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A new highly regioselective method for the synthesis of water-soluble 1,3,4-trisubstituted derivatives of tetrahydropyrimidin-2(1H)-one

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Abstract

In this article, we report a regioselective method for the synthesis of new water-soluble 1,3,4-trisubstituted tetrahydropyrimidin-2(1*H*)-one derivatives containing sodium methanesulfonate fragment in the first position of the heterocycle. The method is based on the reaction of (1-(3,3-diethoxypropyl)ureido)methanesulfonate with aromatic and heterocyclic nucleophiles. The proposed method is distinguished by the possibility of obtaining a wide range of water-soluble substituted tetrahydropyrimidinone derivatives,

the absence of the need to use expensive metal complex catalysts, high product yield, and ease of purification.

Keywords

tetrahydropyrimidin-2(1*H*)-one; electrophilic substitution; *C*-nucleophiles; acetals

Introduction

Currently, cyclic ureas are increasingly being used in the treatment of various diseases in humans and animals [1]. Substituted derivatives of tetrahydropyrimidin-2(1*H*)-one are of particular importance. In 1985, Dieter Seebach demonstrated that *N*,*N*'-dimethylpropylene urea can be used as a polar aprotic organic solvent, thereby replacing hexamethylphosphoramide, which exhibits carcinogenic properties [2–4]. The inhibitory effect of compounds of this class on various enzymes should be noted (Figure 1). Thus, tetrahydropyrimidinones are inhibitors of tubulin (PPB-SOs) [5], HIV protease [6,7], TACE inhibitors [8], and factor Xa [8]. At the same time, the compound shown in Figure 1 is currently under clinical trials (the code name TAK-442). It is quite remarkable that 1,3,4-trisubstituted tetrahydropyrimidinones exhibit antiarrhythmic properties [9], this disease (arrhythmia) affects millions of people around the world [10,11]. However, in a pandemic caused by the SARS-CoV-2 virus, people suffering from cardiac arrhythmia are more susceptible to a complex course of the disease, which often leads to death [12]. In this regard, the development of convenient methods for the synthesis of 1,3,4-trisubstituted tetrahydropyrimidinones is currently very relevant.

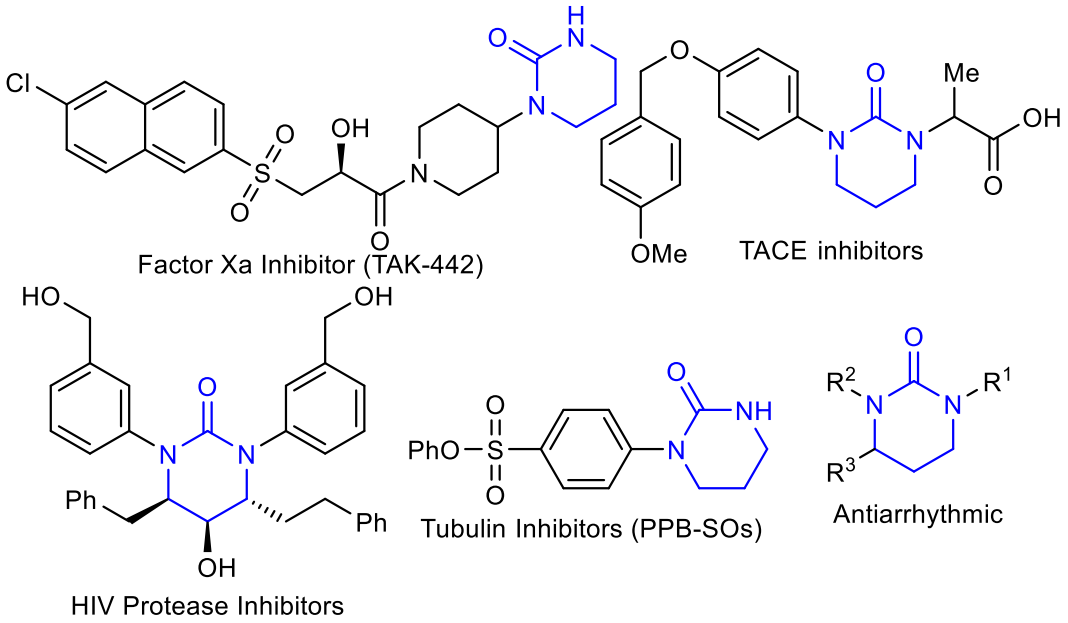


Figure 1: Tetrahydropyrimidin-2-ones of biological importance.

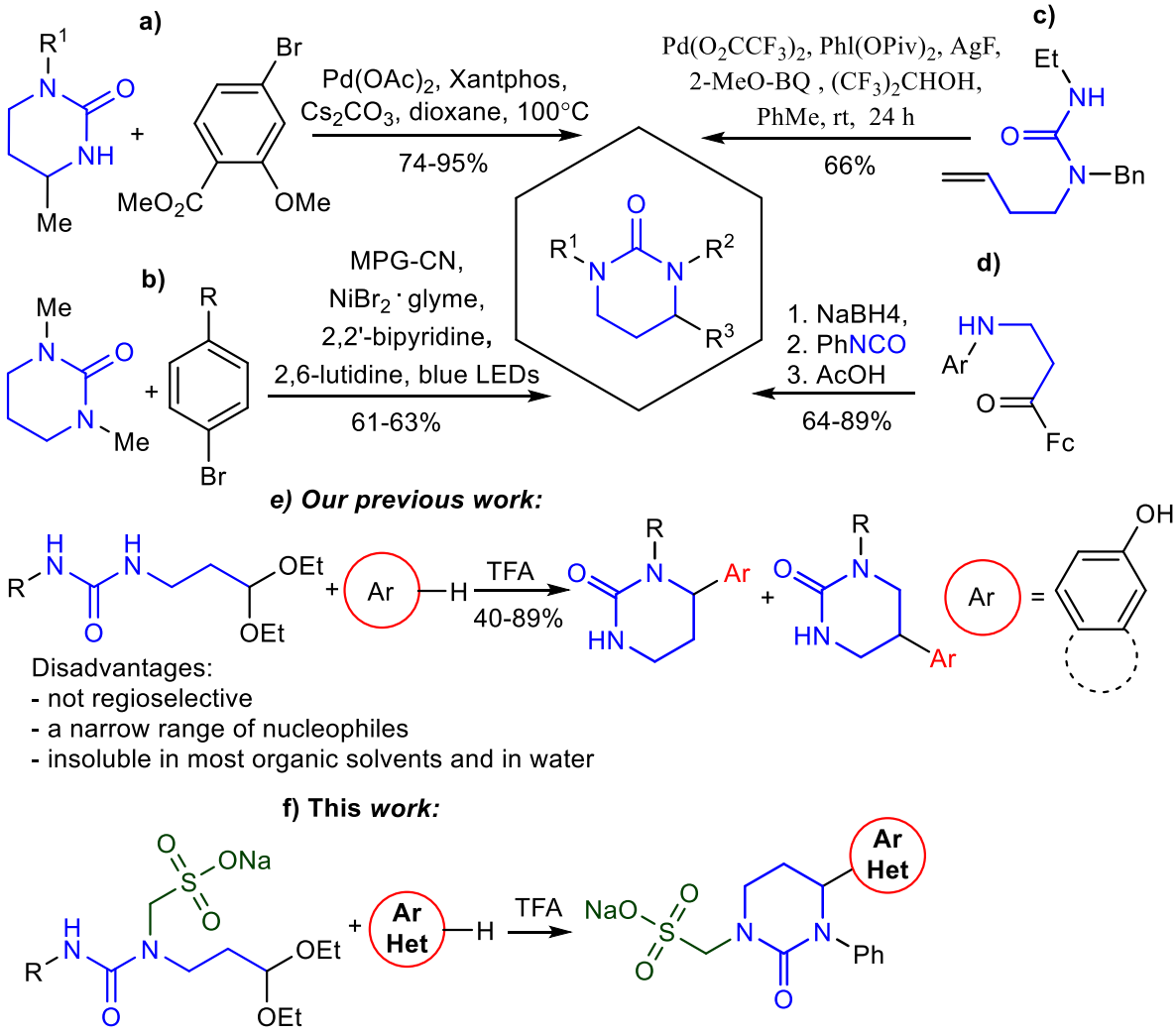
Methods for the synthesis of 1,3,4-trisubstituted tetrahydropyrimidinones can be combined into two large groups. The first group includes methods based on the functionalization of the tetrahydropyrimidine ring (Scheme 1, *a*, *b*) [13,14]. However, this method has a number of disadvantages that limit its wide application in practice. So it is necessary to first obtain a tetrahydropyrimidinone containing substituents either at the nitrogen atoms or at the 4 position of the heterocycle.

The second approach, on the contrary, is based on the closure of acyclic precursors. In 2013, Liu and co-workers (Scheme 1, *c*) described Pd-catalyzed regioselective intramolecular aminofluorination of alkene containing a urea moiety, which lead to 1,3,4-trisubstituted tetrahydropyrimidinone [15]. More recently, the Vukicevic group (Scheme 1, *d*) developed a method for the synthesis of ferrocenyl-containing tetrahydropyrimidinones based on the reduction of amino ketones to amino alcohols, followed by interaction with phenyl isocyanate and cyclization of the resulting urea [16].

Significant disadvantages of the above approaches are the need to use expensive metal-containing catalysts, as well as the need for preliminary synthesis of the starting

compounds with the corresponding functional groups. Therefore, methods requiring inexpensive, readily available reagents and catalysts are of particular interest.

Previously, we developed method of the synthesis of 1,6-disubstituted tetrahydropyrimidin-2(1*H*)-one based on the acid-catalyzed reaction of 1-(3,3-diethoxypropyl) urea derivatives with aromatic nucleophiles (Scheme 1, *e*) [17]. It should be noted that only phenols were used as nucleophiles. A more significant disadvantage of the tetrahydropyridinones obtained in this way is low regioselectivity of the process. The resulting 1,6-disubstituted products had low solubility in most organic solvents and in water as the most important solvent in terms of their potential biological activity.



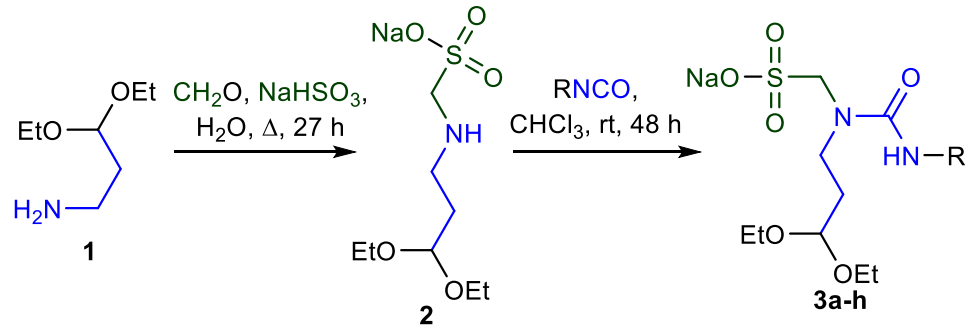
Scheme 1: Synthesis of tetrahydropyrimidin-2(1*H*)-ones.

In this article, we describe a regioselective method for the synthesis of new water-soluble 1,3,4-trisubstituted tetrahydropyrimidinones 4 containing a sodium

methanesulfonate moiety (Scheme 1, *f*). The method is based on the Mannich-type reaction of sodium (1-(3,3-diethoxypropyl)ureido)methanesulfonate with various aromatic and heterocyclic *C*-nucleophiles. An important advantage of the proposed method for the synthesis of potentially biologically active substances is water solubility and the ability to vary widely the substituents at the nitrogen atom and at the carbon atom in the 4 position.

Results and Discussion

We began our study with the synthesis of starting ureas 3 according to a well-known method [18]. By reacting 3,3-diethoxypropan-1-amine **1** with formaldehyde and sodium hydrosulfite in water, sodium ((3,3-diethoxypropyl)amino)methanesulfonate **2** was obtained. The interaction of amine **2** with aryl isocyanates made it possible to obtain sodium (1-(3,3-diethoxypropyl)ureido)methanesulfonates **3a-h**, which were used without further purification (Scheme 2).

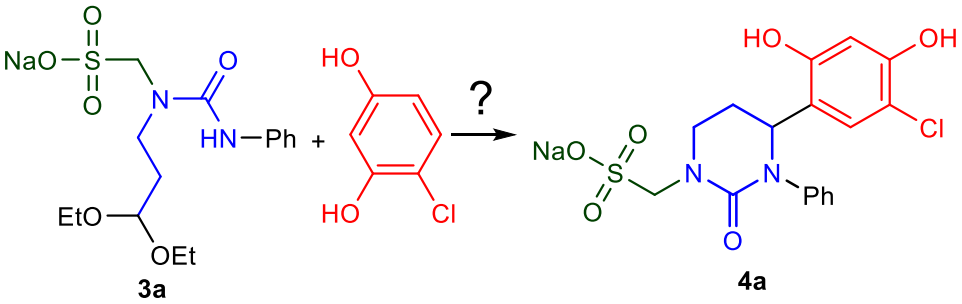


R = Ph (a), 4-ClC_6H_4 (b), 4-MeC_6H_4 (c), 4-$MeOC_6H_4$ (d), 4-FC_6H_4(e), 3-ClC_6H_4 (f), 3-MeC_6H_4 (g), -CH_2-CH_2Cl (h)

Scheme 2: Synthesis of acetals **3**.

Next, we optimized the reaction conditions using acetal **3a** and 4-chlororesorcinol (Scheme 3, Table 1). Since the role of "Green Chemistry" has increased in recent years, we have chosen water as a solvent. Concentrated hydrochloric acid was used as a catalyst. Carrying out the reaction, both at room temperature and at boiling, led to difficult-to-separate mixtures (Table 1, No. 1,2). All attempts to isolate the compounds

individually have not been successful. In this case, the formation of target heterocyclic compounds was not observed. When the reaction was carried out in chloroform at room temperature using trifluoroacetic acid as a catalyst, the formation of tetrahydropyrimidin-2(1*H*)-one **4a** occurred in low yield (Table 1, No. 3). Increasing the reaction temperature did not lead to an increase in the yield of the product (Table 1, No. 4). In this regard, we increased the amount of trifluoroacetic acid by 13 times, which unexpectedly led to an increase in the yield of the target compound to 74% (Table 1, No. 5). An increase in the amount of trifluoroacetic acid to 26 eq made it possible to increase the product yield to 93% (Table 1, No. 6). Thus, these reaction conditions turned out to be optimal.



Scheme 3: Reaction of acetal **3a** and 4-Chlororesorcinol.

Table 1: Screening of the Conditions for the Reaction between acetal **3a** and 4-Chlororesorcinol[a].

Entry	Solvent, temp	Catalyst	Yield[b] (%)
1	H_2O, rt	aq HCl	-
2	H_2O, reflux	aq HCl	-
3	$CHCl_3$, rt	TFA (1 equiv)	36
4	$CHCl_3$, reflux	TFA (1 equiv)	27
5	$CHCl_3$, rt	TFA (13 equiv)	74
6	$CHCl_3$, rt	TFA (26 equiv)	93 (88[c])

[a]**Reaction conditions**: to a mixture of 0.5 g (1.3 mmol) acetal and 0.19 g (1.3 mmol) 4-chlororesorcinea in 20 mL of solvent a catalyst was added, stirred at room temperature for 24 h, or boiled for 10 h.

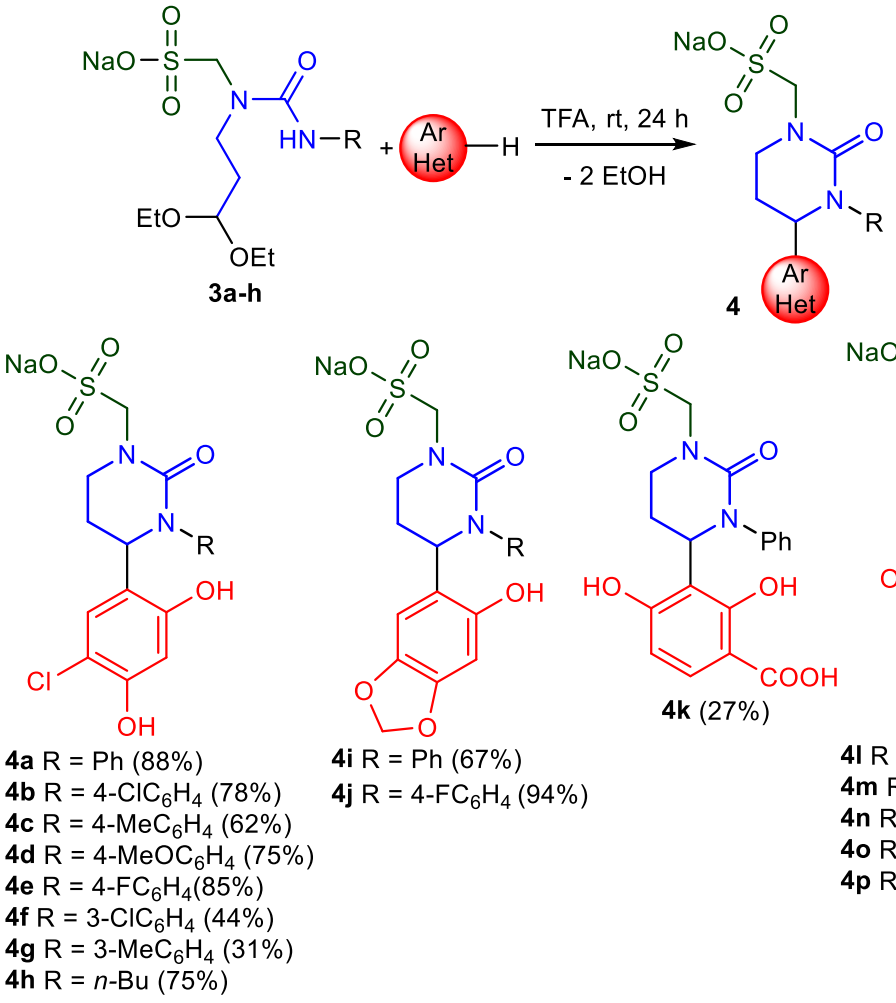
[b]According to NMR data.

[c]Isolated yield.

Next, we studied the interaction of ureas **3b–h** with various phenols (Scheme 4), which are components of various biologically active compounds [19–22]. In all cases, the reaction gave the desired tetrahydropyrimidin-2(1*H*)-ones **4a-k** in good to high yield. The lowest yield of the product was obtained for compound **4k**, which is probably due to a decrease in the nucleophilicity of β-resorcylic acid due to the presence of a strong electron-withdrawing group in the phenol molecule.

No direct correlation was observed between the yields and substituents in the aryl moiety of the starting ureas. However, it was observed that the presence of substituents in the *m*-position of the aryl moiety in ureas contributed to a significant decrease in the yield of the product.

We found that, in addition to aromatic nucleophiles, the heterocyclic analog of phenols, 4-hydroxy-6-methyl-2*H*-pyran-2-one, which is part of the antibiotic Myxopyronins [23] and the anti-inflammatory drug Phaeochromycin A [24], can enter into the reaction. Thus, the reaction of ureas **3** with 4-hydroxy-6-methyl-2*H*-pyran-2-one in chloroform in the presence of trifluoroacetic acid at room temperature led to the formation of tetrahydropyrimidinones series **4l-p**. It should be noted that, as in the previous case, the presence of substituents in the *m*-position of the aryl moiety in ureas also contributed to a decrease in the yield of the product.



4a R = Ph (88%)
4b R = 4-ClC$_6$H$_4$ (78%)
4c R = 4-MeC$_6$H$_4$ (62%)
4d R = 4-MeOC$_6$H$_4$ (75%)
4e R = 4-FC$_6$H$_4$(85%)
4f R = 3-ClC$_6$H$_4$ (44%)
4g R = 3-MeC$_6$H$_4$ (31%)
4h R = *n*-Bu (75%)

4i R = Ph (67%)
4j R = 4-FC$_6$H$_4$ (94%)

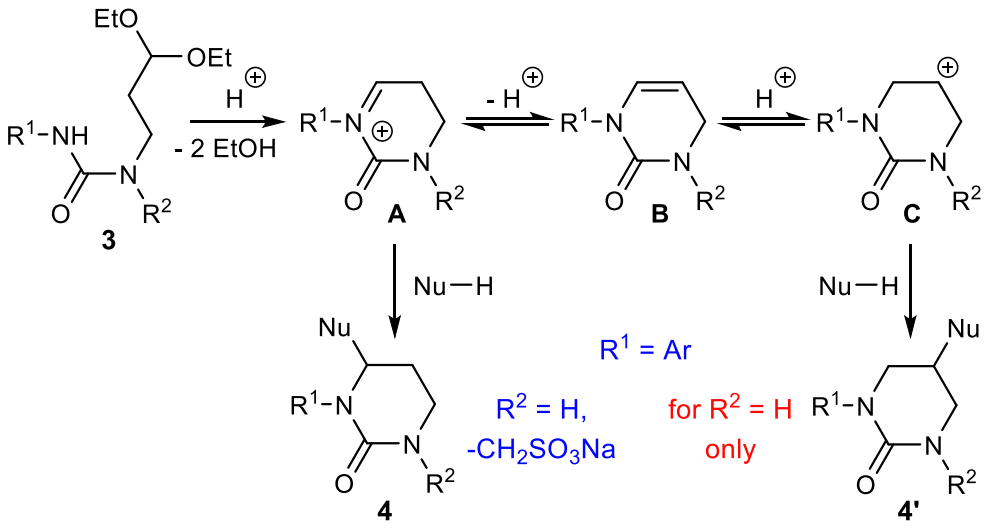
4k (27%)

4l R = Ph (88%)
4m R = 4-ClC$_6$H$_4$ (47%)
4n R = 4-MeOC$_6$H$_4$ (79%)
4o R = 4-FC$_6$H$_4$ (85%)
4p R = 3-ClC$_6$H$_4$ (29%)

Scheme 4: Reaction of acetal **3** with *C*-nucleophiles.

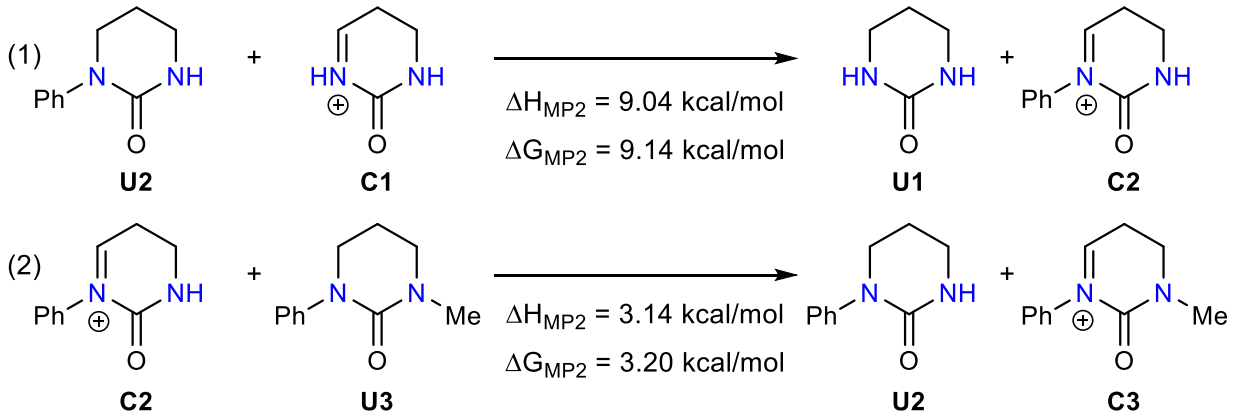
As was noted above, the reaction of ureas **3** with (hetero)aromatic nucleophiles may lead to two regioisomeric products **4** and **4'**. The presumable mechanism of this reaction is depicted on the Scheme 5 [17]. The key step of the reaction is the intramolecular cyclization of the starting urea to give the cyclic acyliminium cation **A**. Further interaction of the cation **A** with (hetero)aromatic nucleophile via the conventional S_EAr mechanism provides the compound **4**. The formation of the regioisomeric compound **4'** may be rationalized by the deprotonation of the iminium ion **A**, which results in the enamide **B**. The re-protonation of the enamide **B** furnishes the carbocation **C**, which subsequently reacts with the nucleophile to give the final regioisomer **4'**. It is of a special note, that the latter process was observed for the previously described *N*-unsubstituted ureas **3** only [17]. No compounds **4'** were detected in present work and the reaction furnished tetrahydropyrimidines **4** exclusively.

Obviously, the relative concentrations of the cations **A** and **C** in the reaction mixture depend on the a) the rate of the deprotonation of the iminium cation **A** and b) the relative stabilities of the cation **A** and **C**. Assuming that the deprotonation of the iminium cation **A** is associated with a relatively low energy barrier [25], the stabilities of the cations should have the greatest impact on the regioisomers distribution.



Scheme 5: Plausible mechanism for the formation of the tetrahydropyrimidinones **4** and **4'**

We speculated that the difference in the regioisomeric outcome of the previously described reaction [17] and the reaction reported herein is due to the presence of the methylsulfonyl substitutuent in the ureas **3a-h**. In order to reveal the influence of the substituents at the nitrogen atoms on the stability of the 2-oxo-2,3,4,5-tetrahydropyrimidin-1-ium cation **A** two isodesmic reactions were designed (Scheme 6). The unsubstituted tetrahydropyrimidin-2-one **U1**, 1-phenyltetrahydropyrimidin-2-one **U2** and 1-methyl-3-phenyltetrahydropyrimidin-2-one **U3** were chosen as the model compounds alongside with corresponding iminium ions **C1-3**. Quantum chemistry calculations were performed for all model compounds at the MP2/6-311+G(d,p) theory level. All optimizations were followed by frequency calculations at the same level of theory in order to check that optimized structures really correspond to true minima. All calculations have been performed with the Gaussian 16 package [26]. The obtained changes in free Gibbs energies and enthalpies for the designed reactions are given on Scheme 6. As seen from the obtained data, the phenyl-substituted iminium ion **C2** is more stable compared to the fully unsubstituted cation **C1** by *ca* 9 kcal/mol (Scheme 6, reaction (1)). This is not of great surprise, taking into account the well-known delocalization of the positive charge across the π-system of aryl moiety. More interestingly, the heat of isodesmic reaction (2) and the change in free Gibbs energy appeared to be 3.14 kcal/mol and 3.20 kcal/mol, respectively. Thus, the presence of methyl substituent at the second nitrogen atom leads to the additional stabilization of the iminium ion **C3**. This is not immediately evident result, given that this substituent is located three bonds away from the cationic center. The more detailed investigation of this phenomenon is underway.



Scheme 6: Designed isodesmic reactions and changes in free Gibbs energy and enthalpy as obtained from quantum chemistry calculations (MP2/6-311+G(d,p), Gaussian 16)

Overall, the obtained results suggest that the *N,N'*-disubstituted tetrahydropyrimidinium ions are more stable compared to their monosubstituted counterparts. Thus, the higher regioselectivity of the reaction in case of ureas **3a-h** may be attributed to this fact.

Conclusion

Thus, we have shown that not only aromatic but also heterocyclic compounds can be used as nucleophiles in the reaction with (3,3-diethoxypropyl)urea derivatives, which made it possible to synthesize water-soluble 1,3,4-trisubstituted derivatives of tetrahydropyrimidine-2(1*H*)-one. Unlike most known approaches to the synthesis of such compounds, the described reaction proceeds under mild conditions, does not require the use of expensive metal complex catalysts, and makes it possible to obtain the target compounds in one stage, without the need to isolate intermediate products.

Experimental

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 600 spectrometer at operating frequency (600 MHz and 150 MHz, respectively) with respect to the residual

proton signals of deuterated solvents (DMSO-d_6). The IR spectra were recorded on a Vector 22 Fourier spectrometer by Bruker in the range of 400-4000 cm^{-1}. Crystalline samples were studied as a suspension in vaseline oil. The melting points were determined in glass capillaries on a Stuart SMP 10 instrument**.** Quantum chemistry calculations were performed with the Gaussian 16 package [26]. Initial structures were fully optimized at the MP2/6-311+G(d,p) theory level. All optimizations were followed by frequency calculations at the same level of theory in order to check that optimized structures really correspond to true minima.

General procedures for the synthesis of acetals 3a-h*.*

13 g (124 mmol) of sodium hydrosulfite were added to 12 mL of 37% formaldehyde solution, and the reaction mixture was boiled for 7 h, then 18 mL (124 mmol) of 3,3-diethoxypropan-1-amine **1** was added and boiled for 20 h. Then the solvent was evaporated in vacuo. 2 g (7.6 mmol) of amine **2** was taken, dissolved in 20 mL of chloroform, 7.6 mmol of isocyanate was added, the mixture was stirred at room temperature for 48 h. The solvent was evaporated in vacuo, acetal **3** was used without further purification.

General procedures for the synthesis of tetrahydropyrimidin-2(1H)-ones 4a-q**.**

To a solution of 1.3 mmol of acetal **3** in 20 mL of chloroform 1.3 mmol of the corresponding nucleophile and 2 mL of trifluoroacetic acid were added, and the reaction mixture was stirred for 24 h at room temperature. Then the solvent was removed in vacuo, the residue was washed with 30 mL of diethyl ether. Additionally, the product was recrystallized in acetone, the resulting white powder was dried in vacuum.

Supporting Information

See Supporting Information File 1 for full experimental data

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