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Synthesis of Nitrogen Heterocycles by Intramolecular Michael Type of Amination via Reduction of Imines with Di-*n*-butyliodotin Hydride (*n*-Bu_2SnIH)

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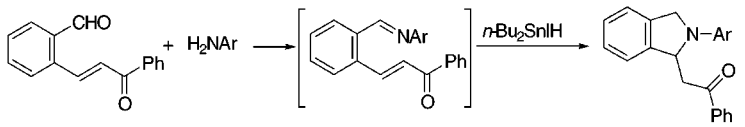
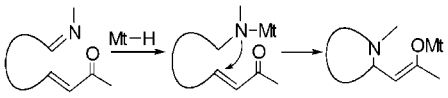
ABSTRACT



Novel nitrogen heterocycles were prepared by a one-pot procedure involving the reductive amination of the bifunctional substrates containing an aldehyde and enone groups with di-*n*-butyliodotin hydride (*n*-Bu_2SnIH).

Intramolecular Michael type amination of ω-amino unsaturated ketones where the amine was created by reductive amination is a good method for the preparation of nitrogen heterocycles because enones are effective electrophiles with amine nucleophiles.[1] However, the method has scarcely been used to build nitrogen heterocycles.[2] This may result from the difficulty of chemoselectively generating an amine. If imine-selective reduction was carried out for a substrate containing both imine and enone functionalities, the 1,4-addition of the generated amine would provide nitrogen heterocycles (Scheme 1).

Scheme 1



However, as far as we know, no imine-selective reductions in the presence of reducible enone functions have been reported so far.[3] Another problem is that imines are generally difficult to isolate because of their instability. This problem could be solved by reductive amination of the aldehyde moiety in the presence of an enone group. We have been developing the unique reactivities of the halogen-substituted tin hydride systems[4] such as *n*-Bu_2SnIH[5a] and *n*-Bu_2SnClH−HMPA[5b,c] which promote effective reductions of enones and imines, respectively. In particular, *n*-Bu_2SnClH−HMPA affords effective reductive aminations.[5d] In this Letter, we describe a facile access to functionalized nitrogen hetero-

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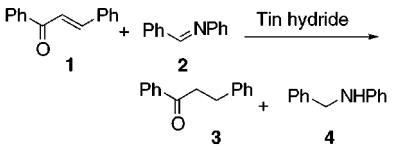
Table 1. Chemoselectivity of Enone vs Imine in the Reduction with Tin Hydrides[a]



Entry	Tin Hydride	Conditions	Yield/% 3	Yield/% 4
1	*n*-Bu_3SnH	rt, 70 h	66	1
2	*n*-Bu_2SnClH	-78°C to rt, 5 h	20	30
3	*n*-Bu_2SnIH	-78°C to rt, 5 h	8	52
4	*n*-Bu_2SnClH - HMPA	-78°C to rt, 5 h	tr	79
5	*n*-Bu_2SnIH - HMPA	-78°C to rt, 5 h	7	71

[a]Enone **1** 1 mmol, imine **2** 1 mmol, Tin hydride 1 mmol, THF 1 mL.

cycles by highly imine-selective reductions with halogen-substituted tin hydride.

To investigate the chemoselectivity of the reduction of enones vs imines with tin hydrides, we initially examined the competitive reaction of equimolar amounts of enone **1** and imine **2** in THF solvent (Table 1). Tri-*n*-butyltin hydride (*n*-Bu_3SnH) slowly reduced enone **1** to give **3** predominantly (entry 1). In contrast, with chloro-substituted tin hydride (*n*-Bu_2SnClH), the reaction proceeded under milder conditions, and amine **4** derived from the reduction of imine was obtained in 30% yield in addition to **3** (entry 2). Interestingly, iodo-substituted tin hydride (*n*-Bu_2SnIH) promoted the predominant formation of **4** (entry 3). The use of penta-coordinate halogenotin hydride complexes, which have previously been reported to provide high imine selectivity over carbonyls,[5b,c] gave **4** effectively (entries 4 and 5). Thus halogenotin hydride derivatives bear imine selectivity even in the presence of enones.

In accordance with the above results, we applied the imine-selective reduction to the synthesis of nitrogen heterocycles. We initially tried to use substrates **7** which contain both enone and imine groups (Table 2). Whereas imines **7** were difficult to isolate, they could be prepared in situ. Namely, the three-component reaction of tin hydride, substrate **5**, and amine **6** was carried out. Starting substrates **5** could be prepared easily from *o*-phthalaldehyde with an appropriate Wittig reagent. *n*-Bu_2SnClH−HMPA and *n*-Bu_2SnIH−HMPA gave the desired isoindoline **8a** in 58% and 53% yields, respectively (entries 1 and 2). Although chlorotin hydride (*n*-Bu_2SnClH) also gave **8a** in 40% yield, product **9** was accompanied in 18% yield by the partial reduction of enone moiety (entry 3). Nonhalogenated tin hydride (*n*-Bu_3SnH) gave **8a** in only 8% yield with complicated mixtures (entry 4). The use of a conventional imine-selective reductant such as $NaBH_3CN$[3b] under the standard conditions resulted in a low yield of **8a** (26%) (entry 5). Interestingly, *n*-Bu_2SnIH afforded **8a** in 64% yield as a sole product (entry 6).[7] Thus reductive amination of the formyl moiety in **5** proceeds, and the resulting tin amide effectively attacks the β-carbon of the remaining enone (Scheme 2).[8] Compared with the results of intermolecular imine-selective reduction in Table 1, iodotin hydride (*n*-Bu_2SnIH) works especially well for the intramolecular reductive amination.[9] Despite a one-pot reaction, no products derived from the reduction of enone or formyl moiety in **5** were obtained.

Scheme 2

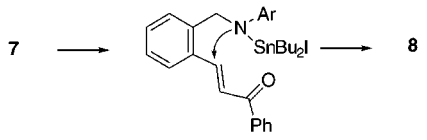
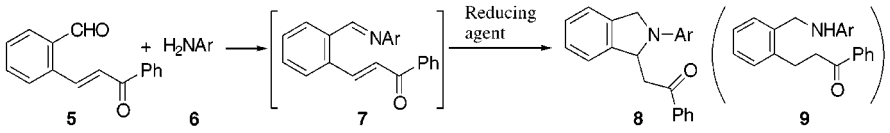


Table 2. Synthesis of Isoindolines by Reductive Amination[a]



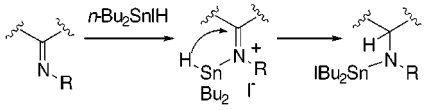
Entry	Ar		Reducing agent	Conditions	Yield/%
1	Ph	**a**	*n*-Bu_2SnClH-HMPA	0 °C, 2 h	58
2			*n*-Bu_2SnIH-HMPA	0 °C, 2 h	53
3			*n*-Bu_2SnClH	0 °C, 3 h	40[b]
4			*n*-Bu_3SnH	0 °C, 48 h	8
5			$NaBH_3CN$[c]	rt, 4 h	26
6			*n*-Bu_2SnIH	0 °C, 2 h	64
7	*p*-$CH_3C_6H_4$	**b**	*n*-Bu_2SnIH	0 °C, 2 h	58
8	*p*-$CH_3OC_6H_4$	**c**	*n*-Bu_2SnIH	0 °C, 2 h	44
9	*p*-ClC_6H_4	**d**	*n*-Bu_2SnIH	0 °C, 2 h	82

[a] Aldehyde **5** 1 mmol, amine **6** 1 mmol, reducing agent1 mmol, THF 1 mL.
[b] Product **9** was obtained in 18% yield. [c]AcOH 1 mmol, MeOH 1mL.

By using *n*-Bu_2SnIH, various aromatic amines could be used to give isoindoline **8** (entries 7−9). In the case of *N*-*p*-chlorophenyl-substituted substrate **7c**, the yield of **8c** was increased up to 82%, where a halogen group on the aromatic ring was not affected (entry 9). In all cases, the use of excess *n*-Bu_2SnIH did not increase the yield of **8** because of the increase of the formation of **9**.

The halogen substituent of the tin hydride is responsible for the high imine selectivity. Thus we assume that the tin halide promotes the formation of an iminium ion as a key intermediate (Scheme 3). The activated imine thus formed

Scheme 3

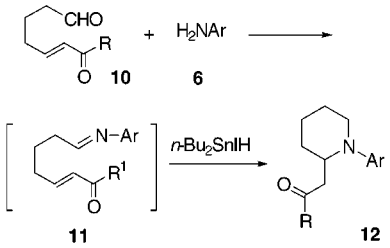


would be reduced more rapidly than other functionalities such as starting aldehydes and enones.

Furthermore, after the imine-selective reduction, the resulting iodo-substituted tin amide bears adequate nucleophilicity to attack the remaining enone because noncyclized secondary amines were not detected in the reaction.

Besides aromatic substrates **5**, aliphatic ones were also applicable for the preparation of nitrogen heterocycles in a similar manner (Table 3). Thus reductive amination of the

Table 3. Synthesis of Piperidines[a]



Entry	R	Ar		Yield of **12** / %
1	Ph	Ph	**a**	56
2		*p*-$CH_3C_6H_4$	**b**	67
3		*p*-ClC_6H_4	**c**	80
4	Me	*p*-ClC_6H_4	**d**	64

[a] Aldehyde **10** 1 mmol, amine **6** 1 mmol, *n*-Bu_2SnIH 1 mmol, THF 1 mL, 0 °C, 2 h.

aldehyde function in **10** with aniline, followed by the intramolecular Michael additin of the resulting tin amide, gave piperidine **12a** in 56% yield in the one-pot procedure (entry 1). Thus, piperidines **12b**−**d** were obtained selectively in good yields (entries 2−4). In all cases, no side reaction such as the reduction of enone or aldehyde was observed.

In this way, various nitrogen heterocycles, isoindolines, and piperidines could be prepared in a one-pot procedure by the imine-selective reduction of in situ formed bifunctional substrates bearing imine and enone functionalities.

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Supporting Information Available: Experimental procedures and IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectra for **8a**−**d** and **12a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The reaction to give isoindoline **8a** was performed as follows. Di-*n*-butyliodotin hydride (*n*-Bu_2SnIH, 1 mmol) was prepared in situ by mixing dibutyltin dihydride (*n*-Bu_2SnH_2, 0.5 mmol) and tin diiodide (*n*-Bu_2SnI_2, 0.5 mmol) in THF (1 mL) at room temperature. To the solution were added substrate **5** (1 mmol) and aniline **6** (1 mmol). After the mixture was stirred at 0 °C for 2 h, MeOH was added, and volatiles were removed under reduced pressure. The residue was chromatographed on silica gel (hexane/EtOAc = 3/1) to afford **8a**.

(8) Although the possibility of the attack of a free amine to enone is not excluded, we think that the more nucleophilic tin amide may play an important role in the cyclization.

(9) Although the higher selectivity of *n*-Bu_2SnIH than pentacoordinate tin reagent is not clear yet, we assume the more acidic *n*-Bu_2SnIH works rather well for the formation of an iminium ion.