

## Oxidative Umpolung

Synthesis of 1,4-Diketones from  $\beta$ -Oxo Esters and Enol Acetates by Cerium-Catalyzed Oxidative Umpolung ReactionIrina Geibel<sup>[a]</sup> and Jens Christoffers<sup>\*[a]</sup>

Dedicated to Professor Siegfried Blechert on the occasion of his 70th birthday

**Abstract:** Cyclic  $\beta$ -oxo esters are converted with enol acetates in a cerium-catalyzed, oxidative Umpolung reaction to furnish 1,4-diketones with up to 95 % yield. Atmospheric oxygen is the oxidant in this process, which can be regarded as ideal from

economic and ecological points of view. Further advantages of this new C–C coupling reaction are its operational simplicity and the application of nontoxic and inexpensive  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  as precatalyst.

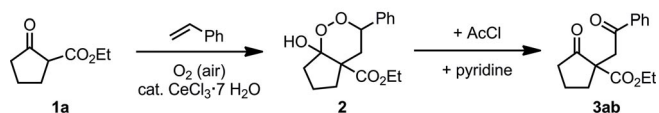
## Introduction

Since they are attractive starting materials for the preparation of furan, thiophene and pyrrole derivatives,<sup>[1]</sup> several procedures for the preparation of 1,4-diketones have been developed. Commonly, the synthesis of 1,4-diketones requires an umpolung strategy,<sup>[2]</sup> for instance, the conjugated addition of acyl-anion equivalents to  $\alpha,\beta$ -unsaturated ketones catalyzed by N-heterocyclic carbenes (Stetter reaction).<sup>[3,4]</sup> The oxidative generation of an electrophilic  $\alpha$ -radical adjacent to a carbonyl group can also be regarded as an umpolung process. The latter can be achieved by starting with  $\alpha$ -halo ketones<sup>[5]</sup> or by the stoichiometric application of metal salts with higher oxidation states like  $\text{Mn}(\text{OAc})_3$ <sup>[6]</sup> or  $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$ .<sup>[7]</sup> 1,4-Diketones can also be prepared from olefins or enol ethers. If hydroperoxides are applied for the generation of ketone  $\alpha$ -radicals, the  $\gamma$ -peroxy ketone products are isolable and can be transformed into 1,4-diketones by a base-mediated disproportionation reaction.<sup>[8]</sup>

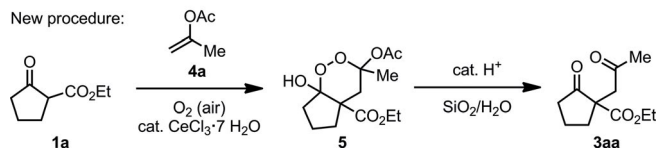
Some time ago, we have reported a cerium-catalyzed, oxidative coupling reaction of  $\beta$ -oxo esters **1** with styrene, which proceeded via 1,2-dioxane derivatives **2** as intermediate products to give 1,4-diketones **3** (Scheme 1, top).<sup>[9]</sup> The use of atmospheric oxygen as oxidative agent and the application of nontoxic and inexpensive  $\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$  as the precatalyst are clearly the advantages of this method compared to the other, above-mentioned umpolung strategies.<sup>[10]</sup> However, the disad-

vantage is the stoichiometric application of pyridine and acetyl chloride in the second step of the reaction to effect the fragmentation of the 1,2-dioxane **2** to the 1,4-diketone **3**. We present herein a new variant with enol acetates **4** instead of styrene, so that the intermediate dioxane derivatives **5** possess two acetal functions (Scheme 1, bottom). Therefore, the cleavage to the 1,4-diketone **3** gets along without the necessity of stoichiometric reagents; acid-catalyzed hydrolysis upon workup is sufficient to achieve the product **3**. Another advantage of the new protocol is the extension of the scope, since the limitation to styrene derivatives as olefins is overcome in favor of 1,4-diketones with an alkyl residue in the side chain.

Previous two-step procedure:



New procedure:



Scheme 1. Cerium-catalyzed, oxidative protocols for the preparation of 1,4-diketones **3** from  $\beta$ -oxo esters **1**. The hitherto existing procedure requires stoichiometric amounts of AcCl and pyridine for the fragmentation of the 1,2-dioxane derivative **2**. In the new procedure, the two acetal functions of the intermediate product **5** are hydrolyzed during the workup procedure.

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## Results and Discussion

In order to access suitable reaction parameters for the target reaction, we began our investigation with the conditions of the previously established two-step procedure for the conversion of oxo ester **1a** with styrene (Table 1, Entry 1). While the  $\alpha$ -hydroxylated compounds **6** were as expected the main product of this conversion,<sup>[11]</sup> we were nevertheless able to detect the

target compound **3aa** by GC–MS and to isolate it with 5 % yield. To identify optimal conditions, we then systematically varied stoichiometry, reaction temperature (23–100 °C), amount of catalyst (0.5–20 mol-%) and solvent [*i*PrOH, 1,1,1,3,3,3-hexafluoroisopropyl alcohol (HFIP), 2,2,2-trifluoroethanol (TFE), AcOH, 2-ethoxyethanol, acetone, toluene, fluorobenzene, benzotrifluoride]. The solvent turned out to be of decisive importance: The use of HFIP allowed for the first time the isolation of compound **3aa** in significant amounts (22 % yield, Entry 2), while the isolated amount of alcohol **6** (9 %) was drastically reduced in favor of the transesterification product **7** (22 %). Ultimately, the reaction conditions optimal for the generation of compound **3aa** were identified (Entry 3): The use of TFE as solvent and 2.5 mol-% of the precatalyst CeCl<sub>3</sub>·7H<sub>2</sub>O at 50 °C gave complete conversion, and the target compound **3aa** was isolated in 53 % yield as the factual exclusive isolable product out of the reaction mixture. As the only unique byproduct the transesterification product **7** was merely detectable, separated by chromatography and isolated in 3 % yield.

Table 1. Optimization of the reaction parameters (representative examples).

Entry	CeCl <sub>3</sub> ·7H <sub>2</sub> O	Solvent	T	Yields <sup>[a]</sup>
1	10 mol-%	<i>i</i> PrOH	30 °C	5 % ( <b>3aa</b> ), 86 % ( <b>6</b> ), 0 % ( <b>7</b> )
2	10 mol-%	HFIP	60 °C	22 % ( <b>3aa</b> ), 9 % ( <b>6</b> ), 22 % ( <b>7</b> )
3	2.5 mol-%	TFE	50 °C	53 % ( <b>3aa</b> ), 0 % ( <b>6</b> ), 3 % ( <b>7</b> )

[a] Yields of isolated products after chromatographic purification.

With the optimized reaction conditions in hand, the scope and limitations of the reaction were evaluated by conversion of various β-oxo esters **1** with enol acetates **4** (Table 2). However, the relative amount of enol ester **4** (1.3–5 equiv.) was individually adjusted for each of the products **3**. For all entries in Table 2 full conversion of the oxo ester component **1** was observed after 18 h reaction time at 40–50 °C. Initially, monocyclic oxo esters **1a–1c** were investigated. While the yield of reaction of cyclopentane derivative **1a** with isopropenyl acetate (**4a**; R = Me) was moderate, but yet preparatively useful (Entry 1: product **3aa**, 53 %), the results obtained with the homologous cyclohexane and -heptane derivatives **1b** and **1c** were inferior (Entries 5 and 7: **3ba**, 27 %; **3ca**, 28 %). This tendency was inverted by application of the acetophenone derivative **4b** (R = Ph; Entries 2, 6 and 8): **3ab** (36 %), **3bb** (46 %), **3cb** (45 %). Furthermore, the cyclopentane derivative **1a** was converted with an electron-deficient and an electron-rich enol ester (**4c**, R = 4-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>; **4d**, R = 4-MeOC<sub>6</sub>H<sub>4</sub>); in both cases the yields were lower (Entries 3 and 4: **3ac**, 19 %; **3ad**, 17 %). Fortunately, the results were significantly improved by utilization of benzo-annulated oxo esters **1**. Indanone derivative **1d** gave good yields with both enol esters **4a** and **4b** (Entries 9 and 10: **3da**, 89 %; **3db**, 82 %). The same is true for the electron-rich, the electron-deficient and the bromo-substituted indanone derivatives **1e**, **1f** and **1g**. Though, the yields with isopropenyl acetate (**4a**)

(Entries 14, 16 and 18: products **3ea**, 44 %; **3fa**, 66 %; **3ga**, 57 %) were good, but slightly lower than with the acetophenone derivative **4b** (Entries 15, 17 and 19: products **3eb**, 95 %; **3fb**, 71 %; **3gb**, 66 %). Conversion of indanone **1d** with nitrophenyl- and methoxyphenyl-substituted enol esters **4c** and **4d** showed decreased yields (Entries 11 and 12: **3dc**, 57 %; **3de**, 45 %), but in contrast to products **3ac** and **3ab** they are now in a preparatively useful range. The conversion of the sterically demanding enol ester **4e** gave only small amounts of the *tert*-butyl-substi-

Table 2. Conversion of various β-oxo esters **1x** with enol acetates **4y** under optimized reaction conditions. The yields of diketones **3xy** are given for isolated products purified by column chromatography.

Entry	Constitution	Product	R	Yield
1		<b>3aa</b>	Me	53%
2		<b>3ab</b>	Ph	36%
3		<b>3ac</b>	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	19%
4		<b>3ad</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	17%
5		<b>3ba</b>	Me	27%
6		<b>3bb</b>	Ph	46%
7		<b>3ca</b>	Me	28%
8		<b>3cb</b>	Ph	45%
9		<b>3da</b>	Me	89%
10		<b>3db</b>	Ph	82%
11		<b>3dc</b>	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	57%
12		<b>3dd</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	45%
13		<b>3de</b>	<i>t</i> Bu	8%
14		<b>3ea</b>	Me	44%
15		<b>3eb</b>	Ph	95%
16		<b>3fa</b>	Me	66%
17		<b>3fb</b>	Ph	71%
18		<b>3ga</b>	Me	57%
19		<b>3gb</b>	Ph	66%
20		<b>3ha</b>	Me	17%
21		<b>3hb</b>	Ph	69%
22		<b>3hc</b>	4-O <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	0%
23		<b>3hd</b>	4-MeOC <sub>6</sub> H <sub>4</sub>	36%
24		<b>3ia</b>	Me	22%
25		<b>3ib</b>	Ph	56%
26		<b>3ja</b>	Me	62%
27		<b>3jb</b>	Ph	77%

tuted product **3de** (Entry 13: 8 %). When tetralone derivatives **1h** and **1i** were submitted to the title reaction, the overall yields declined compared to the indanones (Entries 20, 21, 24 and 25: **3ha**, 17 %; **3hb**, 69 %; **3ia**, 22 %; **3ib**, 56 %). Using the electron-deficient enol ester **4c**, the yield collapsed (Entry 22: **3hc**, 0 %), which is not the case with the electron-rich congener **4d** (Entry 23: **3hd**, 36 %). The chromanone derivative **1j** achieved yields similar to the ones obtained with the CF<sub>3</sub>-substituted indanone **1f** (Entries 26 and 27: **3ja**, 62 %; **3jb**, 77 %). In summary, the benzo-annulated oxo esters **1d–1j** gave generally better yields than the monocyclic compounds **1a–1c** (max. 53 % yield), whereupon the indanone compounds (up to 95 % yield) are superior to the tetralone derivatives (up to 69 %). Regarding both enol acetates **4a** and **4b**, very similar results are obtained in most instances, although (with one exception) the acetophenone derivative **4b** appears to be slightly better. However, it became apparent, that variation of the electron density at the phenyl ring (O<sub>2</sub>N and MeO substitution at enol esters **4c** and **4d**) did not lead to an improvement of productivity.

## Conclusions

The cerium-catalyzed coupling of oxo esters with enol acetates is a new and operationally simple methodology for the synthesis of compounds with 1,4-dioxo constitution. The transformation can formally be considered as an umpolung of reactivity, with atmospheric oxygen being the oxidizing agent. The yields for benzo-annulated oxo esters range from good to excellent (up to 95 %). Monocyclic oxo esters give lower yields (up to 53 %), which are nevertheless still useful from a preparative point of view. In this way, we have successfully developed an attractive alternative to other, classical umpolung strategies, which often require much more elaborated reagents and/or laborious procedures.

## Experimental Section

**Methyl 2-(2-Oxopropyl)-1-indanone-2-carboxylate (3da). Representative Procedure:** CeCl<sub>3</sub>·7H<sub>2</sub>O (15 mg, 40 μmol) was added to a mixture of oxo ester **1d** (300 mg, 1.58 mmol) and isopropenyl acetate (**4a**; 317 mg, 3.16 mmol, 2 equiv.) in 2,2,2-trifluoroethanol (TFE; 1.2 mL), and the resulting mixture was stirred under an aerobic atmosphere at 50 °C for 18 h. Subsequently, all volatile materials

were removed in vacuo, and the residue was purified by column chromatography (SiO<sub>2</sub>; hexanes/MTBE, 1:1; R<sub>f</sub> = 0.20) to furnish the title compound **3da** (345 mg, 1.40 mmol, 89 %) as a colorless oil.

**Supporting Information** (see footnote on the first page of this article): Experimental details and characterization data for starting materials (if not commercially available) and products; copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra of all reported products.

**Keywords:** Umpolung · Oxidation · Cerium compounds · 1,4-Diketones · Enol ester · Oxo esters

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