SYNTHESIS OF 1,3-DIAZASPIRO[5,5]UNDECANES AND 1-THIA-3-AZASPIRO[5,5]UNDEC-2-ENES BY REACTION OF 2-CYANOCYCLOHEXYLIDENEACETYL ISOTHIOCYANATE WITH AMINES AND SODIUM HYDROGEN SULFIDE

Milan DZURILLA, Ondrej FORGÁČ, Peter KUTSCHY, Pavol KRISTIAN, Dušan KOŠČÍK and Ján IMRICH

Department of Organic Chemistry and Biochemistry, P. J. Šafárik University, 041 67 Košice

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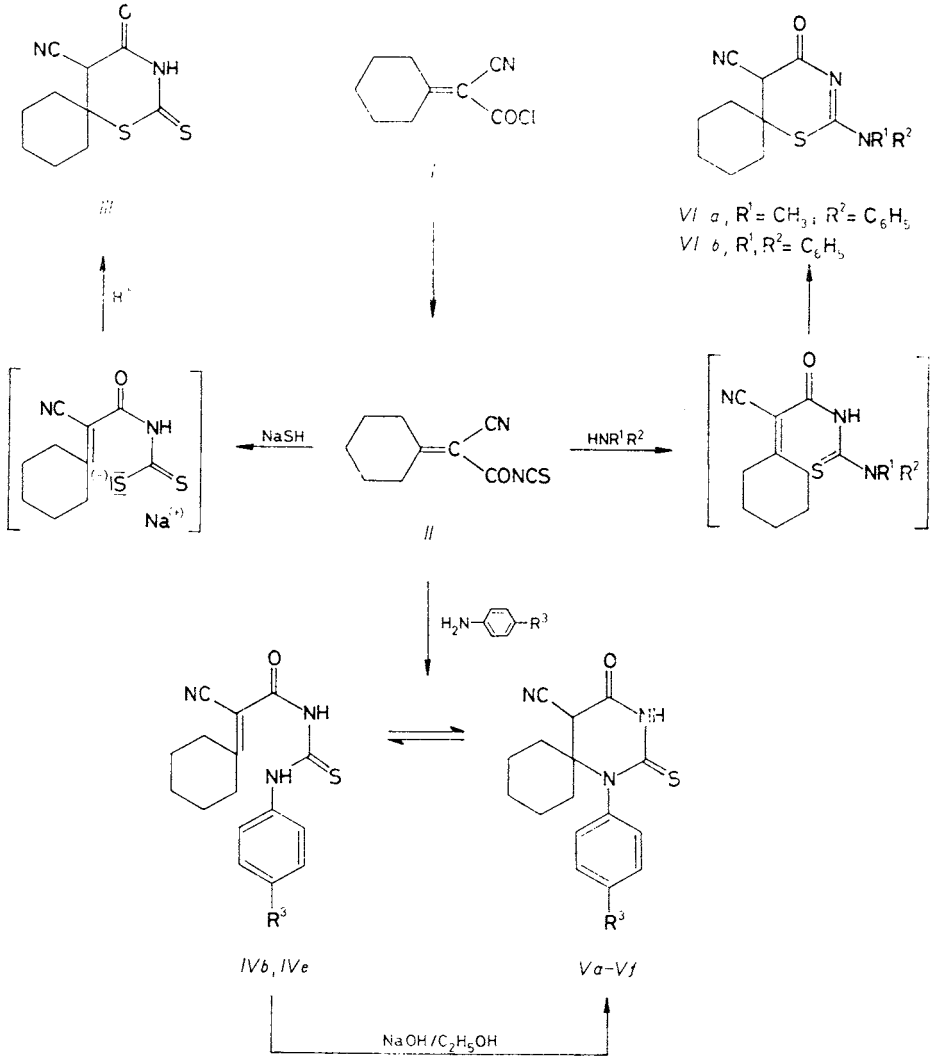
2-Cyanocyclohexylideneacetyl isothiocyanate (*II*) reacts with sodium hydrogen sulfide to give 1-thia-3-azaspiro[5,5]undecane. Reaction of *II* with secondary amines afforded 1-thia-3-azaspiro-[5,5]undec-2-enes whereas primary aromatic amines gave 1,3-diazaspiro[5,5]undecanes under the same conditions. Both types of reactions proceed *via* substituted thioureas which were isolated pure only in the case of 4-methylaniline and 4-methoxyaniline. They were cyclized in alkaline medium to the corresponding diazaspiro derivatives. The structure of the synthesized compounds was confirmed by their elemental analyses and IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy.

The reaction of 3-halogeno-3-cycloalkanoic acids with thioureas is frequently used for the preparation of 1-thia-3-azaspirocycloalkanes[1-4]. 1-Thia-3-azaspiro compounds are converted into isomeric 1,3-diazaspiro derivatives[5], interesting not only from the point of view of synthesis but also because of their biological activity[6,7].

We have found already previously[8] that introduction of an α-cyano group into 3-phenylpropenoyl isothiocyanate makes the double bond more susceptible to nucleophilic addition. Consequently, the corresponding N-(2-cyano-3-phenylpropenoyl)--N'-substituted thioureas undergo a facile cyclization which involves either the sulfur or the nitrogen atom, depending on the reaction conditions. For this reason we focused our attention on the synthesis of spiroheterocyclic compounds by the reaction of 2-cyanocyclohexylideneacetyl isothiocyanate (*II*) with sodium hydrogen sulfide or primary and secondary amines (Scheme 1).

The isothiocyanate *II* was prepared starting from 2-cyanocyclohexylideneacetic acid[9]. The acid was heated with thionyl chloride to give the corresponding chloride (*I*) which was converted to *II* by treatment with freshly prepared lead thiocyanate in anhydrous benzene. Both *I* and *II* are very unstable and their formation was followed by thin-layer chromatography. According to the ^{1}H NMR spectra, they were sufficiently pure for further reactions. In the reaction of *II* with sodium hydrogen sulfide the use of the solid sulfide in acetone proved to be advantageous since in methanolic

solution a decomposition took place, analogously as described for 2-cyano-3-phenylpropenoyl isothiocyanate[10]. After addition of solid sodium hydrogen sulfide the reaction was complete during 30 minutes at room temperature and the resulting 5-cyano-4-oxo-2-thioxo-1-thia-3-azaspiro[5,5]undecane (*III*) was isolated in 21% yield after neutralization with hydrochloric acid.



In formulae *IV*, *V*: *a*, R^3= H; *b*, R^3= CH_3; *c*, R^3= $(CH_3)_2N$; *d*, R^3= OH; *e*, R^3= CH_3O; *f*, R^3= Br.

SCHEME 1

In the reaction of the isothiocyanate *II* with primary amines only 4-methylaniline and 4-methoxyaniline afforded stable thioureas. In the other cases the reaction gave a mixture of the thiourea and the corresponding 1-(4-substituted phenyl)-5-cyano--4-oxo-1,3-diazaspiro[5,5]undecane. The attempted chromatographic separation on silica gel was accompanied by decomposition and the thioureas could not be isolated. No cyclization was observed after refluxing for several hours in benzene, even with boron trifluoride etherate as catalyst[11]. The crude mixture (as well as the isolated thioureas *IVb* and *IVe*) was cyclized in ethanol in the presence of sodium hydroxide at room temperature. Neutralization with hydrochloric acid afforded 1-(4-substituted phenyl)-5-cyano-4-oxo-2-thioxo-1,3-diazaspiro[5,5]undecanes (*Va – Vf*). Secondary amines (diphenylamine, N-methylaniline) reacted with *II* to give the 1-thia--3-azaspiro derivatives *VIa* and *IVb* without isolation of the corresponding thioureas.

Structure of the synthesized 1-thia-3-azaspiro- and 1,3-diazaspiroundecanes was verified by spectral methods. Infrared spectra of the compounds display characteristic absorption bands due to carbonyl stretching vibrations. The 1-thia-3-azaspiro derivatives *VIa* and *VIb* which can exist only in the amino form have carbonyl bands at 1 670 cm^{-1}, in accord with the literature[12]. The carbonyl bands in the spectra of all 1,3-diazaspiro compounds (*Va – Vf*) are markedly shifted to higher frequencies (1 720 – 1 725 cm^{-1}). The assumed structure has been confirmed by ^{13}C NMR spectra: the 1-thia-3-azaspiroundecenes *VIa* and *VIb* as well as 1,3-diazaspiroundecanes *Va – Vf* show carbonyl carbon signals at 168 ppm and 158 ppm, respectively. These two types can be distinguished by means of the signal at 167 ppm due to the C=N group in the 1-thia-3-azaspiro derivatives *VIa* and *VIb* which is not present in the spectra of the 1,3-diazaspiroundecanes (*Va – Vf*). On the other hand, spectra of compounds *Va – Vf* display signals of thiocarbonyl carbon atoms at 178 – 179 ppm whose presence proves that the cyclization involved the nitrogen atom. Also the mass spectra of *Ve* and *VIb* are in accord with the proposed structure, showing molecular ions at *m/z* 329 and 375, respectively.

EXPERIMENTAL

Infrared absorption spectra (wavenumbers in cm^{-1}) were measured on a SPECORD IR-75 spectrometer (Zeiss Jena); ^1H and ^{13}C NMR spectra were taken on a Tesla BS 487A (80 MHz) and TESLA 567 (25, 15 MHz) instrument; internal standard tetramethylsilane, δ-values in ppm. Mass spectra were obtained with an LKB 9000 spectrometer at 70 eV (ionization chamber temperature 190°C). The reaction course was followed by thin-layer chromatography on Silufol plates (Kavalier).

2-Cyanocyclohexylideneacetyl Chloride (*I*)

A mixture of cyclohexylidenecyanoacetic acid[9] (9·78 g; 60 mmol) and thionyl chloride (7·2 ml; 100 mmol) was heated to 80°C until the acid dissolved and then refluxed for 15 min. After cooling, hexane (75 ml) and charcoal were added. The mixture was filtered and thionyl chloride and hexane

were removed under reduced pressure, leaving 9·7 g (79%) of the crude product as yellow viscous oil. IR spectrum ($CHCl_3$): 3 025 (CH), 2 950 and 2 856 (CH_2), 2 224 (C≡N), 1 752 (C=O), 1 561 (C=C). ^{1}H NMR spectrum (C^2HCl_3): 1·75 and 2·73 m, m, 4 H, 6 H, (C_6H_{10}).

2-Cyanocyclohexylideneacetyl Isothicyanate (*II*)

Lead thiocyanate (1·74 g; 5·5 mmol) was added to a solution of 2-cyanocyclohexylideneacetyl chloride (1·83 g; 10 mmol) in anhydrous benzene (50 ml). After refluxing for 3 h, the precipitated $PbCl_2$ was filtered and the benzene driven off *in vacuo*, leaving a red-brown oil (90%). IR spectrum ($CHCl_3$): 3 020 (CH), 2 945 and 2 860 (CH_2), 2 225 (C≡N), 1 940 (NCS), 1 665 (C=O), 1 544 (C=C). ^{1}H NMR spectrum (C^2HCl_3): 1·84 and 2·78 m, m, 4 H, 6 H (C_6H_{10}).

5-Cyano-4-oxo-2-thioxo-1-thia-3-azaspiro[5,5]undecane (*III*)

Solid NaSH (0·72 g; 13 mmol) was added to a stirred solution of 2-cyanocyclohexylideneacetyl isothiocyanate (2·06 g; 10 mmol) in acetone (20 ml). After 30 min the mixture was diluted with water (50 ml) and neutralized with 1M-HCl. The formed oil was extracetd with chloroform, washed with water and dried over anhydrous calcium chloride. Evaporation of the solvent and crystallization of the residue from chloroform–light petroleum afforded 0·5 g (21%) of the title product, m.p. 204°C. For $C_{10}H_{12}N_2OS_2$ (240·4) calculated: 49·97% C, 5·03% H, 11·66% N; found: 50·24% C, 4·87% H, 11·61% N. IR spectrum (KBr): 3 414 (NH), 2 260 (C≡N), 1 728 (C=O). ^{1}H NMR spectrum (C^2HCl_3—$(C^2H_3)_2SO$): 2·33 m, 10 H, (C_6H_{10}); 4·38 s, 1 H, (CH).

N-(4-Substituted phenyl)-N′-2-cyanocyclohexylideneacetylthioureas (*IV*)

A solution of the 4-substituted aniline (10 mmol) in anhydrous benzene or acetone (10 ml) was added dropwise under vigorous stirring to a solution of 2-cyanocyclohexylideneacetyl isothiocyanate (2·06 g; 10 mmol) in anhydrous benzene or acetone (10 ml). After stirring for 30 min the precipitate was filtered, dried and crystallized from acetone–hexane.

N-(4-*Methylphenyl*)-N′-2-*cyanocyclohexylideneacetylthiourea* (IVb), yield 57%, m.p. 152—154°C. For $C_{17}H_{19}N_3OS$ (313·4) calculated: 65·15% C, 6·11% H, 13·41% N; found: 65·24% C, 6·04% H, 13·29% N. IR spectrum (KBr): 2 250 (C≡N), 1 671 (C=O), 1 613 (C=C), 1 550 (NHCS). ^{1}H NMR spectrum ($(C^2H_3)_2SO$): 1·85 and 2·70 m, m, 4 H, 6 H, (C_6H_{10}); 2·48 s, 3 H, (CH_3); 7·45 m, 4 H, (C_6H_4).

N-(4-*Methoxyphenyl*)-N′-2-*cyanocyclohexylideneacetylthiourea* (IVe), yield 41%, m.p. 148 to 149°C. For $C_{17}H_{19}N_3O_2S$ (329·4) calculated: 61·98% C, 5·81% H, 12·76% N; found: 61·73% C, 5·68% H, 12·59% N. IR spectrum ($CHCl_3$): 3 392 (NH), 2 214 (C≡N), 1 678 (C=O), 1 610 (C=C). ^{1}H NMR spectrum ($(C^2H_3)_2SO$): 1·85 and 2·70 m, m, 4 H, 6 H (C_6H_{10}); 3·94 s, 3 H (OCH_3); 7·43 m, 4 H (C_6H_4).

1-(4-Substituted phenyl)-5-cyano-4-oxo-2-thioxo-1,3-diazaspiro[5,5]undecanes *Va*, *Vd*, *Vf*

A solution of the substituted aniline (10 mmol) in benzene (25 ml) was added dropwise with cooling to a stirred solution of isothiocyanate *II* (10 mmol) in benzene (25 ml). After stirring for 2 h, the formed precipitate was filtered, dried, dissolved in ethanol (80 ml) and 2M-NaOH (10 mmol) was added at room temperature in the course of 10 min. After addition of water (100 ml) the mixture was neutralized with 2M-HCl and the precipitate was filtered, dried and crystallized from chloroform–light petroleum.

1-*Phenyl*-5-*cyano*-4-*oxo*-2-*thioxo*-1,3-*diazaspiro*[5,5]*undecane* (Va); yield 74%, m.p. 184–186°C. For $C_{16}H_{17}N_3OS$ (229·4) calculated: 64·19% C, 5·72% H, 14·04% N; found: 64·01% C, 5·59% H, 14·01% N. IR spectrum ($CHCl_3$): 3 360 (NH), 2 241 (C≡N), 1 723 (C=O). ^{1}H NMR spectrum (C^2HCl_3): 1·25 and 1·88 m, m, 4 H, 6 H (C_6H_{10}); 4·80 s, 1 H (CH); 7·35 m, 5 H (C_6H_5). ^{13}C NMR spectrum (C^2HCl_3–$(C^2H_3)_2SO$): 39·86 d, (CH); 63·75 s, (C); 113·54 s, (C≡N); 157·73 s, (C=O); 179·15 s, (C=S).

1-(4-N,N-*Dimethylaminophenyl*)-5-*cyano*-4-*oxo*-2-*thioxo*-1,3-*diazaspiro*-[5,5]*undecane* (Vc), yield 78%, m.p. 181–182°C. For $C_{18}H_{22}N_4OS$ (342·5) calculated: 63·12% C, 6·48% H, 11·36% N; found: 62·96% C, 6·21% H, 16·20% N. IR spectrum ($CHCl_3$): 3 375 (NH), 2 245 (C≡N), 1 720 (C=O). ^{1}H NMR spectrum (C^2HCl_3): 1·13 and 2·00 m, m, 4 H, 6 H (C_6H_{10}); 2·98 s, 6 H ($N(CH_3)_2$); 4·17 s, 1 H (CH); 7·19 m, 4 H (C_6H_4). ^{13}C NMR spectrum (($C^2H_3)_2SO$): 39·64 d, (CH); 39·82 q, (CH_3); 63·28 s, (C); 114·63 s, (C≡N); 158·23 s, (C=O); 178·86 s, (C=S).

1-(4-*Hydroxyphenyl*)-5-*cyano*-4-*oxo*-2-*thioxo*-1,3-*diazaspiro*[5,5]*undecane* (Vd), yield 80%, m.p. 197–198°C. For $C_{17}H_{17}N_3O_2S$ (315·4) calculated: 60·93% C, 5·43% H, 13·23% N; found: 60·71% C, 5·24% H, 13·05% N. IR spectrum (KBr): 2 245 (C≡N), 1 725 (C=O). ^{1}H NMR spectrum (($C^2H_3)_2SO$): 1·09 and 1·65 m, m, 4 H, 6 H (C_6H_{10}); 4·62 s, 1 H (CH); 7·01 m, 4 H (C_6H_4); 8·63 s, 1 H (OH); 10·80 s, 1 H (NH). ^{13}C NMR spectrum (($C^2H_3)_2SO$): 39·71 d, (CH); 63·24 s, (C); 114·43 s, (C≡N); 158·15 s, (C=O); 178·84 s, (C=S).

1-(4-*Bromophenyl*)-5-*cyano*-4-*oxo*-2-*thioxo*-1,3-*diazaspiro*[5,5]*undecane* (Vf), yield 82%, m.p. 195–197°C. For $C_{16}H_{16}BrN_3OS$ (378·3) calculated: 50·18% C, 4·26% H, 11·11% N; found: 50·28% C, 4·12% H, 11·01% N. IR spectrum (KBr): 2 246 (C≡N), 1 720 (C=O). ^{1}H NMR spectrum (C^2HCl_3–$(C^2H_3)_2SO$): 1·12 and 1·75 m, m, 4 H, 6 H (C_6H_{10}); 4·29 s, 1 H (CH); 7·31 m, 4 H (C_6H_4); 12·01 s, 1 H (NH). ^{1} C NMR spectrum (($C^2H_3)_2SO$): 39·71 d, (CH); 63·24 s, (C); 114·43 s, (C≡N); 158·15 s, (C=O); 178·63 s, (C=S).

1-(4-Substituted phenyl)-5-cyano-4-oxo-2-thioxo-1,3-diazaspiro[5,5]undecanes *Vb*, *Ve*

To a solution of the thiourea *IVb* or *IVe* in ethanol (60 ml) was added dropwise 2M-NaOH (5 mmol) under vigorous stirring. After 15 min water (40 ml) was added and the mixture neutralized with 2M-HCl. The precipitate was filtered, dried and crystallized from chloroform–light petroleum.

1-(4-*Methylphenyl*)-5-*cyano*-4-*oxo*-2-*thioxo*-1,3-*diazaspiro*[5,5]*undecane* (Vb), yield 85%, m.p. 181–183°C. For $C_{17}H_{19}N_3OS$ (313·4) calculated: 65·15% C, 6·11% H, 13·41% N; found: 65·21% C, 6·03% H, 13·24% N. IR spectrum ($CHCl_3$): 3 360 (NH), 2 241 (C≡N), 1 725 (C=O). ^{1}H NMR spectrum (C^2HCl_3): 1·13 and 1·88 m, m, 4 H, 6 H (C_6H_{10}); 2·40 s, 1 H (CH_3); 4·23 s, 1 H (CH); 7·19 m, 4 H (C_6H_4); 9·44 s, 1 H (NH). ^{13}C NMR spectrum (C^2HCl_3): 39·79 d, (CH); 64·35 s, (C); 112·88 s, (C≡N); 157·45 s, (C=O); 178·20 s, (C=S).

1-(4-*Methoxyphenyl*)-5-*cyano*-4-*oxo*-2-*thioxo*-1,3-*diazaspiro*[5,5]*undecane* (Ve), yield 80%, m.p. 193–194°C. For $C_{17}H_{19}N_3O_2S$ (329·4) calculated: 61·99% C, 5·81% H, 12·76% N; found: 61·74% C, 5·62% H, 12·58% N. Mass spectrum *m/z* (relative intensity, %): 329 (78, M^+), 165 (100), 123 (31). IR spectrum (KBr): 2 240 (C≡N), 1 723 (C=O). ^{1}H NMR spectrum (C^2HCl_3–$(C^2H_3)_2SO$): 1·13 and 1·87 m, m, 4 H, 6 H (C_6H_{10}); 3·80 s, 3 H (OCH_3); 4·25 s, 1 H (CH); 7·00 m, 4 H (C_6H_4); 11·85 s, 1 H (NH). ^{13}C NMR spectrum (($C^2H_3)_2SO$): 39·62 d, (CH); 55·14 q, (CH_3); 62·27 s, (C); 114·54 s, (C≡N); 158·23 s, (C=O); 178·83 s, (C=S).

5-Cyano-2-methylphenylamino-4-oxo-1-thia-3-azaspiro[5,5]undec-2-ene (*VIa*)

A solution of N-methylphenylamine (1·10 g; 10 mmol) in acetone (10 ml) was added to a stirred

and cooled solution of isothiocyanate *II* (2·05 g; 10 mmol) in acetone (20 ml). After one hour of intensive stirring, the mixture was decomposed by addition of cold water (100 ml) and the formed precipitate was filtered and crystallized from chloroform–light petroleum; yield 0·8 g (33%), m.p. 142—143°C. For $C_{17}H_{19}N_3OS$ (313·4) calculated: 65·15% C, 6·11% H, 13·41% N; found: 65·02% C, 6·21% H, 13·25% N. IR spectrum ($CHCl_3$): 2 235 (C≡N), 1 664 (C=O), 1 507 (NHCS). ^{1}H NMR spectrum (C^2HCl_3): 1·63 m, 10 H (C_6H_{10}); 3·49 s, 3 H (CH_3); 3·68 s, 1 H (CH); 7·31 m, 10 H (C_6H_5, NC_6H_5). ^{13}C NMR spectrum (C^2HCl_3): 14·06 q, (CH_3), 47·18 d, (CH); 52·18 s, (C); 114·67 s, (C≡N); 167·75 s, (C=N); 168·87 s, (C=O).

2-Diphenylamino-5-cyano-4-oxo-1-thia-3-azaspiro[5,5]undec-2-ene (*VIb*)

A solution of diphenylamine (1·76 g; 10 mmol) in anhydrous benzene (5 ml) was added at room temperature to the isothiocyanate *II* (2·06 g; 10 mmol) in the same solvent (5 ml) and the mixture was vigorously stirred for 2·5 h. The precipitate was collected on filter, washed with ether (50 ml), dried and crystallized from carbon tetrachloride; yield 1·3 g (54%), m.p. 114—116°C. For $C_{22}H_{21}N_3OS$ (375·5) calculated: 70·37% C, 5·64% H, 11·19% N; found: 70·15% C, 5·35% H, 11·01% N. Mass spectrum, *m/z* (relative intensity, %): 375 (11 M^+), 254 (26); 169 (100). IR spectrum ($CHCl_3$): 2 235 (C≡N), 1 671 (C=O), 1 475 (NCS). ^{1}H NMR spectrum (C^2HCl_3): 1·69 m, 10 H (C_6H_{10}); 3·68 s, 1 H (CH); 7·28 m, 15 H (C_6H_5, $N(C_6H_5)_2$). ^{13}C NMR spectrum (C^2HCl_3): 46·81 d, (CH); 52·63 s, (C); 114·45 s, (C≡N); 167·83 s, (C=N); 168·47 s, (C=O).

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