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SECTION 9. Chemistry and chemical technology.

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SYNTHESIS AND TRANSFORMATIONS OF SOME TETRAHYDROPYRIMIDINE-5-CARBOXYLATES

Abstract: 2-(methacryloyloxy) ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate, which are cyclic ureas derivatives were synthesized from urea, 2-(methacryloyloxy) ethyl acetoacetate substituted and benzaldehyde.

Key words: Benzaldehyde; single-crystal X-ray study; urea; 2-(methacryloyloxy) ethyl acetoacetate.

Language: English

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1. INTRODUCTION

The pyrimidinethiones display many pharmacological properties, as part of our interest in this kind of materials, we report here the synthesis and crystal structure determination of the title compound^[1]. Our synthesis is based in the Bidjinelli reaction, which consists on a three-component condensation of an aldehyde, a methylene active compound and an urea derivative in acidic media. This procedure is the most simple and useful for the preparation of 3,4-dihydropyrimidine-2(1H) ones^[2-4].

New cyclic ureas were obtained by continuing researches in the field of the synthesis of various classes of organic nitrogen compounds and the study of their transformations. So that first time 2-(methacryloyloxy)ethyl 6-methyl-2-oxo-4-

phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate were obtained for the first time by us based on the trifluoroacetic acid catalyst.

2. EXPERIMENTAL

Chemistry

Synthesis of 2-(methacryloyloxy) ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1)

Urea (1.20 gr, 0.02 mol) is dissolved in 3:1 ratio of acetylacetone (3 ml) and ethyl alcohol (1 ml) and 2-(methacryloyloxy)ethyl acetoacetate (3.82 ml, 0.02 mol) is added on it drop by drop. After being dissolved in magnetic stirrer for 5 minutes benzaldehyde (2.03 ml, 0.02 mol) is added. After determining that the reaction has been fully completed, the solvent is evaporated. Processing of the reaction mixture was carried out by washing the reaction mixture



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with ice water, the precipitate was filtered, washed with 500 ml of water, dried and recrystallized from ethanol (75 ml). The yield is 2.4 g, mp. 211 °C.

Eluent-ethanol:hexane (5:2). ¹H NMR (300 MHz, DMSO-d₆) 5 1.35 (s, 3H, CH₃), 6.8-7.1 (m, H, Ar), 7.4 (m, H, Ar), 9.35 (s, 1H, NH). ¹³C NMR (75 MHz, DMSO-d₆) 5 24, 29, 37, 51, 86, 117, 122, 129, 132, 141, 151, 205 (C=O).

Synthesis of allyl 1-(3-chloro-2-hidroksipropyl)-4-metil-6-phenyl-2-thio-1,2,3,6-tetrahydropyrimidine-5-carboxylate (2)

Allyl 6-methyl-4-phenyl-2-thio-1,2,3,4-tetrahydropyrimidine-5-carboxylate (0,908 gr, 0,0033 mol) is dissolved in 2:1 ratio of acetylacetone (10 ml) and ethyl alcohol (5 ml) and epichlorohydrin (0,26 ml, 0,0033 mol) is added on it drop by drop. After being dissolved in the stirrer for 25 minutes, 0.03 gr. aluminiumchloride catalyst is added on it and mixed by heating at 65-70°C. The progress of the reaction is controlled by Sulifol UV 254 plate. After determining the full completion of reaction, solution is evaporated and is cleansed in ethyl alcohol solution. The white crystalline having the melting temperature of 168°C is obtained.

Eluent-ethanol:hexane (5:2). ¹H NMR (300 MHz, DMSO-d₆) 2.30 (s, 3H, CH₃), 7.06-7.25 (m, H, Ar), 4.81 (H, OH), 9.84 (s, 1H, NH), 3.40, 3.65 (2H, CH₂). ¹³C NMR (75 MHz, DMSO-d₆) 15.5, 49.5, 56,3, 67.8, 71.2, 74.5, 106, 116.4, 127.1, 128.6, 133.5, 138, 158.8, 167.2, 178.4.

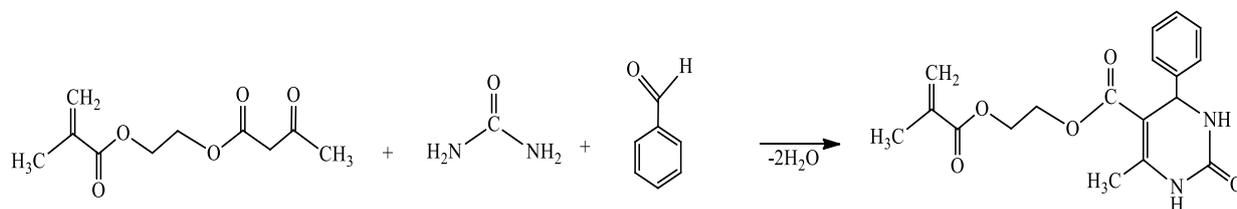
Synthesis of ethyl 1-(2-hidroksibutyl)-4-methyl-6-phenyl-2-thio-1,2,3,6-tetrahydropyrimidine-5-carboxylate (3)

Ethyl 6-methyl-2-thio-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (1.52 gr, 0.02 mol) is dissolved in 2:1 ratio of acetylacetone (12 ml) and ethyl alcohol (5 ml) and 1,2-epoxobutane (2.03 ml, 0.02mol) is added on it drop by drop. After being dissolved in the stirrer for 30 minutes, 0.02 gr. aluminiumchloride catalyst is added on it and mixed by heating at 60-65°C. The progress of the reaction is controlled by Sulifol UV 254 plate. After determining the full completion of reaction, solution is evaporated and is cleansed in ethyl alcohol solution. The white crystalline having the melting temperature of 192°C is obtained.

Eluent-ethanol:hexane (5:2). ¹H NMR (300 MHz, DMSO-d₆) 0.96 (s, 3H, CH₃), 4.59-7.25 (m, 6H, Ar), 4.81 (H, OH), 3.45 (1H, CH), 9.84 (s, 1H, NH), 3.40, 1.48 (2H, CH₂). ¹³C NMR (75 MHz, DMSO-d₆) 14.2, 28.6, 58.9, 61.7, 71.2, 71.6, 104.2, 127.1, 127.9, 128.6, 129.9, 138, 160.3, 167.2, 178.

3. RESULTS AND DISCUSSION

The synthesis of the new compounds is reported in Schemes 1, 2, 3. The reaction of substituted benzaldehyde with methylene active compounds such as 2-(methacryloyloxy)ethyl acetoacetate and urea in the presence of trifluoroacetic acid led to the desired cyclic urea.



Scheme 1

At the next stage we have provided the transformation of obtained compounds. So, by the reaction epichlorohydrin had synthesised

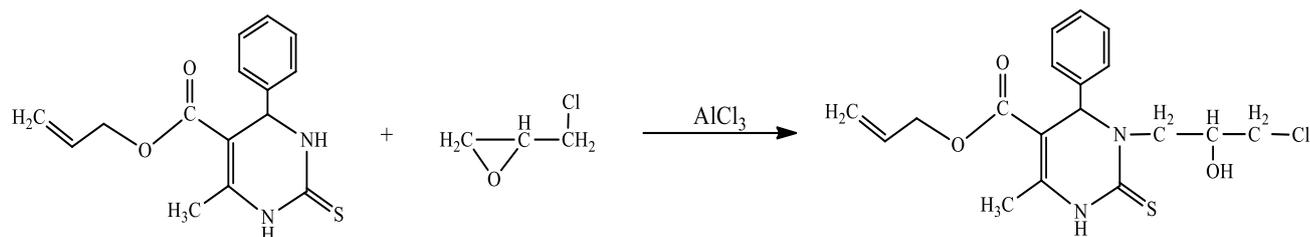
allyl 1-(3-chloro-2-hidroksipropyl)-4-metil-6-phenyl-2-thio-1,2,3,6-tetrahydropyrimidine-5-carboxylate.

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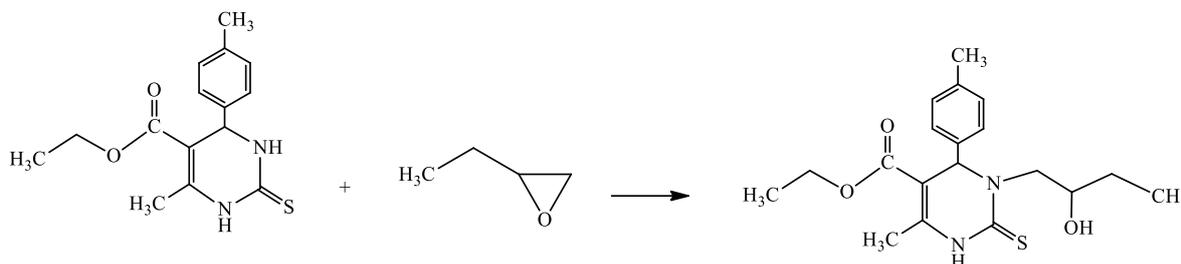
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Scheme 2

At the same time by the reaction 1,2-epoxobutane synthesised ethyl 1-(2-

hidroksibutyl)-4-methyl-6-phenyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxylate.



Scheme 3

The three-component condensation reactions come to an end within 2,5-3 hours at 60-75°C. The synthesized compounds were crystalline and their structure was confirmed by spectral and physico-chemical methods, among which IR, ¹H, ¹³C NMR and X-ray spectroscopy:

The crystal structure of synthesized 2-(methacryloyloxy)ethyl 6-methyl-2-oxo-4-

phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate has been determined with X-ray structure analysis method. The structure and crystalline form of new cyclical compound have been shown in the fig.1 and fig.2. Crystalline compound holds two crystallographical independent molecules.

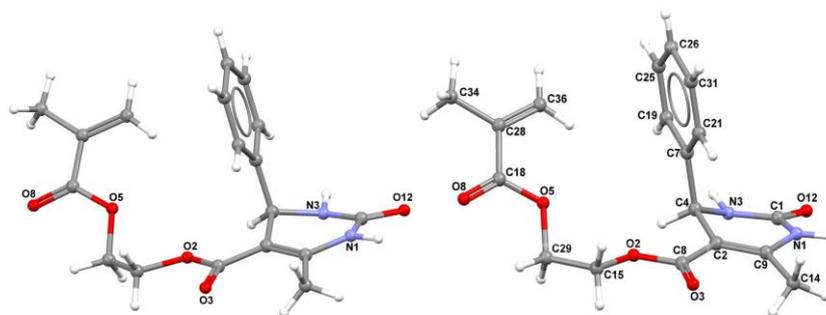


Figure 1 - The molecular structure of the new compound.

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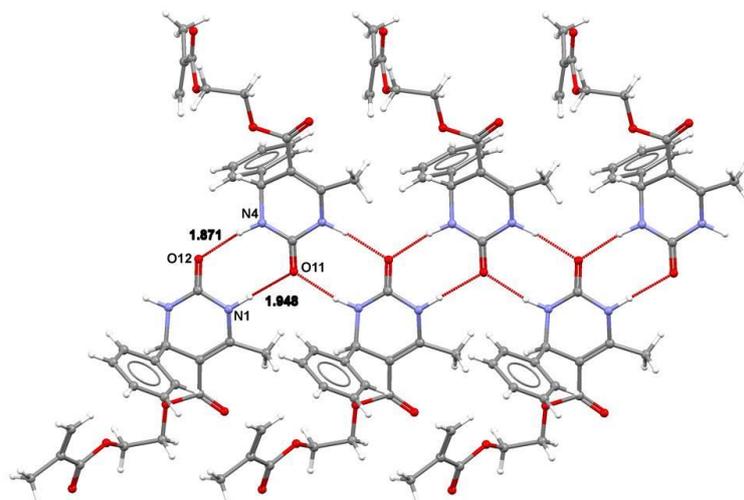


Figure 2 - Packing diagram of the title compound. N—H—O hydrogen bonds are shown as dashed lines. For clarity only one of the disordered components of the phenyl ring is shown.

In the compound, the C8, C9, C11 and C12 atoms of the phenyl ring are disordered over two sets of sites in a 0.60 (3):0.40 (3) ratio. The heterocycle ring is essentially planar and form a dihedral angle of with the phenyl ring. The crystal packing is stabilized by intermolecular N3—H3N···O1 hydrogen bonds (Table 1-3), which link the molecules into chains running

parallel to the b axis (Fig.2), with graph-set notation C(6) [5].

Data collection: *APEX2* [6]; cell refinement: *SAINT-Plus* [7]; data reduction: *SAINT-Plus*; program(s) used to solve structure: *SHELXTL* [8-9]; program(s) used to refine structure: *SHELXTL*; molecular graphics: *SHELXTL*; software used to prepare material for publication: *SHELXTL*.

Table 1

Crystal data and structure refinement for a_a.

Identification code	a_a	
Empirical formula	C ₁₈ H ₂₀ N ₂ O ₅	
Formula weight	344.36	
Temperature	373(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P 21/c	
Unit cell dimensions	a = 16.441(4) Å	a = 90°.
	b = 27.869(6) Å	b = 91.822(5)°.
	c = 7.1837(15) Å	g = 90°.
Volume	3289.8(12) Å ³	
Z	8	
Density (calculated)	1.391 Mg/m ³	
Absorption coefficient	0.102 mm ⁻¹	
F(000)	1456	
Crystal size	0.12 x 0.14 x 0.18 mm ³	
Theta range for data collection	1.916 to 26.998°.	
Index ranges	-20 <= h <= 20, -33 <= k <= 35, -9 <= l <= 9	
Reflections collected	21576	
Independent reflections	6215 [R(int) = 0.0544]	
Completeness to theta = 25.242°	92.7 %	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	6215 / 0 / 455	

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Goodness-of-fit on F^2	1.059
Final R indices [$I > 2\sigma(I)$]	$R^1 = 0.0862$, $wR^2 = 0.1890$
R indices (all data)	$R^1 = 0.1206$, $wR^2 = 0.2065$
Extinction coefficient	n/a
Largest diff. peak and hole	0.491 and -0.311 e. \AA^{-3}

Special details

Geometry. All e.s.d.'s (except the e.s.d. in the dihedral angle between two l.s. planes) are estimated using the full covariance matrix. The cell e.s.d.'s are taken into account individually in the estimation of e.s.d.'s in distances, angles and torsion angles; correlations between e.s.d.'s in cell parameters are only used when they are defined by crystal symmetry. An approximate (isotropic) treatment of cell e.s.d.'s is used for estimating e.s.d.'s involving l.s. planes.

Refinement. Refinement of F^2 against ALL reflections. The weighted R-factor wR and goodness of fit S are based on F^2 , conventional R-factors R are based on F , with F set to zero for negative F^2 . The threshold expression of $F^2 > \sigma(F^2)$ is used only for calculating R-factors (gt) etc. and is not relevant to the choice of reflections for refinement. R-factors based on F^2 are statistically about twice as large as those based on F , and R-factors based on ALL data will be even larger.

Table 2

Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for a_a. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	4377(2)	5866(1)	2262(3)	30(1)
N(1)	8372(2)	4725(1)	11017(4)	23(1)
C(1)	7970(2)	4850(1)	9393(5)	22(1)
O(2)	10562(2)	4190(1)	7716(3)	28(1)
N(2)	6542(2)	5330(1)	5902(4)	26(1)
C(2)	9498(2)	4417(1)	9509(5)	21(1)
O(3)	10796(2)	4197(1)	10777(4)	33(1)
N(3)	8334(2)	4734(1)	7851(4)	23(1)
C(3)	6949(2)	5210(1)	4338(5)	24(1)
O(4)	4063(2)	6419(1)	-835(4)	35(1)
N(4)	6582(2)	5331(1)	2741(4)	25(1)
C(4)	8985(2)	4381(1)	7761(5)	23(1)
O(5)	10892(2)	3631(1)	4709(4)	35(1)
C(5)	5744(2)	5472(1)	5859(5)	24(1)
O(6)	4073(2)	5793(1)	5246(4)	38(1)
C(6)	4563(2)	5770(1)	4061(5)	27(1)
O(7)	3104(2)	6969(1)	-1087(4)	46(1)
C(7)	8654(2)	3884(1)	7352(5)	26(1)
O(8)	11800(2)	3283(1)	2941(4)	50(1)
C(8)	10340(2)	4261(1)	9474(5)	24(1)
C(9)	9167(2)	4569(1)	11078(5)	22(1)
C(10)	6314(2)	6189(1)	2500(5)	30(1)
O(11)	7599(2)	4997(1)	4428(3)	25(1)
C(11)	5949(2)	5696(1)	2635(5)	25(1)
O(12)	7324(2)	5070(1)	9420(3)	27(1)
C(12)	3796(3)	6859(1)	-1188(5)	32(1)
C(13)	5338(2)	5431(1)	7662(5)	28(1)
C(14)	9574(2)	4601(1)	12942(5)	28(1)
C(15)	11354(2)	3984(2)	7530(6)	33(1)
C(16)	5415(2)	5634(1)	4262(5)	26(1)



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C(17)	3566(2)	6026(1)	1842(5)	29(1)
C(18)	11114(3)	3339(2)	3364(6)	36(1)
C(19)	8189(2)	3812(2)	5739(6)	34(1)
C(20)	6721(2)	6317(2)	912(6)	34(1)
C(21)	8791(3)	3504(2)	8498(6)	37(1)
C(22)	6300(3)	6520(1)	3921(6)	37(1)
C(23)	3490(2)	6073(2)	-210(6)	33(1)
C(24)	7103(2)	6755(2)	797(7)	40(1)
C(25)	7872(2)	3372(2)	5320(6)	41(1)
C(26)	8008(3)	2994(2)	6490(7)	43(1)
C(27)	4449(3)	7190(2)	-1704(6)	38(1)
C(28)	10421(3)	3088(2)	2481(6)	41(1)
C(29)	11501(2)	3939(2)	5515(6)	36(1)
C(30)	6686(3)	6950(2)	3801(7)	47(1)
C(31)	8474(3)	3062(2)	8070(7)	47(1)
C(32)	4224(3)	7688(2)	-1877(6)	47(1)
C(33)	7095(3)	7069(2)	2246(7)	47(1)
C(34)	10619(4)	2765(2)	962(8)	73(2)
C(35)	5203(3)	7024(2)	-1952(7)	57(1)
C(36)	9671(3)	3154(2)	3056(6)	43(1)

Table 3**Hydrogen bonds for a_a [Å and °].**

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1)...O(11)#1	0.95	1.95	2.897(4)	176.4
N(2)-H(2)...O(12)	0.95	1.95	2.890(4)	171.8
N(3)-H(3)...O(11)	0.95	1.90	2.802(4)	157.8
N(4)-H(4)...O(12)#2	0.95	1.87	2.809(4)	169.1
C(14)-H(14A)...O(3)	0.96	2.32	2.814(5)	111.0
N(1)-H(1)...O(11)#1	0.95	1.95	2.897(4)	176.4
N(2)-H(2)...O(12)	0.95	1.95	2.890(4)	171.8
N(3)-H(3)...O(11)	0.95	1.90	2.802(4)	157.8
N(4)-H(4)...O(12)#2	0.95	1.87	2.809(4)	169.1
C(14)-H(14A)...O(3)	0.96	2.32	2.814(5)	111.0

Symmetry transformations used to generate equivalent atoms:
 #1 x,y,z+1 #2 x,y,z-1 #3 -x+2,-y+1,-z+1

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