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A Simple One-Pot Procedure for the Conversion of Aldehydes to Methyl Esters

Hakjune Rhee*[a] and Jin Yeon Kim[b]

[a]Department of Chemistry, Hanyang University, Ansan, Kyunggi-Do 425-791, Korea
[b]Department of Chemistry, Seonam University, Namweon, Chunrabuk-Do 590-170, Korea

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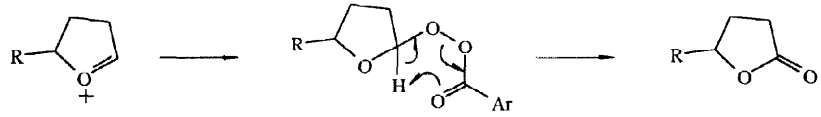
Abstract: Several methyl esters were obtained by an efficient and simple one-pot procedure from the corresponding aldehydes in high yields. This procedure involves dimethyl acetal formation from aldehydes and subsequent oxidation.

Over the last thirty years, a number of methods for the conversion of aldehydes to esters have appeared in the literature.[1] Grieco reported a one-step conversion of protected lactols into lactones,[2] the proposed oxidation mechanism of which was recently proved by the isolation of peroxy intermediate II.[3] Baeyer-Villiger oxidation of ketones and aldehydes



I II

using peracid is frequently the method of choice due to its ease and high productivity.[4] The reaction of acyclic acetal with peracid, however, is known to be sluggish and to provide the carbonate orthoester as the result of dual Baeyer-Villiger oxidation.[5] Since there are a number of methods for the preparation of acetals from the corresponding aldehydes,[6] a method that directly oxidized them to esters would be of great value. We therefore thought that the oxidation of acyclic acetals to esters could be accomplished if the oxidation reaction proceeded *via* rapid fragmentation of the peroxy intermediate rather than *via* Baeyer-Villiger oxidation. Thus, the simultaneous addition of base to the peroxy intermediate could be carried out in order to accelerate the proton elimination.

We report herein a simple one-pot procedure for the conversion of aldehydes to methyl esters. The results are summarized in Table I. It should be noted that the entire reaction sequence was carried out in a one-pot operation from an aldehyde starting material. As shown in Table I, an acetal was prepared from the corresponding aldehyde and trimethyl orthoformate in the presence of Amberlyst® 15 as a catalyst.[7] The acetal formation was monitored by TLC. After aldehyde starting material disappeared, a catalytic amount of $BF_3{\cdot}OEt_2$ and *m*-chloroperbenzoic acid (*m*-CPBA) was added to the reaction mixture. The reaction mixture was then treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) *in situ*. The reaction could also be carried out successfully without base when pure *m*-CPBA was used. However, when base is used, the reaction proceeds more quickly. The addition of DBU to sterically hindered cyclic acetal (protected lactol) actually facilitated the oxidation reaction to produce cyclic lactone.[3]

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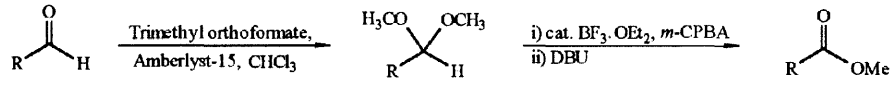

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Table I. One-pot synthesis of methyl esters from the corresponding aldehydes *via* dimethyl acetals.

Entry	Aldehyde	Product	Yield (%)[a]
1	C_6H_5CHO (**1a**)	$C_6H_5CO_2Me$ (**3a**)	95
2	*p*-Me-C_6H_4CHO (**1b**)	*p*-Me-$C_6H_4CO_2Me$ (**3b**)	96
3	*p*-MeO-C_6H_4CHO (**1c**)	*p*-MeO-$C_6H_4CO_2Me$ (**3c**)	93
4	*p*-NO_2-C_6H_4CHO (**1d**)	*p*-NO_2-$C_6H_4CO_2Me$ (**3d**)	65
5	*o*-HO-C_6H_4CHO (**1e**)	*o*-HO-$C_6H_4CO_2Me$ (**3e**)	68
6	$C_6H_5CH_2CHO$ (**1f**)	$C_6H_5CH_2CO_2Me$ (**3f**)	89
7	$CH_3(CH_2)_2CHO$ (**1g**)	$CH_3(CH_2)_2CO_2Me$ (**3g**)	87
8	$CH_3(CH_2)_4CHO$ (**1h**)	$CH_3(CH_2)_4CO_2Me$ (**3h**)	85
9	$CH_3(CH_2)_5CHO$ (**1i**)	$CH_3(CH_2)_5CO_2Me$ (**3i**)	87
10	*trans*-PhCH=CH-CHO (**1j**)	*trans*-PhCH=CH-CO_2Me (**3j**)	83
11	*trans*-PhCH=CMe-CHO (**1k**)	*trans*-PhCH=CMe-CO_2Me (**3k**)	85

a: Yields refer to isolated products.

In summary, we have developed an efficient and simple one-pot procedure for the conversion of various aldehydes to their corresponding methyl esters in high yields through dimethyl acetal formation and the subsequent oxidation using *m*-CPBA and DBU. We are currently investigating the preparation of other alkyl esters and amides using this same methodology.

References

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Experimental Data for

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General. All reactions were carried out under an inert atmosphere of argon. Chloroform was freshly distilled from phosphorus pentoxide prior to use. Liquids reagents and solvents used were reagent grade and purified prior to use, if necessary, by methods reported in the literature. Analytical thin layer chromatography was performed on pre-coated Merck silica gel 60 F254 TLC plate. Small and medium-scale purification were performed by flash column chromatography by using Merck 230-400 mesh silica gel. ^{1}H NMR spectral data were obtained on a Varian Geremi 400 (400MHz) or Varian 300 (300MHz) spectrometer. Proton chemical shifts reported in parts per million (*ppm*) were indirectly referenced to external tetramethylsilane employing resonances due to trace monoprotio-solvent as an internal standard. Coupling constants (*J*) are reported in Hertz (Hz). The *J* values are reported directly as given by the spectrometer, hence slight differences in the coupling constants (*J*) may be noticed. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). The relative areas were determined by electronic integration and reported as number of protons, *e.g.*, 1H. Infrared spectra were recorded using a BioRad FT-IR spectrophotometer with internal calibration. Mass spectra and elementary analysis, ^{13}C NMR spectra were not measured because they were reported on else where. Spectral data of products were compared with those in the Aldrich Library of FT ^{1}H NMR and FT-IR spectra books, and products were indentified.

General procedure. To a solution of 5 mmol aldehyde in dried $CHCl_3$ (15 mL) were added 0.25 g Amberlyst® 15 (wet) ion exchange resin and 20 mmol of trimethyl orthoformate under the argon atmosphere at ambient temperature. The solution was stirred at reflux condition. After being stirred for 3h, a catalytic amount of $BF_3{\cdot}OEt_2$ and 5.0 mmol of *m*-CPBA was added to the reaction mixture, followed by 5.0 mmol of DBU. The resulting reaction mixture was stirred for 1h at ambient temperature. The reaction mixture was diluted with $CHCl_3$ (7 mL) and quenched with 0.5 *N* NaOH solution (15 mL). The organic layer was washed with 0.1 *N* HCl solution (10 mL) while the organic layer was dried over anhydrous sodium sulfate. The desired esters were purified by flash column chromatography.

Preparation of methylbenzoate (3a). To a solution of benzaldehyde (0.51 mL, 5 mmol) in dried $CHCl_3$ (15 mL) were added Amberlyst® 15 (wet) ion exchange resin (0.25 g) and trimethyl orthoformate (1.67 mL, 20 mmol) under the argon atmosphere at ambient temperature. The reaction mixture was stirred for 3h at reflux condition. After the reaction mixture was cooled to ambient temperature, $BF_3{\cdot}OEt_2$ (0.063 mL, 0.50 mmol) and *m*-CPBA (72 %, 1.20 g , 5.0 mmol) were added followed by DBU (1.67 mL, 5.0 mmol) at ambient temperature. The resulting reaction mixture was stirred for 1h and diluted with $CHCl_3$ (7 mL). The reaction was quenched with 0.5 *N* NaOH solution (15 mL) and the organic layer was washed with 0.1 *N* HCl solution (10 mL). The organic layer was dried over anhydrous sodium sulfate, then the filtrate

was concentrated and purified by flash column chromatography to give the desired methylbenzoate (0.65 g, 95 %). TLC (EtOAc/*n*-Hexane = 1:8, v/v), R_f = 0.5. IR(neat) 1729 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.3~8.1 (m, 5H), 3.84 (s, 3H).

Methyl 4-methylbenzoate (3b). Yield 96 %. TLC (EtOAc/*n*-Hexane = 1:8, v/v), R_f = 0.5. IR (neat) 1733 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 8.0 Hz, 2H), 3.82 (s, 3H), 2.31 (s, 3H).

Methyl 4-methoxybenzoate (3c). Yield 93 %. TLC (EtOAc/*n*-Hexane = 1:8, v/v), R_f = 0.4. IR (neat) 1717 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 9.0 Hz, 2H), 3.88 (s, 3H), 3.84 (s, 3H).

Methyl 4-nitrobenzoate (3d). Yield 65 %. TLC (EtOAc/*n*-Hexane = 1:8, v/v), R_f = 0.4. IR (neat) 1719 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 9.2 Hz, 2H), 8.22 (d, J = 8.8 Hz, 2H), 3.99 (s, 3H).

Methyl salicylate (3e). Yield 68 %. TLC (EtOAc/*n*-Hexane = 1:8, v/v), R_f = 0.4. IR (neat) 3189, 1681 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 10.76 (s, 1H), 6.84~7.81 (m, 4H), 3.90 (s, 3H).

Methyl phenylacetate (3f). Yield 89 %. TLC (EtOAc/*n*-Hexane = 1:8, v/v), R_f = 0.5. IR (solution in $CDCl_3$) 1738 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (m, 5H), 3.59 (s, 3H), 3.55 (s, 2H).

Methyl butyrate (3g). Yield 87 %. TLC (EtOAc/*n*-Hexane = 1:8, v/v), R_f = 0.6. IR (solution in $CDCl_3$) 1742 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.32 (s, 3H), 1.95 (t, J = 7.5 Hz, 2H), 1.31 (sextet, J = 7.5 Hz, 2H), 0.61 (t, J = 7.5 Hz, 3H).

Methyl caproate (3h). Yield 85 %. TLC (EtOAc/*n*-Hexane = 1:8, v/v), R_f = 0.6. IR (solution in $CDCl_3$) 1738 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.34 (s, 3H), 1.99 (t, J = 7.5 Hz, 2H), 1.32 (quintet, J = 7.5 Hz, 2H), 1.02 (m, 4H), 0.60 (t, J = 6.9 Hz, 3H).

Methyl enanthate (3i). Yield 87 %. TLC (EtOAc/*n*-Hexane = 1:8, v/v), R_f = 0.6. IR (neat) 1742 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 3.38 (s, 3H), 1.98 (t, J = 7.5 Hz, 2H), 1.33 (m, 2H), 1.03 (m, 6H), 0.60 (t, J = 7.5 Hz, 3H).

Methyl *trans*-cinnamate (3j). Yield 83 %. TLC (EtOAc/*n*-Hexane = 1:8, v/v), R_f = 0.4. IR (neat) 1718 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.68 (d, J = 15.9 Hz, 1H), 7.47 (m, 2H), 7.34 (m, 3H), 6.42 (d, J = 15.9 Hz, 1H), 3.77 (s, 3H).

Methyl α-methyl-*trans*-cinnamate (3k). Yield 85 %. TLC (EtOAc/*n*-Hexane = 1:8, v/v), R_f = 0.3. IR (neat) 1713 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.15-7.31 (m, 6H), 3.63 (s, 3H), 2.08 (s, 3H).