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Novel One-Pot Synthesis of New Derivatives of Dihydropyrimidinones, Unusual Multisubstituted Imidazoline-2-ones: X-ray Crystallography Structure

S. Balalaie[a,*], M. Soleiman-Beigi[a] and F. Rominger[b]

[a]*Department of Chemistry, K.N.Toosi University of Technology, P.O.Box 15875-4416 Tehran -Iran, Fax +98-21-2285 3650*

[b]*Organisch-Chemisches Institut der Universität Heidelberg, Im Neuenheimer Feld 270, D-69120, Heidelberg, Germany*

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Three-component condensation of phenylglyoxal, alkyl acetoacetates or acetylacetone and urea proceeds smoothly, catalyzed by $ZnCl_2$, to afford the corresponding new 3,4- dihydropyrimidinones. This reaction is also catalyzed by $AlCl_3$:$ZnCl_2$ (3:1) under microwave irradiation in solvent-free conditions. One-pot three-component condensation of dimethyl urea, acetylacetone or alkyl acetoacetate and phenylglyoxal catalyzed by $ZnCl_2$ or $AlCl_3$:$ZnCl_2$ (3:1) yields new multisubstituted imidazoline-2-ones derivatives. Structures of products were studied by X-ray crystallographic data. The reaction of phenylglyoxal, urea and β-ketoesters in the presence of hydrochloric acid produces only 5-phenylhydantoins.

Keywords: Dihydropyrimidinones, $ZnCl_2$, $AlCl_3$:$ZnCl_2$ (3:1), Imidazoline-2-one derivatives, X-Ray data, One-pot multicomponent reaction

INTRODUCTION

3,4-Dihydropyrimidin-2-(1H)-one derivatives have received considerable attention within recent years due to their attractive pharmacological profiles. They have emerged as calcium channel blockers [1], antihypertensive agents, alpha-antagonists and neuropeptide (NPY) antagonists [2]. Alkaloids containing the dihydropyrimidine core structure have been isolated from marine sources which demonstrate fascinating biological behavior [3]. Most notably among these are the betzelladine alkaloids, which found to be potent HIVgp-120-CD_4 inhibitors [4]. Thus, the synthesis of this heterocyclic compounds is of much current importance. The simplest and the most straightforward procedure, originally reported by Biginelli in 1893 involves three-component one-pot condensation of an aldehyde, β-ketoester and urea under strong acidic condensation [5]. However, a serious drawback of Biginelli's reaction is low yields in the case of substituted aromatic and aliphatic aldehydes. This had led to the development of multistep strategies that produce somewhat higher overall yields, but lack the simplicity of the one-pot synthesis.

In order to improve the efficiency of the Biginelli reaction, several catalysts including zirconium(IV) chloride [6], indium(III) bromide [7], ytterbium(III) resin [8], ionic liquid $BMImPF_6$ and $BMImBF_4$ [9], ceric ammonium nitrate (CAN) [10], $Mn(OAc)_3.2H_2O$ [11], lanthanide triflate [12], indium bromide [13], lanthanum chloride [14], trifluoroacetic acid (TFA) [15], $BF_3.OEt_2$-CuCl [16], boric acid [17], $CeCl_3.7H_2O$ [18], $Cu(OTf)_2$ [19], lithium bromide [20], silica/sulfuric acid [21], vanadium(III) chloride [22], $FeCl_3.6H_2O$ [23], trimethylsilyl iodide (TMSI) [24], montmorillonite-KSF [25],

*Corresponding author. E-mail: balalaie@kntu.ac.ir

zinc triflate [26], I_2 [27], NBS [28], bismuth triflate [29], NH_2SO_3H [30], $LiClO_4$ [31], lanthanide triflate [32], NH_4Cl [33], heteropolyacid $Ag_3PW_{12}O_{40}$ [34], and polyaniline-bismoclite complex [35] have been developed. Some of these catalysts are very captivating from a synthetic chemist point of view. However, despite the tremendous success of the proposed catalysts, they are still suffering from some drawbacks. For example, some of the catalysts are expensive, complex or unavailable.

In this article, we wish to report a new starting material, phenylglyoxal with an extra ketone as functional group, which provides potential site for further transformation. We also describe a novel and efficient one-pot three component reaction between phenylglyoxal, alkyl acetoacetates (or acetylacetone) and urea catalyzed by either $ZnCl_2$, refluxing in EtOH without any protic acid, or $ZnCl_2$:$AlCl_3$ (1:3) on the surface of silica gel, under microwave irradiation and solvent-free condition. This leads to the synthesis of 3,4–dihydropyrimidine-2-(1H)-one derivatives (Scheme 1). While the use of dimethyl urea, instead of urea, in the three components system leads to the preparation of new derivatives of multisubstituted imidazolin-2-ones (Scheme 2). It should be noted that, very recently, two papers on the use of $ZnCl_2$ as acidic catalyst under solvent-free condition [36] and under high pressure condition [37] *via* a three-component reaction between urea, aldehydes and alkyl acetoacetate for the synthesis of dihydropyrimidinones are reported in the literature.

EXPERIMENTAL

Melting points were determined by an *Electrothermal 9100* melting point apparatus. IR spectra (ν_{max}) were recorded on a Shimadzu IR-408 spectrophotometer using KBr disks. ^1H and ^{13}C NMR spectra in DMSO-d_6 were recorded on a JEOL 90 instrument at 90 MHz and 22.5 MHz, respectively, using TMS as an internal standard. Mass spectral data were obtained by using a GC-MS Shimadzu Qp-1100 (EI 70 eV) instrument. High resolution mass spectra (HRMS) were obtained with a ZAB high resolution mass spectrometer (Vacuum Generators).

The reflections for X-ray diffraction analysis were collected with a Bruker smart CCD difractometer (Mo-Kα, radiation, graphic mono-chromator). Intensities were corrected for Lorentz and polarization effects. Full matrix least squares refinement was carried out against F^2. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were treated using appropriate ring models. Structure solution and refinement were carried out with the SHELXTL (5.0) software package.

CCDC 257035 (**6a**), 257036 (**7**) contain the supplementary crystallographic data for these structures. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; e-mail: deposit@ccdc.cam.ac.uk)

General Procedure for the Synthesis of Dihydropyrimidinone (4a-c)

Method A. A mixture of 1,3-dicarbonyl compound (5 mmol), phenylglyoxal monohydrate (750 mg, 5 mmol) and urea (0.60 g, 10 mmol), $ZnCl_2$ (170 mg, 1.25 mmol) was heated at 80 ºC in ethanol under reflux condition for an appropriate time, as mentioned in Table1. Progress of the reaction was monitored by TLC. After completion of the reaction, the solvent was removed at reduced pressure and ethyl acetate was poured in a flask and was washed with saturated sodium bicarbonate and organic phase was washed with saturated sodium chloride solution and water, dried with anhydrous $MgSO_4$. The solvent was removed by rotary evaporator and the solid was purified by crystallization from a mixture of CH_2Cl_2: petroleum ether.

Method B. A mixture of 1,3-dicarbonyl compound (5 mmol), phenylglyoxal monohydrate (750 mg, 5 mmol) and urea (0.60 g, 10 mmol) was poured on the surface of 1.6 g of silica gel 60 (70-230 mesh) containing 40 mg $AlCl_3$ and 120 mg $ZnCl_2$. The Mixture was mixed thoroughly in a mortar and transferred to a tall beaker. The beaker was covered with a watch glass and irradiated at 850 W for 3-5 min (Table 1). Then, the reaction was allowed to cool to room temperature. Then, 50 ml ethyl acetate was added to the mixture and the mixture was filtered and the solvent was removed under reduced pressure. The residue was purified by crystallization from EtOH: H_2O (2:1)

General Procedure for the Synthesis of Multi-substituted Imidazoline-2-ones (6a-c)

Method A. A mixture of 1,3-dicarbonyl compound (5 mmol), phenylglyoxal monohydrate (750 mg, 5 mmol) and dimethyl urea (0.60 g, 10 mmol), $ZnCl_2$ (170 mg, 1.25 mmol) was heated at 80 ºC in ethanol under reflux condition for an appropriate time, as mentioned in Table 1 (4.5-7 h). The work-up procedure was the same as that for the synthesis of **4a-c.**

Method B. A mixture of 1,3-dicarbonyl compound (5 mmol), phenylglyoxal monohydrate (750 mg, 5 mmol) and dimethyl urea (0.88 g, 10 mmol) was poured on the surface of 1.6g silica gel containing 40 mg $AlCl_3$ and 120 mg $ZnCl_2$. The Mixture was mixed thoroughly in a mortar and transferred to a tall beaker. The beaker was covered with a watch glass and irradiated at 850 W for 4 min (Table 1). The work-up procedure was the same as that for the synthesis of **4a-c**.

General Procedure for the Synthesis of Hydantoins: (8, 9).

A mixture of phenylglyoxal (750 mg, 5 mmol), urea or dimethyl urea (0.88 g, 10 mml) and ethylacetoacetate (0.65 ml, 5 mmol) and 0.9 ml concentrated hydrochloric acid in ethanol was heated for 6 h under reflux condition. The solvent was removed under reduced pressure. Further purification was carried out by crystallization in EtOH.

4-Benzoyl-5-acetyl-6-methyl-3,4-dihydropyridine-2-(1H)-one (4a): R = Me. M.p.: 194 °C; IR (KBr, cm^{-1}) ν = 3275, 2970, 1730, 1695, 1590, 1415 ; ^{1}H NMR (δ, DMSO-d_6) 2.2 (s, 3H, CH_3), 2.3 (s, 3H, CH_3), 5.9 (s, 1H, CH), 7.5 (m, 5H, Ar-H), 7.9 (brs, 1H, N_3-H), 8.0 (brs, 1H, N_1-H) ppm; ^{13}C NMR (δ, DMSO-d_6) 193.9, 174.8, 158.1, 154.4, 136.7, 129.0, 128.6, 127.1, 61.3, 23.2 (2C) ppm; HRMS (EI)$^+$ $C_{14}H_{14}N_2O_3$; Found: 258.1025, Calcd.: 258.1005.

4-Benzoyl-5-methylcarboxylate-6-methyl-3,4-dihydro-pyrimidine-2(1H)-one (4b): R = OMe. M.p.: 204 °C; IR (KBr) ν = 3358, 3228, 3114, 2974, 1698, 1460, 1431; ^{1}H NMR (δ, DMSO-d_6) 2.20 (s, 3H, CH_3), 3.3 (s, 3H, OCH_3), 5.7 (s, 1H, CH), 7.5 (m, 5H, Ar-H), 7.9 (brs, 1H, N_3-H), 8.0 (brs, 1H, N_1-H) ppm; HRMS (EI$^+$) $C_{14}H_{14}O_4N_2$; Found: 274.0969, Calcd.: 274.0954.

4-Benzoyl-5-ethylcarboxylate-6-methyl-3,4-dihydro-pyrimidine-2(1H)-one: (4c) R = OEt. M.p.: 214 °C; IR (KBr, cm^{-1}) ν = 3400, 3225, 3125, 2995, 1720, 1650 , 1595, 1450; ^{1}H NMR (δ, DMSO-d_6) 0.9 (t, 3H, J = 9 Hz, CH_3), 2.20 (s, 3H, CH_3), 3.90 (q, 2H, J = 9Hz, CH_2), 5.60 (s, 1H, CH), 7.50 (m, 5H, Ar-H), 7.90 (brs, 1H, N_3-H), 8.0 (brs, 1H, N_1-H) ppm; ^{13}C NMR (δ, DMSO,d_6): δ = 198.8, 180.7, 165.8, 151.4, 140.5, 135.9, 134.2, 129.6, 59.8, 54.1, 17.8, 17.51 ppm; MS: m/e = 288, 246, 217, 199, 173, 130, 104, 77, 51.

1,3-Dimethyl-4-(4-hydroxy-3pentene-2-one)-5-phenyl imidazoline-2-one (6a). M.p.: 139 °C; IR (KBr, cm^{-1}) ν = 2995, 1710, 1605, 1495, 1410, cm^{-1}; ^{1}H NMR (δ, DMSO-d_6) 1.90 (s, 6H, CH_3), 3.05 (s, 3H, N-CH_3), 3.15 (s, 3H, N-CH_3), 7.40 (m, 5H, Ar-H), 16.90 (s, 1H, OH) ppm; ^{13}C NMR (DMSO-d_6) δ = 194.7, 153.5, 129.5, 129.1, 128.9, 128.4, 123.1, 114.9, 101.8, 28.6, 27.2, 23.3 ppm; HRMS (EI$^+$) $C_{16}H_{18}N_2O_3$; Found: 286.1330, Calcd.: 286.1317.

1,3-Dimethyl-4-(3-hydroxy-3-butene-2-oic acid ethyl ester)-5-phenyl imidazoline-2-one (6c). M.p.: 116-119 °C; IR (KBr, cm^{-1}) 3053, 2973, 1698, 1643, 1589, 1462, 1389 ^{1}H NMR (δ, DMSO-d_6) 1.25 (t, 3H, CH_3), 1.75 (s, 3H, CH_3), 3.20 (s, 3H, N-CH_3), 3.30 (s, 3H, N-CH_3), 4.30 (q, 2H, CH_2), 7.50 (m, 5H, Ar-H), 13.2 (s, 1H, OH) ppm; ^{13}C NMR (δ, DMSO-d_6) 179.7, 172.9, 154.1, 129.6 (2C), 128.9, 128.2, 123.4, 114.4, 91.3, 61.1, 29.1, 27.7, 19.4, 14.1 ppm; HRMS (EI$^+$) $C_{17}H_{20}N_2O_4$; Found: 316.1429, Calcd.: 316.1423.

1,3-Dimethyl-4-(2-oxo-propyl)-5-phenyl imidazoline-2-one (7). M.p.: 90 °C; IR (KBr, cm^{-1}): 2980, 1730, 1665, 1590, 1450; ^{1}H NMR (δ, DMSO-d_6) 2.1 (s, 3H, CH_3), 3.0 (s, 6H, CH_3), 3.70 (s, 2H, CH_2), 7.50 (m, 5H, Ar-H) ppm; ^{13}C NMR (δ, DMSO-d_6) 205.3, 152.8, 129.1, 128.8, 128.6, 127.9, 121.1, 113.9, 38.1, 29.3, 28.4, 27.3 ppm; MS: m/e = 244, (M^+ = 201), 227, 213, 171, 143, 118, 102, 77, 51. HRMS (EI$^+$) $C_{14}H_{16}N_2O_2$; Found: 244.1185, Calcd.: 214.1211.

5-Phenyl imidazoline-2-one (8). M.p.: 176 ºC; IR (KBr, cm^{-1}) 3358, 3228, 3114, 2973, 1696, 1449, 1459; ^{1}H NMR (δ, DMSO-d_6) 5.1 (s, 1H, CH), 7.45 (s, 5H, Ar-H), 8.45 (brs, 1H, N_2-H), 10.80 (brs, 1H, N1-H) ppm; ^{13}C NMR (δ, DMSO-d_6) 61.31, 127.1, 128.6, 129.1, 136.5, 158.1, 174.8, 174.8, 158.1, 136.5, 129.1, 128.6, 127.1, 61.31 ppm; MS: m/e = 176, (M-28 = 148), 148, 133, 104, 77.

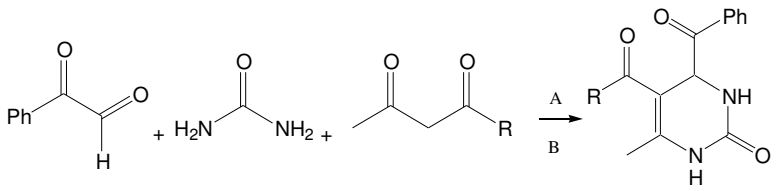
1, 3-Dimethyl-5-phenyl imidazoline-2-one (9). M.p.: 104 °C; IR (KBr, cm^{-1}) 3451, 3033, 2955, 1762, 1737, 1487, 1455; ^{1}H NMR (δ, DMSO-d_6) 2.72 (s, 3H, NCH_3), 2.91 (s, 3H, NCH_3), 5.05 (s, 1H, CH), 7.40 (m, 5H, Ar-H) ppm; ^{13}C NMR (δ, DMSO-d_6) 28.9, 68.1, 129.9, 131.5 (2C), 135.8, 161.0, 175.2; HRMS (EI$^+$) $C_{11}H_{12}N_2$; Found: 204.0901, Calcd.: 204.0899.

RESULTS AND DISCUSSION

Zinc chloride, as a very inexpensive and easily available Lewis acid catalyst, has been widely used in organic reactions. To emphasize the reaction conditions, the reaction between phenylglyoxal, ethyl acetoacetate and urea were selected as a model to examine the effects of catalysts (0-30% mol) and reagents at different reaction temperatures (r.t., 50, 80 °C). Meanwhile, the reaction between phenylglyoxal, ethyl acetoacetate and urea was carried out by different ratios of $ZnCl_2$:$AlCl_3$ on the surface of silica gel. Various yields were obtained for this reaction and the best result was achieved by a $ZnCl_2$:$AlCl_3$ ratio of 1:3. For the synthesis of dihydropyrimidinones, a combinatorial chemistry approach can be applied to exploit this extra ketone functionality and to generate two sets of ready to screen libraries for pharmaceutical activities.

The structures of products **4a-4c** were characterized based on their ^{1}H and ^{13}C NMR, IR and mass spectrometric data. The ^{1}H NMR spectra of compound **4a** in DMSO-d_6 show a singlet at 5.8 ppm which is related to H-4, while the two separated methyl groups resonate at 2.3 and 2.4 ppm. In ^{13}C NMR spectrum of compound **4a**, the peak at 61.3 ppm is related to C-4 (sp^3) which can confirm the formation of product. While, the two different carbonyl groups resonate at 174.8 and 193.8 ppm. HRMS $(EI)^+$ shows a peak at 258.1025 that confirms the product structure. The base peak in mass spectrum is 153.1, which is supposed to be related to a benzoyl group elimination. In ^{1}H NMR spectra of compounds **4a** and **4b**, H-4 resonates at 5.7 and 5.6 ppm, respectively, while in ^{13}C NMR spectrum of **4a**, C-4 resonates at 61.3 ppm.

Since *N,N′*-disubstituted dihydropyrimidinones have pharmaceutical activities and usually are synthesized by multiaddition or substitutional reactions such as Mitsonubo reaction, we used one-pot multicomponent condensation of *N,N′*-dimethyl urea, phenylglyoxal and alkyl acetoacetate (or acetylacetone) for this synthesis. According to the Sweet-Fissekin's mechanism [38], the product of *N,N′*-disubstituted urea should be a *N,N′*-disubstituted dihydropyrimidinone. However, the condensation reaction of phenylglyoxal, alkyl cyanoacetates and *N,N′*-dimethyl urea in the presence of $ZnCl_2$, under reflux condition, and also in the presence of



1 **2** **3a-c** **4a-c**

A: $ZnCl_2$, EtOH,Reflux
B: $ZnCl_2$:$AlCl_3$ (1:3), Silica gel, MW

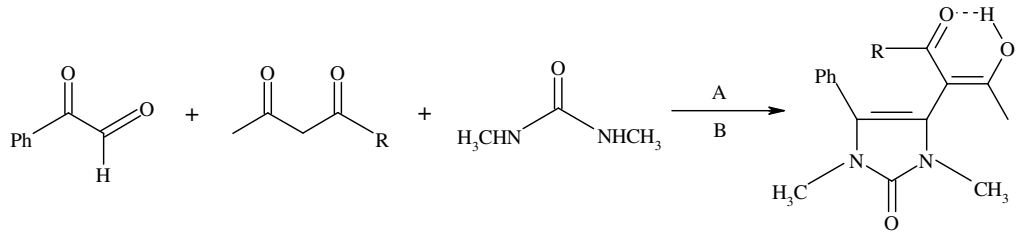
Scheme 1

Table1. Synthesis of Dihydropyrimidinone in Reflux and Microwave Irradiation Conditions

No.	R	Reflux condition		MW condition	
		Yield[a]	Time (h)	Yield[a]	Time (min)
4a	Me	73	4.5	26	3
4b	OMe	67	7	42	5
4c	OEt	59	6	39	4

[a]Yields represent isolated pure crystal based on phenylglyoxal.

$ZnCl_2$:$AlCl_3$ (1:3) supported on silica gel, under microwave irradiation and solvent-free condition, leads to the preparation a new multi-substituted imidazoline-2-one derivative (Scheme 2). In ^{1}H NMR spectrum of compound **6c**, a broad singlet line was found at 13.2 ppm, which could be related to the enolic OH contributing in an intramolecular hydrogen bonding.



A: $ZnCl_2$, EtOH, Reflux
B: $ZnCl_2$:$AlCl_3$ (1:3), Silica gel, MW

Scheme 2

Table 2. Synthesis of Multi-substituted Imidazoline-2-ones (**6a-6c**)

No.	R	Reflux condition		MW condition	
		Yield[a]	Time (h)	Yield[a]	Time (min)
6a	Me	66	5.5	35	3
6b	OMe	56	7	45	5
6c	OEt	50	6	46	4

[a]Yields represent isolated pure crystal based on phenyl glyoxal.

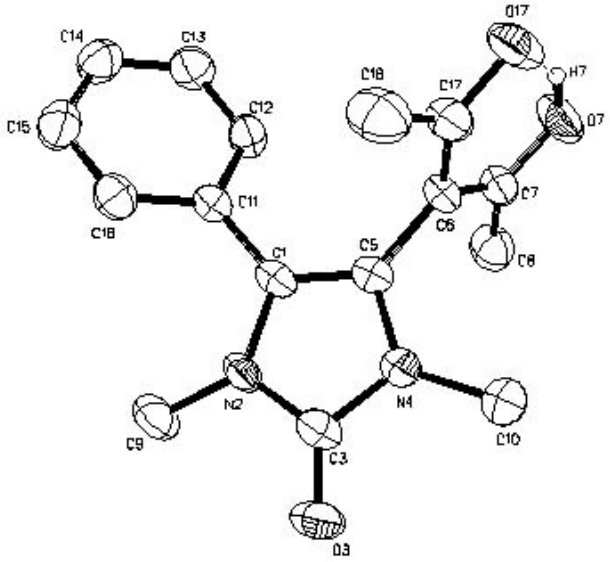
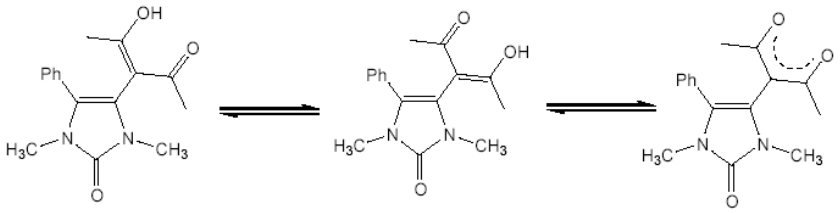


Fig. 1. ORTEP plot of the molecular structure of **6a.**

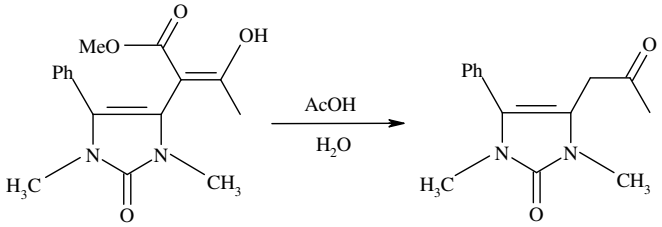
HRMS $(EI)^+$ represents the ion molecular peak at 316.1429 and this mass is belong to dihydropyrimidinone analogue. Figure 1 illustrates the X-ray structure of product, which confirms the existence of intramolecular hydrogen bonding in the molecule.

By checking the ^{13}C NMR spectra, we didn't observe any peak for C-4 at 50-60 ppm, but two separated carbonyl groups at 173.12 and 179.74 ppm were detected. The deshielded carbon atom peak seems to be the carbonyl group contributing in hydrogen bonding. Table 2 contains the entire data for **6a-6c**. ^1H NMR spectrum of compound **6a** illustrates a singlet for two methyl groups and also in its ^{13}C NMR spectrum, one peak for CH_3 groups is observed. It seems that two enolic forms are in equilibrium together and the two methyl groups are equivalent.

In ^1H NMR spectrum of compound **6a**, a broad singlet was



Scheme 3



Scheme 4

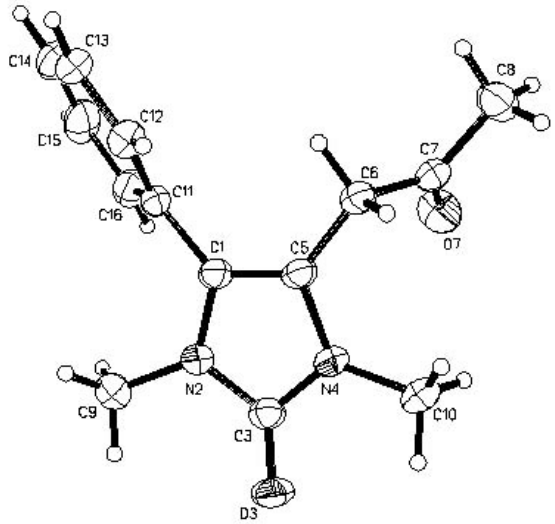


Fig. 2. ORTEP structure of compound **7**.

found at 16.9 ppm which could be related to the intramolecular hydrogen bonding and confirms an enolic form. The phenyl group and two methyl groups in **6c** are distorted and show a minimum interaction between methyl groups and phenyl substitution in imidazoline-2-one ring (Scheme 3).

The bond lengths of C_6-C_7 (1.40 Å) and C_6-C_{17} (1.409 Å) are located between those of single and double bonds, which is due to delocalization of electrons in resonance forms and also equilibration of the enolic structure. Compound **6b** could be converted to **7** after acidic hydrolysis (Scheme 4). Figure 2 illustrates the X-ray structure of compound **7**. The crystallographic data for compounds **6a** and **7** are listed in Table 3.

In ^{1}H NMR spectrum of compound **7**, two singlets were observed at 2.1 and 3.7 ppm due to CH_3 and CH_2 groups. Two *N*-methyl groups resonate at 3.0 ppm and two different

Table 3. Crystal Data and Structure Refinement for **6a** and **7**

	6a	**7**
Empirical formula	$C_{16}H_{18}N_2O_3$	$C_{14}H_{16}N_2O_2$
Formula weight	286.32	244.29
Temperature	200 (2) K	200 (2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
Z	4	4
Unit cell dimensions	a = 15.3220 (2) Å	a = 8.0782 (4) Å
	b = 10.2618 (3) Å	b = 11.9398 (6) Å
	c = 9.9181 (3) Å	c = 13.0812 (6) Å
	α = 90 deg.	α = 90 deg.
	β = 106.611(2)	β = 98.180 (1)
	γ = 90 deg.	γ = 90 deg.
Volume	1494.36 (7) Å^3	1248.87 (11) Å^3
Density (calculated)	1.27 g cm^{-3}	1.30 g cm^{-3}
Absorption coefficient	0.09 mm^{-1}	0.09 mm^{-1}
Crystal shape	polyhedron	polyhedron
Crystal size	0.26 × 0.20 × 0.06 mm^3	0.34 × 0.16 × 0.14 mm^3
Theta range for data collection	2.4 to 23.0 deg.	2.3 to 27.5 deg.
Index ranges	-10 ≤ h ≤ 10, -15 ≤ k ≤ 15, -16 ≤l ≤16	-10 ≤ h ≤ 10, -15 ≤ k ≤ 15, -16 ≤ l ≤ 16
Reflections collected	10504	12793
Independent reflections	2082 (R (int) = 0.0651)	2868 (R (int) = 0.0400)
Observed reflections	1394 (I > 2σ (I))	2013 (I > 2σ (I))
Absorption correction	Semi-empirical from equivalents	Semi-empirical from equivalents
Max. and min. Transmission	0.99 and 0.98	0.99 and 0.97
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	2082 / 0 / 199	2868 / 0 / 166
Goodness-of-fit on F^2	1.02	1.01
Final R indices (I>2□(I))	R1 = 0.043, wR2 = 0.094	R1 = 0.040, wR2 = 0.090
Largest diff. peak and hole	0.21 and -0.19 eÅ^{-3}	0.24 and -0.22 eÅ^{-3}

carbonyl groups at 153 and 205 ppm. HRMS $(EI)^+$ also confirms this structure with a m/e of 244. Figure 3 shows the proposed mechanism for the formation of **4a-c**. Formation of *N*-acyliminium ion intermediate is a key reaction, then Lewis acid can stabilize *N*-acyliminium ion by coordination to the urea oxygen, and also chelation of 1,3-dicarbonyl componenet

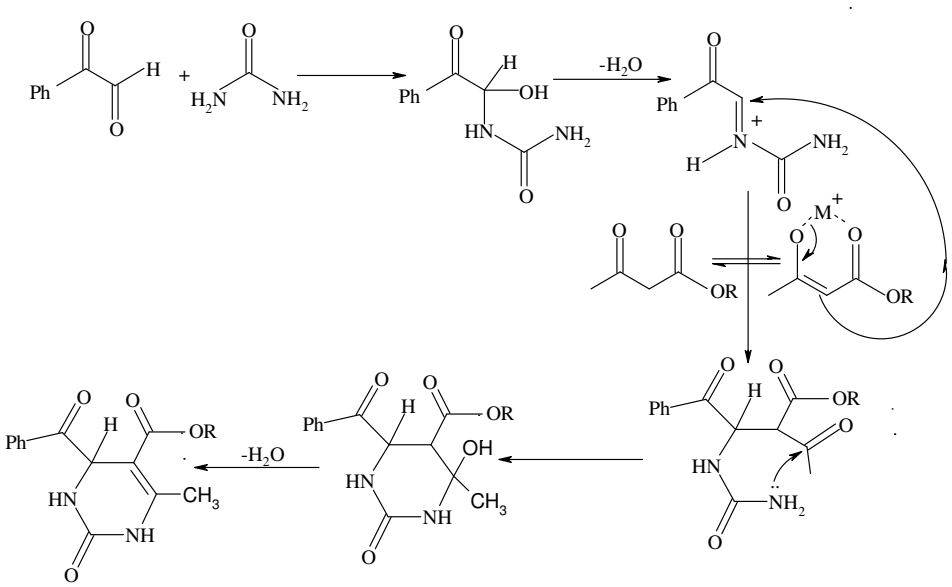


Fig. 3. Proposed mechanism for the synthesis of **4a-c**.

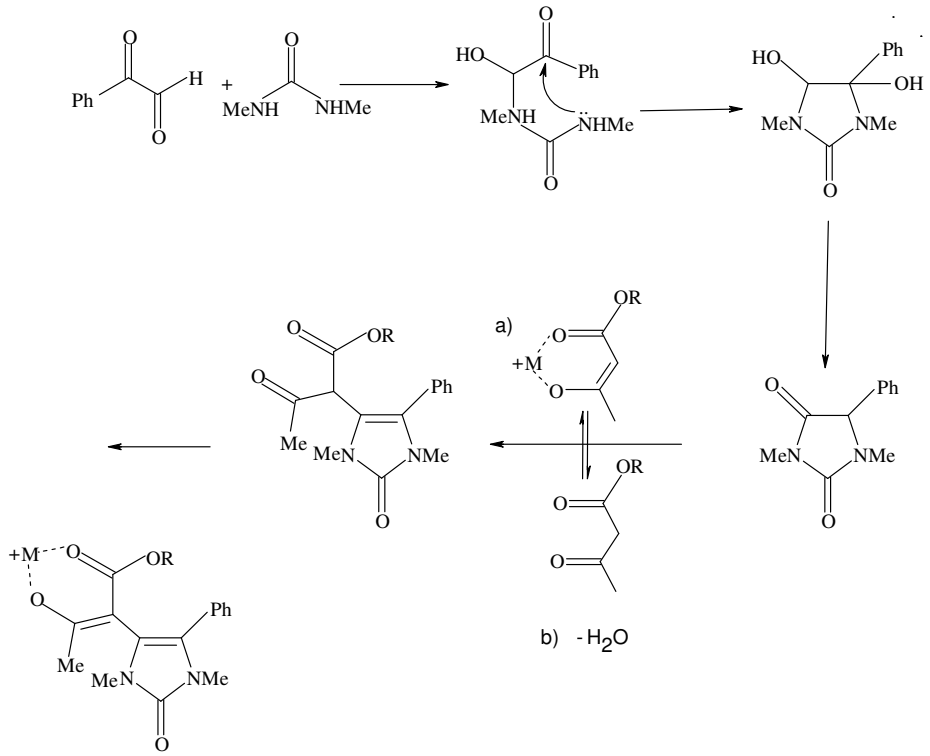


Fig. 4. Proposed mechanism for the synthesis of **6a-c**.

can stabilize the enolic tautomer. Figure 4 shows the formation of compounds **6a-c**. When we used *N,N'*-dimethyl urea, the products were different and, according to the proposed mechanism, imidazoline-2-one derivatives were obtained. In fact, the existence of additional carbonyl group and increased nucleophilicity of nitrogen can change the reaction path; Lewis acid can stabilize the enolic form. Formation of compounds **6a-c** can be confirmed Kappe's mechanism [39].

In another try, the reaction of phenylglyoxal, urea and ethyl acetoacetate in the presence of hydrochloric acid under reflux condition led to the formation of 5-phenylhydantoin (Scheme 5). It is noteworthy that hydantoins are well known for their diverse biological activities and play a key role as antiarrhythmics [40], antitumor [41], and anti-inflammatory [42] agents. They have also been used for the preparation of moistening lotions, increasing HDL cholesterol concentration and as antiserotoninergic agents.

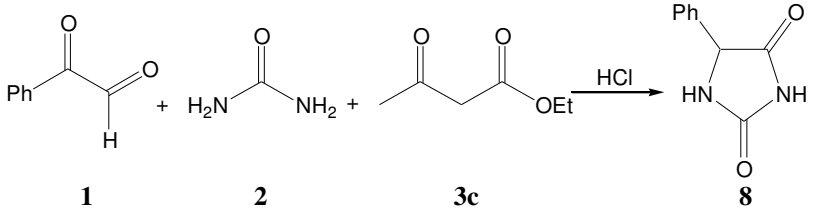
The ^{1}H NMR spectrum of this product shows a broad singlet at 5.2 ppm for the H-5 and two different peaks at 8.45 and 10.8 ppm correlated to N-H. The ^{13}C NMR spectrum consists of a peak at 61.31 ppm due to C-H group. Characteristic carbonyl resonances appear clearly at 158.1 and 174.8 ppm.

Reaction of dimethyl urea, ethyl acetoacetate and phenylglyoxal in the presence of hydrochloric acid refluxing in EtOH leads to the preparation of 1,3-dimethyl-5-phenyl hydantoin (Scheme 5). ^{1}H NMR of compound **8** displays H-4 signal at 5.2 ppm and also in ^{13}C NMR, C-4 is found at 68.1 ppm. It seems that ethyl acetoacetate could not react under these conditions. Formation of hydantoin ring is the driving force for this reaction. HRMS $(EI)^+$ confirms the formation of product **8**. ^{13}C NMR spectrum of compound **8** illustrates two different peaks for -NMe groups at 26.8 and 29.0 ppm. Yields of hydantoins were 90-95%.

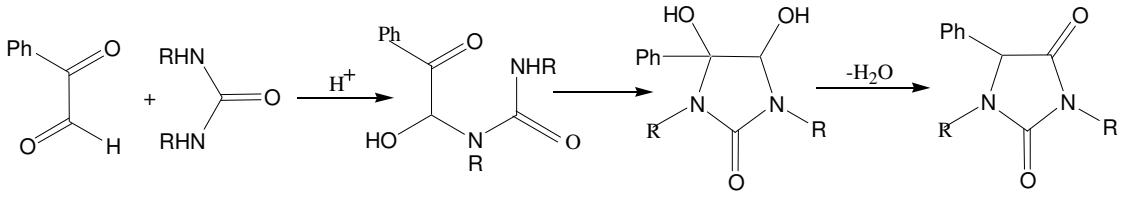
The possible mechanism for the formation of 5-phenylhydantoinis is shown in Scheme 6. Hydrochloric acid can't stabilize the enolic form and, thus, it does not have any role in this reaction.

CONCLUSION

It was found that $ZnCl_2$ is able to catalyze the synthesis of new dihydropyrimidinones, and some multi-substituted imiazoline-2-one derivatives with intramolecular hydrogen bonding. Meanwhile, the reactions are also catalyzed by $ZnCl_2$:$AlCl_3$ (1:3) under solvent-free condition by the aid of



Scheme 5



8 R = H

9 R = Me

Scheme 6

microwave irradiation. Good yields, easy work-up and low reaction time are advantages of this method.

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