THE OXIDATION OF ALDEHYDES TO METHYL ESTERS WITH N-IODOSUCCINIMIDE

Submitted by Penny J. Swartwood

Honors Project

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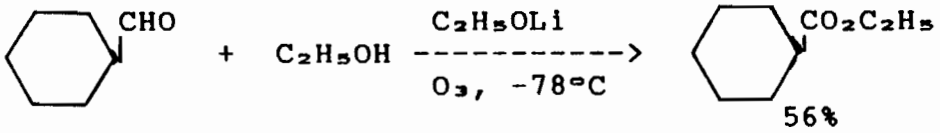
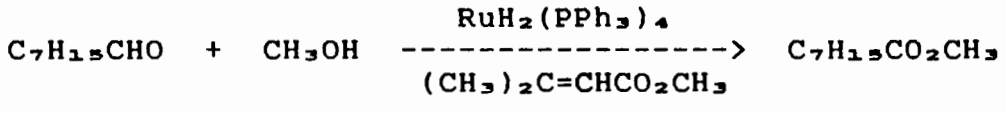
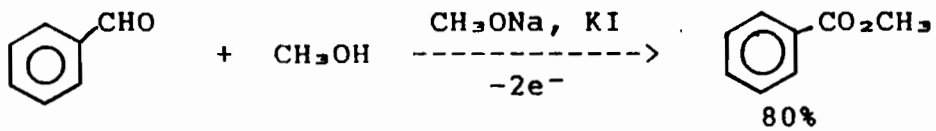
The conversion of aldehydes to esters has traditionally been accomplished by a two step reaction process consisting of an oxidation to the carboxylic acid, followed by an esterification (Solomons, 1984). Recently, a few methods have been developed for accomplishing this transformation in a single step. Djerassi has shown that treatment of alcoholic solutions of aldehydes with ozone produces the corresponding esters (Djerassi, 1978).



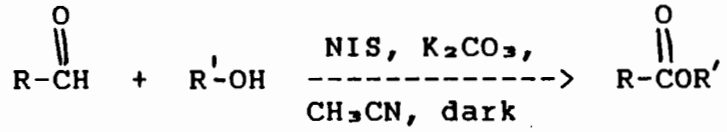
Murahashi has performed similar transformations using catalytic $RuH_2(PPh_3)_4$ (Murahashi, 1987).



Chiba has developed an electro-oxidative approach to the synthesis of methyl esters from aldehydes (Chiba, 1988).

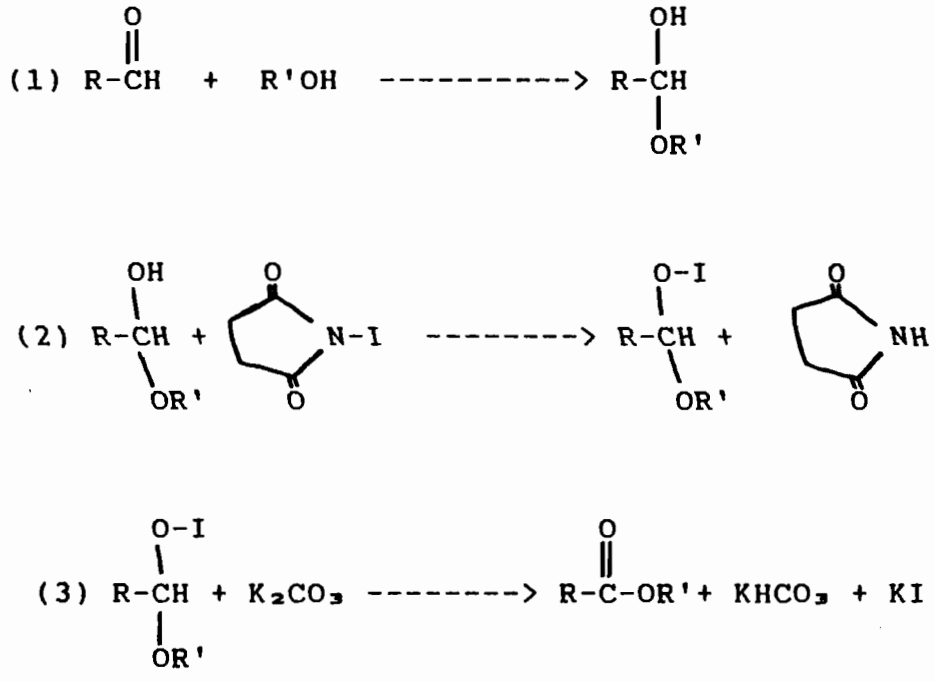


N-Iodosuccinimide (NIS) has been shown to be a versatile reagent for the oxidation of organic compounds (Beebe, 1983). Results in our laboratory indicate that it acts efficiently as an oxidant for accomplishing the aldehyde to ester transformation in one step.



The reaction is thought to proceed as in Scheme 1. The alcohol attacks the electrophilic portion of the aldehyde creating a hemiacetal. This is then oxidized by NIS to form the corresponding hemiacetal hypoiodite. A base induced elimination of hydrogen iodide then produces the observed product.

Scheme 1



Chiba's 1988 oxidation undoubtedly occurs by a similar mechanism. Elimination of hydrogen iodide is thought to occur by an ionic mechanism for several reasons:

1. A moderately strong base is required. Potassium hydrogen carbonate is substituted for potassium carbonate, and the reaction fails to proceed.
2. A polar solvent is needed. When benzene is used as the solvent, the reaction doesn't proceed nearly as well as when the more polar acetonitrile is used as the solvent.
3. Light or oxygen has no positive effect on either the reaction rate or the overall yield.

Since light induced free-radical decomposition pathways exist for hypoiodites, all reactions were performed in the dark (Heusler, 1964).

The overall stoichiometry of the reaction has been found to be one equivalent of aldehyde requiring 1.5 equivalents of NIS. This has been supported by spectrophotometric analyses of the crude reaction mixtures. It has been found that the product iodide anion is converted to the triiodide anion (λ max = 360nm). This assignment is substantiated by an article which reported the triiodide anion to have a λ max of 363nm in acetone (Benesi,1950). Apparently, I^- reacts with an I^+ equivalent, coming from either the NIS or from an alkyl hypoiodite, to form I_2 (λ max of 450nm in acetone). This reacts with another

equivalent of I^- to produce the observed I^{3-}.

RESULTS AND DISCUSSION

The results of this research are shown in Table 1. As can be seen, the transformation is highly successful when methanol is used as the alcohol component to produce methyl esters. Entries 1-4 demonstrate that straight chain aliphatic aldehydes are oxidized quite rapidly with an average reaction time of seven hours. Cyclohexane carboxaldehyde, in entry 5, shows that branching at the alpha carbon has little effect on either the reaction rate or the ultimate yield of the product. Benzaldehyde oxidizes more slowly than its aliphatic counterparts, as shown in entry 6. This sluggishness is thought to be due to the disruption of conjugation which occurs during the hemiacetal formation (see Scheme 1). This results in an unfavorable equilibrium for this step. Modest yields of methyl benzoate were obtained by modifying the reaction conditions as is noted in Table 1. Entries 7 and 8 show that electron poor aromatic aldehydes add methanol more easily than benzaldehyde because they possess a more electrophilic carbonyl moiety. Finally, 2-phenylethanal, in entry 9, once again showed a longer reaction time and a lower yield. In this reaction though, the product yield continually decreased with time. Evidently, another reaction must be occurring. This will be investigated in future

research.

The synthesis of esters of primary alcohols was examined briefly, however the reaction times for these were somewhat longer. This increase could be attributed to a less favorable equilibrium for the addition of bulkier alcohols, in comparison to methanol, to form the corresponding hemiacetals.

Finally, related haloimides such as N-chlorosuccinimide (NCS) and N-bromosuccinimide (NBS) were tried. No reaction was seen between octanal and methanol in the presence of NCS, even at elevated temperatures. However, poor yields of methyl esters were obtained when NBS was used. These yields are not good enough though, to consider either NBS or NCS to be synthetically useful for this transformation.

In terms of the future of this project, sterically hindered aldehydes need to be used to determine the limitations of the process. Also, the reaction needs to be started with the aldehyde precursor, rather than the aldehyde, and proceed to the corresponding ester. Plans have been made to complete this project this summer. When the research has been finished, the material will be submitted for publication.

Table 1 : Synthesis of Methyl Esters[a]

Entry	Aldehyde	Reaction Time (hr)	Yield[b]
1	n-heptanal	4	94%
2	n-octanal	22	81%
3	n-nonanal	7	86%
4	n-dodecanal	9	77%[d]
5	cyclohexane-carboxaldehyde	6	92%
6	benzaldehyde	24	59%[c]
7	m-nitrobenzaldehyde	13	82%[d]
8	3-pyridine-carboxaldehyde	15	80%[d]
9	2-phenylethanal	24	59%[d]

a. Unless otherwise noted reactions were performed with 1 eq aldehyde, 3 eq NIS, 3 eq K_2CO_3, and 5 eq CH_3OH in CH_3CN (0.1 M) at room temperature.
b. Yields determined by gas chromatography unless otherwise noted.
c. 1 eq benzaldehyde, 5 eq NIS, 5 eq K_2CO_3, in CH_3CN, 50 °C
d. Isolated yield

EXPERIMENTAL

INSTRUMENTATION

The reactions were monitored by gas chromatographic analyses on a Hewlett Packard 5700A model equipped with an OV-17 glass column measuring 6ft. x 0.25in., using internal standards of either chlorobenzene or bromobenzene.

STANDARD SOLUTIONS

Standard solutions were prepared for each reaction mixture which contained the aldehyde, the corresponding ester, and an internal standard which separated easily from the other two compounds on the GC. Measured quantities of each of these were put into the standard solution, with acetonitrile being used as the solvent. The standard solutions were then analyzed by gas chromatography. The peak areas for each compound were found by measuring the peak height and multiplying this by the width at half height. These areas and the amount of the compounds in the solution are used to calculate the alpha values which are merely a ratio of either the aldehyde or ester to the internal standard. These values were then used to quantitatively determine the amount of aldehyde and ester present in the reaction mixture.

SAMPLE CALCULATION

$$\alpha_{C_7H_{15}CHO} = \frac{\frac{0.97\text{mmol } C_7H_{15}CHO}{158.75\text{mm}^2 \quad "}}{\frac{1.06\text{mmol}}{210\text{mm}^2} \quad \text{C}_6\text{H}_5\text{Br}} = 1.20$$

PERCENT YIELD CALCULATIONS

The quantities of compounds in the reaction mixture were determined by taking a gas chromatograph of the mixture and measuring the peak areas. These areas are then used with the previously calculated alpha values, and the amount of compound measured into the reaction flask to give the amount of aldehyde or ester present.

SAMPLE CALCULATION

$$C_7H_{15}CHO = (1.20)\left(\frac{0.5\text{mmol } C_6H_5Br}{54\text{mm}^2 \quad "}\right)(42\text{mm}^2) = 0.467\text{mmol}$$

$$\frac{0.467\text{mmol}}{1.07\text{mmol}} \times 100\% = 43.6\%\ C_7H_{15}CHO$$

Where: $1.20 = \alpha_{C_7H_{15}CHO}$

$0.5\text{mmol } C_6H_5Br$ = amount in reaction mixture

54mm^2 C_6H_5Br = peak area from chromatogram

42mm^2 = peak area of $C_7H_{15}CHO$ from chromatogram

1.07mmol = theoretical amount of $C_7H_{15}CHO$ in reaction mixture

REACTION CONDITIONS

Acetonitrile was used as the solvent for all the reactions. It was dried over calcium hydride and distilled before use. The NIS was used as purchased. Finally, all reactions were run under a nitrogen atmosphere.

OXIDATION OF n-HEPTANAL

A mixture of n-heptanal (0.1198g; 1.05mmol), chlorobenzene (0.0577g; 0.513mmol), methanol (81μL; 2mmol), potassium carbonate (0.3457g; 2.5mmole), NIS (0.5625g; 2.5mmol), and acetonitrile (10mL) was put into an oven dried, two-necked reaction flask with a stir bar. The flask was closed with rubber septa and covered with aluminum foil to prevent any light from getting in. The reaction was run at room temperature (22°C). According to GC analyses, after three hours, the reaction seemed to have come to a stop; however, all of the aldehyde had not yet been transformed to the corresponding methyl ester (methyl heptanoate). Thus, more methanol (0.5mmol; 20μL), potassium carbonate (0.5mmol; 0.07g), and NIS (0.5mmol; 0.11g) were added to the flask. After reacting for a total of four and one-half hours, the reaction flask contained 94.1% methyl heptanoate, with 5.54% of the n-heptanal remaining. The reaction was considered to have gone to completion at this point. The reaction mixture was then treated with 5-10mL water and some sodium thiosulfate to destroy the triiodide anion and any remaining NIS. The product

was then extracted using a 1:1 ether/hexane solution. The combined organic layers were subsequently washed with a saturated sodium chloride solution and then dried over anhydrous sodium sulfate. Filtration and solvent removal provided a crude residue which was purified by Kugelrohr distillation. An infrared spectrum was taken of the purified ester with a Mattson Polaris Fourier Transform Infrared Spectrometer. The ester was identified as being methyl heptanoate by comparing its infrared spectrum to that of a standard spectrum for the same compound given in an Aldrich catalog.

OXIDATION OF n-OCTANAL

A mixture of n-octanal (0.1369g; 1.07mmol), bromobenzene (0.0791g; 0.5mmol), methanol (81μL; 2mmol), potassium carbonate (0.3457g; 2.5 mmol), NIS (0.5625g; 2.5mmol), and acetonitrile (10mL) was charged into a reaction flask. The flask was closed and covered. The reaction temperature was room temperature (23°C). After 5 hours, the reaction appeared to have come to a standstill, so more NIS (1 mmol; 0.225g) and potassium carbonate (1mmol; 0.1383g) was added to the flask. Later, when the mixture was checked after reacting for a total of 12 hours, it once again seemed to have come to a stop. At this time, 0.5mmol of NIS (0.112g), of potassium carbonate (0.69g), and of methanol (41μL) were added to the reaction flask. Finally, after a total of 22 hours, the mixture contained 81.1% ester and 2.7% aldehyde. The mixture was worked up as above. The crude ester was purified

with silica gel column chromatography, using 5% ethyl acetate in 30-60 petroleum ether as the solvent. The solvent was evaporated from the product using a rotovap. An infrared spectrum was then taken of the purified product and compared to that of a standard spectrum. From this, the ester could be identified as methyl octanoate.

OXIDATION OF n-NONANAL

A mixture of n-nonanal (0.1467g; 1.03mmol), chlorobenzene (0.0595g; 0.53mmol), methanol (81μL; 2mmol), potassium carbonate (0.3457g; 2.5 mmol), NIS (0.5625g; 2.5mmol), and acetonitrile (10mL) was placed into a reaction flask, which was then closed and covered. The reaction took place at room temperature (22°C). After 3 hours, the reaction seemed to have stopped, so 0.5mmol of methanol (20μL), 0.5mmol of potassium carbonate (0.07g), and 0.5mmol of NIS (0.11g) were added to the flask. After a total reaction time of 7 hours, 85.6% of the mixture was ester, and a trace amount of aldehyde was also present. The mixture was worked up as stated previously, and the crude product was purified through Kugelrohr distillation. An infrared spectrum was taken and compared to a standard spectrum for the compound. The identity of the ester was then known to be methyl nonanoate.

OXIDATION OF n-DODECANAL

A mixture of n-dodecanal (0.1913g; 1.038mmol), bromobenzene (0.0787g; 0.5012mmol), methanol (101.3μL; 2.5mmol), potassium

carbonate (0.3457g; 2.5mmol), NIS (0.5625g; 2.5mmol), and acetonitrile (10mL) was charged into a reaction flask, which was then closed and covered. The reaction temperature was room temperature (24°C). The reaction appeared to stop after 9 hours of reaction time. At this time, more NIS (0.1g; 0.44mmol) and potassium carbonate (0.05g; 0.36mmol) were added. After 11 hours total reaction time, the reaction was assumed to be complete. The mixture was worked up as usual and purified through Kugelrohr distillation. An isolated yield of 78% was achieved. An infrared spectrum was taken of the purified ester and compared to that of a standard. The identity of the ester was found to be that of methyl dodecanoate, as was expected.

OXIDATION OF CYCLOHEXANECARBOXALDEHYDE

A mixture of cyclohexanecarboxaldehyde (0.1166g; 1.04mmol), chlorobenzene (0.0737g; 0.655mmol), methanol (81μL; 2mmol), potassium carbonate (0.3457g; 2.5mmol), NIS (0.5625g; 2.5mmol), and acetonitrile (10mL) was placed into a reaction flask. The flask was then sealed and covered. The reaction took place at room temperature (23°C). The reaction stopped after 4 1/2 hours, and so 0.5mmol of methanol (20μL), 0.5mmol of potassium carbonate (0.07g), and 0.5mmol of NIS (0.11g) were added. After 6 hours, the mixture contained 91.5% ester and 5.17% aldehyde and was considered to have gone to completion. The mixture was worked up as usual, and the ester was purified using Kugelrohr distillation. An infrared spectrum was taken of the pure ester.

This was then compared to the standard spectrum for the ester, and its identity was found to be that of methyl cyclohexanecarboxylate.

OXIDATION OF BENZALDEHYDE

A mixture of benzaldehyde (0.1560g; 1.47mmol), bromobenzene (0.1633g; 1.04 mmol), methanol (119μL; 2.94mmol), potassium carbonate (0.406g; 2.94mmol), NIS (0.828g; 3.68mmol), and acetonitrile (14.7mL) was placed in a reaction flask, which was then sealed and covered. The reaction proceeded at room temperature. After 2.5 hours, there was only 11% ester produced, so the mixture was heated to 43°C. After 11 hours total reaction time, 0.5mmol of the following were added to the flask: NIS (0.166g), potassium carbonate (0.101g), and methanol (31μL). After reacting for a total of 22 hours, the mixture contained only 42% ester. Therefore, isolation of the product was not attempted.

OXIDATION OF BENZALDEHYDE UNDER MODIFIED CONDITIONS

A mixture of benzaldehyde (0.1178g; 1.11mmol), bromobenzene (0.1554g; 0.99 mmol), methanol (449μL; 11.10mmol), potassium carbonate (0.461g; 3.33mmol), NIS (0.749g; 3.33mmol), 18-crown-6 (0.049g; 0.222 mmol), and acetonitrile (11.1mL) was charged into a reaction flask. The flask was then sealed and covered. The reaction took place at 50°C. After 11 hours, 2 mmol of potassium carbonate (0.306g) and 2 mmol of NIS (0.500g) were added to the

reaction. After 24 hours of total reaction time, the mixture consisted of 59% ester and 38% aldehyde. The mixture was worked up as usual. An infrared spectrum was taken and compared to a standard. The identity of the ester was found to be methyl benzoate as predicted.

OXIDATION OF m-NITROBENZALDEHYDE

A mixture of m-nitrobenzaldehyde (0.1511g; 1mmol), methanol (202μL; 5mmol), potassium carbonate (0.4149g; 3mmol), NIS (0.6750g; 3mmol), and acetonitrile (10mL) was charged into a reaction flask. The reaction had to be monitored by TLC plates due to the low volatilities of the various compounds. After 30 minutes, the reaction was checked, using 15% EtOAc in hexane as the solvent. At this point, there was some ester being produced. The reaction was later checked after 11 hours of total time, using 10% EtOAc in hexane as the solvent. At this point, the reaction seemed to have gone to completion. The mixture was worked up as usual. The crude product was purified using silica gel column chromatography. Ten percent EtOAc/hexane was used as the solvent. An isolated yield of 82% was obtained. An infrared spectrum was obtained for the pure ester, and it was compared to that of a standard. The ester was identified as methyl m-nitrobenzoate.

OXIDATION OF 3-PYRIDINECARBOXALDEHYDE

A mixture of 3-pyridinecarboxaldehyde (0.1607g; 1.5mmol), bromobenzene (0.1712g; 1.09mmol), methanol (304μL; 7.50mmol), potassium carbonate (0.6223g; 4.50mmol), NIS (1.012g; 4.50mmol), and acetonitrile (15mL) was placed into a reaction flask. The reaction took place at room temperature. After 11 hours, 0.3mmol of potassium carbonate (0.062g) and of NIS (0.106g) were added to the flask. After 13 hours reaction time, 95% of the mixture consisted of the ester. The mixture was worked up as usual and an infrared spectrum was taken of the purified ester. This was compared to a standard spectrum. The ester was identified as methyl 3-pyridinecarboxylate.

OXIDATION OF n-OCTANAL USING ETHANOL

A mixture of n-octanal (0.1253g; 0.977mmol), bromobenzene (0.1633g; 1.04 mmol), ethanol (285μL; 4.885mmol), potassium carbonate (0.4730g; 3.420mmol), NIS (0.7695g; 3.420mmol), and acetonitrile (10mL) was put into a reaction flask. The reaction proceeded at room temperature. After 22 hours, the mixture contained 67% ester and 27% aldehyde. The reaction was worked up at this point. An infrared spectrum was taken of the purified ester and was compared to a standard spectrum. The ester was identified as ethyl octanoate.

OXIDATION OF 2-PHENYLETHANAL

A mixture of 2-phenylethanal (0.1202g; 1.0mmol), methanol (73μL; 1.8mmol), o-dichlorobenzene (0.0735g; 0.5mmol), potassium carbonate (0.6914g; 5mmol), NIS (0.900g; 4 mmol), and acetonitrile (10mL) was charged into a reaction flask. The reaction temperature was 40°C. After 11 hours 0.5mmol of methanol (20μL), 2mmol of potassium carbonate(0.2766g), 2mmol of NIS (0.4500g), and 2 mL of acetonitrile were added to the reaction flask. After 26 hours, more potassium carbonate (0.225g; 1mmol) and NIS (0.138g; 1mmol) were added to the reaction. After 35 hours, the mixture contained 43% ester and 5% aldehyde. There was a gradual loss of ester yield throughout the later reaction hours. The mixture was worked up at this point. It was decolorized with sodium thiosulfate and water, and extracted with 75% ether/hexane solution. The organic layer was then washed with water. The crude product was purified using silica gel column chromatography. The solvent was 5% EtOAc/hexane solution. The infrared spectrum of the purified product identified it as being methyl 2-phenylethanoate.

OXIDATION OF n-OCTANAL WITH N-CHLOROSUCCINIMIDE (NCS)

A mixture of n-octanal (0.1269g; 0.99mmol), bromobenzene (0.0848g; 0.54mmol), methanol (81μL; 2mmol), potassium carbonate (0.1521g; 1.1mmol), NCS (0.2671g; 2.0mmol), and acetonitrile (10mL) was placed into a reaction flask. The reaction was heated from room temperature to 40°C after 6 hours. When the reaction

was checked last (T + 24 hrs), there was no noticeable reaction taking place. The reaction was abandoned at this time.

OXIDATION OF n-OCTANAL WITH N-BROMOSUCCINIMIDE (NBS)

A mixture of n-octanal (0.1398g; 1.09mmol), bromobenzene (0.0848g; 0.54mmol), methanol (81μL; 2mmol), potassium carbonate (0.1521g; 1.1mmol), NBS (0.3560g; 2.0mmol), and acetonitrile (10mL) was charged into a reaction flask. The reaction was started at 0°C. Showing no apparent reaction after thirty minutes, the mixture was heated to room temperature. It was then heated to 40°C after two additional hours of no reaction. After six hours, the reaction mixture contained 4.1% ester and 63% aldehyde. It was heated to 60°C until 24 hours after the starting time. At this point, the mixture contained 33.4% ester and 3.5% aldehyde. The reaction was stopped at this time. The mixture was worked up as usual, and the product was identified as being methyl octanoate.

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