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USING $RuCl_2(PPh_3)_3$ AND ISOPROPANOL TO REDUCE UNSATURATED ORGANIC COMPOUNDS VIA TRANSFER HYDROGENATION

Diana Matasker*, Dylan Tapp*, and Stephen Anderson†

School of Theoretical and Applied Science, Ramapo College of New Jersey, Mahwah, NJ 07430

Abstract

A series of alkenes and ketones were successfully reduced via transfer hydrogenation using Tris(triphenylphosphine)ruthenium (II) dichloride [$RuCl_2(PPh_3)_3$] as the hydrogen transfer catalyst and isopropanol as the hydrogen transfer agent. Using this method, the ketones acetophenone and cyclohexanone were successfully reduced to 1-phenylethanol and cyclohexanol respectively. The alkenes 1-hexene, cyclohexene and cyclooctene were converted to their equivalent saturated alkanes (hexane, cyclohexane and cyclooctane). In addition, compounds containing both C=C and C=O bonds were also investigated. 5-hexen-2-one produced 2-hexanol as the major product. Chalcones, a class of compounds with conjugated C=O/C=C bonds were also successfully reduced, with 4-methylchalone yielding 3-(4-methylphenyl)-1-phenyl-1-propanol as the product. In these reactions, the generation of acetone, produced when hydrogen was removed from the 2-propanol hydrogen transfer agent, was monitored using infrared spectroscopy and the final products confirmed via gas chromatography where relevant.

†Corresponding author: standers@ramapo.edu
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Introduction

The reduction of unsaturated organic molecules is typically carried out via two traditional methods. One involves the use of reducing agents such as sodium borohydride or lithium aluminum hydride (1). The other involves catalytic hydrogenation, the addition reaction of a C=C or C=O bond with molecular hydrogen gas in the presence of a transition metal catalyst (2). In performing reductions via transfer hydrogenation (3-8), no external source of hydrogen gas is used to perform the reduction. Instead, these employ hydrogen transfer agents (H-TA), molecules that can act as a source of hydrogen. Reagents such as hydrazine/diimide (9), ammonium formate (10) and formic acid (11) have all been used. In addition, various alcohols, including isopropanol (12-18) have been used to perform these reactions. Removal of hydrogen from the each of the H-TA produces a stable product, which acts as a driving force for the reaction. Although each transfer hydrogenation reaction is potentially reversible, using an excess of donor agent appears to prevent this (19). Previous work in the literature has employed both heterogeneous and homogeneous transition metal catalysts to perform the hydrogen transfer (3, 20) using predominantly ruthenium (21-23) rhodium (22, 24-27) or iridium (15) based catalysts. The use of $RuCl_2(PPh_3)_3$ as the catalyst in the reaction has been reported in several previous publications (15, 28, 29). Discussion of the mechanism in these cases involves the starting catalyst being converted to a dihydride species from the reaction with isopropanol and a base. Previous publications by our group (30-32) have shown various transfer hydrogenations using Wilkinson's catalyst [$RhCl(PPh_3)_3$] with isopropanol, with the goal to investigate if the method employed could be extended to a ruthenium catalyst, which would be a considerably cheaper alternative.

Experimental

Materials and Instrumentation

All chemicals were obtained from Sigma-Aldrich and used without further purification. All reactions were performed under an inert atmosphere of nitrogen, and the isopropanol solvent degassed under nitrogen prior to use. Infrared (IR) spectra were recorded on a Thermo Scientific Nicolet 6700 FT-IR Spectrometer. Analysis of reaction products via G.C. were performed on a GOW-MAC Gas Chromatograph using either a 4' x 1 ¼'' 20% CARB.20M on CHROM.-P 80/100 MESH (Column A) or a 4' x 1 ¼'' 20% DC 200 on CHROM-P 80/100 MESH (Column B). Runs were carried out at the specific isotherm temperature noted for each product in the experimental section with a helium carrier gas pressure of 40 psi. Reaction yields for the liquid products were calculated via GC based on area under peak integration calculations as compared to standards. Proton NMR spectra were recorded on a Varian EM360A NMR spectrometer with Anasazi Eft-60.

Synthesis of 1-phenylethanol from acetophenone

$RhCl_2(PPh_3)_3$ (50mg, 0.05mmol) was placed in a 25ml Schlenk tube, and the tube evacuated and refilled with nitrogen several times. Nitrogen purged isopropanol (5ml) was added, followed by acetophenone (0.2ml, 1.7mmol) and KOH (1.5ml, 0.1M sol^n in isopropanol). The reaction was heated under reflux overnight under an atmosphere of nitrogen. The catalyst was allowed to settle, and the infrared spectrum of the reaction liquor was taken to confirm that the starting acetophenone had completely reacted and acetone had been produced. FT-IR of reaction (iPrOH, Fig. 1a): peak at 1680 cm^{-1} went down (C=O of acetophenone), peak at 1711 cm^{-1} produced (C=O of acetone). G.C recorded on Column B at 150^{o}C. RT. of 1-phenylethanol produced (2.25 min) versus 1-phenylethanol standard (2.25 min). Yield ~60 %.

Synthesis of cyclohexanol from cyclohexanone

The above procedure was repeated using cyclohexanone (0.2mL, 1.93mmol) instead of acetophenone. The infrared spectrum of the reaction liquor was taken to confirm that the starting cyclohexanol had completely reacted and acetone had been produced. FT-IR of reaction (iPrOH, Fig. 1b)): peak at 1707 cm^{-1} went down (C=O of cyclohexanone), peak at 1710 cm^{-1} produced (C=O of acetone) produced. The product was confirmed by GC analysis (Column A, 150^{o}C). G.C. (150^{o}C): RT of generated cyclohexanol (4.28 min, Fig. 2a.) versus cyclohexanol standard (4.28 min, Fig. 2b.), compared to starting cyclohexanone standard (3.20 min, Fig.

2c.). Yield ~82 %.

Synthesis of hexane from 1-hexene

The above procedure was repeated using 1-hexene (0.2ml, 1.6mmol) in place of acetophenone. FT-IR of reaction (iPrOH): peak at 1641 cm^{-1} removed (C=C of 1-hexene), peak at 1711 cm^{-1} produced (C=O of acetone).

Synthesis of cyclohexane from cyclohexene

The above procedure was repeated using cyclohexene (0.2mL, 1.97mmol) in place of acetophenone. FT-IR of reaction (iPrOH): peak at 1654 cm^{-1} went down (C=C of cyclohexene), peak at 1711 cm^{-1} produced (C=O of acetone). G.C. (Column A, 100°): RT of generated cyclohexane (32 sec) versus cyclohexane standard (32 sec), compared to starting cyclohexene standard (47 sec). Yield ~20 %.

Synthesis of cyclooctane from cyclooctene

The above procedure was repeated using cis-cyclooctene (0.2mL, 1.54mmol) in place of acetophenone. FT-IR of reaction (iPrOH): peak at 1652 cm^{-1} removed (C=C of cyclooctene), peak at 1711 cm^{-1} produced (C=O of acetone). G.C. (Column A, 80°): RT of generated cyclooctane (4.46 min) versus cyclooctane standard (4.46 min), compared to starting cyclooctene standard (4.95 min). Yield ~40 %.

Synthesis of 2-hexanol from 5-hexen-2-one

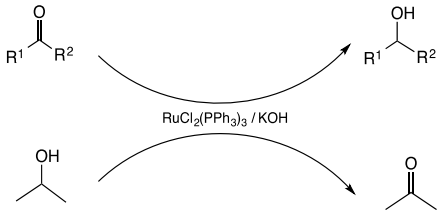
The above procedure was repeated using 5-hexen-2-one (0.2ml, 1.7mmol) in place of acetophenone.. FT-IR of reaction (iPrOH): peaks due to 5-hexen-2-one at 1643 cm^{-1} (C=C) and 1713 cm^{-1} (C=O) removed, peak at 1711 cm^{-1} produced (C=O of acetone). G.C. (Column A, 150°C) RT of 2-hexanol produced (1.45 min) versus 2-hexanol standard (1.44 min), compared to starting 5-hexen-2-one standard (1.25 min) Yield ~ 60 %.

Synthesis of 3-(4-methylphenyl)-1-phenyl-1-propanol from 4-methylchalcone

The above procedure was repeated using 4-methylchalone (0.2g, 0.85mmol) in place of acetophenone. FT-IR of reaction (iPrOH): peaks due to 4-methylchalcone at 1660 cm^{-1} (C=O) and 1601 cm^{-1} (C=C) went down, peak at 1711 cm^{-1} (C=O of acetone) produced. The liquor was decanted from the catalyst, and the solvent removed via rotary evaporator. The residue was extracted into diethyl ether and filtered through a celite pad. The ether was then removed under vacuum and the product isolated. Yield ~ 60 %. ^1H NMR (60 Mhz): δ 7.3 (m, 9H), δ 4.7 (t, 1H), δ 2.6 (m, 2H), δ 2.3 (s, 3H), δ 2.1 (m, 2H).

Results and Discussion

Transfer-hydrogenation involves hydrogen being removed from one species, the hydrogen-transfer agent (H-TA) and donated to the organic substrate being reduced. When isopropanol is used as the donor agent, it is converted to acetone, as can be seen in scheme 1.



Scheme 1: Outline of the transfer hydrogenation of Ketones using $RuCl_2(PPh_3)_3$ and isopropanol

Observing the formation of acetone in the infrared spectra of the reaction mixtures serves as evidence that hydrogen transfer has occurred. Acetone has a characteristic C=O stretch at 1711 cm^{-1}, and its formation can be clearly followed. In addition, as the unsaturated organic substrate adds the transferred hydrogen, any peaks due to the starting material, such as the C=O or C=C bonds, would be expected to go down in the infra-red spectra of the product. Occasionally, the C=O stretch of the starting substrate may be coincidental to that of the generated acetone, and in this case the success of the reaction is not as apparent from the reaction IR spectra. This can be observed by comparing the spectra in Figure 1a to that of 1b.

Fig. 1a shows the IR spectra of the reaction between $RuCl_2(PPh_3)_3$ and acetophenone in isopropanol. (Note: spectra are shows as absorbance, which makes viewing reactions as they proceed easier to observe when overlapped). At the start of the reaction, only the C=O peak of the starting acetophenone is present (1681 cm^{-1}, blue spectrum). On heating the reaction overnight under reflux and recording the IR of the reaction liquor (red spectrum), it can be seen that the peak due to acetophenone is no longer present. The formation of acetone can be observed by the new peak at 1711 cm^{-1} in the reaction product. The IR spectra therefore indicates that acetophenone has reacted and acetone has been produced, showing that hydrogen transfer has occurred. Of note is that the conditions required for this reaction are considerably more severe than when using Wilkinson's catalyst (30). Reductions using $RhCl(PPh_3)_3$ proceeded at room temperature as opposed to the refluxing conditions required for $RuCl_2(PPh_3)_3$. Fig. 1b shows the IR spectra of the equivalent reaction using cyclohexanone as the substrate. The C=O of the starting ketone can be seen at 1707 cm-1 (red spectrum) and the reaction product can be observed in the purple spectrum, showing acetone's C=O peak at 1710 cm^{-1}. Also note that the -OH peaks of the reduced products cannot be observed in the IR spectra, due to the fact that they are recorded in isopropanol solvent, and the limitations of the solvent background removal software.

While the IR spectra of the reactions indicate that hydrogen transfer has occurred, they do not confirm the formation of the expected products. This was achieved by use of Gas Chromatography, with the GC traces of the reaction products compared to those of standards. In the case of 1-phenylethanol produced from acetophenone, the product of the reaction showed a peak in the GC with a RT of 2.25 min, as compared to 2.25 min for the standard

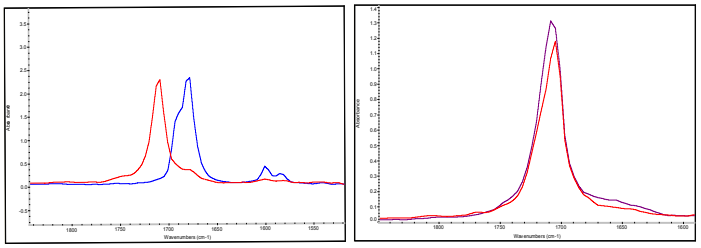


Fig. 1a: IR spectra of acetophenone reduction reaction mixture (left)
Fig. 1b: IR spectra of cyclohexanone reduction reaction mixture (right)

obtained from Sigma-Aldrich. In addition, approximate yields can be estimated from area under the peak comparisons. In this case, the yield of the reaction was approximately 60 %. When the C=O peak of the starting substrate was coincidental with that of the generated acetone in the IR spectra (Fig. 1b), it is also important to compare the data from the starting material in the GC analysis. This is the case with the cyclohexanone reduction, and the GC traces can be seen in Fig. 2.

Fig. 2a shows the GC trace of the reaction liquor, with the generated cyclohexanol showing at RT 4.28 min. The large peak at ~30 sec is the isopropanol solvent. The product standard can be seen in Fig. 2b with RT 4.28 min and the cyclohexanone starting material standard RT at 3.20 min. The yield of cyclohexanol is estimated to be approximately 80% based on area under the peak comparisons to the standard.

The reduction of C=C double bonds of alkenes was also investigated using this method. 1-hexene was first selected as the unsaturated organic substrate, and the reaction followed by Infrared spectroscopy as previously described. In this case, the C=C bond of the 1-hexene can be observed in the IR of the staring reaction mixture at 1642 cm^{-1}. As the 1-hexene reacts, the C=C peak is removed from the IR spectrum and the formation of acetone simultaneously observed at 1711cm^{-1}, indicating that transfer hydrogenation had occurred. However, due to its non-polar nature and relative volatility, both GC columns that were available were unable to successfully resolve the expected hexane from the reaction solvent.

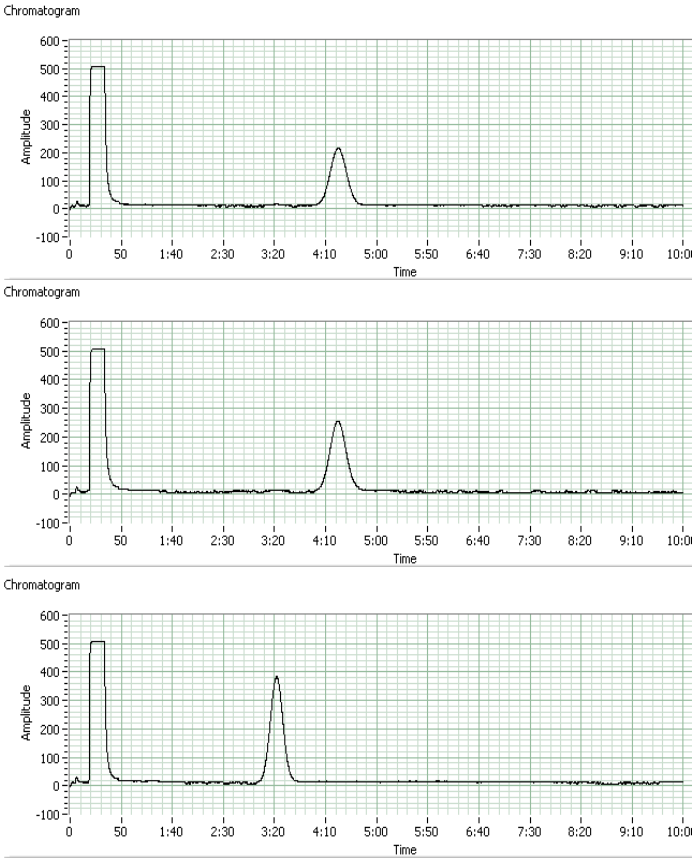


Fig. 2a. G.C. of cyclohexanol produced via transfer hydrogenation of cyclohexanone (Top)
Fig. 2b. G.C.of cyclohexanol standard, in isopropanol. (Middle)
Fig. 2c. G.C.of cyclohexanone (starting material) standard, in isopropanol. (Bottom)

The reduction of cyclohexene was next investigated, with the hope that the GC analysis would be more successful. The IR spectra of the reaction product clearly showed the generation of acetone in the reaction as noted by its characteristic peak at 1711 cm^{-1}. However, a very small peak could still be observed at 1654 cm^{-1} corresponding to the starting material, indicating that the reaction had not gone to completion. Although the G.C. analysis of the product confirmed that some cyclohexane has been produced (RT 32 sec), it also showed the presence of a considerable amount of unreacted cyclohexene (RT 47 sec). The maximum observed yield of product was approximately 20 %. As cyclohexene is itself often employed as a hydrogen transfer agent itself (3), it is perhaps unsurprising that the yield of this reaction is so low. When cyclohexene is used as an H-TA in tandem with a Pd/C catalyst, benzene is produced after it donates hydrogen. We looked for evidence of benzene formation in our system, but none was observed.

Cyclooctene was then studied as a reduction substrate as it was hoped that increasing the ring size from 6 to 8 carbons would make the system considerably more reactive. In this case, the C=C double bond of the starting material at 1652 cm^{-1} is virtually non-existent in the IR spectra of the reduction product, with only the 1711 cm^{-1} peak due to the generated acetone being present. GC analysis shows the generated cyclooctane at RT 4.46 min compared to the product standard (RT 4.46 min). However, the GC trace of the product also shows unreacted starting material, with the cyclooctene showing up at RT 4.95 min. The yield is approximately 40%. Also of note is that the low temperature conditions required to separate cyclooctene and cyclooctane on the GC (80^{o}C) also allowed us to finally see the generated acetone (RT 86 sec) separated from the isopropanol solvent (~2 min) on the GC traces. GC runs recorded at higher temps previously showed these two together, with the small acetone peak being swamped by the large isopropanol solvent peak.

In order to investigate whether both a C=C and C=O bond could be reduced simultaneously, we extended our method by using 5-hexen-2-one as the organic substrate (Fig. 3a). In this case, reduction of both unsaturated functional groups produced 2-hexanol as the major product. The reaction was monitored by IR as before, with the starting material showing peaks at 1643 cm^{-1} (C=C) and 1713 cm^{-1} (C=O). As the reaction proceeds, it can be clearly observed that the C=C peak is removed, indicating that the double bond has been saturated. Confirmation that the C=O group of the starting ketone had reacted was less conclusive because it's carbonyl stretch coincides with that of the acetone produced in the reaction (1711 cm^{-1}). G.C analysis of the product of the reaction (RT 1.45 min) against a standard sample of 2-hexanol (RT 1.44 min) demonstrated that the major product of the reaction was indeed 2-hexanol. However, the GC trace of the product also showed a

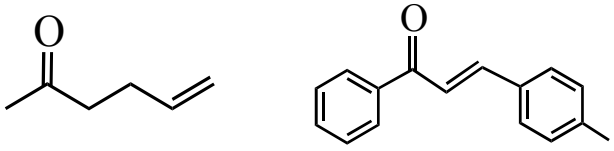


Fig. 3a: Structure of 5-hexen-2-one (left)
Fig. 3b: Structure of 4-methylchalcone (right)

secondary minor peak with RT 1.10 min. This was not due to unreacted starting material, as the 5-hexene-2-one appeared in the GC at RT 1.25min. Recording the GC of a standard sample of 2-hexanone showed a peak at RT 1.10 min, indicating that it was the minor product of the reaction. This implies that reduction of the C=C bond is considerably easier than the C=O bond using this method. The yield of 2-hexanol was approximately 60 % as determined by a peak area calculation.

We next wished to investigate whether this method could be extended to include molecules that contained a conjugated set of C=C/C=O bonds. In the conversion of 5-hexen-2-one to 2-hexanol, the C=O and C=C bonds are not conjugated and are separated by two sp^3 carbons. It was assumed that the reactivity of the unsaturated bonds would be different in a a,b-conjugated system and in a previous paper by our group (32) a series of Chalcones were reduced using Wilkinson's catalyst. In order to test whether this could also be achieved using the $RuCl_2(PPh_3)_3$ catalyst instead, 4-methyl chalcone (Fig. 3b) was selected as it gave the best results previously. As before, the reduction was monitored via infra-red spectroscopy as it proceeded. In the transfer-hydrogenation of 4-methylchalcone, the initial spectrum showed the stretches for the C=O (1660 cm^{-1}) and C=C (1601 cm^{-1}) of the a,b-unsaturated starting material. After reduction was completed, it can be clearly observed that both of these peaks have been removed and that a new peak is seen at 1711 cm^{-1}, corresponding to the generated acetone. Unlike the previous reactions described above, the 4-methylchalcone is a solid at room temperature. After work up and isolation, the product of the reaction was analyzed via ^1H NMR instead of GC. The spectra of the final tetrahydrochalcone product (3-(4-methylphenyl)-1-phenyl-1-propanol was recorded in $CDCl_3$ and compared to the starting 4-methyl chalcone. The sp^2 protons (=C<u>H</u>) of the alkene in the starting material can be observed at δ 8.0 ppm. In the final isolated product, the height of this signal has been considerably reduced, although a small residual peak is still visible, indicating a trace amount of unreacted starting material is still present. The ^1H NMR of the reduced product also shows a new peak at δ 4.6 ppm. This peak appears as a triplet and corresponds to the newly added -C<u>H</u>OH proton.

Conclusion

Based on the results of this study, the reactions described in this paper provide an effective and efficient method of reducing several unsaturated organic substrates via transfer hydrogenation employing isopropanol as the hydrogen transfer agent and $RuCl_2(PPh_3)_3$ as the catalyst. However, as compared to using $RhCl(PPh_3)_3$, the conditions required for the reactions to proceed appear to be more severe with the product yields are somewhat lower.

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