.2.4.2]tetra-deca-2,10-dienes **Va-j** have been obtained from the reaction of 1,4-cyclohexanedione benzoylhydrazone **III** with appropriate nitrilimines **II**. The microanalysis and spectral data of the synthesized compounds are in full agreement with their molecular structure. The microbial features of the synthesized compounds were studied by a known method.

KEYWORDS

Dispiroheterocycles, Benzoylhydrazone, Nitrilimines, Cycloaddition.

RESUMO

A reação de 1,4-ciclohexanaodiona benzoilhidrazona III com as nitriliminas apropriadas II levou a obtenção de vários novos 1,2,4,9,10,12-hexaazadispiro [4,2,4,2]tetra-deca-2,10-dienos Va-j. Os resultados de microanálise e dados espectroscópicos dos compostos sintetizados estão em pleno acordo com as suas estruturas moleculares. Os aspectos e as propriedades microbiais dos compostos sintetizados foram estudados com métodos estabelecidos.

PALAVRAS CHAVE

Dispiroheterociclos, Benzoilhidrazona, Nitriliminas, Cicloadição.

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Graphical abstract

Synthesis of Nitrogen-Containing Dispiroheterocycles (III) Using Nitrilimine

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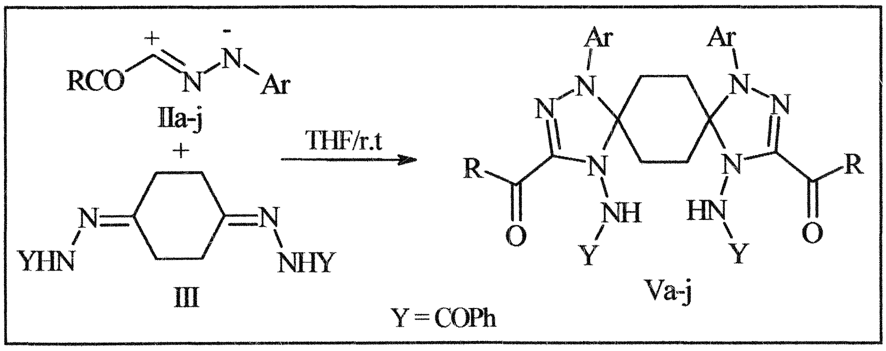

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1. INTRODUCTION

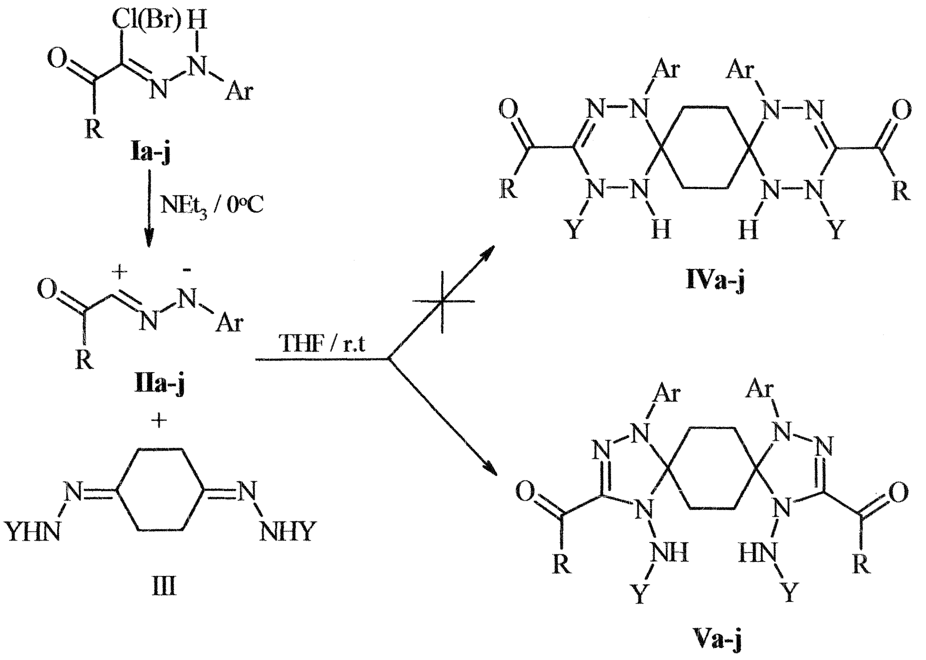
Recently, we described a versatile and efficient one-pot synthesis of hexa and octaazadispiro-heterocyclic compounds utilizing 1,4-cyclohexanedione oxime or methyl hydrazone and nitrilimines, generated in *situ* from the corresponding hydrazonoyl halides by the action of a suitable base [1,2].

As part of our continuing interest in the construction of spiroheterocyclic systems by means of the nitrilimine 1,3-dipolar cycloaddition methodology [3-6], we reported here the reaction of C-substituted-N-arylnitrilimines **II** with 1,4-cyclohexanedione benzoylhydrazone **III** in an attempt to synthesize the hitherto unknown hexaazadispiroheterocyclic compounds **Va-j** with the aim of investigating their biological activities.

2. RESULTS AND DISCUSSION

The hydrazonoyl halides **Ia-j** were prepared by a modified literature procedure and the nitrilimines **2** were generated in *situ* from **I** by reaction with triethylamine (Et_3N). The non isolable nitrilimines **II** reacted readily with 1,4-cyclohexanedione benzoylhydrazone **III** affording the five-membered dispiro heterocycles, 4,12-dibenzoylamino-1,2,4,9,10,12-hexaazadispiro[4.2.4.2]tetradeca-2,10-dienes **Va-j** as cycloaddition products instead of the dispirotetrazine cyclocondensation products **IVa-j** (Figure 1).

It is worth mentioning that, the dispiro-tetrazines were obtained from the reaction of nitrilimines with 1,4-cyclohexanedione methyl hydrazone [1]. This can be explained on the basis of the weak nucleophilicity of the nitrogen atom of the hydrazone carrying the benzoyl group in comparison to that of the nitrogen atom carrying the methyl group in methyl hydrazone.



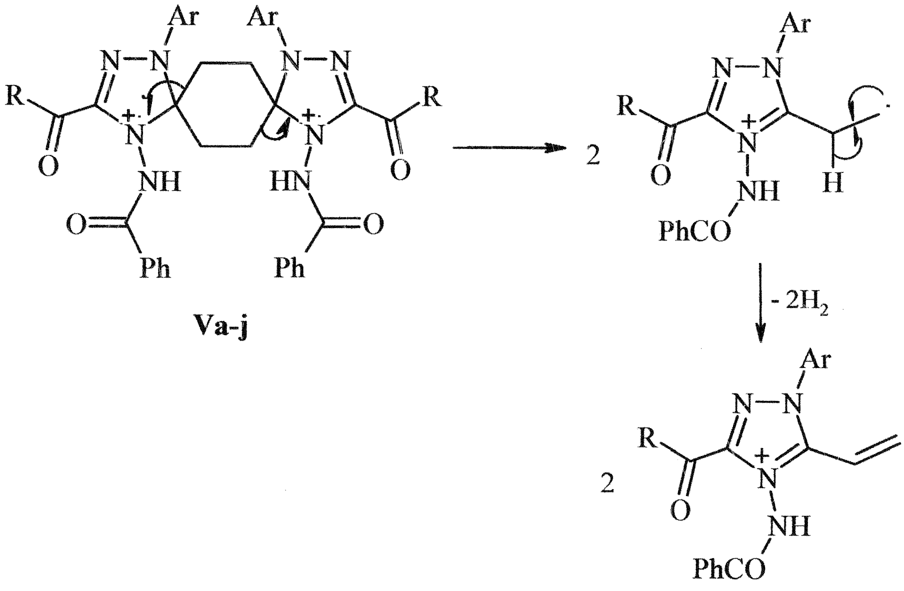
Y = -COPh
Ar = 4-XC$_6$H$_4$-
R/X = **a:** Me/Cl; **b:** Me/Br; **c:** MeO/Cl; **d:** Ph/Cl; **e:** PhNH/H; **f:** PhNH/Cl
g: PhNH/Me; **h:** 2-C$_4$H$_3$O-/Cl; **i:** 2-C$_4$H$_3$S-/Cl; **j:** C$_{10}$H$_7$-/Cl

Figure 1. Synthetic pathway for the preparation of dispiro compounds **Va-j.**

2.1. Spectral data analysis

The structures of the synthesized compounds **Va-j** are confirmed by IR, ^{1}H, ^{13}C NMR and MS spectral data, and are further supported by correct elemental microanalysis and given in the experimental section. The IR spectra for **Va-j** showed the presence of NH absorption bands in the region 3330-3320 cm^{-1}, in addition to tow characteristic bands in the region 1680-1650 cm^{-1} for benzoyl and benzoylamino carbonyl groups.

Their ^{1}H NMR spectra revealed, besides aromatic protons at 8.5-7.1 ppm, a D$_2$O-exchangeble singlet signal in the region 9.7-9.4 ppm assignable to the amide NH of the five-membered dispiro compounds **Va-j**. The NH of the tetrazine structures **IVa-j** is expected to resonate at 4-5 ppm [1]. The entire ^{1}H NMR data are presented in the experimental section. The ^{13}C NMR spectra showed all the signals expected for the proposed structures and, in particular, the C-5 and C-8 signals (spiro carbons) were found at about 97-89 ppm. This is similar to reported values for spiro carbons flanked by two nitrogen atoms in five-membered heterocycles [4-6], which provides strong evidence in support of the structures **Va-j** rather than the six-membered structure **IVa-j**, which is expected to have a C-6 and C-9 signal at about 70 ppm [2], The signal at about 147 ppm was attributed to the C=N of the triazole ring. This assignment is in good agreement with literature data for azomethine carbons. The complete ^{13}C NMR data are presented in the experimental section. Further work on the structures of the synthesized compounds is underway. The electron impact (EI) mass spectra displayed the correct molecular ions ($M^{+\cdot}$) in accordance with the suggested structures. The base peak in all these compounds was that of the conjugated vinyl triazole cation (Figure 2) this fragmentation pattern is well known for cycloalkanones [7].



Vinyl triazole

Figure 2. The main fragmentation of compounds **Va-j**.

2.2. Antimicrobial activity

The synthesized compounds were screened in vitro for their antimicrobial activity against a variety of bacterial strains such as *Euterococci, Escherichia coli*, *Staphylococcus aureus*, *Klebsiella spp*, *Proteus spp*, and fungi such as *Aspergillus niger*, *Candida albicans*, employing the nutrient agar disc diffusion method [8-10] at 10 mg/ml concentration in dimethyl formamide (DMF) by measuring the average diameter of the inhibition zone in mm. The results showed that all the tested compounds showed moderate to weak degree of activity against bacteria and fungi in comparison to DMF which was used as a control.

3. EXPERIMENTAL SECTION

3.1. Reagents and Instrumentation

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 internal reference. Chemical shifts were recorded as δ values in parts per millions (ppm) downfield from 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 **Ia-j** [11-20] and 1,4-cyclohexanedione benzoylhydrazone **III** [21] were prepared according to literature procedures. Tetrahydrofuran (THF) and triethylamine were purchased from Avocado Research Chemicals, England, and used without further purification.

3.2. General procedure for the reaction of nitrilimines II with 1,4-cyclohexanedione benzoylhydrazone III

Triethylamine (0.05 mol, 7 ml) in tetrahydrofuran (10 mL) was added dropwise to stirred mixture of hydrazone **3** (0.025 mol) and the appropriate hydrazonoyl halides **Ia-j** (0.05 mol) in tetrahydrofuran (70 mL) at 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.
The following compounds were synthesized using this method:

3,11-Diacetyl-4,12-dibenzoylamino-1,9-di(4-chlorophenyl)-1,2,4,9,10,12-hexaazadispiro[4.2.4.2]tetradeca-2,10-diene (Va): Yield 47%, m.p. 180-182 °C. IR (KBr): ν 3385 (NH), 1678 (C=O), 1622 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.42-7.12 (m, 10H, arom. protons), 9.44 (s, 2H, 2NH), 2.48 (s, 6H, $2CH_3$), 2.17-2.03 (m, 8H, $4CH_2$). ^{13}C NMR (DMSO-d_6): δ 189.65 (C=O), 147.95 (C=N), 141.46-120.18 (arom. carbons), 87.45 (spiro carbons), 35.07, 34.83 ($2CH_2$), 26.45 (CH_3). MS: m/z = 430 ($M^{+\cdot}$). Anal. Calcd for $C_{24}H_{26}N_6O_2$ (Mw 430.51): C, 66.96; H, 6.09; N, 19.52%. Found: C, 67.18; H, 5.90; N, 19.40%.

3,11-Diacetyl-4,12-dibenzoylamino-1,9-di(4-bromophenyl)-1,2,4,9,10,12-hexaazadispiro[4.2.4.2]tetradeca-2,10-diene (Vb): Yield 45%, m.p. 186-188 °C. IR (KBr): ν 3385 (NH), 1676 (C=O), 1620 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.48-7.14 (m, 8H, arom. protons), 9.42 (s, 2H, 2NH), 2.47 (s, 6H, $2CH_3$), 2.16-2.01 (m, 8H, $4CH_2$). ^{13}C NMR (DMSO-d_6): δ 189.71 (C=O), 147.96 (C=N), 141.94-121.10 (arom. carbons), 87.22 (spiro carbons), 35.10, 34.86 ($2CH_2$), 26.48 (CH_3). MS: m/z = 498/500 ($M^{+\cdot}$, Chlorine isotopes). Anal. Calcd for $C_{24}H_{24}Cl_2N_6O_2$ (Mw 499.40): C, 57.72; H, 4.84; N, 16.83%. Found: C, 57.88; H, 4.74; N, 16.71%.

4,12-Dibenzoylamino-1,9-di(4-chlorophenyl)-3,11-dimethoxycarbonyl-1,2,4,9,10,12-hexaazadispiro[4.2.4.2]tetradeca-2,10-diene (Vc): Yield 50%, m.p. 173-175 °C. IR (KBr): ν 3380 (NH), 1720 (C=O), 1625 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.57-7.20 (m, 8H, arom. protons), 9.60 (s, 2H, 2NH), 3.74 (s, 6H, $2OCH_3$), 2.18-2.04 (m, 8H, $4CH_2$); ^{13}C NMR (DMSO-d_6): δ 156.69 (O-C=O), 147.90 (C=N), 141.90-121.16 (arom. carbons), 88.95 (spiro carbons), 54.22 (OCH_3), 35.56, 34.72 ($2CH_2$). MS: m/z = 530/532 ($M^{+\cdot}$, Chlorine isotopes). Anal. Calcd for $C_{24}H_{24}Cl_2N_6O_4$ (Mw 531.40): C, 54.25; H, 4.55; N, 15.81%. Found: C, 54.46; H, 4.41; N, 15.95%.

3,11-Dibenzoyl-4,12-dibenzoylamino-1,9-di(4-chlorophenyl)-1,2,4,9,10,12-hexaazadispiro[4.2.4.2]tetradeca-2,10-diene (Vd): Yield 52%, m.p. 179-181 °C. IR (KBr): ν 3365 (NH), 1665 (C=O), 1618 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 8.46-7.26 (m, 18H, arom. protons), 9.66 (s, 2H, 2NH), 2.00-1.95 (m, 8H, $4CH_2$). ^{13}C NMR (DMSO-d_6): δ 184.86 (C=O), 148.10 (C=N), 142.15-121.19 (arom. carbons), 91.50 (spiro carbons), 35.54, 34.76 ($2CH_2$). MS: m/z = 622/624 ($M^{+\cdot}$, Chlorine isotopes). Anal. Calcd for $C_{34}H_{28}Cl_2N_6O_2$ (Mw 623.55): C, 65.49; H, 4.53; N, 13.48%. Found: C, 65.30; H, 4.70; N, 13.65%.

4,12-Dibenzoylamino-1,9-diphenyl-3,11-diphenylaminocarbonyl-1,2,4,9,10,12-hexaazadispiro[4.2.4.2]tetradeca-2,10-diene (Ve): Yield 47%, m.p. 196-198 °C. IR (KBr): ν 3375, 3248 (NH), 1655 (C=O), 1615 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 9.70 (s, 2H, 2NH), 8.90 (s, 2H, 2PhNH), 7.76-7.03 (m, 18H, arom. protons), 2.13-2.06 (m, 8H, $4CH_2$). ^{13}C NMR (DMSO-d_6): δ 159.36 (C=O), 147.86 (C=N), 141.43-121.10 (arom. carbons), 89.52 (spiro carbons), 35.50, 34.90 ($2CH_2$). MS: m/z = 652/654 ($M^{+\cdot}$, Chlorine isotopes). Anal. Calcd for $C_{34}H_{30}Cl_2N_8O_2$ (Mw 653.58): C, 62.48; H, 4.63; N, 17.14%. Found: C, 62.30; H, 4.72; N, 17.02%.

4,12-Dibenzoylamino-1,9-di(4-chlorophenyl)-3,11-diphenylaminocarbonyl-1,2,4,9,10,12-hexaazadispiro[4.2.4.2]tetradeca-2,10-diene (Vf): Yield 45%, m.p. 201-203 °C. IR (KBr): ν 3380, 3257 (NH), 1654 (C=O), 1612 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 9.65 (s, 2H, 2NH), 8.87 (s, 2H, 2PhNH), 7.78-7.15 (m, 18H, arom. protons), 2.11-2.05 (m, 8H, $4CH_2$). ^{13}C NMR (DMSO-d_6): δ 159.40 (C=O), 147.84 (C=N), 141.62-116.50 (arom. carbons), 89.60 (spiro carbons), 35.26, 34.90 ($2CH_2$). MS: m/z = 742/744 ($M^{+\cdot}$, Bromine isotopes). Anal. Calcd for $C_{34}H_{30}Br_2N_8O_2$ (Mw 742.48): C, 55.00; H, 4.07; N, 15.09%. Found: C, 55.22; H, 3.95; N, 14.90%.

4,12-Dibenzoylamino-1,9-di(4-methylphenyl)-3,11-diphenylaminocarbonyl-1,2,4,9,10,12-hexaazadispiro[4.2.4.2]tetradeca-2,12-diene (Vg): Yield 48%, m.p. 191-193 °C. IR (KBr): ν 3380, 3260 (NH), 1655 (C=O), 1612 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 9.67 (s, 2H, 2NH), 8.89 (s, 2H, 2PhNH), 7.80-7.13 (m, 18H, arom. protons), 2.26 (s, 6H, $2CH_3$), 2.10-2.04 (m, 8H, $4CH_2$). ^{13}C NMR (DMSO-d_6): δ 159.24 (C=O), 147.90 (C=N), 141.55-119.94 (arom. carbons), 89.65 (spiro carbons), 35.50, 34.96 ($2CH_2$), 23.40 (CH_3). MS: m/z = 612 ($M^{+\cdot}$). Anal. Calcd for $C_{36}H_{36}N_8O_2$ (Mw 612.74): C, 70.57; H, 5.92; N, 18.29%. Found: C, 70.45; H, 4.79; N, 18.42%.

4,12-Dibenzoylamino-1,9-di(4-chlorophenyl)-3,11-di(2-furoyl)-1,2,4,9,10,12-hexaazadispiro[4.2.4.2]tetradeca-2,10-di-ene (Vh): Yield 48%, m.p. 194-196 °C. IR (KBr): ν 3370 (NH), 1665 (C=O), 1615 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.80-7.16 (m, 14H, arom. protons), 9.48 (s, 2H, 2NH), 2.16-2.10 (m, 8H, $4CH_2$); ^{13}C NMR (DMSO-d_6): δ

174.56 (C=O), 148.25 (C=N), 143.20-121.58 (arom. carbons), 94.85 (spiro carbons), 35.41, 34.83 (2CH_2). MS: m/z = 602/604 ($M^{+\cdot}$, Chlorine isotopes). Anal. Calcd for $C_{30}H_{24}Cl_2N_6O_4$ (Mw 603.47): C, 59.71; H, 4.01; N, 13.93%. Found: C, 59.85; H, 3.90; N, 13.85%.

4,12-Dibenzoylamino-1,9-di(4-chlorophenyl)-3,11-di(2-thenoyl)-1,2,4,9,10,12-hexaazadispiro[4.2.4.2]tetradeca-2,10-diene (Vi): Yield 50%, m.p. 180-182 °C. IR (KBr): ν 3375 (NH), 1660 (C=O), 1610 (C=N) cm^{-1}. ^1H NMR (DMSO-d_6): δ 7.84-7.12 (m, 14H, arom. protons), 9.45 (s, 2H, 2NH), 2.15-2.06 (m, 8H, 4CH_2); ^{13}C NMR (DMSO-d_6): δ 175.82 (C=O), 148.30 (C=N), 143.73-121.68 (arom. carbons), 94.64 (spiro carbons), 35.35, 34.66 (2CH_2). MS: m/z = 634/636 ($M^{+\cdot}$, Chlorine isotopes). Anal. Calcd for $C_{30}H_{24}Cl_2N_6O_2S_2$ (Mw 635.60): C 56.69, H 3.81, N 13.22%. Found: C 56.80, H, 3.65; N, 13.06%.

4,12-Dibenzoylamino-1,9-di(4-chlorophenyl)-3,11-di(2-naphthoyl)-1,2,4,9,10,12-hexaazadispiro[4.2.4.2]tetradeca-2,10-diene (Vj): Yield 54%, m.p. 216-218 °C. IR (KBr): ν 3365 (NH), 1650 (C=O), 1605 (C=N). ^1H NMR (DMSO-d_6): δ 8.45-7.22 (m, 22H, arom. protons), 9.72 (s, 2H, 2NH), 2.10-2.03 (m, 8H, 4CH_2). ^{13}C NMR (DMSO-d_6): δ 184.56 (C=O), 148.32 (C=N), 142.12-120.86 (arom. carbons), 91.63 (spiro carbons), 35.30, 34.75 (2CH_2). MS: m/z = 722/724 ($M^{+\cdot}$, Chlorine isotopes). Anal. Calcd for $C_{42}H_{32}Cl_2N_6O_2$ (Mw 723.67): C, 69.71; H, 4.46; N, 11.61%. Found: C, 69.50; H, 4.35; N, 11.70%.

4. CONCLUSION

The nitrilimines reacted with 1,4-cyclohexanedione benzoylhydrazone to form a new dispiroheterocycles, 4,12-dibenzoylamino-1,2,4,9,10,12-hexaazadispiro-[4.2.4.2]-tetradeca-2,10-dienes **Va-j**. All the compounds were screened for their biological activities and displayed weak antibacterial and antifungal activities.

5. ACKNOWLEDGEMENTS

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