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Organotin(IV) Enamines as Selective Reagents: Coupling with α-Halocarbonyls for Synthesis of Substituted Pyrroles

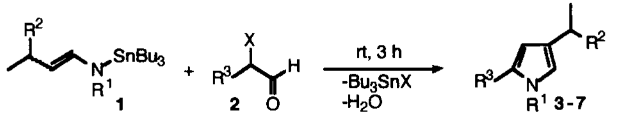
Makoto Yasuda, Junji Morimoto, Ikuya Shibata, and Akio Baba*

Department of Applied Chemistry, Faculty of Engineering, Osaka University,
2-1 Yamadaoka, Suita, Osaka 565, Japan

Abstract: Effective coupling of tin enamines **1** and α-haloaldehydes **2** gave 2,4-disubstituted pyrroles in high yields at room temperature even under aqueous conditions. The reaction with 2-bromoacetophenone gave 3,4-disubstituted pyrroles, while the addition of HMPA changed the selectivity to afford the 2,4-isomer predominantly (27 : 73). © 1997 Elsevier Science Ltd.

We have used organotin(IV) enolates as nucleophiles toward α-halocarbonyl compounds to introduce oxo-functional groups.[1] The reaction of tin enolates with α-halocarbonyls under thermal or Pd-catalyzed conditions often gives furan derivatives *via* the carbonyl addition-cyclization mechanism.[1,2] An organotin enamine[3] which is considered as a homologue of a tin enolate has rarely been utilized for organic syntheses except for the conjugate addition.[4] We wish to report here that organotin(IV) enamines gave 2,4-disubstituted and 3,4-disubstituted pyrroles by coupling with α-halocarbonyls, in which [3+2] cyclization-dehydration took place. Although the [3+2] cyclization process is a very common method for pyrrole syntheses,[5] the generation of water in the dehydration step is often a serious problem. The synthesis of substituted pyrroles from lithium enamine and α-haloketone, for example, has resulted in modest yields,[6] perhaps due to high moisture sensitivity of the lithium reagent. Thus, the stability of metallo-enamine reagents in aqueous conditions is important to obtain high yields of pyrroles. In the present work, we used the tin enamines **1** prepared by stannylation of lithium enamines. They are relatively stable, can be preserved for several weeks, and, moreover, shows high reactivity.

Table 1. Synthesis of Substituted Pyrroles from Tin Enamine **1** and α-Haloaldehyde **2**

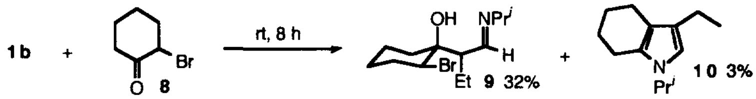


Entry	1	R^1	R^2	2	R^3	X	Pyrrole^a	Yield/%^{b}
1	**a**	*i*-Bu	H	**a**	C_5H_{11}	Br	**3**	>99
2	**b**	*i*-Pr	H	**a**	C_5H_{11}	Br	**4**	>99 (>99)^c
3	**c**	*t*-Bu	H	**a**	C_5H_{11}	Br	**5**	>99
4	**d**	*i*-Pr	Me	**a**	C_5H_{11}	Br	**6**	74
5	**b**	*i*-Pr	H	**b**	Ph	Br	**7**	94
6	**b**	*i*-Pr	H	**c**	C_5H_{11}	Cl	**4**	56
7	**b**	*i*-Pr	H	**c**	C_5H_{11}	Cl	**4**	62^d

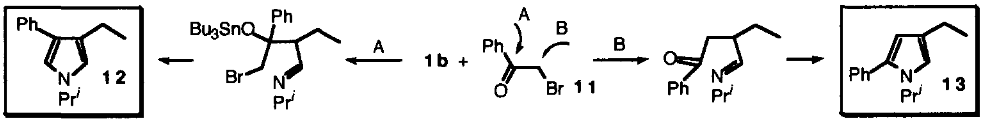
[a] Satisfactory spectroscopic data have been obtained for all products. [b] Yields were determined by GLC.
[c] Solvent, $CHCl_3$-H_2O (1 mL-1 mL). [d] HMPA (1.8 mmol) was added.

The coupling of tin enamines **1** and α-haloaldehydes **2** effectively proceeded at room temperature (Table 1).[7] The quantitative formation of 2,4-disubstituted *N*-alkyl pyrroles **3**-**5** was observed regardless of steric demand around the *N*-atom of enamine (entries 1-3). The quantitative formation of **4** was observed even in $CHCl_3$-H_2O mixed solution (entry 2). An aromatic substituted aldehyde was also applicable to this system (entry 5). The reaction with chloroaldehyde **2c** gave a modest yield. Unfortunately, the addition of HMPA (hexamethylphosphoric triamide) slightly raised the yield (entries 6,7). On the contrary, the lithium enamine generated by treatment of the parent aldimine (butylidene isopropylamine) with LDA afforded a lower yield (49%) of pyrrole **4** in the reaction with α-bromo aldehyde **2a**.

The reaction of tin enamine **1b** with 2-bromocyclohexanone **8** afforded the hydroxy imine derivative **9** and a trace amount of pyrrole **10**, perhaps because the conformational strain retarded the cyclization to **10**. This result showed the inherent nucleophilicity of tin enamines toward carbonyl moieties.



The reaction of **1b** with 2-bromoacetophenone **11** gave two types of substituted pyrroles, **12** and **13** (93 : 7), at 60 °C for 48 h.[8] In contrast to the case of α-haloaldehydes, the addition of HMPA accelerated the reaction and reversed the selectivity (27 : 73). DMF also reversed the selectivity. We assume that the high coordination of tin enamine by HMPA would cause the halide substitution (route B), although we do not have sufficient evidence in this regard.[9]



Additive	Time/h	Yield/%	**12**:**13**
none[a]	48	34	93: 7
DMF[b]	2	26	38:62
HMPA[b]	2	47	27:73

Tin enamine **1b** (1.2 mmol), haloketone **11** (1.0 mmol), 60 °C.
[a] $CHCl_3$ (10 mL). [b] Additive (4.8 mmol), $CHCl_3$ (1 mL).

Although the full scope of this pyrrole ring construction system by the coupling of tin enamines **1** and halocarbonyls remains to be established, it promises to be a useful alternative to conventional protocols.

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7. The general procedure is as follows: A mixture of tin enamine **1** (1.2 mmol) and haloaldehyde **2** (1.0 mmol) in solvent (1 mL) was stirred at room temperature for 3 h under nitrogen. Diethyl ether (100 mL) and aqueous NH_4F (15%; 40 mL) were added, and the organic layer was separated and washed with water (50 mL × 2), dried ($MgSO_4$) and evaporated. The crude product was purified by distillation under reduced pressure.
8. ^1H NMR (270 MHz, $CDCl_3$) signals of pyrrole ring protons: **8**: δ 6.78 (d, 1H, $J = 2.44$ Hz), 6.56 (m, 1H). **9**: δ 6.65 (m, 1H), 6.01 (d, 1H, $J = 1.95$ Hz).
9. We have reported spectroscopic evidence of the HMPA-coordinated tin enolate (ref 5c).

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