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Grindstone chemistry: a highly efficient and green method for synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones by L-tyrosine as an organocatalyst: a combined experimental and DFT study†

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A single step, mild, environmentally friendly green method has been developed for the synthesis of physiologically active 3,4-dihydropyrimidin-2-(1*H*)-ones employing L-tyrosine as catalyst under solvent-free conditions at room temperature *via* grinding. The procedure is efficient, time saving and gives high-yields. The structures and purity of these compounds were confirmed by FT-IR, NMR (^{1}H and ^{13}C) and HRMS spectral analysis. DFT calculations have been used to show the effectiveness of L-tyrosine as a suitable catalyst for the above reaction.

Introduction

Development of less hazardous synthetic methodologies for organic reactions is one of the most sought after problems in contemporary research. For synthesis of complex molecules employing environment friendly green methods, reactions conducted in aqueous media have received much attention.[1a] But there have been associated drawbacks as well; primarily owing to very poor ability of water in solubilizing organic reactants making the reaction mixture heterogeneous.[1b] This difficulty can be overcome using phase transfer catalysts but this will cause the process to be more expensive.[1b] Reactions in dry media or under solvent free condition are especially appealing, as they provide an opportunity to work in an open vessel, thus avoiding the risk of high internal pressure development and with the possibility of up-scaling the reaction to the larger scale.[1c] Recently, grindstone chemistry has been shown to be a highly viable green and rapid method for the synthesis of organic compounds without the complicacies associated with the use of different solvents, including water.[2a] The proposed technique does not require external heating, leading to energy efficient synthesis and may be regarded as more economical and ecologically favorable procedure in chemistry.[2b] Toda and co-workers showed that many of the exothermic organic reactions can be performed in good yield using mortar and pestle only.[2a] Grindstone chemistry has been shown to be a very useful method for desktop as well as kilogram scale synthesis.[2a]

3,4-Dihydropyrimidines are well-known for their wide range of bioactivities and their applications in the field of drug research.[3–6] 3,4-Dihydropyrimidin-2-(1*H*)-ones (DHPMs) have high pharmacological value and they are used as calcium channel blockers,[7] alpha-1a-antagonists,[8] antihypertensive agents and neuropeptide Y (NPY) antagonists.[9] Their derivatives also exhibit a wide spectrum of biological effects including antifungal, antiviral, anticancer, and anti-inflammatory effects.[10] Several bioactive marine alkaloids have the dihydropyrimidin-5-carboxylate core in their molecules.[11] Batzelladine alkaloids A and B from the sponge of *Batzella* sp. inhibit the binding of HIV gp-120 to human CD4 receptor.[12] Nitractin was first reported in 1960s as an agent against the trachoma group of viruses.[13a] Monastrol, a thio derivative of DHPM has been identified as a compound that acts as a cell-permeable molecule to block mitosis cell division by specifically inhibiting the motor activity of the mitotic kinesis Eg5.[13b]

Search for more suitable preparation of DHPMs continue today. Recently many improved procedures have been reported using $CuCl_2$–H_2O,[14] L-proline,[15] praseodymium methanesulfonate,[16] phenyl pyruvic acid,[17] chloroacetic acid,[18] TMSCl,[19] Lewis acids,[20] $InCl_3$,[21] $InBr_3$,[22] $CdCl_2$,[23] heteropolyacids[24] as catalyst in Biginelli reaction. In addition, methods employing microwaves,[25] ultrasound,[26] solid and fluorous phase syntheses[27] have been reported.

Hitherto, all these methodologies have come up with drawbacks such as prolonged reaction time, tedious catalyst preparation and work up, formation of inevitable sticky products and exhaustive usage of solvents. Development of organocatalytic processes in which the reactions are catalyzed by organic molecules is an important area for the green synthesis.[28a] Recently, Yadav and co-workers[28b] reported the application of L-proline as catalyst in Biginelli reaction for the synthesis of

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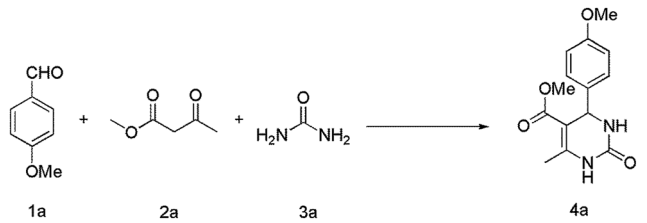


Scheme 1 Synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones.

dihydropyrimidin-2-(1*H*)-ones (thiones). A natural bi-functional organocatalyst phytic acid has also been reported by Guo and co-workers[28c] in Biginelli 3,4-dihydrppyrimidin-2-(1*H*)-one synthesis. Sinha and co-workers[28d] reported glycine nitrate catalyzed DHPM synthesis under microwave condition. Our aim is to develop a fully green synthesis of various 3,4-DHPMs at room temperature and we have selected L-tyrosine as the catalyst for this purpose. The choice of L-tyrosine is based on the fact that it is an efficient, bi-functional, zwitterionic and eco-friendly organocatalyst capable of playing multiple catalytic roles as an acid and base. Though L-tyrosine used in psychiatric disorder, schizophrenia,[28e] its catalytic activity in various organic transformations is till unnoticed. The one report of the catalytic ability of L-tyrosine is reflected in its application in Knoevenagel condensation reaction under grindstone condition.[28f]

To the best of our knowledge, the Biginelli reaction under grinding condition was first reported by Bose and co-workers[28g] using *p*-TSA as catalyst. In this report they used only aromatic aldehydes, ethyl acetoacetate and urea for the synthesis of 3,4-DHPMs. Very recently, Safari and co-workers reported diarylpyrimidones synthesis by Fe_3O_4–CNT nanocomposites *via* grinding using aldehydes, urea and ketone.[28h] As a part of the continuous efforts for employing grinding methodology, herein we report the synthesis of 3,4-DHPMs (Scheme 1) using various types of aldehydes (such as alkyl, aromatic and heterocyclic), 1,3-diketones (acetyl acetone, methyl acetoacetate and ethyl acetoacetate) and urea (or thiourea) using L-tyrosine as catalyst under solvent-free condition at room temperature. Another major aspect of our work is that the appreciably higher catalytic activity of L-tyrosine compared to that of glycine has been corroborated by means of DFT calculation.

Results and discussions

Traditional condition for Biginelli reactions commonly require a large excess of one of the reagents, large amounts of catalyst, high temperatures, several hours reactions and occasionally the presence of co-catalyst.[29]

Our initial efforts were focused on the search of a catalyst, which would be useful in grindstone methodology to carry out the synthesis of DHPMs at room temperature. For our purpose, L-tyrosine was chosen as the preferred catalyst. We first started to investigate the Biginelli reaction (Scheme 1) with 4-methoxy benzaldehyde (1 mmol), urea (1 mmol) and methyl acetoacetate (1 mmol) in presence of L-tyrosine (10 mol%) as catalyst under solvent free grinding condition using mortar and pestle. This model reaction afforded compound **4a** (Table 3) in 87% yield. The yield of the reaction is optimum under grinding method using L-tyrosine (10 mol%) at room temperature. Increment in the amount of the catalyst to 20 mol% (Table 1, entry 6) did not show any improvement in the yield, whereas the yield was found to be lesser when the amount of the catalyst was reduced to 5 mol% (Table 1, entry 5). Another significant observation is that the reaction is more successful considering time and yield at room temperature than microwave condition (Table 1, entry 7).

In Table 1 we also compare the catalytic activity of L-tyrosine with others amino acid catalysts such as glycine, L-proline and L-serine under grinding methodology for the synthesis of compound **4a**. L-Proline and glycine both are effective catalysts for various organic reactions such as Biginelli reaction, but

Table 2 Comparison of L-tyrosine with other Brønsted acid catalysts for the synthesis of **4a**

Entry	Catalyst	Catalyst load (mol%)	Time (min)	Yield[a] (%)
1	L-Tyrosine	10	15	87
2	Camphorsulphonic acid	10	60	50
3	Oxalic acid	10	120	45
4	$HClO_4$	10	60	57

[a] Isolated yield.

Table 1 Optimization of the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-one (**4a**)

Entry	Catalyst	Catalyst load (mol%)	Solvent	Time (min)	Yield[a] (%)
1	Glycine	10	Ethanol (reflux at 80 °C)	50	50
2	Glycine	10	Solvent free (grinding method, rt)	60	30
3	L-Tyrosine	10	Ethanol (reflux at 80 °C)	45	60
4	L-Tyrosine	10	Solvent free (grinding method, rt)	15	87
5	L-Tyrosine	5	Solvent free (grinding method, rt)	30	59
6	L-Tyrosine	20	Solvent free (grinding method, rt)	15	87
7	L-Tyrosine	10	Microwave	20	41
8	L-Serine	10	Solvent free (grinding method, rt)	30	73
9	L-Proline	10	Solvent free (grinding method, rt)	50	35

[a] Isolated yield.

Table 3 One-pot, L-tyrosine catalyzed synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones and thiones[a]

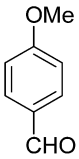
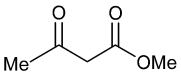
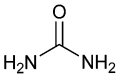
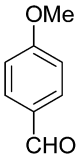
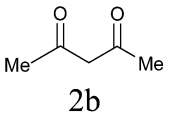
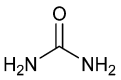
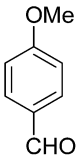
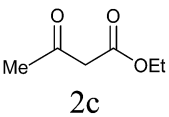
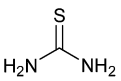
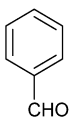
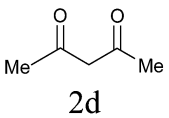
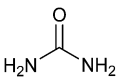
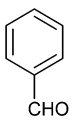
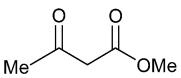
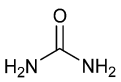
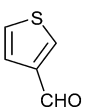
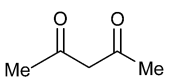
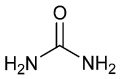
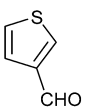
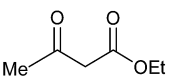
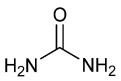
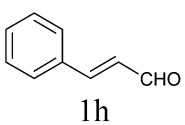
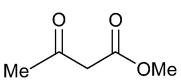
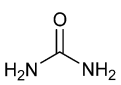
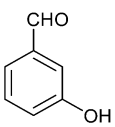
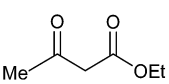
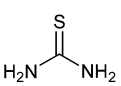
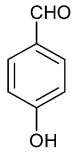
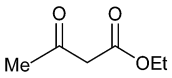
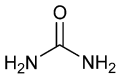
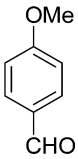
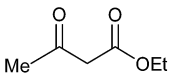
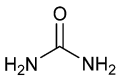
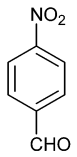
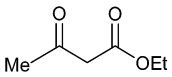
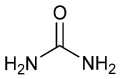
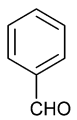
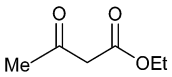
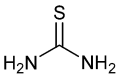
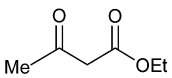
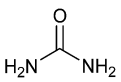
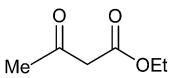
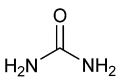
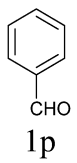
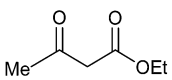
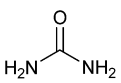
Entry	Aldehydes	1,3-Diketone	Urea/thiourea	Time (min)	Yield[b] (%)
1	 1a	 2a		15	87 (**4a**)
2	 1b	 2b		10	91 (**4b**)
3	 1c	 2c		10	82 (**4c**)
4	 1d	 2d		10	89 (**4d**)
5	 1e	 2e		15	85 (**4e**)
6	 1f	 2f		10	81 (**4f**)
7	 1g	 2g		5	89 (**4g**)
8	 1h	 2h		15	83 (**4h**)
9	 1i	 2i		20	91 (**4i**)

Table 3 (*Contd.*)

Entry	Aldehydes	1,3-Diketone	Urea/thiourea	Time (min)	Yield[b] (%)
10	 1j	 2j		20	83 (**4j**)
11	 1k	 2k		10	85 (**4k**)
12	 1l	 2l		15	88 (**4l**)
13	 1m	 2m		15	87 (**4m**)
14	$CH_3(CH_2)_2CHO$ 1n	 2n		20	82 (**4n**)
15	HCHO 1o	 2o		15	90 (**4o**)
16	 1p	 2p		15	84 (**4p**)

[a] Reaction conditions: aldehyde (1 mmol), urea (1 mmol), 1,3-dicarbonyl compounds (1 mmol) and L-tyrosine (10 mol%) ground at room temperature. [b] Isolated yield (after recrystallization). All compounds have been characterized by IR, NMR and HRMS data.

under room temperature grinding condition L-tyrosine is significantly more effective. L-Serine was also found to be a better catalyst compared to both glycine and L-proline for the synthesis of compound **4a** (yield 73%) in grinding condition at room temperature, but not as effective as L-tyrosine.

For the model reaction (**4a**) we have also compared the catalytic activity of other Brønsted acids with L-tyrosine under grinding condition and the details are given in Table 2.

A broad range of structurally diverse 1,3-dicarbonyl compounds, aldehydes and urea were subjected under this protocol to produce the corresponding DHPMs (Table 3). Many of the pharmacologically significant substitution patterns have been introduced efficiently. Aromatic aldehydes were found to produce the corresponding DHPMs in high yield irrespective of their electronic effects. Aldehydes with heterocyclic ring afforded higher yields (Table 3, **4f** and **4g**). Thiourea was also used in similar success (Table 3, **4c**, **4i** and **4m**) which are of much interest with regard to the biological activity.[13]

To demonstrate the efficiency of the chosen catalyst, a blank reaction (*i.e.* without catalyst) was carried out for entry 2 and no

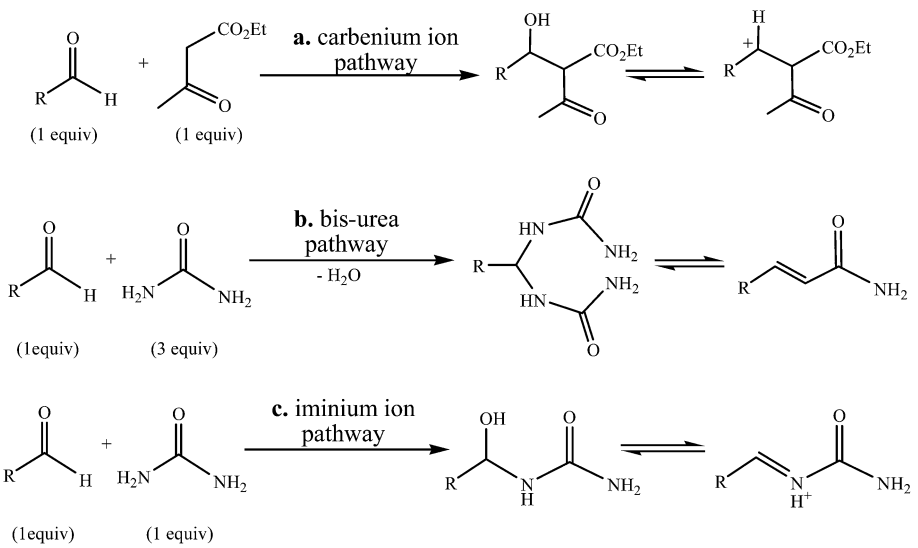
suitable result has been observed. It is important to note that this procedure is much simpler and faster than the protocols published till date. It requires neither tedious work up procedure nor column chromatographic purification. The grinding reaction mixture was quenched with water to remove the catalyst and finally we got the precipitate of DHPMs. To probe the probable mechanism of L-tyrosine mediated Biginelli reaction three different routes (Scheme 2) were investigated: (a) carbenium ion pathway,[30a] (b) bis-urea pathway[30b] and (c) iminium ion pathway.[30c]

When 4-methoxy benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol) and L-tyrosine (10 mol%) were ground for 15 min, no product was obtained which rules out the possibility of the carbenium ion pathway.[30a] Next to investigate the possibility of bis-urea pathway, urea (3 mmol) was ground with 4-methoxy benzaldehyde (1 mmol) for 15 min and no derivative was obtained, which rules out the idea of bis-urea pathway.[30b] Finally, to investigate the iminium pathway, 4-methoxybenzaldehyde (1 mmol) and urea (1 mmol) were ground for 15 min in L-tyrosine (10 mol%), subsequently ethyl acetoacetate (1 mmol) was added and again ground for 5 min and we got the desired product (Table 3, **4k**, yield 85%).[30c] Neto and co-workers demonstrated that urea excess is the worst condition for the Biginelli reaction when iminium-based mechanism is favoured.[30d] So, we completely avoided using excess urea in any of the reaction reported here and always used it in equimolar amount with aldehyde and 1,3-diketone. Recently, it has been demonstrated that electrospray ionization mass spectrometry is an excellent tool to study the Biginelli intermediates formed during the transformation. We observed two distinct peaks at *m*/*z* value of 178.03 and 198.08 in the mass spectra for **4g** and **4h** that corresponds to the two iminium intermediates (mass of iminium intermediate + Na^+), respectively. This fact reinforces our initial finding that the reaction follows the iminium ion pathway (c) as shown in Scheme 2.

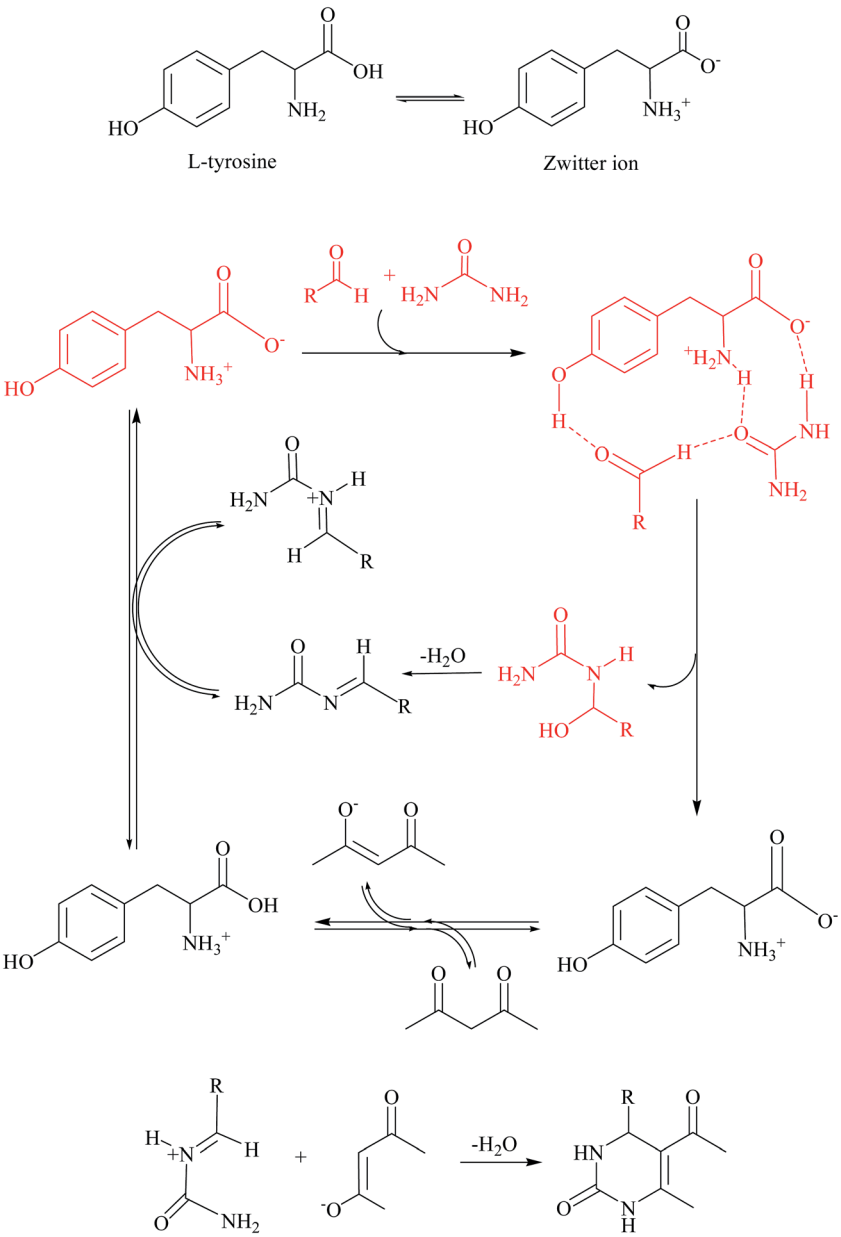
A reaction mechanism for the Biginelli condensation *via* iminium intermediate has been proposed in Scheme 3. This intermediate is formed by reaction of aldehyde and urea in presence of the catalyst and is then stabilized by Zwitterionic form of L-tyrosine through H-bonding interaction. Subsequent addition of 1,3-diketone to the acyl imine, followed by cyclization and dehydration, produces the corresponding DHPMs. It is worthwhile to mention here that the all the synthesized DHPMs (Table 3; **4a–4p**) were found to be racemic in nature. In fact, it has been shown that L-proline and its corresponding hydrochloride catalyzed reaction, too, resulted in racemic DHPMs.[15,28b] The chiral center in the DHPMs originates at the carbonyl carbon of the reactant aldehyde during the addition of iminium ion intermediate and enolic form of 1,3-dicarbonyls. The fact that we obtained products with a chiral centre as a racemic mixture indicates that L-tyrosine does not participate in this particular step as it would have facilitated formation of one enantiomer over the other due to the catalyst's own chirality.

From the results given in Table 1 it can be noted that under room temperature grinding condition there is a significant difference in product yield when two different amino acid catalysts are used; for **4a** glycine catalyzed reaction gave very poor yield (30%) whereas for L-tyrosine the yield is considerably higher (87%). So, it is clearly evident that L-tyrosine is a highly efficient catalyst for Biginelli reaction under room temperature grinding condition but the same is not true for glycine. This large difference in catalytic activity between the two amino acid catalysts must be due to the marked difference in their molecular geometries and consequently, in chemical properties, too. The phenolic group present in L-tyrosine must be actively taking part in the catalytic process by reducing the transition energy and hence increasing reaction rate compared to that in glycine, which is reflected in higher product yield.

We propose here that it is the intermolecular hydrogen bonding interaction between the catalyst and the reactant species that makes the reaction facile under mild grinding



Scheme 2 Probable reaction mechanisms for Biginelli reaction.



Scheme 3 Proposed mechanistic pathway of Biginelli reaction by L-tyrosine as catalyst. The rate determining step, for which DFT calculation has been carried out, is shown in red [for iminium ion pathway, this particular step is the slowest step[31]].

condition. To support the above proposition, we have modeled the potential energy surface of the rate determining step (RDS) employing electronic structure calculation by density functional theoretical methods. In Biginelli reaction, formation of $RCH(OH)NHCONH_2$ by addition of urea with aldehyde (shown in red in Scheme 3) is known to be the slowest step.[31] The following step is faster and involves release of water molecule leading to the iminium intermediate. In our study, too, the mass spectra showed peaks corresponding to the iminium intermediates only and no signature for its precursor could be identified. The above facts confirm that the addition of urea and aldehyde is the RDS of Biginelli reaction when it follows iminium ion pathway.

When compared against glycine, L-tyrosine through its Ph–OH group can provide extra H-bonding site that facilitates the reaction by further stabilization of the activation complex. Here, we have taken the smallest aldehyde (*i.e.* formaldehyde; R=H in Scheme 3). The reactant complex, transition state and product complex involving glycine are designated here as GRC, GTS and GPC, respectively and similarly TRC, TTS and TPC imply same species when L-tyrosine acts as a catalyst. The optimized geometries of these species are shown in Fig. 1 along with the H-bond lengths.

The hydrogen bonded complex formed by the catalyst, urea and formaldehyde was found to be enjoying greater stabilization in TRC compared to that in GRC. In both cases, urea is

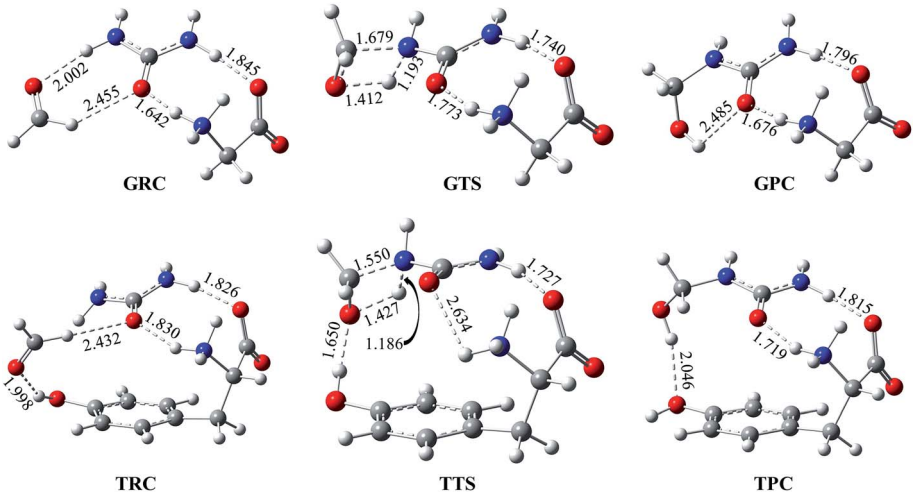


Fig. 1 Molecular geometries of reactant, product and transition complexes involving glycine and L-tyrosine catalysts optimized at B3LYP/6-311++G(d,p) level. Hydrogen-bond lengths are given in Å.

bound to the amide group of the amino acid catalyst by two H-bonds, one between the amine hydrogen of urea and carboxylate oxygen of the amino acid and the other between the carbonyl oxygen of the former and the ammonium hydrogen of the latter. It is the aldehyde whose binding pattern was found to differ significantly when two different amino acids were taken as catalyst. For both of them, the hydrogen atom of formaldehyde is bonded to the carbonyl oxygen of urea. But the carbonyl oxygen of formaldehyde forms H-bond with the phenolic hydrogen of L-tyrosine in TRC, but it is bonded to the hydrogen of free amino group of urea in GRC. This difference in the conformation of formaldehyde has twofold effects on the potential energy surface of the RDS step. Firstly, binding energies of the complexes involving L-tyrosine and glycine are different, the first one being larger in magnitude. Secondly, which is more important from our viewpoint, this results in a considerable difference between the barriers of activation involving the two catalysts, the one with glycine *i.e.* GTS (46.0 kcal mol^{-1}) requires ~12 kcal mol^{-1} higher energy than that needed with L-tyrosine *i.e.* TTS (34.4 kcal mol^{-1}). This large increment in the reaction barrier makes glycine to be much less effective in catalyzing the reaction which we have found to be done efficiently by L-tyrosine. The relative energies of all the species studied here are shown schematically in Fig. 2. The energies of all species were computed relative to the isolated urea, formaldehyde and catalyst molecules.

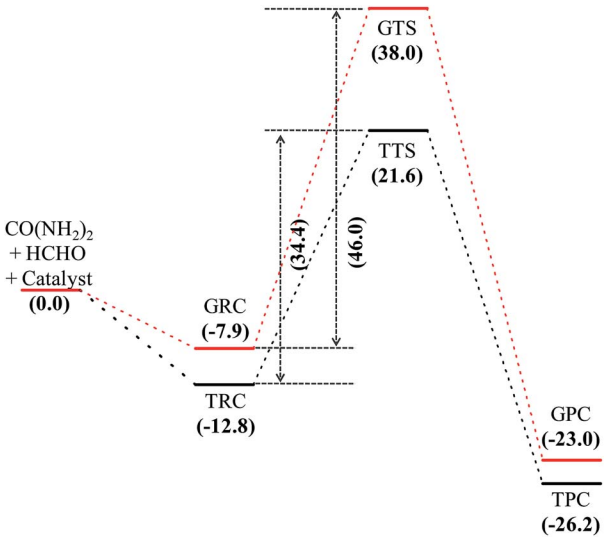


Fig. 2 Relative energies (in kcal mol^{-1}) of reactant, product and transition complexes involving glycine (in red) and L-tyrosine (in black) catalysts calculated by single point energy calculation at M06-2X/6-311++G(d,p) using the optimized geometries calculated at B3LYP/6-311++G(d,p) level.

When the reactant and product complexes along with the transition states are scrutinized from a closer quarter (Fig. 1), it can be observed that the formaldehyde moiety undergoes a significant reorientation with respect to the urea molecule during the process for glycine, whereas for L-tyrosine it hardly needs to change its orientation. The dihedral angle between the formaldehyde C=O and the urea C–N (closer to the formaldehyde) are −130°, −114° and −110° for TRC, TTS and TPC, respectively, whereas these values are −178°, −90° and −70° for GRC, GTS and GPC, respectively. So it is directly evident that during the transformation of GRC to GTS, formaldehyde undergoes a rotation of ~90° along an axis perpendicular to C=O. But TRC–TTS transformation requires only ~15° rotation in similar manner which should be much easier to perform. More importantly, this rotational reorientation disrupts the H-bond formed by carbonyl oxygen of formaldehyde in GRC but no such effect is seen during TRC–TTS conversion where the said oxygen is H-bonded with the phenolic OH of L-tyrosine in both TRC and TTS. On the contrary, the said H-bond becomes even stronger in TTS than that in TRC, its length being 1.650 Å in the former and 1.998 Å in the later. We conclude here that these two reasons are primarily responsible for the large difference in barrier heights for the reaction catalyzed by glycine and L-tyrosine. We may add to the above facts that this

difference will get even more widened for reactions involving bulkier aldehydes as their reorientation will require much larger energy compared to formaldehyde.

Another notable observation was that when the reaction (for entry **4a**) was carried out using two more amino acids, namely L-proline and L-serine (Table 1), it was found that the former one (entry 9) gave yield that was comparable to what was obtained with glycine. On the other hand, the latter one (entry 8) gave appreciably high yield (albeit lower than that for L-tyrosine). Here, too, the difference between these two catalysts is that while L-serine has an extra hydrogen bonding site (hydroxyl group) like L-tyrosine, L-proline lacks such a feature similar to glycine. In order to provide further support to the computational results we carried out the reaction with formaldehyde, ethyl acetoacetate and urea using both glycine and L-tyrosine as catalysts. It was found that in this case, too, that latter proved to be a more efficient catalyst (Table 3, **4o**, yield 90%) than the former (yield 52%), but the difference in yield is not as large as was found for the aromatic aldehyde (Table 1, entry 2 and 4).

Conclusions

We have developed an eco-friendly novel method for the synthesis of DHPMs catalyzed by L-tyrosine in high yield. The remarkable features of this procedure are solvent free, grinding methodology, high conversion rates and operational simplicity. Compared to the previously reported methods, most of which required elevated temperatures, this methodology proceeds smoothly at room temperature and therefore is able to sustain a large number of functional groups. Mild reaction conditions, fully green and clean reaction profile, shorter reaction time and wide range of substrate applicability are the key advantages of this methodology.

Experimental

Melting points were uncorrected. IR spectra were recorded as KBr pellets on a Perkin Elmer 782 spectrophotometer. The ^{1}H NMR and ^{13}C NMR spectra in DMSO were run on a Bruker AM-300L instrument operating at 300 MHz and 75 MHz respectively. Electrospray mass spectra were recorded on a Waters Micromass Q-Tof micro™ mass spectrometer. Optical rotations are measured in 241 Perkin Elmer polarimeter.

General procedure for the synthesis of 3,4-dihydropyrimidine-2-ones

A mixture of aldehyde (1 mmol), urea (1 mmol) and 1,3-diketone (1 mmol) was ground together in a mortar and pestle in presence of L-tyrosine (10 mol%) as catalyst at room temperature. For the few minutes later formation of a syrupy solution was observed. The reaction was monitored by TLC. After completion of the reaction the syrupy reacting mixture was treated with water to remove the catalyst and white coloured solid product was formed. The solid product was filtered and the product was recrystallized from ethanol–ethyl acetate (1 : 1) mixture.

Calculation

Molecular geometries of all the species involved in the RDS of the reaction, their H-bonded complexes, and the corresponding transition states have been optimized by density functional theoretical (DFT) methods employing B3LYP functional and 6-311++G(d,p) basis set. Single point energy calculations have been carried out at the M06-2X/6-311++G(d,p) level using the optimized geometries calculated at B3LYP/6-311++G(d,p) level. Basis set superposition errors (BSSEs) for all the complexes and the transition states were corrected employing the single point counterpoise method proposed by Boys and Bernardi.[32] Normal mode frequencies were calculated for all species to ascertain that optimized geometries corresponded to minima in the potential energy surfaces characterized by no imaginary frequencies and transition complexes corresponded to first order saddle points characterized by a single imaginary frequency. The Gaussian 09 program package[33] was used to perform all the calculations reported herein.

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