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STUDY OF LITHIUM ALUMINIUM HYDRIDE REDUCTION OF 5-ACETYL-1,6-DIMETHYL-4-PHENYL-3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONE †

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Abstract. *In this paper, we investigated the $LiAlH_4$-reduction of 5-acetyl-1,6-dimethyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (N-methylated Biginelli compound). Following the reduction and SiO_2-promoted dehydration, (Z)-5-ethylidene-1-methyl-6-methylene-4-phenyltetrahydropyrimidin-2(1H)-one was isolated as the major product (33% yield). Chromatographic separation of the reaction products also allowed us to isolate (yield in parentheses) and fully spectrally characterize: 1,6-dimethyl-4-phenyl-5-vinyl-3,4-dihydropyrimidin-2(1H)-one (20%), 5-ethyl-1,6-dimethyl-4-phenyl-3,4-dihydro-pyrimidin-2(1H)-one (9%), 5-(1-hydroxyethyl)-1,6-dimethyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (5%). A possible mechanism explaining the formation of these products is proposed.*

Key words: *Biginelli product, $LiAlH_4$-reduction, dehydration, NMR spectroscopy, structural elucidation*

1. INTRODUCTION

Biginelli compounds (3,4-dihydropyrimidin-2-(1*H*)-ones[1] and the corresponding thiones), derived from the acid-catalyzed condensation of a *β*-keto carbonyl compound, aldehyde and (thio)urea building blocks, have enjoyed a massive surge of popularity for an entire century since the discovery by Pietro Biginelli (Li and Corey, 2005). The DHPM scaffold is featured in a wide range of medicinally important compounds (Kappe, 2000a). For example, monastrol, the most well-known DHPM molecule, arrests cells in

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[1] The acronym DHPM has also been adopted for this class of compounds and is often used in literature.

mitosis by specifically inhibiting Eg5, a member of the Kinesin-5 family, and is considered a lead compound in the search for new anti-cancer drugs (Li and Corey, 2005). The scope of the Biginelli reaction can be significantly broadened by a variation of all three building blocks, giving access to combinatorial libraries of densely functionalized molecules in a single synthetic step (Kappe, 2000b).

We showed recently that $LiAlH_4$-reduction of Biginelli compounds can lead to additional molecular diversification (Zlatković and Radulović, 2016). The reduction of 1-(*N*)-methylated Biginelli compounds gave the corresponding alcohols (4-aryl-5-hydroxymethyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-ones) which readily dehydrated (under weakly acidic conditions) to vicinal bis(*exo*-methylene) derivatives. We also showed that the reduction with $LiAlH_4$ of a Biginelli compound derived from acetyl acetone(5-acetyl-1,6-dimethyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one, **1**) gave the corresponding 5-(1-hydroxyethyl)-1,6-dimethyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (**2**) as the major product; we did not, however, identify any of the side products of the reaction nor did we investigate dehydration of alcohol **2**. This paper intends to close the gap left in our previous report. Thus, our aim was to isolate and spectrally characterize products formed during the reduction ($LiAlH_4$) of compound **1** and subsequent dehydration of compound **2**. Also, we propose a plausible mechanistic pathway for the formation of these compounds.

2. MATERIALS AND METHODS

2.1. General

All chemicals were obtained from Sigma-Aldrich (St. Louis, USA) or Carl Roth (Karlsruhe, Germany) and were used as purchased, with the exception of solvents which were redistilled before use in an all glass apparatus. All reactions were performed in oven-dried glassware under an atmosphere of dry nitrogen. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III spectrometer (Bruker, Fällanden, Switzerland) operating at 400 and 100.6 MHz, respectively. 2D experiments (NOESY, and gradient HSQC and HMBC) were run on the same instrument with the built-in Bruker pulse sequences. NMR spectra were measured at 25 °C in $CDCl_3$ with tetramethylsilane (TMS) as an internal reference. Chemical shifts (δ) are reported in parts per million and referenced to tetramethylsilane (δ_H = 0 ppm) in ^{1}H NMR spectra and/or to solvent signals (residual $CHCl_3$: δ_H = 7.26 ppm, and $^{13}CDCl_3$: δ_C = 77.16 ppm) in heteronuclear 2D spectra. Scalar couplings are reported in hertz (Hz). Elemental microanalysis of carbon and hydrogen was carried out with a Carlo Erba 1106 microanalyzer (Carlo Erba, Milan, Italy) and their results agreed favorably with the calculated values. Mass spectra were recorded on a Hewlett Packard 5975B mass selective detector coupled with a Hewlett Packard 6890N gas chromatograph equipped with a fused silica capillary column DB-5MS (5% phenylmethylsiloxane, 30 m x 0.25 mm, film thickness 0.25μm, Agilent Technologies, USA). The injector and interface were operated at 250 °C and 320 °C, respectively. Oven temperature was raised from 70 °C to 310 °C at a heating rate of 5 °C/min and then isothermally held for 10 min. As a carrier gas, He at 1.0 mL/min was used. The samples (1 mg per 1 mL of an appropriate solvent) were injected in a pulsed-split mode (the flow was 1.5 mL/min for the first 0.5 min and then set to 1.0 mL/min throughout the rest of the analysis; split ratio, 40:1). MS Conditions: ionization voltage, 70 eV, acquisition mass

range, 35–650 amu, scan time, 0.32 s. Preparative medium-pressure liquid chromatography (MPLC) was performed with a pump module C-601 and a pump controller C-610 Work-21 pump (Büchi, Flawil, Switzerland) and was carried out on pre-packed column cartridges (40 mm × 75 mm, silica-gel 60, particle size distribution 40–63 μm, Büchi, Flawil, Switzerland). Pre-coated Al silica gel plates (Kieselgel 60 F_{254}, 0.2 mm, Merck, Germany) were used for analytical TLC analyses. The spots on TLC plates were readily visualized by UV light (254 nm) and by spraying with vanillin-sulfuric acid reagent (6% vanillin [w/v] and 1% H_2SO_4 [v/v] in ethanol) followed by short, gentle heating.

2.2. $LiAlH_4$ reduction of 5-acetyl-1,6-dimethyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (1) and the isolation of products 2-5

Biginelli product **1**(244 mg, 1 mmol)[2] was suspended in 10 mL of diethyl ether with the aid of ultrasound (5 min), and lithium aluminium hydride (5 mmol, 190 mg) was slowly added in the course of 5 min. The reaction mixture was stirred under an atmosphere of nitrogen for 3 h and the excess of $LiAlH_4$ was decomposed by successive addition of H_2O (0.5 mL), 15% NaOH aq. soln (0.5 mL), and again H_2O (0.5 ml). The mixture was extracted with CH_2Cl_2, dried over anhydrous $MgSO_4$ and evaporated *in vacuo*. The raw products were dissolved in 5 ml of ethyl acetate, after which 2.5 g of silica gel was added, and the mixture was refluxed for 15 min. After the removal of the solvent, the product absorbed on silica gel was charged on top of a column of silica gel and was flushed with ethyl acetate-hexane (1:2, v:v) mixture. Products **2**-**5** were separated in this way.

*5-(1-hydroxyethyl)-1,6-dimethyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one* (**2**): Yield: 12 mg (4.9%). Spectral data of this compound were consistent with the data already published in Zlatković and Radulović (2016).

*5-ethyl-1,6-dimethyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one* (**3**): Yield: 20 mg (8.8%).^{13}C-NMR (100.6 MHz, $CDCl_3$)[3]: δ = 13.0 (C-9), 14.3 (C-7), 23.0 (C-8), 29.8 (-NMe), 58.2 (C-4), 111.2 (C-5), 126.9 (C-2′), 127.0 (C-4′), 128.7 (C-3′), 129.1 (C-6), 143.6 (C-1′), 154.5(C-2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.85 (3H, *t*, *J*= 7.5 Hz), 1.80 (1H,*dq*, *J*=15.0, 7.5 Hz, H-8), 1.94 (3H, H-7), 2.01 (1H,*dq*, *J*=15.0, 7.5 Hz, H-8), 3.16 (3H, NMe), 4.73 (H-4), 5.34 (1H, NH), 7.22-7.34 (5H, ArH). EI-MS (*m/z*, rel. int.): 230 (M^+, 16), 153 (100), 201 (51).

*1,6-dimethyl-4-phenyl-5-vinyl-3,4-dihydropyrimidin-2(1*H*)-one* (**4**): Yield: 45 mg (19.7%). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 14.3 (C-7), 30.2 (NMe), 54.4 (C-4), 110.5 (C-5), 111.0 (C-9), 126.4 (C-2′), 127.9 (C-4′), 128.9 (C-3′), 131.2 (C-8), 135.0 (C-6), 142.5 (C-1′), 154.3 (C-2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 2.17 (3H, s, H-7), 3.21 (3H, *s*, NMe), 4.85 (1H, *d*, *J* = 17.2 Hz, H-9 *trans* to H-8), 4.90 (1H, *d*, *J* = 11.2 Hz, H-9 *cis* to H-8), 5.11 (1H, *d*, *J* = 2.8 Hz, H-4), 5.52 (1H, *br s*, NH), 6.62 (1H, *dd*, *J* = 17.2, 11.2 Hz, H-8), 7.22-7.35 (5H, ArH).EI-MS (*m/z*, rel. int.): 228 (M^+, 30), 227 (18), 151 (100).

*(Z)-5-ethylidene-1-methyl-6-methylene-4-phenyltetrahydropyrimidin-2(1*H*)-one* (**5**): Yield: 75 mg (32.9%). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ = 14.0 (C-9), 30.3 (NMe), 52.1 (C-4), 88.4 (C-7), 123.0 (C-8), 125.6 (C-2′), 127.6 (C-4′), 128.8 (C-3′), 131.1 (C-5), 141.4 (C-1′), 144.0 (C-6), 153.6 (C-2); ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.87 (3H, *s*, H-9), 3.12 (3H, *s*, NMe), 4.09 (1H, *br s*, H-7_{out}), 4.40 (1H, *br s*, H-7_{in}), 5.26 (1H, *d*, *J* = 4.4

[2]5-acetyl-1,6-dimethyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one was prepared according to the procedure in our previous study (Zlatković and Radulović, 2016).

[3] The numbering scheme used in this paper can be found in Fig. **1**.

Hz, H-4), 6.17 (1H, *s*, H-8), 6.17 (1H, *br s*, NH), 7.19-7.38 (5H, ArH). EI-MS (*m/z*, rel. int.): 228 (M^+, 42), 227 (14), 151 (100).

3. RESULTS AND DISCUSSION

3.1. Reduction of 5-acetyl-1,6-dimethyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (1)

As we have already shown (Zlatković and Radulović, 2016), $LiAlH_4$-reduction of Biginelli compound **1** leads to the formation of alcohol **2** as the major product. The relative stereochemistry (*S**, *R**) of this product was not addressed in this study but was assigned according to Zlatković and Radulović (2016). Dehydration of alcohol **2** does not occur in a significant extent during the reaction workup or during chromatography when the sample is "wet-loaded" onto a SiO_2 column. However, we noticed that during dry-loading at elevated temperatures, silica gel acts as an acid catalyst and induces dehydration.

Raw reaction products of $LiAlH_4$-reduction of compound **1** were without prior separation subjected to dehydrating condition by refluxing them ethyl acetate in the presence of silica gel at *ca*. 77 °C. The obtained mixture was chromatographed on a silica gel column and compounds **2**-**5** were isolated in pure state. A small, residual amount of alcohol **2** was recovered (less than 5%), and the overwhelming majority of the products (> 60%) comprised dehydration products **3**-**5**.

A possible mechanism that would account for the formation of compounds **3**-**5** is given in Fig. 1. All reactions proceed through a common intermediate, the conjugated iminium cation **i**. Michael addition of a hydride to C-8 in **i** leads to the formation of compound **3**. Acid-catalyzed dehydration of alcohol **2** gives diene **5** as the product; this is probably a result of proton loss from intermediate **i** (Fig. 1). Finally, two possible pathways could be proposed for the formation of compound **4** – it formed either from diene **5** via a [1,5]-hydride shift or by tautomerism of **i**, or both paths could be operational. It is very likely that at least small amounts of **4** are generated from **i** – we observed that a $NaBH_4$-reduction of compound **1** yielded compound **4** (yield: *ca*. 5%) as the sole dehydration product when the reaction is quenched by a base. This ruled out compound **5** as the precursor of **4**, since acidic conditions are necessary for the formation of diene **5**.

3.2. Structural elucidation of compounds 3-5

The structure of compound **3** was solved in a straightforward manner since it was analogous to the structure of 5-ethyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (the reduction product of a urea-derived Biginelli compound) that we have previously synthesized and spectrally characterized (Zlatković and Radulović, 2016). An additional signal (at 29.8 ppm, originating from the -NMe group from the methylurea block) was observed for compound **3** in its ^{13}C-NMR spectrum. Protons attached to this carbon correlated in the HMBC spectrum to both C-2 and C-6 (δ154.5and 129.1, respectively, Fig. 2) atoms across 3 bonds; the chemical shift of C-5 (δ 111.2) carbon was assigned from its coupling with H-9 methyl group. Finally, H-8 hydrogens (a pair of diastereotopic protons) showed cross-peaks in the HMBC spectrum with two sp^2 carbons (C-5 and C-6).

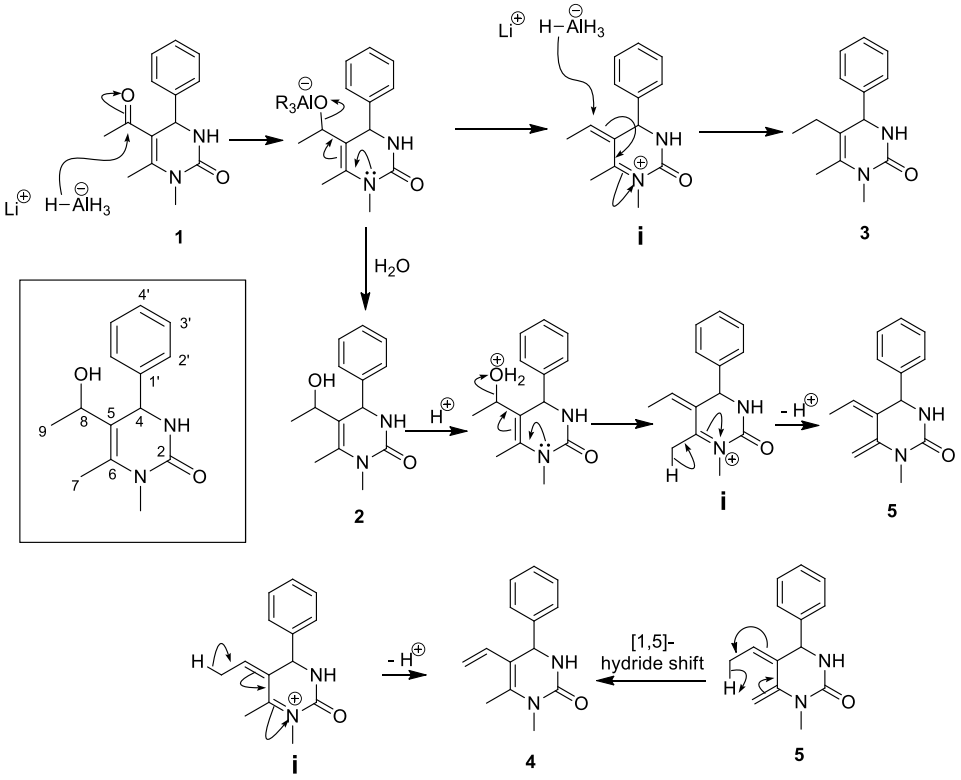

Fig. 1 A proposed mechanism scheme for the formation of products **2**-**5**.
Carbon-numbering scheme used in this study is illustrated on compound **2**.

The presence of a vinyl group in compound **4** was immediately obvious from the proton signal at 6.62 ppm. This signal was split (coupling constants of 17.2 and 11.2 Hz) as a result of *trans* and *cis* coupling with terminal alkene protons attached to C-9; H-9 atoms correlated in the HMBC spectrum with C-5 carbon; the remaining quaternary carbon (C-6) could also be assigned from its correlation in the HMBC spectrum; it showed cross-peaks with H-7 and -NMe methyl protons.

The connectivity in diene **5** was easily inferred from its 2D spectra: *exo*-methylene protons at C-7 coupled to C-5 and C-6 carbons; the third proton attached to a double bond (H-8, *quartet*) was split with a vicinal *J*-value and also showed correlations with C-5 and C-6 atoms. The only uncertainty left, the stereochemistry of C(5)=C(8) double bond was resolved with data from the NOESY spectrum – H-9 protons (δ 1.87) and the proton at 4.40 ppm showed a correlation which is possible only if both were oriented inwards, i.e. we concluded that the double had a *Z*-stereochemistry.

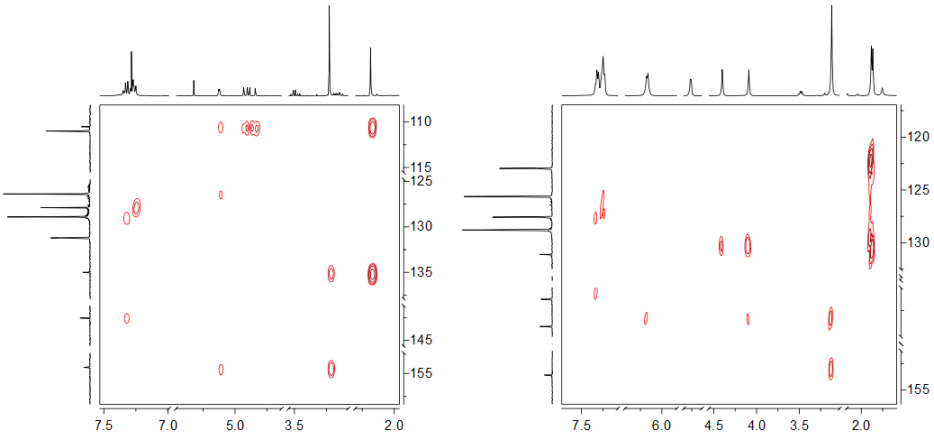

Fig. 2 HMBC spectra (expanded regions) of compounds **4** and **5**

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REDUKCIJA5-ACETIL-1,6-DIMETIL-4-FENIL-3,4-DIHIDROPIRIMIDIN-2(1*H*)-ONA LITIJUM-ALUMINIJUM-HIDRIDOM

*U ovom radu ispitana je redukcija 5-acetil-1,6-dimetil-4-fenil-3,4-dihidropirimidin-2(1*H*)-ona (*N*-metilovanog Biđinelijevog proizvoda) litijum-aluminijum-hidridom. Kao najzastupljeniji proizvod reakcije, nakon redukcije I dehidratacije na silica gelu, izolovan je (*Z*)-5-etiliden-1-metil-6-metilen-4-feniltetrahidropirimidin-2(1*H*)-on u prinosu od 33%. Hromatografskim razdvajanjem prečišćeni su I ostali proizvodi:4-fenil-1,6-dimetil-5-vinil-3,4-dihidropirimidin-2(1*H*)-on (prinos: 20%), 5-etil-1,6-dimetil-4-fenil-3,4-dihidropirimidin-2(1*H*)-on (9%) i5-(1-hidroksietil)-1,6-dimetil-4-fenil-3,4-dihidropirimidin-2(1*H*)-on (5%). Predložen je mogući mehanizam koji objašnjava nastajanje ovih proizvoda.*

Ključne reči: *Biđinelijev proizvod, redukcija litijum-aluminijum-hidridom, dehidratacija, NMR spektroskopija, određivanje strukture*