DOI: 10.1002/ejoc.200500927

One-Pot Synthesis of Heterocycles Initiated by Chemoselective Reduction of Bifunctional Carbonyl Compounds

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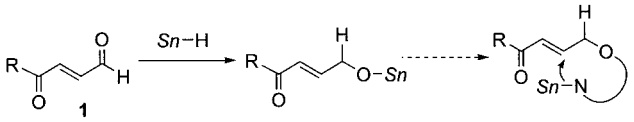
Keywords: Tin hydride / Reduction / Heterocycles / One-pot synthesis

One-pot syntheses of a variety of heterocyclic compounds initiated by the chemoselective reduction of the formyl groups in bifunctional carbonyl compounds **1** with the Bu_3SnH/HMPA system have been achieved.

Tin–oxygen bonds can easily be generated by the addition of organotin nucleophiles to carbonyl compounds.[1] The reduction of carbonyl compounds by tributyltin hydride (Bu_3SnH) is one well known method.[2] Although the reactions proceed under mild and neutral conditions, the resulting tin alkoxides have only rarely been used for further transformations, most tin–oxygen bonds being hydrolyzed to provide alcohols. However, tin–oxygen and –nitrogen bonds have high nucleophilicity, higher in some cases than those of the corresponding free alcohols and amines.[3] Here we report one-pot syntheses of heterocycles initiated by the chemoselective reduction of the formyl groups of bifunctional compounds **1**,[4] with the generated tin–oxygen bonds acting as key intermediates (Scheme 1).



Scheme 1. Reaction concept for the synthesis of heterocycles.

The choice of reducing agent is important for the selective reduction of the formyl groups in compounds **1**, because of the coexisting reactive enone functionalities. As shown in Table 1, use of conventional agents such as $LiAlH_4$ and $NaBH_4$ resulted in complex reaction mixtures (Entries 1–3), while tributyltin hydride (Bu_3SnH) itself has little reducing ability (Entry 4). The Bu_3SnH reaction[5] catalyzed by Lewis acids gave only **2a**, though in moderate yields (Entries 5 and 6). We had already developed Bu_3SnH/HMPA to effect chemoselective reduction of formyl groups under mild conditions,[6] and here Bu_3SnH/HMPA was found to reduce the formyl group of **1a** in the highest yield (Entry 7). Dibutylchlorotin hydride (Bu_2ClSnH) complex[7] also gave a good yield of **2a** (Entry 8).

As shown in Scheme 2, we next tried to prepare heterocycles through initiation by tin hydride reduction in one-pot procedures. Thus, after the chemoselective reduction of the formyl group of **1**, the generated tin–oxygen bond of **A** was allowed to react with an isocyanate.[8] The resulting tin–nitrogen bond of **B** successively added to the enone moiety in conjugate fashion to give the 2-oxazolidinones **3**.

We have recently reported the synthesis of nitrogen heterocycles initiated by the allylation of **1**,[9] by treatment with dibutylchlorotin nucleophiles (Bu_2ClSn-allyl)/HMPA. The reason why dibutylchlorotin derivatives worked well is their high reactivity towards the formyl groups of **1** in the initial allylation, whilst allylic tributyltin compounds, (Bu_3Sn-allyl)/HMPA, show no reactivity towards **1**. In the tin hydride-initiated reductions presented here, use of the dibutylchlorotin hydride system (Bu_2ClSnH/HMPA) and subsequent treatment with BuN=C=O gave the desired 2-oxazolidone **3a** in only 37% yield, although the initial reduction of the formyl group proceeded effectively (see Table 1, Entry 8). In contrast, the reduction of **1** with tributyltin nucleophile (Bu_3SnH/HMPA) and subsequent treatment with BuN=C=O afforded **3a** in a good yield (84%).[10]

The role of the Sn–N bond of **B** is clearly important, because the linear compound **4**, which bears no tin moiety, did not afford intramolecular conjugate addition under the same conditions (Scheme 3).

While the reason why the $ClBu_2SnN$- nucleophile did not work well here in comparison with the reaction involving allylation[9] is not yet clear, Bu_3SnN moieties have fundamentally higher nucleophilicity than $ClBu_2SnN$ moieties because of the presence of the electron-withdrawing Cl sub-

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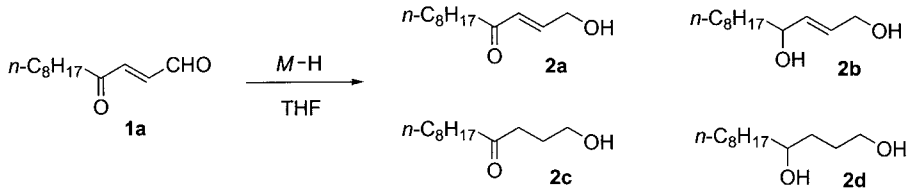
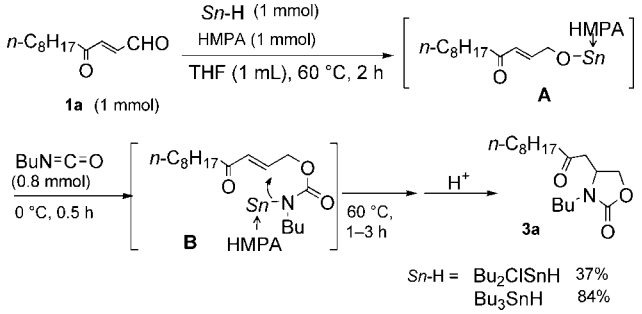
Table 1. Chemoselective reduction of the formyl group in **1a**.[a]

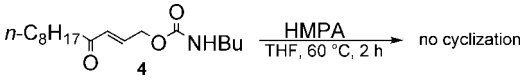


Entry	Reducing agent (M–H)	Conditions	Product and yield [%][a,b]
1	DIBAL (1 equiv.)	0 °C, 5 h	**2a** 25%, **2b** 31%
2	$NaBH_4$ (1 equiv.)	r.t., 1.5 h	**2d** 61%
3	$LiAlH_4$ (1 equiv.)	0 °C, 1 h	**2b** 33%, **2c** 12%
4	Bu_3SnH (1 equiv.)	r.t., 23 h	trace
5	Bu_3SnH (1 equiv.)/$ZnCl_2$ (0.1 equiv.)	r.t., 23 h	**2a** 40%
6	Bu_3SnH (1 equiv.)/$MgBr_2$ (0.1 equiv.)	r.t., 14 h	**2a** 35%
7	Bu_3SnH/HMPA (1 equiv.)	r.t., 3 h	**2a** 56%
8	Bu_3ClSnH/HMPA (1 equiv.)	r.t., 3 h	**2a** 51%

[a] M–H 1 mmol, **1a**: 1 mmol, THF 1 mL. [b] Isolated yield.

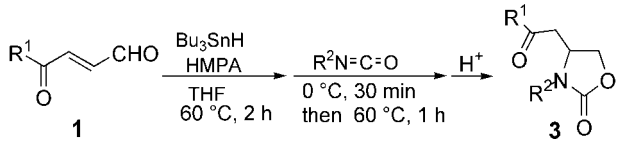


Scheme 2. One-pot synthesis of 2-oxazolidinones.



Scheme 3.

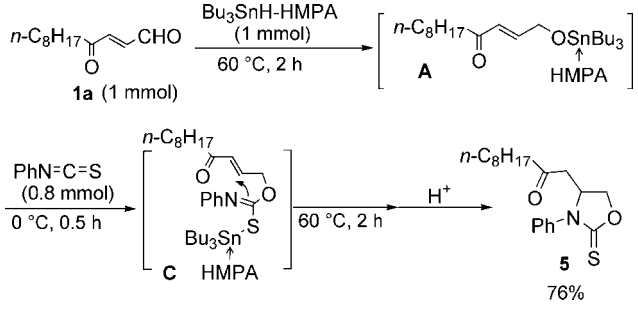
Table 2. Synthesis of 2-oxazolidones.



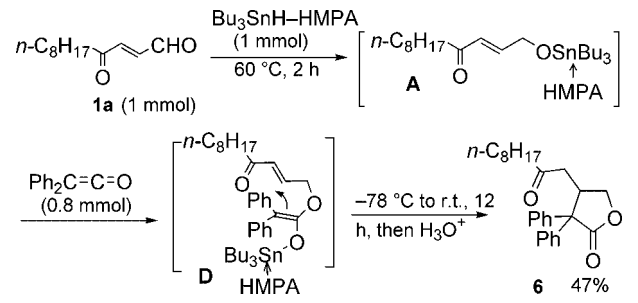
Entry	R^1 (**1**)	R^2 (**2**)	Product	Yield [%] [a][b]
1	n-C_8H_{17} (**1a**)	Bu	**3a**	84
2		$H_2C{=}CHCH_2$	**3b**	73
3		$ClCH_2CH_2$	**3c**	75
4		$PhCH_2$	**3d**	70
5		$(CH_3)_2CH$	**3e**	87
6		Ph	**3f**	85
7	$Ph(CH_2)_3$ (**1b**)	Bu	**3g**	56
8	Ph (**1c**)	Bu	**3h**	38
9	p-ClC_6H_4(**1d**)	Bu	**3i**	42

[a] **1** (1 mmol), Bu_3SnH/HMPA (1 mmol), isocyanates (0.8 mmol), THF (1 mL). [b] Based on isocyanate. Isolated yield.

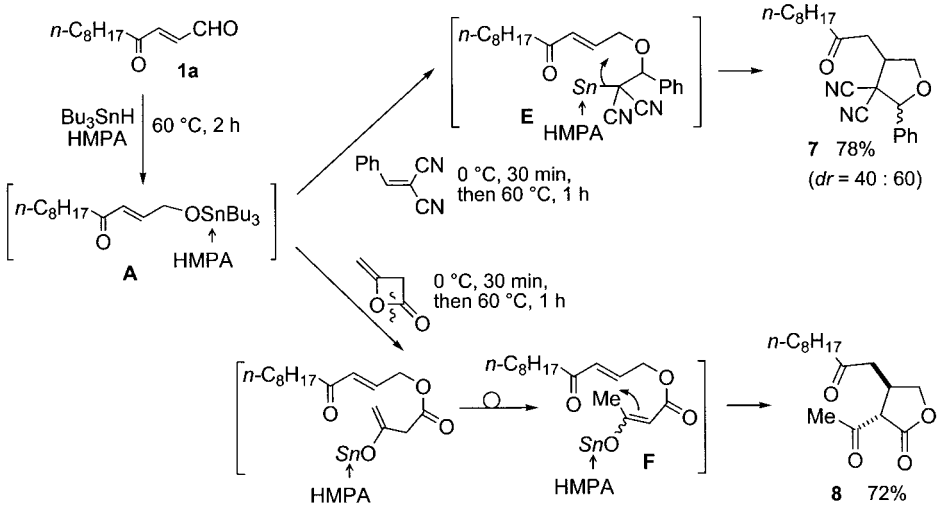
stituents in the latter case. Hence, Bu_3SnN moieties worked effectively in the presented conjugate addition. HMPA also plays an important role in the conjugate addition besides the chemoselective reduction of the formyl group in **1**, in the generation of nucleophilic pentacoordinate tin amides **B**.[11] It is clear that no intramolecular conjugate addition takes place in the absence of HMPA, because the $ZnCl_2$-catalyzed Bu_3SnH reduction (Table 1 Entry 5) and subsequent treatment with BuN=C=O at 60 °C for 2 h gave only the linear compound **4**. As shown in Table 2, various 2-oxazolidones **3** were prepared by Bu_3SnH/HMPA. Aliphatic, allylic, secondary alkyl, and aromatic isocyanates were reactive towards **1a**, giving the corresponding 2-oxazolidones **3a**–**3f** in good to excellent yields (Entries 1–6). Use



Scheme 4. Synthesis of an oxazolidine-2-thione.



Scheme 5. Synthesis of a γ-lactone.



Scheme 6. Synthesis of the cyclic ether **7** and the α-acyl-γ-lactone **8**.

of substrates **1c** and **1d** with aromatic ketone moieties also gave 2-oxazolidones **3h** and **3i** (Entries 8 and 9).

The advantages of this method include the potential to use other heterocumulenes instead of isocyanates, giving a variety of heterocycles.[12,13] Use of phenyl isothiocyanate afforded oxazolidine-2-thione **5** (Scheme 4). In this case, it was known that the tin–oxygen bond should add across the C=S bond of an isothiocyanate to give **C** because of the strong affinity of tin towards a sulfur atom.[8b] The subsequent intramolecular conjugate addition occurs from the terminal imino nitrogen atom.

As shown in Scheme 5, use of diphenylketene afforded the γ-lactone **6** through the intramolecular conjugate addition of tin enolate **D**. The conjugate addition occurred through *C*-alkylation of the tin enolate. This result is in contrast to our previous intramolecular reactions with alkyl halides to cause *O*-alkylation.[14] Electrophiles other than heterocumulenes were also applicable (Scheme 6). An electrophilic alkene reacted with the Sn–O bond of **A** to give intermediate **E**, and intramolecular addition then proceeded to give the cyclic ether **7** in a one-pot procedure. When **A** was treated with diketene, the α-acyl-γ-lactone **8** was obtained, so the ring cleavage of diketene must have occurred at the acyl carbon–oxygen bond.[15] After isomerization to the stable tin enolate **F**, the intramolecular conjugate addition took place.

In summary, one-pot syntheses of a variety of heterocycles initiated by chemoselective reduction of enals **1** have been established.

Supporting Information (see footnote on the first page of this article): Experimental details and characterization data.

Acknowledgments

This research was carried out at the Strategic Research Base "Handai FRC" supported by the Japanese Government's Special Coordination Fund for Promoting Science and Technology, and was supported by The Sumitomo Foundation (050432) and a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture.

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Received: November 28, 2005
Published Online: January 24, 2006

