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COMMUNICATION

Thiourea dioxide promoted efficient organocatalytic one-pot synthesis of a library of novel heterocyclic compounds†

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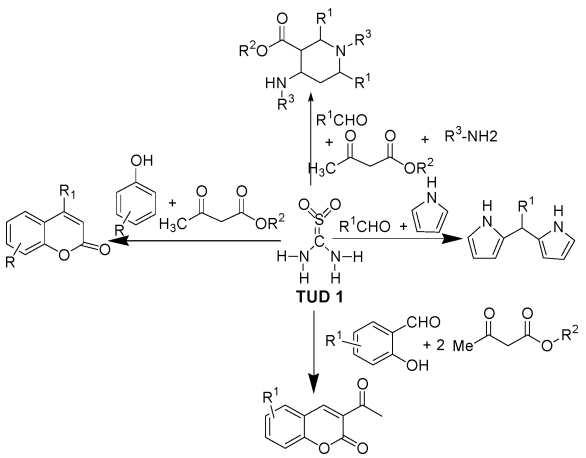
The utility of thiourea dioxide as an efficient organocatalyst for the library synthesis of novel heterocyclic compounds *via* one-pot multicomponent coupling reactions is disclosed. Thiourea dioxide is an inexpensive and readily accessible catalyst, resulting in better product yields as compared to the corresponding thiourea as catalyst. Thiourea dioxide is found to be insoluble in various organic solvents and therefore at the end of the reaction products can be separated by extraction with diethyl ether and the recovered catalyst can be used several times with consistent catalytic activity.

Development of "greener synthetic methodologies" along with fast access toward the desired compounds is one of the prime objectives to speed up current organic synthesis.[1] In this regard, several advancements such as microwave synthesis,[2] use of ionic liquids,[3] sonication,[4] multicomponent couplings[5] and combinatorial synthesis[6] have been recognized to be efficient tools to accelerate the reaction rates. Among them, multicomponent coupling reactions (MCRs) represent a valuable synthetic approach for the library synthesis of novel heterocyclic compounds of tremendous importance.[7] Synthesis of these compounds by an MCR approach provides a number of advantages over conventional synthesis, such as simple synthesis, lower costs, shorter reaction times, and environmental friendliness. Among the recently developed advancements, the discovery of catalysis by small organic molecules termed as "organocatalysts" has become a break-through, which offers numerous advantages including lower activation energy, high stability, metal free environment, reduced toxicity, and mild reaction conditions.[8] Small molecules such as urea[9] and thiourea[10] derivatives due to their strong hydrogen-bonding activity have also emerged to be potential organocatalysts in developing a variety of synthetically important organic reactions. Owing to the growing environmental concerns, there is continued pressure on chemical and pharmaceutical industries to reduce chemical waste. In this regard utilization of heterogeneous catalysts may offer the advantages of facile recovery and recycling of the catalyst.[11]

Thiourea dioxide (TUD)[12] easily prepared by the oxidation of thiourea with hydrogen peroxide is highly stable and possesses the ability to activate organic substrates through hydrogen bonding. Owing to the presence of two extra oxygen atoms it forms strong hydrogen bonding and can provide higher activation than the corresponding thiourea. In addition, thiourea dioxide is insoluble in common organic solvents and therefore can easily be recovered at the end of the reaction for its reuse. Despite its high potential, the use of thiourea dioxide as organocatalyst for organic reactions is not much reported in the literature.[13] So far, to the best of our knowledge except our report, there is no report available on the use of TUD as an organocatalyst for organic transformations[13]

Our previous results led us to explore the potential of TUD as organocatalyst for developing "greener" methodologies for other organic reactions as well. Accordingly we planned to use TUD as catalyst to develop an efficient organocatalytic multicomponent synthetic approach for the library synthesis of novel heterocycles of potential biological applications for various purposes (Scheme 1).



Scheme 1 TUD catalyzed one-pot synthesis of heterocycles.

Initially, the catalytic efficiency of the thiourea dioxide and thiourea was tested for the reaction of salicylaldehyde (2 mmol) and ethyl acetoacetate (2 mmol) under solvent free conditions. The reaction was found to occur very slowly and provided a poor yield of the corresponding product. On the other hand, the reaction occurred efficiently in the presence of a catalytic amount of TUD and provided excellent product yield (>90%) as listed in Table 1, entry 1. In the absence of catalyst, no reaction was occurred under described reaction conditions. Next, we studied the effect of various solvents such as acetonitrile, dichloromethane, water

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Table 1 TUD mediated synthesis of functionalized coumarins[a]

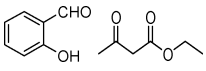
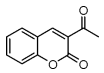
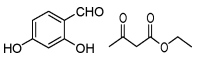
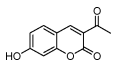
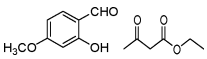
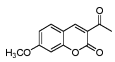
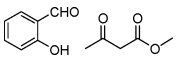
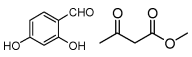
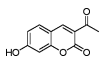
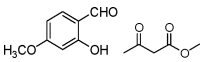
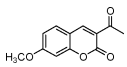
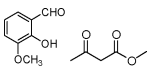
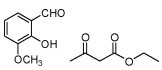
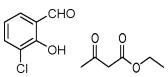
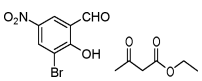
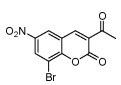
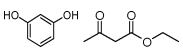
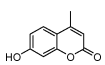
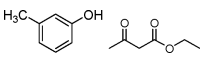
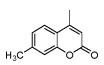
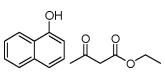
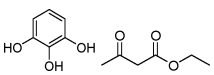
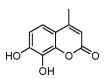
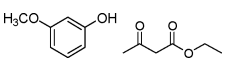
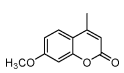
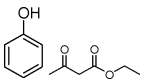
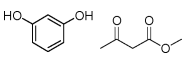
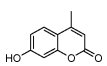
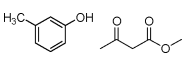
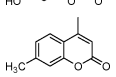
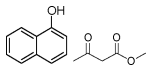
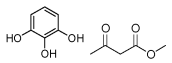
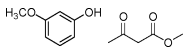
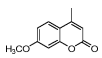
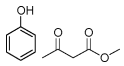
Entry	Substrate	Product	Time (h)	Yield (%)[b]
1			—	—[c]
			4.0	85. 60[d], 60[e]
			5.0	65[f]
			4.0, 3.5	90[g] 92[h]
			4.0	40[i], 65[j], 72[k], 85[l], 82[m], 86[n]
2			4.0	84
3			4.0	84
4			4.0	86
5			4.0	85
6			4.0	83
7			4.0	83
8			4.0	85
9			8.0	65
10			12.0	40
11			3.5	90
12			3.0	90
13			4.0	85
14			4.0	90
15			4.0	90
16			5.0	59
17			3.5	90
18			3.0	90

Table 1 (*Contd.*)

Entry	Substrate	Product	Time (h)	Yield (%)[b]
19			4.0	85
20			4.0	90
21			4.0	90
22			5.0	60

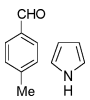
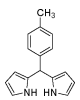
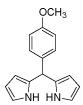
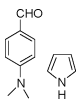
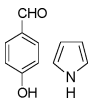
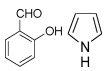
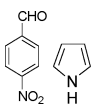
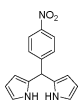
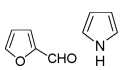
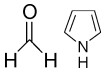
[a] Reaction conditions: hydroxyl aromatic compound (2 mmol), β-keto ester (2 mmol), TUD (5 mol%) under solvent free conditions. [b] Isolated yields. [c] Without catalyst. [d] By using urea as catalyst. [e] Using thiourea as catalyst. [f] Using TUD 2 mol%. [g] 10 mol%. [h] 20 mol%. [i] Using water as solvent. [j] In acetonitrile solvent. [k] In dichloroethane. [l] Using methyl acetoacetate. [m] Using *tert*-butyl acetoacetate. [n] Using acetylacetone.

and no solvent under similar reaction conditions. The results revealed solvent free condition to be the best choice for the present transformation. Low yield of the product was obtained when water was employed as the solvent. The reaction was significantly affected by increasing the amount of TUD from 2 to 5 mol%, whereas no improvement could be observed upon increasing the catalyst loading to 10 mol% (Table 1, entry 1). Other β-keto esters such as methyl acetoacetate, *tert*-butyl acetoacetate and acetyl acetone were also proved to be an excellent substrate, giving good yields of the corresponding product under identical reaction conditions (Table 1, entry 1).

Since the thiourea dioxide is insoluble in common organic solvents it can be considered as a heterogeneous catalyst. To investigate the reusability of the catalyst which is one of the most important features of heterogeneous catalysts, we studied the reaction of salicylaldehyde and ethyl acetoacetate under similar reaction conditions. At the end of the reaction, the reaction mixture was diluted with the diethyl ether to extract the reaction products. The insoluble TUD could easily be separated form the reaction mixture by simple filtration and was successfully reused for subsequent experiments (4 runs) with high catalytic efficiency.

The scope of the reaction under optimized conditions was explored using a variety of substituted salicylaldehydes and other 1,3-dicarbonyl compounds, the results are summarized in Table 1 (entry 1–8). In general, all the salicylaldehydes bearing functional groups at different positions reacted with ethyl or methyl acetoacetate smoothly to give the corresponding heterocyclic products in good to excellent yields. Next, we studied the coupling of various hydroxyl aromatic compounds such as phenol and resorcinol with ethyl acetoacetate under the described reaction conditions, an the results are summarized in Table 1 (entry 9–20). In all cases the reaction was found to occur efficiently and the provided corresponding heterocyclic compounds, coumarins, in almost quantitative yields. Furthermore we studied the reaction of various aldehydes (1 mmol) with pyrrole (2 mmol) under the described experimental conditions (Table 2, entry 1–9). In general aromatic aldehydes bearing both electron donating or withdrawing groups were found to react smoothly and provided excellent yield of the corresponding products. However, the reaction of aliphatic

Table 2 TUD mediated synthesis of heterocyclic dipyrromethanes[a]

Entry	Substrate	Product	Reaction time (min)	Yield (%)[b]
1			15	80, 70[c], 62[d]
2			15	80
3			15	75
4			18	70
5			18	69
6			30	70
7			30	72
8			30	80
9			30	65

[a] Reaction conditions aldehyde (2 mmol) and pyrrole (4 mmol), catalytic amount of TUD (5 mol%). [b] Isolated yields. [c] Using thiourea as catalyst. [d] Using urea as catalyst.

Table 3 TUD-catalyzed synthesis of piperidines[a]

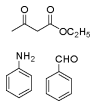
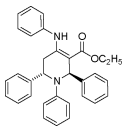
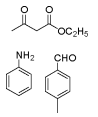
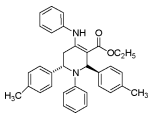
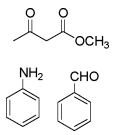
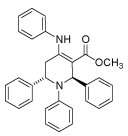
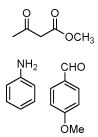
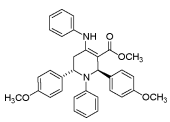
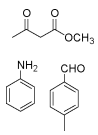
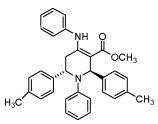
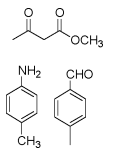
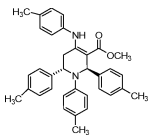
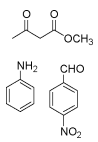
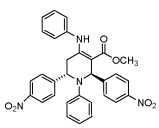
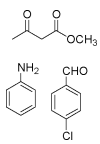
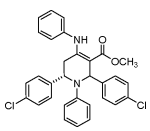
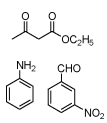
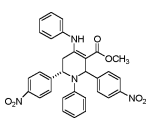
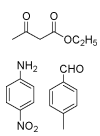
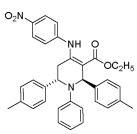
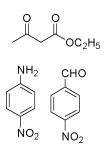
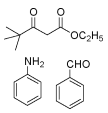
Entry	Substrate	Product	Reaction time (h)	Yield (%)[b]	*anti*/*syn*
1			4	80, 65[c], 55[d]	97/3
2			4	85	94/6
3			4.5	82	97/3
4			4.5	85	96/4
5			6.0	80	95/5
6			5.0	85	96/4
7			10	50	85/15
8			8	90	92/8
9			10	50	90/10
10			12	50	86/14
11		—	12	trace	—

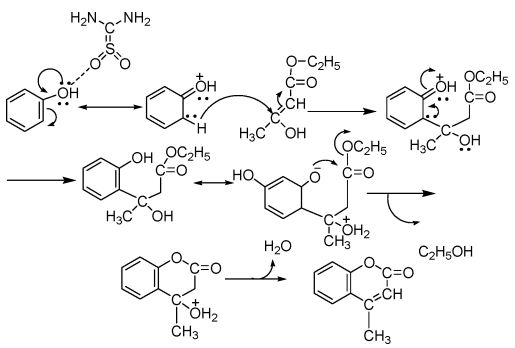
Table 3 (*Contd.*)

Entry	Substrate	Product	Reaction time (h)	Yield (%)[b]	*anti*/*syn*
12		—	—	—	—

[a] Reaction conditions: β-keto ester (1.0 mmol), aldehyde (2.0 mmol), amine (2 mmol), and TUD (5 mol%) under solvent free conditions. [b] Isolated yields. [c] Using thiourea as catalyst. [d] Using urea as catalyst.

aldehydes was found to be slow with the formation of very poor yield of the desired product, as shown in (Table 2, entry 9). Lastly, we studied the synthesis of functionalized tetrahydropyridines *via* the one-pot coupling of β-keto ester, aromatic aldehyde, and amine under the similar reaction conditions (Table 3, entry 1–12). In general, aromatic aldehydes bearing electron-donating or electron-withdrawing functional groups at different positions reacted faster and afforded high to excellent yield of the corresponding products. On the other hand, aromatic amines were found to be effective substrates and afforded the corresponding tetrahydropyridine derivatives in high yields. However, aliphatic amines were found to be less reactive substrates and gave moderate yields, probably due to the higher basicity of aliphatic amines. All the compounds were characterized by comparing their physical and spectral data with those of authentic sample. The purity of the products was identified by ^{1}H NMR spectroscopy.

The exact mechanism of the reaction is not known at this stage; however a proposed mechanism for this reaction may involve the activation through hydrogen bonding between TUD and substrates. The probable mechanism for the synthesis of coumarin is shown in Scheme 2. The presence of two more oxygen atoms in TUD may possibly be responsible for its higher catalytic activity as compared to the thiourea and it can promote several other transformations in a similar fashion.



Scheme 2 Probable mechanistic pathway.

In conclusion, we have developed an efficient organocatalytic synthetic approach for the synthesis of a series of pharmacologically important heterocyclic compounds *via* a one-pot multi-component coupling reaction by using a catalytic amount of TUD under solvent free conditions. The salient features of this procedure are the easy synthesis and facile recovery of the catalyst, mild reaction conditions, clean reaction profiles, inexpensive starting materials, and environmentally friendly protocol. Owing to its strong hydrogen bonding ability TUD can also be served as an efficient organocatalyst for other organic transformations also.

Experimental

Synthesis of thiourea dioxide[11]

Thiourea (45 g) was added into hot water (350 ml) at 40 °C and the resulting mixture stirred to dissolve the thiourea completely. Further, the aqueous solution of thiourea thus prepared was cooled and added to hydrogen peroxide (aq. 50 wt%, 80 ml) slowly at a rate such that the solution temperature was held below 10 °C. Thereafter, the solution was cooled to 0 °C. and stirring continued for about 30 min to allow the crystals to be aged. After the crystallization, the resulting solid–liquid mixture was filtered off immediately at 0 °C and the crystals so obtained were dried at 50 °C, yield of thiourea dioxide 40 g (64%).

General procedure for the preparation of functionalized coumarins (Table 1, entry 1–20)

To a mixture of salicylaldehyde or hydroxyl aromatic compound (phenol, resorcinol) (2 mmol) and β-keto ester (2 mmol) was added a catalytic amount of TUD (5 mol%). The resulting mixture was heated with stirring at 80 °C for the time as given in Table 1. The progress of the reaction was monitored by TLC (SiO_2). After the completion of the reaction, the reaction mixture was diluted with diethyl ether to isolate the product. The recovered catalyst was separated by filtration for its reuse. The organic solvent was evaporated under reduced pressure to afford the crude product, which was then purified by column chromatography by using ethyl acetate and hexane (4 : 6) as eluent.

General procedure for the synthesis of derivatives of dipyrromethanes (Table 2, entry 1–9)

Into a stirred mixture of aldehyde (2 mmol) and pyrrole (4 mmol), a catalytic amount of TUD (5 mol%) was added. The resulting mixture was stirred at room temperature. Progress of the reaction was checked by TLC (SiO_2). At the end of the reaction, the reaction mixture was subjected to usual work-up to afford the corresponding dipyrromethane. The crude product was purified by column chromatography by using ethyl acetate: hexane (4 : 6) as eluent.

General experimental procedure for the synthesis of functionalized piperidines (Table 3, entry 1–12)

A mixture of β-keto ester (1.0 mmol), aldehyde (2.0 mmol), amine (2 mmol), and TUD (5 mol%) was stirred at room temperature for an appropriate time (Table 3). After completion of the reaction, as indicated by TLC, the mixture was diluted with ethyl acetate (20 ml), washed with water and dried with anhydrous Na_2SO_4. The filtrate was concentrated to yield crude product was purified by silica gel column chromatography.

Acknowledgements

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