doi:10.1246/cl.2012.920

Combined Thiourea Dioxide–Water: An Effective Reusable Catalyst for the Synthesis of Polyhydroquinolines via Hantzsch Multicomponent Coupling

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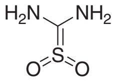
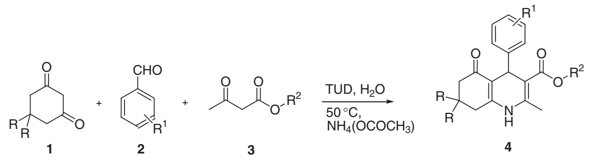
Thiourea dioxide in water was found to be an efficient and reusable organocatalytic system for the one-pot synthesis of polyhydroquinoline derivatives via the Hantzsch-type coupling of aldehyde, dimedone, acetoacetate, and ammonium acetate under mild reaction conditions. Operational simplicity, the use of an economically affordable catalyst, environmentally benign conditions, high product yields, and reusability of the catalyst system were the advantageous features of the developed method.

Multicomponent coupling reactions (MCRs) have been acknowledged as highly valuable synthetic tools for the construction of complex molecular structures with minimum reaction steps and simple workup procedures.[1] Several advanced techniques such as microwave reactions,[2] sonication,[3] organocatalysis,[4] and combinatorial chemistry[5] have been established to accelerate these reactions. In the recent decades, increasing environmental and economical considerations worldwide have led to the search for enviroeconomic synthetic methods for chemical reactions.[6] In this regard, efforts are being made to replace the expensive and hazardous metal-based catalysts with organocatalysts, which are safe, less expensive, easily accessible, harmless, and environmentally benign. In addition, the use of water as the reaction medium is highly desired to make the chemical reactions more environmentally as well as economically viable. During the course of our investigations, we have established the use of thiourea dioxide,[7] which can be easily prepared by the oxidation of thiourea with hydrogen peroxide, as an efficient organocatalyst for the synthesis of novel heterocyclic compounds via multicomponent coupling reactions.[8] As a continuation of our work on multidisciplinary synthetic approaches, we now plan the synthesis of polyhydroquinolines with various substituents. 4-Substituted 1,4-dihydropyridines (1,4-DHPs), an important class of medicinal compounds,[9] exhibit a number of therapeutic properties, i.e., they act as Ca^{2+} channel blockers,[10] vasodilators, and bronchodilators, and as anti-atherosclerotic, antitumor, geroprotective, hepatoprotective, and antidiabetic agents.[11,12] Conventionally, these compounds are synthesized by the condensation of aldehyde with ethyl acetoacetate and ammonia in acetic acid or alcohol.[13,14] However, these methods suffer from several drawbacks such as long reaction times, the need for toxic organic solvents, and low yields. In recent years, several improved protocols, including those involving the use of microwaves,[15] organocatalysts,[16–18] TMSCl-NaI,[19] metal triflates,[20] ionic liquids,[21] ceric ammonium nitrate,[22] supported reagents, and polymers, have been developed. Again, the use of volatile solvents, high temperatures,[23] expensive or hazardous catalysts that are harmful to the environment, and long reaction times restricts the utility of these efficient approaches. Consequently, there is scope for further development of an efficient, environmentally benign, and cost-effective methodology for the synthesis of these valuable compounds. Herein, we report a convenient, enviroeconomic, and practical approach for the one-pot synthesis of polyhydroquinoline derivatives via the Hantzsch-type condensation of aldehydes, dimedone, ethyl- or methyl acetoacetate, and ammonium acetate in the presence of a catalytic amount of thiourea dioxide in water under mild reaction conditions (Scheme 1). The present methodology is particularly promising for the large-scale preparation of polyhydroquinoline derivatives, where cost, safety, and hazards are the prime factors of concern. The use of thiourea dioxide (TUD) in water is advantageous as it allows for recycling of the catalyst without any loss in activity.



Thiourea dioxide (TUD)



4a, R = H, R^1 = H; $R^2 = CH_3$
4b, R = H, R^1 = H; $R^2 = C_2H_5$
4c, R = H, R^1 = 4-Cl; $R^2 = CH_3$
4d, R = H, R^1 = 4-Cl; $R^2 = C_2H_5$
4e, R = H, $R^1 = 4\text{-}CH_3$; $R^2 = CH_3$
4f, R = H, $R^1 = 4\text{-}CH_3$; $R^2 = C_2H_5$
4g, R = H, $R^1 = 4\text{-}OCH_3$; $R^2 = CH_3$
4h, R = H, $R^1 = 4\text{-}OCH_3$; $R^2 = C_2H_5$
4i, R = H, $R^1 = 4\text{-}NO_2$; $R^2 = CH_3$
4j, R = H, $R^1 = 4\text{-}NO_2$; $R^2 = C_2H_5$
4k, $R = CH_3$, R^1 = H; $R^2 = CH_3$
4l, $R = CH_3$, R^1 = H; $R^2 = C_2H_5$
4m, $R = CH_3$, R^1 = 4-Cl; $R^2 = CH_3$
4n, $R = CH_3$, R^1 = 4-Cl; $R^2 = C_2H_5$
4o, $R = CH_3$, $R^1 = 4\text{-}CH_3$; $R^2 = CH_3$
4p, $R = CH_3$, $R^1 = 4\text{-}CH_3$; $R^2 = C_2H_5$
4q, $R = CH_3$, $R^1 = 4\text{-}OCH_3$; $R^2 = CH_3$
4r, $R = CH_3$, $R^1 = 4\text{-}OCH_3$; $R^2 = C_2H_5$
4s, $R = CH_3$, $R^1 = 4\text{-}NO_2$; $R^2 = CH_3$
4t, $R = CH_3$, $R^1 = 4\text{-}NO_2$; $R^2 = C_2H_5$

Scheme 1. TUD-catalyzed synthesis of polyhydroquinoline derivatives.

At first, we carried out the reaction of benzaldehyde, dimedone, ethyl acetoacetate, and ammonium acetate in the presence of a catalytic amount of TUD (2 mol %) in water (2 mL) at 50 °C to afford the corresponding polyhydroquinoline. After the completion of the reaction, the product was isolated by filtration. The aqueous layer containing TUD was washed with diethyl ether to remove traces of the organic reactants. The recovered aqueous solution of TUD was reused as such for the subsequent reaction. The recyclability of the developed catalyst was checked for seven runs (Table 1). The yield of the product and reaction time were almost the same during these experiments, indicating the efficient recycling of the aqueous solution of TUD. In a controlled blank experiment, the reaction of dimedone, benzaldehyde, and methyl acetoacetate in water did not produce any product in the absence of TUD, even after a

Table 1. Results of recycling experiments[24]

Run	1	2	3	4	5	6	7
Yield/%	94	94	92	93	93	92	93

Table 2. TUD-catalyzed synthesis of polyhydroquinolines[a]

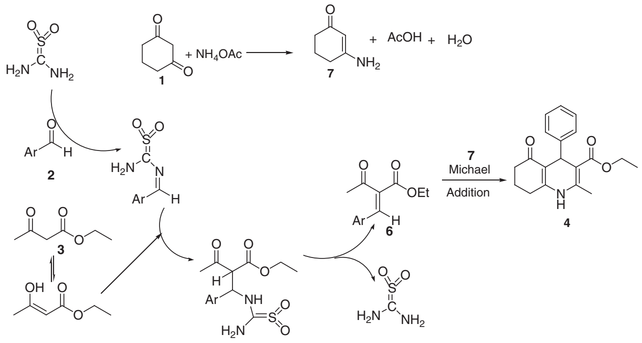
Entry	R	R^1	R^2	Product	Yield/%[b]
1	H	H	CH_3	**4a**	92
2	H	H	C_2H_5	**4b**	94
3	H	4-Cl	CH_3	**4c**	91
4	H	4-Cl	C_2H_5	**4d**	91
5	H	4-CH_3	CH_3	**4e**	92
6	H	4-CH_3	C_2H_5	**4f**	92
7	H	4-OCH_3	CH_3	**4g**	91
8	H	4-OCH_3	C_2H_5	**4h**	91
9	H	4-NO_2	CH_3	**4i**	89
10	H	4-NO_2	C_2H_5	**4j**	89
11	CH_3	H	CH_3	**4k**	92
12	CH_3	H	C_2H_5	**4l**	94
13	CH_3	4-Cl	CH_3	**4m**	94
14	CH_3	4-Cl	C_2H_5	**4n**	93
15	CH_3	4-CH_3	CH_3	**4o**	91
16	CH_3	4-CH_3	C_2H_5	**4p**	91
17	CH_3	4-OCH_3	CH_3	**4q**	90
18	CH_3	4-OCH_3	C_2H_5	**4r**	90
19	CH_3	4-NO_2	CH_3	**4s**	85
20	CH_3	4-NO_2	C_2H_5	**4t**	85

[a]Reaction conditions: aldehyde **2** (1 mmol), dimedone **1** (1 mmol), alkyl acetoacetate **3** (1 mmol), and ammonium acetate (1 mmol), TUD (2 mol %), H_2O 2 mL as solvent at 50 °C, reaction time 2 h.[24] [b]Isolated yields.

Table 3. TUD-catalyzed synthesis of polyhydroquinolines in large-scale reaction (gram-scale reaction)[a]

Entry	R	R^1	R^2	Product	Yield/%[b]
1	H	H	CH_3	**4a**	90
2	H	H	C_2H_5	**4b**	91
3	H	4-Cl	CH_3	**4c**	90
4	H	4-Cl	C_2H_5	**4d**	91
5	H	4-CH_3	CH_3	**4e**	90

[a]Reaction conditions: aldehyde **2** (50 mmol), dimedone **1** (50 mmol), alkyl acetoacetate **3** (50 mmol), and ammonium acetate (50 mmol), TUD (2 mol %, 1 mmol), H_2O 100 mL as solvent at 50 °C, reaction time 3 h. [b]Isolated yields.



Scheme 2. Proposed mechanism for TUD-catalyzed polyhydroquinoline synthesis.

prolonged reaction time (24 h). Next, we extended the reaction to various aromatic, aliphatic, unsaturated, and heterocyclic aldehydes using the developed protocol. The results of these experiments are presented in Table 2. All the substrates reacted efficiently and afforded almost quantitative yields of the corresponding polyhydroquinolines. The developed method is very simple and convenient and can tolerate a variety of other functional groups such as methoxy, nitro, hydroxy, and halides under the given reaction conditions. Both electron-rich and electron-deficient aldehydes reacted efficiently, leading to high yields of the product. The use of just 2 mol % of TUD in water was sufficient to push the reaction forward. Further increase in the catalyst concentration (5 and 10 mol %) in water did not lead to any significant improvement in the yield of the polyhydroquinolines. Further, we obtained the coupling products selectively without any evidence for the formation of by-products. We also attempted to use the developed protocol for the large-scale synthesis of polyhydroquinolines; these results are summarized in Table 3. As shown, the developed catalytic method was found to be promising for the gram-scale synthesis of the desired products.

The exact mechanistic pathway for this reaction is not known at this stage; however, the possible mechanism is shown in Scheme 2. In the presence of TUD in water, **2** and **3** react to give **6** by the Knoevenagel condensation; another intermediate **7** is the ester enamine, which is produced by the condensation of **1** with ammonia (from ammonium acetate). Intermediates **6** and **7** react by the Michael addition to produce the final product **4**. The formation of Knoevenagel product **6** was confirmed by carrying out the reaction of benzaldehyde and ethyl acetoacetate in the presence of a catalytic amount of TUD in water.

In conclusion, we have described a very convenient, environmentally benign, and practical approach for the preparation of polyhydroquinoline derivatives via the Hantzsch-type condensation reaction by using an aqueous solution of thiourea dioxide as a reusable catalyst. The important features of the present method are as follows: the use of an inexpensive catalyst, recyclability of the catalyst, easy experimental procedures, easy workup, and high yields.

We gratefully acknowledge the kind permission of Director, IIP, to publish these results. SV thanks CSIR for his fellowship. Analytical division of the Institute is acknowledged for assistance in the analysis (IR and NMR) of the products. DST, New Delhi, is acknowledged for the research funding.

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24 **Experimental procedure for the synthesis of polyhydroquinoline derivatives 4**: Into a stirred mixture of aromatic aldehyde **2** (1 mmol), dimedone **1** (1 mmol), alkyl acetoacetate **3** (1 mmol), and ammonium acetate (2 mmol) was added TUD (2 mol %). The reaction mixture was slowly heated to 50 °C and continued the reaction to the time as mentioned in Table 2. Progress of reaction is monitored by TLC. After completion of the reaction, the mixture was cooled to 10 °C. The solid mixture so obtained was added in ethyl acetate to recover the thiourea dioxide. The recovered catalyst was isolated by filtration and reused for next experiments. The filtrate was concentrated under reduced pressure and purified by column chromatography. The crude product was finally recrystallize from ethanol to afford the pure product. The products were identified by comparing their physical and spectral data with the reported compound.