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Retro-Claisen Condensation with Fe^{III} as Catalyst under Solvent-Free Conditions

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Dedicated to Dr. J. S. Yadav on the occasion of his 60th birthday

Keywords: Iron / Cleavage reactions / Esters / Regioselectivity / Retro reactions

An iron(III) salt catalyzed retro-Claisen condensation between an alcohol and a 1,3-diketone was investigated. The mechanism involves the formation of a metal-induced six-membered cyclic transition state and cleavage of the C_{sp^2}–C_{sp^3} bond. Regioselective esterification and one-pot conversion of silyl ethers into esters with good yields was observed. Simple reaction conditions, high yields, and broad scope of the reaction illustrate the good synthetic utility of this method.

Introduction

For many decades, both in the history of mankind and in organic chemistry research, esters have been leading an important role in daily life, as well as in academic and industrial laboratories. Because of this essentiality we need an efficient method for the synthesis of esters.[1] Over the past decades, so many protocols have been established for the synthesis of esters, including condensation of alcohols and carboxylic acids;[2–4] acid anhydrides[5] or acyl halides;[6] transesterification;[7] ester-interchange reactions;[8] iron-, copper-, and ruthenium-catalyzed reactions of aldehyde and alcohols;[9] mercury- and tin-catalyzed reactions of carboxylic acids with acetylenes;[10] enzyme-catalyzed methods;[11] and the preparation of amides.[12] All these methods have disadvantages like in Fischer esterification: the use of concentrated aqueous HCl or H_2SO_4 may lead to many side products and the need for tedious procedures to isolate the product. Exercise with acid anhydrides and acid halides is very carcinogenic and they are toxic in nature. Transesterification, ester-interchange reactions, mercury-catalyzed reactions, and enzyme-catalyzed methods need tedious reaction conditions and difficult work-up procedures. In most of these methods, hazardous solvents are used and the conversions are expensive and environmentally unfavorable. In modern times, esterification[13] by carbon–carbon bond cleavage has received much attention, because new skeletons can be constructed directly by using such reactions. Recently in 2007, Kuninobu, Takai et al. worked on esterification by C–C bond cleavage by using $In(OTf)_3$.

Iron is very useful and one of the most abundant metals on the earth. In the recent past, iron-based catalysis has become a powerful tool for organic synthesis. Because of its low cost, environmentally benign characteristics, and significant reactivity, efforts have been directed to employ iron as an efficient catalyst for various organic transformations.[14,15] This inspired us to focus on the synthesis of esters in the presence of iron.

Herein we report a solvent-free, inexpensive, and commercially available ferric chloride catalyzed synthesis of esters. This reaction proceeds through carbon–carbon bond cleavage by a metal-induced six-membered cyclic transition state with excellent yields. The solvent-free approach is simple with amazing versatility. The reaction did not proceed in the absence of a catalyst.

Results and Discussion

In a preliminary reaction, 2,4-pentanedione (**1**) was treated with 2,3-dihydro-1*H*-inden-2-ol (**2a**) in the presence of $FeCl_3$ (10 mol-%) as catalyst at 80 °C under solvent-free conditions for 16 h to afford 2,3-dihydro-1*H*-inden-2-yl acetate (**3a**) in 98% yield (Scheme 1). Acetone was formed as a side product was removed by aqueous work-up. The structure of **3a** was established by ^1H NMR spectroscopy, in which the conspicuous presence of a signal due to the *acetyl* group at δ = 2.00 (s, 3 H) ppm along with other signals for 2,3-dihydro-1*H*-inden-2-yl acetate.

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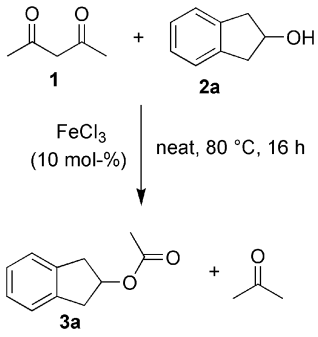


Scheme 1.

To investigate the scope of the reaction, several Lewis acids were used as catalysts (Table 1) under neat conditions. The reactivity of anhydrous $FeCl_3$ (**3a**, 98% yield) differs from that of $FeCl_3·6H_2O$ (**3a**, 83% yield; Table 1), whereas the use of $Fe(OTf)_3$ afforded almost the same yields as those obtained with $FeCl_3$. Nevertheless, $La(NO_3)_3$ afforded **3a** in 0% yield and $LaCl_3$ provided 15% yield only (Table 1). $BiCl_3$ and $AlCl_3$ offer considerable yields apart from the remaining Lewis acids in Table 1.

Table 1. Effect of catalyst on the retro-Claisen condensation between alcohol and 1,3-diketone.[a]

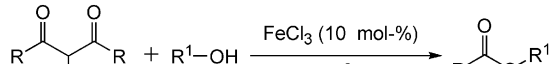
Entry	Catalyst	% Yield[b]
1	$FeCl_3$	98
2	$FeCl_3·6H_2O$	83
3	$FeCl_2$	47
4	$Fe(OTf)_3$	98
5	$LaCl_3$	15
6	$La(NO_3)·6H_2O$	0
7	CAN	0
8	$AlCl_3$	73
9	$Bi(NO_3)_3$	0
10	$BiCl_3$	93
11	$ZnCl_2$	trace
12	$ZnBr_2$	trace
13	$Zn(OTf)_2$	30
14	BF_3 Et_2O	0
15	BBr_3	0
16	Catalyst free	0

[a] Reaction conditions: 2,4-pentanedione (1 equiv.), 2,3-dihydro-1*H*-inden-2-ol (1 equiv.), catalyst (10 mol-%), 80 °C, 16 h. [b] Isolated yield.

After optimizing the scope and limitations of the reaction, we investigated the advantageous role and efficiency of this method by treating various 1,3-diketones with a variety of structurally diverse alcohols. We observed outstanding results. All of the reactions were carried out in the presence of $FeCl_3$ as catalyst without the use of any kind of hazardous solvent; the corresponding esters were obtained in high yields (Tables 2 and 3).

The reactions of acyclic (**2b**, **2c**) and cyclic (**2a**, **2d**) alcohols with acyclic 1,3-dicarbonyl compounds like pentane-2,4-dione (**1**) and 3-methylpentane-2,4-dione (**2**) afforded THE corresponding acetylated products in good yields (Table 2, Entries 1 and 2). Similarly, when alcohols **2a**, **2b**, and **2f** were treated with 1,3-diphenylpropane-1,3-dione (**4**), the corresponding benzoylated products were obtained. Nevertheless, with the use of 1-phenylbutane-1,3-dione (**3**), we observed high selectivity and the corresponding benzoates were predominantly afforded (Table 2, Entry 3). Usually the acetylation and benzoylation of hydroxy groups is very important in the synthesis of natural products and carbohydrate chemistry. In general, acetylation and benzoylation are carried out by using highly corrosive acetyl halides, benzoyl halides, and their acid anhydrides. In this aspect, our new protocol is very useful for synthetic organic chemistry.

Table 2. Iron-catalyzed reaction of acyclic 1,3-dicarbonyl compounds with aliphatic alcohols.



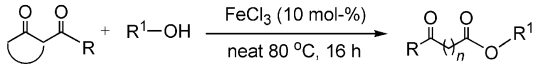
Entry	1, 3-Dicarbonyl compound	ROH	Product	% Yield[b]
1	1	2b	3b	98
		2c	3c	96
2	2	2b	3b	95
		2a	3a	93
		2d	3d	96
3	3	2a	3e	93
		2b	3f	96
		2g	3g	94
4	4	2a	3e	89
		2b	3f	91
		2f	3h	97

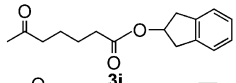
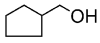
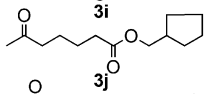
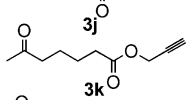
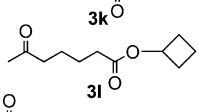
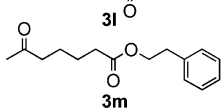
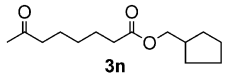
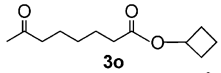
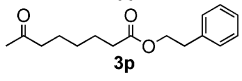
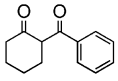
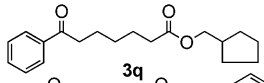
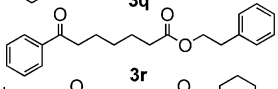
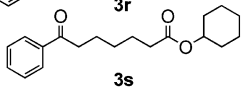
[a] Reaction conditions: 1,3-dicarbonyl compound (1 equiv.), alcohol (1 equiv.), $FeCl_3$ (10 mol-%), neat, 80 °C, 16 h. [b] Isolated yield.

Further, we employed the reaction to cyclic 1,3-diketones, namely, 2-acetylcyclopentanone (**5**), 2-acetylcyclohexanone (**6**), and 2-benzylcyclohexanone (**7**), with alcohols **2a**, **2b**, **2g**, **2h**, **2i**, and **2j** to obtain the corresponding keto esters (Table 3) in high yields with good atom economy. These esters might be useful in organic chemistry research, as intermediates for the total synthesis of bioactive natural products.

We observed regioselectivity for substrates **3** (Table 2), where the esterification occurred exclusively on the carbonyl group next to the benzyl group, affording predominantly the corresponding benzoates in excellent yields. Nevertheless, on substrates **7** (Table 3), esterification occurred exclusively on the carbonyl group in the cyclohexanone ring to give the corresponding ring-opened keto esters in high

Table 3. Iron-catalyzed reaction of cyclic 1,3-dicarbonyl compounds with cyclic and aliphatic alcohols.



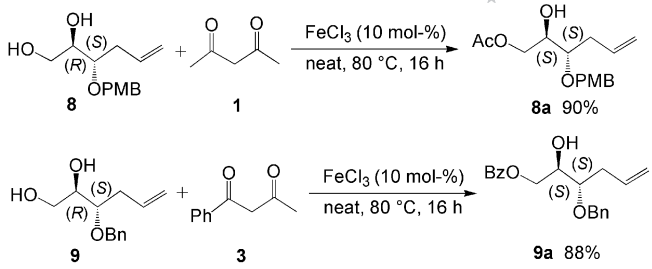
Entry	1,3-Dicarbonyl compound	ROH	Product	% Yield[b]
1	 5	2a	 3i	91
		 2g	 3j	94
		 2h	 3k	98
		 2i	 3l	93
		2b	 3m	97
2	 6	2g	 3n	95
		2i	 3o	94
		2b	 3p	98
3	 7	2g	 3q	94
		2b	 3r	97
		 2j	 3s	93

[a] Reaction conditions: 1,3-dicarbonyl compound (1 equiv.), alcohol (1 equiv.), $FeCl_3$ (10 mol-%), neat, 80 °C, 16 h. [b] Isolated yield.

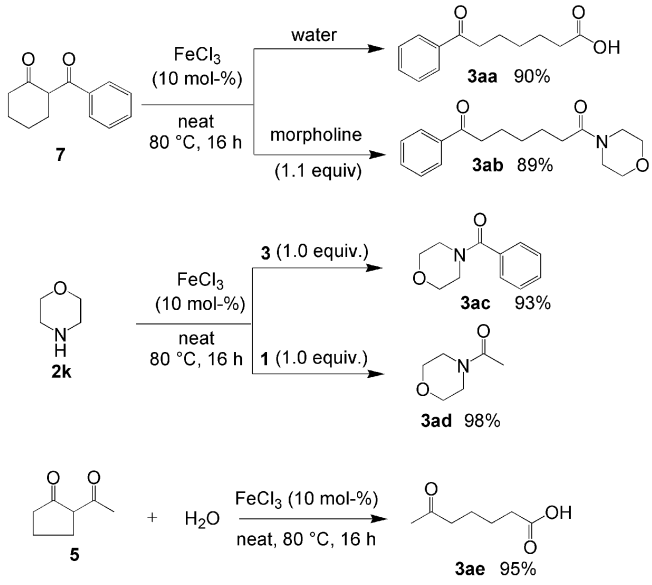
yield. It is evident that epimerization may take place in the case of some optically active compounds.

In the synthesis of bioactive natural products and carbohydrate chemistry, regioselective protections are fundamental and important. In this connection, our new method is useful for synthetic organic chemistry. We also examined the regioselective characteristics of this method by treating substrates **8** and **9** with 2,4-pentanedione (**1**) and 1-phenylbutane-1,3-dione (**3**); esterification occurs exclusively on the primary hydroxy group with a unimolar stoichiometry and predominantly afforded corresponding products **8a** (90%) and **9a** (88%; Scheme 2) under same reaction conditions.

By using the same protocol, 1,3-diketones reacted with water and secondary amines instead of hydroxy compounds. The reactions proceeded smoothly, affording the corresponding acids and amides in excellent yields (Scheme 3).

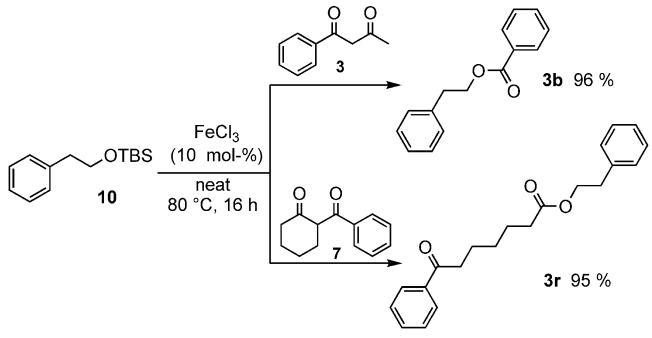


Scheme 2. Isolated yields of the products are given.



Scheme 3. Isolated yields of the products are given.

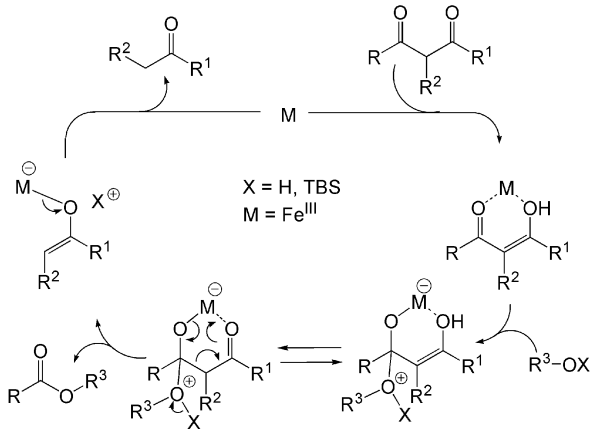
To investigate the substrate scope and potential of the new method, we carried out esterification on a substrate containing sensitive protecting groups like silyl ethers (TBS group, **10**) and obtained amazing results. When the reaction was carried out in the presence of $FeCl_3$ under solvent-free conditions at 80 °C for 16 h with the use of 1-phenylbutane-1,3-dione (**3**) and 2-benzyl cyclohexanone (**7**) in one pot, products **3b** (96%) and **3r** (95%) were obtained in high yields (Scheme 4).



Scheme 4. Isolated yields of the products are given.

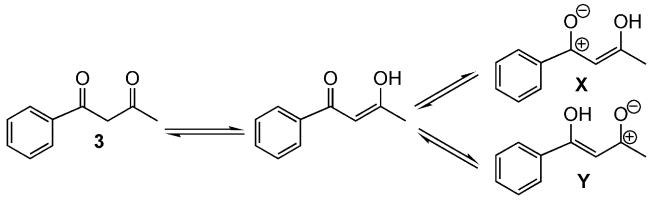
The reaction proceeds through metal-induced formation of a six-membered cyclic transition state and C_{sp^2}–C_{sp^3} bond breakage. The reaction mechanism mimics the retro-

Claisen condensation. Because of their strong oxophilicity, variable valency, and strong Lewis acidity, iron(III) salts catalyze the reaction by involving a six-membered cyclic transition state (Scheme 5).



Scheme 5. Proposed mechanism for the formation of ester.[11a]

In Scheme 6, it is evident that the benzylic carbocation (in isomer X) is more stable and readily available for a longer period of time than the aliphatic carbocation (in isomer Y), which facilitates regioselective nucleophilic attack predominantly on the carbonyl group next to the benzyl group rather than the non-benzylic carbonyl group.



Scheme 6. Proposed mechanism for the possibility of substrate regioselectivity.

Conclusions

In conclusion, we have developed an iron-catalyzed synthesis of esters by treating 1,3-dicarbonyl compounds with alcohols. These reactions proceed by nucleophilic attack of the alcohol at one of the carbonyl groups of the 1,3-diketone followed by carbon–carbon bond cleavage, which occurs through a six-membered cyclic transition state in a retro-Claisen condensation manner. Water, secondary amines, and silyl ethers can also be used as nucleophiles. We observed regioselective esterification with the use of the same protocol.

Experimental Section

General Esterification Procedure: The 1,3-diketone (1.0 mmol) was added to the hydroxy compound (1.0 mmol) in a 10-mL round-bottomed flask, followed by the addition of $FeCl_3$ (10 mol-%) under solvent-free and closed-vessel conditions. The reaction mixture was stirred for 16 h at 80 °C. The reaction was monitored by TLC. After completion of the reaction, the reaction mixture was dissolved in DCM (5 mL) and washed with distilled water. The organic layer was dried with Na_2SO_4, and the solvent was evaporated under vacuum. Column chromatography afforded product **3a** as a pale yellowish oil in 96% yield. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.16 (m, 4 H), 5.48 (m, 1 H), 3.27 (dd, J = 6.7, 16.6 Hz, 2 H), 2.95 (dd, J = 3.0, 16.6 Hz, 2 H), 2.00 (s, 3 H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$, 25 °C): δ = 171.4, 140.5 (2 C), 126.8 (2 C), 124.5 (2 C), 75.4, 39.8 (2 C), 21.6 ppm. IR: $\tilde{\nu}$ = 1734.8 cm^{-1}. MS (ESI): m/z = 199 [M + 23].

Supporting Information (see also the footnote on the first page of this article): General information and procedures, characterization data of the prepared compounds.

Acknowledgments

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