Synthesis of 5-amino-pyrazol-4-*N*'-[*bis*(metylthio)-methylene]carbohydrazide

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Recibido: 4 de octubre de 2001. Aceptado: 5 de junio de 2002.

Palabras clave: síntesis, 5-aminopirazoles, ceten-S,S-acetales, 1,3-ditietanos.
Key words: synthesis, 5-aminopyrazoles, keten-S,S-acetals, 1,3-dithiethanes.

RESUMEN. La síntesis de anillos pirazólicos ha sido ampliamente estudiada en los últimos años con el propósito de hallar nuevas moléculas con potencial actividad biológica. Esto se ha logrado ciertamente, pues actualmente varios medicamentos contienen este tipo de estructura como principio activo. Entre ellos deben destacarse analgésicos, antinflamatorios y sedantes. En este trabajo se reporta la síntesis de nuevos compuestos de estructura 5-aminopirazólica mediante la reacción de los alquenos o ditietanos *push pull* derivados de las *N*'-[*bis*(metiltio)-metilen]cianoacetahidrazidas con dinucléofilos adecuados. Los mejores resultados se lograron en la reacción del alqueno *push pull N*'-[*bis*(metiltio)metilen]-2-ciano-3,3-[*bis*(metiltio)]acrilhidrazida con hidracinas e hidracidas en presencia de un exceso de estos agentes dinucleofílicos (alqueno/dinucléofilo 1:2,5). La ciclización intramolecular que ocurre en el intermediario de la reacción se produce sin la participación del grupo carbonílico amídico, lo que corrobora la mayor reactividad del grupo ciano ante el ataque del grupo NH. Los resultados permitieron comprobar el mayor carácter *push pull* del enlace olefínico en comparación con el azometínico, ya que en el primer sistema se estabiliza más el enlace polarizado. Se pudo demostrar que en general, los mejores rendimientos se logran utilizando los ceten-S,S-acetales como agentes electrofílicos. Los compuestos de interés se obtuvieron en un solo paso de síntesis con rendimientos superiores a los reportados para sistemas similares de anillos. Todos los productos sintetizados se caracterizaron adecuadamente mediante análisis elemental cuantitativo y con el empleo de varios métodos espectroscópicos como espectroscopias infrarroja y resonancia magnética nuclear, así como por espectrometría de masas.

ABSTRACT. The synthesis of pyrazolic ring systems has been widely studied in the last years with the purpose of finding new molecules with potential biological activity. It has been certainly achieved since now a days, several medications contain this kind of structures as active principle. Between them, analgesics, antiinflammatories, and sedatives are to be emphasized. In this work, the synthesis of new compounds of 5-aminopyrazolic structure by means of the reaction between the alkene and dithiethane *push pull* derived from *N*'-[*bis*(methylthio)methylene]-cyanoacethydrazide and appropriate dinucleophiles is reported. The best results were achieved by reaction of the alkene *push pull N*'-[*bis*(methylthio)methylene]-2-cyano-3,3-[*bis*(methylthio)]acrylhydrazide with hydrazine and hydrazide when an excess of the dinucleophiles was used (1:2.5). The intramolecular cyclization occurring in the reaction intermediate takes place without participation of the amidic carbonyl, which shows the greater reactivity of the cyano group regarding the NH attack. The results allow to verify the greater *push pull* character of the ethylene bond than the azometinic one for the reason that in the former the polarized bond will be more stabilized. It could be demonstrated in general, that the better yields were achieved by using the keten-S,S-acetals as electrophilic agents. The goal compounds could be obtained in just one step with higher yields than the reported for similar ring systems. The characterization of the products was carried out by means of elemental quantitative analysis and several spectroscopic methods: Infra Red and Nuclear Magnetic Resonance Spectroscopies and Mass Spectrometry.

INTRODUCTION

Researches into pyrazolic compounds and its derivatives have been stimulated during the last years because some of these compounds have shown biological activity.[1-5]

As a frequently reported method to obtain such compounds, the reaction ceten-S,S-acetals or N,S-analogs with dinucleophiles, could be mentioned.[6-8]

Recently the new ceten-S,S-acetal **1** and the dithietane **3** derived from *N*'-[*bis*(methylthio)methylene]-cyanoacetohydrazide[9] were prepared. This fact enables the preparation of new heterocyclic compounds with potential biological activity.[10]

Therefore, the reactions of **1** and **3** with dinucleophiles R-NHNH$_2$ were investigated in this paper.

MATERIAL AND METHODS

Melting points were determined in Boetius hot stage microscope and are uncorrect. The recording of NMR spectra was performed on a Bruker AC 250 F spectrometer. All NMR spectra were recorded as dimethyl sulfoxide solutions, chemical shifts being given as δ values with respect to tetramethylsilane as the internal standard. The IR spectra were measured with a on a Philips PU-9426FTIR spectrometer as potassium bromide pellets. Mass spectra (EI) were obtained with a JEOL JMS DX 300 spectrometer under normal conditions. Mycroanalyses were performed on an EAGER-200 Summary.

EXPERIMENTAL PART

Synthesis of *N*'-[*bis*(methylthio)-methylene]2-cyano-3,3-*bis*-(methylthio)acrylhydrazide 1

2.03 g (0.01 mol) of *N*'-[*bis*(methylthio)methylene]cyanoacetohydrazide[9] was added to a solution of 0.23 g Na in 10 mL EtOH and stirred at room temperature for 15 min . Then, 2.5 mL carbon disulphide was added dropwise, solution of 0.23 g Na in 10 mL EtOH and 2.5 mL CH_3I. The mixture was stirred at room temperature 1 h and poured into 50 mL of ice water. The formed solid was filtered, washed and recrystallized from EtOH.

White needles; yield 2.21 g (72 %), m.p. 144-146 °C .

IR(KBr): $\nu_{max.}$(cm^{-1}) = NH 3 400; CN 2 220; CO 1 680.

^{1}H-NMR (DMSO-d_6): δ(ppm) = 2.43(s,3H-SCH_3); 2.48(s,3H-SCH_3); 2.54(s,3H-SCH_3); 2.51(s,3H-SCH_3); 10.9(s,1H-NH).

^{13}C-RMN (DMSO-d_6): δ(ppm) = 14.44(SCH_3); 14.63(SCH_3); 17.96(SCH_3); 18.11(SCH_3); 92.45 (C-CN); 119.23(CN); 142.83 (C=N); 177.72(C-SCH_3); 186.21 (CO).

MS-EI (70 eV): m/z(%) = 307 (M^+:1.3); 260(100); 172(75); 129(8); 91(29); 75(48); 47(17); 45(27).

$C_9H_{13}N_3OS_4$(307).

Elemental analysis:

Calculated:

C 35.17; H 4.23; N 13.68; S 41.69.

Found:

C 35.32; H 4.50; N 14.06; S 41.34.

Synthesis of 5-amino-3-methylthio-pyrazol-4-*N*'-[*bis*(methylthio)-methylene]carbohydrazide 2. General procedure

N'-[*bis*(methylthio)methylene]2-cyano-3,3-*bis*(methylthio)acrylhydrazid 1 [0.01 mol (3.07g)] was dissolved in 15 mL ethanol. Then, 0.025 mol N-nucleophile in 10 mL EtOH was added dropwise and the mixture was heated at refluxed until TLC showed the absence of starting material ($CHCl_3$:MeOH; 5:1). Finally, the solution was concentrated and the formed solid was filtered, washed and recrystalized from EtOH.

5-amino-3-methylthio-pyrazol-4-*N*'-[*bis*(methylthio)methylene]-carbohydrazide 2a

Green needles; yield 2.03 g (70 %), m.p. 179-81 °C . Reaction time: 2 h .

IR(KBr): $\nu_{max.}$(cm^{-1}) = NH_2, NH 3 480; 3 350; 3 250; CO 1 680; C=N 1 640.

^{1}H-NMR (DMSO-d_6): δ(ppm) = 2.3(s,3H-SCH_3); 2.4(s,3H-SCH_3); 2.5(s,3H-SCH_3); 6.4(s,2H-NH_2); 10.2 (s,1H-NH); 12.1(s,1H-NH).

^{13}C-RMN (DMSO-d_6): δ(ppm) = 14.62(SCH_3); 15.01(SCH_3); 17.01 (SCH_3); 93.97(C -CO); 141.29(C=N); 146.7(C-NH_2); 153.06(C-SCH_3); 159.16 (CO).

MS-EI (70 eV): m/z(%) = 291 (M^+,1.6); 244(56); 196(28); 156(100); 114(21); 91(14); 75(27); 47(69).

$C_8H_{13}N_5OS_3$ (291).

Elemental analysis:

Calculated:

C 32.98; H 4.46; N 24.05; S 32.98.

Found:

C 32.98; H 4.84; N 24.23; S 32.67.

5-amino-1furoyl-(2)-3-methylthio-pyrazol-4-*N*'-[*bis*(methylthio)-methylene]carbohydrazide 2b

Greace needles; yield 2.19 g (57 %), m.p. 158 °C . Reaction time: 3 h .

IR(KBr): $\nu_{max.}$(cm^{-1})= NH_2, NH 3 420, 3 350, 3 250; =CH 3 040; CO 1 680i and 1 660; C=N 1 610; C=C 1 520.

^{1}H-NMR (DMSO-d_6): δ(ppm) = 2.4(s,3H-SCH_3); 2.5(s,4H-SCH_3); 2.6 (s,3H-SCH_3); 7.1(s,2H-NH_2); 6.7 (m,1H-H_4fur); 7.3(m,1H-H_3fur); 8.1 (m,1H-H_5fur); 10.1(s,1H-NH).

MS-EI (70 eV): m/z(%) = 385 (M^+:0.8); 338(60); 290(25); 250 (100); 47(20).

$C_{13}H_{15}N_5O_3S_3$ (385).

Elemental analysis:

Calculated:

C 40.51; H 3.89; N 18.18; S 24.93.

Found:

C 40.28; H 3.92; N 18.65; S 24.42.

5-amino-1-phenil-3-methyltio-pyrazol-4-*N*'-[*bis*(methylthio)-methylene]carbohydrazide 2c

Yellow needles; yield 2.86 g (78 %), m.p. 178-80 °C . Reaction time: 8 h .

IR(KBr): $\nu_{max.}$(cm^{-1}) = NH_2, NH 3 440, 3 300, 3 250; =CH 3 020; CO 1 660.

^{1}H-NMR (DMSO-d_6): δ(ppm) = 2.4(s,3H-SCH_3); 2.5(s,4H-SCH_3); 2.6(s,3H-SCH_3); 6.6(s,2H-NH_2); 7.6 (m,5H-$H_{arom.}$); 10.1(s,1H-NH).

^{13}C-RMN (DMSO-d_6): δ(ppm) = 14.64(SCH_3); 15.05(SCH_3); 16.26 (SCH_3); 94.84(C-CO); 123.50 ($C_{2,6}$benc.); 127.54(C_4benc.); 129.39($C_{3,5}$benc.); 137.36(C_1benc.); 143.12(C=N); 148.05 (C-NH_2); 151.38(C-SCH_3); 159.17 (CO).

MS-EI (70 eV): m/z(%) = 367 (M^+:1.2); 319(90); 272(10); 232(100); 47(20).

$C_{14}H_{17}N_5OS_3$ (367).

Elemental analysis:

Calculated:

C 45.77; H 4.63; N 19.07; S 26.15.

Found:

C 45.34; H 4.42; N 18.57; S 26.59.

Synthesis of 1,3-dithiethane-2,4-diylidene-bis{*N*'-[*bis*(methylthio)methylene]}cyanoacetohydrazide 3

N'-[*bis*(methylthio)methylene]-cyanoacetohydrazide (9) [2.03 g (0.01 mol)] was suspended in 5 mL absolute ethanol. Then, a solution of 0.23 g Na in 10 mL EtOH and 0.01 mol ClCOOEt in 2.5 mL carbon disulphide was added dropwise. Finally, the mixture was stirred 1 h at room temperature. The formed solid was filtered, washed with EtOH and recrystallized from EtOH-DMF.

Dithiethane-2,4-diylidene-bis{*N*'-[*bis*(methylthio)methylene]}cyanoacetohydrazide 3

Orange solid; yield 3.47g (71 %), m.p. 185 °C(D).

IR(KBr): $\nu_{max.}$(cm^{-1}) = NH 3 400; CN 2 220; CO 1 650.

MS-EI (70 eV): m/z(%) = 490(M^+:1.3), 443(7), 395(6), 198(7), 155(8), 141(10), 110(17), 91(100), 47(53).

$C_{14}H_{14}N_6O_2S_6$ (490).

Elemental analysis:

Calculated:

C 34.28; H 2.85; N 17.14; S 39.68.

Found:

C 34.77; H 2.62; N 17.63; S 39.18.

Synthesis of 5-amino-3-mercapto-pyrazol-4-*N*'-[*bis*(methylthio)-methylene]carbohydrazide 4. General procedure

1,3-Dithiethane-2,4-diylidene-*bis*{*N*'-[*bis*(methylthio)methylene]} cyanoacetohydrazide **3** [0.005 mol (0.5 g)] was added in 10 mL ethanol-DMF (1:1). Then the mixture was heated and stirred for 15 min . After adding dropwise 0.025 mol N-nuclephile in 10 mL EtOH, the mixture was heated at refluxed until TLC showed the absence of startig material ($CHCl_3$:MeOH; 5:1). The product was then extracted with cloroform and the solvent was eliminated under reduced pressure. The solid was washed and recrystallized from EtOH.

5-Amino-1H-3-mercapto-pyrazol-4-*N*'-[*bis*(methylthio)-methylene]carbohydrazide 4 a

Yellow needles; yield 1.82 g (66 %), m.p. 190-191 °C . Reaction time: 4 h .

IR(KBr): $\nu_{max.}$(cm^{-1}) = NH_2, NH 3 460, 3 250, 3 260; CO 1 690; C=N 1 640.

^{1}H-NMR (DMSO-d_6): δ(ppm) = 2.4(s,1H-SH); 2.3(s,3H-SCH_3); 2.5 (s,3H-SCH_3); 6.5(s,2H-NH_2); 10.1 (s,1H-NH); 11.8(s,1H-NH).

^{13}C-RMN (DMSO-d_6): δ(ppm) = 14.24(SCH_3); 14.750(SCH_3); 95.10(C -CO); 142.22(C=N); 147.220(C-NH_2); 145.20(C-SH); 158.25(CO).

MS-EI (70 eV): m/z(%) = 277 (M^+:1.2); 230(45); 142(100); 75(27); 47 (25).

$C_7H_{11}N_5OS_3$ (277).

Elemental analysis:

Calculated:

C 30.32; H 3.97; N 25.27; S 34.65.

Found:

C 30.89; H 3.48; N 24.95; S 34.21.

5-Amino-1-furoyl-(2)-3-mercapto-pyrazol-4-*N*'-[*bis*(methylthio)-metylen]carbohydrazide 4b

Beige needles; yield 1.66 g (45 %), m.p. 182-184 °C . Reaction time: 5 h .

IR(KBr): $\nu_{max.}$(cm^{-1}) = NH_2, NH 3 450, 3 350, 3 240; =CH 3 040; CO 1 690; CO 1 670; C=N 1 620; C=C 1 520.

^{1}H-NMR (DMSO-d_6): δ(ppm) = 3.1(s,1H-SH); 2.3(s,3H-SCH_3); 2.5 (s,4H-SCH_3); 6.9(s,2H-NH_2); 6.7 (m,1H-H_4fur); 7.4(m,1H-H_3fur); 8.4 (m,1H-H_5fur); 10.3(s,1H-NH).

MS-EI (70 eV): m/z(%) = 371 (M^+:0.9); 324(70); 236(100); 47(40).

$C_{12}H_{13}N_5O_3S_3$ (371).

Elemental analysis:

Calculated:

C 38.81; H 3.50; N 18.86; S 25.87.

Found:

C 39.02; H 3.22; N 18.35; S 25.51.

5-Amino-1-phenyl-3-mercapto-pyrazol-4-*N*'-[*bis*(methylthio)-methylene]carbohydrazide 4c

Yellow needles; yield 2.54 g (72 %), m.p. 183-185 °C . Reaction time: 8 h .

IR(KBr): $\nu_{max.}$(cm^{-1}) = NH_2, NH 3 450, 3 320, 3 250; =CH 3 020; CO 1 670; 600-700.

^{1}H-NMR (DMSO-d_6): δ(ppm) = 3.1(s,1H-SH); 2.3(s,3H-SCH_3); 2.4 (s,4H-SCH_3); 6.9(s,2H-NH_2); 7.5 (m,5H-$H_{arom.}$); 10.2(s,1H-NH).

^{13}C-RMN (DMSO-d_6): δ(ppm) = 14.35(SCH_3); 14.85(SCH_3); 94.92(C-CO); 125.80($C_{2,6}$benc.); 128.10(C_4benc.); 130.54($C_{3,5}$benc.); 138.10(C_1benc.); 143.81(C=N); 147.62(C-NH_2); 144.72 (C-SH); 159.12(CO).

MS-EI (70 eV): m/z(%) = 353 (M^+: 0.8); 339(56); 218(100); 47(35).

$C_{13}H_{15}N_5OS_3$ (353).

Elemental analysis:

Calculated:

C 44.19; H 4.24; N 19.83; S 27.19.

Found:

C 44.54; H 3.87; N 19.43; S 26.99.

RESULTS AND DISSCUSION

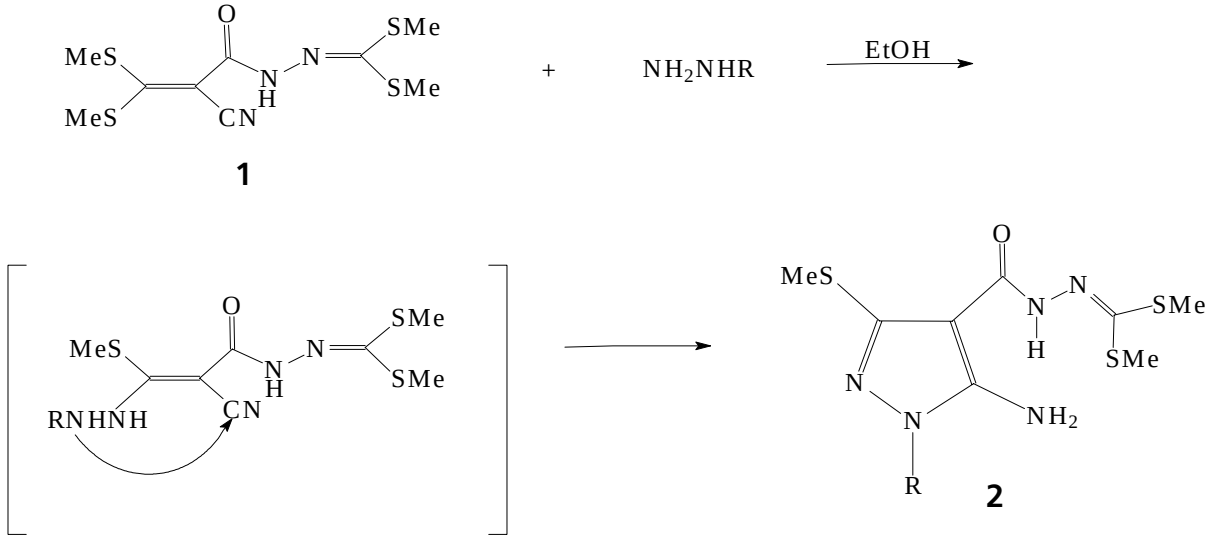
Reaction of *N*'-[*bis*(methylthio)-methylene]2-cyano-3,3-*bis*-(methylthio)acrylhydrazide 1 with dinucleophiles

It is known that by reactions of ethylene *push pull* with dinucleophiles the best yields are obtained by using an excess of the latter.[11] In this case the best results were achieved by carryng out the reactions with proportion ethylene-dinucleophile: 2:5

The yields of desired products increase by using hydrazines instead hydrazides due surely to the less nucleophilic character of the latters. The preference for the intramolecular cyclization showed in the scheme 1 corroborate the greater reactivity of the cyano group by the NH attack. When the reaction was carried out with 2,4-dinitrophenylhydrazine, good results were not obtained.

The 5-amino-pyrazol-4-*N*'-[*bis*-(methylthio)methylene]-carbohydrazide structure of compounds **2** was confirmed by NMR, IR and mass spectra. IR spectra showed cleary the dissappearance of the CN-band of the starting material. In the ^{1}H and ^{13}C-NMR spectra only three CH_3S signals could be observed, indicating that an initial substitution of such a group had taken place.

The obtained results demonstrate the greater push pull character of the ethylenic bond than the azomethinic one for the reason that in the former two electrons withdrawing groups on the nucleophilic C-atom have comparatively an enhanced stabilizing effect over the polarized bond. Therefore the interaction of nucleophile takes place preferably on the electrophilic C-atom of the ethylene.



2	R
a	H
b	COFu
c	Ph

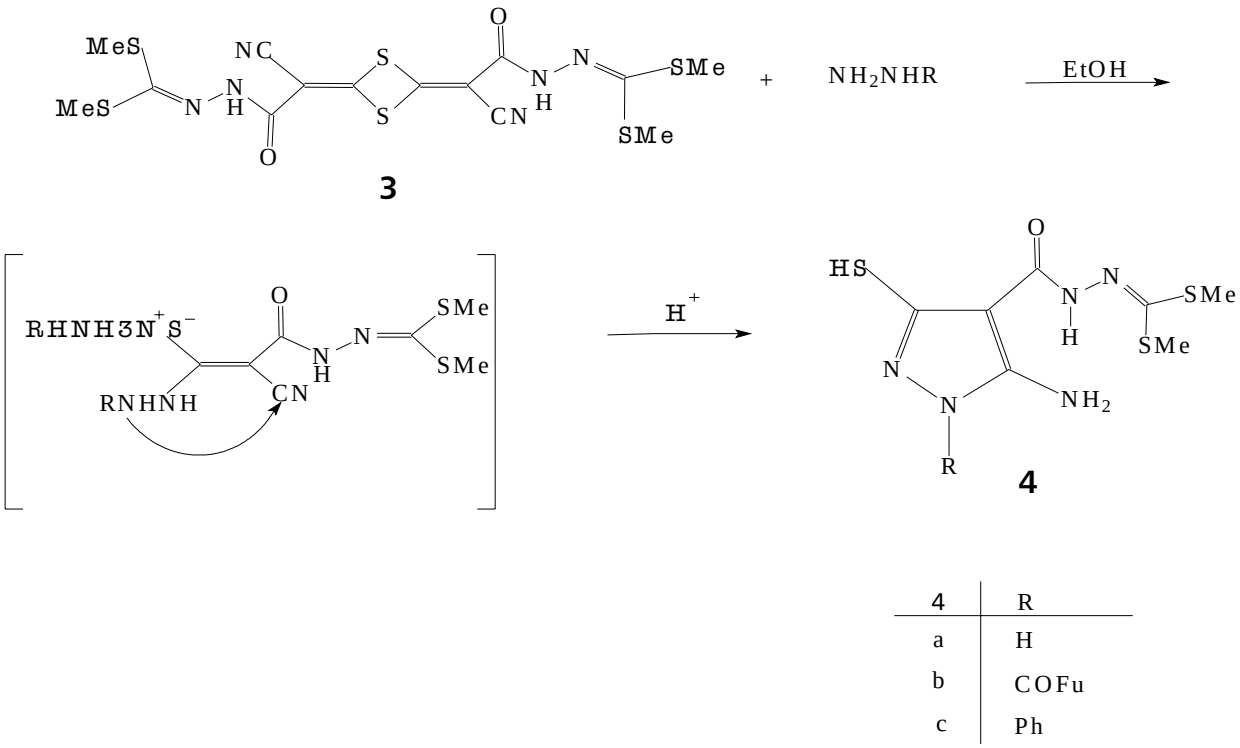
Scheme 1

Reaction of 1,3-dithiethane-2,4-diylidene-*bis*{*N*'-[*bis*(methylthio)methylene]}cyanoacetohydrazide 4 with dinuleophiles

Taking into account that **1** and **3** have similar structure, the analog pyrazolic compounds **4** were obtained by reaction of dithiethane **3** with the corresponding nucleophilic agents

According to experiences of Almeida and co-workers,[12] dimethylformamide-cloroform mixture was used as solvent in the reactions of this type. Under these conditions, good results were obtained. It should be mentioned that the dithiethane **3** are little soluble in this solvent, however its solubility was increased progresively by heating the reaction mixture.

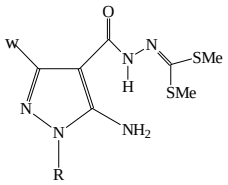
As can be seen from the date given in Table 1, the better results were obtained by using the keten-S,S-acetals as electrophilic agents in coincidence with author's findings about the synthesis of heterocyclic systems.



4	R
a	H
b	COFu
c	Ph

Scheme 2

Table 1. 5-Amino-pyrazol-4-*N*'-[*bis*(methylthio)methylene]carbohydrazide.



Compound	W	R	Yield (%)	Time (h)
2a	SMe	H	70	2
2b	SMe	COFu	57	3
2c	SMe	Ph	78	8
4a	SH	H	66	4
4b	SH	COFu	45	5
4c	SH	Ph	72	8

Spectral date of compounds **2** and **4** are identical. Mass spectra have a great significance by structural characterization. The α-cleavage induced by the CO group gives place to very intense oxonium ions. This fact is highly expressive for corroborating the presence of pyrazolic ring in the structure.

CONCLUSIONS

The synthesis of pyrazols starting from keten-S,S-acetal **1** or dithietane **3** by reaction with nucleophilic hydrazines and hydrazides is characterized by its simplicity and permits the preparation of great number of different pyrazoles.

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