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Short Communication

## Novel $\alpha$ -ketoesters from $\beta$ -diketones via a vanadium-mediated tandem transformation under an oxygen atmosphere



Yi Xiao <sup>a,b,c</sup>, Yue Xia <sup>b</sup>, Chunying Rong <sup>b</sup>, Hongmei Huang <sup>b,\*</sup>, Liqiu Mao <sup>a,b,c</sup>, Zaihui Fu <sup>a,b,c</sup>, Ningya Yu <sup>a,b,c</sup>, Dulin Yin <sup>a,b,c,\*\*</sup>

<sup>a</sup> Institute of Fine Catalysis and Synthesis, Hunan Engineering Laboratory for Petrochemical Materials, Hunan Normal University, Changsha 410081, PR China

<sup>b</sup> Key Laboratory of Chemical Biology and Traditional Chinese Medicine Research (Ministry of Education of China), Hunan Normal University, Changsha 410081, PR China

<sup>c</sup> National & Local Joint Engineering Laboratory for New Petro-chemical Materials and Fine Utilization of Resources, Hunan Normal University, Changsha 410081, PR China

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#### 1. Introduction

 $\alpha$ -Ketoesters are key intermediates for the synthesis of important substances such as optically active compounds, proteinase inhibitors and heterocycles [1]. Strategies for the one-pot synthesis of  $\alpha$ -ketoesters include the addition of Grignard reagents to oxalates or oxalyl chlorides and the Pd-catalyzed double carbonylation of halides [2,3]. However, these methodologies and related approaches often require harsh conditions [4] (e.g., low temperature [2], high CO pressure [3], and use of toxic SeO<sub>2</sub> [5]) and additives [6], which often result in relatively low atom efficiency.

Tandem reactions are powerful tools in green synthesis because of their step economy, operational simplicity and environmental friend-liness [7]. Furthermore, one-pot tandem protocols facilitate the preparation of novel compounds that are inaccessible by conventional step-by-step approaches [8]. Thus, many precious metals (e.g., Pd, Ru, Rh, Ir, and Au) [8], small molecules (e.g., H<sub>2</sub>O and cinchona alkaloid derivatives) [7,9] and enzymes [10] have been extensively explored in tandem catalysis.

Vanadium, which plays a vital role in chemistry and life sciences, is abundant and relatively inexpensive. Since the discovery of vanadium-dependent haloperoxidase (V-HPO) by Vilter in 1983,

#### ABSTRACT

Novel  $\alpha$ -ketoesters were conveniently synthesized from acetylacetone and analogs via a vanadium-mediated one-pot tandem process. These advanced  $\alpha$ -ketoesters could be selectively prepared under additive-free, mild conditions, viz., 1 atm O<sub>2</sub> pressure and 50–80 °C. DFT calculations were performed to provide insights into the detailed mechanism of the tandem transformation.

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vanadium complexes have gained increasing attention for their catalytic potential [11–13]. To date, these complexes have been widely used as catalysts in addition, condensation, cyclization, and oxidation reactions owing to the Lewis acidity and redox capabilities of V<sup>5+</sup> and V<sup>4+</sup> [14,15]. The inherently multifunctional nature of vanadium makes it a good candidate for a catalyst in tandem reaction. However, the use of vanadium catalyst in O<sub>2</sub>-driven green tandem process remains relatively unexplored probably because of reaction complexity and catalyst compatibility issues [8]. Herein, we report the first example of the facile synthesis of novel advanced  $\alpha$ -ketoesters via a vanadium-catalyzed one-pot tandem process using O<sub>2</sub> as the terminal oxidant.

### 2. Experimental

#### 2.1. General

All chemicals were commercially available and used without further purification. FT-IR spectra of samples were measured on an Avatar-370 spectrometer. UV–Vis spectra of the oxovanadium complexes were recorded with the Shimadzu UV-2450 UV–Vis spectrophotometer. <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of the isolated products were recorded on a Bruker 500-MHz NMR spectrometer. Gas chromatography was run on Agilent 6890 equipped with a DB-5 (30 m × 0.25 mm × 0.25 µm) column. Mass spectra were performed on a Varian Saturn 2100T GC-MS instrument. Density functional theory calculations for the key species at the B3LYP/6-31 + G(d) level have been performed on the Gaussian 03 software package.

<sup>\*</sup> Corresponding author. Tel.: +86 731 88872576; fax: +86 731 88872531.

<sup>\*\*</sup> Correspondence to: D. Yin, Key Laboratory of Chemical Biology and Traditional Chinese Medicine Research (Ministry of Education of China), Hunan Normal University, Changsha 410081, PR China. Tel.: +86 731 88872576; fax: +86 731 88872531.

*E-mail addresses:* huanghongmei@hunnu.edu.cn (H. Huang), dulinyin@126.com (D. Yin).

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#### 2.2. Synthesis of catalysts

Oxovanadium complexes were prepared by a modified method reported in the literature using 8-hydroxyquinoline (Q) and its halogen-substituted derivatives as the model ligands [16]. A mixture of 30 wt.% aq.  $H_2O_2$  (10 mmol) and 10 mL tetrahydrofuran was added into a three-necked flask containing  $V_2O_5$  (5 mmol) and 10 mL water. Then a solution of 8-hydroxyquinoline (Q, 20 mmol), 5-chloro-8-hydroxy-7-iodoquinoline (Q', 20 mmol) or 5,7-dichloro-8-hydroxyquinoline (Q'', 20 mmol) in tetrahydrofuran (40 mL) was added and the pH value of the solution was adjusted to 6–7 with ammonia. After refluxing for 2 h, the resulting solution was filtered to give black 8-quinolinolato vanadium complex after washing for three times with ethanol. Bis(8-hydroxyquinolinato) oxovanadium ( $Q_2VO$ ),  $Q'_2VO$  and  $Q''_2VO$  were obtained as black powders in 70%–79% yield.

For comparative studies, we used manganese complexes due to their cheapness, versatility in oxidation, and potential applicability as bifunctional redox-Lewis acid catalysts in tandem process [17]. Bis(8-hydroxyquinolinato) manganese ( $Q_2Mn$ ) was prepared from 5 mmol Mn(OAc)<sub>2</sub> and 10 mmol 8-hydroxyquinoline ligand in tetra-hydrofuran by the procedure described above.  $Q_2Mn$  was obtained as a pale yellow powder in 68% yield.

#### 2.3. Transformation of $\beta$ -diketones

A mixture of acetylacetone (58 mmol) and catalyst (0.07–0.14 mmol, unless otherwise stated) was placed into a three-necked flask. Then the one-pot tandem reaction was performed at 80 °C or specific temperature for the appropriate time under 1 atm O<sub>2</sub> supplied continuously by a commonly used water-seal system [18]. A small amount of mixture was taken out using a syringe. After centrifugation, the mixture was analyzed with an Agilent-6890 gas chromatograph. The identification of products was done by GC-MS (Varian Saturn 2100T; injector temperature: 250 °C, column temperature from 80 °C to 200 °C for  $\beta = 7$  °C/min). The resulting product was purified by silica gel column chromatography using a mixed solvent of n-hexane and ethyl acetate (3:1, v/v) as the eluent. The isolated product was determined by <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>), <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>), GC-MS and FT-IR analysis. Transformation of other  $\beta$ -diketones was performed according to the procedure described above.

#### 3. Results and discussion

#### 3.1. FT-IR spectra of samples

The FT-IR spectra of vanadium complexes **Q<sub>2</sub>VO**, **Q'<sub>2</sub>VO** and **Q''<sub>2</sub>VO** are shown in Fig. 1. The characteristic stretching frequencies for 8-hydroxyquinoline ligands can be observed at 1566–1574 ( $\nu_{(C=N)}$ ), 1483–1497 cm<sup>-1</sup> ( $\nu_{(C=C)}$ ), 1450–1466 cm<sup>-1</sup> ( $\nu_{(C=C)}$ ) and 1369–1377 cm<sup>-1</sup> ( $\nu_{(C=N)}$ ), respectively [19,20]. It is noteworthy that **Q<sub>2</sub>VO**, **Q'<sub>2</sub>VO** and **Q''<sub>2</sub>VO** showed strong V=O stretch around 960 cm<sup>-1</sup> (955, 962 and 960 cm<sup>-1</sup>, respectively), indicative of mononuclear complexes [21]. Complex **Q<sub>2</sub>Mn** also shows major bands between 1300 and 1600 cm<sup>-1</sup>, which correspond to characteristic stretching frequencies of 8-hydroxyquinoline ligand (Fig. A. 1).

#### 3.2. Tandem transformation of $\beta$ -diketones under O<sub>2</sub>

We began our studies by investigating the influence of different vanadium and manganese catalysts on the tandem reaction of acetylacetone (acacH). The results of these studies are shown in Table 1. When catalyzed by **Q**<sub>2</sub>**VO**, the transformation of acacH proceeded at 80 °C under 1 atm O<sub>2</sub> to give a new  $\alpha$ -ketoester, 4-oxo-2-penten-2-ylpyruvate (**3**), in relatively high yield (37.4%, Table 1, entry 1). The structure of **3** was unambiguously identified by <sup>13</sup>C NMR, <sup>1</sup>H NMR, GC-MS and FT-IR analysis. Other metal salts studied were shown to be less effective in the tandem process (entries 10–13). In the absence of catalyst or O<sub>2</sub>, the tandem



Fig. 1. FT-IR spectra of Q<sub>2</sub>VO, Q'<sub>2</sub>VO and Q"<sub>2</sub>VO.

reaction hardly proceeded, whereas the presence of pyridine exhibited only minor influence on the yield of **3** (entries 3, 14 and 15). It is interesting to note that the reaction leading to **3** catalyzed by **Q<sub>2</sub>VO** can proceeded at lower temperatures (50–60 °C, entries 5 and 6), although the conversion of acacH was slow. These results show that the vanadium complex can efficiently serve as a multifunctional catalyst for the tandem transformation of acacH to give **3** and has promising potential as a biomimetic activator of O<sub>2</sub> at mild temperatures.

Comparison of entry 4 with entry 7 in Table 1 showed that Q greatly improved the catalytic efficiency of vanadium compounds (per V atom). In addition, a manganese center could also be tuned by Q to improve the selectivity for product **3** (entries 10 and 11), which is consistent with our recent report on the green oxidation of alcohols using a Q derivative catalyst Q<sub>3</sub>Mn [16]. Not surprisingly, halogen-substituted ligands Q' and Q" inhibited the activity of the catalyst in the tandem reaction (entries 2, 8 and 9), probably because of the electron-withdrawing effect of the halogen substituents.

Next, we explored the scope of the tandem transformation with a variety of  $\beta$ -diketones using **Q**<sub>2</sub>**VO** as the catalyst (Table 2). Interestingly, the tandem reaction seemed to be substrate-selective. Fairly good yields were obtained when using analogs bearing an acacH subunit (entries 1–3), while ethyl acetoacetate, which has no acacH subunit, was unreactive (entry 7). Other  $\beta$ -diketones containing  $\alpha$ -CF<sub>3</sub> or phenyl

Table 1
Tandem transformation of acacH mediated by various catalysts under 1 atm of O <sub>2</sub> <sup>a</sup> .

Entry	Catalyst (mmol)	Time (h)	T (°C)	Conversion (%) <sup>b</sup>	Selectivity (%) <sup>b</sup>
1	Q <sub>2</sub> VO (0.14)	8	80	47.8	78.2
2	Q <sub>2</sub> VO (0.07)	8	80	20.7	76.8
3 <sup>c</sup>	Q <sub>2</sub> VO (0.07)	8	80	14.7	76.2
4	Q <sub>2</sub> VO (0.07)	8	70	16.9	76.3
5	Q <sub>2</sub> VO (0.07)	8	60	3.3	72.7
6	Q <sub>2</sub> VO (0.07)	8	50	0.4	72.5
7	V <sub>2</sub> O <sub>5</sub> (0.07)	8	70	13.5	68.0
8	Q'2VO (0.07)	8	80	18.6	53.6
9	Q"2VO (0.07)	8	80	15.7	49.5
10	Q <sub>2</sub> Mn (0.1)	8	80	2.1	66.7
11	$Mn(OAc)_2(0.1)$	8	80	4.4	34.1
12	$Cu(OAc)_2(0.1)$	24	80	0.8	<15.0
13	FeCl <sub>3</sub> (0.1)	24	80	0.6	0
14	None (0)	24	80	Trace	0
15 <sup>d</sup>	Q <sub>2</sub> VO (0.07)	8	80	0	0

 $^{\rm a}\,$  AcacH (58 mmol), catalyst (0.07–0.14 mmol), O\_2 (1 atm), 8–24 h, 50–80 °C.

<sup>b</sup> Determined by GC.

<sup>c</sup> Pyridine (6 mmol) was added.

<sup>d</sup> The reaction was performed under 1 atm of N<sub>2</sub>.

groups (entries 4–6) were not good substrates for the tandem process, and only decomposition products such as trifluoroacetic acid or benzoic acid were obtained.

Insight into the reaction mechanism was further explored using acetylacetone as the model molecule. The presence of high-valent  $V^{4+}$  and  $V^{5+}$  species in the tandem transformation of acetylacetone was supported by UV–Vis spectroscopy, though they have not been isolated. At different time intervals aliquot of the reaction mixture was taken out with the help of a syringe and then analyzed. It is interesting to note that intensity at ~572 nm due to the characteristic d–d transition of  $V^{4+}$  gradually decreased with time, suggesting that  $V^{4+}$  was slowly oxidized to  $V^{5+}$  in the **Q**<sub>2</sub>**VO** catalytic system (Fig. 2) [22]. Color changes of the reaction solution from black to red-brown also verified the change. However, the  $V_2O_5$  catalytic system displays a new broad band at ~582 nm after 8 h (Fig. A. 2), suggesting in situ production of the V<sup>4+</sup> center (blue in color) which may remain relatively stable under aerobic conditions [23].

Radical species play a decisive role in the activation of dioxygen, as reported in refs. [24,25]. To confirm the involvement of radical intermediate in the above tandem transformation of acetylacetone, an effective free-radical inhibitor was added. The results in Fig. 3 show that the free-radical inhibitor hydroquinone (HQ) drastically reduced the yield of **3**, indicating the importance of free radicals in the tandem transformation.

From our results and previous studies, it can be deduced that the vanadium-mediated tandem transformation of acetylacetone can be readily carried out through consecutive oxidation, addition, and dehydrogenation under an  $O_2$  atmosphere, leading to the formation of **3** (Scheme 1).

In order to elucidate the mechanistic details of the transformation, density functional theory (DFT) calculations for the key species **I–V** (mimicking the catalytic process of Fe<sup>2+</sup>-dependent acacH dioxygenase [24]) were performed at the B3LYP/6–31 + G(d) level of theory. The results of these calculations indicate that concerted peroxo radicals **I** and **II** are involved in the transformation. This is probably due to the coordination of carbonyl oxygen to the metal, which is promoted by the Lewis acidity of vanadium [14]. The optimized structure of **II** is also stereochemically favorable for the conversion of **II** to **III** since the O0group is adjacent to the CH• group (Fig. 4A). Further calculations show that the energy dramatically changes with the structural alterations of critical vanadium (30.2 kcal mol<sup>-1</sup>) is apparently lower than that of manganese (37.1 kcal mol<sup>-1</sup>), which is consistent with the higher product yields obtained using the vanadium complex catalysts.

#### Table 2

Tandem transformation of  $\beta$ -diketones catalyzed by **Q<sub>2</sub>VO** under 1 atm of O<sub>2</sub><sup>a</sup>.



Entry	$R_1$	R <sub>2</sub>	Time (h)	T (°C)	GC yield $(\%)^{b}$ ( <sup>c</sup> )
1	Me	Me	36	80	54.9 (43.7)
2	Et	Et	72	80	51.7 (35.0)
3	i-Pr	<i>i</i> -Pr	72	80	60.5 (41.2)
4	Me	CF <sub>3</sub>	72	80	Trace
5 <sup>d</sup>	CF <sub>3</sub>	CF <sub>3</sub>	72	65	Trace
6	Me	Ph	72	80	0
7	Me	$OC_2H_5$	72	80	0

<sup>a</sup> β-Diketone (acacH 58 mmol, others 4 mmol in 2 mL 1,2-dichloroethane), catalyst ( $Q_2VO$  0.14 mmol for acacH, others 0.06 mmol),  $O_2$  (1 atm), 36–72 h, 65–80 °C.

<sup>b</sup> Determined by GC.

<sup>c</sup> Yield of isolated product.

<sup>d</sup> Temperature was chosen based on the boiling point of substrate.



Fig. 2. UV–Vis spectra of the reaction system ( $\sim$ 0.1  $\mu$ L) in 3 mL acetonitrile. Reaction conditions: 0.14 mmol Q<sub>2</sub>VO in 58 mmol acacH, 1 atm O<sub>2</sub>, 80 °C.

It can be expected that intermediates **1** (methylglyoxal) and **2** will be difficult to isolate and characterize experimentally in the presence of **Q<sub>2</sub>VO** since the two species are reactive [26,27]. Fortunately, the main by-product in the first step of the transformation (oxidative cleavage), acetic acid, was detected by GC-MS, which strongly implies the existence of **1**. The addition of **1** to **2** over vanadium [14,28] or proton [29] (H<sup>+</sup> appears to be dispensable, see Table 1, entry 3) and the aerobic oxidation of **2** to **3** via vanadium would proceed easily and quickly [27]. Thus the observation of intermediate **2** is possible using less active catalysts **Q'<sub>2</sub>VO** or **Q''<sub>2</sub>VO**. This is good evidence for the fact that the same intermediate is formed in the reaction using catalyst **Q<sub>2</sub>VO**.

#### 4. Conclusions

In summary, we have developed a novel vanadium-mediated tandem process for the transformation of acacH and its analogs into  $\alpha$ -ketoesters that are inaccessible by conventional step-by-step approaches. In particular, these advanced  $\alpha$ -ketoesters can be selectively prepared under additive-free, mild conditions (1 atm O<sub>2</sub> pressure and 50–80 °C). DFT calculations performed to provide insights into the reaction mechanism indicate the involvement of peroxo radicals



**Fig. 3.** Influence of HQ on the yield of **3**, catalyzed by  $Q_2VO$  (0.07 mmol in 58 mmol acacH) at 80 °C under 1 atm of O<sub>2</sub> (0.02 or 0.08 equiv HQ w.r.t acacH was added, respectively).



Scheme 1. Proposed path for the tandem transformation via vanadium using acetylacetone as the model molecule.

in the tandem process, an observation supported by experimental results. Attempts to improve the transformation efficiency of this new process are now in progress. Further investigation will be focused on the systemic mechanism of vanadium-based biomimic activation of dioxygen and related tandem catalysis in the green synthesis of substituted analogs of **3**.



**Fig. 4.** (*A*) Optimized structure of **II**. The arrows that point from the C(5), H(6) and O(14) atoms indicate the directions of motion. (*B*) Calculated energy profiles for the species transformation catalyzed by  $VO^{2+}$  (from **I** to **V**) or  $Mn^{2+}$ .

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.catcom.2013.03.037.

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