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Oxidative Esterification of Aldehydes with Urea Hydrogen Peroxide Catalyzed by Aluminum Chloride Hexahydrate

Sin-Ae Lee, Yoon Mi Kim, and Jong Chan Lee*

*Department of Chemistry, Chung-Ang University, Seoul 06974, Korea. *E-mail: jclee@cau.ac.kr*

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Esters are some of the most important functional groups in organic chemistry and have been found in the sub-structure of a variety of natural products, industrial chemicals, and pharmaceuticals.[1] Numerous methods have been reported for the preparation of various esters.[2] One of the most common methods is the reaction of activated carboxylic acid derivatives with alcohols. In this method, prior to the reaction with alcohols, carboxylic acids must be converted to reactive intermediates such as acid chlorides, anhydrides, or 1-hydroxybenzotriazoles.[3] Other more efficient and economically advantageous approaches include the direct esterification of aldehydes with alcohols in the presence of various oxidants.[4] A variety of transition-metal-based catalysts like vanadium,[5] iridium,[6] palladium,[7] copper,[8] rhodium,[9] and gold[10] were utilized for oxidative esterification of aldehydes. In addition, a variety of oxidative systems were developed for direct esterification, which include Br_2,[11] I_2/PhI(OAc)$_2$,[12] *N*-halosuccinimide,[13] pyridinium hydrobromide perbromide,[14] NaOCl/NaI,[15] potassium peroxymono-sulfate,[16] B(C_6F_5)$_3$/TBHP,[17] and trichloroisocyanuric acid.[18] However, all of the above methods usually require the use of stoichiometric amounts of reagents, toxic transition metals, expensive catalysts, or harsh reaction conditions. Recently, aqueous hydrogen peroxide mediated oxidative esterification has become more popular for the direct esterification of aldehydes. A few transition metal complexes such as methyltrioxorhenium,[19] V_2O_5,[20] titanosilicate,[21] and Ni(II) complex,[22] were reported in the literature to effect the hydrogen peroxide mediated oxidative esterification of aldehydes. Very recently, Wu *et al.* reported an environmentally friendly method for the oxidative methyl esterification of aromatic aldehydes utilizing aqueous hydrogen peroxide with readily available calcium chloride or magnesium chloride.[23] However, even by virtue of this method in the preparation of aromatic methyl esters, one might occasionally encounter inconveniences in terms of low isolated yields, long reaction times, and a narrow range for the applicable aromatic aldehydes. In particular, this method gives low yields for both aldehydes containing electron donating substituents in aromatic rings and heterocyclic aldehydes. Therefore, development of a more general, efficient, and greener protocol for the esterification of aldehydes with readily available catalyst is still desirable.

In search of a new oxidative esterification method, our attention was directed to the utilization of readily available aluminum(III) chloride hexahydrate as the catalyst since it possesses high Lewis acidity and low toxicity. Aluminum(III) chloride hexahydrate, well-known as a promising environmentally benign reagent, has found wide utility for a variety of organic transformations.[24] Initial attempts at the esterification of benzaldehyde using aqueous 30 wt % hydrogen peroxide with aluminum(III) chloride hexahydrate in methanol at 60°C for 12 h gave only 58% yield for the desired methyl benzoate. However, we found that replacement of aqueous hydrogen peroxide with urea hydrogen peroxide (UHP) gave methyl benzoate with a significantly better yield of 90%. Although UHP has found applications in various organic transformations,[25] to the best of our knowledge there is no precedent for the application of UHP for oxidative esterification. Further attempts at the esterification of benzaldehydes in methanol with various catalysts like $ZnCl_2$, $ZnBr_2$, $MgCl_2$, $MgBr_2$, $CaCl_2$, or $CaBr_2$ in the presence of UHP gave only moderate yield lower than 70%. Therefore use of UHP in combination with aluminum(III) chloride hexahydrate is distinctively more reactive for the direct transformation of benzaldehyde to methyl benzoate. Replacement of methanol by other larger alcohols in the present reaction conditions led to somewhat lower yields as shown in the Table 1. With highly hindered t-butanol or less nucleophilic phenol, no reaction occurs under the same reaction conditions. Various aldehydes undergo oxidative esterification to the corresponding methyl esters in high yields upon treatment with urea hydrogen peroxide and catalytic amounts of aluminum(III) chloride hexahydrate in methanol as shown in Table 2. In a typical experiment 1.0 mmol of aryl/alkyl aldehyde was reacted with 5.0 mmol of UHP and 10 mol % of aluminum chloride hexahydrate in 4.0 mL of methanol at 60°C to give the desired methyl esters. All of the reactions tested in this study were completed within 8–12 h. The present protocol was sufficiently reactive for various types of aromatic, aliphatic, and heterocyclic aldehydes. Aromatic aldehydes with electron donating or electron withdrawing substituents gave equally high yields. Sterically demanding aldehydes such as 2,4-dimethoxybenzaldehydes and 2,4-dichlorobenzaldehyde were smoothly converted into the

Table 1. Effect of different alcohols for esterification of benzaldehyde.[a]

Entry	Alcohols	Yield(%)[b]
1	MeOH	90
2	MeOH	58[c]
3	EtOH	83
4	*i*-Propyl alcohol	60
5	*i*-BuOH	N.R.[d]
6	PhOH	N.R.[d]

[a] Reaction conditions: 1.0 mmol benzaldehyde, 5.0 mmol of UHP, 10 mol % of $AlCl_3 \cdot 6H_2O$, 3.0 mL of alcohol, 12 h, 60°C.
[b] Isolated yield.
[c] Yield obtained replacing UHP by aqueous 30% H_2O_2.
[d] No reaction.

corresponding methyl esters with high yields (entries **5** and **8**). Moreover, aliphatic aldehydes and heterocyclic aldehydes also afforded high yields of the corresponding methyl esters. (entries **14–18**). In all of the cases tested, carboxylic acid by-products were detected in negligible amounts. Hence, the present reaction conditions provide a solution to the previously reported difficulties in the metal halide catalyzed esterification of aromatic aldehyde with electron donating substituents and heterocyclic aldehydes.[23] However, this procedure does not work for oxidative esterification of unsaturated aldehyde like cinnamaldehyde.

The transformation of the aldehydes to the corresponding esters probably occurred with the initial formation of hemiacetal intermediates and subsequent oxidation of the hydroxyl group of hemiacetal with UHP/aluminum(III) chloride hexahydrate to give methyl esters as proposed in other analogous Lewis acid catalyzed esterification of aldehydes.[17,20]

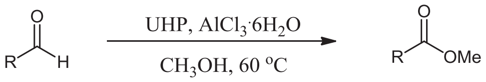
In summary, we have developed a new, environmentally benign and highly efficient oxidative preparation of methyl esters by the reaction of various aldehydes with UHP in methanol catalyzed by readily accessible aluminum(III) chloride hexahydrate. This new greener and cost effective direct esterification method can serve as a useful alternative to existing protocols.

Experimental Section

All the alcohols and aldehydes were purchased from Aldrich (St. Louis, MO, USA) and used as received. The reactions were checked by TLC using Silica gel plates. Merck silica gel 60 (230–400 mesh; Darmstadt, Germany) was used for flash column chromatography. ^1H NMR spectra were measured with the Varian Gemini 2000 (300 MHz; Palo Alto, CA, USA) spectrometer tetramethylsilane as an internal standard and $CDCl_3$ as a solvent. All products were known and identified by comparison of their ^1H NMR spectra with those of reported literature data.

General Procedure. A mixture of aldehyde (1.0 mmol), aluminum chloride hexahydrate (10 mol %), and urea hydrogen peroxide (5.0 mmol) was stirred in methyl alcohol (4.0 mL) at 60°C for 8–12 h. After cooling the mixture

Table 2. AlCl3 catalyzed oxidative esterification of aldehyde in methanol.



Entry	Aldehyde	Esters	Yield (%)[a]
1	PhCHO	PhCOOMe	90
2	4-$CH_3C_6H_4CHO$	4-$CH_3C_6H_4COOMe$	92
3	2-$CH_3OC_6H_4CHO$	2-$CH_3OC_6H_4COOMe$	90
4	4-$CH_3OC_6H_4CHO$	4-$CH_3OC_6H_4COOMe$	91
5	2,4-$(CH_3O)_2C_6H_4CHO$	2,4-$(CH_3O)_2C_6H_4COOMe$	87
6	2-ClC_6H_4CHO	2-ClC_6H_4COOMe	93
7	4-ClC_6H_4CHO	4-ClC_6H_4COOMe	95
8	2,4-$(Cl)_2C_6H_4CHO$	2,4-$(Cl)_2C_6H_4COOMe$	92
9	4-BrC_6H_4CHO	4-BrC_6H_4COOMe	92
10	4-FC_6H_4CHO	4-FC_6H_4COOMe	92
11	4-CNC_6H_4CHO	4-CNC_6H_4COOMe	90
12	4-$NO_2C_6H_4CHO$	4-$NO_2C_6H_4COOMe$	73
13	2-Naphtaldehyde	Methyl-2-naphthoate	98
14	$CH_3(CH_2)_4CHO$	$CH_3(CH_2)_4COOMe$	75
15	$CH_3(CH_2)_6CHO$	$CH_3(CH_2)_6COOMe$	82
16	$C_6H_{11}CHO$	$C_6H_{11}COOMe$	76
17	2-Furaldehyde	2-Furoic acid methyl ester	82
18	Thenaldehyde	Methylthiophene-2-carboxylate	84

[a] Isolated yields.

to room temperature the product was extracted into ethyl acetate (3 × 20 mL), washed with water and dried over sodium sulfate. The combined ether extracts were concentrated under reduced pressure and the crude product was purified by flash column chromatography (ethyl acetate/*n*-hexane = 1:4, v/v) to give the desired methyl ester.

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