New method for synthesis of pyrazolo[1,5-a]pyrimidines from cyanoacetohydrazide and *push pull systems*

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Palabras clave: pirazolo(1,5-a)pirimidinas, cianoacetohidrazida, sistemas *push pull*, reacción de substitución-eliminación.
Key words: pirazolo(1,5-a)pyrimidines, cyanoacetahydrazide, *push pull* systems, substitution-elimination reaction.

RESUMEN. En los últimos años ha sido presentada mucha evidencia experimental sobre la considerable actividad biológica que poseen las pirazolo[1,5-a]pirimidinas haciendo posible su amplia utilización en la industria farmacéutica. Esto ha motivado que la síntesis de estos heterociclos condensados se haya llevado a cabo con creciente interés. El propósito de este trabajo fue desarrollar un nuevo método de síntesis de estos compuestos con buen rendimiento y pureza, más sencillo que los reportados para obtener compuestos similares. Para ello, se tuvo en cuenta la presencia de los centros reactivos de los alquenos y ditietanos *push pul*l que posibilitara la ciclización intramolecular con posterioridad al ataque nucleofílico inicial de la cianoacetohidrazida. Se estudió el comportamiento de las reacciones tanto en medio alcohólico como en dimetilformamida. En todos los casos, se obtuvieron los mejores resultados utilizando el disolvente dipolar aprótico que permite la estabilización de los estados de transición polares formados durante el transcurso de la reacción. Se demostró la menor reactividad de los ditietanos *push pull* comparado con los ceténS,S-acetales. El esquema de reacción presentado parte del mecanismo general de reacción propuesto por Rappaport para la reacción entre nucléofilos etilenos *push pull. La* estructura de los intermediarios más estables fue establecida a partir de los cálculos realizados con el programa MOPAC Ver. 6. Los productos sintetizados se caracterizaron adecuadamente por medio del análisis elemental cuantitativo y varias técnicas espectroscópicas como IR, RMN, incluyendo el método COLOC, y la Espectrometría de Masas.

ABSTRACT. Experimental evidence on the powerful biological activity of pirazolo[1,5-a]pyrimidines] has been supported by several reports in the last years, which has made possible their wide utilization in the pharmaceutical industry. For this reason, the synthesis of these condensed heterocycles has been carried out with increasing interest. The purpose of the work was to develop a new simpler synthesis method with good yields and purity than those reported for obtaining similar structures. Therefore the presence of reactive centres in alquene and dithiethane *push pull* systems was taken into account making possible the intramolecular cyclization subsequently to the initial nucleophilic attack of the cyanoacetahydrazide. The reaction behavior was studied in aloholic medium as dimethylformamide. In all cases, best results were achieved by using the aprotic dipolar solvent since it allows the stabilization of the polar transition states formed through the reaction course. It was demonstrated that the dithiethanes are less reactive than the keten-S,S-acetals. A reaction scheme is showed which is agreement with the general reaction mechanism proposed by Rappaport for the interaction between nucleophiles and *push pull* ethylenes. The structures of the most stable intermediate was established on the basis of the calculations performed by means of the MOPAC 6.0 program. The compounds synthesized were characterized adequately by means of their elemental quantitative analysis and several spectroscopic techniques IR, NMR, including the COLOC method, and the Mass Spectrometry.

INTRODUCTION

The synthesis of pyrazolo[1,5-a]pyrimidines and derivatives has attracted attention in the last year due to their interesting pharmacological properties.[1-5] Starting from cyanoacetohydrazide and cinnamonitrile derivatives, the goal compounds could be obtained in just one step, but with low yield due to the formation of several by-products.[6] When the reactions of polarized ethylenes with other nucleosides are employed, two steps are generally needed and the reaction mixture has to be heated for a few hours.[7,9]

In this paper the authors report the direct synthesis of the pyrazolo[1,5-a]pyrimidines from cyanoacetohydrazide and *push pull* systems. For this purpose, it was taken into account that the presence of appropriate reactive center in the ketene-S,S-acetals and 1,3-dithiethanes used as *push pull* systems, makes it possible the necessary intramolecular cyclizations subsequently to the initial nucleophilic attack of the cyanoacetohydrazide. The developed method is quite simple and allows the preparation of new heterocyclic compounds of potential biological activity with good yields and purity.

EXPERIMENTAL PART

Melting points were determined on a Boetius hot-stage microscope and are incorrect. The ^{1}H-NMR and ^{13}C-NMR spectra were measured us-

ing a Bruker AC 250 F spectrometer. All NMR spectra were recorded as dimethylsulfoxide solutions, chemical shifts being given as δ values with respect to tetramethylsilane as the internal standard. The IR spectra were measured with a Philips PU-9426 FTIR spectrometer as potassium bromide pellets. Mass spectra (70 eV) were obtained with a JEOL DX 300 apparatus with direct inlet. Microanalysis was carried out by means of the microanalytical service of the Rostock University. The reactions were monitored by TLC performed on silica-gel plates (Merck 60-F) and using chloroform:methanol, (3:1) as eluent. The calculations were executed on an IBM PC 80486 DX/ 33MHZ by means of the program MOPAC Ver. 6.0 using PM3 Hamiltoniam. Mycroanalysis were performed on an EAGER-200 summary.

Synthesis of 5-amino-6H-2-methylthio-7-oxo-pyrazolo[1,5-a]pyrimidines 3. General procedure

0,01mol (0,99 g) cyanoacetohydrazide **1** y 0,01 mol keten-S,S-acetal **2** were dissolved in 5 mL dimethylformamide and stirred at room temperature until the starting materials had reacted completely. (TCL; $CHCl_3$:MeOH 5:1). Then the mixture was poured into 50 mL of ice water. The formed solid was filtered, washed with water and recrystallized form EtOH-DMF.

5-amino-6H-2-methylthio-7-oxo-pyrazolo[1,5-a]pyrimidine-3-methylcarboxylate 3a

White solid; yield 2,10 g (83 %); m.p. 187 - l90 °C . Reaction time: 3 h .

IR(KBr): $\nu_{max.}/cm^{-1}$ = NH_2 3 450, 3 350; CO 1 740; CO 1 690; C=N 1 620; C=C 1 540.

^{1}H-RMN (DMSO-d_6): δ/ppm = 2,41(s,3-SCH_3); 3,73(s,3-OCH_3); 4,57(s,2-CH_2); 7,61(s,2-NH_2).

^{13}C-RMN (DMSO-d_6): δ/ppm = 12,13(SCH_3); 27,09(CH_2); 50,78 (OCH_3); 91,68(C-CO);

114,56(C-NH_2); 153,58(N-C-N); 153,86(C-SCH_3); 162,65 (CO) ;165,06 (CO).

MS-EI (70 eV): m/z (%) = 254(M^+, 95); 187(40); 155(100); 84(59); 68(33).

$C_9H_{10}N_4O_3S$ (254 g · mol^{-1}).

Analysis

Calculated:

C 42,51 H 3,93 N 22,04 S 12,59.

Found:

C 42,08 H 3,97 N 22,43 S 12,91.

5-amino-6H-2-methylthio-7-oxo-pyrazolo[1,5-a]pyrimidine-3-ethylcarboxilate 3b

White solid; yield 2,27 g (85 %); m.p. 189-l90 °C . Reaction time: 3 h .

IR(KBr): $\nu_{max.}/cm^{-1}$ = NH_2 3 450, 3 350; CO 1 730; CO l 680; C=N 1 620; C=C 1 540.

^{1}H-RMN (DMSO-d_6): δ/ppm = 1,38(t,3-CH_3); 2,49(s,1-SCH_3); 4,35 (q,2-OCH_2); 4,55(s,2-CH_2); 7,9(s,2-NH_2).

^{13}C-RMN (DMSO-d_6): δ/ppm = 12,91(SCH_3); 13,37(CH_3); 26,61(CH_2); 60,43(OCH_2); 91,00(C-CO); 113,49(C-NH_2); 153,34(N-C-N), 153,80(C-SCH_3); 162,98(CO); 166,12(CO).

MS-EI (70 eV): m/z (%)= 268 (M^+,90); 201(50); 155(100); 84(65); 68(20).

$C_{10}H_{12}N_4O_3S$ (268 g · mol^{-1}).

Analysis

Calculated:

C 44,77 H 4,47 N 20,89 S 11,94.

Found:

C 44,29 H 3,98 N 21,02 S 11,53.

5-amino-6H-2-methylthio-7-oxo-piyrazolo[1,5-a]pyrimidina-3-carbonitrile 3c

Beige solid; yield 21,79 g (81%); m.p. 193-l95 °C . Reaction time: 8 h .

IR(KBr): $\nu_{max.}/cm^{-1}$ = NH_2 3 450, 3 325; CN 2 220; CO 1 690; C=N 1 620; C=C 1 520

^{1}H-RMN (DMSO-d_6): δ/ppm = 2,90(s,3-SCH_3); 4,56(s,2-CH_2); 8,1(a,2-NH_2).

^{13}C-RMN (DMSO-d_6): δ/ppm = 12,17(SCH_3); 27,20(CH_2); 82,57(C-CN); 114,69(C-NH_2); 115,24(CN); 153,57(N-C-N); 153,97(C-SCH_3); 165,50(CO).

MS-EI (70eV): m/z (%) = 221 (M^+,93); 166(10); 154(43); 84(70); 68(30).

$C_8H_7N_5OS$ (221 g · mol^{-1}).

Analysis

Calculated:

C 43,43 H 3,16 N 31,67 S 14,47.

Found:

C 43,10 H 3,25 N 31,45 S 14,25.

5-amino-6H-2-methylthio-7-oxo-pyrazolo[1,5-a]pyrimidine-3-N(fur-2-il-methyl)carbamide 3d

Beige solid; yield 2,00 g (63 %); m.p. 163-l65 °C . Reaction time: 12 h .

IR(KBr): $\nu_{max.}/cm^{-1}$ = NH_2, NH 3 450, 3 350, 3 200 ; CO 1 700; CO 1 680; C=N 1 630; C=C 1 520 *me.*

^{1}H-RMN (DMSO-d_6): δ/ppm = 2,49(s,3-SCH_3); 4,5(s,2-CH_2); 4,8(d,2-CH_2-NH); 6,4(m,$_2$-H_3,H_4fur); 7,5 (m,1-H_5fur); 7,6(s,2-NH_2); 8,9(a,1-NH-CH_2).

^{13}C-RMN (DMSO-d_6): δ/ppm = 13,19(SCH_3); 27,40(CH_2); 36,02(CH_2-NH); 85,83(C-CO); 107,89(C3 fur); 110,38(C4 fur); 142,16(C5 fur); 148,16(C2 fur); 114,92(C-NH_2); 152,28(N-C-N); 153,97(C-SCH_3); 165,02(CO); 168,02(CO-NH).

MS-EI (70 eV): m/z (%) = 319(M^+, 85); 252(35); 156(58); 96(100); 81(48); 84(38); 68(25).

$C_{13}H_{13}N_5O_3S$ (319 g · mol^{-1}).

Analysis

Calculated:

C 48,90 H 4,07 N 21,94 S 10,03.

Found:

C 48,45 H 3,71 N 22,08 S 9,62.

Synthesis de 5-amino-6H-2-mercapto-7-oxo-pyrazolo[1,5-a]pyrimidines 6. General procedure

0,01 mol (0,99 g) de cyanoacetohydrazide **1** y 0,005 mol dithietane **5** were dissolved in 5 mL dimethylformamide and stirred at room temperature until the starting materials had reacted completely (TCL; $CHCl_3$:MeOH 5:1). After the mixture was allowed to stand for a while, an orange precipitate was separate by decantation and discared. The liquid layer was then poured into 50 mL of ice water. The formed solid was filtered, washed with water and recrystallized frorm EtOH-DMF.

5-amino-6H-2-mercapto-7-oxo-pyrazolo[1,5-a]pyrimidine-3-methylcarboxylate 6a

Yellow solid; yield 1,60 g (67 %); m.p. l90 °C . Reaction time: 6 h .

IR(KBr): $\nu_{max.}/cm^{-1}$ = NH_2 3 450, 3 350; CO 1 720; CO 1 680; C=N 1 610; C=C 1 520.

^{1}H-RMN (DMSO-d_6): δ/ppm = 1,30(s,1-SH); 3,93(s,3-OCH_3); 4,51(s,2-CH_2); 8,10(a,2-NH_2).

^{13}C-RMN (DMSO-d_6): δ/ppm = 28,16(CH_2); 51,42(OCH_3); 91,28(C-CO); 115,31(C-NH_2); 144,83(C-SH); 152,22(N-C-N); 162,18(CO); 166,29 (CO).

MS-EI (70 eV): m/z (%)= 240 (M^+, 88); 207(38); 141(100); 84(40); 68(38).

$C_8H_8N_4O_3S$ (240 g · mol^{-1}).

Analysis

Calculated:

C 40,00 H 3,33 N 23,33 S 13,33.

Found:

C 39,61 H 3,07 N 23,01 S 13,73.

5-amino-6H-2-mercapto-7-oxo-pyrazolo[1,5-a]pyrimidina-3-ethylcarboxylate 6b

Yellow solid; yield 1,60 g (63 %); m.p. 193-195 °C . Reaction time: 6 h .

IR(KBr): $\nu_{max.}/cm^{-1}$ = NH_2 3 400, 3 350; CO 1 710; CO l 680; C=N 1 620; C=C 1 540.

^{1}H-RMN (DMSO-d_6): δ/ppm = 1,20(t,3-CH_3); 1,30(s,1-SH); 4,29(q,2-OCH_2); 4,50(s,2-CH_2); 8,10(a,2-NH_2).

^{13}C-RMN (DMSO-d_6): δ/ppm = 13,20(CH_3); 28,40(CH_2); 63,20(OCH_2); 91,30(C-CO); 115,70(C-NH_2); 145,23 (C-SH); 152,90(N-C-N); 161,30(CO); 165,90(CO).

MS-EI (70 eV): m/z (%) = 254(M^+, 90); 221(40); 141(65); 84(50); 68(34).

$C_9H_{10}N_4O_3S$ (254 g · mol^{-1}).

Analysis

Calculated:

C 42,51 H 3,93 N 22,04 S 12,59.

Found:

C 42,28 H 3,97 N 22,43 S 12,97.

5-amino-6H-2-mercapto-7-oxo-pyrazolo[1,5-a]pyrimidine-3-N(fur-2-il-*methyl)carbamide* 3c

Yellow solid; yield**:** 1,83 g (60 %); m.p. 198-199 °C. Reaction time: 16 h .

IR(KBr): $\nu_{max.}$/cm^{-1} **=** NH_2, NH 3 400, 3 300, 3 250; CO 1 700; CO 1 670; C=N 1 620; C=C 1 510.

^{1}H-RMN (DMSO-d_6): δ/ppm = 1,30(s,1-SH); 4,50(s,2-CH_2); 4,90(d,2-CH-NH); 6,40(m,2-H3,H4fur); 7,40 (m,1-H5fur); 7,90(s,2-NH_2); 8,90(a,1-NH-CH_2).

^{13}C-RMN (DMSO-d_6): δ/ppm = 27,95(CH_2); 37,21(CH2-NH); 86,64(C-CO); 108,24; (C3 fur); 111,27(C4 fur); 143,26(C5 fur); 149,35(C2 fur); 115,12(C-NH_2); 147,10; (C-SH); 152,28(N-C-N); 163,45(CO); 168,49 (CO-NH).

MS-EI (70 eV): m/z (%) = 305(M^+, 75); 124(60); 96(100); 81(48); 84(38); 68(25).

$C_{12}H_{11}N_5O_3S$ (305 g . mol^{-1}).

Analysis

Calculated:

C 47,21 H 3,60 N 22,95 S 10,49.

Found:

C 47,03 H 3,23 N 22,61 S 10,29.

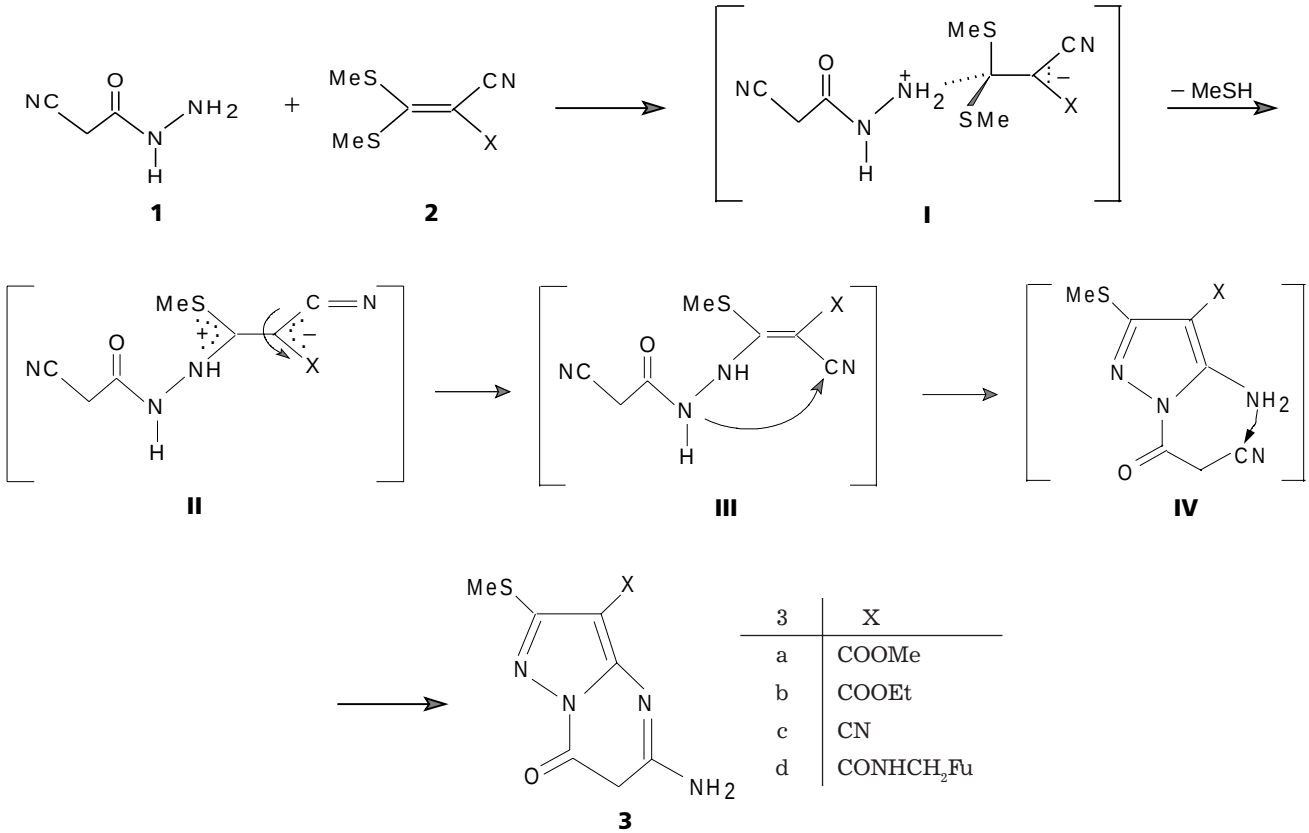
RESULTS AND DISCUSSION

Reaction of cyanoacetohydrazide 1 and ketene-S,S-acetals 2

In agreement with the general reaction mechanism established by Rappaport[10] for the interaction between nucleophiles and *push pull* ethylenes, the following route is proposed for the reaction of cyanoacetohydrazide with keten-S,S-acetals (Scheme 1).

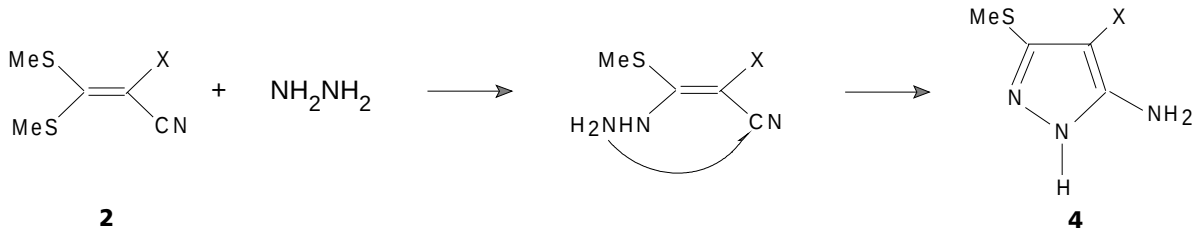
As a consequence of nucleophilic attack of the $NHNH_2$ group on the electophilic C atom of the keten-S,S-acetal, the not isolable intermediate I is formed. The latter is stabilized by loss of a mercaptane molecule producing the alkene E (intermediate II) which is more stable than the Z isomer.[11] This alkene has a very low rotational barrier as a result of the high polarization of the double bond (*push pull* efect).[12] Besides it has to be taken in account that the replacement of a SMe group by $NHNHCOCH_2CN$ strengthens the above described effect, due to the larger electron donating capacity of the nitrogenous groups. Consequently the intramolecular cyclization showed in the conformer III is carried out due to the largest electrophilic character of the cyano group with respect to the ester and amide groups. In this way the intermediate IV is obtained, which contains substituents able to interacting amoug themselves to get finally to the condensated system **3.**

According to the earlier reports of other authors about the reactions of the cyanoacetohydrazide **1** with several nucleophilic agents, it was decided to begin our experiences in alcohol solution. In this medium yields were always less than 50 % although under reflux for 8-16 h . Besides the main product **3**, the compound **4** is obtained with approximately 40 % yield. Its formation could be explained trough the reaction of *push pull* ethylene and the hydrazine formed by ethanolysis of



*Reaction of cyanoacetohydrazide **1** and ketene-S,S-acetals **2**.*

Scheme 1



Scheme 2.

the cyanoacehydrazide, as following (Scheme 2).

When the reaction was carried out in dimethylformamide, even at room temperature and by much shorter times, the average yields of the main compound **3** were increases considerably.

By using dimethylformamide as solvent, the ethanolysis of cyanoacetohydrazide was firstly eliminated. On the other hand, the polar transition states throughout the course of reaction were stabilized adequately.

IR-Spectra of compounds **3a**, **3b** and **3d** showed the disappearance of the corresponding CN-bands of cyanoacetohydrazide. Besides in the ^{1}NRM Spectra the absence of a CH_3S signal could be observed as evidence that initial substitution of this group in the *push pull* system had taken place.

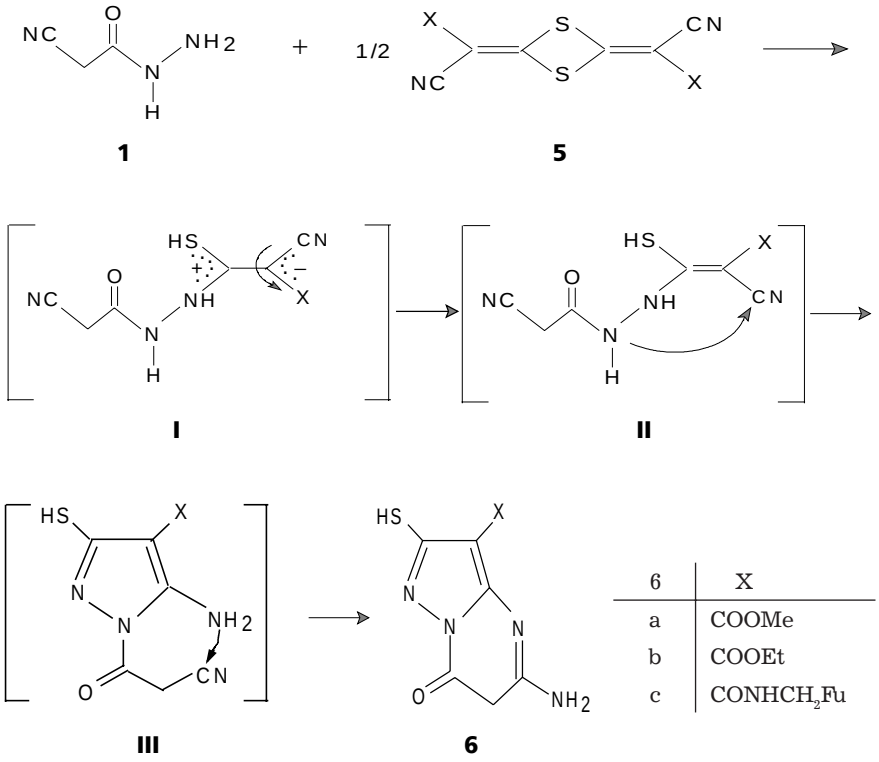
Also the ^{13}C-NMR Spectra are good according to the proposed structures. The quaternary C atoms were identified and assigned correctly by using DEPT and COLOC techniques.

Reaction of cyanoacetohydrazide 1 and push pull 1,3-dithietanes 5

In the same manner as in the case of keten-S,S-acetals, the use ethanol as solvent gave place to low yields of desired products **6** became of ethanolysis and formation of several by-products. Nevertheless, when the reaction of **1** with 1,3-dithietanes **5** was carried out in dimethylformamide the yields of **6** were increased to moderate values. In all cases a by product of lower RF value could be obtained in 8-10 % yields. The latter was not possible to be characterized totally because of its lack of stability.

According to the experiences of Peseke (K. Peseke, personal comunication) about the reactions of *push pull* dithiethanes the reaction could be schematized (Scheme 3).

It was observed that the better results are obtained by using the ketene-S,S-acetals as electrophilic agents (Table 1).



6	X
a	COOMe
b	COOEt
c	$CONHCH_2Fu$

*Reaction of cyanoacetohydrazide **1** and push pull 1,3-dithietanes **5**.*

Scheme 3.

Table 1. Yields and reaction times for the synthesis of the substituted pyrazolo[1,5-a]pyrimidines **3** and **6** using ethanol and dimethylformamides as solvent.

Compound	W	X	Yield		Time	
			(EtOH)	(DMF)	(EtOH)	(DMF)
			(%)		(h)	
3a	SMe	COOMe	47	83	8	3
3b	SMe	COOEt	46	85	8	3
3c	SMe	CN	43	81	10	8
3d	SMe	$CONHCH_2Fu$	39	63	16	12
6a	SH	COOMe	45	67	10	6
6b	SH	COOEt	43	63	10	6
6c	SH	$CONHCH_2Fu$	25	60	16	16

Fu C_4H_3O.

CONCLUSIONS

The reactions of cyanoacetohydrazide **1** with alkenes dithiethanes **5** p*ush pull using aprotic dipolar solvent as dimethylformamide allows to obtain* pyrazolo[1,5-a]pyrimidines **3** and **6** which have not been reported with good yields. This method is more simple and faster than other descripted procedures for analogous compounds.

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RESULTADOS CIENTIFICOS DESTACADOS MINISTERIO DE EDUCACION SUPERIOR DE CUBA

CARACTERISTICAS FISICO-QUIMICAS Y DISPONIBILIDAD BIOLOGICA DE FUENTES MINERALES CUBANAS PARA LA ALIMENTACION ANIMAL

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San José de las Lajas, La Habana.

Se estudiaron las características físico-químicas y la biodisponibilidad de 15 fuentes minerales cubanas con posibilidades de uso en la alimentación animal. Por primera vez, se evaluaron química y biológicamente la roca fosfórica cubana y sus fosfatos derivados, sulfatos de microelementos, zeolitas, bentonitas y otros residuos como suplemento mineral, combinando métodos in vivo e in vitro.

Se emplearon herramientas novedosas como: el fluido ruminal y el contenido intestinal del cerdo para determinar la solubilidad de los microelementos a nivel del tracto gastrointestinal; técnicas isotópicas para la producción endógena del calcio y el fósforo; la estimación directa de la biodisponibilidad de macro y microelementos como componentes de medios de cultivo para estudios de microbiología, como terapéuticos y profilácticos en ovinos y equinos, así como por su valor potencial en la activación de los procesos de fermentación en estados líquido y sólido.

Los resultados arrojaron que el calcio y el fósforo de la roca fosfórica cubana responden a la estructura de la hidroxiapatita en la que el flúor se encuentra principalmente en forma de fluoruro de calcio. Se demostró la esencialidad del flúor y se identificaron el hueso y la orina como tejidos idóneos para el diagnóstico y prevención de la fluorosis en especies domésticas al establecer la ruta metabólica del microelemento. La caliza fosfatada del yacimiento "Loma de Candela", posee características similares a la "limestone" de importación por su poder estabilizador para vacas lecheras y por la calidad de la cáscara del huevo. Se demostró que los minerales contenidos en los sulfatos de hierro, cobre, cobalto y manganeso se encontraban disponibles para rumiantes y monogástricos. Se estableció que las zeolitas naturales procedentes del yacimiento "Tasajera", no poseían capacidad estabilizante, pero regulaban el medio interno debido a su poder de intercambio catiónico y su elevado contenido de ceniza ácido insoluble resultó un marcador indirecto para medir su nivel de inclusión en piensos comerciales. La bentonita sódica protegió a la proteína dietética del ataque de microorganismos del rumen. Los minerales contenidos en la excreta bovina se encuentran disponibles para la fermentación de la caña de azúcar en estado sólido.

Este material constituye un valioso documento que de forma integral, pone a disposición de científicos, productores y estudiantes, un grupo de metodologías novedosas científicamente avaladas que permiten conocer el valor potencial de fuentes minerales, lo que propiciará la toma de decisiones al momento de su inclusión en las raciones para rumiantes y monogástricos.

Estos resultados contaron con la colaboración de instituciones de los Ministerios de la Agricultura, de la Industria Básica y del Interior.