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A Catalytic Oxidative Esterification of Aldehydes Using V_2O_5–H_2O_2

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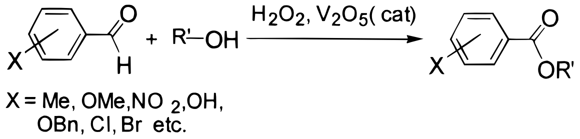
ABSTRACT



Aldehydes, in the presence of methanol, undergo oxidative transformation to the corresponding esters upon treatment with catalytic amounts of vanadium pentoxide in combination with oxidant hydrogen peroxide. Mild reaction conditions, shorter reaction times, high efficiencies, cost-effectiveness, and facile isolation of the desired products make the present methodology a practical alternative.

Oxidative transformation of aldehydes to esters is often required, and hence much effort has been devoted to find newer methods and newer reagents effective for this type of oxidative transformation.[1,2] Catalyst methyltrioxorhenium(VII), with hydrogen peroxide as oxidant, and a cocatalyst such as bromide or chloride ions is an efficient combination for the transformation of aldehydes to esters.[3] Unfortunately, many of these procedures often require a large excess of reagents, expensive catalysts, dry solvent, an inert atmosphere, and photochemical conditions, causing severe economic problems upon scale-up. Moreover, at times, poisonous and polluting reagents, mediators, and cocatalysts are required along with longer reaction times and drastic reaction conditions. Also these reagents do not always prove to be satisfactory for specific oxidation of aldehydes in systems containing deactivating groups and olefinic functions. We have therefore sought to develop a highly facile, cost-effective, and environmentally friendly catalytic route for esterification of aldehydes and now report success in this endeavor.

Recently we have reported a method for the oxidative transformation of tetrabutylammonium bromide to the corresponding tribromide (Br_3^-) using V_2O_5 as catalyst and H_2O_2 as oxidant.[4] Utilizing the *in situ* generated active brominating agent (Br_3^-) we have successfully brominated a wide spectrum of organic substrates.[5] On the basis of the versatility of the combination of V_2O_5–H_2O_2 as oxidant, we chose to examine its efficacy in the controlled oxidation of aldehydes to esters in the presence of an alcohol. In this Letter we report V_2O_5–H_2O_2-mediated oxidative esterification of wide varieties of aldehydes to the corresponding methyl esters with high yields in a single step. Our method has advantages over previous methods with respect to environmentally benign catalyst and reagent, cost-effectiveness, high efficiency, mild reaction conditions, shorter reaction times, and facile isolation of required products.

In a typical reaction, to an ice cooled solution of aldehyde (1 mmol) in methanol (5 mL) containing 70% $HClO_4$ (0.6 mmol) is slowly added a solution of V_2O_5 (0.04 mmol) dissolved in H_2O_2 (4 mmol) ca. 5 °C. The reactiom times are as shown for each substrate in Table 1.

Mechanistically, it seems plausible that the aldehyde is oxidized with V_2O_5–H_2O_2 to the corresponding acid, which is esterified immediately with alcohol. However when benzoic acid is used instead of benzaldehyde (**1**) under identical conditions, no methyl benzoate could be obtained. It is most probable that this oxidation of aldehydes in an

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[2] March, J. *Advanced Organic Chemistry*; John Wiley & Sons: New York, 1992; p 1196.

[3] Espenson, J. H.; Zhu, Z.; Zauche, T. H. *J. Org. Chem.* **1999**, *64*, 1191–1196.

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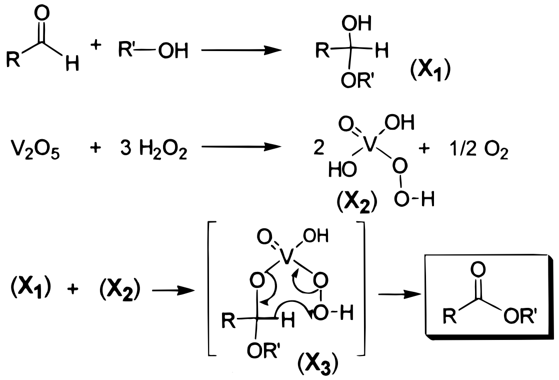
Table 1. Oxidative Esterification[a] of Aldehydes to Corresponding Methyl Esters with $V_2O_5-H_2O_2$

substrate	time/h	product[c]	yield (%)[d]	ester (%)[d,e]
benzaldehyde (**1**)	3.0	methyl benzoate	100	100
m-bromobenzaldehyde (**2**)	0.75	methyl *m*-bromobenzoate	100	96
p-methylbenzaldehyde (**3**)	0.5	methyl *p*-methylbenzoate	100	100
o-hydroxybenzaldehyde (**4**)	7.5	methyl *o*-hydroxybenzoate	93	100
o-methoxybenzaldehyde (**5**)	5.0	methyl *o*-methoxybenzoate	100	91
p-hydroxybenzaldehyde (**6**)	2.5	methyl *p*-hydroxybenzoate	100	100
p-methoxybenzaldehyde (**7**)	3.0	methyl *p*-methoxybenzoate	100	100
4-hydroxy-3-methoxybenzaldehyde (**8**)	6.0	methyl 4-hydroxy-3-methoxybenzoate	83	100
3,4-dimethoxybenzaldehyde (**9**)	5.0	methyl 3,4-dimethoxybenzoate	85	97
p-chlorobenzaldehyde (**10**)	5.5	methyl *p*-chlorobenzoate	100	100
p-nitrobenzaldehyde (**11**)	0.5[b]	methyl *p*-nitrobenzoate	100	100
p-benzyloxybenzaldehyde (**12**)	5.0	methyl *p*-benzyloxybenzoate (**15**)	100	100
2-furaldehyde (**13**)	2.0	methyl 2-furoate	100	100
cinnamaldehyde (**14**)	2.0[b]	methyl cinnamate	95	100

[a] Reactions were monitored by TLC, GC. [b] The reaction was performed at reflux temperature after addition of the reagent under ice-cooled conditions. [c] Confirmed by comparison with IR and ^1H NMR of the authentic sample. [d] Determined by GC. [e] The balance is the carboxylic acid.

alcoholic medium proceeds through a hemiacetal (X_1) → vanadium hemiacetal intermediate (X_3) → ester, as indicated in Scheme 1.

Scheme 1. Proposed Mechanism of Esterification



Aldehyde under acidic conditions reacts with alcohol to form hemiacetal (X_1). It is envisaged that the initially formed hemiacetal (X_1) reacts with peracid (X_2), which results from the addition of H_2O_2 to vanadium(V) oxide to form a vanadium hemiacetal type intermediate (X_3).[6] The conjugate base of the peracid (X_3) is an excellent leaving group for nucleophilic displacement.[6] Subsequent elimination produced the desired product and releases the catalyst. We believe that formation of the hemiacetal intermediate (X_1) is necessary. In the absence of alcohol, aldehydes are rapidly oxidized to their corresponding acids. The success of the reaction is dependent upon the selective oxidation of the hemiacetal hydroxy moiety (X_1) in the presence of a much higher concentration of alcohol. Selective oxidation of a more substituted alcohol has been observed with other oxidizing agents such as CrO_3[2] and NIS.[7]

Under these conditions activated, deactivated, conjugated, and hindered aldehydes can all be oxidized to the corresponding methyl esters in excellent yields. Typically, a $V_2O_5-H_2O_2$-catalyzed reaction of benzaldehyde (**1**) with methanol gave methyl benzoate in quantitative yield. Under similar experimental conditions, *m*-bromobenzaldehyde (**2**) and *p*-methylbenzaldehyde (**3**) produced the corresponding methyl esters, methyl *m*-bromobenzoate and methyl *p*-methylbenzoate, respectively, in very high yields in a short time. The reaction of aromatic aldehydes with *o*-substituted compounds such as *o*-hydroxybenzaldehyde (**4**) and *o*-methoxybenzaldehyde (**5**) to yield esters is more sluggish, as compared to the corresponding *p*-substituted substrates *p*-hydroxybenzaldehyde (**6**) and *p*-methoxybenzaldehyde (**7**). This could be attributed to an unfavorable equilibrium to hemiacetal due to steric strain as proposed in Scheme 1.

Steric interaction could also be responsible for the slow reaction rate of trisubstituted aldehydes such as 4-hydroxy-3-methoxybenzaldehyde (**8**) and 3,4-dimethoxybenzaldehyde (**9**). Aromatic aldehydes substituted with electron-withdrawing groups at the *p*-position such as *p*-chlorobenzaldehyde (**10**) and *p*-nitrobenzaldehyde (**11**) react slowly. Only 10% conversion to methyl *p*-nitrobenzoate is observed in 5 h for the deactivated substrate (**11**), under the reaction conditions. However, refluxing the reaction in a water bath can accelerate the reaction rate as demonstrated in the case of *p*-nitrobenzaldehyde (**11**). Importantly, no other side products are obtained during reflux. Substrate *p*-benzyloxybenzaldehyde (**12**) reacts slowly to give methyl *p*-benzyloxybenzoate (**15**)[8] in quantitative yield.

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(7) McDonald, C.; Holcomb, H.; Kennedy, K.; Kirkpatrick, E.; Leathers, T.; Vanemon, P. *J. Org. Chem.* **1989**, *54*, 1213−1215.

(8) Selected data for methyl *p*-benzyloxybenzoate (**15**): mp 95-96 °C; IR (KBr) 2950, 1716, 1608, 1511, 1460, 1439, 1393, 1321, 1280, 1255, 1173, 1116, 1009, 855, 773, 748, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.88 (s, 3H, -OCH_3), 5.12 (s, 2H, ArCH_2), 6.99 (d, J = 9 Hz, 2H, ArH), 7.30−7.45 (m, 5H, ArH), 7.99 (d, J = 9 Hz, 2H, ArH).

Principles of oxidative transformation can also be extended to heterocyclic aldehydes as well. Thus, 2-furaldehyde (**13**) could be smoothly converted to methyl 2-furoate in quantitative yield. The efficacy of the methodology is further demonstrated by esterification of unsaturated aldehyde such as cinnamaldehyde (**14**). Longer reaction times under the given conditions (30% in 7 h) can be due to an unfavorable equilibrium in hemiacetal formation, due to disruption of conjugation. Here again, refluxing the reaction mixture in a water bath can enhance the reaction rate and improve the yield (95% in 2 h).

A minor amount of carboxylic acids is also obtained for substrates **2**, **5**, and **9**. The esters formed do not hydrolyze under the reaction conditions to acids; thus the minor amounts of acids obtained are due to the overoxidation of aldehydes.

In the above systems, H_2O_2 does not bring about esterification without the catalyst (V_2O_5) and the catalyst alone fails to bring about esterification. The reactions can be carried out even in the absence of any external acid, but reactions are rather sluggish. It may be mentioned here that analogous to methyltrioxorhenium(VII) mediated esterification,[3] addition of a catalytic amount of bromide ion greatly enhances the rate, the details of which will be reported subsequently.

In conclusion, the present method represents a simple, yet highly efficient method for the synthesis of esters from corresponding aldehydes under mild conditions. We have enough evidence that the methodology may work equally well for the synthesis of other esters. The reagent is cheap and nontoxic, and the inorganic salts are removed easily. Although the literature enumerates a number of procedures for conversion of aldehydes to esters, the simplicity, environmental acceptability, and inexpensiveness of our procedure makes it a practical alternative. Its synthetic application to other esters and detailed reaction mechanism are currently under investigation and will be reported in due course.

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Supporting Information Available: Detailed experimental procedures for esterification of *p*-hydroxy benzaldehyde (**6**) to methyl *p*-hydroxybenzoate and *p*-nitrobenzaldehyde (**11**) to methyl *p*-nitrobenzoate and their characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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