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PEG-embedded thiourea dioxide (PEG.TUD) as a novel organocatalyst for the highly efficient synthesis of 3,4-dihydropyrimidinones

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ABSTRACT

The host–guest complex between polyethylene glycol and thiourea dioxide (PEG.TUD) was prepared via different approaches involving co-crystallization method and by a chemical reaction. The resulting PEG.TUD complex was found to be very active and recyclable catalyst for the direct synthesis of 3,4-dihydropyrimidinones via Biginelli condensation and provided high product yields. Interestingly, the corresponding poly(ethylene glycol)–thiourea complexes, PEG.TU, were found to be unreactive and no reaction occurred under similar reaction conditions.

Multi-component coupling reactions (MCR's), involving the inherent formation of several bonds in one step, have proven to be efficient and powerful tool for the rapid formation of complex heterocyclic compounds in recent years.[1] The unique features of these reactions are their operational simplicity, structural diversity, versatility, high synthetic efficiency, atom-economy, and single step synthesis without isolating the intermediates. The synthesis of 3,4-dihydropyrimidinones via one-pot condensation of aldehyde, β-dicarbonyl compound, and urea/thiourea known as Biginelli reaction[2] is one of the most recognized and often used MCR's for the synthesis of these valuable heterocyclic compounds.

3,4-Dihydropyrimidinones are remarkably important heterocyclic units that possess a wide spectrum of therapeutic and pharmacological applications including antiviral, antitumor, antibacterial, and anti-inflammatory activities.[3] They also have emerged as calcium channel blockers, antihypertensive agents, and α-1a-adrenergic antagonists. Furthermore, several alkaloids containing the dihydropyrimidine nucleus obtained form marine sources are well known to show interesting biological activities.[4] Owing to the wide synthetic utility and potential applications, the synthesis of this heterocyclic nucleus is of much importance. A number of improved methods involving the use of transition-metal-based catalysts/reagents,[5] ionic liquids,[6] polymer immobilized reagents,[7] microwave,[8] and ultrasound irradiation[9] have been recently reported for their synthesis. However, most of them suffer from the drawbacks, such as the use of toxic metals, volatile organic solvents, high cost, low yields, longer reaction times, and harsh reaction conditions. Therefore, it is still needed to develop an efficient and cost-effective method for the synthesis of these valuable compounds. Development of organocatalytic processes in which the reactions are catalyzed by small organic molecules has become an area of tremendous importance in current organic synthesis particularly from the green chemistry point of view.[10] Unlike the conventional catalysis, these organocatalysts are advantageous in many ways like high stability, availability of the catalyst, metal free nature, reduced toxicity, and simple reaction conditions and can promote a chemical reaction through different activation modes. Small organic molecules, such as urea and thiourea derivatives due to their strong hydrogen bonding ability have been distinguished as efficient organocatalysts and their versatility as a general acid catalyst has been successfully demonstrated by several groups.[11] Nevertheless a number of reports related to the organocatalytic multi-component reactions have been reported in the literature.[12] However, among the known organocatalysts, L-proline and its derivatives have been widely used in various MCR's such as aldol reaction,[13] Robinson annulation,[14] Mannich reactions,[15] Michael reactions,[16] Diels–Alder reactions,[17] Baylis–Hillman reactions,[18] and aza-Morita–Baylis–Hillman reactions.[19] Recently, Yadav et al.[20] reported the application of L-proline as catalyst in Biginelli reaction for the synthesis of dihydropyrimidin-2-ones (thiones). Feng and co-workers[21] reported an enantioselective Biginelli reaction by using a simple chiral secondary amine and achiral Brønsted acid via a dual-activation route. Suzuki et al.[22] reported the hydrazine type organocatalysts for Biginelli condensation. However, to the best

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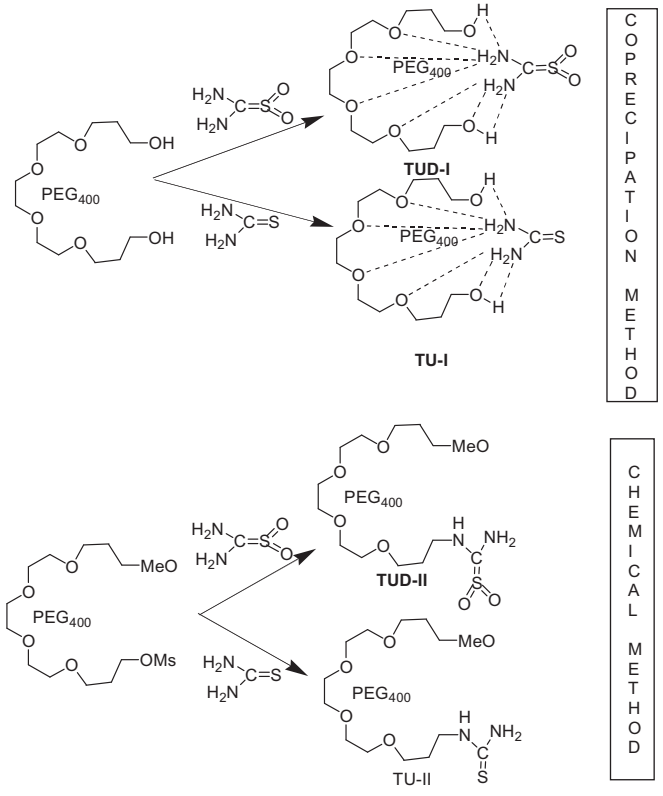
of our knowledge there is no literature report on the use of host–guest complex type organocatalysts for organic transformation.

In the present Letter, we wish to report a first successful development of the PEG-embedded thiourea dioxide (PEG.TUD) host–guest complex as a highly efficient, cost effective and recyclable catalyst for the synthesis of 3,4-dihydropyrimidinones by a three-component condensation, that is, Biginelli reaction. The required PEG.TUD complex could readily be prepared from poly(ethylene)glycol and thiourea dioxide (TUD)[23] either by co-crystallization or via a chemical approach as shown in Scheme 1. For the comparison purpose we also prepared the corresponding polyethylene glycol–thiourea (PEG.TU) complexes in a similar manner (Scheme 1). In the co-crystallization method, PEG_{400} was dissolved in a methanol solution saturated with thiourea dioxide (TUD) and the resulting solution was stirred until a white precipitate appeared. The resulting precipitate was separated by filtration, washed with diethylether, and dried under vacuum to give white solid, PEG.TUD **I**. Following the chemical approach,[24] the reaction of TUD and $MeOPEG_{400}$ in a fixed molar ratio (1:2) in dry DMF at 80 °C for 5–6 h followed by usual work-up could easily give a white powdered PEG.TUD **II** in high yields. Similarly, the corresponding PEG–thiourea complexes, that is, PEG.TU **I** and PEG.TU **II** were prepared as shown in Scheme 1. The thermal stability of the complexes (PEG.TUD **I–II** & PEG.TU **I–II**) was determined by thermogravimetric analysis (TGA), the complexes were found to be quite stable up to 170–180 °C and could be completely decomposed around 300–350 °C.

At first we studied the reaction between 4-chlorobenzaldehyde, ethyl acetoacetate, and urea by using the catalytic amount of synthesized complexes (PEG.TUD **I–II** and PEG.TU **I–II**) in order to evaluate their catalytic potential. The reaction was continued at 50 °C under stirring until the mixture became solidified. Surprisingly, the PEG–thiourea (PEG.TUD **I–II**) complexes did not show any catalytic activity and starting materials could be recovered at the end of the reaction; whereas, PEG–thiourea dioxide complexes (PEG.TUD **I–II**) showed excellent catalytic efficiency and provided corresponding 3,4-dihydropyrimidinone in almost quantitative yield within shorter reaction times. The results of these experiments are presented in Table 1 (entry 1). Next, we carried out the recycling experiments of the PEG.TUD complexes **I–II** by using the 4-chlorobenzaldehyde, ethyl acetoacetate, and urea as a representative example. After completion of the reaction, the catalyst could readily be recovered by precipitation with diethyl ether and reused for subsequent experiments (5 runs). However, the filtrates so obtained were concentrated and subjected to usual work-up to obtain the pure product. During the course of this study, the PEG.TUD **II** complex did not show any significant decrease in the catalytic activity; whereas PEG.TUD **I**, showed slight decrease in catalytic activity with each passing run and after 8 runs, it showed very poor catalytic activity and provided poor yield of the desired product. This is probably due to the leaching of the thiourea dioxide from the support in PEG.TUD **I**, in which thiourea is bonded to the support via physical attraction forces. On the other hand, in PEG.TUD **II**, thiourea is attached to the support by covalent bonding, preventing the leaching of thiourea dioxide from the PEG support during the reaction. Further, the leaching of the organic molecule TUD from the support in PEG.TUD **I** was established by heating the catalyst in ethanol at 50 °C for 3 h. After cooling the reaction mixture at room temperature, the catalyst was separated by precipitation with diethyl ether and the resulting filtrate was concentrated and charged with chlorobenzaldehyde, ethyl acetoacetate, and urea. The reaction was continued under optimized reaction conditions without adding further amount of the catalyst. The reaction was found to progress well and afforded corresponding 3,4-dihydropyrimidinone in almost similar yield, confirming the leaching of TUD from catalyst **I**. These facts established that the PEG.TUD complex **II** was a truly heterogeneous catalyst which could be reused with consistent catalytic efficiency for several runs. Further, we used only PEG.TUD **II** to extend the reaction with a variety of aromatic, aliphatic, heterocyclic aldehydes, dicarbonyl compounds, and urea/thiourea under similar reaction conditions (Scheme 2).[25]

The results of these experiments are summarized in Table 1. All the aldehydes either containing electron donating or withdrawing

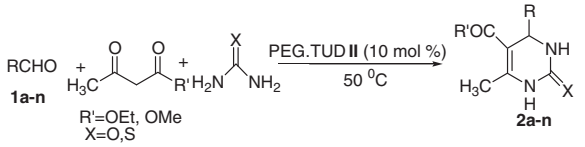


Scheme 1. Synthesis of PEG.TUD and PEG.TU complexes.

Table 1
PEG.TUD **II** catalyzed synthesis of 3,4-dihydropyrimidinones[a]

Entry	Product	R	R′	X	Yield[b] (%)
1	**2a**	4-ClC_6H_4	OEt	O	97, 95[c], –[d], –[e], –[f], 85[g]
2	**2b**	C_6H_5	OEt	O	98
3	**2c**	4-$CH_3C_6H_4$	OEt	O	96
4	**2d**	4-$CH_3OC_6H_4$	OEt	O	96
5	**2e**	4-$NO_2C_6H_4$	OEt	O	95
6	**2f**	2-ClC_6H_4	OEt	O	94
7	**2g**	*n*-$CH_3CH_2CH_2$	OEt	O	92
8	**2h**	2-Furyl	OEt	O	90
9	**2i**	C_6H_5	OMe	O	96
10	**2j**	4-$NO_2C_6H_4$	OMe	O	92
11	**2k**	4-$CH_3OC_6H_4$	OMe	O	90
12	**2l**	4-ClC_6H_4	OMe	O	92
13	**2m**	2-Furyl	OMe	O	89
14	**2n**	C_6H_5	OEt	S	98
15	**2o**	4-$CH_3C_6H_4$	OEt	S	96
16	**2p**	4-$NO_2C_6H_4$	OEt	S	94

[a] Reaction condition: aldehyde (2 mmol), urea/thiourea (2 mmol), β-dicarbonyl compound (2 mmol), PEG.TUD **II** (10 mol %) at 50 °C.
[b] Isolated yields.
[c] By using PEG.TUD **I** as catalyst.
[d] By using PEG.TU **I** as catalyst.
[e] By using PEG.TU **II** as catalyst.
[f] Blank experiment in the absence of catalyst.
[g] By using thiourea dioxide as catalyst.



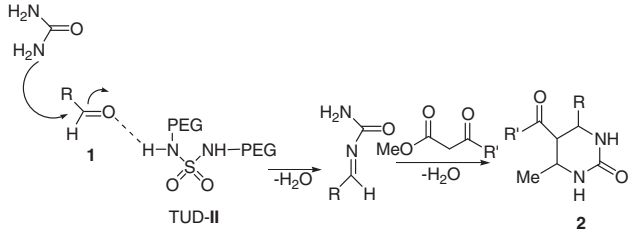
2a, R=4-ClC$_6$H$_4$, R'=OEt; X=O
2b, R=Ph, R'=OEt; X=O
2c, R=4-CH$_3$C$_6$H$_4$, R'=OEt; X=O
2d, R=4-CH$_3$OC$_6$H$_4$, R'=OEt; X=O
2e, R=4-NO$_2$C$_6$H$_4$, R'=OEt; X=O
2f, R=2-ClC$_6$H$_4$, R'=OEt; X=O
2g, R=CH$_3$(CH$_2$)$_2$; X=O
2h, R=2-Furyl, R'=OEt; X=O
2i, R=C$_6$H$_5$, R'=OMe; X=O
2j=R=4-NO$_2$C$_6$H$_4$, R'=OMe; X=O
2k, R=4-CH$_3$OC$_6$H$_4$,R'=OMe; X=O
2l, R=4-ClC$_6$H$_4$,R'=OMe; X=O
2m, R=2-Furyl, R'=OMe; X=O
2n, R=Ph, R'=OEt; X=S
2o, R=4-CH$_3$C$_6$H$_4$, R'=OEt; X=S
2p, R=4-NO$_2$C$_6$H$_4$, R'=OEt; X=S

Scheme 2. Biginelli condensation by using PEG.TUD **II**.

groups were smoothly converted into their corresponding 3,4-dihydropyrimidinones in excellent yields. Similarly, β-ketoesters, such as ethyl acetoacetate and methyl acetoacetate smoothly reacted under these reaction conditions. Further, the use of thiourea in place of urea afforded corresponding 3,4-dihydropyrimidinones-2(1*H*)-thiones, which also exhibit a number of interesting biological activities. Use of organic solvents, such as acetonitrile and ethanol did not enhance the reaction rates to any significant extent and, therefore, all the experiments were carried out under solvent-free conditions. It is worthy to mention that the reaction between 4-chlorobenzadehyde, ethyl acetoacetate, and urea did not proceed even after 24 h in the absence of catalyst under otherwise similar reaction conditions (Table 1, entry 1). Similarly, the use of thiourea dioxide alone as a catalyst showed poor catalytic efficiency than PEG.TUD **II**, indicating the important role of PEG support in making the reactions faster. The reaction was found to be very slow at room temperature, whereas, 50 °C was found to be optimum for this reaction. Further increase in reaction temperature did not affect the rate of the reaction to any considerable extend.

The exact mechanism of the reaction is not clear; the probable mechanism of the reaction may involve the activation via the strong hydrogen bonding ability of the PEG.TUD **II** with oxygen of the carbonyl group as shown in Scheme 3. This activation will be promoting the formation of acylimine intermediate by the reaction of aldehyde with urea/thiourea. In analogy to the well established mechanism,[26] the generation of acylimine intermediate is the key step, which subsequently reacts with β-dicarbonyl compound followed by cyclodehydration to give corresponding 3,4-dihydropyrimidinones. Further studies to establish the mechanistic pathway for the present reaction are currently under progress.

In summary, we have developed for the first time a novel and recyclable host–guest type PEG-embedded thiourea dioxide (PEG.TUD) organocatalysts for the efficient synthesis of 3,4-dihydropyrimidinones. The key advantages, such as ease of synthesis, fast reaction rates, use of cost effective, environmentally acceptable substances like PEG, and recycling without loss in activity make this method more efficient and open an avenue to explore the potential of this cost-effective catalyst for developing many other synthetic methodologies.



Scheme 3. Plausible mechanistic pathway.

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24. *Synthesis of PEG.TUD **II***: A mixture containing thiourea dioxide (2 mmol, 0.2 g) and $MeOPEG_{400}$ (4 mmol, 2.0 g) in dry DMF (15 ml) was heated at 80 °C over night. After being cooled to room temperature, the reaction mixture was concentrated under reduced pressure and the residue obtained was treated with diethyl ether. The white precipitate thus obtained was isolated by filtration, washed thoroughly with 2-propanol and diethyl ether, and dried under vacuum to yield PEG.TUD **II**, yield (1.8 g, 82%). PEG.TU **I** & PEG.TU **II** were prepared exactly as PEG.TUD **I** and PEG.TUD **II**, respectively.
25. *General experimental procedure*: A stirred mixture containing the aldehyde (2 mmol), urea/thiourea (2 mmol), β-dicarbonyl compound (2 mmol), and TUD **II** (10 mol %) was heated at 50 °C until the mixture became solidified. After completion, resulting solid was separated and washed with hot ethanol. The catalyst could readily be recovered from the filtrate by the precipitation using diethylether. The crude product was purified by recyrstallization with ethanol to afford the pure 3,4-dihydropyirimidinones. All the products were characterized by comparing their physical (mps) and spectral data (IR & ^{1}H NMR) with the authentic compounds.
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