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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

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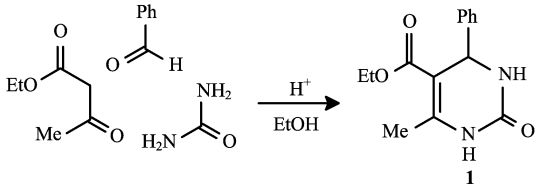
An efficient and environmentally friendly procedure for the one-pot synthesis of 13-acetyl-9-methyl-11-oxo-8-oxa-10,12-diazatricyclo[7.3.1.$0^{2,7}$]trideca-2,4,6-triene from salicylaldehyde, acetylacetone and urea via Biginelli condensation and intramolecular Michael-addition by using magnesium bromide as an inexpensive and easily available catalyst in a solvent-free condition is described. The structural elucidation of the product is reported by ^{1}H- and ^{13}C-NMR spectra. The product can also be identified by its EI TOF mass spectrometry based on the molecular ion at m/s 246(10%) and on the fragment ions in which two nitrogen atoms are remained. Three kinds of characteristic fragmentation pathways from the molecular ion were observed. One is the loss of the OH radical to form the dihydropyrimidinone cation at m/z 229(48%), followed by elimination of a molecular methane forming the pyrimidinone cation at m/z 213(27%). The second is the cleavage of the C_6H_4OH radical, and the formation of the dihydropyrimidinone cation at m/z 153(24%). The third one is the loss of MeC=O radical to afford the oxygen-bridged fragment ion at m/z 203(33%).

Key words: Oxygen-bridged dihydropyrimidinone, Intramolecular Michael-addition, One-pot solvent-free synthesis, NMR, EI-TOFMS

I. INTRODUCTION

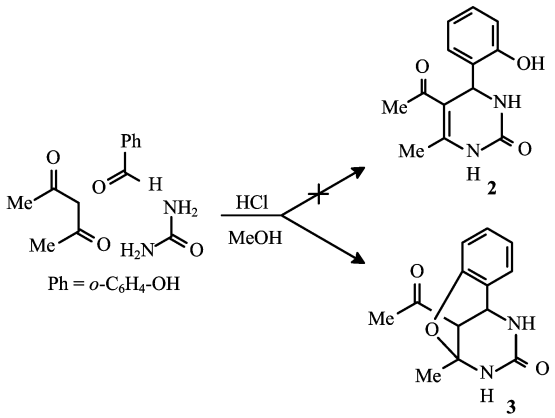
During the past decade, dihydropyrimidinones, an important class of compounds, have become increasingly significant due to their therapeutic and pharmacological properties [1]. They have emerged as integral backbones of several calcium channel blockers, antihypertensive agents and alpha-1a-antagonists [2]. Recently several isolated marine alkaloids with biological activities were found containing a 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 a Biginelli reaction [1], of an aromatic aldehyde, urea and ethyl acetoacetate in ethanolic solution (Scheme 1).



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).



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 work in the synthesis and characterization of Biginelli dihydropyrimidinones and Hantzsch dihydropyridines [5–7], 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 its fragmentation processes using accurate masses. 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 ∼5 ppm allowing, in many cases, unambiguous assignment and definitive designation of the fragmentation path-

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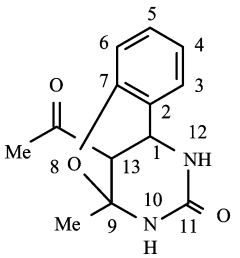
way. This leads to an easier interpretation of the product ion spectrum. Therefore, oa-TOFMS is invaluable for the structural characterization of trace amounts of pyrimidines [7–9].

TABLE I ^{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	5.25d (2.22)	H-4
6.75−7.20m(4H)	H_{arom}	7.22−7.35m(5H)	H_{arom}
6.75−7.20m(1H)	H−N	7.81brs	H−N
7.45brs	H−N	9.16brs	H−N
3.37d (2.17)	H-13	–	–
2.28s	CH_3CO	2.28s	CH_3CO
1.64s	CH_3	2.10s	CH_3



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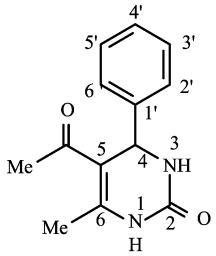

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TABLE II ^{13}C-NMR spectral data of **3** compared with **4**

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	CH_3CO	30.2	CH_3CO
30.2	CH_3	18.8	CH_3

II. EXPERIMENTAL

A. Apparatus and reagents

All chemicals were obtained from commercial sources and used without further purification. The melting point was uncorrected. IR spectrum was run on a Bruker spectrometer and expressed in cm^{-1} (KBr). ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker AVMCE-300 MHz 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 0.1 mA. The sample was 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.

B. Synthesis

Acetylacetone (10 mmol), salicylaldehyde (10 mmol), urea (15 mmol) and magnesium bromide (1 mmol, 10 mol%) were heated to 100°C while stirred, for 90 min. After cooling, the reaction mixture was poured onto crushed ice (50 g) and stirred for 5−10 min. The separated solid was filtered via suction, washed with ice-cold water (2×50 mL) and then recrystallized from ethanol to afford a pure product (2.14 g) with yield of 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) are given in Table I and II, and the accurate MS data in Table III. IR (KBr), ν (cm^{-1}): 3239 (NH), 1713 (C=O, acetyl), 1697 (C=O, NH-CO-NH), 1588, 1508, 1459 (aromatic C=C).

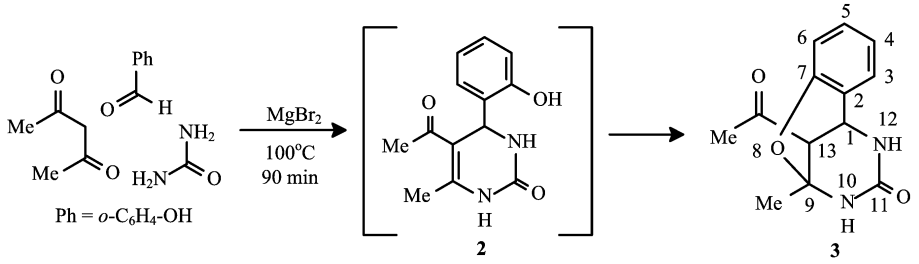
III. RESULTS AND DISCUSSION

A. Synthesis and NMR characterization

In our research work $MgBr_2$, $ZnCl_2$ and $Mg(ClO_4)_2$ have been used as catalysts for Biginelli reaction. In the case of $MgBr_2$ we found that its chemical yield was higher than others. In addition $MgBr_2$ is easily available, inexpensive, and is safer than other compounds. $ZnCl_2$ and $Mg(ClO_4)_2$ are too moisture sensitive. In solvent free condition $Mg(ClO_4)_2$ is explosive. Therefore we identified $MgBr_2$ as the best catalyst for this reaction.

In the course of our work towards the solvent-free one-pot synthesis of dihydropyrimidinones using magnesium bromide as a catalyst [5] by the use of the same procedure, we observed that the product derived from the condensation reaction involving salicylaldehyde, acetylacetone and urea showed a NMR spectrum inconsistent with the expected structure of dihydropyrimidinone (3) (Scheme 3).

Structure **3** is assigned to this product on the basis of comparisons of its ^{1}H- and ^{13}C-NMR spectra (Table I and II) with those of a similar structural dihydropyrimidinone **4**, reported in the previous paper [5]. The presence of a new proton signal at 3.37 ppm as a doublet (2.17 Hz) in the ^{1}H spectrum of compound **3** was



Scheme 3

TABLE III Exact masses and predicted elemental composition for the fragments of **3**

Ion	Measured mass/Da	Calculated mass/Da	Error/mDa	Relative abundance[a]	Elemental composition	Assigment
M	246.0999	246.1004	−0.5	10	$C_{13}H_{14}N_2O_3$	Molecular ion
a	229.1021	229.1021	4.4	48	$C_{13}H_{13}N_2O_2$	$\mathbf{M}^{+\cdot}$-OH·
b	213.0705	213.0664	4.1	27	$C_{12}H_9N_2O_2$	**a**-CH_4
c	170.0649	170.0606	4.3	38	$C_{11}H_8NO$	**b**-HNCO
d	153.0732	153.0664	6.8	24	$C_7H_9N_2O_2$	**m**-C_6H_4OH
e	203.0857	203.0821	3.6	33	$C_{11}H_{11}N_2O_2$	**M**-MeCO·
f	160.0783	160.0762	2.1	8	$C_{10}H_{10}NO$	**e**-HNCO
g	43.0221	43.0184	3.7	100	C_2H_3NO	$MeCO^+$

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

assigned to H-13, implying the proton was 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 conclusion was supported by the presence of a double doublet (2.11 and 2.07 Hz) signal at 4.62 ppm, 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 5.25 ppm with only a doublet (2.22 Hz) 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 1.64 ppm (assigned to CH_3), are located in 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**.

The above conclusion from ^{1}H-NMR is supported by ^{13}C-NMR. There are two carbon signals at 83.6 and 50.1 ppm 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 204.2 ppm in the spectrum of **3**, assigned to C=O, which has a lower field than that (194.2 ppm) of **4**, because of the donating electron of double bond conjugation in the molecule of **4**.

The production of **3** can be explained by the isomerization reaction (intramolecular Michael addition) of the dihydropyrimidinone **2** which was initially formed by Biginelli reaction [1, 5] (Scheme 3). The preparation of the dihydropyrimidinone 2 derived from salicylaldehyde was first described in 1932 [10]. Its structure was disproved, when exclusive formation of the bridged compound was obtained under HCl catalysis [11]. 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, therefore this dihydropyrimidinone promptly isomerizes to its cyclic isomer in the presence of magnesium bromide, which can be considered as conformationally rigid calcium channel blockers [11–13]. To the best of our knowledge this is the first time where a bridged polycyclic derivative of type **3** has been synthesized under solvent free conditions.

In the case of using ethyl acetoacetate ($CH_3-CO-CH_2-COO-C_2H_5$) instead of acetylacetone ($CH_3-CO-CH_2-CO-CH_3$) as a starting material in this reaction (remain salicylaldehyde), the Biginelli product can also be an oxygen-bridged compound. But the chemical yield was lower and the reaction time was longer. It should be noted that in continuation of our research work we will use ethyl acetoacetate and thiourea as new starting materials for this reaction.

B. Structure characterization using TOFMS

1. The molecular ion

An evident peak at m/s 246.0999 Da was found (Table III) in the mass spectrum, which corresponds to the molecular ion **M**, $[C_{13}H_{14}N_2O_3]^{\cdot+}$ (calc. 246.1004 Da, 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 abundance (R.A.) of molecular ion M is 10%, which indicates the oxygen-

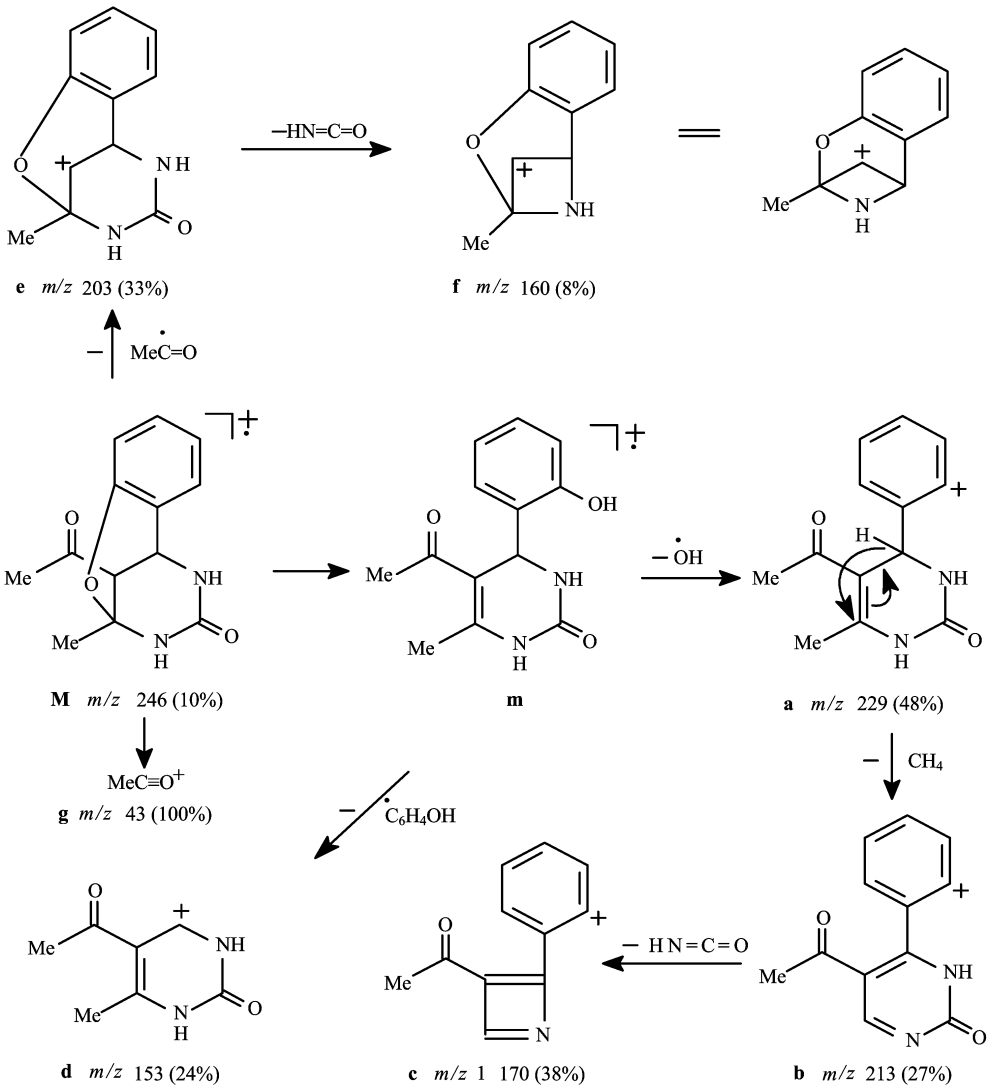


FIG. 1 Fragmentation pathway of compound **3**

bridged compound **3** is fairly stable under 70 eV EI condition.

2. Fragmentation

Significant peaks with accurate masses in EI mass spectrum of compound **3** examined are summarized in Table III, and the possible fragmentation pathways are shown in Fig. 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 **M** 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 then is 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 characteristic cleavage for dihydropyrimidinones [7]. Loss of MeC=O radical from **M** afforded cation **e** at m/z 203 (33%), $[C_{11}H_{11}N_2O_2]^+$, 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 **g** by an α-cleavage from **M**. As shown in Fig. 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.

IV. CONCLUSION

We have described an efficient, high yield 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. Furthermore, we confirmed the structure as an oxygen-bridged compound rather than a free hydroxyl dihydropyrimidinone using the detailed information from NMR and TOFMS spectra.

V. ACKNOWLEDGMENT

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