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Heterocyclic Synthesis Using Nitrilimines: Part 5. Synthesis of Some Novel Spiro Heterocycles

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A new class of spiro-triazoles (**4a-m**) were synthesized from the reaction of corresponding nitrilimines **2** with substituted heterocyclic benzoylhydrazones **3** in good yields. The spectral data of the new synthesized compounds are in full agreement with their molecular structure.

Key Words: Cycloaddition, benzoylhydrazones, nitrilimines, spiro-triazoles.

Introduction

1,2,4-Triazoles and their derivatives represent one of the most biologically active classes of compounds, possessing a wide spectrum of activities. The 1,2,4-triazole nucleus is associated with diverse pharmacological properties such as antibacterial, antifungal, hypoglycemic, antihypertensive, analgesic and antitumoral activities[1−10]. The synthesis of polymers derived from triazoles is currently the most practical application of this heterocyclic system[11]. 1,3-Dipolar cycloaddition reactions of nitrilimines with dipolarophiles containing a carbon-nitrogen double bond represent an important synthetic route to substituted 1,2,4-triazoles[11].

Nitrilimines are reported to react differently with hydrazones: the reaction with methylhydrazones of aliphatic aldehydes and ketones provides the tetrahydro-1,2,4,5-tetrazines[12−14]. On the other hand, methylhydrazones of aromatic aldehydes give a mixture of cyclic tetrazines and corresponding open-chain structures[15]. Simple hydrazones react in a similar manner, giving the acyclic electrophilic addition products, which, upon heating with activated charcoal, give dihydro-1,2,4,5-tetrazines[16] or amidrazones[14]. In a continuation of our work concerning the utility of nitrilimines in the synthesis of heterocyclic spiro compounds, we investigated the reaction of different C-substituted-N-arylnitrilimines with 1-methyl, 1-isopropyl and 1-benzyl-4-piperidone benzoylhydrazones in order to prepare a new series of substituted spiro-triazoles.

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Experimental

Melting points were determined in open capillaries on an Electrothermal Melting Temperature apparatus and are uncorrected. The IR spectra were obtained using a Satellite 3000 Mid infrared spectrometer in KBr pellets. The ^{1}H NMR and ^{13}C spectra were recorded on a Bruker instrument (400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C) in $CDCl_3$ using TMS as internal reference. All chemical shifts (δ) were reported in ppm from internal TMS. Electron impact mass spectra were run on an LCT Electrospray mass spectrometer. Elemental analysis was performed at Cairo University, Egypt. The hydrazonoyl halides **1** and 1-substituted-4-piperidone ketohydrazones **3**were prepared according to the literature[17−23].

Preparation of substituted heterocyclic spiro compounds (4a-m):

General procedure: Triethylamine (0.05 mol) in absolute THF (10 mL) was dropwise added to a stirred solution of appropriate hydrazonoyl halides **1** (0.01 mol) and the respective 1-substituted-4-piperidone benzoylhydrazones **3** (0.02 mol) in THF (100 mL) at room temperature. Stirring was continued overnight. The solvent was then evaporated in vacuo, and the residue was washed with water to get rid of the triethylamine salt, followed by chromatograph on silica-gel plates (eluent chloroform) and then recrystallization from ethanol. The following compounds were synthesized using this method:

4-Benzoylamino-1-(4-chlorophenyl)-8-methyl-3-(2-naphthoyl)-1,2,4,8-tetraaza-spiro[4.5] dec-2-ene (4a): Yield: 70% ; M.p. 173-175 ^{o}C; Analysis (% Calculated/found) for $C_{31}H_{28}ClN_5O_2$ C: 69.20/69.40, H: 5.25/5.10, N: 13.02/12.90; MS ($M^{+\cdot}$ = 537/539); IR (ν/cm^{-1}): 3325 (N-H), 1680 (Ph-C=O), 1645 (Ar-C=O); ^{1}H NMR (δ/ppm): 9.20 (1H, s, N-H), 8.90-7.26 (16H, m, Ar-H), 2.80-1.80 (8H, m, $4CH_2$), 2.36 (3H, s, CH_3); ^{13}C NMR (δ/ppm): 183.60 (Ar-C=O), 169.10 (Ph-C=O), 146.20 (C=N), 141.50-115.50 (C=C, Ar), 86.90 (spiro carbon), 53.10, 31.10 ($4CH_2$), 46.50 (CH_3).

4-Benzoylamino-1-(4-chlorophenyl)-8-isopropyl-3-(2-naphthoyl)-1,2,4,8-tetra-azaspiro[4.5] dec-2-ene (4b): Yield: 75% ; M.p. 186-188 ^{o}C; Analysis (% Calculated/ found) for $C_{33}H_{32}ClN_5O_2$ C: 70.02/69.80, H: 5.70/5.80, N: 12.37/12.50; MS ($M^{+\cdot}$ = 565/567); IR (ν/cm^{-1}): 3320 (N-H), 1680 (Ph-C=O), 1640 (Ar-C=O); ^{1}H NMR (δ/ppm): 9.10 (1H, s, N-H), 8.85-7.25 (16H, m, Ar-H), 2.80-1.80 (8H, m, $4CH_2$), 2.40 (1H, m, CH), 1.2 (6H, d, $2CH_3$); ^{13}C NMR (δ/ppm): 183.40 (Ar-C=O), 169.00 (Ph-C=O), 146.30 (C=N), 141.50-115.50 (C=C, Ar), 86.70 (spiro carbon), 52.80, 31.00 ($4CH_2$), 47.10 (CH), 27.60 ($2CH_3$).

4-Benzoylamino-8-benzyl-1-(4-chlorophenyl)-3-(2-naphthoyl)-1,2,4,8-tetraaza-spiro[4.5] dec-2-ene (4c): Yield: 72% ; M.p. 184-186 ^{o}C; Analysis (% Calculated/found) for $C_{37}H_{32}ClN_5O_2$ C: 72.36/72.50, H: 5.25/5.10, N: 11.40/11.30; MS ($M^{+\cdot}$ = 613/615); IR (ν/cm^{-1}): 3325 (N-H), 1680 (Ph-C=O), 1645 (Ar-C=O); ^{1}H NMR (δ/ppm): 9.20 (1H, s, N-H), 9.00-7.26 (21H, m, Ar-H), 3.20 (2H, s, CH_2-Ph), 2.80-1.70 (8H, m, $4CH_2$); ^{13}C NMR (δ/ppm): 183.50 (Ar-C=O), 169.10 (Ph-C=O), 146.30 (C=N), 142.30-125.50 (C=C, Ar), 86.90 (spiro carbon), 53.00, 31.10 ($4CH_2$), 49.70 (CH_2-Ph).

4-Benzoylamino-8-methyl-1-phenyl-3-phenylaminocarbonyl-1,2,4,8-tetraaza-spiro[4.5] dec-2-ene (4d): Yield: 80% ; M.p. 185-187 ^{o}C; Analysis (% Calculated/ found) for $C_{22}H_{26}N_6O_3$ C: 62.54/62.70, H: 6.20/6.00, N: 19.89/20.10; MS ($M^{+\cdot}$ = 422); IR (ν/cm^{-1}): 3350 (PhN-H), 3330 (N-H), 1675 (Ph-C=O), 1655 (Ar-C=O); ^{1}H NMR δ/ppm: 9.20 (1H, s, N-H), 8.80 (1H, s, Ph-NH), 7.70-7.20 (14H, m, Ar-H), 2.80-1.60 (8H, m, $4CH_2$), 2.30 (3H, s, CH_3); ^{13}C NMR (δ/ppm): 169.4 (Ph-C=O), 159.6 (Ar-C=O),

146.40 (C=N), 141.80-115.60 (C=C, Ar), 87.20 (spiro carbon), 53.10, 31.20 ($4CH_2$), 46.60 (CH_3).

4-Benzoylamino-8-isopropyl-1-phenyl-3-phenylaminocarbonyl-1,2,4,8-tetraaza-spiro[4.5] dec-2-ene (4e): Yield: 75% ; M.p. 173-175 ^{o}C; Analysis (% Calculated/found) for $C_{29}H_{32}N_6O_2$ C: 70.14/69.90, H: 6.49/6.60, N: 16.92/17.10; MS ($M^{+\cdot}$ = 496); IR (ν/cm^{-1}): 3350 (PhN-H), 3325 (N-H), 1670 (Ph-C=O), 1650 (Ar-C=O); ^{1}H NMR (δ/ppm): 9.20 (1H, s, N-H), 8.70 (1H, s, Ph-NH), 7.60-7.20 (14H, m, Ar-H), 2.80-1.80 (8H, m, $4CH_2$), 2.40 (1H, m, CH), 1.2 (6H, d, $2CH_3$); ^{13}C NMR (δ/ppm): 169.20 (Ph-C=O), 159.80 (Ar-C=O), 146.20 (C=N), 142.80-125.60 (C=C, Ar), 87.20 (spiro carbon), 53.00, 31.10 ($4CH_2$), 47.10 (CH), 27.70 ($2CH_3$).

4-Benzoylamino-8-benzyl-1-phenyl-3-phenylaminocarbonyl-1,2,4,8-tetraaza-spiro[4.5] dec-2-ene (4f): Yield: 90% ; M.p. 168-170 ^{o}C; Analysis (% Calculated/found) for $C_{33}H_{32}N_6O_2$ C: 72.77/72.50, H: 5.92/6.10, N: 15.43/15.50; MS ($M^{+\cdot}$ = 544); IR (ν/cm^{-1}): 3350 (PhN-H), 3330 (N-H), 1675 (Ph-C=O), 1650 (Ar-C=O); ^{1}H NMR (δ/ppm): 9.30 (1H, s, N-H), 8.80 (1H, s, Ph-NH), 7.80-7.20 (19H, m, Ar-H), 3.10 (2H, s, CH_2-Ph), 2.90-1.70 (8H, m, $4CH_2$); ^{13}C NMR (δ/ppm): 169.20 (Ph-C=O), 159.90 (Ar-C=O), 146.30 (C=N), 142.00-122.60 (C=C, Ar), 87.40 (spiro carbon), 53.20, 31.20 ($4CH_2$), 50.10 (CH_2-Ph).

3-Benzoyl-4-benzoylamino-1-(4-chlorophenyl)-8-methyl-1,2,4,8-tetraazaspiro-[4.5]-dec-2-ene (4g): Yield: 85% ; M.p. 152-154 ^{o}C; Analysis (% Calculated/found) for $C_{27}H_{26}ClN_5O_2$ C: 66.46/66.70, H: 5.36/5.20, N: 14.35/14.20; MS ($M^{+\cdot}$ = 487/489); IR (ν/cm^{-1}): 3330 (N-H), 1675 (Ph-C=O), 1630 (Ar-C=O); ^{1}H NMR (δ/ppm): 9.40 (1H, s, N-H), 8.30-7.20 (14H, m, Ar-H), 3.00-1.80 (8H, m, $4CH_2$), 2.40 (3H, s, CH_3); ^{13}C NMR (δ/ppm): 183.80 (Ar-C=O), 169.00 (Ph-C=O), 146.20 (C=N), 141.00-121.40 (C=C, Ar), 86.60 (spiro carbon), 53.10, 31.10 ($4CH_2$), 46.60 (CH_3).

3-Benzoyl-4-benzoylamino-1-(4-chlorophenyl)-8-isopropyl-1,2,4,8-tetraaza-spiro[4.5]dec-2-ene (4h): Yield: 75% ; M.p. 196-198 ^{o}C; Analysis (% Calculated/ found) for $C_{29}H_{30}ClN_5O_2$ C: 67.50/67.30, H: 6.87/7.00, N: 13.57/13.50; MS ($M^{+\cdot}$ = 515/517); IR (ν/cm^{-1}): 3325 (N-H), 1670 (Ph-C=O), 1625 (Ar-C=O); ^{1}H NMR (δ/ppm): 9.30 (1H, s, N-H), 8.20-7.20 (14H, m, Ar-H), 2.90-1.60 (8H, m, $4CH_2$), 2.40 (1H, m, CH), 1.3 (6H, d, $2CH_3$); ^{13}C NMR (δ/ppm): 183.90 (Ar-C=O), 169.10 (Ph-C=O), 146.20 (C=N), 141.00-121.50 (C=C, Ar), 86.70 (spiro carbon), 52.90, 31.10 ($4CH_2$), 47.40 (CH), 27.8 ($2CH_3$).

3-Benzoyl-4-benzoylamino-8-benzyl-1-(4-chlorophenyl)-1,2,4,8-tetraazaspiro- [4.5]-dec-2-ene (4i): Yield: 80% ; M.p. 178-180 ^{o}C; Analysis (% Calculated/found) for $C_{33}H_{30}ClN_5O_2$ C: 70.27/70.50, H: 5.36/5.20, N: 12.42/12.30; MS ($M^{+\cdot}$ = 563/565); IR (ν/cm^{-1}): 3330 (N-H), 1675 (Ph-C=O), 1625 (Ar-C=O); ^{1}H NMR (δ/ppm): 9.50 (1H, s, N-H), 8.20-7.20 (19H, m, Ar-H), 3.30 (2H, s, CH_2-Ph), 3.00-1.70 (8H, m, $4CH_2$); ^{13}C NMR (δ/ppm): 184.00 (Ar-C=O), 169.10 (Ph-C=O), 146.30 (C=N), 142.00-125.60 (C=C, Ar), 86.80 (spiro carbon), 53.30, 31.20 ($4CH_2$), 49.90 (CH_2-Ph).

4-Benzoylamino-1-(4-chlorophenyl)-8-methyl-3-(2-thenoyl)-1,2,4,8-tetraaza-spiro[4.5]dec-2-ene (4j): Yield: 75% ; M.p. 190-192 ^{o}C; Analysis (% Calculated/found) for $C_{25}H_{24}ClN_5O_2S$ C: 60.78/61.00, H: 4.90/4.80, N: 14.18/14.30; MS ($M^{+\cdot}$ = 477/479); IR (ν/cm^{-1}): 3320 (N-H), 1680 (Ph-C=O), 1665 (Ar-C=O). ^{1}H NMR (δ/ppm): 9.20 (1H, s, N-H), 8.30-7.15 (12H, m, Ar-H), 2.80-1.70 (8H, m, $4CH_2$), 2.40 (3H, s, CH_3); ^{13}C NMR (δ/ppm): 174.30 (Ar-C=O), 169.40 (Ph-C=O), 146.50 (C=N), 141.20-120.10 (C=C, Ar), 87.00 (spiro carbon), 53.20, 31.20 ($4CH_2$), 46.70 (CH_3).

4-Benzoylamino-8-benzyl-1-(4-chlorophenyl)-3-(2-thenoyl)-1,2,4,8-tetraaza-spiro[4.5]dec-2-ene (4k): Yield: 70% ; M.p. 183-185 ^{o}C; Analysis (% Calculated/ found) for $C_{31}H_{28}ClN_5O_2S$ C: 65.31/65.20, H: 4.95/5.10, N: 12.28/12.10; MS ($M^{+\cdot}$ = 569/571); IR (ν/cm^{-1}): 3325 (N-H), 1675 (Ph-C=O), 1660 (Ar-C=O); ^{1}H NMR (δ/ppm): 9.30 (1H, s, N-H), 8.30-7.16 (17H, m, Ar-H), 3.40 (2H, s, CH_2-Ph), 3.00-1.80 (8H, m, 4CH_2); ^{13}C NMR (δ/ppm): 174.20 (Ar-C=O), 169.30 (Ph-C=O), 146.30 (C=N), 142.10-121.10 (C=C, Ar), 87.20 (spiro carbon), 53.30, 31.30 (4CH_2), 50.10 (CH_2-Ph).

4-Benzoylamino-1-(4-chlorophenyl)-3-(2-furoyl)-8-methyl-1,2,4,8-tetraazaspiro-[4.5]dec-2-ene (4l): Yield: 74% ; M.p. 179-181 ^{o}C; Analysis (% Calculated/found) for $C_{22}H_{24}ClN_5O_3$ C: 62.83/63.00, H: 5.06/4.90, N: 14.65/14.70; MS ($M^{+\cdot}$ = 477/479); IR (ν/cm^{-1}): 3325 (N-H), 1675 (Ph-C=O), 1660 (Ar-C=O); ^{1}H NMR (δ/ppm): 9.10 (1H, s, N-H), 8.00-7.10 (12H, m, Ar-H), 2.80-1.60 (8H, m, 4CH_2), 2.40 (3H, s, CH_3); ^{13}C NMR (δ/ppm): 173.60 (Ar-C=O), 169.40 (Ph-C=O), 146.50 (C=N), 141.60-120.60 (C=C, Ar), 87.10 (spiro carbon), 53.20, 31.10 (4CH_2), 46.60 (CH_3).

4-Benzoylamino-8-benzyl-1-(4-chlorophenyl)-3-(2-furoyl)-1,2,4,8-tetraazaspiro-[4.5]dec-2-ene (4m): Yield: 78% ; M.p. 162-164 ^{o}C; Analysis (% Calculated/found) for $C_{31}H_{28}ClN_5O_3$ C: 67.20/67.40, H: 5.09/5.00, N: 12.64/12.50; MS ($M^{+\cdot}$ = 553/555); IR (ν/cm^{-1}): 3330 (N-H), 1675 (Ph-C=O), 1660 (Ar-C=O); ^{1}H NMR (δ/ppm): 9.20 (1H, s, N-H), 8.20-7.2 (17H, m, Ar-H), 3.20 (2H, s, CH_2-Ph), 2.90-1.80 (8H, m, 4CH_2); ^{13}C NMR (δ/ppm): 173.50 (Ar-C=O), 169.40 (Ph-C=O), 146.40 (C=N), 142.20-121.50 (C=C, Ar), 87.20 (spiro carbon), 53.20, 31.20 (4CH_2), 50.00 (CH_2-Ph).

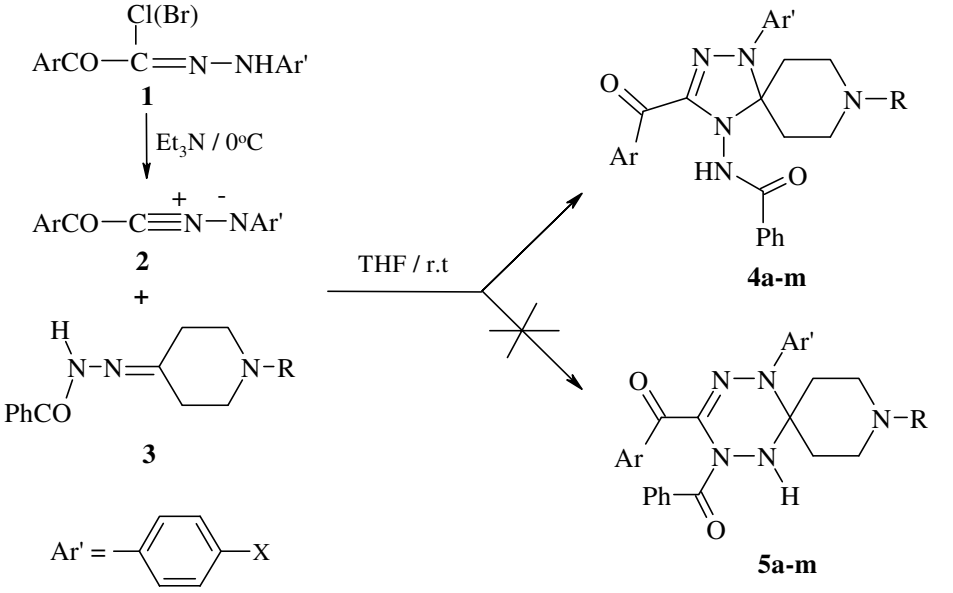
Results and Discussion

The reaction was carried out by applying a 2-fold excess of the benzoylhydrazones **3** with hydrazonoyl halides **1** (precursors of nitrilimines **2**) in tetrahydrofuran in the presence of triethylamine (Scheme). The reaction is found to give the 5-membered spiro heterocycles, 1,2,4,8-tetraazaspiro[4,5]dec-2-enes (**4a-m**) as cycloaddition products instead of the spiro-tetrazine cyclocondensation products (**5a-m**). It is worth mentioning that the tetrazines were obtained from the reaction of nitrilimines with methyl hydrazones of aliphatic aldehydes and ketones[12−14]. This can be explained on the basis of the weak nucleophilicity of the nitrogen atom of the hydrazones carrying the benzoyl group in comparison to that of the nitrogen carrying the methyl group in methyl hydrazones.

Spectral data analysis

The structures of the title compounds (**4a-m**) are confirmed by IR,^{1}H, ^{13}C NMR and MS spectral data, and are further supported by correct elemental microanalysis (experimental part). IR spectra reveal the presence of NH absorption bands in the region 3330-3320 cm^{-1}, in addition to 2 characteristic signals at about 1670 cm^{-1} for the benzoyl carbonyl group (Ph-C=O) and 1660 cm^{-1} (Ar-C=O) (see experimental part). The absorption band for NH of the ring in tetrazines (**5**) is expected to appear at about 3200 cm^{-1}[12−14]. The ^{1}H NMR spectra show a signal at 9-9.5 ppm, which is characteristic for the amide NH of the 5-membered ring compounds (**4a-m**). The NH of the 6-membered ring structure (**5**) is expected to resonate at 4-5 ppm[12−14]. The entire ^{1}H NMR data are presented in the experimental part. The ^{13}C NMR spectra display the characteristic signals of the suggested structures. The signal for C-5 (spiro carbon)

resonates at about 90 ppm. This is similar to reported values of spiro carbons flanked by 2 nitrogens in 5-membered heterocycles[22,24–26]. This provides strong evidence in support of structures (**4a-m**) rather than the 6-membered heterocyclic structures (**5**), which is expected to have a C-6 signal at about 70 ppm[12–14]. The signal at about 146 ppm is attributed to the C-3 carbon of the triazoles. This assignment is in good agreement with literature data for azomethine carbons[25,26]. The detailed ^{13}C NMR data are presented in the experimental part.



Entery	Ar	R	X
a	2-Naphthyl	$-CH_3$	Cl
b	2-Naphthyl	$-CHMe_2$	Cl
c	2-Naphthyl	$-CH_2Ph$	Cl
d	PhNH-	$-CH_3$	H
e	PhNH-	$-CHMe_2$	H
f	PhNH-	$-CH_2Ph$	H
g	Ph	$-CH_3$	Cl

Entery	Ar	R	X
h	Ph	$-CHMe_2$	Cl
i	Ph	$-CH_2Ph$	Cl
j	2-Thienyl	$-CH_3$	Cl
k	2-Thienyl	$-CH_2Ph$	Cl
l	2-Furyl	$-CH_3$	Cl
m	2-Furyl	$-CH_2Ph$	Cl

Scheme. Synthetic pathway for the preparation of compounds (**4a-m**).

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