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Reduction of α , β -unsaturated nitroolefins into nitroalkanes with Hantzsch ester promoted by isothiouronium salts

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Introduction

Nitroalkanes are versatile and inexpensive candidates for feedstocks in organic synthesis, and they are easily transformed into a wide variety of functional moieties such as nitrile oxide, amine, and carbonyl group via the corresponding reactions.^[1] Several synthetic methods have been proposed for the reduction of α,β -unsaturated nitroolefins^[2] into nitroalkanes, but they have some drawbacks in chemoselective reactions.^[3] Borohydride is the most common reducing agent used to synthesize nitroalkanes from nitroolefins, but a dimeric by-product is obtained because of the addition of the nitronate intermediate to the starting α,β -unsaturated nitroolefin. Reduction of nitroolefins with lithium aluminum hydride also leads to the formation of by-products such as hydroxyl amines, oximes, and amines.^[3e]

Hantzsch esters have been identified as powerful biomimetic reducing agents^[4] that can overcome some of the drawbacks associated with typical reducing agents such as metal hydrides and hydrogen gas/metal systems.^[5] Selective reduction of nitroolefins

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Scheme 1. Reduction of α,β -unsaturated nitroolefins using S-benzyl isothiouronium iodide.

into nitroalkanes has been carried out using Hantzsch esters, promoted by catalysts such as acetic acid,^[2b] silica gel,^[2c,f] and thiourea.^[2g,7b] During the course of our studies on isothiouronium salts as novel combination catalysts with Hantzsch esters,^[6] we discovered that *S*-benzyl isothiouronium iodide was more effective than *S*-benzyl isothiouronium chloride for the reductive amination of aldehydes.^[6d] This recipe of *S*-benzyl isothiouronium iodide and Hantzsch esters is herein applied to the reduction of α,β -unsaturated nitroolefins into nitroalkanes, resulting in a more effective and chemoselective combination. Isothiouronium units have recently been reported as a novel class of hydrogen-bonding motifs for anion molecular recognition.^[7] Some advantages of the isothiouronium is more acidic than that of thiourea, resulting in stronger hydrogen bonding; (ii) the isothiouronium group can be easily prepared by the reaction of thiourea with general halides.^[8] We demonstrate that isothiouronium iodide works as an effective organocatalyst for the reduction of nitroolefins (Scheme 1).

Results and discussion

Hydrogen bonding between the isothiouronium catalyst and the nitro group might mechanically decrease the lowest unoccupied molecular orbital (LUMO) activation energy of the alkene, thus increasing the reaction rate (Scheme 1).^[2g] Nitrostyrene 1a was chosen for the model reaction (Table 1), which provided the corresponding nitroalkane in the presence of 0.1 equiv. isothiouronium iodide in 74% and 96% yields in CH₂Cl₂ and CH₃OH at 60 °C, respectively (entries 1 and 2). Decreasing the catalyst loading to 5 mol% led to a lower yield of 2a in 73% (entry 3). When the reaction was carried out at room temperature, the yield was further reduced to 51% (entry 4). The reaction executed under the same conditions but without the catalyst gave the product in only 35% yield (entry 5). Therefore, 10 mol% catalyst loading was selected for further investigation. Then, different solvents were screened to optimize the reaction. Methanol, which dissolved the catalyst adequately, was selected as the best solvent, while benzene, toluene, tetrahydrofuran, and dioxane, in which the catalyst was insoluble, were less effective for this reaction. The most significant benefit of the isothiouronium catalyst over thiourea was that it showed strong hydrogen-bonding interactions with the nitro group even in a polar protic solvent such as methanol.^[2g,8]

			NO ₂ NO ₂	+ Ar + NO	Ar NO ₂
	1a H ₂ N	NH ₂	2a	3a	
Entry	Catalyst loading (mol%)	Solvent	Time (h)	Temperature (°C)	Yield of 2a (%)
1	10	CH ₂ Cl ₂	12	Reflux	74 (0) ^a
2	10	MeOH	7	60	96 (45) ^a
3	5	MeOH	7	60	73
4	10	MeOH	24	RT	51
5	0	MeOH	7	60	35

Table 1. Optimization of reaction conditions for the model reaction.

^aYields in the parentheses were obtained from using the excess tetrabutylammonium acetate (1.5 equiv.).

To examine the hydrogen bonding between the nitrostyrene substrate and the catalyst, excess acetate anion, which is known to bind strongly with the isothiouronium ion, was added to the reaction mixture.^[9] The reaction gave very low yields of the products (entries 1 and 2), implying that the acetate anion hampered the binding between the catalyst and the nitro group. On the basis of the experimental results, we propose that the isothiouronium ion intensely promotes the reduction via hydrogen bonding with the nitro group.

After establishing the optimal reaction conditions, we next investigated the reduction of a variety of nitroolefin substrates in methanol at 60 °C (Table 2). This protocol worked well for nitroolefins containing aromatic (entries 1–8) and heterocyclic (entries 9 and 10) substrates. Electron-withdrawing and electron-donating substituents at different positions on the aromatic ring of the nitroolefins were investigated, and in all cases, the desired products were obtained in high yields, regardless of the type of substituent and substituent position. It is noteworthy to mention that, nitro (entry 1), cyano (entry 6), and carbonyl (entry 7) substituents on the aromatic ring were not reduced at all. Additionally, in a nitroolefin with two conjugated carbon–carbon double bonds, only the double bond adjacent to the nitro group was selectively reduced even when the excess reducing agent was employed (entry 8). α,β -Unsaturated carbonyl compounds such as cyclohexenone and cinnamaldehyde did not react under these conditions, and the starting material was recovered. This result indicated that the present protocol allows for the chemoselective reduction of α,β -unsaturated nitroolefins.

Conclusion

In summary, we have developed a highly chemoselective method for the reduction of α,β -unsaturated nitroolefins into nitroalkanes, promoted by S-benzyl isothiouronium iodide. S-Substituted isothiouronium organocatalysts might work well even in polar protic solvents such as methanol via effective hydrogen bonding.

Table 2.	The	reaction	scope	for	the	reduction	of	nitroolefins.
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Entry	Nitroolefins 1	Nitroalkanes 2	Reaction time (h)	Yield (%)
1	NO2 1a		7	96 ^a
2	1b	2b	16	81 ^b
3	Br NO ₂	Br NO ₂	5	76
4			6	76
5	Me 1e	Me 2e	9	79
6	NC NO2	NC NO ₂	6	95
7			7	82
8	1h	^{NO2} 2h	22	51
9		^{NO2} 2i	9	91
10	SNO2 1j	SNO ₂ 2j	9	85

^alsothiouronium chloride and isothiouronium bromide gave 78% and 83% yields, respectively. ^blsothiouronium chloride and isothiouronium bromide gave 63% and 81% yields, respectively.

Experimental detail

All reagents and solvents were purchased and used without further purification. Airand moisture-sensitive reactions were carried out under a nitrogen atmosphere. TLC was developed on Merck silica gel 60 F254 aluminum sheets. ¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra were recorded in CDCl₃ (solvent). Chemical shifts are presented in parts per million (ppm), downfield from tetramethylsilane as the internal standard. HRMS profiles were recorded on a Micromass Q-TOF instrument (ESb ion mode).

General procedure for the reduction of nitroolefins into nitroalkanes

To a mixture of nitroolefins 1 (0.70 mmol) and Hantzsch ester (0.20 g, 0.77 mmol) in methanol (5 mL), S-benzyl isothiouronium iodide (21 mg, 0.07 mmol) was added and stirred at 60 °C for 5–22 h. The methanolic mixture was concentrated, and then, cold CH_2Cl_2 was added. The isothiouronium iodide was precipitated out, filtered, and washed three times with CH_2Cl_2 . The filtrate was concentrated and purified using flash column chromatography to provide the desired nitroalkanes 2. All the nitroalkanes obtained herein were characterized by their NMR spectra, which were compared with the literature data.^[6c]

Selected product

1-Aceto-3-(2-nitroethyl)benzene (2 g).^[5c]

Colorless oil; IR (neat): $\nu_{\text{max}} = 1681$, 1547, 1267 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): $\delta = 2.60$ (s, 3H), 3.38 (t, J = 7.2 Hz, 2H), 4.65 (t, J = 7.2 Hz, 2H), 7.20–7.90 (m, 4 H); ¹³C NMR (75 MHz, CDCl₃): $\delta = 26.62$, 33.18, 75.87, 127.59, 128.21, 129.32, 133.18, 136.41, 137.93, 197.69; HRMS (ESI) calcd. for C₁₀H₁₂NO₃ [M + H⁺]: 194.0817, found: 194.0817.

Full experimental details, ¹H, and ¹³C NMR spectra. This material can be found in the "Supplementary Content" section of this article's webpage.

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