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Thiourea dioxide with TBHP: a fruitful and greener recipe for the catalytic oxidation of alcohols†

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Sanny Verma, Raghuvir Singh, Deependra Tripathi, Piyush Gupta, Gajendra Mohan Bahuguna and Suman L. Jain*

Thiourea dioxide, owing to its hydrogen bonding ability, has been established as an exceptional, widely applicable organocatalyst. In the present paper, thiourea dioxide, an organocatalyst, in combination with *t*-butyl hydroperoxide (TBHP), a non-toxic and environmentally benign oxidant, serves to be a greener and more fruitful approach for the oxidation of alcohols to corresponding carbonyl compounds in excellent yields under mild reaction conditions.

During the past decade, molecules derived from urea and (thio)urea have emerged to be an important class of small molecule organocatalyst.[1] The prominent feature of these catalysts is their ability to form double hydrogen bonds with the substrates, which provides an inimitable approach of activation to a chemical reaction. In view of the similar mode of activation, very recently thiourea dioxide (TUD),[2] readily prepared by the reaction of thiourea and hydrogen peroxide, has proven to be a promising organocatalyst for a number of challenging transformations.[3] The oxidation of alcohols to their corresponding carbonyl compounds is one of the most fundamental transformations in both academia and industrial manufacturing.[4] Traditionally, the oxidation of alcohols is accomplished using stoichiometric amounts of metallic oxidants, mainly chromium and manganese reagents,[5] which produces copious amounts of toxic and hazardous metallic waste. As a consequence, a number of catalytic methods by using metallic derivatives with clean oxidants such as O_2, H_2O_2 and alkyl peroxides have been developed.[6–8] Unfortunately, most of the existing processes are performed by using costly and toxic metal based catalysts. From the standpoint of green chemistry, chemical transformations that use organic catalysts, or organocatalysts, have become an area of contemporary research in recent years.[9] The use of organocatalysis is preferred as it offers the prospect of savings in cost, time, and energy, and a reduction in chemical waste. To the best of our knowledge there are limited literature reports on the use of organocatalysts[10] or metal free systems[11] for the oxidation of alcohols and there is no literature report using an organocatalyst with TBHP as an oxidant for this transformation. Very recently, Mlochowski *et al.* reviewed the oxidation of various organic compounds with hydroperoxides (such as *tert*-butyhydroperoxide and hydrogen peroxide) catalyzed by non-heavy metal containing low-molecular-weight compounds and enzymes including perhydrates, hydroperoxysulfonylhalides, oxazilidines, hydroperoxyflavines, aminoacids, polyaminoacids, cyclodextrins, bases, acids and urea.[12] Our research is inspired by a recent report by Tripathi and Mukherjee [13] describing the *N*-bromosuccinimide (NBS)-mediated oxidation of alcohols catalyzed by thiourea derivatives as the organocatalyst. The main drawbacks of this method are the use of NBS as an oxidant, producing brominated by-products, as well as longer reaction times. To overcome the drawbacks associated with this method, we envisioned that the catalytic efficiency of alcohol oxidation could be improved by modifying the structure of the catalyst and therefore we planned to use thiourea dioxide as a catalyst, which, owing to the presence of two extra oxygen atoms, can form stronger hydrogen bonds to provide higher activation than the corresponding thiourea.

In continuation of our on-going studies on organocatalytic transformations, herein we report thiourea dioxide (TUD) (Fig. 1) as a convenient and cost effective organocatalyst, allowing a fruitful and efficient oxidation of a variety of alcohols to the corresponding carbonyl compounds by using *tert*-butyl hydroperoxide (TBHP) as a terminal oxidant under simple experimental conditions (Scheme 1).

We started our study by comparing the catalytic activities of thiourea and thiourea dioxide (TUD) **1** for the oxidation of benzhydrol by using 5 mol % catalysts in acetonitrile at 65 °C in the presence of TBHP (1.5 M solution in dodecane) for 4 h. As

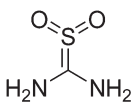
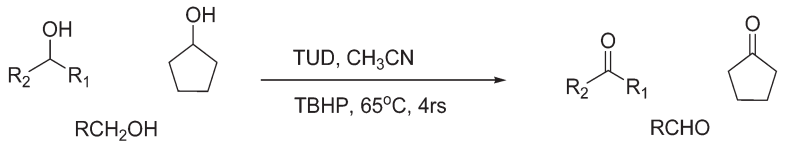


Fig. 1 Thiourea dioxide (TUD) **1**.

Chemical Sciences Division, CSIR-Indian Institute of Petroleum, Mohkampur, Dehradun-248005, India. E-mail: suman@iip.res.in

† Electronic supplementary information (ESI) available: Copies of ^1H and ^{13}C NMR spectra of the products are given in the supporting information. See DOI: 10.1039/c3ra21971b



Scheme 1 Oxidation of alcohols.

expected, thiourea was found to be a less active catalyst and provided incomplete oxidation of benzhydrol (30%), whereas thiourea dioxide exhibited excellent activity and afforded complete conversion with the 94% isolated yield of the benzophenone (Table 1, entry 1). Similarly, the oxidation of benzhydrol, cyclopentanol and 4-methyl benzyl alcohol was studied by using thiourea as a catalyst under identical experimental conditions. The results of these experiments are summarized in Table 1 (entry 2,5,8). In all cases thiourea exhibited lower catalytic acitivity and afforded a poorer yield of the oxidized products than thiourea dioxide. In the absence of TUD, the oxidation of benzhydrol was found to be very slow and yielded only 20% conversion even after a prolonged reaction time (8 h). The reaction was found to be slow at room temperature and 65 °C was found to be the optimum for the present transformation.

This led us to extend the scope of the reaction and consequently we performed the oxidation of a variety of alcohols including primary, secondary and 1,2-diols under described reaction conditions. These results are summarized in Table 1. As shown in Table 1, all the substrates were efficiently converted to their corresponding carbonyl compounds and afforded a high to excellent yield of the desired products. Benzyl alcohol and its derivatives containing electron donating and withdrawing groups in the aromatic ring, *i.e.*, 4-methyl-, 4-methoxy, 4-chloro-, 3-nitro-, and 2,4,6-trimethybenzyl alcohols were selectively oxidized to their corresponding benzaldehydes and 2,4,6-trimethyl benzaldehyde, respectively, without any evidence for the formation of the corresponding acids instead of their oxidation products. Compared to benzylic alcohols, aliphatic alcohols showed relatively lower activities in the oxidation. In the case of secondary alcohols, those having carbonyl groups at an adjacent position, such as benzoins, were found to be the most reactive compared to the aromatic groups containing secondary alcohols. Aliphatic alcohols and unactivated secondary alcohols such as borneol were also conveniently oxidized to the corresponding ketones and afforded higher yields of the corresponding ketones. In order to explore the further utility of the catalytic system, we studied the oxidation of various 1,2-diols under similar reaction conditions, providing 1,2-diones in moderate to higher yields.

Compared to the recent report by Tripathi and Mukherjee,[13] our method provides a number of advantages such as the use of an environmentally benign oxidant in place of NBS, shorter reaction times (4 h as compared to 34 h), and higher product yields (>85%) with the selective formation of desired products.

In order to establish the mechanism, we determined the Hammett correlation for studying the influence of the electronic effects of the substituents on the rate of the reaction. The oxidation of a series of 4-X-substituted benzyl alcohols (X-$ArCH_2OH$), where X is NO_2, Cl, Me, or OMe, was investigated with the TUD/TBHP system under the described reaction conditions. Each one of these precursors was treated with the unsubstituted benzyl alcohol to determine the relative reactivity ratio k_x/k_H, by determining the relative amounts of the two resultant aldehydes (X-ArCHO and PhCHO, respectively) by GC analysis. According to the Hammett equation ($\log k_x/k_H = \rho\sigma$), the log k_x/k_H ratios were plotted *vs.* the substituent constant σ of the substituent X. The linear plot with the negative value of rho ($\rho = -2.31$) indicates the formation of the positive charge in the rate determining step of the reaction (Fig. 2). Based on this finding, it is proposed that the intermolecular hydrogen bonding between thiourea dioxide (Lewis base) and TBHP might be increasing the electrophilic character of peroxy oxygen atom of the TBHP. This activated oxygen subsequently reacts with the nucleophilic alcoholic group and, at the same time, assists the leaving group (^{t}BuOH and H_2O) in departing from the reactive intermediate (Scheme 2). The presence of electron donating groups in substituted benzyl alcohols increases the nucleophilic character of the OH group, which in turn might be responsible for the increased reaction rates in the case of substrates having electron donating substituents.

In conclusion, we have developed a greener and fruitful approach for the oxidation of a variety of alcohols by using thiourea dioxide, an organocatalyst, in conjunction with TBHP, a non-toxic and environmentally benign oxidant, to give carbonyl compounds in high to excellent yields. The remarkable advantage of the developed protocol is the facile synthesis, inexpensive higher catalytic activity as compared to the thiourea derivatives. Furthermore, the developed protocol provides selective oxidation of primary alcohols to aldehydes in higher to excellent yields, which is very useful from synthetic viewpoints. We further believe that the use of TUD as an organocatalyst will open several new prospective routes towards developing the greener and sustainable chemical synthesis.

Experimental

General

All commercially available substrates and solvents were used as received. The melting points were determined in open-capillaries on a Buchi apparatus and are uncorrected. The IR spectra were recorded on a Perkin-Elmer FT-IR X 1760 instrument. Elemental analyses were carried out by using an ASTM D-3828 (Kjeldhal method). ^{1}H NMR and ^{13}C NMR were recorded on a Bruker AVANCE III-500 MHz NMR spectrometer using TMS as an internal reference.

Table 1 Oxidation of alcohols, diols and α-hydroxyketones[a]

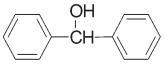
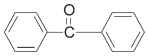
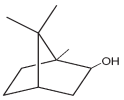
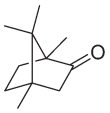
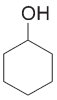
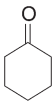
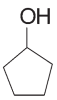
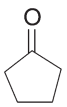
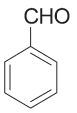
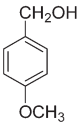
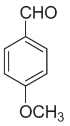
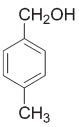
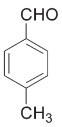
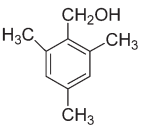
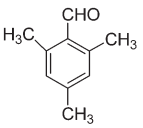
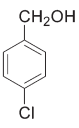
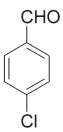
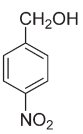
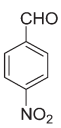
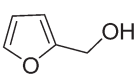
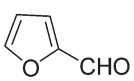
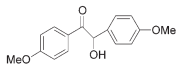
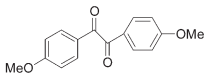
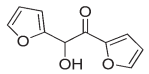
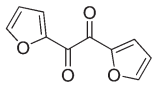
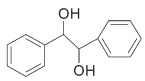
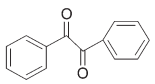
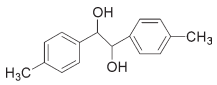
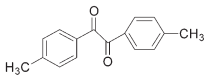
Entry	Substrate	Product	Time(h)	Yield (%)[b]
1			4, 8[c]	94, 30[d], 20[c]
2			4	90, 45[d]
3			4	76
4			4	85
5			4	90, 55[d]
6			4	92
7			4	90
8			4	92, 76[d]
9			4	90
10			4	88
11			4	80
12			4.5	90

Table 1 (*Continued*)

Entry	Substrate	Product	Time(h)	Yield (%)[b]
13			2.5	95
14			2.5	96
15			4.5	90
16			4.5	86
17			4.5	89

[a] Reaction conditions: substrate (1 mmol), TUD (5 mol %), TBHP (1.5 eq.), at 65 °C. [b] Isolated yields. [c] Blank experiment in the absence of the catalyst. [d] Control experiments by using thiourea as a catalyst under otherwise similar experimental conditions.

Synthesis of thiourea dioxide. Thiourea (0.5 mol, 32 g) was dissolved in water (300 ml) which gave a clear solution on stirring. Then ammonium bicarbonate (8 g L^{-1}) solution was added drop wise into the aqueous solution of thiourea to maintain the pH of the solution between 5.0 and 5.5. The resulting solution was cooled to 8 °C, at this temperature 50 wt% hydrogen peroxide (75 g) was added to the thiourea solution over a period of 90 min under vigorous stirring. The mixture continued to stir at this temperature for further 60 min and the resulting thiourea dioxide was separated. The precipitated thiourea dioxide was obtained by filtration, dried under vacuum for 3 h and kept under vacuum. Yield, 30 g (80%); IR (KBr) cm^{-1}: 3262, 3055, 2784, 2217, 1699, 1066, 1027. The elemental analysis values of the prepared thiourea dioxide were: calcd (found); C% 11.11 (11.08); H% 3.73 (3.82); N% 25.91 (24.86).

General experimental procedure for the oxidation of alcohols. To the stirred mixture of alcohol (1.0 mmol), anhydrous TBHP in dodecane (1.5 mmol) and acetonitrile (2 ml) was added to the catalyst TUD (5 mol %). The resulting mixture was stirred and refluxed at 65 °C for the time reported in Table 1. Progress of the reaction was monitored by TLC. After completion, the reaction mixture was concentrated under reduced pressure and the obtained residue was dissolved in diethyl ether and filtered to remove TUD. The organic layer was washed with water, dried and concentrated under reduced pressure. Again, the crude compound was diluted with dichloromethane (10 ml) and the organic layer was washed with brine solution (5 ml × 2). The organic layer was separated, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified with column chromatography (SiO_2) using ethyl acetate–hexane (1 : 9) as the eluent. The selectivity and conversion were determined by high resolution GC–MS analysis; however the identity of the products was confirmed by comparing their physical and spectral data with the known compounds.

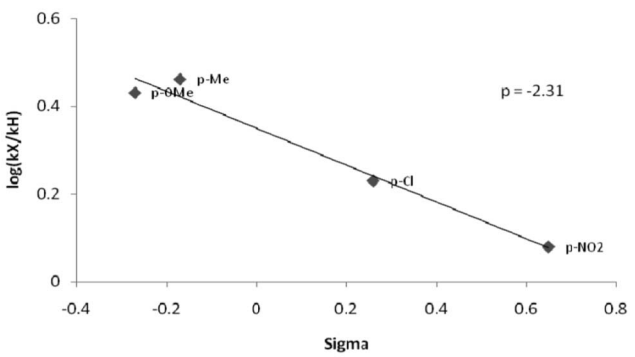
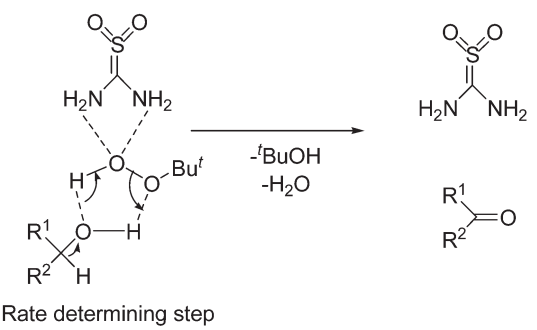


Fig. 2 Hammett plot for the oxidation of 4-X-substitutedbenzyl alcohols with the TUD/TBHP system.



Scheme 2 Possible mechanistic pathway.

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