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Reductive Reformatsky–Honda Reaction of α,β-Unsaturated Esters: Facile Formation of 1,3-Dicarbonyl Compounds and β-Hydroxy Esters

Kazuyuki Sato,[a] Motoyuki Isoda,[a] Shizuka Ohata,[a] Shuhei Morita,[a] Atsushi Tarui,[a] Masaaki Omote,[a] Itsumaro Kumadaki,[a] and Akira Ando[a,*]

[a] Faculty of Pharmaceutical Sciences, Setsunan University, 45-1, Nagaotoge-cho, Hirakata, Osaka 573-0101, Japan
Fax: (+81)-72-866-3142; phone: +81-72-866-3140; e-mail: aando@pharm.setsunan.ac.jp

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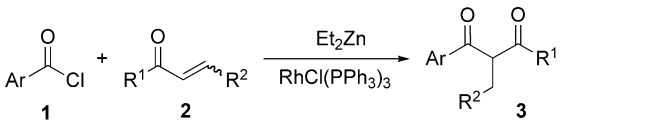
Abstract: The reaction of tris(triphenylphosphine)-rhodium chloride [$RhCl(PPh_3)_3$] with diethylzinc (Et_2Zn) easily afforded a rhodium-hydride complex that effects the 1,4-reduction of α,β-unsaturated esters to give rhodium enolates. Formation of the rhodium enolate is followed by transmetalation with the zinc species to give a Reformatsky-type reagent, and this reacts with various acid chlorides at the α-position to give β-keto esters. The Reformatsky-type reagent also reacts with various electrophiles such as aldehydes, ketones and acid anhydrides to give the corresponding products in which the electrophiles were introduced reductively at the α-position of α,β-unsaturated esters.

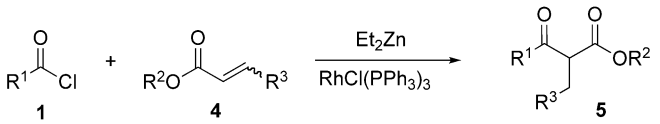
Keywords: α-acylation; 1,3-dicarbonyl compounds; β-hydroxy esters; reductive coupling; Reformatsky–Honda reaction; rhodium

Introduction

It is well known that 1,3-dicarbonyl compounds are key intermediates for the synthesis of various heterocyclic compounds that, in turn, are one of the most important components in medicines and natural products.[1] However, surprisingly, there is only a limited number of procedures for a direct synthesis of 1,3-dicarbonyl compounds, especially 1,3-diketones, this is due to the higher acidity of the α-hydrogen of the 1,3-dicarbonyl compounds than that of the starting carbonyl compounds.[2–4] We recently reported the direct synthesis of 1,3-diketones (**3**) by using Rh-catalyzed reductive α-acylation of α,β-unsaturated ketones (**2**) (Scheme 1).[5] The acylation proceeded at the α-position of the α,β-unsaturated ketones, since the Rh−H complex that was easily derived from the combination of $RhCl(PPh_3)_3$ with Et_2Zn properly acted as the key intermediate.[6] On the other hand, there are a lot of methodologies to synthesize β-keto esters, but their one-pot synthesis from α,β-unsaturated ester using hydroacylation is rare.[7] We herein would like to report the Rh-catalyzed reductive α-acylation of α,β-unsaturated esters (**4**) with various acid chlorides (**1**) to give the corresponding β-keto esters (**5**) in a one-pot procedure (Scheme 2).



Scheme 1. The direct synthesis of 1,3-diketones.



Scheme 2. Rh-catalyzed reductive α-acylation of α,β-unsaturated esters.

Results and Discussion

Reductive α-Acylation of α,β-Unsaturated Esters

Based on the previous conditions,[5] we examined the reaction of methyl acrylate (**4a**) with benzoyl chloride

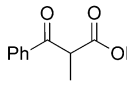
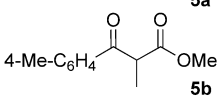
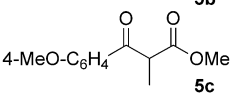
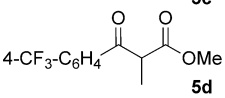
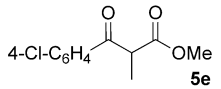
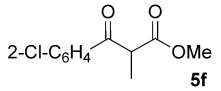
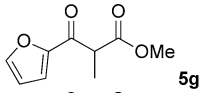
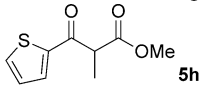
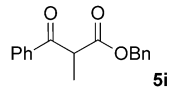
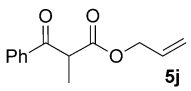
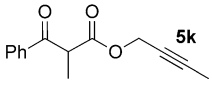
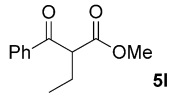
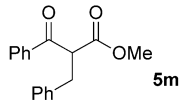
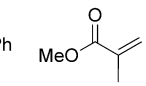
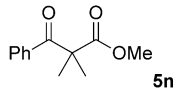
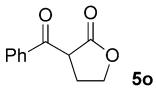
(**1a**). As expected, the reaction proceeded smoothly and gave the desired product (**5a**) in good yield. Then, we optimized the conditions for this reaction, and the best result was obtained in the original conditions [conditions A: 2 mol% of $RhCl(PPh_3)_3$ in THF at 0 °C]. Next, the reactions using various acid chlorides (**1**) and α,β-unsaturated esters (**4**) were examined under these conditions. These results are summarized in Table 1.

Although the electronic features of the acid chlorides somewhat affected the yields and the reaction rates, all acid chlorides gave the corresponding products in moderate to good yields as shown in entries 2–6. Heterocyclic acid chlorides also gave the corresponding β-keto esters in moderate to good yields as shown in entries 7 and 8. On the other hand, other α,β-unsaturated esters except benzyl acrylate gave poor results (entries 9–15). In particular, substituents on the β-position of **4** significantly decreased the yield. In addition, the reaction of acetyl chloride with phenyl acrylate gave the corresponding the product (**5p**) in 39% yield, but the using of an aliphatic acid chloride made the reaction mixture dirty (result was not shown in Table 1).

We therefore examined some additives in the reaction with methyl crotonate, and found that the addition of 1,5-cyclooctadiene (COD) dramatically improved the rate and the yield as shown in entry 12 [conditions B: 2 mol% of $RhCl(PPh_3)_3$ with 6 mol% of COD in THF at 0 °C]. Although the role of COD has not been clarified yet, it suppressed the side products. Thus we reexamined all reactions by using the conditions B. The yields and/or the rates of **5j–l**, and **5o** were improved by using COD, although further improvement in the yields of **5a–i** was not observed. Especially, it is interesting that **5j** and **5k** having an unsaturated alkoxy group were obtained in moderate yields without intramolecular cyclization.

Table 1. Scope and limitation of the Rh-catalyzed reductive α-acylation.

1 **4** **5**

Entry	1 R¹	4 R²	4 R³	Cond.[a]	Time [h]	5	Yield[b] [%]
1	Ph	Me	H	A	2	 **5a**	77
2	4-Me-C_6H_4	Me	H	A	3	 **5b**	75
3	4-MeO-C_6H_4	Me	H	A	7	 **5c**	64
4	4-CF_3-C_6H_4	Me	H	A	3	 **5d**	55
5	4-Cl-C_6H_4	Me	H	A	5	 **5e**	66
6	2-Cl-C_6H_4	Me	H	A	5	 **5f**	65[c]
7		Me	H	A	24	 **5g**	49
8		Me	H	A	3	 **5h**	64
9	Ph	Bn	H	A	9	 **5i**	59
10	Ph	allyl	H	A B	24 24	 **5j**	18 40
11	Ph	2-butynyl	H	A B	24 24	 **5k**	17 35
12	Ph	Me	Me	A B	24 1	 **5l**	27 67
13	Ph	Me	Ph	A B	24 24	 **5m**	ND ND
14	Ph			A B	24 24	 **5n**	ND ND
15	Ph			A B	4 1	 **5o**	39[c] 35[c]

[a] *Conditions A:* 2 mol% of $RhCl(PPh_3)_3$ in THF at 0 °C. *Conditions B:* 2 mol% of $RhCl(PPh_3)_3$ with 6 mol% of COD in THF at 0 °C.

[b] Isolated yield.

[c] Mixture yield of the tautomer.

Mechanistic Studies

Initially, we had thought that the Rh-catalyzed α-acylation proceeded through a rhodium enolate (**6**) that led to a Rh(III) complex (**7**) as mentioned in the previous paper.[5] Nonetheless, the whole yields of β-keto esters (**5**) were fairly low to moderate in comparison with the synthesis of 1,3-diketones. It, however, is clear that Rh–H complex would be involved in the reaction, since the reaction did not give the desired product in the absence of Rh catalyst. In addition, a reductive double aldol-type product was obtained, when the reaction by using benzoyl chloride with 2 equivalents of methyl acrylate was examined during the optimization of the reaction conditions. These results would suggest the existence of another mechanism, and we arrived at the conclusion that the Rh-catalyzed reductive α-acylation might proceed through zinc enolate (**8**) as shown in Figure 1.

To clarify the above mechanism, we examined some reactions as shown in Scheme 3. In the reaction of benzalacetone with benzoyl chloride, the corresponding 1,3-diketone was obtained in a good yield [Eq. (1)]. However, methyl cinnamate did not give the α-acylation product (**5m**) but was recovered as shown in Eq. (2). These results would relate to the capability of 1,4-reduction to Rh–H. In other words, an α,β-unsaturated ketone would be more susceptible to 1,4-reduction compared with an α,β-unsaturated ester, thus the reductive α-acylation might proceed even though an α,β-unsaturated ketone that has a substituent on the β-position. On the other hand, methyl vinyl ketone did not give the reductive aldol product, but methyl acrylate gave the corresponding product in an excellent yield in the reaction with benzaldehyde [Eq. (3) and Eq. (4)]. These results suggest that the stronger nucleophilicity of zinc enolate (**8**) from an ester might play an important role in the reaction.

From the above results, we proposed the following catalytic cycle (Figure 2). $RhCl(PPh_3)_3$ reacted with Et_2Zn to give the rhodium hydride complex (**11**) through the ethyl rhodium complex (**9**) along with the elimination of ethylene. The 1,4-reductive addition of

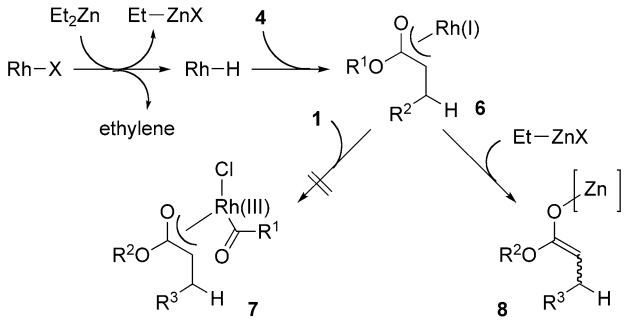
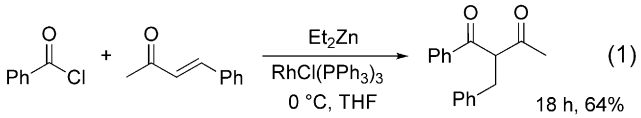
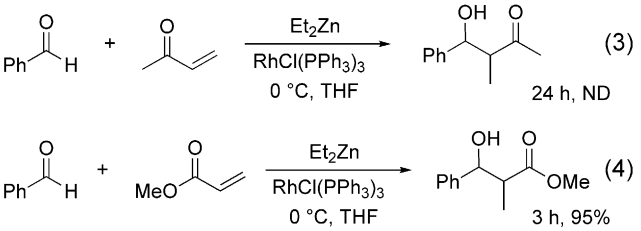


Figure 1. Participation of another mechanism through a zinc enolate.

Reductive α-acylation with benzoyl chloride



Reductive aldol reaction with benzaldehyde



Scheme 3. Mechanistic studies on the Rh-catalyzed reductive coupling reaction.

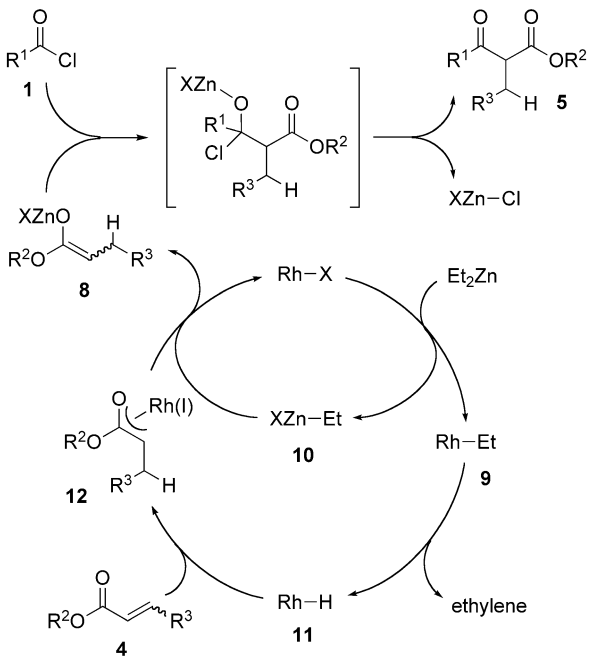
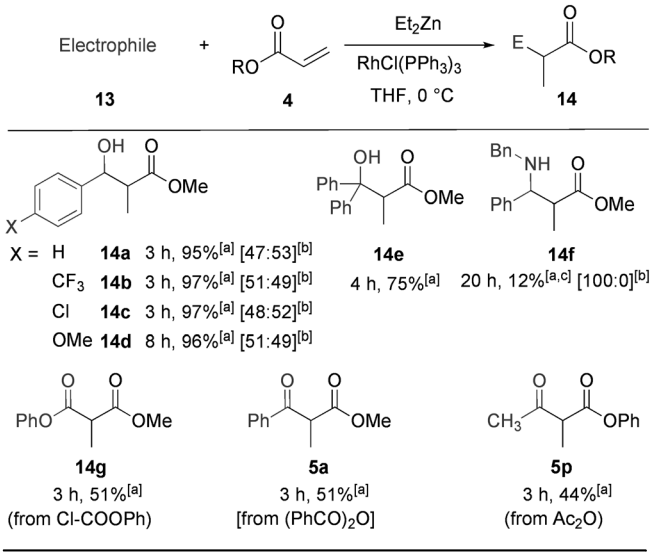


Figure 2. Plausible reaction mechanism.

11 to α,β-unsaturated ester to form rhodium enolate (**12**) is followed by transmetalation with zinc species to give a Reformatsky-type reagent (**8**). This reagent **8** promptly reacted with acid chlorides (**1**) to give the corresponding β-keto esters (**5**). However, the stronger nucleophilicity of **8** relative to a corresponding intermediate that is derived from α,β-unsaturated ketone led to the generation of side products, and then the yields of the β-keto ester might be decreased.

Table 2. Rh-Catalyzed reductive Reformatsky–Honda reaction with various electrophiles.



[a] Isolated yield.
[b] Diastereomeric ratio [*syn*:*anti*] after purification.
[c] β-Lactam product was isolated in 70%, and its diastereomeric ratio was *syn*:*anti* = 81:19.

Reductive Reformatsky–Honda Reaction with Various Electrophiles

The reductive α-acylation was assumed to proceed through zinc enolate (**8**). If so, the reaction could be applied to other electrophiles. Honda et al. reported a rhodium-catalyzed Reformatsky-type reaction by using the combination of Et_2Zn with $RhCl(PPh_3)_3$ (called the Reformatsky–Honda reaction). They applied the reaction to aldehydes and ketones or imines to give the corresponding Reformatsky-type products.[8] On the other hand, various intermolecular reductive aldol-type reactions toward aldehydes using metals such as copper,[9] cobalt,[10] and rhodium catalysts[11] have recently been reported, and they are showing synthetic versatility with high stereoselectivity. In addition, there are now similar aldol-type reactions *via* isomerization of allylic and/or homoallylic alcohols.[12] Thus we applied the reaction to various electrophiles (Table 2).

As expected, aldehydes and also a ketone gave the corresponding products in good to excellent yields, although their diastereomeric selectivities will need to be improved in the future. In the reaction with *N*-benzylidenebenzylamine (**13f**), the corresponding β-lactam product (**15f**) was isolated in 70% yield as the main product, and the total yields with uncyclized β-amino ester (**14f**) were also good. Furthermore, the reaction with phenyl chloroformate gave the corresponding 1,3-diester (**14g**). Acid anhydrides also reacted smoothly, and the desired products (**5a** and **5p**) were obtained in moderate yields. On the other hand, the reaction with other electrophiles such as phenyl formate, allyl acetate, allyl bromide and cyclohexyl bromide did not give any products at all. These results could be attributed to the nucleophilicity and/or steric effect of the Reformatsky-type reagent.

Conclusions

In conclusion, we have synthesized various β-keto esters from α,β-unsaturated esters with acid chlorides in moderate to good yields. The reactions proceeded smoothly and introduced the acyl groups at the α-position of the α,β-unsaturated esters, although the yield was strongly affected by the substrates. Furthermore, we proposed a plausible reaction mechanism, and applied this Reformatsky-type reaction to various electrophiles in good to excellent yields. Now we are trying to develop a stereoselective reductive aldol-type reaction based on this reaction.

Experimental Section

General Procedure for the Synthesis of β-Keto ester (5) (Conditions A)

α,β-Unsaturated ester (**4**, 2 mmol) and acid chloride (**2**, 4 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 the mixture was stirred at same temperature. The mixture was quenched with 10% HCl and extracted with AcOEt. The AcOEt layer was washed with saturated NaCl and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by column chromatography to give **5**.

General Procedure for the Synthesis of β-Keto Ester (5) (Conditions B)

To a solution of $RhCl(PPh_3)_3$ (2 mol%) in THF (5 mL) was added 1,5-cyclooctadiene (6 mol%), then the mixture was stirred at ambient temperature for 30 min. After this time, the mixture was cooled to 0 °C, α,β-unsaturated ester (**4**, 2 mmol) and acid chloride (**2**, 4 mmol) were added. Then, 1.0 M Et_2Zn in hexane (3 mmol) was gradually added to the mixture at 0 °C, and the mixture was stirred at same temperature. The mixture was quenched with 10% HCl and extracted with AcOEt. The AcOEt layer was washed with saturated NaCl and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by column chromatography to give **5**.

General Procedure for the Reaction with Electrophile (13)

α,β-Unsaturated ester (**4**, 2 mmol) and electrophile (**13**, 4 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 the mixture was stirred at same temperature. The mixture was quenched with 10% HCl and extracted with AcOEt. The AcOEt layer was washed with saturated NaCl and dried over $MgSO_4$. The solvent was removed under vacuum, and the residue was purified by column chromatography to give the corresponding product (**14**).

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