Synthesis of 2-Monosubstituted Pyrroles by Intramolecular Addition of Amines via Reductive Amination with Dibutyliodotin Hydride Complex (Bu_2SnIH–HMPA)

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Abstract: Various 2-monosubstituted pyrroles were prepared in a one-pot procedure via the reductive amination of formyl groups of multifunctional substrates **1** by using Bu_2SnIH–HMPA system.

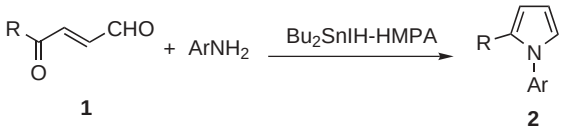
Key words: pyrroles, reductive amination, tin hydride, complex

We have been developing the unique reactivities of the halogen-substituted tin hydride systems such as Bu_2SnIH and Bu_2SnClH–HMPA which promote effective reduction of imines.[1] In particular, Bu_2SnClH–HMPA affords effective reductive amination to give a wide range of secondary and tertiary amines in one pot procedures.[2] Pyrroles are important heterocycles broadly used in materials science[3] and found in naturally occurring and biologically important molecules.[4] Accordingly, substantial attention has been paid to develop efficient methods for the synthesis of pyrroles, most known methods are for forming 2,5-di- or polysubstituted pyrroles. Convenient methods have scarcely reported for the construction of 2-monosubstituted pyrrole ring.[5] Herein we wish to report a novel, and efficient method for construction of 2-monosubstituted pyrroles via the reductive amination by di-*n*-butyliodotin hydride (Bu_2SnIH)–HMPA system.

As shown in Table 1, first, it was found that enal **1a** in the presence of iodotin hydride in THF at 0 °C for 2 hours underwent reductive amination with *p*-chloroaniline to give secondary amine **3a** in 74% yield (entry 1).[6,7] Although no cyclization occurred, this result indicates that reductive amination was carried out effectively without affecting the remaining enone functionality in **1a**. Chloro-substituent on nitrogen aromatic ring was not reduced. After the reductive amination, heating the mixture at 80 °C for 2 hours afforded pyrrole **2a** in 22% yield with 60% of **3a** (entry 2). In this case, 1,4-dioxane was used as a solvent to heat the reaction mixture at 80 °C. Noteworthy is that under the same conditions, pyrrole **2a** was obtained in 81% yield in the presence of an equimolar amount of HMPA (entry 3), in which non-cyclized product **3a** was not obtained at all. The iodo-substituent on the tin center was essential for the cyclization because chlorotin derivative, Bu_2SnClH–HMPA, gave no pyrrole **2a** at all where only **3a** was obtained under the same conditions (entry 4).

Various aromatic amines were applicable to give pyrroles **2b**–**d** in one-pot procedures by the reductive amination of **1** using Bu_2SnIH–HMPA system followed by heating at 80 °C (entries 5–7). In the case of **1b**, pyrrole **2e** was also obtained (entry 8). Enal having aromatic ketone **1c** was also reactive to give the corresponding pyrroles **2f**–**h** where reductive amination was carried out at –40 °C (entries 9–11).

A plausible reaction course is indicated in Scheme 2. Initially, reductive amination occurs by mixing Bu_2SnIH–HMPA with starting substrate **1** and an aromatic amine (Scheme 1).



1 **2**

Scheme 1

It is cleared that halogenotin hydride bears high imine-selectivity because formyl and enone groups of **1** were not reduced at all. In the next stage, the resulting tin-nitrogen bond adds to the remaining ketone moiety in **1** by heating. At the last stage, the elimination of tin hydroxide gives pyrroles **2**. The reaction was carried out in a one-pot procedure hence no intermediates were isolated. The substituent and ligand in the tin complex play important roles for the synthesis of pyrroles. Bu_2SnIH–HMPA is a trigonal bipyramidal structure in which iodine substituent occupies apical position.[8] The Sn-halogen bond is responsible for high imine-selectivity, which promotes the formation of an iminium ion (I). As a result, electrophilicity of imine is increased.[1,2] The activated imine thus formed would be reduced more rapidly than any other functionalities such as starting formyl and enone moieties. After the imine-selective reduction, tin-nitrogen bond is formed. High coordination of tin is important for the intramolecular addition. Namely, in the pentavalent tin amide (II), the tin-nitrogen bond occupying the apical position bears adequate nucleophilicity to the remaining carbonyl groups.[9,10]

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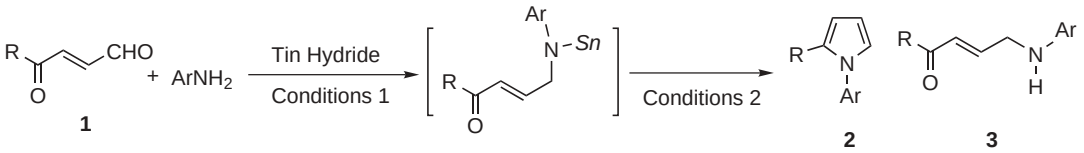
Table 1 One-Pot Synthesis of 2-Monosubtituted Pyrroles **2**[a]



Entry	R	Ar	Tin hydride	Solvent	Conditions 1	Condtions 2	Product [Yield (%)]
1	n-C_8H_{17} (**1a**)	p-ClC_6H_4	Bu_2SnIH	THF	0 °C, 2 h	0 °C, 2 h	**3a** (74)
2			Bu_2SnIH	Dioxane	0 °C, 2 h	80 °C, 2 h	**2a** (22) **3a** (60)
3			Bu_2SnIH–HMPA	Dioxane	0 °C, 2 h	80 °C, 2 h	**2a** (81)
4			Bu_2SnClH–HMPA	Dioxane	0 °C, 2 h	80 °C, 2 h	**3a** (98)
5		Ph	Bu_2SnIH–HMPA	Dioxane	0 °C, 2 h	80 °C, 2 h	**2b** (54)
6		p-Tol	Bu_2SnIH–HMPA	Dioxane	0 °C, 2 h	80 °C, 2 h	**2c** (60)
7		p-$MeOC_6H_4$	Bu_2SnIH–HMPA	Dioxane	0 °C, 2 h	80 °C, 2 h	**2d** (66)
8	$PhCH_2CH_2CH_2$ (**1b**)	p-ClC_6H_4	Bu_2SnIH–HMPA	THF	0 °C, 2 h	80 °C, 2 h	**2e** (60)
9	Ph (**1c**)	p-ClC_6H_4	Bu_2SnIH–HMPA	THF	–40 °C, 2 h	60 °C, 2 h	**2f** (46)
10		Ph	Bu_2SnIH–HMPA	THF	–40 °C, 2 h	60 °C, 2 h	**2g** (41)
11		p-$MeOC_6H_4$	Bu_2SnIH–HMPA	THF	–40 °C, 2 h	60 °C, 2 h	**2h** (49)

[a] Compound **1** 1 mmol, $ArNH_2$ 1 mmol, tin hydride 1 mmol, (HMPA 1 mmol), 1 1 mmol, solvent 1 mL.

In conclusion, various 2-monosubstituted pyrroles 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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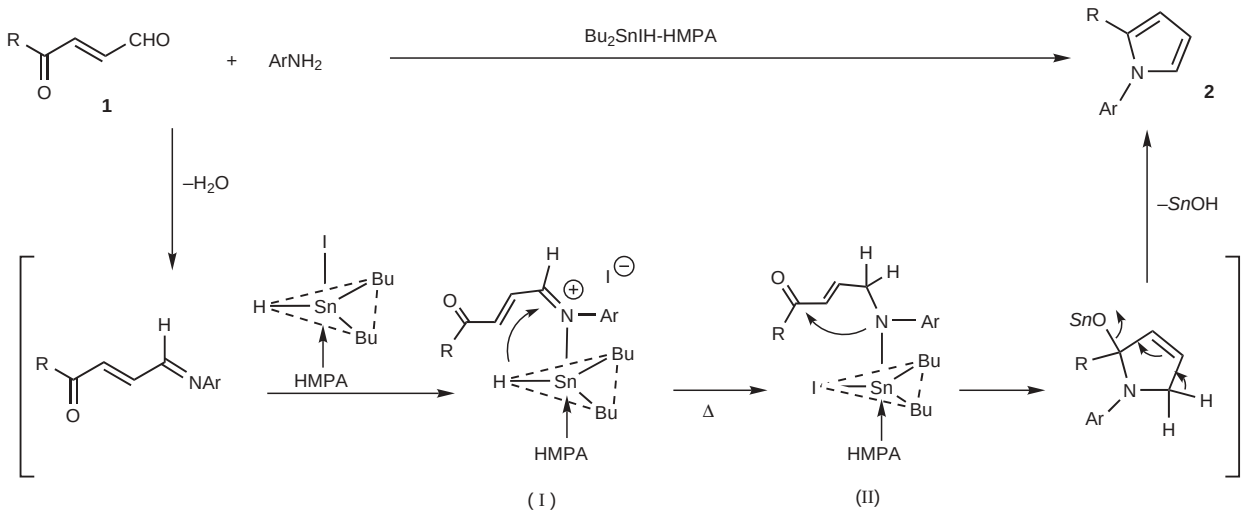

Scheme 2 A plausible reaction mechanism

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(7) **Typical Experimental Procedure** (see Table 1, entry 3). To a dry nitrogen-filled 10 mL round-bottomed flask containing di-*n*-butyltin dihydride (Bu_2SnH_2, 0.166 g, 0.5 mmol) in 1,4-dioxane (1 mL) was added di-*n*-butyltin diiodide (Bu_2SnI_2, 0.243 g, 0.5 mmol) and HMPA (0.180 g, 1 mmol) at r.t. After stirring at r.t. for 10 min, the resulting solution of di-*n*-butyliodotin hydride (Bu_2SnIH, 1 mmol) was cooled to 0 °C. Carbonyl substrate(**1a**) (0.196 g, 1 mmol), and *p*-chloroaniline (0.128 g) were added successively, and stirring was continued at 0 ºC for 2 h. The IR absorption band of Sn-H (1850 cm^{-1}) disappeared, which indicated the formation of stannylamide (II). The mixture was heated to 80 ºC and stirred for 2 h. The reaction was quenched with MeOH (0.5 mL), and the residue was chromatographed on silica-gel column [FL100-DX (Fuji silysia)]. Elution with hexane gave pyrrole **2a** (0.234 g, 81%).
Spectral data of representative products are as follows.
Compound **2a**. IR: 1596, 1496 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 0.86 (t, *J* = 6.83 Hz, 3 H), 1.21–1.30 (m, 10 H), 1.44–1.55 (m, 2 H), 2.49 (t, *J* = 7.81 Hz, 2 H), 6.04–6.06 (m, 1 H), 6.21 (t, *J* = 2.93 Hz, 1 H), 6.67–6.69 (m, 1 H), 7.22 (d, *J* = 8.79 Hz, 2 H), 7.39 (d, *J* = 8.79 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ = 14.08, 22.63, 26.65, 29.13, 29.27, 29.30, 31.57, 31.80, 107.10, 108.26, 121.30, 127.30, 129.18, 132.77, 134.21, 139.06. HRMS: calcd for $C_{18}H_{24}NCl$: 289.1597. Found: 289.1597.
Compound **2e**. IR: 1496 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 1.75–1.87 (m, 2 H), 2.51–2.59 (m, 4 H), 6.06–6.09 (m, 1 H), 6.18–6.21 (m, 1 H), 6.66–6.68 (m, 1 H), 7.05–7.35 (m, 9 H). ^{13}C NMR ($CDCl_3$): δ = 26.09, 30.67, 35.29, 107.39, 108.32, 121.46, 125.71, 127.19, 128.25, 128.31, 129.20, 132.76, 133.49, 138.87, 141.86. HRMS: calcd for $C_{19}H_{18}NCl$: 295.1128. Found: 295.1125.
Compound **2f**. IR: 1600, 1492 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 6.35–6.38 (m, 1 H), 6.42–6.44 (m, 1 H), 6.90–6.91 (m, 1 H), 7.09 (d, *J* = 8.40 Hz, 2 H), 7.13–7.24 (m, 5 H), 7.28 (d, *J* = 8.40 Hz, 2 H). ^{13}C NMR ($CDCl_3$): δ = 109.60, 110.99, 124.16, 126.49, 126.76, 128.18, 128.32, 129.13, 132.19, 132.59, 133.79, 139.01. HRMS: calcd for $C_{16}H_{12}NCl$: 253.0658. Found: 253.0653.

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(10) It seems that chlorodibutyltin amide moiety (Bu_2ClSnN-) does not has enough nucleophilicity to cause cyclization because of the electron withdrawing character of Cl-substituent (entry 4).