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Direct Synthesis of 1,3-Diketones by Rh-Catalyzed Reductive α-Acylation of Enones

Kazuyuki Sato, Satoshi Yamazoe, Rie Yamamoto, Shizuka Ohata, Atsushi Tarui, Masaaki Omote, Itsumaro Kumadaki, and Akira Ando*

Faculty of Pharmaceutical Sciences, Setsunan University, 45-1, Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan

aando@pharm.setsunan.ac.jp

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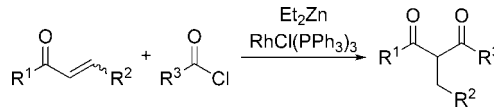
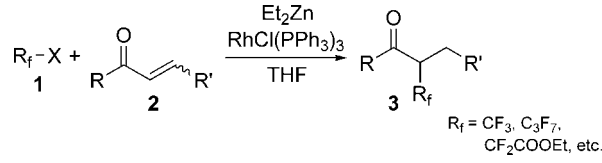
ABSTRACT



1,3-Diketones were synthesized from α,β-unsaturated ketones by treatment with acid chlorides and Et_2Zn in the presence of $RhCl(PPh_3)_3$. This is a very simple and extremely chemoselective reaction to give the adduct at the α-position of α,β-unsaturated ketones.

1,3-Diketones are very important compounds in organic chemistry, because they exhibit some biological activities themselves, such as antioxidants, antitumors, and antibacterial activities,[1] and are also key intermediates to various heterocyclic compounds.[2] To date, there are many reports for the synthesis of 1,3-diketones by oxidation of aldol-type compounds, hydroxylation of alkynones, oxidative cleavege of 1,4-dienes, and so on. However, surprisingly, only a limited number of procedures for a direct synthesis of 1,3-diketones from ketones has been reported,[3] because 1,3-diketones synthesized from acid chlorides or esters with various metal enolates of ketones have a problem in their chemoselectivity owing to the higher acidity of the α-hydrogen of 1,3-diketones than that of starting ketones. In addition, the regioselectivity also became a problem, when metal enolates of aliphatic ketones were used as starting materials which have α-hydrogens at both sides of the carbonyl group. Although, recently, some chemists reported new methods to solve this difficulty, the direct synthesis of 1,3-diketones has not been satisfactory and is still strongly desired.[4,5]

Scheme 1. Rh-Catalyzed α-Fluoroalkylation Reaction



Herein, we would like to report a simple and novel synthesis of 1,3-diketones using an Rh catalyst.

(1) (a) Kel'in, A. V. *Curr. Org. Chem.* **2003**, *7*, 1691–1711. (b) Kel'in, A. V.; Maioli, A. *Curr. Org. Chem.* **2003**, *7*, 1855–1886.

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(3) For the synthesis of 1,3-diketones using metal enolates: (a) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E *Tetrahedron Lett.* **2002**, *43*, 2945–2948. (b) Nishimura, Y.; Miyake, Y.; Amemiya, R.; Yamaguchi, M. *Org. Lett.* **2006**, *8*, 5077–5080. (c) Lim, D.; Fang, F.; Zhou, G.; Coltart, D. M. *Org. Lett.* **2007**, *9*, 4139–4142.

(4) For the synthesis of 1,3-diketones using transition metals: (a) Ikeda, Z.; Hirayama, T.; Matsubara, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 8200–8203. (b) Fukuyama, T.; Dai, T.; Minamino, S.; Omura, S.; Ryu, I. *Angew. Chem., Int. Ed.* **2007**, *46*, 5559–5561.

(5) For the synthesis of 1,3-diketones from benzotriazoles or acyl cyanides: (a) Katritzky, A. R.; Pastor, A *J. Org. Chem.* **2000**, *65*, 3679–3682. (b) Wiles, C.; Watts, P.; Haswell, S. J.; Pombo-Villar, E. *Chem. Commun.* **2002**, *10*, 1034–1035. (c) Katritzky, A. R.; Meher, N. K.; Singh, S. K. *J. Org. Chem.* **2005**, *70*, 7792–7794. (d) Shen, Z.; Li, B.; Wang, L.; Zhang, Y. *Tetrahedron Lett.* **2005**, *46*, 8785–8788. (e) Lim, D.; Fang, F.; Zhou, G.; Coltart, D. M. *Org. Lett.* **2007**, *9*, 4139–4142.

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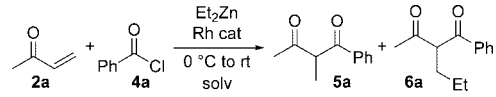
Table 1. Optimization of α-Acylation Reaction



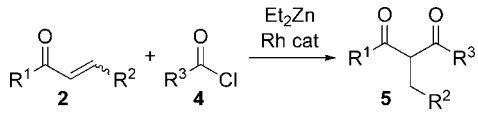
entry	**2a** (equiv)	Rh cat (mol%)	Et_2Zn (equiv)	solv	time (h)	yield of **5a**[a] (%)	yield of **6a**[a] (%)
1	1.5	$RhCl(PPh_3)_3$ (1)	1.5	THF	26.5	27	17
2	1.5	$RhCl(PPh_3)_3$ (2)	1.5	THF	5	45	0
3	1.5	$RhCl(PPh_3)_3$ (5)	1.5	THF	5	44	0
4	1.5	none	1.5	THF	2	0	62
5	2.0	$RhCl(PPh_3)_3$ (2)	1.5	THF	24	62	0
6	2.0	$RhCl(PPh_3)_3$ (2)	1.5	Et_2O	24	trace	35
7	2.0	$RhCl(PPh_3)_3$ (2)	1.5	1,4-dioxane	24	29	15
8	2.0	$RhCl(PPh_3)_3$ (2)	1.5	DME	24	43	trace
9	2.0	$RhCl(PPh_3)_3$ (2)	1.5	CH_2Cl_2	24	trace	25
10	2.0	$RhCl(PPh_3)_3$ (2)	1.5	toluene	24	trace	23
11	2.0	$RhCl(PPh_3)_3$ (2)	1.5	CH_3CN	24	trace	20

[a] Isolated yield.

Recently, we have reported a novel trifluoromethylation at the α-position of α,β-unsaturated ketones (**2**) by treating it with CF_3-I (**1a**) and Et_2Zn in the presence of $RhCl(PPh_3)_3$.[6] This reaction proceeded smoothly, and it could be applied to other halofluoroalkyl compounds (**1**; R_f-X) instead of CF_3-I to give α-R_f ketones (Scheme 1).[7]

In the Rh-catalyzed α-fluoroalkylation, we found that a rhodium hydride complex, which formed from $RhCl(PPh_3)_3$ with Et_2Zn, played an important role, and clarified the reaction mechanism by using a deuterated Zn reagent.[7]

Scheme 2. Rh-Catalyzed Reductive α-Acylation of α,β-Unsaturated Ketones



Based on this result, we expected if the reaction would proceed by using acid chlorides (**4**) instead of R_f-X (**1**), the acyl group could be introduced at the α-position of α,β-unsaturated ketones to give the 1,3-diketones (**5**) reductively (Scheme 2).

Using the previous condition,[6,7] we examined the reaction of methyl vinyl ketone (**2a**) with benzoyl chloride (**4a**) as shown in entry 2 of Table 1. As expected, the reaction proceeded and gave the desired product (**5a**) in a moderate yield. Decreasing the amount of Rh catalyst (1 mol %) led to a low yield along with a side product (**6a**). However, the yield did not improve even if 5 mol % of the Rh catalyst was used (entries 1−3). In entry 4, only the byproduct (**6a**) was obtained in the absence of Rh catalyst. It means that the Rh catalyst is involved in the formation of **5a**. So, we examined other rhodium catalysts instead of $RhCl(PPh_3)_3$, but the yield and/or the selectivity could not be improved. Next, we examined the effect of solvents as shown in entries 6−11. The ethereal solvents such as 1,4-dioxane or DME gave the product, whereas the other solvents did not improve the yield, unfortunately.

Then, using the optimum reaction condition (entry 5 in Table 1), we attempted to synthesize a variety of 1,3-diketones (**5**) to establish the scope of this method. The results are summarized in Table 2.[8]

The reaction of methyl vinyl ketone (**2a**) with benzoyl chloride (**4a**) gave the desired 1,3-diketone (**5a**) without a decrease of the yield even at 0 °C (entry 2). As shown in entries 1−8, most enones gave the corresponding 1,3-diketones (**5**) in good yields, regardless of whether they were cyclic or acyclic. However, enones that have two substituents on the β-carbon or have a bulky substituent (*t*Bu) next to the carbonyl group did not give the products (entries 3 or 7) but propiophenone was obtained in a considerable yield.

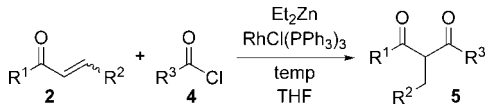
Furthermore, the reaction using various acid chlorides gave the products as shown in entries 9−15. Electronic effects of acid chlorides affected the yields and the reaction rate. Electron donating groups decreased the yields and prolonged the reaction time (entries 9 and 10). On the other hand, electron withdrawing groups on the acid chlorides improved the yields and the rate, although the *o*-substituent on the aromatic ring decreased the yield probably due to the steric hindrance (entries 11−13). Also, the heteroaromatic acid chlorides gave the desired 1,3-diketones in good yields as shown in entries 14 and 15.

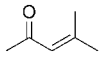
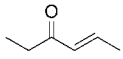
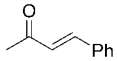
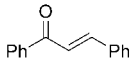
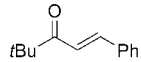
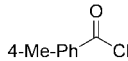
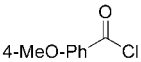
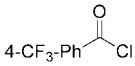
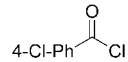
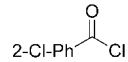
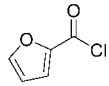
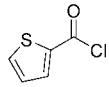
We think that the mechanism of this reaction is similar to the previous α-fluoroalkylation of α,β-unsaturated ketones (Figure 1).[7] More specifically, $RhCl(PPh_3)_3$ reacted with Et_2Zn to give a rhodium hydride complex (**8**) through an

(6) (a) Sato, K.; Omote, M.; Ando, A.; Kumadaki, I. *Org. Lett.* **2004**, *6*, 4359–4361. (b) Sato, K.; Omote, M.; Ando, A.; Kumadaki, I. *Org. Synth.* **2006**, *83*, 177–183.

(7) Sato, K.; Ishida, Y.; Murata, E.; Oida, Y.; Mori, Y.; Okawa, M.; Iwase, K.; Tarui, A.; Omote, M.; Kumadaki, I.; Ando, A. *Tetrahedron* **2007**, *63*, 12735–12739.

Table 2. Synthesis of Various 1,3-Diketones by Using Rh-Catalyzed α-Acylation



entry	2	4	temp (°C)	time (h)	yield of 5[a] (%)
1			0 to rt	24	62
2			0	3	61
3			0 to rt	24	0[b]
4			0	5	79
5			0	18	64
6			0	7	74
7			0	24	0[b]
8			0	24	81[c]
9			0	24	57
10			0	27	51
11			0	1	74[c]
12			0	3	70
13			0	5	57[c]
14			0	3	66
15			0	3	55

[a] Isolated yield. [b] Propiophenone was obtained in a considerable yield. [c] Mixture yield of the tautomer.

ethyl rhodium complex (**7**) along with the elimination of ethylene. The 1,4-reduction of enone (**2**) by **8** to form rhodium enolate (**9**) is followed by oxidative addition of acid chlorides (**4**) to give another rhodium complex (**10**). The reductive elimination generated the desired α-acylation product (**5**) and regenerated a rhodium catalyst.

In entries 3 and 7 of Table 2, the desired 1,3-diketone (**5**) was not obtained at all. We think that the enone in entry 3 would be prevented from the 1,4-reduction with the rhodium hydride (**8**) by the two substituents at the β-position. On the other hand, the reason why the reaction did not give the product in entry 7 would be that the oxidative addition of acid chloride could not proceed easily.

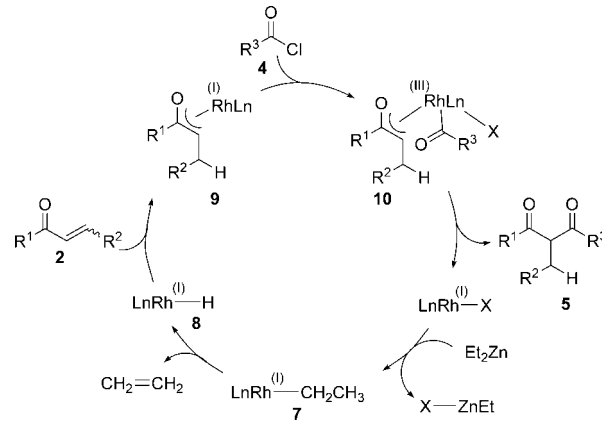
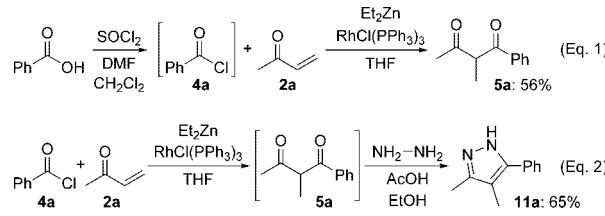


Figure 1. Reaction mechanism for Rh-catalyzed reductive α-acylation of enones.

Aiming the further application of this reaction, we attempted a one-pot rhodium catalyzed α-acylation using a carboxylic acid. Thus, benzoic acid was treated with $SOCl_2$ to form benzoyl chloride (**4a**) followed by the reductive α-acylation with **2a** to give the 1,3-diketone (**5a**) without a significant decrease of the yield (eq 1 in Scheme 3). This result suggests that carboxylic acids could be used instead of unstable acid chlorides.

Scheme 3. Application for One-Pot Synthesis of a 1,3-Diketone or a Pyrazole



Furthermore, 1,3-diketones are one of the useful key-intermediates to give various heterocyclic compounds which are involved in natural compounds and/or medicines. Especially, the most prevalent method of obtaining pyrazoles is by the reaction of 1,3-diketones with hydrazine or its derivatives.[9] So, we applied the reaction to one-pot synthesis of a pyrazole. That is, the 1,3-diketone (**5a**) derived from **4a** and **2a** was subjected to the cyclization by treatment with hydrazine. This reaction proceeded

(8) General procedure for reductive α-acylation: α,β-Unsaturated ketone (**2**; 4 mmol) and acid chloride (**4**; 2 mmol) were added to a solution of $RhCl(PPh_3)_3$ (2 mol %) in THF (5 mL) at 0 °C. Then, 1.0 M Et_2Zn in hexane (3 mmol) was gradually added to the mixture at 0 °C and was stirred at same temperature for the reaction time shown in Table 2. The mixture was quenched with 10% HCl and extracted with AcOEt. The AcOEt layer was washed with sat. NaCl and dried over $MgSO_4$. The solvent was removed *in vacuo*, and the residue was purified by column chromatography to give the corresponding 1,3-diketone (**5**).

(9) (a) Kost, A. N.; Grandberg, I. I. *Adv. Heterocycl. Chem.* **1966**, *6*, 347–429. (b) Heller, S. T.; Natarajan, S. R. *Org. Lett.* **2006**, *8*, 2675–2678.

smoothly to give a pyrazole (**11**) in a good yield, as expected (eq 2 in Scheme 3).

In conclusion, we synthesized various 1,3-diketones from α,β-unsaturated ketones and acid chlorides in good yields. The reaction proceeded smoothly, and gave the products regioselectively at the α-position of enones. Furthermore, it could be applied to the one-pot synthesis of a 1,3-diketone or a pyrazole. There are a few reports for the direct synthesis of 1,3-diketones which can lead to various heterocyclic compounds. In particular, this regioselective synthesis has never been reported to the best of our knowledge. Therefore, we believe that this reaction would become an important method for synthesis of such compounds.

Supporting Information Available: Experimental details and characterization of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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