S-Benzyl Isothiouronium Chloride as a Recoverable Organocatalyst for the Direct Reductive Amination of Ketones with Hantzsch Ester

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Abstract: The direct reductive amination of ketones using the Hantzsch ester in the presence of *S*-benzyl isothiouronium chloride as a recoverable organocatalyst is reported. A wide range of ketones as well as amines were found to give the expected products in moderate to excellent yields.

Key words: *S*-benzyl isothiouronium chloride, reductive amination, ketones, amines, hydrogen bond

Reductive amination is one of the oldest, but most powerful and widely used methods of accessing different kinds of amines, which are indispensable building blocks in natural products, pharmaceuticals, and agrochemicals.[1] Previous reports indicate that there are two general approaches to transforming ketones into amines. The first is an indirect/stepwise method whereby the intermediate ketimines are pre-formed and then reduced in an independent step.[2] This method is not straightforward because some ketimines are unstable and difficult to isolate.[3] Therefore, direct reductive amination, in which the ketone, amine, and reducing agent are all present at the outset of the reaction, avoiding the isolation of ketimine intermediate, is much more convenient and extremely attractive. However, the choice of reducing agent is critical to the success of the reaction, because the ketimine should be reduced selectively in the presence of the ketone.[4] In previous reports, Hantzsch esters were shown to be powerful biomimetic reductants, because they overcome some of the problems encountered with traditional reductive reagents such as hydrogen gas/metal and metal hydrides, for instance, their limitations in the case of sensitive, acid-labile, or polyfunctional substrates.[5d] The reductive amination of ketones using Hantzsch esters has been developed with effective catalysts such as the Lewis acid scandium triflate $Sc(OTf)_3$,[5a,b] binol phosphoric acid,[5c,e,f] and thiourea.[5d] Recently, we reported *S*-benzyl isothiouronium chloride[6] as a novel noncovalent organocatalyst for the direct reductive amination of aldehydes using Hantzsch esters.[7] Herein, we wish to introduce the use of this system in the direct reductive amination of ketones. A wide range of ketones as well as amines were investigated, and the recyclability of the *S*-benzyl isothiouronium chloride catalyst is also described.

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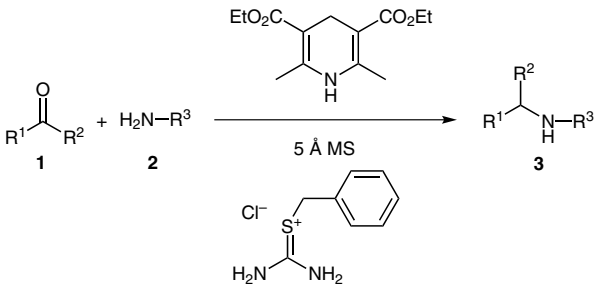
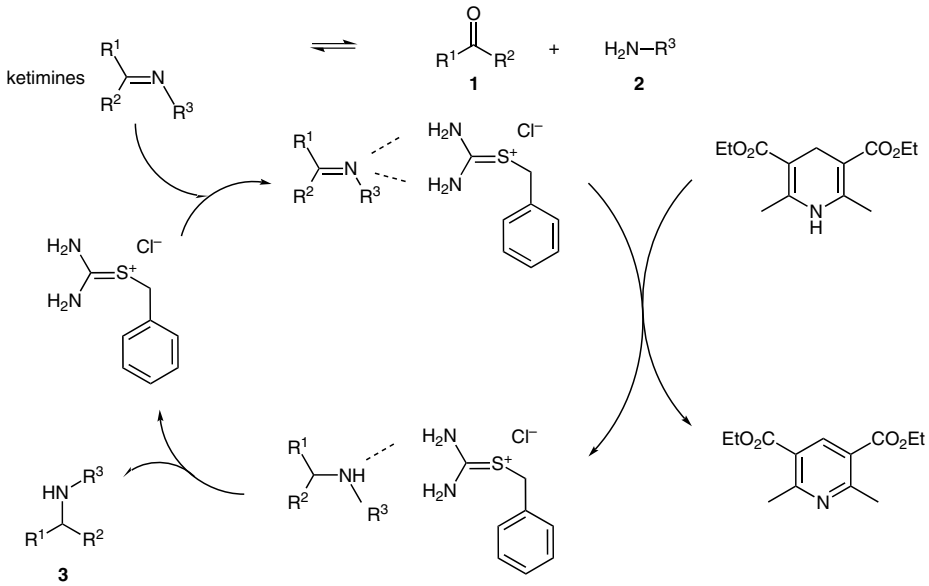
The development of acid- and metal-free catalysts still remains a challenging task. The advent of organocatalysts has led to the discovery of new activation modes and novel transformations. Isothiouronium salts have been explored quite recently as a new class of hydrogen-bonding subunit for the purpose of anion recognition.[8] The isothiouronium group as an anion-binding site has several advantages: (i) it enhances the NH acidity compared to the corresponding thiourea, and (ii) the chemical modification is readily varied using synthetic methods to make several types of functional molecular systems.[8f] Therefore, the isothiouronium salt might be expected to act as an activator for the reductive amination of ketones (Scheme 1).



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

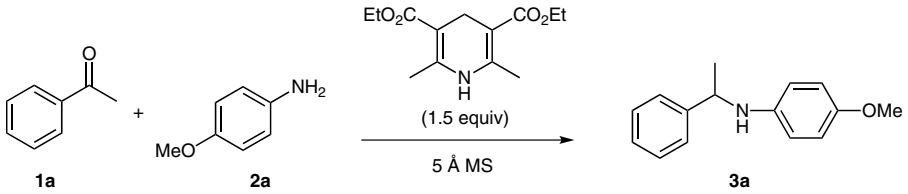
Mechanistically, this reaction includes two steps: (i) the first step is the equilibrium of the ketone and amine with the ketimine; (ii) in the second step, due to the formation of strong hydrogen bonds between the C=N moiety of the ketimine intermediate and the isothiouronium moiety of the catalyst, the reduction of the Hantzsch ester is expected to be accelerated (Scheme 2).[5d]

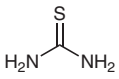
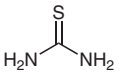
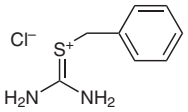
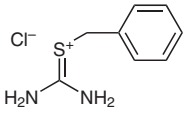
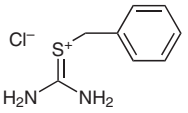
With this mind, our initial study began with the reaction of acetophenone, *p*-anisidine, and the Hantzsch ester in the presence of *S*-benzyl isothiouronium chloride as an organocatalyst (Table 1). To identify the hydrogen bond between the respective ketimine and *S*-benzyl isothiouronium chloride catalyst, a ^{1}H NMR spectrophotometric method was developed that involved monitoring the changes in the spectra of the catalyst in the presence of the excess ketimine (10 equiv) in DMSO-d_6. The protons of the -NH and -CH_2Ph moieties of the *S*-benzyl isothiouronium chloride catalyst were shifted from δ = 9.37 to 9.45 ppm and from δ = 4.55 to 4.58 ppm, respectively,



Scheme 2 Proposed mechanism of the hydrogen-bond catalyzed direct reductive amination of ketones using *S*-benzyl isothiouronium chloride

Table 1 Direct Reductive Amination of Ketones



Entry	Catalyst	Equiv	Solvent	Temp (°C)	Time (h)	Yield of **3a** (%)
1	none	0	MeOH	70	48	0
2	none	0	toluene	70	48	<5
3	$Sc(OTf)_3$	0.1	benzene	r.t.	24	75[a]
4	phosphoric acid	0.1	benzene	50	24	87[b]
5		0.1	toluene	50	48	88[c]
6		0.1	MeOH	70	48	0
7		0.1	toluene	70	48	91 (0)[d]
8		0.1	MeOH	70	48	73 (0)[d]
9		0.05	toluene	70	48	60

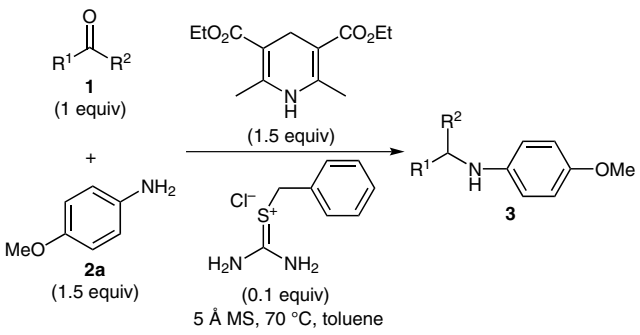
[a] Yield from ref.[5b]
[b] Yield from ref.[5c]
[c] Yield from ref.[5d]
[d] Yields in parentheses were obtained in the presence of excess tetrabutyl ammonium acetate (1.5 equiv).

showing the hydrogen bonding interaction between them. However, upon adding excess acetophenone, the ^{1}H NMR spectra of the catalyst remained almost unchanged. Without *S*-benzyl isothiouronium chloride, no transformation into the product **3a** was observed (Table 1, entries 1 and 2). In addition, *S*-benzyl isothiouronium chloride was completely inactive in the presence of excess tetrabutyl ammonium acetate (TBAA), which could successfully break the hydrogen bond between the *S*-benzyl isothiouronium chloride and ketimine due to the stronger coordination of the acetate anion with the isothiouronium moiety (Table 1, entries 7 and 8).[9,10] From these experimental data, we concluded that this reaction relies exclusively on hydrogen bonding activation by the *S*-benzyl isothiouronium catalyst.

The best yields for this reversible reaction were obtained when a slight excess (1.5 equiv) of the amine and Hantzsch ester were used with respect to the ketone (1 equiv) and 5 Å molecular sieves were used to remove the water formed. Toluene was the most suitable solvent (Table 1, entry 7);[11] although this solvent did not dissolve the *S*-benzyl isothiouronium chloride, it allowed the catalyst to be easily separated from the reaction mixture and facilitated its recovery and reuse. Interestingly, whereas the known thiourea catalyst did not work in protic methanol solvent (Table 1, entry 6),[5d] the *S*-benzyl isothiouronium chloride catalyst functioned well to give the required product in 73% yield (Table 1, entry 8); thus, one advantage of the use of isothiouronium over thiourea is that a higher binding interaction could be achieved even in polar protic solvents, as known in anion recognition.[8] Compared with the previously developed catalysts (Table 1, entries 3, 4, and 5),[5b–d] *S*-benzyl isothiouronium chloride was an effective metal- and acid-free catalyst for the reductive amination of aldehydes[7] and ketones, primarily because of its high hydrogen-bond forming ability, which allows it to function even in protic solvents, and because of its easy recovery.

With the optimized reaction conditions in hand, we investigated the scope and limitations of the organocatalytic reduction of a range of ketones with *p*-anisidine (Table 2). The latter substrate was chosen because the *p*-methoxyphenyl group of this amine can be oxidatively removed from the resulting secondary amine to produce a primary amine, which renders the whole protocol more versatile.[12] To our delight, for all of the ketones considered, including aromatic, aliphatic, aliphatic cyclic, and heterocyclic ketones, the expected products were obtained in moderate to excellent yields. Aliphatic and cyclic aliphatic ketones were the most reactive (Table 2, entry 7 and 8). The aromatic ketone with a nitro substituent, which might form a hydrogen bond with the catalyst, furnished low yield (Table 2, entry 4). Notably, no reduction of the nitro group (Table 2, entry 4) or double bond (Table 2, entry 8) was observed. The reactions proceeded in good yields even with sterically hindered ketones (Table 2, entries 9, 10 and 11).

Table 2 Scope of Ketones



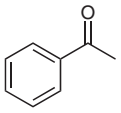
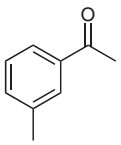
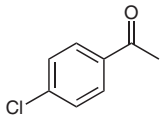
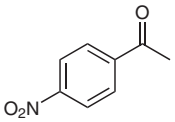
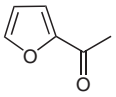
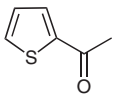
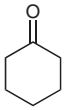
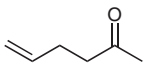
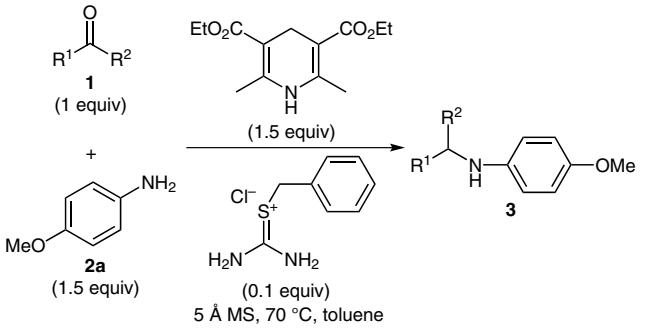
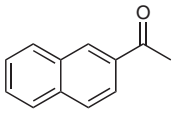
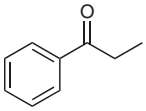
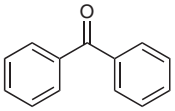
Entry	Ketone **1**	**3**	Time (h)	Yield (%)[a]
1	 **1a**	**3a**	48	91
2	 **1b**	**3b**	48	87
3	 **1c**	**3c**	48	65
4	 **1d**	**3d**	72	45
5	 **1e**	**3e**	72	73
6	 **1f**	**3f**	48	80
7	 **1g**	**3g**	48	98
8	 **1h**	**3h**	48	92

Table 2 Scope of Ketones (continued)



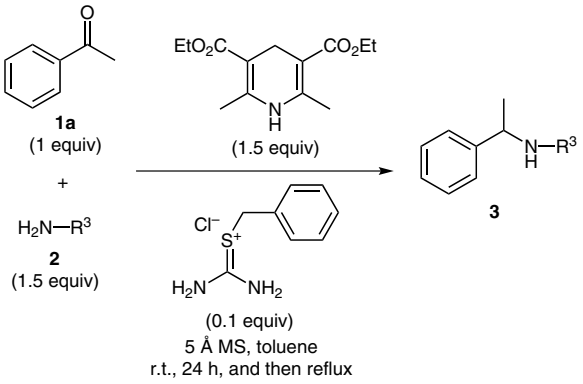
Entry	Ketone **1**	**3**	Time (h)	Yield (%)[a]
9	 **1i**	**3i**	72	83
10	 **1j**	**3j**	72	67
11	 **1k**	**3k**	96	56[a]

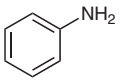
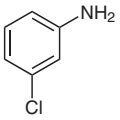
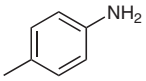
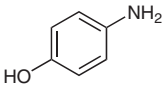
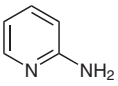
[a] Yield obtained at r.t. for 24 h and then at reflux temperature.

The scope of amines was also examined with acetophenone (Table 3). Initially, the reaction was performed at 70 °C; however, with aniline this did not lead to a high yield and increasing the temperature to reflux gave an even poorer result. The yield was improved by first conducting the reaction at room temperature for 24 hours and then at reflux temperature (Table 3, entry 1). Under these conditions, the reaction with aromatic amines containing either an electron-withdrawing substituent (chloride) or an electron-donating substituent (methyl and hydroxy), proceeded smoothly to give good yields of the expected products (Table 3, entries 2–4). In addition, a free hydroxy group was tolerated under the reaction conditions (Table 3, entry 4). However, the heterocyclic amine **2f** reacted with more difficultly (Table 3, entry 5) and the aliphatic amine was completely unreactive (Table 3, entry 6).

Finally, a striking feature of this method was the recovery of the *S*-benzyl isothiouronium chloride catalyst. Under heterogeneous reaction conditions, *S*-benzyl isothiouronium chloride was easily recovered by simple filtration and reused with no significant change in its efficiency (Table 4).

Table 3 Scope of Amines



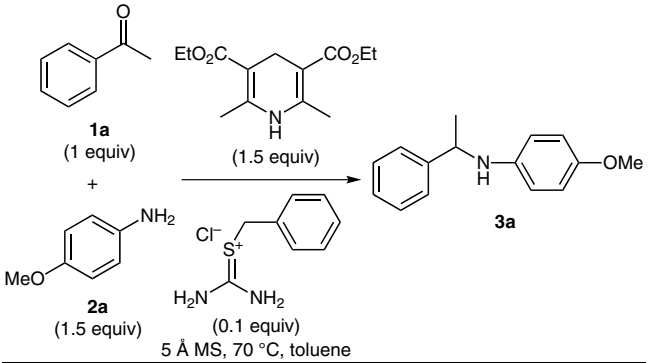
Entry	Amine **2**	**3**	Time (h)	Yield (%)
1	 **2b**	**3l**	72	82 (70)[a]
2	 **2c**	**3m**	96	81
3	 **2d**	**3n**	72	78
4	 **2e**	**3o**	96	76
5	 **2f**	**3p**	96	55
6	$Me(CH_2)_7NH_2$ **2g**	**3q**	96	0

[a] Yield in parenthesis was obtained at 70 °C.

In summary, *S*-benzyl isothiouronium chloride has been successfully developed as a novel class of noncovalent organocatalyst for the direct reductive amination of ketones. A wide range of ketones as well as amines were found to give the expected products in moderate to excellent yields. The isothiouronium catalyst has certain valuable characteristics such as high hydrogen-bonding propensity and the ability to be recovered and reused. In addition, we expect that the isothiouronium organocatalyst should be readily modifiable, allowing the development of chiral organocatalysts for asymmetric syntheses that may even be

used in polar protic solvent systems. A chiral isothiouronium organocatalyst will be reported in due course.

Table 4 Recovery of the Catalyst



Run	Yield of recovered catalyst (%)	Yield of **3a** (%)
1	80	91
2	81	86
3	78	88
4	80	85

All reagents and solvents were obtained from commercial suppliers and were used without further purification. All air- and/or moisture-sensitive reactions were carried out under an argon atmosphere. The products were purified by using flash column chromatography. TLC was developed on Merck silica gel 60 F254 aluminum sheets. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AMX300 spectrometer operating at 300 and 75 MHz, respectively, using $CDCl_3$ as solvent. HRMS were measured with a Micromass Q-TOF instrument (ES+ ion mode).

Direct Reductive Amination of Ketones; General Procedure

A solution of ketone **1** (0.54 mmol, 1 equiv) and amine **2** (1.5 equiv) in toluene (4 mL) was treated with the Hantzsch ester (1.5 equiv), *S*-benzyl isothiouronium chloride (0.1 equiv) and 5 Å MS (1 g). The reaction mixture was stirred either at 70 °C or first at r.t. for 24 h and then heated at reflux. Upon the completion of the reaction, the mixture was filtered and washed several times with CH_2Cl_2. The filtrate was evaporated and then purified by flash column chromatography to obtain the pure amine **3**. The residue in the filter was washed several more times with MeOH and the filtrate was evaporated to recover the *S*-benzyl isothiouronium chloride catalyst. All amines except **3m** and **3o** were characterized by comparison with reported spectroscopic data.

Compound 3m

Yield: 101 mg (81%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (d, *J* = 6.2 Hz, 3 H), 4.01 (br s, 1 H), 4.38 (q, *J* = 6.2 Hz, 1 H), 6.20–7.30 (m, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.7, 53.4, 111.5, 113.1, 117.2, 125.8, 127.1, 128.7, 130.1, 134.8, 144.6, 148.4.

High-resolution mass spectroscopy did not produce a signal for the molecular ion $[M + H]^+$, but rather gave a signal at *m*/*z* 230.0375, which corresponds to the fragment of the ketimine produced by oxidation of the amine under HRMS conditions.

Compound 3o

Yield: 88 mg (76%); yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.40 (d, *J* = 6.3 Hz, 3 H), 3.40 (br s, 1 H), 4.31 (q, *J* = 6.3 Hz, 1 H), 6.33 (d, *J* = 8.0 Hz, 2 H), 6.50 (d, *J* = 8.0 Hz, 2 H), 7.10–7.30 (m, 5 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9, 54.4, 115.0, 116.1, 125.9, 126.8, 128.6, 141.6, 145.4, 147.6.

High-resolution mass spectroscopy did not produce a signal for the molecular ion $[M + H]^+$, but rather gave a signal at *m*/*z* 212.0888, which corresponds to the fragment of the ketimine produced by oxidation of the amine under HRMS conditions.

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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