## Unusual Aluminum Hydride-mediated Reduction of N-(γ- or δ-Oxoacyl)oxazolidinone

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Reduction of N-( $\gamma$ -oxoacyl)oxazolidinone with a borohydride reagent, such as NaBH<sub>4</sub> or LiBEt<sub>3</sub>H, resulted in formation of the corresponding lactone or lactol. In contrast, when an aluminum hydride reagent was used instead of a borohydride reagent, reduction of N-( $\gamma$ - or  $\delta$ -oxoacyl)oxazolidinone proceeded unexpectedly to give not the corresponding lactone or lactol, but a tetrahydrofuran or tetrahydropyran derivative, respectively, containing an oxazolidino group.

Reduction using a metal hydride reagent is an important reaction in synthetic organic chemistry. Metal hydride reagents are useful for the reduction of polarized multiple bonds, such as a carbonyl or cyano group. Almost all metal hydride reagents contain boron or aluminum atoms. Among the available metal hydride reagents, diisobutylaluminum hydride (DIBAL) often is the first choice for transformation of an ester, carboxamide, or nitrile into an aldehyde.<sup>1</sup>

Reduction of N-( $\gamma$ - or  $\delta$ -oxoacyl)oxazolidinone **1** with a metal hydride reagent was expected to give the corresponding  $\gamma$ - or  $\delta$ -lactone **2** or lactol **3** (Scheme 1). The reduction of N-(4-oxo-4-phenylbutanoyl)oxazolidinone (**1a**) yielded the corresponding lactone **2** or lactol **3** when a borohydride reagent [e.g., NaBH<sub>4</sub>, Zn(BH<sub>4</sub>)<sub>2</sub>, or LiBEt<sub>3</sub>H] was used. However, no lactone or lactol was isolated when N-(5-oxo-5-phenylpentanoyl)oxazolidinone (**1c**) was used as a substrate.

In contrast, when an aluminum hydride [e.g., bis(2-methoxyethoxy)aluminum hydride (Red-Al<sup>®</sup>), LiAlH<sub>4</sub> (LAH), or DIBAL] was used as a reductant, the corresponding tetrahydrofuran or tetrahydropyran derivative **4** was provided as the main product, not the lactone **2** (Scheme 2).

Starting materials 1a-1c were prepared in high yield from condensation of carboxylic acid with oxazolidinone in the presence of water-soluble carbodiimide hydrochloride (WSC HCl) and 4-dimethylaminopyridine (DMAP). The first examination involved the reduction of 1 with several types of



Scheme 1. Reduction of N-( $\gamma$ - or  $\delta$ -oxoacyl)oxazolidinone 1 to lactone 2 or lactol 3 using borohydride reductant.



Scheme 2. Reduction of 1 with aluminum hydride reductant.

borohydride reagents. Results of the reduction of **1a** or **1c** with various borohydride reagents are shown in Table 1. Using sodium borohydride, the reduction of **1a** in THF–H<sub>2</sub>O afforded the corresponding lactone **2a** (Entry 1). The reduction of **1a** with Zn(BH<sub>4</sub>)<sub>2</sub> or LiBH<sub>4</sub> also resulted in the formation of **2a** in moderate yield (Entries 2 and 3). Because LiBEt<sub>3</sub>H (Super Hydride<sup>®</sup>) is a powerful reductant for reducing an ester to an alcohol, the reduction of **1a** with 2 equivalents of LiBEt<sub>3</sub>H gave the corresponding lactol **3a** (Entries 4 and 5). *N*-(5-Oxo-5-phenylpentanoyl)oxazolidinone (**1c**) also was examined (Entries 6 and 7). The *N*-(5-hydroxy-5-phenylpentanoyl)oxazolidinone (**5**) was produced by reaction of **1c** with NaBH<sub>4</sub> in moderate yield (Entry 6 and Figure 1). In contrast to the reaction with Zn(BH<sub>4</sub>)<sub>2</sub>, <sup>1</sup>H NMR analysis of the crude mixtures indicated no formation of the corresponding lactone and lactol (Entry 7).

The second examination involved the reduction of 1 with aluminum hydrides (Table 2). Reduction using lithium aluminum hydride (LAH) resulted in formation of an unexpected product (Entry 1). The <sup>1</sup>HNMR and MS spectra revealed that the structure of the product was a diastereomeric mixture of tetrahydrofuran derivative 4a containing an oxazolidinone group at position 2 of the tetrahydrofuran ring. In contrast, 4a and also 3a was obtained when Red-Al<sup>®</sup> instead of LAH was used as a reductant (Entry 2). In addition, the use of DIBAL increased the yield of 4a (Entry 3). Analysis using integration of the <sup>1</sup>H NMR spectra indicated that the ratio of major 4a to minor 4a was 57:43. A comparison among the three types of aluminum hydride showed that DIBAL was the best reductant for formation of 4a (Entries 1-3). In addition, the yield of 4a was independent of the reaction solvent (Entries 3-5). Reduction of another starting material such as 1b with DIBAL also resulted in yield of the corresponding tetrahydrofuran derivative 4b (Entry 6). Fortunately, each diastereomer could be isolated by

Table 1. Reduction of 1 with borohydride reductants

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Entry	Subst.	Reductant /mol equiv	Solvent	Time /h	Temp. /°C	Product	Yield /%
1	1a	NaBH <sub>4</sub> /3.5	THF-H <sub>2</sub> O	0.5	RT	2a	56
2	1a	Zn(BH <sub>4</sub> ) <sub>2</sub> /1.5	THF	4	-20-RT	2a	41
3	1a	LiBH <sub>4</sub> /1.0	THF	2	0	2a	47
4	1a	LiBEt <sub>3</sub> H/1.0	THF	0.5	-78	2a (3a)	30 (15)
5	1a	LiBEt <sub>3</sub> H/2.1	THF	0.5	-78	3a	61
6	1c	$NaBH_4/1.0$	$THFH_2O$	0.5	RT	5	37
7	1c	$Zn(BH_4)_2/1.0$	THF	0.25	0	—	

Figure 1. Structure of 5.

Table 2. Reduction of 1 with aluminum hydride reductants

Entry	Subst.	Reductant	Solvent	Time	Temp.	Product
		/mol equiv		/h	/°C	(Yield/%)
1	1a	LAH/1.0	THF	1.5	-60	<b>4a</b> (26)
2	1a	Red-Al <sup>®</sup> /1.5	THF	1.5	-40	<b>4a</b> (<6) <sup>a</sup> , <b>3a</b> (46)
3	1a	DIBAL/2.2	THF	0.5	-40	<b>4a</b> (62) <sup>b</sup>
4	1a	DIBAL/2.2	Toluene	0.5	-40	<b>4a</b> (68)
5	1a	DIBAL/2.2	$CH_2Cl_2$	0.5	-40	<b>4a</b> (61), <b>3a</b> (6)
6	1b	DIBAL/2.5	$CH_2Cl_2$	2.0	-40	4b (67) <sup>c</sup> , 3b (10)
7	1c	DIBAL/2.2	THF	0.5	-40	<b>4c</b> (39), <b>3c</b> (40)
8	1c	DIBAL/2.2	Toluene	0.5	-40	<b>4c</b> (30), <b>3c</b> (59)
9	1c	DIBAL/2.2	$CH_2Cl_2$	0.5	-40	<b>4c</b> (87) <sup>d</sup> , <b>3c</b> (8)

<sup>a</sup>**4a** was difficult to isolate without contamination by by-products. All ratios were determined using integration of <sup>1</sup>H NMR spectra. <sup>b</sup>57:43. <sup>c</sup>58:42. <sup>d</sup>56:44.



Figure 2. NOESY correlations for 1a and 1b.

preparative TLC. When *N*-(5-oxo-5-phenylpentanoyl)oxazolidinone (1c) was used as the substrate, the corresponding tetrahydropyran derivative mixture 4c was produced. However, yields of 4c depended on the reaction solvent (Entries 7–9). Among the three solvents used,  $CH_2Cl_2$  performed the best in the present reaction system. In addition, 4c was given as a 56:44 mixture of diastereomers, determined by integration of <sup>1</sup>H NMR spectra.

*cis-trans* Assignments in **4a** and **4b** were based on NOESY analysis (Figure 2). The aromatic proton of the major product at the *ortho* position showed NOESY cross-peaks with two methine protons at the 2- and 5-positions of the tetrahydrofuran ring. However, no cross-peak was observed for the methine protons at the 2- and 5-positions of the tetrahydrofuran ring. These data suggest that the stereochemistry of the major product was *trans*. In contrast, the aromatic proton of the minor product had a NOESY cross-peak only with the 5-position on the tetrahydrofuran ring. Together with the cross-peak at the methine protons of the 2- and 5-positions of the tetrahydrofuran ring, these data indicate that the stereochemistry of the minor product was *cis*. The stereochemistry of **4c** was not clear from the NOESY spectrum; however, the stereochemistry of the major product is probably *trans*.

Scheme 3 shows the proposed reaction mechanism of the present reduction. In the initial step, generation of cyclic aluminum alkoxide 6 resulted from reduction of the ketone group of 1. In the next step, 6 released the oxazolidinone anion to give the corresponding lactone 2 and/or lactol 3 when a borohydride was used (route A). In contrast, when an aluminum hydride was used, the aluminum oxide species, not the oxazolidinone anion, was eliminated from 6 to form the iminium salt 7. In the final step, 7 was reduced by the aluminum hydride to yield 4 as the final product (route B).

Aluminum oxide species, such as dialuminum oxide and aluminum hydroxide, can act as a leaving group. The first report of this phenomenon by Newman et al. described the formation of aluminum oxide species as a leaving group during reduction



Scheme 3. Proposed reaction mechanism for the reduction.



Scheme 4. Reduction of  $\gamma$ - or  $\delta$ -oxocarboxamide with DIBAL.

of carboxamide with LAH to the corresponding amine.<sup>2</sup> Brown reported that AlH<sub>3</sub> or LAH reduced ketoximes to primary amines.<sup>3</sup> In the reduction of a specific ketoxime utilizing LAH<sup>4</sup> or DIBAL,<sup>5</sup> a rearranged product arose from an initial Beckmann rearrangement of the ketoxime prior to reduction. All of these reports, as well as the present results, indicate that the leaving ability of aluminum oxide species is greater than that of boron oxide species. Therefore, only aluminum oxide species can act as leaving groups.

To reveal the scope and limitation, reduction of the amide with DIBAL was examined (Scheme 4). Although the reduction of **8** with DIBAL was complicated, the corresponding  $\gamma$ -hydroxycarboxamide **10** was isolated in moderate yield only. Furthermore, when **9** was used as a substrate, unfortunately, a similar result was given.

In conclusion, a new role for aluminum hydride reagents was discovered and described. Further investigation of the limitations of this reaction system and new functional transformations using aluminum hydrides is needed.<sup>6</sup>

This paper is dedicated to Professor Teruaki Mukaiyama in celebration of the 40th anniversary of the Mukaiyama aldol reaction.

## **References and Notes**

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