Tributyltin Hydride in NMP-Promoted Reduction of Acid Chlorides to Aldehydes under Transition-Metal-Free Conditions

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Received 17 December 2009

Abstract: Tributyltin hydride in *N*-methyl-2-pyrrolidinone (NMP) was used for the partial reduction of various functionalized acid chlorides at room temperature. This transition-metal-free procedure allows the synthesis of a range of (hetero)aromatic- and aliphatic aldehydes in good to excellent yields.

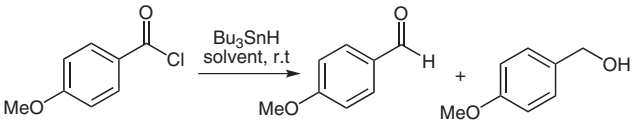
Key words: acid chlorides, aldehydes, reduction, tributyltin hydride, *N*-methyl-2-pyrrolidinone, free-metal conditions

The partial reduction of acid chlorides to aldehydes seems to be a simple reaction, yet this type of transformation remains a desirable tool. Over the past decades, a variety of methods have been developed. Besides the traditional hydrogenolysis with $Pd/BaSO_4$ (Rosenmund reduction),[1] many metallic hydrides have been extensively used for such transformations, including, lithium or sodium tri-*t*-butoxyaluminium hydride,[2] sodium borohydride,[3] hypervalent silicon hydrides,[4] transition-metal borohydrides,[5] anionic transition-metal reductants,[6] and others.[7] However, such methods have limitations, which include over-reduction, lack of generality, low yield and functional group incompatibility. Alternative methods involve the use of organosilicon[8] or tributyltin hydrides[9] in the presence of a transition-metal catalyst. Since the pioneering work of Guibé, tributyltin hydride[9a,10] mediated reduction of acid chlorides to aldehydes in the presence of palladium catalyst appears to be superior and this procedure has been successfully applied to the synthesis of complex molecules.[11]

As part of our research program on the hydrostannation of arylalkynes[12] and enynes,[13] we have noticed the crucial influence of the solvent, particularly with *N*-methyl-2-pyrrolidinone (NMP), where a partial addition of tributyltin hydride across the carbon–carbon triple bond occurred in the absence of palladium catalyst. These findings have prompted us to investigate the particular reactivity of the Bu_3SnH/NMP system toward other functionalities, such as the partial reduction of acid chlorides under metal-free conditions. Herein, we wish to report on our successful results.

First, we studied the reduction of 4-methoxybenzoyl chloride (**1a**) as a model substrate. The results, summarized in Table 1, showed that treatment of **1a** with Bu_3SnH (1.1 equiv) in tetrahydrofuran (THF) was ineffective, and only trace amounts of over-reduced **3a** was detected (entry 1). For comparison, with addition of tetrakis(triphenylphosphine)palladium(0) (5 mol%), Bu_3SnH in THF was found to affect the reduction of **1a**, furnishing 4-methoxybenzaldehyde (**2a**) in 72% yield along with a small amount of benzyl alcohol (**3a**; <5%, data not shown). When the reaction was carried out without transition-metal catalyst in *N*,*N*-dimethylacetamide (DMA) or *N*,*N*′-dimethyl propyleneurea (DMPU) as solvents, the conversion rose to ~50%, but a noticeable amount of over-reduced **3a** was detected in the crude reaction mixture (entries 2 and 3). Finally, when the reaction was performed in NMP as solvent, we were pleased to observe that the reduction of **1a** with Bu_3SnH (1.05 equiv) at room temperature for one hour successfully furnished the desired 4-methoxybenzaldehyde (**2a**) in 81% yield (entry 5). Only a trace of over-reduced by-product **3a** was detected.

Table 1 Effect of Solvents on the Reduction of 4-Methoxybenzoyl Chloride (**1a**) to Aldehyde **2a** with Bu_3SnH under Metal-Free Conditions



1a **2a** **3a**

Entry	Solvent	Time (h)	Temp (°C)	Bu_3SnH (equiv)	Ratio (%)[a] **1a/2a/3a**
1	THF	1	r.t.	1.1	96:0:4
2	DMA	1	r.t.	1.05	46:44:10
3	DMPU	1.5	r.t.	1.05	43:50:7
4	DMF	2	r.t.	1.05	90:10:0
5	NMP	1	r.t.	1.05	10:85[b]:5
6	NMP	8	r.t.	1.05	15:47:38
7	NMP	1	50	1.05	12:70:18
8	NMP	1	r.t.	1.5	22:48:30

[a] Determined by the ^1H NMR ratio of the crude product.
[b] Compound **2a** was isolated in a 81% yield after column chromatography.

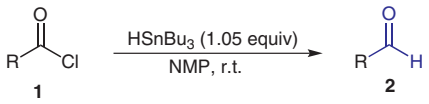
SYNLETT 2010, No. 7, pp 1101–1103
Advanced online publication: 23.03.2010
DOI: 10.1055/s-0029-1219796; Art ID: D36709ST

Increasing the reaction time, the temperature, or the amount of Bu_3SnH led to a decline in yield of aldehyde **2a** with increased formation of the over-reduced by-product **3a** (entries 6–8). In our system, it appeared that the use of NMP heightened the reactivity of the tributyltin hydride to the point that acid chloride **1a** could be converted into the aldehyde **2a** without the need for a palladium catalyst.

With optimized conditions in hand,[14] our investigation shifted to an exploration of the reaction scope, and a series of commercially available acid chlorides was reacted with the Bu_3SnH/NMP system at room temperature, as shown in Table 2.

The partial reduction of acid chlorides **1a–o** with Bu_3SnH in NMP led to aldehydes **2a–o**, respectively, in good yields, without exception, demonstrating a broad reaction scope and tolerance of a range of functional groups. Aromatic acid chlorides **1a–f**, bearing an electron-donating group, were successfully transformed into their corresponding aldehyde derivatives **2a–f** in good to excellent yields (entries 1–6). It should be noted that the position of the substituent on the aromatic ring had no influence on either the yield or selectivity. An important aspect of this transition-metal-free procedure is the survival of an *O*-allyl protecting group during the Bu_3SnH partial reduction (entry 6). It should be noted that such a transformation could not be selectively realized under the Guibé protocol [$Bu_3SnH/Pd(PPh_3)_4$/THF] as these conditions are well known to result in cleavage of an *O*-allyl ether function.[15] As shown in entries 8–10, the presence of an electron-withdrawing group on the aryl ring also did not affect the yield of the reduction, and the reaction provided aldehydes **2h–j** in good yields. It is particularly notable that a potentially reducible NO_2 substituent was tolerated under the reaction conditions (74%, entry 9). The reduction of other aromatic and heteroaromatic systems, such as 1-naphthoyl acid chloride (**1k**) or 2-thienoyl acid chloride (**1l**) by Bu_3SnH in NMP worked equally well, to give **2k** and **2l** in 90% and 93% yield, respectively (entries 11 and 12). α,β-Unsaturated acid chloride **1m** (entry 13) reacted well with 1.05 equivalents of tributyltin hydride in NMP to give the α,β-unsaturated aldehyde **2m** in a good 85% yield with no trace of the saturated aldehyde. Because few methods could achieve complete efficiency with both aromatic and aliphatic acid chlorides, it was important to test the partial reduction of aliphatic substrates. Thus, as shown in entry 14, the Bu_3SnH/NMP protocol was found to be optimal for the conversion of aliphatic acid chloride **1n** into aldehyde **2n**, demonstrating the generality of the method. Finally, the reduction of citronelloyl chloride (**1o**; entry 15), gave only citronellal (**2o**), which is in contrast to the reduction of **1o** in the presence of azobis(isobutyronitrile) (AIBN), which has been reported to give the cyclic compound menthone.[16] This observation led us to exclude a radical mechanism for the Bu_3SnH/NMP-mediated reduction of acid chlorides.

Table 2 Reduction of Acid Chlorides with the $HSnBu_3$/NMP System at Room Temperature



1 2

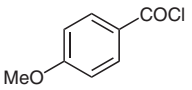
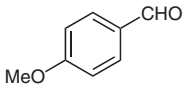
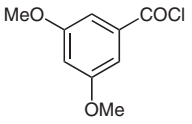
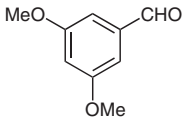
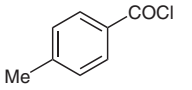
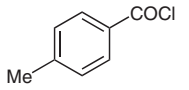
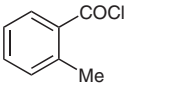
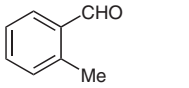
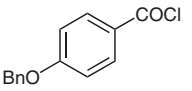
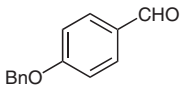
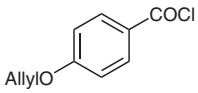
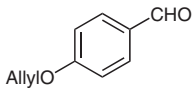
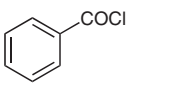
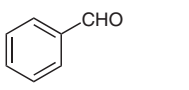
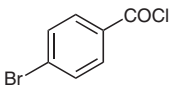
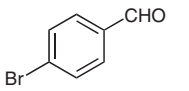
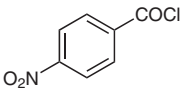
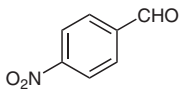
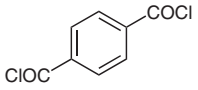
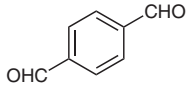
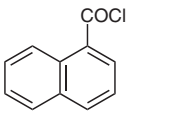
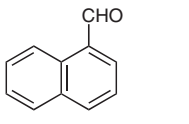
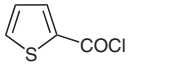
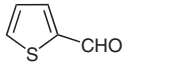
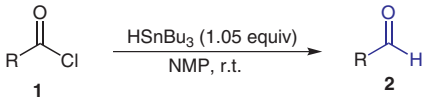
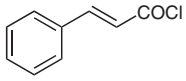
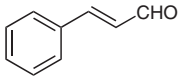
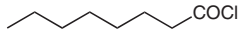
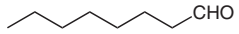
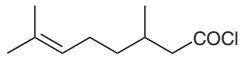
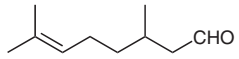
Entry	Acide chloride **1**	Aldehyde **2**	Yield (%)[a]
1	 **1a**	 **2a**	81
2	 **1b**	 **2b**	60
3	 **1c**	 **2c**	80
4	 **1d**	 **2d**	87
5	 **1e**	 **2e**	63
6	 **1f**	 **2f**	70
7	 **1g**	 **2g**	87
8	 **1h**	 **2h**	90
9	 **1i**	 **2i**	74
10	 **1j**	 **2j**	86[b]
11	 **1k**	 **2k**	90
12	 **1l**	 **2l**	93

Table 2 Reduction of Acid Chlorides with the $HSnBu_3$/NMP System at Room Temperature (continued)



1 2

Entry	Acide chloride **1**	Aldehyde **2**	Yield (%)[a]
13	 **1m**	 **2m**	85
14	 **1n**	 **2n**	96
15	 **1o**	 **2o**	65

[a] Isolated pure product after column chromatography.
[b] Bu_3SnH (2.1 equiv) was used.

In summary, we have developed a simple, efficient and general process for the partial reduction of acid chlorides using tributyltin hydride in NMP at room temperature. This mild and transition-metal-free procedure works well with (hetero)aromatic as well as aliphatic acid chlorides and allows the efficient preparation of a variety of functionalized aldehydes in good to excellent yields. In the present method, the survival of an *O*-allyl ether function, which is commonly used as an alcohol-protecting group, must be highlighted as it constitutes a real advantage when compared with palladium-catalyzed procedures. Due to its simplicity and versatility, we believe that this methodology should find broad applications in synthetic organic chemistry.

Acknowledgment

The CNRS is gratefully thanked for support of this research.

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