

Chemoselective Conversion from α -Hydroxy Acids to α -Keto Acids Enabled by Nitroxyl-Radical-Catalyzed Aerobic Oxidation

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S Supporting Information

ABSTRACT: The chemoselective oxidation of α -hydroxy acids to α -keto acids catalyzed by 2-azaadamantane *N*-oxyl (AZADO), a nitroxyl radical catalyst, is described. Although α -keto acids are labile and can easily release CO₂ under oxidation conditions, the use of molecular oxygen as a cooxidant enables the desired chemoselective oxidation.



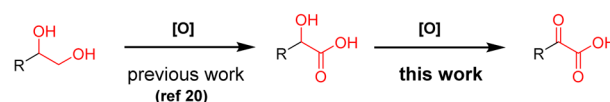
α -Keto acids and their esters exhibit unique structures that directly connect a keto carbonyl group and a carboxyl group. On the basis of the characteristic structures of α -keto acids, it is inferred that the C–C bonds linking the above-mentioned groups are easily cleaved to release CO₂,¹ and the acidity of the α -proton of the keto carbonyl group and electrophilicity of the keto carbonyl group are relatively high. These properties enable various remarkable transformations of α -keto acids and their esters.^{2–9} One of the most prominent reactions is the amide-forming reaction developed by Bode and co-workers, taking advantage of the efficient coupling between α -keto acids and hydroxylamines.² Another important reaction is decarboxylative coupling, which exploits the ability of α -keto acids to easily produce an acyl radical with the release of CO₂ under oxidation conditions.^{3–8} In addition, several transition-metal-catalyzed decarboxylative coupling reactions using α -keto acids as acyl anion equivalents have also been reported.⁹ α -Keto acids are mainly used as coupling partners in the above-mentioned decarboxylative coupling reactions, whereas α -keto esters are widely used as platform molecules for the development of catalytic reactions.¹⁰ α -Keto esters readily enolize to react with electrophiles under mild acidic or basic conditions.¹¹ Owing to the high electrophilicity of α -keto esters, many nucleophiles can also readily functionalize them.¹² These properties of α -keto esters enable them to compensate for catalytic activity. In particular, these properties are beneficial for organocatalysis, and an array of valuable organocatalytic reactions using α -keto esters have been developed.¹³ Thus, the number of useful reactions using α -keto acids and their esters is increasing, and these potential utilities in organic synthesis are growing. Due to this growth, the demand for the development of efficient preparation methods of α -keto acids is increasing. However, unfortunately the preparation methods of α -keto acids are rather limited. Although the α -keto ester is relatively easily available, its hydrolysis to α -keto acids often gives rise to undesired side reactions and epimerization owing to the lability of α -keto acids and their esters.¹⁴ Wasserman's protocol using cyanophosphorus ylides and Bode's modified protocol using cyanosulfur ylides are the predominant methods for the

preparation of α -keto acids.¹⁵ These protocols require the oxidative deprotection of phosphorus ylide or sulfur ylide, and the subsequent hydrolysis of acyl cyanides is accompanied by the stoichiometric amount of waste originated from phosphorus reagents and sulfur reagents.

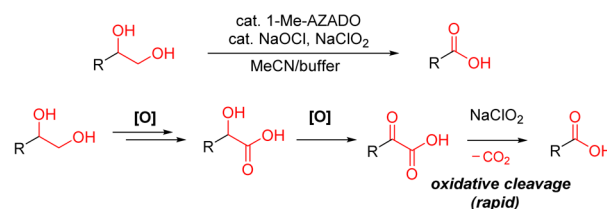
On the other hand, the preparation method of α -keto acids by sequential oxidations from 1,2-diols is a promising approach, which is highly atom-economical and does not require deprotection and hydrolysis (Scheme 1A). It is important to

Scheme 1. Chemoselective Oxidation towards α -Keto Acids

A) A preparation method of α -keto acids by sequential oxidations



B) Previous study: Oxidative cleavage^{21a}

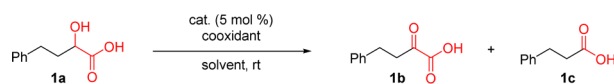


note that sequential oxidation affords α -keto acids without homologation, whereas Wasserman's protocol, Bode's protocol, etc. are accompanied by homologation.^{14,15} Various 1,2-diols are available from the biomass and are prepared by the dihydroxylation of terminal alkenes,^{16,17} hydrolysis of epoxides,¹⁸ and other methods,¹⁹ and we have developed chemoselective oxidation from 1,2-diols to α -hydroxy acids.²⁰ Thus, in order to develop a preparation method based on sequential oxidations, chemoselective oxidation from α -hydroxy acids to

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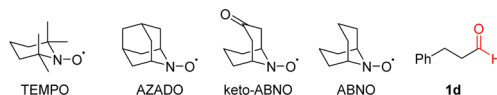
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Table 1. Optimization of the Reaction Conditions



entry	cat.	cooxidant	additive	solvent	time (h)	yield (%) ^a		
						1a	1b	1c
1	TEMPO	NaOCl	10 mol % <i>n</i> Bu ₄ NBr, 10 mol % KBr	CH ₂ Cl ₂ /sat. NaHCO ₃	4	11	8	69
2	TEMPO	PhI(OAc) ₂	—	CH ₂ Cl ₂	4	0	0	34 (37) ^b
3	TEMPO	PhIO	5 mol % Sc(OTf) ₃	CH ₂ Cl ₂	5	68	16	4 (10) ^b
4	TEMPO	TCCA	2.0 equiv of NaHCO ₃	CH ₂ Cl ₂	6	0	44	40
5	TEMPO	oxone	20 mol % <i>n</i> Bu ₄ NBr	CH ₂ Cl ₂	6	63	19	5
6	TEMPO	I ₂	—	toluene/sat. NaHCO ₃	6	91	0	0
7	AZADO	air (balloon)	20 mol % NaNO ₂	AcOH	2	<5	92	0
8	TEMPO	O ₂ (balloon)	20 mol % NaNO ₂	AcOH	2	85	5	0
9	AZADO	air (balloon)	20 mol % NaNO ₂	AcOEt	2	49	42	0
10	AZADO	air (balloon)	20 mol % NaNO ₂	acetone	2	78	11	0
11	AZADO	air (balloon)	20 mol % NaNO ₂	H ₂ O	2	79	18	0
12	AZADO	air (balloon)	20 mol % NaNO ₂	toluene	2	<5	94	0
13	AZADO	air (balloon)	20 mol % NaNO ₂	MeCN	2	0	95	0
14	keto-ABNO	air (balloon)	20 mol % NaNO ₂	MeCN	2	42	50	0
15	ABNO	air (balloon)	20 mol % NaNO ₂	MeCN	2	20	73	0

^aDetermined by ¹H NMR. ^bYield of **1d**.



α -keto acids is an issue that needs to be resolved. Owing to the difficulty associated with oxidation, we have observed that α -keto acids immediately cause decarboxylation to yield one-carbon-shorter carboxylic acids under oxidation conditions (Scheme 1B).²¹ Although limited examples employing Dess-Martin oxidation and a few other protocols are reported, the development of a conventional method for chemoselective oxidation is strongly desired.^{22,23} Dess-Martin oxidation yields a stoichiometric amount of waste from Dess-Martin periodinane, which creates a problem that is associated with the purification of the desired α -keto acid (*vide infra*). With regard to the realization of efficient oxidation from α -hydroxy acids to α -keto acids, we have obtained important results indicating that the oxidative cleavage is not caused by the nitroxyl radical catalyst, but by the cooxidant.^{21a} We assumed that a mild cooxidant compatible to α -keto acids enables the catalytic oxidation from α -hydroxy acids to α -keto acids.

On the basis of this assumption, we investigated the applicability of the reported 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO)-catalyzed oxidation protocols to the oxidation of α -hydroxy acids employing 2-hydroxy-4-phenylbutanoic acid (**1a**) as a substrate (Table 1).²⁴ Most of these protocols result in the production of a moderate yield of **1b** at most, because NaOCl,^{24a} PhI(OAc)₂,^{24b} PhIO,^{24f} trichloroisocyanuric acid (TCCA),^{24g} and Oxone^{24c} cause the oxidative cleavages to yield **1c** and **1d**, and the oxidation of **1a** does not proceed using the TEMPO-iodine protocol^{24d} (entries 1–6). In contrast, the desired α -keto acid **1b** was obtained in high yield by the AZADO-catalyzed aerobic oxidation,²⁵ although a low yield of **1b** was obtained when TEMPO was used instead of AZADO as a catalyst even under an O₂ atmosphere (balloon) (entries 7 and 8).^{24e} When AcOH was used as a solvent, the reaction terminated before **1a** was completely consumed, and small amounts of **1a** were recovered. In our previous study involving the use of normal secondary alcohols that do not have an acidic

functional group, the acidity of AcOH is necessary and no reaction occurred in neutral solvents such as MeCN and toluene. Interestingly, the oxidation of α -hydroxy acid **1a** occurred in aprotic solvents and water, without the need for an acid additive (entries 9–13). The reaction completed in MeCN to provide α -keto acid **1b** in high yield, without the recovery of **1a** (entry 13). Keto-ABNO- and ABNO-catalyzed aerobic oxidation afforded moderate yields of **1b** together with the recovery of **1a** (entries 14 and 15).²⁶

Under the optimized conditions, we investigated the substrate scope of chemoselective oxidation (Table 2). A broad range of α -hydroxy acids were efficiently oxidized to provide the corresponding α -keto acids in high yield (entries 1–13). Various functional groups such as ester, silyl ether, benzyl carbamate, alkene, and alkyne are tolerated (entries 3–5, 9–13). Proline-derived β -amino α -hydroxy acid **13a** was effectively oxidized to β -amino α -keto acid **13b** without any racemization, and valine-derived acyclic β -amino α -hydroxy acid **14a** afforded β -amino α -keto acid **14b** with minimum racemization. Unfortunately, the α -hydroxy acids generating α -keto acids with activated methylene such as **15a** did not yield the desired products, although the reason is not clear.

In our previous aerobic oxidation reaction, AcOH plays an indispensable role, presumably because the generation of NO_x from NaNO₂ requires an acid.²⁵ Consistent with the previous observation, the oxidation of α -hydroxy ester **16** did not proceed under similar conditions (Scheme 2). On the other hand, the reaction proceeded in the presence of 1 equiv of α -keto acid **1b** to provide α -keto ester **17** in good yield. These results indicate that α -hydroxy acids and α -keto acids themselves promote the reaction as acids, instead of AcOH.

Finally, we examined the oxidation of α -hydroxy acid **1a** employing conventional methods, i.e. Swern oxidation, TPAP oxidation, IBX, and Dess-Martin oxidation. From the results of our study, it was inferred that Swern oxidation and TPAP

Table 2. Substrate Scope of the AZADO-Catalyzed Chemoselective Oxidation

entry	α -hydroxy acid	α -keto acid	yield (%)
1			89
2 ^a			86
3			77
4			88
5			87
6			95 ^b
7			98
8			99
9			79
10			83
11 ^c			88
12			85 (er >99:1) ^d
13			86 (er 95:5) ^d
14			not detected

^aMeCN/H₂O (1:1) was used as a solvent. ^bIsolated as a methyl ester by a treatment with CH₂N₂. ^c10 mol % of AZADO was used. ^dEnantiomeric ratio was determined by chiral-HPLC as a methyl ester.

oxidation resulted in the production of α -keto acid in low yield, whereas IBX and Dess-Martin oxidation of **1a** effectively proceeded. Acid–base extraction of the reaction mixture yields a mixture of the desired product **1b** and residual iodine reagents together with small amounts of byproducts (Figure 1A). Owing to the high polarity and acidity of α -keto acids, it is difficult to separate the desired α -keto acid **1b** from the residual

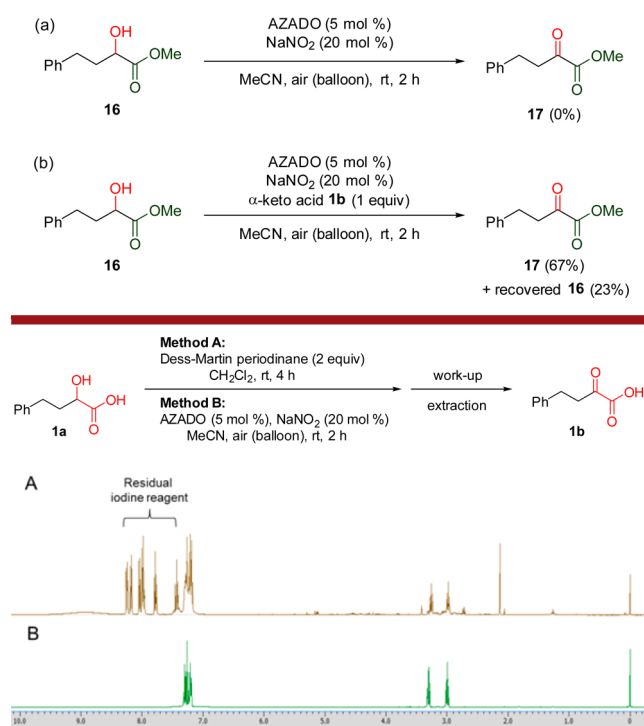
Scheme 2. Control Experiments


Figure 1. ¹H NMR spectra of crude materials after acid–base extraction. (A) Dess-Martin oxidation (Method A). (B) AZADO-catalyzed aerobic oxidation (Method B).

iodine reagents and the byproducts. In contrast, the AZADO-catalyzed aerobic oxidation yields the α -keto acid **1b** in high purity after acid–base extraction. Any noticeable byproduct and residual reagent are not detected, as shown in Figure 1B, without further purification.

In conclusion, we have realized oxidation from α -hydroxy acids to α -keto acids. By the combination of this oxidation with the chemoselective oxidation from 1,2-diols to α -hydroxy acids, α -keto acids can be prepared from the readily available 1,2-diols. The compatibility of molecular oxygen as a mild cooxidant embodies the preparation of labile α -keto acids under oxidation conditions. This oxidation attributed to a catalytic amount of AZADO and NaNO₂ to produce a minimum amount of waste, which not only is environmentally benign but also makes the purification of highly polar α -keto acids simple. This chemoselective oxidation is likely to expand the utility of α -keto acids having valuable reactivity in organic synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01964.

Experimental procedures and spectroscopic data (PDF)

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Notes

The authors declare no competing financial interest.

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