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Water-tuned tautomer-selective tandem synthesis of the 5,6-dihydropyrimidin-4(3*H*)-ones driven under the umbrella of the sustainable chemistry

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ABSTRACT: The selective synthesis of 5,6-dihydropyrimidin-4(3*H*)-one scaffold (precursor of dihydrouracil) was a quite difficult synthetic challenge which has not been achieved so far. For the first time, in this paper, green, selective and high-yields approach to forty novel 5,6-dihydropyrimidin-4(3*H*)-ones (DHPMs) by one-pot reaction of aldehydes, Meldrum's acid and isothioureas under solvent-free conditions in the presence of water as an additive is presented. In the majority of cases, introduced methodology gave an unprecedented tautomer-selective fashion towards targeted compounds with excellent tautomeric purity (>99.9%), which reached 100% in few cases. The molecular structure of the five compounds has been determined by X-ray crystallography. In each one of them very short length for the corresponding N2–C1 bond was noticed, making them especially structurally interesting. This experimental fact can imply a highly localized electron π density in this part of each heterocyclic ring. The obtained experimental results which figure out from NMR and ESI-MS study indicate that this Biginelli-type reaction smoothly proceeds in a one-pot mode, pointing out to the three-step tandem process

going via Knoevenagel, aza-Michael and retro-Diels-Alder reactions. The presented strategy also was followed by advantages: reduction amount of waste, excellent values of green chemistry metrics (cEF, EcoScale and GCIS) and it is a first eco-friendly strategy towards to DHPMs scaffold.

Keywords: Biginelli-Atwal reaction; solvent-free; dihydrouracil; diazoles; tautomer-selective; short C=N bond; green metrics

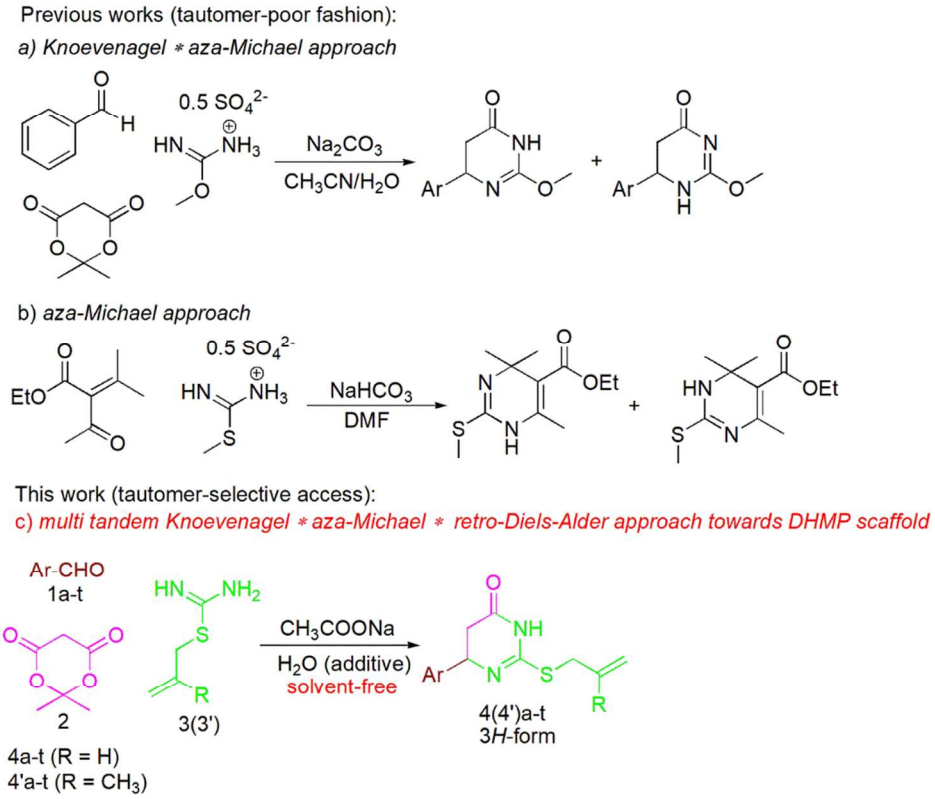
Introduction

Since the conventional chemical manufacturing processes for preparing of different pharmaceutical and other relevant molecules produces large amounts of waste and toxic by-products[1] it is essential to develop methods which satisfy green principle.[2,3] All chemical transformations should be promoted in eco-friendly medium with advantages such as the easy work-up, nontoxicity, nonflammability and high heat capacity.[4] To realize these requirements, synthesis of some important compounds is performed in water,[5] ionic liquids,[6] lemon juice,[7] bio-based chemicals[8] and supercritical fluids[9] as an environmentally friendly and sustainable medium. The last few years especially appealing are reactions under solvent-free conditions, driven by grindstone[10-13] or "in the presence of water" methodology.[14-16] Generally, the reactions carried out under mentioned conditions displayed shorter reaction times, higher yields and selectivity, reduction of reaction waste when compared with the same processes carried out in some organic solvents. An additional bonus of solvent-free chemistry consists in the fact that it avoids the serious environmental concerns associated with the traditional methods, as well as in possibility to perform the multigram scale synthesis of important bioactive compounds.[17]

Dihydropyrimidinones (DHPMs) are an important class of heterocyclic compounds in medicinal chemistry, due to their diverse pharmacological activities, which occupied the attention of many scientists.[18-21] They exhibit different biopotentials, such as antimitotic,[22] antiproliferative,[23] and cytotoxic activities.[24] For some DHPMs, it has been found to be antivirals and antibacterial, adrenergic receptor antagonists, calcium channel modulators and mitotic kinesin inhibitors.[25] Some DHPMs such as risperidone and paliperidone (9-hydroxy-risperidone) are applied for the treatment of schizophrenia.[26,27] The pyrimidine-based compounds, containing the conjugated π-system display fluorescent properties and are successfully used as electronic and photonic materials.[28-30] Most of DHPMs, earlier described in the literature, were prepared via very

important Biginelli multicomponent reaction under acid-catalyzed conditions.[31-34] However, Atwal proposed a different approach to obtained DHPMs in 1987, which allowed using of isouronium salts and enones under basic conditions.[35,36]

Traditional methods leading to DHPM scaffold via Atwal's modification of Biginelli reaction have been carried out in hazardous, toxic organic solvents and reagents such as acetonitrile,[37] ethanol/Et_3N,[38] dimethylacetamide,[39] trifluoroacetic acid[39] and *N*-methyl-2-pyrrolidone.[40] Previously, all these methods have led to undesirable drawbacks such as complicated two steps procedures, difficult isolation, the application of special apparatus (*e.g.*, microwave irradiation), limited-scope procedure, *etc*.



Scheme 1. Different strategies towards dihydropyrimidine scaffolds.

The crucial DHPMs scaffold is 5,6-dihydropyrimidin-4(3*H*)-one which presents backbones or toolkit to access dihydrouracil, that is well-known as an intermediate in the catabolism of uracil,[41] one of the fundamental building block of life. In earlier published method few examples of the 5,6-dihydropyrimidin-4-ones were observed as a mixture of prototropic tautomers with

very unfavorable purity **(Scheme 1**, **a**).[37] In one variation of Biginelli-Atwal reaction poor selectivity has been achieved (**Scheme 1**, **b**).[42] Both protocols carried out with solvents indicate that high tautomer purity (≥99%), in Atwal's modification of Biginelli reaction, was quite problematic synthetic challenge and it has not been achieved so far. Bearing in mind mentioned facts, our combined experiences and interest in green[43,44] and multicomponent synthesis[45-47] prompted us to explore, develop novel and at the same time greenness synthetic strategy for the synthesis of 6-aryl-5,6-dihydropyrimidin-4(3*H*)-ones on a highly tautomer-selective manner.

To our delight, we wish to report the highly tautomeric pure synthesis of forty novel 6-aryl-5,6-dihydropyrimidin-4(3*H*)-ones (**4a-t** and **4'a-t**) "in the presence of water" under soft basic solvent-free conditions (**Scheme 1**, **c)**.

Results and Discussion

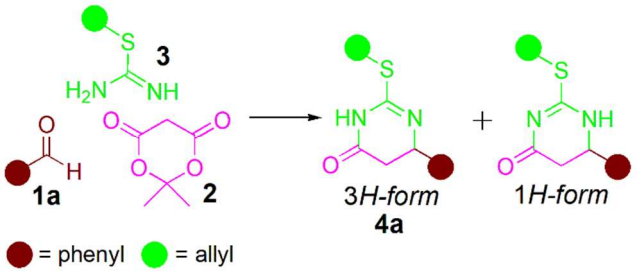
A simple, green, efficient, and convenient solvent-free method for the soft base catalyzed synthesis of forty novel 6-aryl-5,6-dihydropyrimidin-4(3*H*)-ones (**4a-t** and **4'a-t**) from different aldehydes (**1**), Meldrum's acid (**2**) and S-allyl- (**3**) or S-methallyl isothiourea (**3'**) in the presence of water as additive in mortar with pestle is depicted on **Scheme 1**.

Following our goal to develop green and selective methodology towards DHPMs with the significant reduction of waste we started with a screening of reaction conditions where the reaction of benzaldehyde **1a** with **2** and **3**, was selected as a model reaction to produce **4a** (Table 1).

We first explore the applicability of various bases followed with a thermal setup to find the high-yielding methodology which driven by grindstone solvent-free methodology. In the light of this, some weak bases such as $NaHCO_3$, Na_2CO_3, CH_3COONa and [Bmim][HCO_3] were used. Unfortunately, after homogenization 1 and 1.5 eq. of $NaHCO_3$, Na_2CO_3, CH_3COONa with above-mentioned substrates under solvent-free conditions at room temperature appropriate Knoevenagel's adduct as sole product in moderate yields was obtained. Same happened when we added 5 eq. of each base at 50 ^oC, none of these reactions led to the targeted products even after a long time of grinding. Nevertheless, the catalytic amount (20 mol%) of soft base ionic liquid (IL) [Bmim][HCO_3] at 50 ^oC produced targeted products but in low yields (**Table 1**, entry 1) after complicated workup. Then, under thermal screening and with addition of 100 mol% of IL yields

were slightly better at 70 °C and 100 °C but still unsatisfactory (entry 2 and 3, up to 42%). This manner was followed with moderate tautomeric purity (by NMR 3H : 1H= 79:21). As a last resort, we performed reactions "in the presence of water", so the next experiments were conducted with 0.5 mL of water as an additive and 1 eq. $NaHCO_3$, Na_2CO_3 and [Bmim][HCO_3]. For all of them, we achieved moderate yields of targeted compound (up to 52%). Although these bases provided appropriate product, by using of 20 mol% of CH_3COONa in the presence 0.5 mL of water through 3h significantly better yields (entry 4, 91% of **4a**) were achieved that combined with exclusively tautomer-purity 3H : 1H = 99.9% : 0.1% for **4a** (**Figure S81**).

Table 1. Conditions screening



Entry	Conditions[a]	Isolated yield of **4a** (%)	3*H*:1*H*[d] (%)
1	[Bmim][HCO_3] 20 mol%, 50 °C	24	n.d.
2	[Bmim][HCO_3] 1 eq., 70 °C	27	n.d.
3	[Bmim][HCO_3], 1 eq., 100 °C	42	79 : 21
4[b]	CH_3COONa H_2O (0.5 mL)	91	99.9 : 0.1
5	CH_3COONa H_2O (0.75 mL)	88	99.1 : 0.9
6	CH_3COONa H_2O (1.0 mL)	85	99.4 : 0.6
7	CH_3COONa H_2O (10 mL)[c]	-	-
8	CH_3COONa 20% aq. CH_3COOH	-	-
9	CH_3COONa 0.5 mL CH_3COOH, ^{i}PrOH or ^{t}BuOH	-	-
10	CH_3COONa, CH_3CN+H_2O (18 + 0.5	71	81 : 19

mL)

[a] Conditions in entries 7-9 are produces only Knoevenagel product, [b] Entries 4-10 carried out at 50 ^{o}C with 20 mol% of CH_3COONa, [c] water as solvent, and [d] ratio was determinate by using HPLC and NMR (entry 3 and 10).

Additionally, we investigated the effect of different quantity of water and type of proton source (alcohols and acid) under same conditions. Obtained results suggested that loading volume of water, which ranged from 0.5 mL to 1 mL (entry 4-6), did not have a significant effect on yields and purity of **4a**. We have also tested the effect of water as the solvent (entry 7) and under this condition appropriate Knoevenagel's adducts fall out of solution in nearly quantitative yields. By using acetic acid and its aqueous solutions as well as ^{i}PrOH and ^{t}BuOH as a proton source, sole Knoevenagel's product appeared (entry 8 and 9), without the presence of the traces of **4a**. Additionally, by varying the molar ratio of **3** and **1a**, from 1.5:1 to 2:1 we have not achieved any effect on yields. When optimal reaction conditions were applied in the solvent mixture (acetonitrile + water = 18mL+ 0.5mL) **4a** was isolated in moderate yield (71%) which followed with poor selectivity 3H : 1H = 81% : 19% (entry 11). Similar conditions when using acetonitrile result in an unfavorable mixture of products. Obtained results demonstrated the importance of the presence of water as an additive and at the same time pointed out to the advantage of solvent-free methodology. Results which are obtained from optimization screening clearly indicates that the optimal reaction condition was of 20 mol% CH_3COONa in the presence 0.5 mL of water at 50 ^{o}C with molar ratio 1:1. In addition, to check the reproducibility, the method was performed three times without any appreciable loss in terms of selectivity and yield of **4a**.

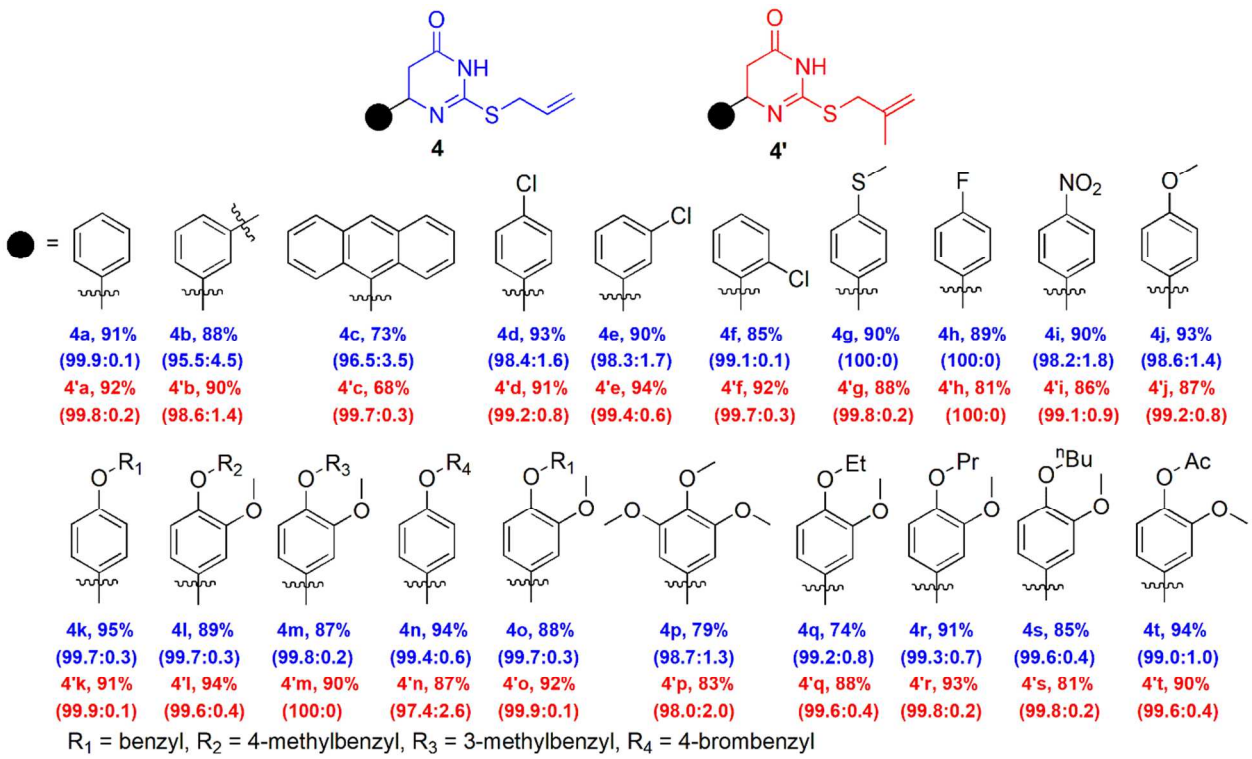


Figure 1. Structures, isolated yields (%) of **4a-t** and **4'a-t** and them purity which presented as ratio 3H : 1H in % (in brackets). Purity was determinate by using HPLC technique (see SI).

With optimized reaction conditions in hand, we evaluated the substrate scope regarding aldehydes and biazanucleophyles (**Scheme 1** and **Figure 1**). Initially, a wide range of different aldehydes **1b-t**, **2** and biazanucleophyles **3** or **3'** were subjected to optimized conditions and after simple workup, the newly-synthesized products were isolated.

The structures of obtained products **4a-t** and **4'a-t** are depicted in **Figure 1**. Generally, good-to-excellent yields were achieved, however, the best yield (95%) was achieved in the synthesis of **4k** from **1k**, **2** and **3**. Also, it was found that electron-donating as well as an electron-withdrawing group at aromatic rings of aldehydes did not have a significant impact on the yield of targeted products. For example, *p*-nitrobenzaldehyde **1i** (strong electron-withdrawing group) and *p*-methoxybenzaldehyde **1j** (electron-donating group) gave excellent yields for **4i**, **4'i**, **4j** and **4'j**: 90%, 86%, 93% and 87%, respectively. However, the exception was the aldehyde 1c which contains bulky anthracenyl group that led to lower yields of **4c** (73%) and **4'c** (68%), pointing that the presence of high steric hindrance lowered the reaction efficiency.

The forty newly-synthesized compounds (**4a-t** and **4'a-t**) were characterized by IR, NMR, MS and X-ray crystallography. The NMR (^{1}H and ^{13}C) spectra are given in Supporting Information (SI) (**Figures S1-S80**). The ^{1}H NMR data for all products shown slightly broadened singlet located in range 8.5-9.5 ppm related to imino N-H proton pointing that all products exist in 3H-form. In the crystalline state **4** and **4'** exists in the 3H-form according to X-ray crystallographic analysis (**Figure 3**). In addition, to determine purity (%) we separated and measured ratio 3H : 1H by using of LC-MS/MS (see SI). Obtained results indicate that our green methodology gave tautomer-enriched manner for access to the 5,6-dihydropyrimidin-4(3*H*)-ones with a measured ratio of 3H : 1H up to 99.9% : 0.1% (**Figures 1** and **S81-S120**). Especially, in few cases (**4g**, **4h**, **4'h** and **4'm**) absence of 1H-form was achieved. The tautomeric ratios remained unaffected standing in the solution and when the concentrations varied showing that N-H proton (3H-form) unlikely to tautomerize into 1H-form in solution. As support, unusually short C=N bond distance as explained in section with crystal structure description of five compounds points on an absence of electron π delocalization along N=C-NH fragment. As well-known, π-electron delocalization plays a crucial role in tautomeric systems and its presence or absence strongly influence on final tautomeric distribution.[48,49]

To elucidate the function of water as proton source in the synthesis we performed some control experiments. Consequently, we investigated the isotope labelling using deuterium oxide (instead of H_2O) in the hope that will give us valuable information how water contributed reaction. Under optimized conditions, we isolated **4a-*d*$_3$** as sole deuterated product and without unlabeled product **4a** (**Figure 2**). Compounds **2** and **3** did not show labelled properties in the control experiments under same conditions.

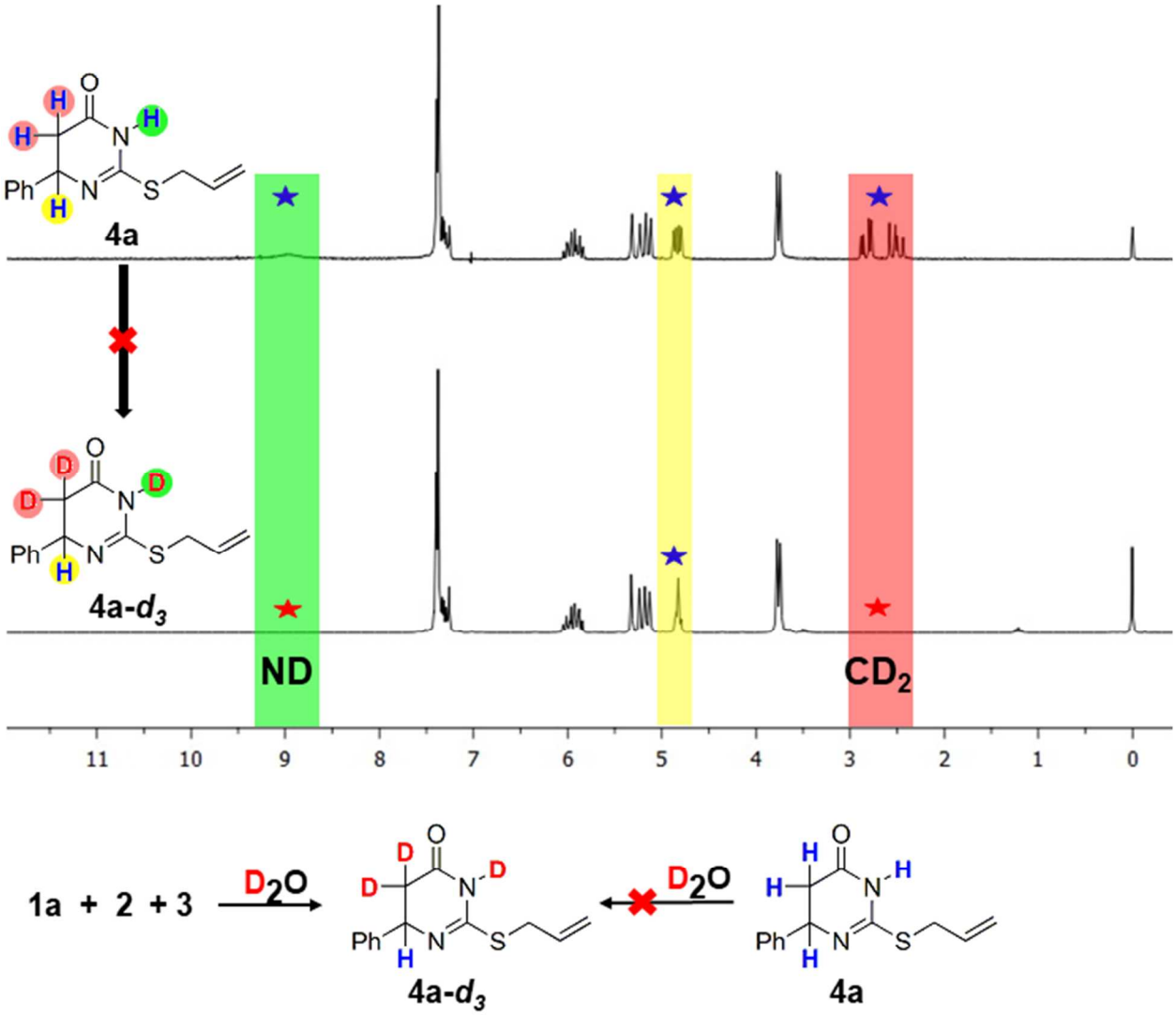
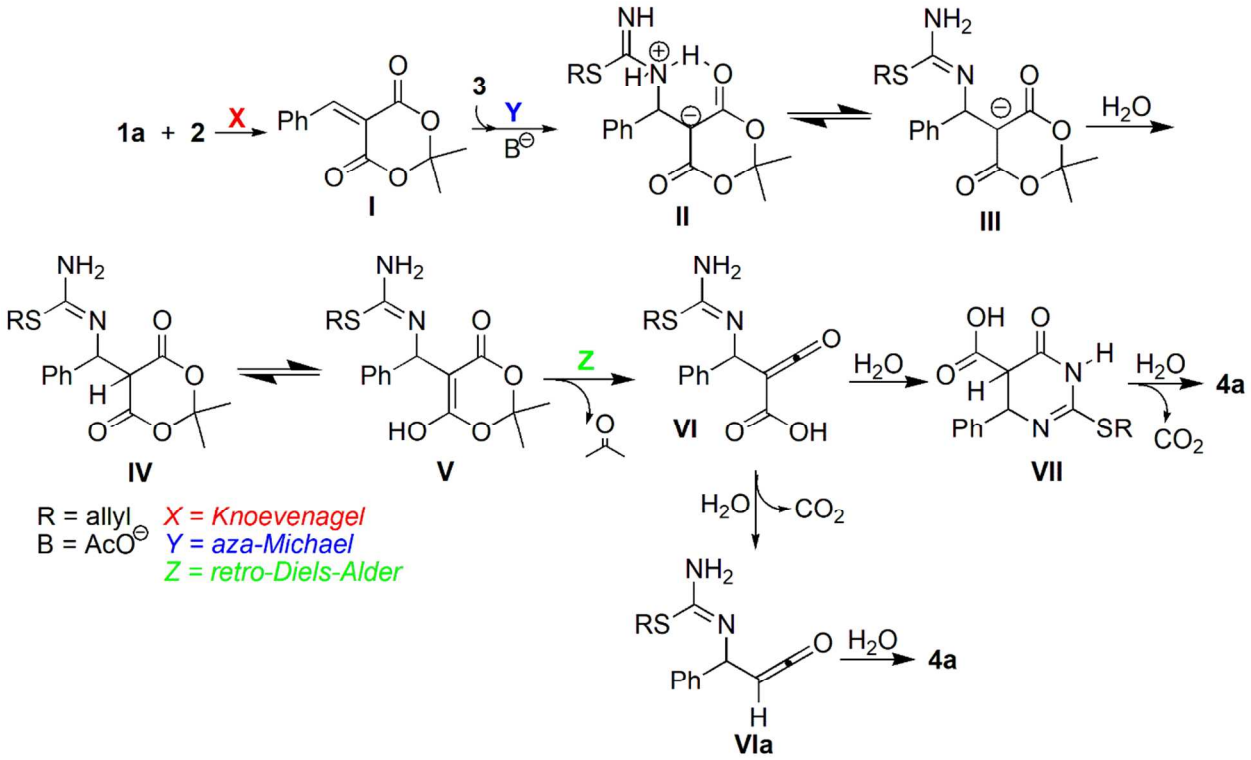


Figure 2. Overlap of ^{1}H NMR spectra of **4a** (top) and **4a-*d*$_3$** (bottom)

As can be seen from the overlap of ^{1}H (**Figure 2**) and ^{13}C NMR (**Figure S128**) spectra of **4a** and **4a-*d*$_3$** absence of an appropriate signal of α-methylene protons and appropriate carbons from CH_2CO fragment approve that *α*-carbon is fully deuterated. Then, the signal of a benzylic proton is simplified from doublet of doublet in **4a** into broadened singlet which appeared in **4a-*d*$_3$** (yellow shadow, **Figure 2**) pointing to the absence of through space CD_2-CHBz proton coupling (**Figure S130**), which we have already detected in NOESY spectra of **4a** (**Figure S129**). On the first look, although the reaction was driven under the solvent-free condition we have assumed

that H/D exchange happened between in situ formed **4a** and D_2O, on the solid-additive (water) surface to produce **4a-*d*$_3$**. Hence, we explore control reaction to investigated isotopic labelling properties of protons in **4a** skeleton under optimized conditions. Interestingly, however, protons in **4a** did not show exchangeable properties under solvent-free conditions approving that direct conversion of pre-formed **4a** into **4a-*d*$_3$** in the presence of D_2O was not possible (**Figure 2**). Additionally, in basic CD_3CN/D_2O solution, NH proton in **4a** showed isotopic labelling properties, however, α-methylene protons were not labelled (**Figure S132**). Considering, we proposed that the deuteration is most likely take place during formation some stable intermediates which are formed on the reaction path. To address this issue, we were monitored reaction mixture (**1a** + **2** + **3**) by using of ESI-MS technique in positive and negative mode (**Figure S131**).

Based on NMR and ESI-MS experimental observation we suggested followed mechanistic proposal (**Scheme 2**). On the starting point substrates (**1a** and **2**) are furnished benzylidene adduct **I** (*m/z* 233 $[M + H]^+$) over Knoevenagel reaction. Then it reacted with **3** via the aza-Michael step as a Michael acceptor releasing the hydrogen-bridged cyclic zwitter ion **II** (*m/z* 349 $[M]^+$). Intermediate **II** gave anionic intermediate **III** (*m/z* 349 $[M + H]^+$) which in the presence of water produces intermediate **IV** (*m/z* 349 $[M]^+$). Then, this one undergoes retro-Diels-Alder step (cycloreversion) to generate carboxyketene **VI** (*m/z* 291 $[M + H]^+$). Finally, carboxyketene have two possible destinies. The first one, it could be directly intramolecular trapped by nucleophilic NH_2 group furnishing *β*-keto acid **VII** (*m/z* 290 $[M]^+$), which suffers by intermolecular rearrangement, underwent elimination of CO_2 to afford **4a** (*m/z* 247 $[M + H]^+$). The second one, **4a** can occur via ketene **VIa** (*m/z* 246 $[M + H]^+$) which made over decarboxylation of carboxyketene **VI**. Carboxyketene has been detected as likely intermediate in the reaction of Meldrum's acids with nucleophilic reagents in multicomponent/domino process.[50]



Scheme 2. The proposed mechanism of the reaction.

Molecular and crystal structures of 4f, 4'c, 4'd, 4'g and 4's

The molecular structure of the compounds **4f**, **4'c**, **4'd**, **4'g** and **4's** (**Figure 3**) is determined by single-crystal X-ray diffraction analysis (**Table S1**). All five molecules are characterized by a similar structural fragment which consists of the DHMP ring bearing the phenyl substituent at chiral C4 and the methylallylthio or allylthio group at atom C1 (**Figure 3**). The overlay of these fragments (**Figures 4** and **S122**) reveals a very similar half-chair conformation of the central six-membered ring, where the C4 atom significantly deviates [0.510(3) to 0.623(3) Å] from the least-squares plane of the other five atoms [rms deviations of fitted atoms N2/C1/N1/C2/C3 range from 0.053 to 0.078 Å].

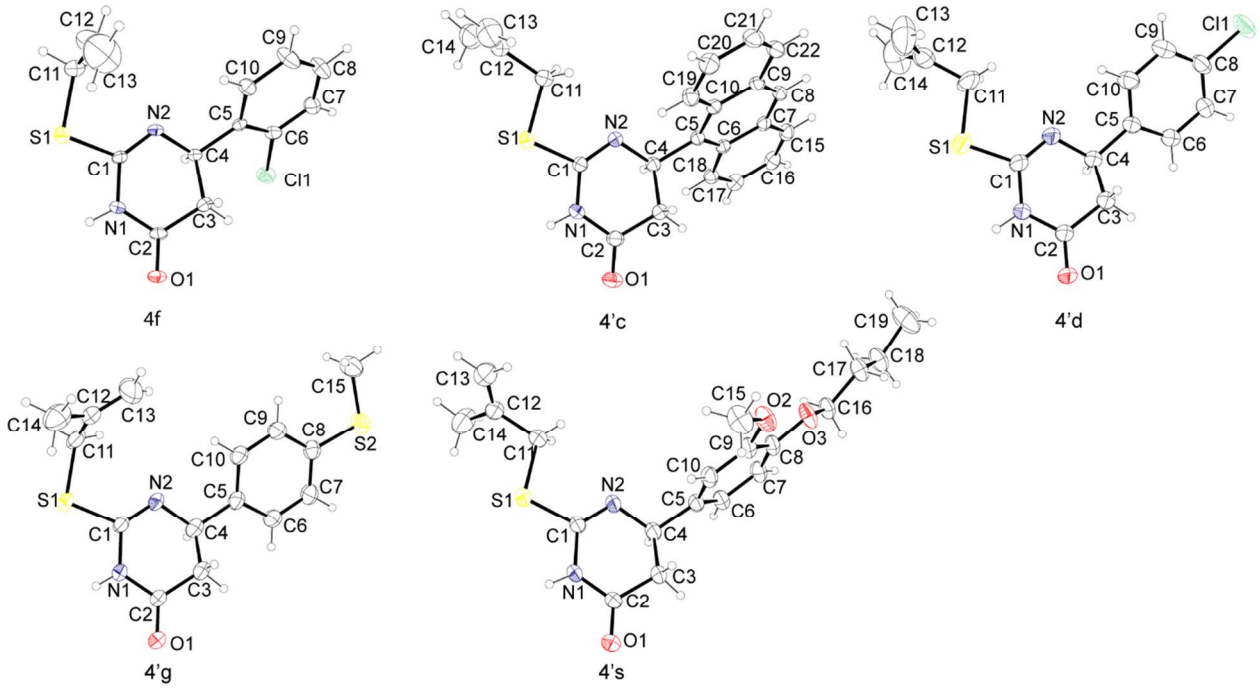


Figure 3. Molecular structure of the compounds **4f**, **4'c**, **4'd**, **4'g** and **4's** (CCDC 1829873-1829877) with 40% probability displacement ellipsoids and the atom-labelling scheme.

According to **Figure 4** the five molecules mainly differ in two respects, i.e. the different inclination of the aromatic fragment relative to the heterocyclic ring and the dissimilar orientation of their S-substituents (see **Figure S123** and torsion angles in **Table S2**). A comparison of structural parameters (**Table S3**) indicates similar bond lengths and angles for the five molecules. It is especially interesting to notice that the all five molecules display very short length for the corresponding N2–C1 bond (average value of 1.26 Å); this can imply a highly localized electron π density in this part of each heterocyclic ring.

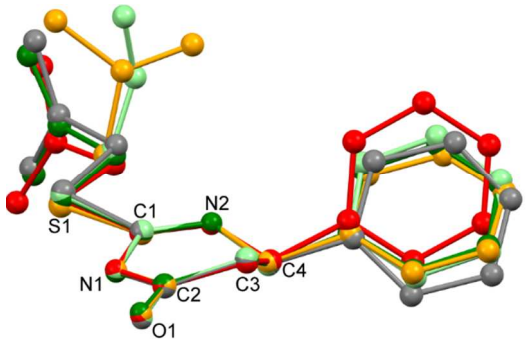


Figure 4. The overlay of five molecules (see **Figure 3**) based on a least-squares fit of atoms from the heterocyclic rings.

A CSD (Cambridge Structural Database) search[51] for heterocyclic structures comprising the similar N atom bonded to two carbon atoms shows that only 1% of the archived crystal structures (**Figure S124a**) contains the N–C bonds with the lengths similar to N2–C1 bond of the present compounds. Results of the CSD search also show that the difference between the bond lengths of two N-C bonds formed by the same N atom rarely reaches 0.21 Å as is the case with the N2–C1 and N2–C4 bonds in the present structures (see **Figure S124b**). Single-crystal X-ray diffraction experimental information and detailed description of the **4f**, **4'c**, **4'd**, **4'g** and **4's** crystal structures can be found in SI.

Green validation of applied method

To validate presented methodology on an example of synthesis **4a** we are used complete E-factor (cEF),[54,55] EcoScale[1] as well-known green analytic tools. Compared with established literature procedures (see SI) presented method is followed with significantly lower cEF = 25.9 and higher value of EcoScale = 91.5. Consequently, a lower cEF and at the same time higher EcoScale means fewer amounts of waste and points out that applied chemical process has the positive environmental impact. In addition, we compared results which obtained under solvent-free (Table 1, entry 4) and in solvent conditions (entry 10) by using green chemistry innovation scorecard-GCIS.[55,56] GCIS presents one graphical output, which clearly and effectively illustrates the impact of the innovative procedure on waste reduction during the synthesis. As can be seen from data which are outlined in **Figure 5**, method in the solvent and solvent-free produce 1.03 more and 2.05 times less waste, respectively, compared to the industry average.

"Excellent" relative process greenness (RGB) properties in both protocols was achieved. However, solvent-free strategy upgraded RPG value approximately 2.5 times by 128% (in the solvent) to 326% (solvent-free) and at the same time reducing the amount of waste by 40.4 kg per kg product. Hence, the solvent-free method is followed by significantly higher process improvements (innovation impact quadrant, **Figure 5**), compared to the method which carried out in the solvent. Finally, obtained results from GCIS indicates that solvent-free method gave significantly better efficiency towards to DHMP scaffold which is followed by significantly better RGB value, innovation impact as well as reduction of the quantity of reaction waste (**Figure 5**).

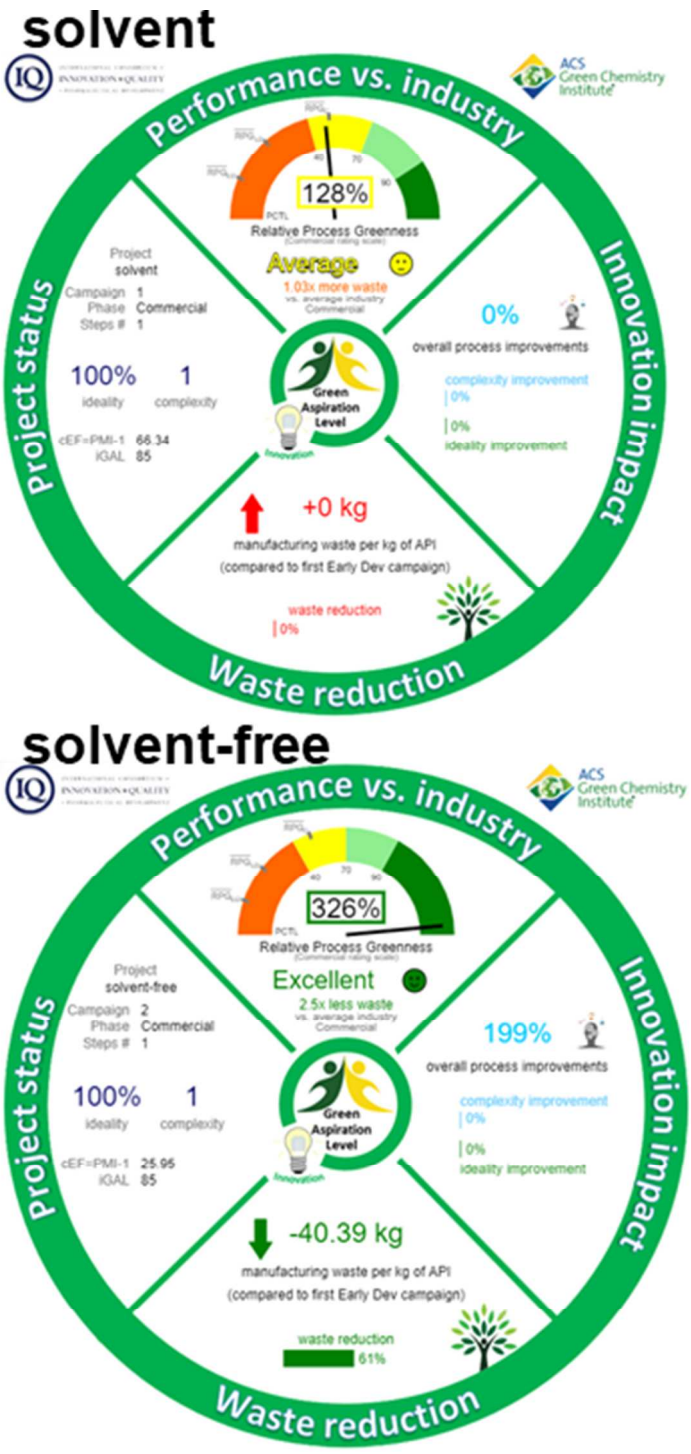


Figure 5. Green chemistry innovation scorecard for solvent (top) and solvent-free driven protocol (bottom).

Conclusion

In summary, an elegant and high-yielding solvent-free methodology driven by solvent-free route and "in the presence of water" for the environmentally friendly synthesis of forty novel 5,6-dihydropyrimidin-4(3*H*)-ones under soft basic conditions with high tolerance to various substrates has been developed. In the majority of cases, the high-to-excellent yields of appropriate products (up to 95%) and at the same time high selectivity for each of them (3H : 1H = >99.9% : 0.1%) was achieved. The molecular structures of the compounds **4f**, **4'c**, **4'd**, **4'g** and **4's** has been determined by single-crystal X-ray diffraction analysis. In each one of them, very short length for the corresponding N2–C1 bond (average value of 1.26 Å) was noticed. According to CSD analysis, only 1% of the N-heterocyclic structures contains the N–C bond with the lengths comparable to N2–C1 bond. This feature makes the present compounds especially interesting from the structural point of view.

Additionally, reduction of waste (confirmed by using green chemistry innovation scorecard) and excellent values of green chemistry metrics (cEF and EcoScale) in the synthesis of 6-aryl-5,6-dihydropyrimidin-4(3*H*)-one motifs, has been realized. The use of green compatible approach which followed with simple work-up, extended substrate scope regarding aldehyde (twenty) and biazanucleophyles (two), requires no chromatographic purification, reduction of waste and at the same time possibility for functionalization of synthesized heterocycles makes presented strategy very suitable for one-pot conversion of similar substrates into corresponding products. Allylic-decorated 6-aryl-5,6-dihydropyrimidin-4(3*H*)-ones will be an excellent toolkit for the lead-oriented synthesis of targeting medicinally relevant motifs, which is developing in our laboratory.

Experimental

General information

All substrates (allyl chloride 99.5 %, methallyl chloride 97 %, thiourea 99%, 2,2-dimethyl-1,3-dioxane-4,6-dione 98% and aldehydes) were purchased from Sigma. The vanillic aldehydes (**1l**, **1m**, **1o**, **1q-t**) were synthesized according to the previously described methodology.[52,53] HPLC-grade acetonitrile, methanol and water were purchased from Sigma-Aldrich (St. Louis, MO, USA). Formic acid (*p.a.*) was obtained from Merck (Darmstadt, Germany). The melting points

(mp) were determined on a Mel-Temp apparatus and are uncorrected. The IR spectra were recorded by a Perkin–Elmer Spectrum One FT-IR spectrometer on a KBr pellet. The NMR spectra of compounds **4** and **4'** (**Figures S1-S80**) were performed in DMSO-d_6, $CDCl_3$ or mixture DMSO-d_6 : $CDCl_3$ with TMS as the internal standard on a Varian Gemini 200 MHz NMR spectrometer (^{1}H at 200 and ^{13}C at 50 MHz). ^{1}H NMR data are presented in followed order: chemical shifts (ppm), multiplicity (s = singlet, d = doublet, dd = doublet od doublet, t = triplet, q = quartet, qd = quartet of doublet, m = multiplet, and br. s. = broad singlet), number of protons, coupling constants *J* (Hz) and type of carbon group where is appropriate proton attached. LC-MS/MS system consisted of Shimadzu (Kyoto, Japan) components: two LC-30AD UPLC pumps connected in binary gradient mode, DGU-20A degassing unit, SIL-30AC autosampler, CTO-20AC column oven, CBM-20A system controller and LCMS 8040 triple-quadrupole mass spectrometer. Waters Symmetry® C18 reversed-phase column (150 x 4.6 mm, 5 µm) was employed for the separation of isomers 3H and 1H. Mass spectrometer operated in Q3 scan mode (unit resolution), selected m/z range was 100-1000, scan speed was 909 u/sec. Ionization was performed in ESI+ mode, interface voltage was set to +4.5 kV after several trials to accomplish the best yield for the molecular ion and avoid in-source fragmentation. Temperatures of the interface, desolvation line and heat block were set to 350 °C, 250 °C and 400 °C respectively. Drying gas (N_2) flow was 15 l/min and nebulizing gas flow was 3 l/min. Electrical parameters (pre-filter and quadrupole voltages) were optimized using PPG for the positive and raffinose for negative ionization according to the in-built auto-tune procedure of the instrument. Princip of analysis, chromatograms and MS spectra of **4a-t** and **4'a-t** are given in SI (**Figures S81-S120**).

Experimental procedure for preparation of diazoles 3 and 3'

Twice redistilled allyl or *β*-Methallylchloride (100 mmol) was added to a solution of thiourea (9.12 g, 120 mmol) in water (50 mL), and the mixture was stirred at 80 ^{o}C for 6 h. The solution was cooled at room temperature, acetone (50 mL) was added and put in the refrigerator during the night. White shine crystals of obtained products S-allyl or S-methallylisothiouronium hydrochloride were precipitated, filtrated, washed with acetone and vacuum dried. Then, isothiouronium hydrochloride salts were ground in a mortar with $NaHCO_3$, dissolved in ethanol, filtered and after the removed solvent was obtained **3** and **3'**.

General experimental procedures for synthesis of 6-aryl-5,6-dihydropyrimidin-4(3*H*)-ones **4 and 4'**

In a mortar with pestle crystalline S-allyl or S-methallylisothiourea (5 mmol) with 5 mmol of appropriate aldehyde (**1a-t**) was ground 10 minutes. Then, Meldrum's acid (0.720 g, 5 mmol) and sodium acetate (0.082 g, 20 mol%) were added and homogenized in mortar with pestle. After 30 minutes water (0.5 mL) was added and then homogenized periodically (20 min.) through 3h at 50 ^{o}C. Upon completion of the reaction (followed with TLC) in the resultant paste 15 mL 70% methanol-water solution was added, obtained products (**4** or **4'**) fall out of the solution in pure form, isolated via filtration, washed with hot water and air-dried. All experimental data (mp, IR, NMR, LC/MS and X-ray crystallography data) are given in SI.

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Supporting Information

The NMR, MS spectra and chromatograms, as well as the X-ray crystallography and green metrics data are provided in Supporting Information.

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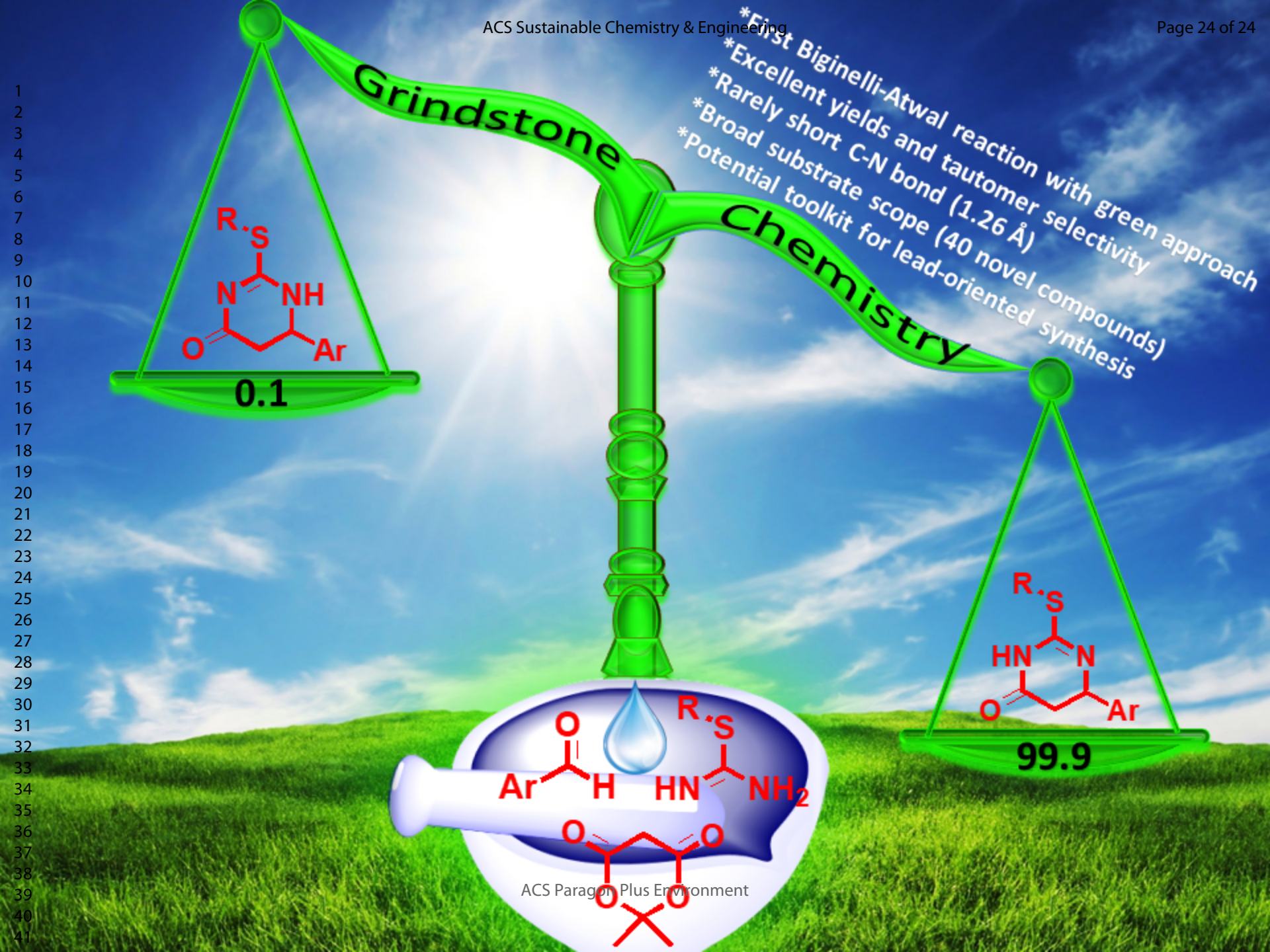
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