Direct reductive amination of aldehydes and ketones mediated by a thiourea derivative as an organocatalyst Yi-Bo Huang and Chun Cai*

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The direct reductive arylamination of arylaldehydes and ketones has been achieved using a selective imine activation by a hydrogen bond of a thiourea derivative. This mild, acid- and metal-free process requires a catalytic amount of N,N'-bis[3,5-bis(trifluoromethyl)phenyl]thiourea, the Hantzsch 1,4-dihydropydine diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate as hydride source and activated 5Å-molecule sieve as dehydrant. The method is adaptable for the synthesis of various amines.

Keywords: thiourea derivative, reduction, organocatalyst, hydrogen bond, amination

Chiral amines are key structural units in many biologically active natural products and pharmaceuticals.^{1,2} Reductive amination is an effective method for the synthesis of various amines in which the carbonyl component is treated with an amine and reductant in a "one-pot" fashion. Thus, many methods have been reported to accomplish this direct process.³⁻⁶ Some classic methods such as the procedure of Borch^{7,8} rely on a Brønsted acid or Lewis acid to facilitate the formation of the intermediate imines and to activate the C=N for preferential reduction in the presence of a carbonyl compound.

Nevertheless, application of these methods to sensitive, acid-labile or polyfunctional substrates is limited. Many of these procedures seem not to be adaptable for asymmetric variants.³ This leads to the development of novel catalysts for a mild direct reductive amination.

We report here the direct reductive amination of aldehyde and ketone based on a hydrogen bond for imine activation, based on Menche's reports of thiourea-catalysis applied to the direct reductive amination.^{9,10} In Menche's reports, this acid-free reaction is mediated by thiourea as a simple organocatalyst. Unfortunately the reaction time was long and the catalyst loading was large. We considered that a some modified thiourea derivative might catalyse these reactions,¹¹⁻¹⁴ and thought that an electron-deficient thiourea derivative could accelerate this process effectively. In addition, we examined the scope of the method for the synthesis of various amines is described in our studies.

Biosynthetically, amines may be derived by the reductive amination of carbonyl groups by NADH-transferases or by the vitamin B_6 pathway.¹⁵ During the biosynthetic process NADH acts as reducing agent and some enzyme may activate the imine by hydrogen bond. To mimic the key feature of biosynthetic pathway, the combination of a Hantzsch 1,4-dihydropydine and thiourea derivative was selected as the basis for our studies.

Only a few reports describe the reduction of imines by the Hantzsch 1,4-dihydropydine 3, and these reactions proceeded in low yield and required an extended reaction time. Lewis

acid activation¹⁶ of the imine significantly improved this result. The groups of Rueping¹⁷ and List¹⁸ have recently reported on the organocatalytic, asymmetric hydrogenation of imines by **3** in the presence of a chiral Brønsted acid. Unfortunately, these methods have not been adaptable for direct reductive amination.

We studied the direct reductive amination of aldehydes and ketones mediated by N,N'-bis[3,5-bis(trifluoromethyl) phenyl]thiourea **4** using the Hantzsch 1,4-dihydropyridine **3** as the reducing agent as shown in Scheme 1. We hoped to obtain better results with a thiourea derivative rather than with thiourea itself.

First, we began to explore the direct reduction of benzaldehyde and *p*-anisidine using Hantzsch 1,4-dihydropydine as a model reaction. The comparative catalytic activities of thiourea and its derivative were examined (see Table 1). Obviously, the electron deficient thiourea catalyst was more active than thiourea. As shown from entries 3 to 5, the reaction yields were excellent. It showed that thiourea derivative **4** was so efficient that the catalyst loading could be decreased to 0.01equiv. In addition, this direct reduction cannot happen in the absence of catalyst.

We then studied the scope of this procedure for the synthesis of sterically, electronically and functionally diverse amines (5a-m) (see Table 2). Electron-deficient (entry 3) and electron-rich (entry 4) aromatic aldehydes were both easily transformed into the products. Furthemore no reduction of nitro group (entry 3) was observed and free hydroxyl was tolerated (entry 5). In addition, an electron-deficient aromatic aldehyde afforded higher yields than an electron-rich aromatic aldehyde.

From entries 6 to 10, diverse aromatic amines were easily reacted with aromatic aldehydes. This showed that the approach can be applied to various aromatic amines. Some yields of the products were good (entries 6-8), whilst the yields of other products were moderate (entries 9-10). Functional groups such as the nitro group and the hydroxyl group in the amino substrate **2** were also tolerated during the reaction process.





Table 1 Direct amination of benzaldehyde and p-anisidine under different conditions



Entry	Catalyst/Equiv.	Conditions ^a	Yield/% ^b 22%	
1	Thiourea (0.1)	R.t. CH ₂ Cl ₂ 24 h		
2	Thiourea (1.0)	R.t. $CH_{2}CI_{2}$ 24 h	58%	
3	Thiourea derivative 4 (0.1)	R.t. CH ₂ Cl ₂ 15 h	92%	
4	Thiourea derivative 4 (0.01)	R.t. CH ₂ Cl ₂ 15 h	90%	
5	Thiourea derivative 4 (0.01)	35 °C CH ₂ Cl ₂ 15 h	92%	
6	None	50 °C, Toluene, 24 h	trace	

^a2.0 mmol benzaldehyde, 2.2 mmol *p*-anisidine, 2.4 mmol Hantzsch 1,4-dihydropydine, 5Å-molecule sieve (activated)1.0 g, solvent 10 mL.

^blsolated yield using column chromatography.

Table 2 Direct reduction reaction of substitute benzaldehyde and diverse aniline^a

Entry	R ¹	R²	R ³	Product	M.p./°C		Yield ^b /%
					Observed	Reported	
1	Ph	Н	Ph	5a	_	_22	75
2	4-CI–C ₆ H₄	Н	Ph	5b	50–52	51–52 ²⁰	81
3	$4-O_2N-C_6H_4$	Н	Ph	5c	67–69	67–69 ²⁰	90
4	4-MeO−C ₆ H₄	Н	Ph	5d	63–65	63–64 ²⁰	70
5	2-HO–C ₆ H _₄	Н	Ph	5e	110–112	113–114 ²⁰	75
6	Ph	Н	4-MeO–C ₆ H₄	5f	48–50	48.6–48.9 ⁶	90
7	Ph	Н	4-HO–C ₆ H _₄	5g	88–90	89–90 ²⁰	84
8	$4-O_2N-C_6H_4$	Н	4-MeO–C ₆ H₄	5ĥ	97–99	97.7–97.9 ⁶	93
9	4-MeO−C ₆ H₄	Н	4-MeO–C ₆ H ₄	5i	92–94	91–93 ²²	75
10	4-MeO–C ₆ H ₄	Н	$4-O_2N-C_6H_4$	5j	140-142	140–141 ²²	79
11	PhCH=CH	Н	Ph	5k	-	_21	65
12	Ph	CH ₃	4-MeO–C ₆ H₄	51	56–58	56.3–56.7 ⁶	80 ^c
13	Cyclohexanone	0	4-MeO–C ₆ H ₄	5m	_	_10	85 ^c

^aAldehyde or ketone 2.0 mmol, amine 2.2 mmol, 2.4 mmol Hantzsch 1,4-dihydropydine, 5Å molecule sieve (activated)1.0 g, CH₂Cl₂10 mL, reaction time 15 h.

^bisolated yield by column chromatography.

^cReaction time extended to 24 h.

We found that a C=C double bond in the substrate was not reduced during the reaction (entry 11). Aliphatic ketone and aromatic ketone were reduced directly to amine with good yields (entries 12 and 13). But the reaction time was extended to 24 h.

In summary, we have developed a method for the direct reductive amination of aldehydes and ketones based on the imine activation of hydrogen bond of thiourea derivative. The protocol is mild and acid-free, together with the high chemoselctivity.

Experimental

Reagents were obtained from commercial sources. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker AM 400 spectrometer using TMS as an internal standard, chemical shift values were given in ppm. Mass spectra were obtained on a Sectorfield-MS. Elemental analyses were conducted using a Yanaco MT-3CHN elemental analyser. Melting points were uncorrected. All products were known compounds and were identified by comparing their physical and spectra data with those reported in the literatures.^{6,10,19-22}

General procedure of synthesis of 4

A mixture of 3,5-bis(trifluoromethyl)aniline (50 mmol) and triethylamine (60 mmol) in THF (300 mL) was added to a 500 mL three-necked flask. A mixture of thiophosgene (22 mmol) in THF (50 mL) was added dropwise to the stirred solution at -5-0 °C. After addition, the yellow suspension (a white solid precipitated) was stirred at room temperature. After 24 h the bulk of the solvent

was removed on a rotary evaporator under reduced pressure. The concentrated brown-coloured residue was added to water (200 mL), and the aqueous layer was extracted with diethyl ether (2×80 mL). The combined organic layers were washed with brine (1×80 mL) and dried over sodium sulfate. After filtration and evaporation of the solvent, the red-brown solid crude product was purified by recrystallisation from chloroform twice. Then pure thiourea derivative catalyst was dried *in vacuo* at 70 °C.

General procedure for the direct reductive amination of aldehyde and ketone

In a typical experiment, the aldehyde or ketone **1** (2.0 mmol) and the amine **2** (2.2 mmol) in CH_2Cl_2 (10 mL) was treated with the Hantzsch 1,4-dihydropydine **3** (2.4 mmol), thiourea derivative catalyst **4** (0.02 mmol) and MS 5Å (1.0 g). The mixture was stirred at room temperature under nitrogen atmosphere. After 15 h, the crude product was filtered. Then the solvent was evaporated, the residue was purified by column chromatography on silica gel using mixtures of PE and EtOAc as elutant to give the product amines **5a**-**m** in pure form.

N,N'-bis[3,5-*bis*(*trifluoromethyl*)*phenyl*]*thiourea* (4):¹⁹ M.p. 172–173 °C, ¹H NMR(d_4 -methanol) δ : 7.27–7.33 (6H, m), 7.68(2H, s), ¹³C NMR(d_4 -methanol) δ : 120.47, 123.17, 125.87, 132.67, 142.51, 182.20. HRMS Calcd C₁₇H₈N₂SF₁₂: 500.0216. Found: 498.6. Anal Calcd for C₁₇H₈N₂SF₁₂: C, 40.81; H, 1.61; N, 5.60. Found: C, 40.69; H, 1.65; N 5.68%.

N-benzyl-p-anisidine (**5f**)⁶: M.p. 48–50 °C, ¹H NMR(CDCl₃) δ : 3.73(3H, s), 4.28(2H, s), 6.60(2H, dt, J = 9.0, 3.0 Hz), 6.77(2H, dt, J 9.0, 2.9 Hz), 7.25(1H, tt, J 6.9, 2.1 Hz), 7.30–7.37(4H, m); ¹³C NMR(CDCl₃) δ : 49.2, 55.8, 114.0, 114.8, 127.0, 127.4, 128.4, 139.5, 142.2, 152.0 Anal. Calcd for C₁₄H₁₅NO: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.87; H, 7.21; N, 6.58%.

N-(1-phenylethyl)-p-anisidine (51):⁶ M.p. 56–58 °C, ¹H NMR $(CDCl_3)$ δ : 1.49 (3H, d, J = 6.6 Hz), 3.69 (3H, s), 4.40 (1H, q, J = 6.8 Hz), 5.40 (1H, brs), 6.47 (2H, d, J = 8.8 Hz), 6.69 (2H, d, J = 8.8 Hz), 7.21 (1H, tt, J = 7.1, 1.7 Hz), 7.29–7.37 (4H, m); ¹³C NMR(CDCl₃) δ: 25.1, 54.2, 55.7, 114.5, 114.7, 125.9, 126.8, 128.6, 141.5, 145.5, 151.9. Anal. Calcd for C₁₅H₁₇NO: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.01; H, 7.78; N, 6.12%.

Received 11 August 2009; accepted 16 October 2009 Paper 09/0732 doi: 10.3184/030823409X12561332783406 Published online: 16 November 2009

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