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Improved Procedure for the Oxidative Cleavage of Olefins by OsO_4–$NaIO_4$

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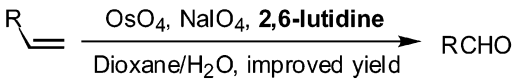
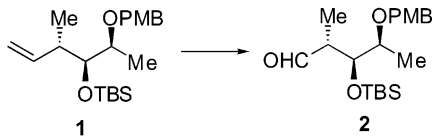
ABSTRACT



Oxidative cleavage of olefins by OsO_4–$NaIO_4$ sometimes suffers from low yields due to the formation of side products. It is found that the addition of 2,6-lutidine can suppress the side reactions and dramatically improve the yield of this classic reaction.

In connection with a project in our laboratory, we needed to convert olefin **1** to aldehyde **2** via an oxidative cleavage reaction (Scheme 1).[1] Due to the presence of the *para*-methoxybenzyl protecting group, ozonolysis did not give satisfactory results. Therefore, we decided to apply the well-known OsO_4−$NaIO_4$ protocol.

Scheme 1



The oxidative cleavage of the double bond of compound **1** under the standard literature conditions of OsO_4−$NaIO_4$[2] gave the desired aldehyde **2** in only 60∼64% yield (Table 1, entry 1). We found that the relatively low yield was due to the formation of about 25−30% α-hydroxy ketone **3**, presumably formed via the over-oxidation of the diol intermediate. Others have also reported the formation of α-hydroxy ketones as side products under the standard literature conditions.[3] Although we did not find many examples that actually reported α-hydroxy ketone as the side product, we noticed that the tedious two-step procedure (dihydroxylation employing OsO_4−NMO or Sharpless asymmetric dihydro-oxylation followed by oxidative cleavage by $NaIO_4$) was employed much more often than the one-step protocol (OsO_4−$NaIO_4$).[4] This prompted us to investigate the possibility of improving this classic oxidative cleavage reaction.

Since the reaction media was acidic (pH = 2), we thought that buffering the reaction might change the outcome of the reaction. Deionized water was replaced with the phosphate buffer (pH = 7). But the reaction appeared to be very slow, and no selectivity was observed (Table 1, entry 2). We next examined the effect of the addition of powdered K_2CO_3. Surprisingly, TLC showed very good selectivity, and only a trace amount of compound **3** was formed (Table 1, entry 3). But the reaction was very slow and never went to completion after 24 h. This experiment indicated that it was possible to inhibit the formation of compound **3** by the addition of a weak base. However, more experiments were needed to search for the "ideal base" that could inhibit the formation of compound **3** at a reasonable reaction rate. It is known

(1) Yu, W.; Zhang, Y.; Jin. Z. *Org. Lett.* **2001**, *3*, 1447.
(2) Pappo, R.; Alen, D. S., Jr.; Lemieux, R. U.; Johnson, W. S. *J. Org. Chem.* **1956**, *21*, 478.
(3) (a) Grant, P. K.; Hanton, L. R.; Lynch, G. P.; Robinson, W. T.; Wong, G. *Aust. J. Chem.* **1994**, *47*, 71. (b) Lohray, B. B.; Bhushan, V.; Kumar, R. K. *J. Org. Chem.* **1994**, *59*, 1375.
(4) There are numerous examples of using the two-step procedure to cleave olefins. The following are some of the recent applications: (a) Francavilla, C.; Chen, W.; Kinder, F. R. Jr. *Org. Lett.* **2003**, *5*, 1233. (b) Wang, Z.; Moloney, M. G. *Tetrahedron Lett.* **2002**, *43*, 9629. (c) Taylor, R. E.; Chen, Y.; Beatty, A. *J. Am. Chem. Soc.* **2003**, *125*, 26. (d) Roush, W. R.; Bannister, T. D.; Wendt, M. D.; Jablonowski, J. A.; Scheidt, K. A. *J. Org. Chem.* **2002**, *67*, 4275.

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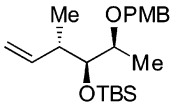
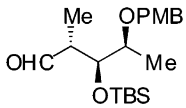
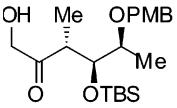
Table 1. Effects of Various Bases on the Rate of Reaction and Product Distribution

entry	substrates	conditions[a]	product 1	product 2
1	 **1**	No base	 **2** 60-64%	 **3** 30-25%
2	**1**	Buffer=7.0	very slow reaction	no selectivity
3	**1**	K_2CO_3 (5.0 eq.)	very slow reaction	trace
4	**1**	Pyridine (2.0 eq.)	faster reaction, but epimerization	trace
5	**1**	2,6-*t*-butylpyridine (2.0 eq.)	no effect	
6	**1**	2,6-lutidine (2.0 eq.)	90%	6%

[a] Reaction conditions: OsO_4 (0.02 equiv), $NaIO_4$ (4.0 equiv), dioxane−water (3:1).

that the rate of formation of osmium(VI) ester complexes could be dramatically increased by the addition of an excess of tertiary amine such as pyridine.[5] When pyridine was added, the reaction was indeed faster, and the selectivity was excellent (Table 1, entry 4). Only a trace amount of compound **3** was isolated. Unfortunately, we also observed the formation of the epimer of the methyl group at the α-position of the aldehyde **2**, which was formed via the enolization of the aldehyde by pyridine. To avoid the base-promoted enolization, 2,6-di-*tert*-butylpyridine was employed (Table 1, entry 5). However, no effect was observed. These findings logically led us to investigate the use of 2,6-lutidine as the base. To our delight, we found that 2 equiv of 2,6-lutidine effectively suppressed the formation of compound **3** and dramatically improved the yield of the desired aldehyde **2** to 90% along with only 6% of the side product **3**. Furthermore, the reaction was faster and was complete in 2 h without epimerization of the methyl group at the α-position of the aldehyde **2**.

The amazing inhibiting effect of 2,6-lutidine led us to study its broad scope in a variety of substrates (Table 2).[6] In the absence of 2,6-lutidine, the reaction of compound **4** with OsO_4−$NaIO_4$ gave only 44% yield of the desired product **5** (Table 2, entry 1). Although structurally compound **4** is very similar to compound **1** except for the different protecting group at the homoallylic alcohol, we noticed that the oxidative cleavage reaction of compound **4** under the classic conditions (without 2,6-lutidine) was very messy, and many side products were formed (we did not try to characterize each side product). Amazingly, the yield of the desired aldehyde **5** was improved to 83% with the addition of 2,6-lutidine. It appeared that 2,6-lutidine inhibited several uncharacterized side reactions at the same time. The reaction of compound **6** under the classic conditions was quite slow and gave only 34% yield of the desired product **7** along with a 48% recovery of the starting material after the reaction was stirred at room temperature for 20 h (Table 2, entry 2). It was noted that longer reaction times resulted in even lower yield due to cleavage of the acid-labile TBS protecting group. In the presence of 2,6-lutidine, the same reaction was complete in 20 h and afforded 99% yield of compound **7**. Both inhibiting and rate acceleration effects by 2,6-lutidine were quite obvious in this instance. Similar effects were also observed in compound **8** (Table 2, entry 3). Compound **10** gave only 42% yield of the desired aldehyde **11** (Table 2, entry 4). But the yield was improved to 71% when 2 equiv of 2,6-lutidine was added. It should be noted that 2,6-lutidine also served as a weak base to neutralize the acid generated in the reaction to prevent the cleavage of the TES group. Compound **12**, an internal olefin, gave only 28% yield of the aldehyde **13** under the classic conditions. However, the yield was improved to 77% after the addition of 2,6-lutidine (Table 2, entry 5).

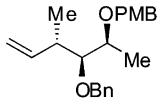
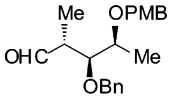
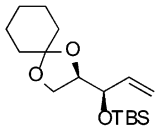
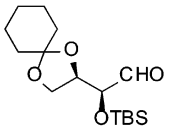
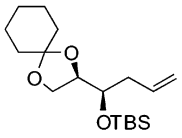
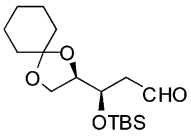
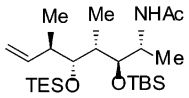
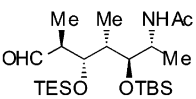
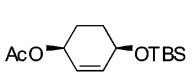
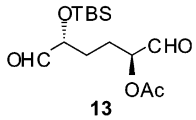
A typical procedure for the improved OsO_4−$NaIO_4$ oxidative cleavage reaction follows: To a solution of compound **1** (296 mg, 0.812 mmol) in dioxane−water (3:1, 8 mL) were added 2,6-lutidine (0.189 mL, 1.62 mmol), OsO_4 (2.5% in 2-methyl-2-propanol, 165 mg, 0.016 mmol), and $NaIO_4$ (695 mg, 3.25 mmol). The reaction was stirred at 25 °C and monitored by TLC. After the reaction was complete, water (10 mL) and CH_2Cl_2 (20 mL) were added. The organic layer was separated, and the water layer was extracted by CH_2Cl_2 (10 mL) three times. The combined organic layer was washed with brine and dried over Na_2SO_4. The solvent was removed, and the product was purified with silica gel column chromatography to afford aldehyde **2** (268 mg, 90%) as a colorless oil.

In conclusion, we have successfully developed an improved procedure for the classic OsO_4−$NaIO_4$-mediated oxidative cleavage reaction. We have demonstrated that 2,6-lutidine (or pyridine where epimerization is not likely to be an issue) can effectively suppress the formation of α-hydroxy ketone side products, accelerate the rate of the desired

(5) Criegee, R.; Marchand, B.; Wannowlus, H. *Justus Liebigs Ann. Chem.* **1942**, *550*, 99. (b) Schroder, M. *Chem. Rev.* **1980**, *80*, 187 and references therein.

(6) All compounds were fully characterized.

Table 2. Superior Improvement of the Oxidative Cleavage of Olefins

entry	substrate[a]	product	time, yield (without 2,6-lutidine)	time, yield (with 2,6-lutidine)
1	 **4**	 **5**	1 h, 44%	1 h, 83%
2	 **6**	 **7**	20 h, 34%	20 h, 99%
3	 **8**	 **9**	3 h, 21%[b]	3 h, 81%
4	 **10**	 **11**	3 h, 42%	3 h, 71%
5	 **12**	 **13**	24 h, 28%	24 h, 77%

[a] Reaction conditions: OsO_4 (0.02 equiv), $NaIO_4$ (4.0 equiv), 2,6-lutidine (2.0 equiv), dioxane−water (3:1). [b] Starting material (48%) was recovered.

reaction, and dramatically improve the reaction yield. In addition, 2,6-lutidine can also be used as a weak base to neutralize the acid generated in the reaction to prevent the cleavage of acid-labile protecting groups. Furthermore, we have noted that 2,6-lutidine can suppress some other side reactions that are not characterized at the present time. It is our conviction that this new procedure will find wide application in organic synthesis. The mechanistic explanation of the inhibiting effect of 2,6-lutidine is currently under investigation and will be reported in due course.

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