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Synthesis of Some Spiro Piperidino-1,2,4-triazolidines and Aziridines

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ABSTRACT: *The oxidative cyclization of the thiosemicarbazones of 4-piperidones* **(2)** *furnished spiro piperidino-1,2,4-triazoles* **(3,4,5)**, *while the pyrolysis of* **5** *led to spiro piperidinoaziridines* **(6)**. *The new compounds were characterized by IR and* ^{1}*H NMR spectral data.*© 1999 John Wiley & Sons, Inc. Heteroatom Chem 10: 313–317, 1999

INTRODUCTION

In recent times, we have been interested in exploiting the α-keto methylene functionality of cyclic ketones to build 1,2,3-selena/thiadiazoles via their semicarbazones [1]. Prompted by the successful results on this front, we considered the possibility that the thiosemicarbazones of cyclic ketones could also lead to novel heterocycles. Further, in continuation of our work to develop some interesting spiro heterocyclic systems [2] and in view of our unsuccessful results in the synthesis of spiro piperidino aziridines [3], herein, we report the synthesis of spiro piperidinotriazoles **(3,4,5)** and their reactivity leading ultimately to spiro piperidinoaziridines **(6)**. Moreover, it is well documented that the piperidines, 1,2,4-triazolidines, and aziridines are known to be reactive intermediates and pharmacological agents [4].

RESULTS AND DISCUSSION

To accomplish this goal, the 4-piperidones **(1)** were condensed with thiosemicarbazide to provide the respective thiosemicarbazono-4-piperidines **(2)**, which, on oxidative pentannulation with hydrogen peroxide [4], led to spiro piperidinotriazolidinethiones **(3)**. The compounds, **3**, on treatment with iron pentacarbonyl [5] in the presence of potassium hydroxide, furnished the corresponding spiro triazolidines **(4)**, as depicted in Scheme 1 (see Table 1).

The conversion of each thiosemicarbazone **(2)** to the respective spiro triazolidinethione **(3)** involves a free-radical mechanism [6]. Accordingly, only one isomer is selectively obtained in which the NHCS group is *cis* with respect to the adjacent axial hydrogens. This could be explained on the basis that, during cyclization, the heterocyclic ring was preferably formed such that the NHCS group would be equatorial at the spiro carbon. The mode of cyclization and the stereochemical conformations of the compounds **3** and **4** were confirmed by spectral inspections. The IR spectrum (ν, cm^{-1}) of **3** showed bands around 3290–3410 (NH) and 1190–1240 (C=S). The disappearance of the latter in the case of **4** confirms its reduction. The ^{1}H NMR spectra (δ) of **3** was a replica of **1** except for its NH absorptions of the triazolidine ring. This absorption, which should normally appear at 6.00–8.55, however, merged with those of the aromatic protons and appeared at around 6.50–8.00. The peaks corresponding to NH dissappeared on deuteration. The $C_{3'}$–H in **4a–d** are isochronous and appeared as a sharp singlet around 6.55 instead of appearing as an AB quartet or as two doublets. However, in **4e–j**, these two protons are anisochronous and showed two doublets at 5.60 and 6.65 with the J value of 12.5 Hz, typical of a geminal coupling, and thus indicating that they are diastereotopic [7]. Apart from this, in the latter, the two

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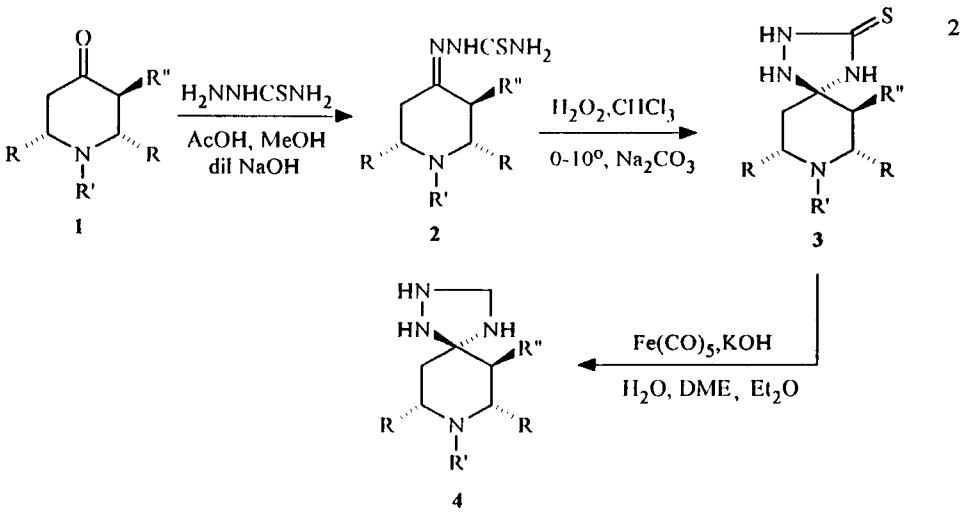


	R	R′	R″		R	R′	R″
a	H	H	H	**f**	Ph	H	C_2H_5
b	H	CH_3	H	**g**	Ph	H	iso-C_3H_7
c	H	CH_2Ph	H	**h**	Ph	$COCH_3$	CH_3
d	H	CO_2Et	H	**i**	Ph	NO	CH_3
e	Ph	H	CH_3	**j**	4-OMePh	H	CH_3

SCHEME 1

TABLE 1 Physical Data of Compounds **2–6**

Product	*M.p* (°C)	*Yield* (%)	*Product*	*M.p* (°C)	*Yield* (%)
2a	160–161	76	**4a**	131–132	62
2b	158–159	73	**4b**	111–112	59
2c	163–164	80	**4c**	98(dec)	53
2d	145–146	66	**4d**	92–93	56
2e	133–134	76	**4e**	116–117	61
2f	148–149	72	**4f**	112–113	60
2g	154–155	70	**4g**	96(dec)	60
2h	197–198	68	**4h**	92–93	55
2i	168–169	75	**4i**	114–115	58
2j	159–160	78	**4j**	136–137	60
3a	86–87	61	**5a**	110–111	58
3b	72–73	64	**5b**	136–137	62
3c	95–96	55	**5e**	128–129	64
3d	72–73	64	**5h**	116–117	61
3e	90–91	61	**6a**	91–92	49
3f	91–92	61	**6b**	114–115	54
3g	89–90	63	**6e**	110–111	52
3h	84–85	58	**6h**	97–98	50
3i	69–70	63			
3j	121–122	59			

Satisfactory elemental analyses were obtained for representative examples of each series C ± 0.32, H ± 0.15, N ± 0.21.

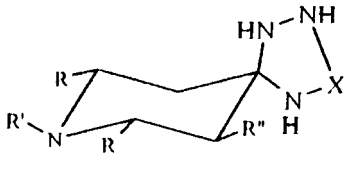
benzylic protons at C_2 and C_6 showed *J* values around 11.5 Hz (see Table 2), indicating that these hydrogens are axially oriented. Consequently, the bulkier phenyl groups would occupy the equatorial position in the rigid chair conformation of the piperidine ring, indicating that the geometry of the parent moiety was retained. From these observations, it was tentatively concluded that the triazolidinethione and triazolidine rings in **3** and **4**, which themselves are nearly planar, are almost perpendicular to the average plane of the piperidine moiety (see Figure 1). Furthermore, in both the heterocyclic systems, the NH couplings were not observed clearly, indicating the rapid exchangeability of these protons in the solvent ($CDCl_3$) taken.

The reactivity of **4** was investigated by choosing representative examples (see Tables 1 and 2). The compounds **4**, on treatment with diethyl azodicarboxylate (DEAD) [8], in the presence of triphenylphosphine at 0–5°C, undergo dehydrogenation, furnishing the spiro piperidinotriazolines (**5**). Pyrolysis of each **5** with copper powder [9] resulted in the formation of the corresponding spiro piperidinoaziridine (**6**), with the *syn*-elimination of nitrogen (see Scheme 2).

The IR spectra of **6** displayed absorptions in the region 3300–3440 due to NH stretching. In the ^1H

TABLE 2 ^{1}H NMR Spectral Data of **3,4**, and **6**

Product	*^{1}H NMR δ (coupling constants)*
3a	2.65 (t, J = 6.1 Hz, 4H, H-2&6), 2.21 (t, J = 6.1 Hz, 4H, H-3&5), 2.02 (bs, 1H, H-1).
3c	2.82 (t, J = 5.8 Hz, 4H, H-2&6), 2.40 (s, 2H, H-CH_2Ph), 2.24 (t, J = 5.8 Hz, 4H, H-3&5).
3f	4.08 (dd, J = 3.5 & 11.5 Hz, 1H, H-6ax), 3.72 (d, J = 10.9 Hz, 1H, H-2ax), 2.70 (dd, J = 3.5 & 12.4 Hz, 1H, H-5eq), 2.59 (dd, J = 11.5 & 12.4 Hz, 1H, H-5ax), 2.01 (bs, 1H, H-1), 1.54–1.61 (m, 1H, H-3ax), 1.13–1.16 (m, 2H, H-$\underline{CH_2}CH_3$), 0.77 (t, 3H, H-$CH_2\underline{CH_3}$).
3h	3.96 (dd, J = 4.0 & 11.0 Hz, 1H, H-6ax), 3.69 (d, J = 11.2 Hz, 1H, H-2ax), 2.68 (dd, J = 4.0 & 12.6 Hz; 1H, H-5eq), 2.50 (dd, J = 11.0 & 12.6 Hz, 1H, H-5ax), 2.43 (s, 3H, H-$COCH_3$), 1.69–1.78 (m, 1H, H-3ax), 0.98 (d, J = 6.9 Hz, 3H, H-CH_3).
3j	4.00 (dd, J = 4.2 & 11.6 Hz, 1H, H-6ax), 3.80 (s, 3H, H-OCH_3) 3.78 (s, 3H, H-OCH_3), 3.54 (d, J = 11.7 Hz, 1H, H-2ax), 2.77 (dd, J = 4.2 & 12.0 Hz, 1H, H-5eq), 2.48 (dd, J = 11.7 & 12.0 Hz, 1H, H-5ax), 1.98–1.90 (m, 1H, H-3ax), 0.96 (d, J = 6.8 Hz, 3H, H-CH_3).
4a	6.36 (s, 2H, H-3′), 2.69 (t, J = 6.5 Hz, 4H, H-2 & 6), 2.28 (t, J = 6.5 Hz, 4H, H-3&5), 2.00 (bs, 1H, H-1).
4b	6.42 (s, 2H, H-3′), 2.62 (t, J = 6.0 Hz, 4H, H-2&6), 2.42 (s, 3H, H-CH_3), 2.15 (t, J = 6.0 Hz, 4H, H-3&5).
4e	6.39 (d, J = 12.5 Hz, 1H, H-3′), 5.98 (d, J = 12.5 Hz, 1H, H-3′), 4.05 (dd, J = 3.8 & 11.5 Hz, 1H, H-6ax), 3.56 (d, J = 11.8 Hz, 1H, H-2ax), 2.72 (dd, J = 3.8 & 12.4 Hz, 1H, H-5eq), 2.50 (dd, J = 11.5 & 12.4 Hz, 1H, H-5ax), 2.29–2.00 (m, 1H, H-3ax), 1.76 (d, J = 6.0 Hz, 3H, H-CH_3).
4h	6.34 (d, J = 12.8 Hz, 1H, H-3′), 5.68 (d, J = 12.8 Hz, 1H, H-3′), 3.98 (dd, J = 3.8 & 11.5 Hz, 1H, H-6ax), 3.66 (d, J = 11.2 Hz, 1H, H-2ax), 2.60 (dd, J = 3.8 & 12.1 Hz, 1H, H-5eq), 2.56 (dd, J = 11.5 & 12.1 Hz, 1H, H-5ax), 2.45 (s, 3H, H-$COCH_3$), 2.01–1.84 (m, 1H, H-3ax), 0.76 (d, J = 6.1 Hz, 3H, H-CH_3).
4j	6.60 (d, J = 12.5 Hz, 1H, H-3′), 5.74 (d, J = 12.5 Hz, 1H, H-3′) 3.96 (dd, J = 4.1 & 11.2 Hz, 1H, H-6ax), 3.81 (s, 3H, H-OCH_3), 3.76 (s, 3H, H-OCH_3), 3.50 (d, J = 11.5 Hz, 1H, H-2ax), 2.79 (dd, J = 4.1 & 12.6 Hz, 1H, H-5eq), 2.39 (dd, J = 11.2 & 12.6 Hz, 1H, H-5ax), 2.01–1.84 (m, 1H, H-3ax), 0.77 (d, J = 6.1 Hz, 3H, H-CH_3).
5a	6.75 (s, 2H, H-3′), 2.66 (t, J = 6.2 Hz, 4H, H-2&6), 2.45 (t, J = 6.2 Hz, 4H, H-3&5), 2.06 (bs, 1H, H-1).
5e	6.56 (d, J = 12.8 Hz, 1H, H-3′), 6.01 (d, J = 12.8 Hz, 1H, H-3′), 4.15 (dd, J = 4.1 & 11.2 Hz, 1H, H-6ax), 3.61 (d, J = 11.5 Hz, 1H, H-2ax) 2.81 (dd, J = 4.1 & 12.1 Hz, 1H, H-5eq), 2.61 (dd, J = 11.2 & 12.1 Hz, 1H, H-5ax), 2.20–1.91 (m, 1H, H-3ax), 1.42 (d, J = 6.3 Hz, 3H, H-CH_3).
6a	2.72 (t, J = 6.1 Hz, 4H, H-2&6), 2.48 (s, 2H, H-3′), 2.39 (t, J = 6.1 Hz, 4H, H-3&5), 2.01 (bs, 1H, H-1).
6b	2.68 (t, J = 6.3 Hz, 4H, H-2&6), 2.46 (s, 2H, H-3′), 2.25 (t, J = 6.3 Hz, 4H, H-3&5), 2.01 (s, 3H, H-CH_3).
6e	3.98 (dd, J = 3.6 & 11.2 Hz, 1H, H-6ax), 3.54 (d, J = 11.5 Hz, H-2ax), 2.68 (d, J = 12.3 Hz, 1H, H-3′), 2.50 (d, J = 12.3 Hz, 1H, H-3′), 2.28 (dd, J = 3.6 & 12.5 Hz, 1H, H-5eq), 2.18 (dd, J = 11.2 & 12.5 Hz, 1H, H-5ax), 1.84–1.60 (m, 1H, H-3ax), 0.77 (d, J = 6.0 Hz, 3H, H-CH_3).
6j	4.12 (dd, J = 4.1 & 11.1 Hz, 1H, H-6ax), 3.90 (s, 3H, H-OCH_3), 3.84 (s, 3H, H-OCH_3), 3.66 (d, J = 11.2 Hz, 1H, H-2ax), 2.72 (d, J = 12.8 Hz, 1H, H-3′), 2.69 (d, J = 12.8 Hz, 1H, H-3′), 2.48 (dd, J = 4.1 & 12.5 Hz, 1H, H-5eq), 2.31 (dd, J-11.1 & 12.5 Hz, 1H, H-5ax), 1.90–1.51 (m, 1H, H-3ax), 0.77 (d, J = 6.1 Hz, 3H, H-CH_3).



3; X = CS
4; X = CH_2

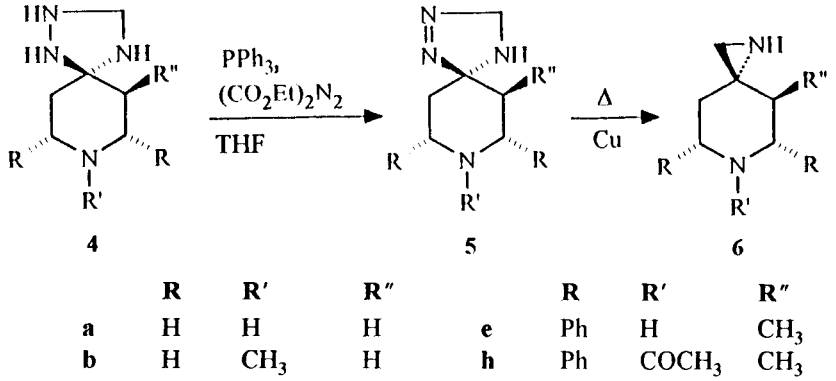
FIGURE 1

NMR spectra of **6a,b**, the methylene protons at C_3 appeared as a singlet at 2.60, while in **6f,j**, they resolved as two distinct doublets 2.65, 2.42 (J_{AB} = 12.2 Hz) in analogy with **4** (see Table 2). Thus, the NH of the aziridine ring in **6** presumably would be in an equatorial position relative to the spiro carbon atom. The resonance signals due to NH were not, however, resolved clearly.

Compounds **4** and **6** showed the first preliminary semiquantitative antimicrobial activity tests by the Vincent and Vincent method [10] and the Horsfall and Rich method [11] against the strains of bacteria [*Staphylococcus aureus, Bacillus subtilis (gram + ve),* and *Escherichia coli (gram − ve)*] and fungi (*Curvurlaria lunata, Fusarium solani,* and *Helminthosporium oryzae*). Further studies of biological activity are in progress.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. The purity of the compounds was checked by TLC (silica gel H, BDH, ethyl acetate/hexane, 1:3). The IR spectra were recorded on a Perkin-Elmer grating infrared spectrophotometer, model 337 in KBr pellets. The ^{1}H NMR spectra were recorded in $CDCl_3$/DMSO-d_6 on a Bruker Spec-



	R	R′	R″		R	R′	R″
a	H	H	H	**e**	Ph	H	CH_3
b	H	CH_3	H	**h**	Ph	$COCH_3$	CH_3

SCHEME 2

trospin varian EM-360 spectrophotometer (90 MHz) with TMS as an internal standard. The elemental analyses were performed at Dr. Reddy's Research Foundation, Hyderabad, India.

The piperidones, **1a–d** were commercially available, and **1e–j** were obtained by the condensation of araldehydes with appropriate ketones and ammonium acetate in alcohol [12].

Thiosemicarbazono-4-piperidines (2)

A mixture of thiosemicarbazide (20 mmol), 4-piperidone (20 mmol), and glacial acetic acid (5 mL) was added to methanol (25 mL) and refluxed for 3–4 hours. The progress of the reaction was monitored by TLC. After completion of the reaction, the contents were concentrated, cooled, and poured onto ice-cold water. To this mixture, 10% sodium hydroxide solution was added, and the solid that separated was filtered off, dried, and recrystallized from methanol to obtain pure **2**.

Spiro Piperidino[4,5]1′,2′,4′-triazolidino-3′-thiones (3)

A solution of each **2** (10 mmol) in chloroform (25 mL) at 5°C was treated with excess hydrogen peroxide (30%, 10 mL) and stirred for 3–4 hours. After completion of the reaction, chloroform (15 mL) was added to the reaction mixture, and the organic layer was separated, washed with 10% sodium carbonate solution, and dried (Na_2SO_4). Evaporation of the solvent under vacuo gave the respective **3**, which was purified by recrystallization from methanol.

Spiro Piperidino[4,5′]1′,2′,4′-triazolidines (4)

A mixture of iron pentacarbonyl (50 mmol), potassium hydroxide (2 g), and water (15 mL) was refluxed in 1,2-dimethoxyethane (50 mL) for 1.5 hours [to generate iron tetracarbonyl hydride ion ($HFe(CO)_4^-$)]. To this, each thioketone **3** (25 mmol) in 1,2-dimethoxyethane (20 mL) was added portionwise, and the resulting mixture was refluxed for 10 hours. The solution was cooled and filtered. The solvent was removed from the filtrate under reduced pressure to provide a yellow semisolid. The latter was extracted with dichloromethane (25 mL), washed with water, and dried (Na_2SO_4). Removal of the solvent afforded the product **4**, which was purified by filtration through a column of silica gel.

Spiro Piperidino[4,5′]1,2,4-triazolines (5)

Each compound **4** (15 mmol) was added to a solution of diethyl azodicarboxylate (15 mmol) and triphenylphosphine (2 g) in dry tetrahydrofuran (15 mL), protected from sunlight, at 0–5°C. The contents were stirred for 4–5 hours and allowed to attain room temperature. After completion of the reaction, the contents were poured onto the crushed ice (200 g). The crude substance obtained was chromatographed to provide pure **5**.

Spiro Piperidino[4,2′]aziridines (6)

A solution of each **5** (15 mmol) in dichloromethane (25 mL) with copper powder (500 mg) was slowly heated under a nitrogen atmosphere to cause evaporation of the solvent in such a way that the solid matter covered the walls of the flask. Then the contents were heated to 160–180°C in an oil bath for 15 minutes under similar conditions. After completion of the reaction, chloroform (15 mL) was added to the contents, and the solution was chromatographed on silica gel to yield pure **6**.

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