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Efficient One-Pot Synthesis and Characterization of 13-Acetyl-9-methyl-11- oxo-8-oxa-10,12-diazatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene

Salehi Hojatollah[1*], Rabbani Mohammad[1], Li Qian-Rong[2], Guo Qing-Xiang[3]

[1] Nuclear Research Center, Atomic Energy Organization of Iran, P.O.Box: 11365-3486, Tehran-Iran
[2] Structure Research Laboratory;
[3] Department of Chemistry, University of Science and Technology of China, Hefei 230026, China

ABSTRACT

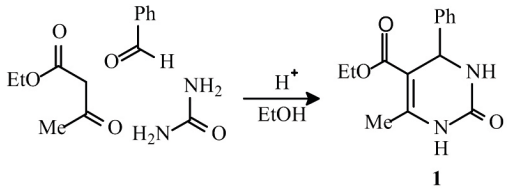
An efficient and environmentally friendly procedure for the one-pot synthesis of 13-acetyl-9-methyl-11-oxo-8-oxa-10,12-diazatricyclo [7.3.1.$0^{2,7}$] trideca-2,4,6-triene from salicylaldehyde, acetylaceton and urea via Biginelli condensation and intramolecular Michael-addition by using magnesium bromide as an inexpensive and easily available catalyst under solvent-free condition is described. The structural elucidation of the product is also described by ^{1}H- and ^{13}C-NMR spectra and the detailed fragmentation routs of EI-TOFMS.

Keywords: Oxygen-bridged dihydropyrimidinone; Intramolecular Michael-addition; One-pot-solvent-free synthesis; NMR and EI-TOFMS

INTRODUCTION

During the past decade, dihydropyrimidinones, an important class of compounds, have become increasingly significant due to their therapeutic and pharmacological properties[1]. They have emerged as integral backbones of several calcium channel blockers, antihypertensive agents and alpha-1a-antagonists[2]. Recently several isolated marine alkaloids with biological activities were also found containing the dihydropyrimidinones core. Most notably among them are betzelladine alkaloids, which have been found to be potent HIVgp-120-CD4 inhibitors[3].

Dihydropyrimidinones (**1**) can be synthesized by a simple one-pot condensation termed as Biginelli reaction[1] of an aromatic aldehyde, urea and ethyl acetoacetate in ethanolic solusion (Scheme 1).



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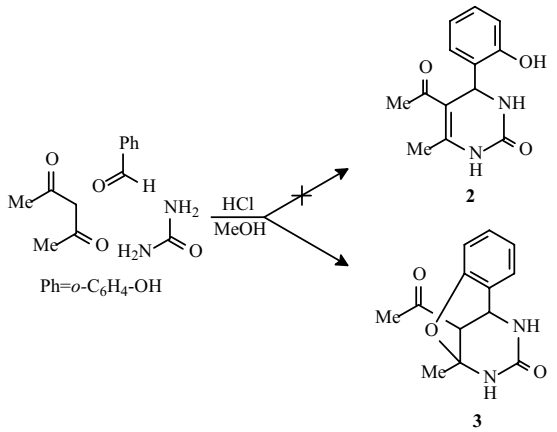
Scheme 1

However, by the use of salicylaldehyde as the aldehyde reagent, the Biginelli product will be an oxygen-bridged compound rather than a free hydroxyl compound (**2**). 13-acetyl-9-methyl-11-oxo-8-oxa-10,12-diazatricyclo [7.3.1.$0^{2,7}$] trideca-2,4,6-triene (**3**) is an example of this kind of compound, which was synthesized by Rehani *et al*, using the traditional Biginelli reaction in boiling methanol in the presence of conc. HCl[4] (Scheme 2).

* Corresponding author: E-mail: hsalehi@aeoi.org.ir



Scheme 2

Nevertheless, there is no detailed information about ^{13}C-NMR and MS spectra for identification of the structure in the reference [4]. Continuing our recent works in synthesis and characterization of Biginelli dihydropyrimidinones and Hantzsch dihydropyridines[5-7], here we wish to report solvent-free one-pot synthesis and characterization of the title compound using both of ^{1}H- and ^{13}C-NMR. Furthermore, the time-of-flight (TOF) mass spectrum of the compound was studied to establish their fragmentation processes in view of what follows. One difficulty with the characterization of pyrimidinones or its isomers is that often they are only isolated *in vitro* or *in vivo* in very small quantities when used for medicine, thus precluding facile characterization by nuclear magnetic resonance (NMR) spectroscopy. A time-of-flight mass spectrometer (oa-TOFMS) allows fast acquisition of full spectra, with high sensitivity and elevated resolution (~8000 FWHM) and usually allows product ions to be assigned by a mass accuracy of ~5ppm allowing, in many cases, unambiguous assignment and definitive designation of the fragmentation pathway. This leads to an easier interpretation of the product ion spectrum. Therefore, oa-TOFMS is invaluable for the structural characterization of trace amounts of pyrimidines [7].

EXPERIMENTAL

1. Apparatus and Reagents

All chemicals were obtained from commercial sources and used without further purification. Melting point is uncorrected. IR spectrum was run on a Bruker spectrometer and expressed in cm^{-1} (KBr). ^{1}H- and ^{13}C NMR spectrum were recorded on a Bruker AVMCE-300MHz in DMSO-d_6 solution. Electron impact (EI) mass spectrum was recorded using a GCT-TOF mass spectrometer (Micromass, Manchester, UK) in positive ion mode at a resolution of 8000 (FWHM) by direct probe introduction at a nominal electron energy of 70 eV. Accurate mass measurement was obtained by calibration and single point lock-mass correction at *m/z* 218.9856 using heptacosafluorotributylamine (PFTBA) as internal reference. The source temperature was set at 200°C and the trap current at 100 μA. The samples were volatilized from a heated insertion probe in the source. Sample analysis, exact mass measurement and elemental composition determination were performed automatically using the OpenLynx software within MassLynx.

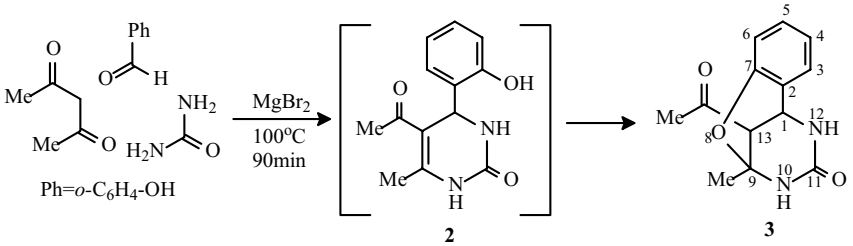
2. Synthesis

Acetylaceton (10mmol), salicylaldehyde (10mmol), urea (15mmol) and magnesium bromide (1mmol, 10 mol%) were heated at 100°C under stirring for 90 min. After cooling, the reaction mixture was poured onto crushed ice (50 g) and stirred for 5-10 min. The solid separated was filtered under suction, washed with ice-cold water (2×50 ml) and then recrystallized from ethanol to afford pure product (2.14g, yield=87%), which is much higher than that of the reaction (52%) reported by Rehani *et al* [4] . m.p. 200-202°C. ^{1}H- and ^{13}C-NMR data (in DMSO-d_6) see Table 1 and 2, and the accurate MS data see Table 3. IR (KBr), υ (cm^{-1}): 3239 (NH), 1713 (C=O, acetyl), 1697 (C=O, NH-CO-NH), 1588, 1508, 1459 (aromatic C=C).

RESULTS AND DISCUSSION

1. Synthesis and NMR Characterization

In the course of our work for the solvent-free one-pot synthesis of dihydropyrimidinones using magnesium bromide as a catalyst[5] we have observed that the product derived from the condensation reaction involving salicylaldehyde, acetylaceton and urea showed NMR spectrum inconsistent with the expected structure of dihydropyrimidinon (**2**) (Scheme 3).



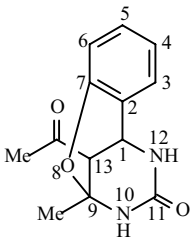
Scheme 3

Structure **3** is assigned to this product on the base of the comparisons of its ^{1}H- and ^{13}C-NMR spectra (Table 1 and 2) with those of a similar structural dihydropyrimidinon **4**, which was reported in the previous paper5.

The presence of a new proton signal at 3.37ppm as a doublet (2.17Hz) in the ^{1}H spectrum of compound **3** is assigned to H-13, implying the proton connected to a sp^3 carbon and the lack of a double bond between C_9 and C_{13}, or the presence of an oxygen-bridge. This conclude was supported by the presence of a double doublet (2.11 and 2.07Hz) signal at 4.62ppm, assigned to H-1, due to the presences of one proton at the C_{13} and one proton at the NH. In the case of **4**, the corresponding signal appeared at 5.25ppm with only a doublet (2.22Hz) for the proton at C_4 because of the presence of only one proton (NH) adjacent to C_4. Furthermore, three signals at 4.62 (H-1), 7.45 (assigned to N-H) and 1.64ppm (assigned to CH_3), are located at higher fields than those of respective proton signals (H-4, N-H and CH_3) for **4** at 5.25, 9.19 and 2.10 ppm respectively. These facts indicate that there is no double bond between C_9 and C_{13} in the molecule of **3**.

Table 1. ^{1}H-NMR spectral data of **3** compared with **4**

Compound **3**		Compound **4**	
δ (ppm)	Proton	δ (ppm)	Proton
4.62dd (2.11, 2.07)	H-1	**5.25**d (2.22)	H-4
6.75~7.20m(4H)	H_{arom}	7.22-7.35m(5H)	H_{arom}
6.75~7.20(1H)	H-N	7.81brs	H-N
7.45brs	H-N	**9.16**brs	H-N
3.37d (2.17)	H-13	-	-
2.28s	CH_3 CO	**2.28**s	CH_3 CO
1.64s	CH_3	**2.10s**	CH_3



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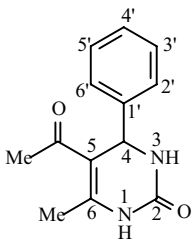

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The above conclusion from ^{1}H-NMR is supported by ^{13}C-NMR. There are two carbon signals at 83.6 and 50.1ppm in the ^{13}C spectrum of **3**, assigned to C-9 and C-13 respectively, which are much higher fields than the respective signals for **4**, namely, 148.0 (C-6) and 109.5 (C-5) ppm, respectively. Another signal at 204.2ppm in the spectrum of **3**, assigned to C=O, which is lower field than that (194.2ppm) of **4,** because of the donating electron of double bond conjugation in the molecule of **4**.

Table 2. ^{13}C-NMR spectral data of **3** Compared with **4**

Compound **3**		Compound **4**	
δ (ppm)	Carbon	δ (ppm)	Carbon
47.1	C-1	53.8	C-4
126.2	C-2	144.2	C-1′
129.5	C-3	126.3	C-2′
120.5	C-4	128.4	C-3′
129.1	C-5	127.2	C-4′
116.8	C-6	128.4	C-5′
151.1	C-7	126.3	C-6′
83.6	C-9	**148.0**	C-6
155.0	C-11	152.0	C-2
50.1	C-13	**109.5**	C-5
204.2	C=O	**194.2**	C=O
29.2	**C**H_3CO	**30.2**	**C**H_3CO
23.8	CH_3	**18.8**	CH_3

The production of **3** can be explained by the isomerization reaction (intramolecular Michael addition) of the dihydropyrimidinon **2** which was initially formed by Biginelli reaction [1,5] (Scheme 3). The preparation of the dihydropyrimidinon **2** derived from salicylaldehyde was first described in 1932[8]. Its structure was disproved, when exclusive formation of bridged compound was obtained under HCl catalysis[9]. This finding suggests that the steric proximity[2] of the OH substituent in the *ortho* position of the aromatic ring, and the C-6 carbon of the pyrimidine ring enables the formation of a six-membered ring via intramolecular Michael addition, therfore this dihydropyrimidinone promptly isomerizes to its cyclic isomer in the presence of magnesium bromide, which can be considered as conformationally rigid calcium channel blockers[9-11]. To the best of our knowledge this is the first time which bridged polycyclic derivative of type **3** has been synthesized under solvent free conditions.

2. Structure Characterization using TOFMS

2.1 The molecular ion

An evident peak at *m/s* 246.0999 was found (Table 3) in the mass spectrum, which corresponds to the molecular ion $\mathbf{3M}^{\cdot+}$, $[C_{13}H_{14}N_2O_3]^{\cdot+}$ (calc. 246.1004, ppm error -2.2). The mass accuracy of the molecular mass is only –0.5 mDa or 2 ppm, which confirms its elemental compositions. The relative abundances (R.A.) of molecular ions $\mathbf{M}^{+}$ is 10%, which indicates the oxygen-bridged compound **3** is fairly stable under 70eV EI condition.

2.2 Fragmentation

Table 3. Exact masses and predicted formulas for the fragments of **3**

Ion	Measured mass (Da)	Calculated mass (Da)	Error (mDa)	Relative abundance[a]	Elemental composition	Assigment
3M	246.0999	246.1004	-0.5	10	$C_{13}H_{14}N_2O_3$	Molecular ion
3a	229.1021	229.1021	4.4	48	$C_{13}H_{13}N_2O_2$	$\mathbf{M}^{+\cdot}$-OH·
3b	213.0705	213.0664	4.1	27	$C_{12}H_9N_2O_2$	**a**-CH_4
3c	170.0649	170.0606	4.3	38	$C_{11}H_8NO$	***b***-*HNCO*
3d	153.0732	153.0664	6.8	24	$C_7H_9N_2O_2$	***m***-C_6H_4OH
3e	203.0857	203.0821	3.6	33	$C_{11}H_{11}N_2O_2$	*M-MeCO·*
3f	160.0783	160.0762	2.1	8	$C_{10}H_{10}NO$	**e**-HNCO
3g	43.0221	43.0184	3.7	100	C_2H_3O	$MeCO^+$

[a] Expressed as % of base peak (I/%).

Significant peaks with accurate masses in EI mass spectrum of compound **3** examined are summarized in Table 3, and the possible fragmentation pathways are shown in Figure 1. A peak at *m/z* 229 (48%), $[C_{13}H_{13}N_2O_2]^+$ corresponds to dihydropyrimidinone cation **a** by loss of radical OH from the phenolic radical cation **m**, which comes from the molecular ion $\mathbf{M}^{+\cdot}$ by cleavage of the ether (oxygen bridge) bond accompanied by a hydrogen migration and formation of a double bond. The cation **a** eliminates CH_4 accompanied by a hydrogen 1,3-migration, forming the pyrimidinone cation **b** at *m/z* 213 (27%), $[C_{12}H_9N_2O_2]^+$, which then further undergoes a cyclic cleavage and expulses NH=C=O (43 Da) forming the nitrogen heterocyclobutadiene ion **c** at *m/z* 170 (38%), $[C_{11}H_8NO]^+$. Another fragmentation route from **m** is the cleavage of the C_6H_4OH radical, and the formation of fragment **d** at *m/z* 153 (24%), $[C_7H_9N_2O_2]^+$, which is a character cleavage for dihydropyrimidinones [7]. Loss of MeC=O radical from $\mathbf{M}^{+\cdot}$ afforded cation **e** at *m/z* 203 (2%), $[C_{11}H_{11}N_2O_2]^+$, which then further undergoes a cyclic cleavage and expulses NH=C=O forming the nitrogen heterocyclobutane ion **f** at *m/z* 160 (8%), $[C_{10}H_{10}NO]^+$. Finally, a fragment with high abundance as the base peak (100%) at *m/z* 43, $[C_2H_3O]^+$ appears in the spectrum, which corresponds to acetyl cation **3g** by an α-cleavage from $\mathbf{3M}^{+\cdot}$. As shown in Figure 1, the fragmentation routes of compound **3** are quite different from those of dihydropyrimidinones[7], which confirms its structure as the dihydropyrimidinone isomer **3** with an oxygen-bridged bond.

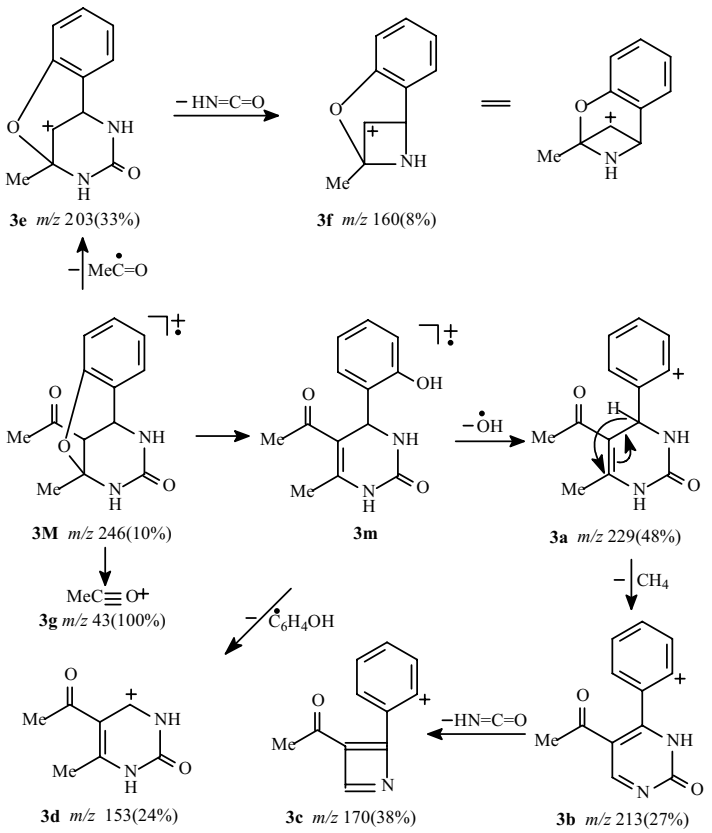

Fig. 1. Fragmentation pathway of compound **3**

CONCLUSION

We have described an efficient and environmentally friendly procedure for the one-pot synthesis of 13-acetyl-9-methyl-11-oxo-8-oxa-10,12-diazatricyclo [7.3.1.$0^{2,7}$] trideca-2,4,6-triene with high yield, and confirmed the structure of the oxygen-bridged compound rather than a free hydroxyl dihydropyrimidinone using the detailed information from NMR and TOFMS spectra.

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