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On water synthesis of the novel 2-oxo-1,2,3,4-tetrahydropyrimidines

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ABSTRACT

A simple *on water* approach for the synthesis of novel tetrahydropyrimidine (THPM) derivatives has been developed under a green and sustainable fashion. For the first time, a deuterated Biginelli's hybrid was synthesized. Novel THPMs are suitable for further derivatization and could be an excellent toolkit for lead-oriented synthesis and/or cross-coupling reactions.

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1. Introduction

The Biginelli reaction is well-known multicomponent reaction through which is possible to access 2-oxo- and 2-thioxo-1,2,3,4-[former tetrahydropyrimidines-THPMs name 34dihydropyrimidine-2(1H)-ones(thiones)]. This reaction was found by Pietro Biginelli in 1893 [1]. Since then, the synthetic potential of the mentioned reaction has been ignored, and this discovery has been put undercover by the scientific community. In the second half of the 20th century (1980s) a significant exploration of Biginelli chemistry started after decades of silence and disregarding that discovery. The principal reason for this action was the discovery in the terms of great and broad biological potential that Biginelli's products possess. From the 1980s until now, over 70 000 Biginellilike compounds have been synthesized (source SciFinder). A significant number of THPM derivatives have been found to be potent calcium-channel blockers, antihypertensive agents, adrenergic antagonists, mPGES-1 inhibitors, antimicrobials, anticancer, and antivirals agents [2-4]. They were also used as a tool for combinatorial [5] as well as material science [6–8]. From a structural point of view, the Biginelli reaction is attractive because substituents attached at THPM core can be readily transformed into

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https://doi.org/10.1016/j.tet.2020.131790 0040-4020/© 2020 Elsevier Ltd. All rights reserved. different functional groups required for some further synthetic manipulation. Considering, many different methods and catalysts have been applied for accessing THPMs [9]. Almost all the THPM derivatives were synthesized directly *via* one-pot fashion [10,11]. Although there were six diversity points at the THPM core (N1, C2, N3, C4, C5, and C6) that could be furthermore functionalized, the most interesting seemed to be the derivatization of the substituent at the C6 position (Fig. 1, methyl group). Functionalization (bromination) of the methyl group from THPM was easily reached by substitution reaction, giving the 6-bromomethyl and 6-dibromomethyl THPM derivatives as products [12,13]. Another way implies catalytic olefination of a methyl group at the C6 using benzaldehyde under high temperature, hazardous solvents, and catalysts consumption [13–15].

Therefore, the behavior of THPM core under hydrolytic conditions was very interesting (Fig. 1) [16–20]. Pietro Biginelli noted that the presence of KOH (in water under reflux) initiated deep decomposition of the THPM core into benzaldehyde, ammonia, and potassium carbonate [1]. Lately, Zigeuner showed that the N₁-unsubstituted THPMs were inactive under the hydrolytic conditions (5% KOH, reflux) [19,20]. Also, some data showed that the THPM can react with excess benzaldehyde and KOH in boiled 70% EtOH, while the appropriate product was isolated in moderate yield (<50%). It was also published that the N₁-unsubstituted THPMs can easily undergo to hydrolysis/decarboxylation process giving a





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Fig. 1. Derivatization of THPM at C6 position.

complicated mixture of the products [17]. Based on the literature survey, we also found some contradictory data in Dhankar and Shutalev results [16,18], although both reactions were done under nearly the same hydrolytic conditions (Fig. 1). Shutalev and Aksinov performed the reaction to obtain product **A** (Fig. 1) by boiling two equivalents of THPMs in 2.5% sodium hydroxide water solution without loading the aldehyde [18]. Lately, Dhankar performed the reaction under the same fashion, but with the stronger alkaline conditions (5% and 10% aq. NaOH), obtaining product **B** [16]. At the same time, Kappe discussed the poor reactivity of ester group of THPMs towards the hydrolysis [21]. So, many available data are limited and there is a need for further investigations in this area.

Taking into account disagreements between the reported results and our interest in green [22–25] and Biginelli chemistry [26–29], we investigated the reactivity towards hydrolysis of such an important position (methyl at C6) at THPM core in reaction with different aromatic aldehydes.

2. Results and discussion

Our investigations began with conditions screening. For the model reaction, we used **1a** (1eq.), benzaldehyde (1eq. of **2a**'), and two equivalents of different bases (LiOH, NaOH, KOH, K₂CO₃, Li₂CO₃ and Cs₂CO₃) under *on water* and solvent-free mode (Table 1).

All the applied modes that included the application of all bases at room temperature produced product in traces. However, under higher temperature conditions (70 °C), the best yields were obtained *via on water* fashion, for all applied bases. Among applied

| Table 1 | | | | |
|--------------|--------|----------|-------------|--|
| Optimization | of the | reaction | conditions. | |

| Base | Yields of 3a' (%) | | |
|---------------------------------|-------------------|--------------|--|
| | on water | solvent-free | |
| LiOH | 47 | _ | |
| NaOH | 84 | <10 | |
| КОН | 77 | <10 | |
| K ₂ CO ₃ | 51 | - | |
| Li ₂ CO ₃ | <10 | - | |
| Cs ₂ CO ₃ | <10 | - | |
| | | | |

bases, the best yields for 3a' were noted when applied NaOH (84%), KOH (77%) or K₂CO₃ (51%) at 70 °C through 4 h reaction time. Other bases gave lower yields compared to NaOH for the same temperature and reaction time. In the next experiments, we loaded 10 and 20eq. of NaOH to investigate the effects of base excess on the yields. Achieved results indicated that the excess of sodium hydroxide does not have an influence on the yield of **3a'**. Synthesis of **3a'** in low concentration of aqueous sodium hydroxide solution (0.75%) was investigated. Therefore, under this reaction mode yield of 3a' was significantly lower (42%). The crucial effect on the yield has had the concentration of applied base and temperature. In further experiments, instead of THPM methyl ester (1a) we explored the reactions between ethyl (1b), benzyl (1c), and allyl (1d) esters with 2a' in the presence of 2eq. NaOH. As expected, lower yields were achieved (75%, 71%, and 81% of 3a' for applied 1b, 1c, and 1d, respectively) compared to ones obtained applying methyl ester 1a.

Respecting optimization, the best-yielding reaction condition was as follows: 1a (5 mmol), 1eq. of 2a' (5 mmol) and 2eq. of NaOH (10 mmol, 7.5% aq. solution) via on water at 70 °C through 4 h. To demonstrate the substrate scope of the method, we applied optimized reaction conditions to the other aromatic aldehydes (Fig. 2) and THPMs (Fig. 3). After a simple work-up (see ESI), the newly synthesized products were isolated and characterized (Figs. S1-S19). The structures and isolated yields of products 3a'-i' are outlined in Fig. 2. Generally, good-to-excellent yields were noted, but the best yield was realized for **3h'**. Also, in the case of utilization THPMs 1a" and 1b" in reaction with 2a', good yields of targeted products 3a'a" and 3a'b" were achieved (Fig. 3). Taking into account that investigated reactions have been done under on water fashion, it is reasonable to explore the destiny of protons from water molecules [30]. In order to track the route of protons through the reaction, the next experiment was carried out using NaOD/D₂O instead of NaOH/H₂O. To our delight, deuterated THPM **3a'-d₂** was isolated in good yield (82%), proving the role of protons from water (Fig. 4). In addition, the same deuteration manner appeared using NaOH/D₂O. Based on NMR spectra, two protons and their appropriate carbons peaks disappeared due to deuteration (Figs. S24-S27). Because of the presence of deuterons in the molecule 3a '-d2, signals of adjacent protons (benzylic and benzylidene) were simplified into a singlet. However, we assumed that H/D exchange

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= methyl (a, 84%), ethyl (b, 75%), benzyl (c, 71%), allyl (d, 81%)

Fig. 2. General outline for the synthesis of 3a'-i'; reaction conditions as follow: 1 (5 mmol), 1eq. of 2a'-i' (5 mmol) and 2eq. of NaOH (10 mmol, 7.5% aq. solution) at 70 °C.



Fig. 3. Olefination of different THPMs (1a'', 1b'') with 2a'.



Fig. 4. On-D₂O synthesis of **III-d** and **3a**'- d_2 (top); Proposed mechanism, deuterons are given in red.

happened between 3a' and D_2O , on the organic-water interface. Hence, we explored the control reaction by investigating isotopic labeling properties of protons in 3a' skeleton under optimized conditions. However, protons in 3a' did not display exchangeable properties, approving that direct conversion of 3a' into $3a'-d_2$ in NaOD/D₂O was not possible (Fig. 4).

We proposed that the deuteration most likely took place during the formation of some stable intermediates which were formed on the reaction path. Hence the control experiments were performed in NaOD/D₂O, and intermediate III-d was isolated (Figs. 4, S28 and S29). Also, nondeuterated intermediate III was obtained by using NaOH/H₂O (Figs. S30 and S31). Using system NaOD/D₂O in refluxing CD₃OD inseparable mixture of deuterated and nondeuterated THPM were produced in very low yields [17]. Mentioned facts and achieved results imply that reaction of THPMs with NaOH needed to carry out under on water fashion and at the same time in the absence of organic solvents. Also, the presence of deuterons in the final product pointed out that the reaction probably involved interfacial proton transfer from water to intermediate (III-d), and then to the product $(3a'-d_2)$ at the organic-water interface. Considering the experimental examinations and the results, we proposed a followed mechanistic path (Fig. 4). In the first step, 1a

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underwent hydrolysis to producing **I**. Then, the intermediate **I** underwent the decarboxylation through **II**, giving intermediate **III-***d*. Finally, **III-***d* formed carbanion **IV**, that in reaction with carbonyl moiety from aldehyde forms **V**, that gave product **3a**'-*d*₂.

Molecular structures of **3a**' and **3e**' are confirmed by singlecrystal X-ray analysis (Fig. 5). Both compounds crystallized in the triclinic space group P-1 but only **3a**' incorporates one molecule of DMSO in the asymmetric unit of the unit cell. Regardless of this structural difference in crystal state and the fact that DMSO forms a relatively strong N1–H···O2 hydrogen bond with **3a**' molecule (see Fig. 5 and Table S2), both compounds exhibit similar conformation (Fig. S32). Namely all atoms in **3a**' and **3e**' are placed in two planes. The smaller plane is defined by the C5–C10 phenyl ring while the rest of the atoms define another plane. These two parts of molecules are interconnected through the C4–C5 bond which is the longest C–C bond in both crystal structures (See Table S1).

The spatial orientation of the C5–C10 phenyl ring regarding the six-membered heterocyclic ring is very similar in both compounds (Fig. S32). Thus the C3–C4–C5–C6 torsion angle is -84.0(3)and $-84.5(2)^{\circ}$ in **3a**' and **3e**' respectively. The crystallographic analysis also confirmed that the C11-C12 bond [1.333(4) and 1.327(3) Å in **3a**' and **3e**' respectively] has a double bond character in both structures. Corresponding N-C bonds (N1-C1 vs. N2-C1 and N1-C2 vs. N2-C4) in two molecules display some differences in bond lengths (Table S1) and it can be explained by the influence of C4 which is only sp³ hybridized atom. Both compounds form centrosymmetric dimers in the crystal lattice with two molecules interconnected by two relatively strong N-H…O1 hydrogen bonds (Table S2). The main difference between the two molecules is that they use different N-H groups for hydrogen bonding within the dimers (Fig. S33). The geometrical parameters of all hydrogen bonds are given in Table S2.

3. Materials and methods

3.1. General experimental procedures

Tetrahydropyrimidines 1a-d, 1a" and 1b" were synthesized following our published method [27]. Aromatic aldehydes and sodium deuteroxide solution were purchased from Sigma. The melting points (mp) were determined on a Mel-Temp apparatus and are uncorrected. The NMR spectra of compounds (Figs. S1-S31) were performed in DMSO-d₆ on a Varian Gemini 200 MHz NMR spectrometer (¹H at 200 and ¹³C at 50 MHz). Abbreviations for the NMR signal that were used are: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, m = multiplet, and br. s. = broad singlet. Mass spectrometry was performed by Waters Micromass Quattro II triple quadrupole mass spectrometer and MassLynx software for control and data processing. Electrospray ionization in the positive mode was used. The electrospray capillary was set at 1.0 kV and the cone at 5 V. The ion source temperature was set at 140 °C and the flow rates for nitrogen bath and spray were 500 l/h and 50 l/h, respectively. The collision energy was 10 eV.

3.2. General procedures for synthesis 3a'-i', 3a'a'', 3a'b'' and $3a'-d_2$

In 25 ml round-bottom flask 5 ml 7.5% NaOH water solution (2eq., 10 mmol, 0.400 g in 5 ml) and temperature raised to 70 °C. Then, 5 mmol of aromatic aldehyde and 5 mmol of appropriate THPM were added. The reactants swam on water and the reaction mixture was stirred for 4 h. Reaction progress was followed by TLC. Target products fall out as solid, then hot mixture was filtered off, washed with 50% ethanol, and dried in vacuum. The same procedures for the synthesis of $3a'-d_2$ were used, but with the



Fig. 5. Crystal structure and atom-numbering scheme of 3a' (top) and 3e' (bottom). Displacement ellipsoids are drawn at the 40% probability level. Hydrogen bonds between molecule 3a' and DMSOare shown in light blue dotted lines.

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exception that instead of NaOH/H2O we applied NaOD/D2O at 70 $^\circ\text{C}$ through 12 h.

3.3. Synthesis of intermediate III and III-d

In 10 ml round-bottom flask benzaldehyde (1 mmol) and THPM **1a** (1 mmol) were added in 2 ml 7.5% NaOH/H₂O (for synthesis of **III**) or NaOD/D₂O (for synthesis of **III-d**) at 70 °C. To track decarboxylation in both reactions, every half hour ¹H NMR spectra were recorded. Then, reactions mixtures after cooling down, were filtrated, and washed with 50% ethanol, and dried in vacuum, to give products **III** or **III-d**. the Products were recrystallized from mixture EtOAc/MeOH (3:1).

4. Conclusion

In summary, an elegant, catalyst-free, and green synthesis of novel tetrahydropyrimidines (THPMs) *via on water* fashion has been developed. In the majority of cases, good-to-excellent yields were achieved. The synthesized compounds possess disubstituted benzylidene fragments that are exclusively found as *E*-isomers. This feature makes the benzylidene decorated THPMs especially interesting for the future application in cross-coupling chemistry. During deuterium labeling experiments, two deuterated compounds (intermediate and target product) were isolated proving the presence of the reactive anionic species on the reaction path. From 1893 (the discovery of THPM by Biginelli) to the present, only a few attempts demonstrate the reactivity of THPM core towards hydrolysis. Bearing in mind that among the published results have been disagreements, we believe that the presented results are of great importance for the future development of Biginelli's chemistry.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2020.131790.

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