New method for synthesis of triazolo[1,5-a]pyridines from *N*'-[*bis*(methylthio)methylene]cyanoacetohydrazide and *push pull systems*

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Palabras clave: síntesis, piridinas, cianoacetahidracidas, sistemas push pull.
Key words: synthesis, pyridines, cyanoacethydrazides, push pull systems.

RESUMEN. La *N*'-[*bis*(metiltio)metilen]cianoacetahidrazida derivada de la cianoacetahidrazida presenta una estructura adecuada para formar, en medio básico, el carbanión metileno. En este trabajo se estudió el comportamiento de este agente nucleofílico en reacciones con alquenos y ditietanos *push pull* para obtener heterociclos del tipo de triazolo[1,5-a]piridinas de potencial actividad biológica. Las triazolo[1,5-a]piridinas con compuestos importantes por su utilización como fármacos. Su obtención comprende, usualmente varios pasos de síntesis y en los casos más sencillos, no se obtienen buenos rendimientos. En este trabajo se describe la síntesis directa de un nuevo sistema del tipo de triazolo[1,5-a]piridina. Este significa una ventaja con relación a los otros métodos descritos. Todas las reacciones se ensayaron a temperatura ambiente utilizando diferentes medios básicos sin resultados satisfactorios. Los mejores rendimientos se obtuvieron con calentamiento a reflujo usando etóxido de sodio. Se proponen los mecanismos de reacción que pueden explicar claramente la formación de los heterociclos condensados a partir del ataque nucleofílico del carbanión de la *N*'-[*bis*(metiltio)metilen]cianoacetahidrazida al carbono electrofílico de los ceten-S,S-acetales y los ditietanos *push pull*. Las pruebas preliminares efectuadas a los nuevos productos arrojaron resultados alentadores con relación a su bioactividad. Los rendimientos de las triazolo[1,5-a]piridinas sustituidas obtenidas a partir de la *N*'-[*bis*(metiltio)metilen]cianoacetahidrazida 1 y los alquenos *push pull* 1 son superiores a las obtenidas con los ditietanos *push pull* 4. Los productos 3 y 5 fueron caracterizados mediante análisis elemental cuantitativo y varias técnicas espectroscópicas (IR, RMN-^{1}H y ^{13}C y espectrometría de masas).

ABSTRACT. The *N*'-[*bis*(methylthio)methylen]cyanoacethydrazides derived from cyanoacethydrazide possess the structural requirements for the formation, in basic media of methylenic carbanions which make possible the synthesis of interesting heterocyclic systems with potential activity. On the other hand, it is known that the triazolo[1,5a]pyridines are very useful compounds as pharmaceutical agents for the treatment of several diseases. Their synthesis usually requires several steps and even in the most simple cases, good yields could be not achieved. In this paper, the direct synthesis of new triazolo[1,5a]pyridines is described , which is advantageous in relation to the other methods reported. All reactions were carried out at room temperature using several basic media without satisfactory results. The best yields could be obtained by reflux temperature in presence of sodium ethoxide. Reaction mechanisms were proposed, which explain clearly the formation of these condensed heterocycles starting from the nucleophilic attack of the corresponding carbanion to the electrophilic C-atom of keten-S,S-acetals and dithiethane *push pull* systems. The best results were obtained with the former ethylenic ones. The compounds synthesized were characterized through their quantitative elemental analysis and spectroscopic techniques (IR, ^{1}H and ^{13}C-NMR and mass spectrometry).

INTRODUCTION

1,2,4-triazolo[1,5-a]pyridines have been previously described as very interesting compounds from pharmacological point of view.[1-5] This fact has atractted a great interest, thus there are several studies on the reactivity and structure of these compounds.[6-9]

Their synthesis usually requires several steps with separate formation of each ring. Although some procedures starting from the pyridine ring are known,[10-12] most of them involve the construction of the triazole ring first.[13,14] These compounds have also been prepared by ring transformation of isomeric triazolo[3,4-a]pyridines[15] and from 2-thioxopyrone.[16]

A one step synthesis of triazolo-[1,5-a]pyridine in anion form from 2-acyl-2-cyanoacetohydrazide and arylidencyanonitrile is reported.[17-19] However, in the described method, reaction mixtures have to be refluxed for a relative long time and moderate yields of the goal compounds have been achieved.

The direct synthesis of a new system of triazolo[1,5-a]pyridines form acyclic starting materials: *N´*-[*bis*-(methylthio)methylene]cyanoacetohydrazide and *push pull systems* as the keten-S,S-acetals and 1,3-dithiethanes is described in this paper.

This new method only involves one step and satisfactory results can be obtained. Besides reaction times are short, fundamentally when

keten-S,S-acetals are used as electrophilic agents.

The authors have recently reported the synthesis of *N´*-[*bis*-(methylthio)methylene]cyanoacetohydrazide from cyanoacetohydrazide, CS_2 and CH_3I in basic medium with very good yield.[20] This compound **1** contains an acidic methylene group which is able in an appropriate basic medium to attack the electrophilic C-atom of ethylene and dithiethane *push pull systems*.

EXPERIMENTAL PART

Melting points were determined on a Boetius hot stage microscope and are incorrected. The ^{1}H-NMR and ^{13}C-NMR spectra were performed on a Bruker AC 250 F spectrometer. All NMR spectra were recorded in dimethylsulfoxide solutions, chemical shifts being given as δ values with regards to tetramethylsilane as the internal standard. IR spectra were recorded on a Philips PU-9426FTIR spectrometer as potassium bromide pellets. Mass spectra (EI) were obtained using an JEOL JMS DX 300 spectrometer under normal conditions. Microanalyses were performed on an EAGER-200 Summary.

Synthesis of N´-[*bis*(methylthio)-methylene]cyanoacetohydrazide 1

A solution of 0.46 g Na (0.02 mol) in 20 mL EtOH was added 0.99 g (0.01mol) of cyanoacetohydrazide. Inmediately a mixture of carbon disulphide (2,5mL) and methyl iodide (3 mL) was dropped . The mixture was left at room temperature and after 24 h, 20 mL of water were added. The formed solid was filtered and recrystallized from EtOH.

White needles; yield 1.93 g (95 %), m.p. 113-115 ºC .

IR(KBr): $\nu_{max.}$(cm$^{-1)}$ = NH 3 200; CN 2 235; CO 1 650.

^{1}H-NMR (DMSO-d_6): δ(ppm) = 2.45(s,3H-SCH_3); 2.55(s,3H-SH_3); 3.75(s,2H-CH_2); 9.1(s,1H-NH).

^{13}C-RMN (DMSO-d_6): δ(ppm) = 15.19 (SCH_3); 15.81(SCH_3); 24.88-(CH_2); 113.79(CN); 149.71(C=N); CO(162.66).

MS-EI (70 eV): m/z (%) = 203-(M^+,89); 188(19); 156(100); 128(31); 91(81); 74(59); 67(88); 47(74); 45(74)

$C_6H_9N_3OS_2$ (203).

Calculated (%):
C 35.46; H 4.43; N 20.68; S 31.52.
Found (%):
C 35.33; H 4.50; N 20.50; S 31.16.

Synthesis of 6-cyano-1*H*-2,7-dimethylthio-5-oxo-1,2,4-triazolo[1,5-a]pyridines 3

A solution of 0.23 g Na (0.01 mol) in 20 mL EtOH (0.5 mol/L) was added to the mixture of *N´*-[*bis*(methylthio)methylene]-cyanoacetohydrazide **1** (2.03 g, 0.01 mol) and the corresponding keten-S,S-acetal (0.01 mol). The reaction mixture was refluxed until TLC showed the absence of starting materials. After neutralizing with 50 % hydrocloric acid, a solid was isolated and identified as triazolo[1,5-a]pyridines **3.** The filtered solid were washed with water and recrystallized from EtOH-DMF.

6-cyano-1*H*-2,7-dimethylthio-5-oxo-1,2,4-triazolo[1,5-a]pyridine-8-methylcaboxylate 3a

Beige solid; yield 2.26 g (73 %), m.p. 260 ºC (decomposition). Reaction time: 30 min .

IR(KBr): $\nu_{max.}$(cm^{-1}) = NH 3 325; CN 2 225; CO 1 720; CO 1 680; C=N 1 620.

^{1}H-NMR(DMSO-d_6): δ(ppm) = 2.4 (s,3H-SCH_3); 2.6(s,3H-SCH_3); 3.9 (s,3H-OCH_3); 8.1(a,1H-NH).

^{13}C-RMN (DMSO-d_6): δ(ppm) = 13.1 (SCH_3); 14.3(SCH_3); 52.2(OCH_3); 82.2(C-CN); 93.1(C-CO); 115.8(CN); 152(C-NH); 153.9(N-C-SCH_3); 154.7 (CO); 161.8(CO); 164.3(C-C-SCH_3).

MS-EI (70 eV): m/z (%) = 310 (M^+,100); 295(25); 263(15); 216(60); 74(25); 47(25).

$C_{11}H_{10}N_4O_3S_2$ (310).
Calculated (%):
C 42,58; H 3,22; N 18,06; S 20,64.
Found (%):
C 42,92; H 3,00; N 17,65; S 20,73.

6-cyano-1*H*-2,7-dimethylthio-5-oxo-1,2,4-triazolo[1,5-a]pyridine-8-ethylcaboxylate 3b

Beige solid; yield 2,26 g (74 %), m.p. 265 ºC (decomposition). Reaction time: 30 min .

IR(KBr): $\nu_{max.}$(cm^{-1}) = NH 3 350; CN 2 220; CO 1 710; CO 1 680; C=N 1 610.

^{1}H-NMR (DMSO-d_6): δ(ppm) = 1,4 (t,3H-CH_3); 2.6(s,3H-SCH_3); 2.8(s,3H-SCH_3); 3.8(q,2H-OCH_2); 7.9 (s,1H-NH).

^{13}C-RMN (DMSO-d_6): δ(ppm) = 13.2(SCH_3); 14.1(SCH_3); 13.5(CH_3); 65.2(OCH_2); 84.3(C-CN); 95.2(C-CO); 115.5(CN); 151.4(C-NH); 153.2(N-C-SCH_3); 155(CO); 161.9(CO); 165.1(C-C-SCH_3).

MS-EI (70 eV): m/z (%) = 324 (M^+,100); 319(35); 277(10); 74(25); 47(35).

$C_{12}H_{12}N_4O_3S_2$(324).
Calculated (%):
C 44,44; H 3,70; N 17,28; S 19,75.
Found (%):
C 44,83; H 3,28; N 17,00; S 19,92.

6-cyano-1*H*-2,7-dimethylthio-5-oxo-1,2,4-triazolo[1,5-a]pyridine-6,8-dicarbonitrile 3c

Beige solid; yield 1.96 g (69 %), m.p. 268 ºC (decomposition). Reaction time: 45 min .

IR(KBr): $\nu_{max.}$(cm^{-1}) = NH 3 350; CN 2 220,2 210; CO 1 680, C=N 1 620.

^{1}H-NMR (DMSO-d_6): δ(ppm) = 2.6 (s,3H-SCH_3); 2.8(s,3H-SCH_3); 7.8 (a,1H-NH).

^{13}C-RMN (DMSO-d_6): δ(ppm) =13.5(SCH_3);15.1(SCH_3);70.9(C-CN); 86.6(C-CN) 115.9(CN); 117.1(CN); 151.6(C-NH); 152.9(N-C-SCH_3); 154.7(CO); 163.2(C-C-SCH_3).

MS-EI (70 eV): m/z (%) = 277 (M^+,100); 262(15); 230(12); 74(22); 47(21).

$C_{10}H_7N_5OS_2$ (277).
Calculated (%):
C 43.32; H 2,52; N 25,27; S 23,10.
Found (%):
C 42,91; H 2,35; N 25,34; S 23,33.

Synthesis of 6-cyano-1*H*-7-mercapto-2-methylthio-5-oxo-1,2,4-triazolo[1,5-a]pyridines 5

A solution of 0.23 g Na in 20 mL EtOH (0.5 mol/L was added to the mixture of N´-[*bis*(methylthio)-methylene]cyanoacetohydrazide **1** (2.03 g; 0.01 mol) and the corresponding dithietane (0.005 mol). The reaction mixture was refluxed until TLC showed the absence of starting materials. After neutralizng with 50 % hydrocloric acid, a solid was isolated and identified as triazolo[1,5-a]pyridines **5.** The filtered solid was washed with water and recrystallized from EtOH-DMF.

6-cyano-1H-7-mercapto-2-methylthio-5-oxo-1,2,4-triazolo[1,5-a]pyridine-8-ethylcarboxylate 5a

Beige solid; yield 1.92 g (65 %), m.p. 210 ºC (decomposition). Reaction time: 5 h .

IR(KBr): $\nu_{max.}$(cm^{-1}) = NH 3 350; SH 2 550; CN 2 220; CO 1 700; CO 1 680; C=N 1 620.

^{1}H-NMR (DMSO-d_6): δ(ppm) =2.6(s,3-SCH_3); 3.1(s,3-SH); 3.8(s,3-OCH_3); 8.8(s,1-NH).

^{13}C-RMN (DMSO-d_6): δ(ppm) = 13.7(SCH_3); 51.8(OCH_3); 83.2(C-CN) 92.4(C-CO); 115.6(CN); 144.5(C-NH); 151(C- SCH_3); 154.2(CO); 162.3(CO); 165(C-SH).

MS-EI (70 eV): m/z (%) = 296(M^+, 100); 249(13); 74(28); 47(20).

$C_{10}H_8N_4O_3S_2$(296).
Calculated (%):
C 40,54; H 2,70; N 18,91; S 21,62.
Found (%):
C 40,08; H 3,19; N 18,42; S 22,00.

6-cyano-1*H*-7-mercapto-2-methylthio-5-oxo-1,2,4-triazolo[1,5-a]pyridine-8-ethylcarboxylate 5b

Beige solid; yield 1,86 g (60 %), m.p. 250 ºC (decomposition). Reaction time: 5 h .

IR(KBr): $\nu_{max.}$(cm^{-1}) = NH 3 350; SH 2 250; CN 2 220; CO 1 700; CO 1 680; C=N 1620.

^{1}H-NMR (DMSO-d_6): δ(ppm) = 1.5 (t,3-CH_3); 2.6(s,3-SCH_3); 3.1(s,1-SH); 3.9(q,2-OCH_2); 8.1 (s,1-NH).

^{13}C-RMN (DMSO-d_6): δ(ppm) = 13.4(SCH_3); 13.4(CH_3); 64.8(OCH_2); 82.7(C-CN); 92.3(C-CO); 115.4(CN); 145(C-NH); 152.2(C- SCH_3); 153.2 (CO); 162.3(CO); 166.2(C-SH).

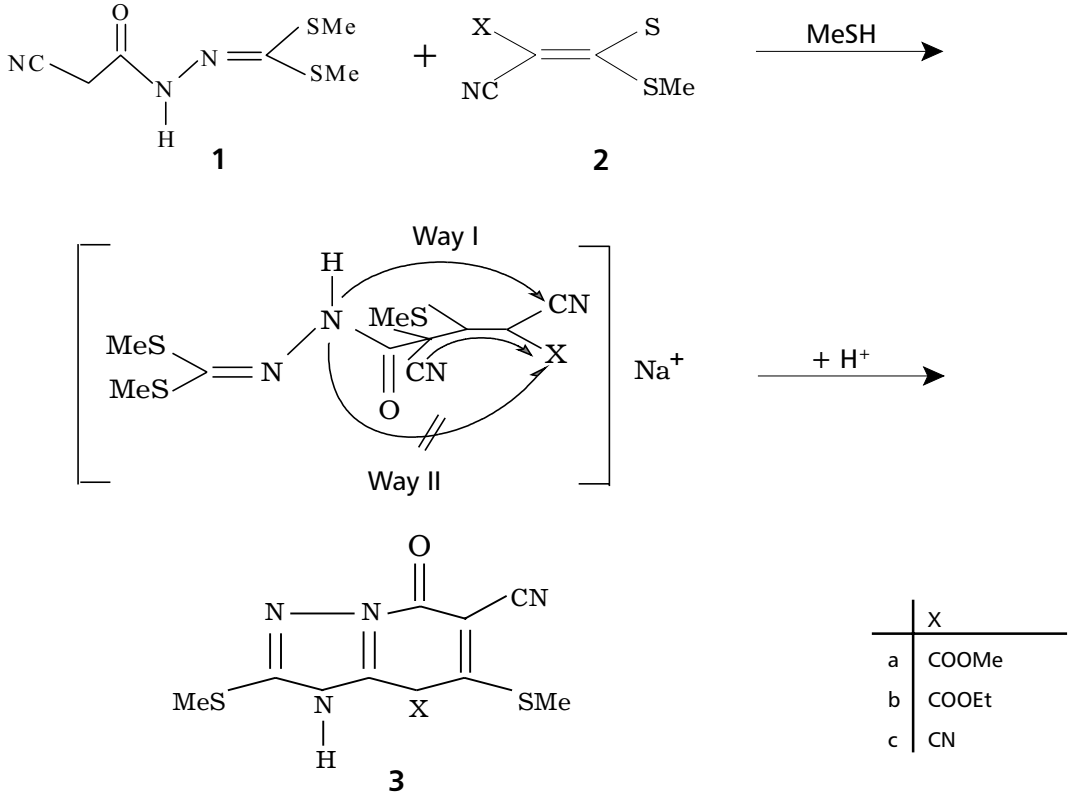
MS-EI (70 eV): m/z (%) = 310(M^+, 100); 263(12); 74(31); 47(25).

$C_{11}H_{10}N_4O_3S_2$(310).
Calculated (%):
C 42,58; H 3,22; N 18,06; S 20,64.
Found (%):
C 42,85; H 3,20; N 18,32; S 20,21.

RESULTS AND DISCUSSION

Reactions of *N´*-[*bis*(methylthio)-methylene]cyanoacetohydrazide 1 with keten-S,S-acetals 2

In agreement of general reaction mechanism established by Gompper[21] a way is proposed for this process:



Scheme 1

By means of the initial attack of the corresponding carbanion of **1,** the not isolable open chain intermediate I is formed by substitution of a methylthio group. Intramolecular cyclizations then leads to the compound **3.**

This reaction was carried out at room temperature using K_2CO_3/ DMF or NaEtO/EtOH as basic solutions. Under these conditions, good results were not obtained. However, when the mixture was heated at reflux temperature for a short time in alcoholic solution of NaOEt, the reaction proceeded easily with good yields.

The structure of compounds **3** was confirmed by NMR, IR and mass spectra. In the ^{1}H-NMR spectra two CH3S signals and the corresponding NH signal were found. Also the ^{13}C-NMR spectra are in good agreement with the proposed structures showing very cleary the six signals corresponding to the quaternary C atoms. The mass spectra showed very intense molecular ions in correspondence with the great stability of the heterocyclic system.

Reactions of *N´*-[*bis*(methylthio)-methylene]cyanoacetohydrazide 1 with dithietane *push pull* 4

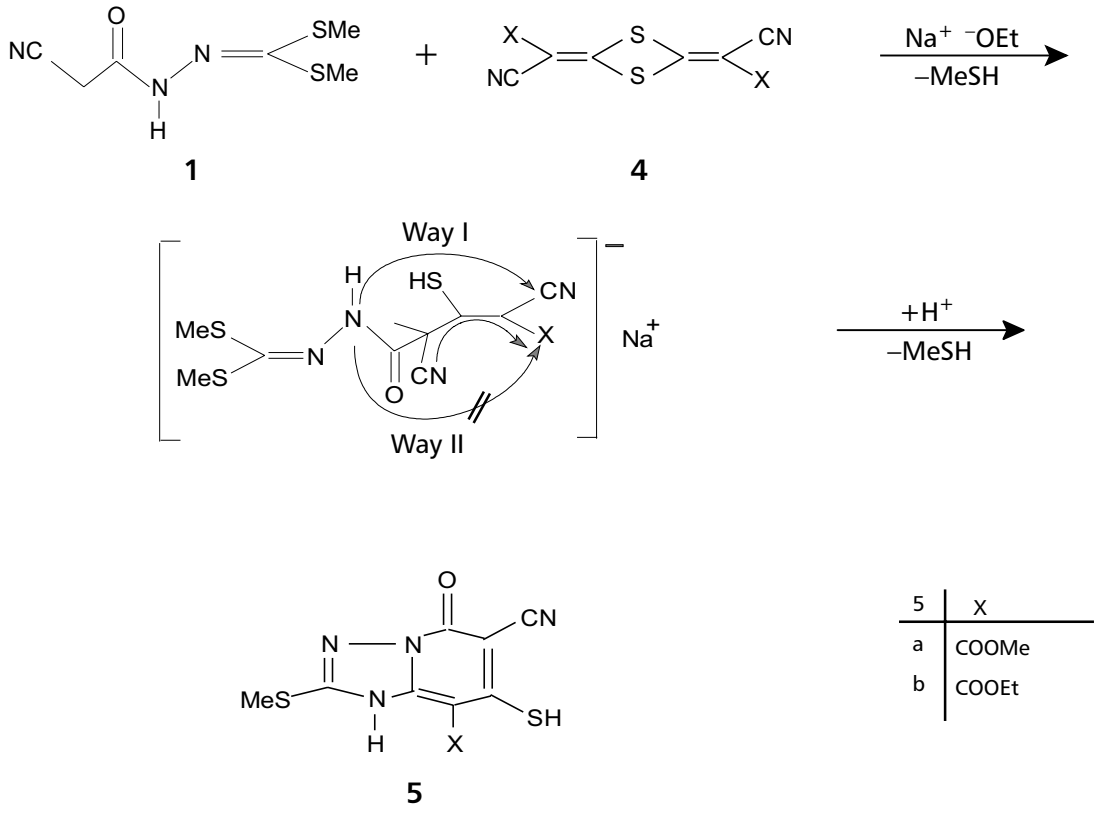
In accordance with the experiences described above for the keten-S,S-acetals, the reaction of **1** with **4** was carried out under the same conditions (sodium ethoxide-ethanol, reflux temperature). In all cases, triazolo[1,5-a]pyridines **5** were obtained with moderate yields.

The reaction could be illustrated by means of scheme 2.

Nevertheles, it must be mentioned that in these cases, as in the method of synthesis for pirazolo[1,5-a]pyrimidenes reported elsewhere,[22] the use of ketene-S,S-acetals as *push pull* system afforded better results than the corresponding dithiethanes.

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Scheme 2

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