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Organocatalytic Approach for Transfer Hydrogenation of Quinolines, Benzoxazines and Benzothiazines

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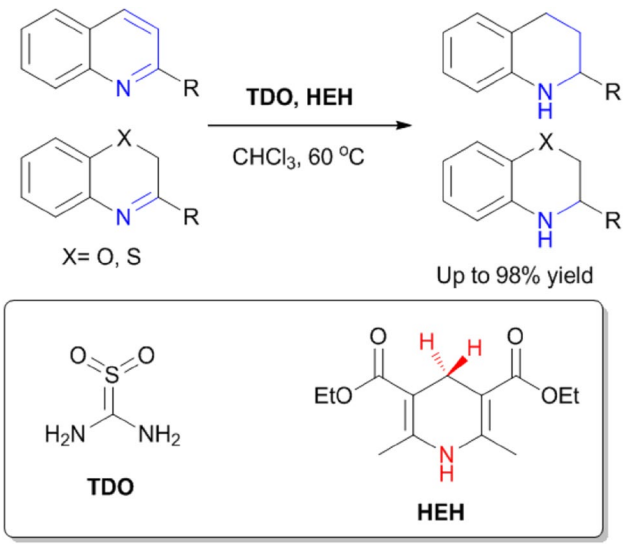
Abstract This study reports on the thiourea dioxide catalyzed transfer hydrogenation of diverse C=N–containing heterocyclic compounds with Hantzsch ester as the hydrogen source. With this cost effective and readily available catalyst, a wide range of 2-substituted quinolines, 3-substituted-2H-1,4-benzoxazines and 3-substituted-2H-1,4-benzothiazines were efficiently reduced to the corresponding tetrahydroquinolines, dihydro-2H-benzoxazines and dihydro-2H-benzothiazines under mild conditions.

Graphical Abstract This study reports on the first thiourea dioxide catalyzed transfer hydrogenation of 2-substituted quinolines, 3-substituted-2H-1,4-benzoxazines and 3-substituted-2H-1,4-benzothiazines with Hantzsch 1,4-dihydropyridine as the hydrogen source.



Keywords Thiourea dioxide · Transfer hydrogenation · Quinoline · Benzoxazine · Benzothiazine

1 Introduction

The use of small molecule metal-free hydrogen-bond in catalysis is an important frontier of research in recent years [1–6]. In this context, a number of classes of compounds have been introduced including binols [7], silanediols [8, 9], squaramides [10–13], and α,α,α,α-tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOLs) [14, 15], but no species have received more attention than thioureas [16–21]. Thioureas have two N–H bonds, which can activate substrate via hydrogen bonding and facilitate a nucleophilic attack [22, 23]. In addition, their catalytic properties are possible to be

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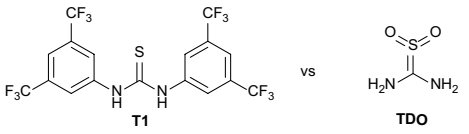


Scheme 1 Schreiner thiourea (**T1**) and thiourea dioxide (**TDO**)

intricately tuned through the systematic adjustment of their structures by incorporation of various substituents or chiral building blocks [24, 25]. Among thiourea-based derivatives reported, *N,N′*-bis(trifluoromethyl)phenylthiourea [(3,5-$(CF_3)_2C_6H_3NH)_2CS$] (**T1**), also known as Schreiner's thiourea [26–28], has stood to be a privileged catalyst for a plethora of chemical transformations [29]. While the past 20 years have seen many examples of H-bond activation with **T1** under remarkably mild conditions and with high reactivity, no profitable practical applications have yet been developed. This is mainly because of the cost of **T1** and considerably tedious separation process after the reaction (Scheme 1).

Recently, thiourea dioxide, one of the best known reducing agents in textile, paper and other industries, has started to serve as a new arsenal in organocatalysis, as it shows stronger hydrogen bonding activation than thiourea itself owing to the presence of two extra electronegative oxygen atoms [30]. Sain and co-workers reported that thiourea dioxide was an efficient organocatalyst for the synthesis of a series of heterocyclic compounds via one-pot multicomponent coupling reactions [31]. Jain and co-workers demonstrated that thiourea dioxide in combination with *t*-butyl hydroperoxide (TBHP) served to be a fruitful and greener recipe for the catalytic oxidation of sulfides and alcohols [32, 33]. Mansoor et al. developed a simple and highly efficient TDO-catalyzed one-pot synthesis of pyrano[4,3-*b*] pyran derivatives in water [34]. Bhale and Patel groups reported the efficient synthesis of 1,8-dioxooctahydoxanthenes and 1,4-dihydropyrano[2,3-*c*]-pyrazole-5-carbonitrile derivatives in aqueous media, respectively [35, 36]. Although the exact mechanisms for these transformations are unknown at current stage, most of its catalytic activity was attributed to H-bond interaction with the substrates. In view of the great potential utilization of TDO as an alternative H-bond catalyst, together with our recently developed **T1**-catalyzed biomimetic reduction of quinolines [37], as well as other hydrogenation of quinolines [38–41], we reasoned that it might be possible to replace **T1** with TDO in the transfer hydrogenation of quinolines with Hantzsch ester as the hydrogen source [42–44]. Similarly, this strategy can even be further extended to the reduction of benzoxazines and benzothiazines. This would not only be the first example of TDO-catalyzed transfer hydrogenation of these substrates, but also give direct access to the biologically relevant building blocks, 1,2,3,4-tetrahydroquinolines, dihydro-2H-benzoxazines and dihydro-2H-benzothiazines (Scheme 2).

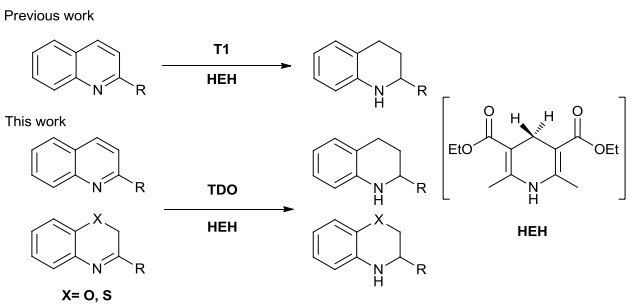
2 Experimental

2.1 Materials

Unless otherwise noted, all materials were obtained from commercial suppliers and were used without further purification. Solvents for chromatography were of technical grade and were distilled prior to use. Solvents used in the reactions were reagent grade. For thin-layer chromatography (TLC), silica gel plates coated glass plates (Haiyang) were used and chromatograms were visualized by irradiation with UV light. Column chromatography was performed using silica gel (200–300 mesh) from Haiyang. Solvent mixtures are understood as volume/volume.

2.2 Instrumentation

All NMR experiments were performed on a Bruker Avance 400 MHz NMR spectrometer equipped with a 5 mm BBO probe at 295 K. The data were collected and processed by TOPSPIN software (Bruker) running on a PC with Microsoft Windows 7. Proton and ^{13}C chemical shifts were referred to the solvent signal ($CDCl_3$) at 7.26 and 77.23 ppm, respectively. Data are presented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, cm = complex multiplet) and coupling constant in Hertz (Hz). Infrared (IR) spectra were scanned with thermo NICOLET 6700 in terms of frequency of absorbtion (cm^{-1}). GC analyses were carried out with a SHIMADZU GC-2010 Plus gas chromatograph equipped with a Agilent J&W scientific fused silica GC column



Scheme 2 Thiourea catalyzed transfer hydrogenations with HEH

(30 m × 0.250 mm, 0.25 micron HP-5 stationary phase: (5%-Phenyl)-methylpolysiloxane) using nitrogen as carrier gas; T-program standard 60–250 °C (15 °C/min heating rate), injector and transfer line 250 °C.

2.3 General Procedure for Transfer Hydrogenation of 2-Substituted Quinolines

An oven-dried flask was fitted with magnetic stirring bar and charged with 2-substituted quinoline (0.10 mmol), thiourea dioxide (1 mol%), Hantzsch dihydropyridine (2.5 equiv.) and chloroform (1 mL). The resulting mixture was stirred at 60 °C for 24–48 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using hexane/EtOAc (20:1) as eluent to yield the corresponding 1,2,3,4-tetrahydroquinolines.

2.4 General Procedure for Transfer Hydrogenation of 3-Substituted-2H-1,4-Benzoxazines

An oven-dried flask was fitted with magnetic stirring bar and charged with 3-substituted-2H-1,4-benzoxazine (0.10 mmol), thiourea dioxide (1 mol%), Hantzsch dihydropyridine (1.3 equiv.) and chloroform (1 mL). The resulting mixture was stirred at 60 °C for 16 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using hexane/EtOAc (15:1) as eluent to yield the corresponding products.

2.5 General Procedure for Transfer Hydrogenation of 3-Substituted-2H-1,4-Benzothiazines

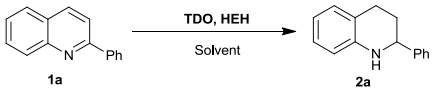
An oven-dried flask was fitted with magnetic stirring bar and charged with 3-substituted-2H-1,4-benzothiazine (0.10 mmol), thiourea dioxide (10 mol%), Hantzsch dihydropyridine (1.3 equiv.) and chloroform (1 mL). The resulting mixture was stirred at 60 °C for 48 h. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel using hexane/EtOAc (15:1) as eluent to yield the corresponding products.

3 Results and Discussion

3.1 Optimization of TDO Catalyzed Transfer Hydrogenation of 2-Phenylquinoline

To test our hypothesis, we first examined the reduction of 2-phenyl quinoline with TDO as a catalyst. To our delight, in the presence of 20 mol% of TDO and 2.5 equiv. of HEH, the reaction proceeded smoothly in toluene at 60 °C, giving a 77% conversion of substrate at 24 h (Table 1, entry 1). It should be noted that TDO, sparingly soluble in toluene, has been able to promote this transformation. Encouraged by this result, we further investigated solvent effects on reaction outcomes (Table 1, entries 2–9). Without regard to the solubilities of TDO in common organic solvents, when the reaction was carried out in polar solvents such as EtOAc, DMF, MeOH, THF, and EtOH, it gives the conversions in the range of 34–86%, presumably due to competitive H-bond interaction in these solvents. $CHCl_3$ and CH_3CN proved to be optimal solvents for this transformation, furnishing the product in excellent conversions (entries 2 and 4). Using $CHCl_3$ as the solvent, we evaluated other reaction parameters including temperature and catalyst loadings. The reaction proceeds slowly as the temperature decreases (entries 10–12). Notably, the catalyst loading could be reduced to 1 mol% without obvious compromise of the conversion

Table 1 Optimization of transfer hydrogenation of 2-phenylquinoline



Entry[a]	Catalyst (mol%)	Solvent	Conversion[b] (%)
1	20	Toluene	77
2	20	$CHCl_3$	98
3	20	EtOAc	52
4	20	CH_3CN	97
5	20	DMF	34
6	20	MeOH	53
7	20	THF	86
8	20	EtOH	84
9	20	CH_2Cl_2	39[c]
10	20	$CHCl_3$	74[d]
11	20	$CHCl_3$	44[c]
12	20	$CHCl_3$	8[e]
13	10	$CHCl_3$	92
14	5	$CHCl_3$	91
15	3	$CHCl_3$	90
16	1	$CHCl_3$	88
17	0.1	$CHCl_3$	40[f]
18	0	$CHCl_3$	6

[a]The reactions were performed with 2-phenylquinoline (0.10 mmol) and HEH (0.25 mmol) in 1 mL of solvent at 60 °C for 24 h

[b]Conversion is determined by GC analysis with tridecane as the internal standard.

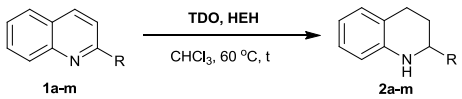
[c]At 40 °C

[d]At 50 °C

[e]At r.t.

[f]48 h

Table 2 Transfer hydrogenation of 2-substituted quinolines



Entry[a]	R	Time (h)	Yield[b] (%)
1	Phenyl	24	87 (85)[c]
2	4-Methylphenyl	48	90
3	4-Isopropylphenyl	48	83
4	4-Methoxyphenyl	48	84
5	1,1′-Biphenyl-4-yl	48	80
6	2,4-Dimethylphenyl	48	88
7	4-Chlorophenyl	24	89
8	4-Bromophenyl	24	87
9	2-Fluorophenyl	24	86
10	*n*-Butyl	24	77
11	Methyl	24	80
12	2-(3,4-Methylenedioxy-phenyl)ethyl	24	84
13	Vinyl	24	69 [d]

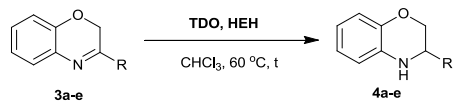
[a]All reactions were performed with quinoline (0.10 mmol) and HEH (0.25 mmol) in the presence of 1 mol% of thiourea dioxide at 60 °C in 1 mL of $CHCl_3$

[b]Yield of isolated product after column chromatography

[c]With 1.025 g of 2-phenylquinoline

[d]Affording 2-ethyl-1,2,3,4-tetrahydroquinoline as product

Table 3 Transfer hydrogenation of 3-substituted-2H-1,4-benzoxazines



Entry[a]	R	Time (h)	Yield[b] (%)
1	Phenyl	16	98
2	4-Methylphenyl	16	96
3	4-Methoxyphenyl	16	92
4	4-Bromophenyl	16	89
5	4-Chlorophenyl	16	89

[a]All reactions were performed with 2 H-1,4-benzoxazine (0.10 mmol) and HEH (0.13 mmol) in the presence of 1 mol% of thiourea dioxide at 60 °C in 1 mL of $CHCl_3$

[b]Yield of isolated product after column chromatography

(entries 13–16), suggesting that TDO is even more efficient than **T1** in accelerating this transformation. A control experiment showed that no reaction took place in the absence of TDO, indicating the crucial role of TDO in substrate activation (Table 1, entry 18).

3.2 Scope of TDO Catalyzed Transfer Hydrogenation of 2-Phenylquinoline

Subsequently, the optimized conditions were used for further evaluation of the substrate scope (Table 2). Various 2-substituted quinolines were subjected to this transfer hydrogenation reactions and smoothly converted into 1,2,3,4-tetrahydroquinolines in high to excellent yields (entries 1–12). Substrates with electron-donating substituents on 2-phenyl ring need longer time to give a satisfactory yield (Table 2, entries 2–6). The halogen substituents (F, Cl, Br) at 2-phenyl ring slightly improved the reactivity and afforded the desired product in high yields within 24 h (Table 2, entries 7–9). In addition, 2-butyl and 2-methyl quinolines also proceeds smoothly, affording the product with 77% yield (Table 2, entries 10–11). This new methodology is also applicable to the production of biologically active alkaloid galipinine (Table 2, entry 12). Notably, when 2-vinylquinoline was employed as the substrate, a product of 2-ethyl-1,2,3,4-tetrahydroquinoline was afforded (Table 2, entry 13). From a practical point of view, a gram-scale experiment with 2-phenylquinolines (1.025 g) has also been performed, giving the product in 85% yield (Table 2, entry 1).

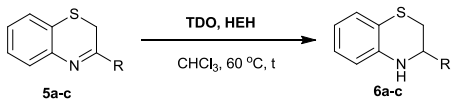
3.3 TDO Catalyzed Transfer Hydrogenation of 3-Substituted-2H-1,4-Benzoxazines

In view of the structural similarities of quinolines with benzoxazines and benzothiazines, we further extended this protocol to these two types of substrates, as the reduced products dihydro-2H-benzoxazines and dihydro-2H-benzothiazines are of great interest in pharmaceuticals [45–47]. Benzoxazine **3a** was initially tested as a benchmark for comparison to quinolines. Gratifyingly, in the presence of 1 mol% of TDO and 1.3 equiv. of HEH, benzoxazine **3a** was successfully converted to 3-phenyl-substituted product **4a** with 98% yield, which exhibited higher reactivity than quinoline derivatives, since the reaction can be completed in less reaction time (16 vs. 24–48 h). Substitutions with either electron-donationg or -withdrawing groups at 3-substituted phenyl ring showed marginal effect on reactivities and all the corresponding products **4b–e** were obtained in high to excellent yields (Table 3).

3.4 TDO Catalyzed Transfer Hydrogenation of 3-Substituted-2H-1,4-Benzothiazines

After transfer hydrogenation of quinolines and benzoxazines were established with this organocatalytic protocol, we next turned our attention to the reduction of benzothiazines, which was generally considered to be challenging substrates for transition metal catalysts because of the

Table 4 Transfer hydrogenation of 3-substituted-2H-1,4-benzothiazines



Entry[a]	R	Time (h)	Yield[b] (%)
1	Phenyl	48	78
2	4-Methoxyphenyl	48	81
3	4-Bromophenyl	48	80

[a]All reactions were performed with 2H-1,4-benzothiazine (0.10 mmol) and HEH (0.13 mmol) in the presence of 10 mol% of thiourea dioxide at 60 °C in 1 mL of $CHCl_3$

[b]Yield of isolated product after column chromatography

poison of sulfur-containing compounds to them. Initially, In the presence of 1 mol% of TDO, when 3-phenyl substituted benzothiazine **5a** was used as a model substrate, the reaction proceeded much slowly and was not completed even with prolonged reaction time (48 h). Pleasingly, simply increasing the catalyst loading to 10 mol% could greatly improve the catalytic activities of TDO and all substrates **5a–c** exhibited good reactivaties in the transfer hydrogenation reaction, furnishing the corresponding dihydro-2H-benzothiazines **6a–c** in good yields (Table 4).

4 Conclusions

In conclusion, we have developed an efficient transfer hydrogenation of C=N-containing heterocyclic derivatives including quinolines, benzoxazines and benzothiazines with thiourea dioxide as a cost effective and readily available catalyst and HEH as the hydrogen source. This method represents not only the first example of thiourea dioxide-catalyzed transfer hydrogenation of these substrates, but also give direct access to the biologically relevant building blocks, 1,2,3,4-tetrahydroquinolines, dihydro-2H-benzoxazines and dihydro-2H-benzothiazines under mild reaction conditions. Further studies will be directed to the further application of thiourea dioxide in organocatalytic transformations and potential utilization of chiral thiourea dioxides for asymmetric transfer hydrogenation of heterocyclic compounds.

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References

1. Taylor MS, Jacobsen EN (2006) Angew Chem Int Ed 45:1520–1543
2. Doyle AG, Jacobsen EN (2007) Chem Rev 107:5713–5743
3. Yu X, Wang W (2008) Chem Asian J 3:516–532
4. Wende RC, Schreiner PR (2012) Green Chem 14:1821–1849
5. Phipps RJ, Hamilton GL, Toste FD (2012) Nat Chem 4:603–614
6. Auvil TJ, Schafer AG, Mattson AE (2014) Eur J Org Chem 13:2633–2646
7. Yu S, Pu L (2015) Tetrahedron 71:745–772
8. Tran NT, Wilson SO, Franz AK (2011) Org Lett 14:186–189
9. Schafer AG, Wieting JM, Fisher TJ, Mattson AE (2013) Angew Chem 125:11531–11534
10. Alemán J, Parra A, Jiang H, Jørgensen KA (2011) Chem Eur J 17:6890–6899
11. Storer RI, Aciro C, Jones LH (2011) Chem Soc Rev 40:2330–2346
12. Tsakos M, Kokotos CG (2013) Tetrahedron 69:10199–10222
13. Chauhan P, Mahajan S, Kaya U, Hack D, Enders D (2015) Adv Synth Catal 357:253–281
14. Seebach D, Beck AK, Heckel A (2001) Angew Chem Int Ed 40:92–138
15. Pellissier H (2008) Tetrahedron 64:10279–10317
16. Kotke M, Schreiner P (2009) In: Pihko PM (ed) (Thio) urea organocatalysts. Wiley, Weinheim, pp 141–351
17. Zhang Z, Schreiner PR (2009) Chem Soc Rev 38:1187–1198
18. Connon SJ (2006) Chem Eur J 12:5418–5427
19. Takemoto Y (2010) Chem Pharm Bull 58:593–601
20. Serdyuk OV, Heckel CM, Tsogoeva SB (2013) Org Biomol Chem 11:7051–7071
21. Fang X, Wang C-J (2015) Chem Commun 51:1185–1197
22. Schreiner PR (2003) Chem Soc Rev 32:289–296
23. Takemoto Y (2005) Org Biomol Chem 3:4299–4306
24. Jakab G, Tancon C, Zhang Z, Lippert KM, Schreiner PR (2012) Org Lett 14:1724–1727
25. Fan Y, Kass SR (2016) Org Lett 18:188–191
26. Schreiner PR, Wittkopp A (2002) Org Lett 4:217–220
27. Wittkopp A, Schreiner PR (2003) Chem Eur J 9:407–414
28. Lippert KM, Hof K, Gerbig D, Ley D, Hausmann H, Guenther S, Schreiner PR (2012) Eur J Org Chem 30:5919–5927
29. Zhang ZG, Bao ZB, Xing HB (2014) Org Biomol Chem 12:3151–3162
30. Makarov SV, Horvath AK, Silaghi-Dumitrescu R, Gao Q (2014) Chem Eur J 20:14164–14176
31. Verma S, Kumar S, Jain SL, Sain B (2011) Org Biomol Chem 9:6943–6948
32. Kumar S, Verma S, Jain SL, Sain B (2011) Tetrahedron Lett 52:3393–3396
33. Verma S, Singh R, Tripathi D, Gupta P, Bahuguna GM, Jain SL (2013) RSC Adv 3:4184–4188
34. Ghashang M, Mansoor SS, Aswin K (2014) Chin J Catal 35:127–133
35. Bhale PS, Dongare SB, Mule YB (2014) Chem Sci Trans 4:246–250
36. Vekariya RH, Patel KD, Patel HD (2016) Res Chem Intermed 42:4683–4696
37. Qiao X, Zhang Z, Bao Z, Su B, Xing H, Yang Q, Ren Q (2014) RSC Adv 4:42566–42568
38. Rueping M, Antonchick AP, Theissmann T (2006) Angew Chem Int Ed 45:3683–3686
39. Guo QS, Du DM, Xu J (2008) Angew Chem Int Ed 47:759–762
40. Tu X-F, Gong L-Z (2012) Angew Chem Int Ed 51:11346–11349
41. Wang WB, Lu SM, Yang PY, Han XW, Zhou YG (2003) J Am Chem Soc 125:10536–10537

42. Ouellet SG, Walji AM, Macmillan DWC (2007) Acc Chem Res 40:1327–1339
43. Zheng C, You SL (2012) Chem Soc Rev 41:2498–2518
44. Herrera RP (2016) Top Curr Chem 374:29
45. Urbanski T, Radzikowski C, Ledochowski Z, Czarnocki W (1956) Nature 178:1351–1352
46. Achari B, Mandal SB, Dutta PK, Chowdhury C (2004) Synlett 14:2449–2467
47. Alipour M, Khoobi M, Emami S, Fallah-Benakohal S, Ghasemi-Niri SF, Abdollahi M, Foroumadi A, Shafiee A (2014) Daru 22:1