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S-Benzyl isothiouronium chloride as a recoverable organocatalyst for the direct reductive amination of aldehydes

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ABSTRACT

The direct reductive amination of aldehydes using *S*-benzyl isothiouronium chloride as a recoverable organocatalyst for the activation of the imine intermediate through hydrogen bonding is described. A mild and operationally simple fragment coupling procedure was accomplished with a wide range of aldehydes as well as amines in good to excellent yields. In addition, the *S*-benzyl isothiouronium chloride catalyst was easily recovered by simple filtration and reused without any drop in its efficiency.

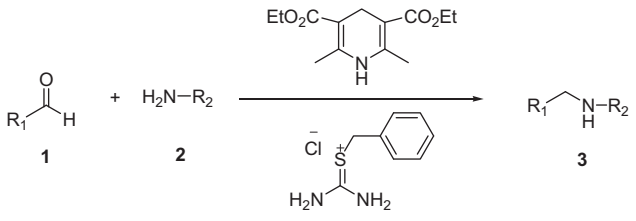
Introduction

Reductive amination is one of the most powerful methods of accessing the C–N bond, a key structural feature in natural products and pharmaceuticals,[1] in particular, when the carbonyl component is reacted directly with the amine and reducing agent, avoiding isolation of the imine intermediate.[2,3] Hantzsch ester has proven to be a powerful reductive reagent, since it permits some of the problems encountered with the traditional reductive reagents, viz. hydrogen gas/metal and metal hydrides, to be overcome, such as their limitations in the case of sensitive, acid-labile, or polyfunctional substrates.[4] However, in some cases, this reducing agent was found to be ineffective without catalysis.[2]

Thioureas are powerful organocatalytic systems and can provide considerable reaction rate acceleration through hydrogen bond interactions.[5] Isothiouroniums have been explored as prospective replacements of thioureas in the area of anion binding to enhance the acidity of the NH moieties and allow more hydrogen bonding.[6] Kilburn and co-workers reported isothiouronium based organocatalysis for enantioselective Michael addition of cyclohexanone to *trans*-beta-nitrostyrene with high conversion and stereoselectivity, as well as lower catalyst loading compared to the same thiourea based model.[7] In addition, there are many ongoing attempts to increase the efficiency of the catalysts by introducing various strategies, such as immobilizing them onto a solid support[8] or using the fluorous technique[9] to facilitate their recovery and reuse. Herein, we wish to introduce *S*-benzyl isothiouronium chloride as a novel organocatalyst with high efficiency, selectivity, and easy recovery for the direct reductive amination of aldehydes using Hantzsch ester.

Results and discussion

The hydrogen bond catalyzed direct reductive amination of aldehydes using thiourea derivatives has been reported by several groups.[3,9] This encouraged us to explore *S*-benzyl isothiouronium chloride,[6,10] which is expected to have more hydrogen bonding than the corresponding thiourea due to the enhancement of the acidity of the NH moieties,[6] in this field (Scheme 1). We first investigated the reaction of benzaldehyde with aniline and Hantzsch ester in the presence of *S*-benzyl isothiouronium chloride (Table 1). We found that benzaldehyde **1a** could be condensed and reduced to the corresponding amine **3q** without catalysis with 55% yield in 24 h. Schreiner and Zhang assumed that the auto-oxidation of



Scheme 1. The direct reductive amination of aldehydes using *S*-benzyl isothiouronium chloride.

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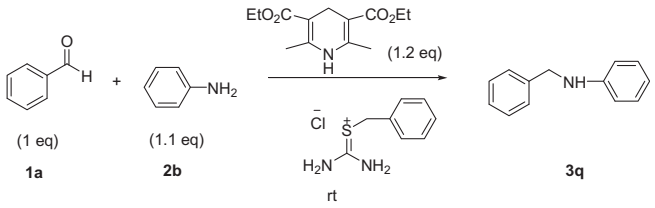
E-mail address: thkim@chonnam.ac.kr (T.H. Kim).

Table 1
Optimization of isothiouronium-catalyzed reductive amination of aldehydes

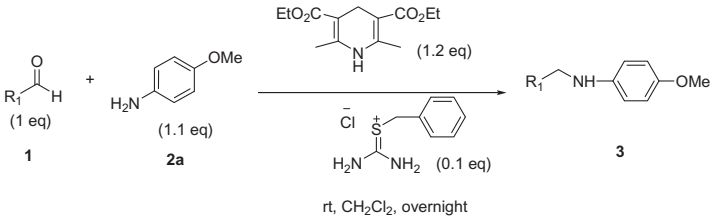


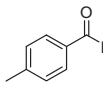
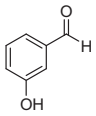
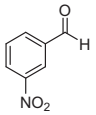
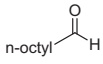
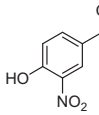
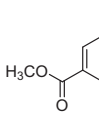
Entry	Catalyst (mol %)	Time (h)	Solvent	Yield **3q** (%)
1	0	24	CH_2Cl_2	55
2	5	12	CH_2Cl_2	85
3	10	12	CH_2Cl_2	99
4	10	12	THF	84
5	10	12	Dioxane	82
6	10	12	Benzene	85
7	10	12	Toluene	89
8	10	12	MeOH	99
9	10	12	EtOH	90

1a produced sufficient quantities of benzoic acid that could catalyze the reaction as well.[3c] The desired amine **3q** was obtained in nearly quantitative manner in the presence of 10 mol % of *S*-benzyl isothiouronium chloride as the catalyst in dichloromethane and methanol solvent (Table 1, entries 3 and 8) at room temperature. This is quite different from the results obtained using thiourea as the catalyst, in which protic solvents such as methanol display limited applicability and the reaction must be carried out at 70 °C in the presence of molecular sieve 5 Å to separate the water generated during the formation of the imine.[3] It is worth noting that the reaction using *S*-benzyl isothiouronium chloride proceeded under heterogeneous conditions in dichloromethane[10] and, therefore, the *S*-benzyl isothiouronium chloride catalyst was easily recovered by simple filtration and reused effectively. Due to owning the higher hydrogen bond, the *S*-benzyl isothiouronium chloride gave the above valuable characteristics as compared with the corresponding thiourea. By converting the thiourea to the isothiouronium salt via alkylation, the catalyst becomes reusable. This finding introduces a new simple strategy for organocatalyst recovery and reuse, not possible with the corresponding thiourea.

Under the optimal conditions, our experiments were carried out at mild room temperature in the heterogeneous condition of the *S*-benzyl isothiouronium chloride catalyst in dichloromethane, thus allowing for its convenient recovery and without the need for the molecular sieve which has generally been a necessary additive to prevent the deleterious impact of water on both the formation of the iminium and hydride reduction step.[11] We next examined the scope and limitation of the aldehydes in the organocatalytic reduction with *p*-anisidine (Table 2) rather than aniline because the *p*-methoxyphenyl group can be oxidatively removed from the resulting amine to produce a primary amine, which renders the whole protocol more versatile.[12] In the case of aromatic, aliphatic, heterocyclic, and cyclic aldehydes **1**, the desired product amines **3** were obtained in high yields. No reduction of the nitro (entries 6 and 12), nitrile (entry 14), and carbonyl (entries 15 and 16) moieties were observed and free hydroxyls were tolerated (entries 4, 12 and 15). Aliphatic aldehydes reacted with more difficulty and required a higher temperature such as 70 °C in toluene to obtain a high yield (entries 10 and 11). Heterocyclic aldehydes (entries 7,

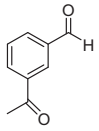
Table 2
Scope of aldehydes



Entry	Aldehydes **1**	Product amines **3**	Yield (%)
1	 **1a**	**3a**	95
2	 **1b**	**3b**	93
3	 **1c**	**3c**	90
4	 **1d**	**3d**	87
5	 **1e**	**3e**	99
6	 **1f**	**3f**	84
7	 **1g**	**3g**	99
8	 **1h**	**3h**[a]	85
9	 **1i**	**3i**	81
10	 **1j**	**3j**[a]	82
11	 **1k**	**3k**[a]	98
12	 **1l**	**3l**[a]	81
13	 **1m**	**3m**	99
14	 **1n**	**3n**	99
15	 **1o**	**3o**	84

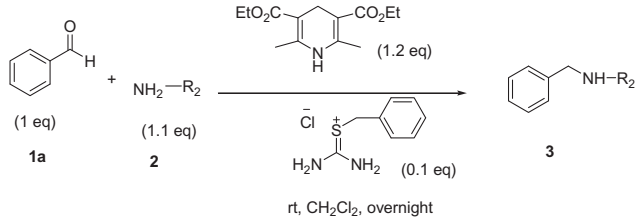
(*continued on next page*)

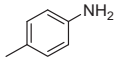
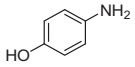
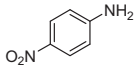
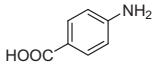
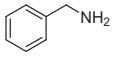
Table 2 (*continued*)

Entry	Aldehydes **1**	Product amines **3**	Yield (%)
16	 **1p**	**3p**	87

[a] Toluene, 70 °C.

Table 3
Scope of amines

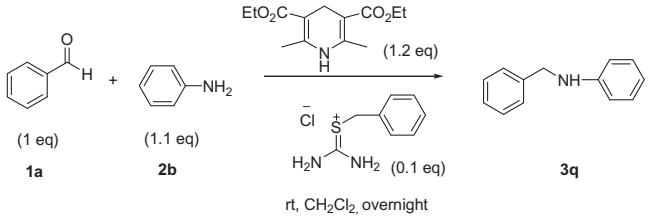


Entry	Amines **2**	Product amines **3**	Yield (%)
1	 **2b**	**3q**	99
2	 **2c**	**3r**	92
3	 **2d**	**3s**	93
4	 **2e**	**3t**	97
5	 **2f**	**3u**	92
6	 **2g**	**3v**[a]	99
7	 **2h**	**3w**	94
8	 **2i**	**3x**[a]	92

[a] Toluene, 70 °C.

8, and 13) also proceeded in good yield. Pleasingly, all of the amines listed in Table 3 functioned successfully, thus demonstrating the wide range of functional groups that can be used with our protocol. In addition, one remarkable point that should be mentioned here is that high selectivity is obtained in this reaction. Only the carbonyl group of the aldehyde was reduced in the presence of a ketone, ester, and acid (entries 15 and 16 in Table 2 and entry 7 in Table 3). Finally, the *S*-benzyl isothiouronium chloride catalyst can be easily recovered by simple filtration and reused with no significant change in its efficiency (Table 4). Compared with the same model based on thiourea,[3a] the isothiouronium catalyst showed a higher yield and milder reaction conditions, for example, from 70 °C to room temperature, as well as easier recovery and reuse. The extension of the scope of the *S*-benzyl isothiouronium chloride catalyst to other reactions, for example, the direct reductive amination of ketones, is currently under our consideration.[13]

Table 4
Recovery of the catalyst



Recycle	Yield of recovered catalyst (%)	Yield of product **3q** (%)
1st	96	99
2nd	95	97
3rd	96	98
4th	97	95

Conclusions

In summary, *S*-benzyl isothiouronium chloride was explored as an effective organocatalyst for the direct reductive amination of aldehydes. A mild and operationally simple fragment coupling procedure was developed, which functions with a wide range of aldehydes as well as amines in good to excellent yield. The *S*-benzyl isothiouronium chloride catalyst can be easily recovered by simple filtration and reused with no drop in its efficiency. Compared with the same model based on thiourea, the isothiouronium catalyst showed higher yield and milder reaction conditions, as well as easier recovery and reuse.

Acknowledgments

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Supplementary data

Supplementary data (typical reaction procedure, spectral data and copies of NMR data of all compounds **3**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.07.024.

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10. The *S*-benzyl isothiouronium chloride catalyst is commercially available and soluble in methanol and ethanol, but not in dichloromethane, THF, dioxane, benzene or toluene.
11. Typical procedure for the direct reductive amination of aldehydes, synthesis of **3p**

    A solution of the aldehyde **1p** (55 mg, 0.37 mmol) and amine **2a** (50 mg, 0.41 mmol) in CH_2Cl_2 (5 ml) was treated with Hantzsch ester (110 mg, 0.44 mmol) and *S*-benzyl isothiouronium chloride (7.5 mg, 0.037 mmol). The mixture was stirred at room temperature for 12 h, and then filtered and washed several times with CH_2Cl_2 to recover the catalyst. The filtrate was evaporated and the residue was purified by flash chromatography on silica gel (*n*-hexane–ethyl acetate = 9:1) to obtain the pure amine products **3p** as yellow oil (82 mg, 0.32 mmol, 87%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.5–8 (8H, m), 4.35 (2H, s), 3.73 (3H, s), 2.60 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.2, 152.3, 142.0, 140.4, 137.4, 132.2, 128.9, 127.2, 114.9, 114.2, 55.8, 48.9, 26.7; HRMS $[M+H]^+$ *m*/*z* expected for 256.1338, obtained 256.1335.
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13. Preliminary results show that the direct reductive amination of acetophenone and *p*-anisidine could be obtained in 90% yield when *S*-benzyl isothiouronium chloride catalyst was used.