Regioselective Catalytic Dehydrogenation of Aldehydes and Ketones

Youval Shvo* and Anan Haj Ichia Arisha

School of Chemistry, Raymond and Beverly Sackler School of Exact Sciences, Tel Aviv University, Tel Aviv, 69978, Israel

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A simple one-step reaction inducing regioselective introduction of a double bond into an aliphatic molecular framework is a desirable synthetic tool.

Selective dehydrogenation is an important reaction in organic chemistry as well as in biochemical processes, with chloranil and DDQ being the classic and useful stoichiometric dehydrogenation reagents in organic chemistry. Substitution reactions of the α-position of ketones with halogens,[1] sulfur,[2] and selenium[3] groups, with subsequent elimination of these groups, are stoichiometric and cumbersome procedures for the preparation of α,β-unsaturated ketones.

Certain transition metal complexes catalyze dehydrogenation reactions of saturated ketones to α,β-unsaturated ketones. Among those are the $Pd(OAc)_2/Cu(II)/O_2$ dehydrogenation system[4] applied directly to ketones, and Pd−phosphine complexes acting indirectly on the silyl enol ethers of aldehydes and ketones in the presence of allyl carbonate,[5] and on allyl enol carbonates.[6]

We have discovered a new reaction condition whereby aldehydes and cyclic ketones are *directly* transformed into their α,β-unsaturated derivatives with moderate to good yields, under mild conditions with *no* prior derivatization and in the *absence* of oxygen. The reaction consisted of heating a THF (or DMF) solution of the saturated carbonyl compound, allyl diethyl phosphate (ADP), and sodium carbonate (or sodium bicarbonate) in the presence of 4 mol % $Pd(OAc)_2$ to yield the desired product. The progress of the reaction was monitored by GC. The reaction products (known compounds) were identified by NMR, IR, and MS, and by comparison with authentic samples. The stoichiometry of the reaction, exemplified with aldehyde and a ketone, is shown in Scheme 1.

Propylene was determined by trapping the evolved gas in Br_2/CCl_4 solution.[7] The stereochemistry of the conjugated double bond was established by ^1H NMR spin decoupling experiments. The results of various experiments are presented in Table 1.

Both allyl diethyl phosphate (ADP) and sodium carbonate (or bicarbonate) were found, by control experiments, to be essential for the above reaction. Noteworthy are the findings that, neither allyl alcohol, nor allyl acetate, carbonate, tosylate, and bromide induce the above reaction in THF. Thus *allyl phosphate* is a critical component of this new reaction.

Our preliminary investigation of the scope of this rection indicated that, while aldehydes and cycloalkanones are reactive, neither simple acyclic ketones, nor esters, lactones, and nitriles were reactive in the above reaction. This behavior may conceivably be related to the higher acidity[8] of the α-H atoms of aldehydes and cycloalkanones relative to acyclic ketones, esters, and nitriles, assuming that the enolization of the carbonyl compound is associated with the rate-determining step of the deydrogenation reaction. This assumption will be checked in future mechanism studies. The presence of triphenylphosphine did not affect the reaction. No black Pd deposit could be observed during the reaction.

The formation of phenyl allyl ether as a byproduct in expt 2 (Table 1) indicates that the primary product, cyclohexenone, is being further dehydrogenated to give phenol, which in the basic reaction solution is being allylated by the ADP to give the phenyl allyl ether. This was further demonstrated in expt 3 by prolonging the reaction time, and in expt 6 where excess ADP and prolonged reaction time generated the phenyl allyl ether as the main reaction product, as shown in Scheme 2. All of the above compounds were detected by GC during the progress of the reaction. As formulated above, 3 mol of ADP are required to obtain the final product. This has been also demonstrated with α-tetralone (expt 8) using a 2.7/1 molar ratio of ADP/α-tetralone, which resulted in the formation of allyl 1-naphthyl ether with high selectivity. It should be noted that ADP/sodium carbonate ratio was always kept at least at a 1:1 ratio.

Thus, the above reaction provides a simple, catalytic, good yield route for the conversion, under mild conditions, of cyclohexanone, and substituted cyclohexanones, directly to phenyl allyl ethers.

The 2- and 4-methyl-substituted cyclohexanones were also studied briefly (expts 4 and 5). The reaction with 2-methylcyclohexanone proved to be nonselective (expt 5), inasmuch as the two isomeric products were formed in a ratio of ca. 1:2.

An additional interesting aspect of the above reaction system is its capacity to catalytically oxidize alcohols to ketones. Thus, cyclohexanol, with excess ADP, was also transformed into phenyl allyl ether (expt 7). This demonstrates that cyclohexanols can also be used as the starting materials for the aromatic ethers.

In the same fashion, the 3-hydroxy group of cholesterol was converted to the ketone under the standard reaction conditions (Table 1, expt 9), followed by the introduction of two double bonds, consequently forming cholesta-1,4,6-trien-3-one in 75% isolated yield, as shown in Scheme 3. A 3/1 ratio of ADP/cholesterol had to be used, since lower ratios resulted in a mixture of products. The ready dehydrogenation of the steroidal system is significant.

Three saturated aldehydes were examined (expts 10−12), all resulting in the formation of the corresponding α,β-unsaturated aldehydes in 55−59% yield (THF). In a larger scale experiment, 2-octenal, derived from octanal,

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Scheme 1

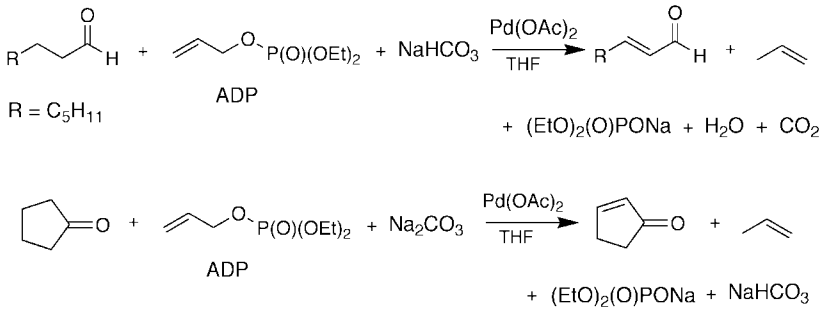
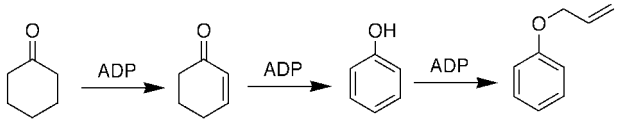


Table 1.[a]. Experimental Data for Dehydrogenation Reactions with $Pd(OAc)_2$

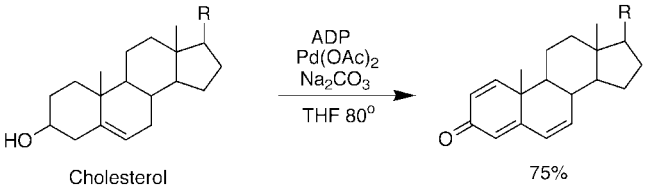
expt	allyl/base (mmol)	substrate (mmol)	time (h)	conv[b] (%)	products (yield %)[b]
1	ADP (5) Na_2CO_3 (6)	cyclopentanone (5)	21	86	2-cyclopenten-1-one (63)
2	ADP (5) Na_2CO_3 (6)	cyclohexanone (5)	5	61	2-cyclohexen-1-one (71), allyl phenyl ether (3.3)
3	ADP (5) Na_2CO_3 (6)	cyclohexanone (5)	24	79	2-cyclohexen-1-one (59), phenol (4.3), allyl phenyl ether (5.6)
4	ADP (5) Na_2CO_3 (6)	4-methylcyclohexanone (5)	21	82	4-methyl-2-cyclohexen-1-one (73)
5	ADP (5) Na_2CO_3 (6)	2-methylcyclohexanone (5)	21	42	6-methyl-2-cyclohexen-1-one (53), 2-methyl-2-cyclohexen-1-one (24)
6	ADP (10) Na_2CO_3 (12)	cyclohexen-3-one (5)	21	79	allyl phenyl ether (67), phenol (6)
7	ADP (13.5) Na_2CO_3 (15)	cyclohexanol (2.5)	43	95	allyl phenyl ether (44), 2-cyclohexen-1-one (10), phenol (3.3)
8	ADP (13.5) Na_2CO_3 (13)	α-tetralone (5)	16	97	allyl 1-naphthyl ether (59), 1-naphthol (1.7)
9	ADP (5.85) Na_2CO_3 (7)	cholesterol (1.67)	40	100	cholesta-1,4,6-trien-3-one (75)
10	ADP (5) $NaHCO_3$ (6)	octanal (5)	19	97	2-octenal (59)
11	ADP (5) $NaHCO_3$ (6)	decanal (5)	16	94	2-decenal (57)
12	ADP (5) $NaHCO_3$ (6)	pentanal (5)	16	92	2-pentenal (55)
13[a]	AMC (11) K_2CO_3 (13)	cyclohexanone (5)	23	98	phenol (30), 2-cyclohexen-1-one (2.5), phenyl allyl ether (4.7)
14[a]	ADP (5) $NaHCO_3$ (6)	octanal (5)	5	85	2-octenal (42)
15	ADP (5) $NaHCO_3$ (6)	citral (5)	20	88[c]	3,7-dimethyl-2,4,6-heptatrienal (32)[c]

[a] Reaction conditions: reactions 1−12 and 15 were carried out in THF (4 mL), and reactions 13 and 14 in DMF (4 mL). 4 mol % of $Pd(OAc)_2$ with respect to substrates was used in all experiments. All reactions were carried out at 86 °C under argon. [b] Conversions and yields were determined quantitatively by an internal standard method using gas chromatography and are accurate to ±5%. The product of expt 9 was isolated by column chromatography (see Experimental Section). [c] The conversion and yield of this experiment were estimated from the appropriate GC peak areas.

Scheme 2



Scheme 3



was isolated in 50% yield after distillation (see Supporting Information). The main byproducts of these reactions are the allyl esters of the respective acids of the aldehydes. Their mode of formation has not yet been determined. The use of sodium bicarbonate rather than carbonate with aldehydes gave better yields of the dehydrogenated aldehydes.

No reaction could be observed with cyclohexanone by replacing the allyl diethyl phosphate (ADP) with allyl methyl carbonate (AMC) in THF. However, using AMC, and also replacing the solvent THF by DMF, resulted in the conversion of cyclohexanone to mainly phenol with 30% yield (expt 13). This solvent effect was further investigated with octanal. In Figure 1, the rate of dehydrogenation of octanal with ADP in the two solvents, under identical conditions (see expt 10, Table 1), was compared. Clearly the reaction is significantly faster in DMF than in THF, where a reaction induction period was noted. The above rate difference may be attributed to the greater solubility of the carbonate salt in the more polar DMF reaction solution. However, the observed increase in the rate of formation of the allyl octanoate byproduct in DMF resulted in a lower yield compared to THF (expts 10 and 14, Table 1).

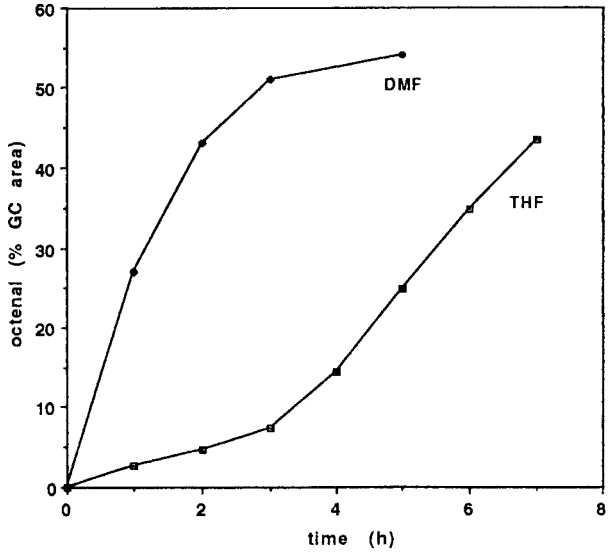
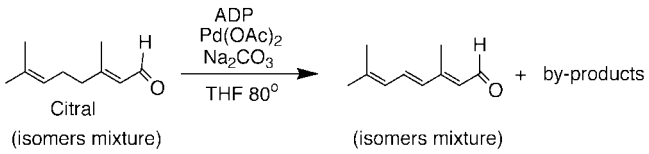


Figure 1. Rates of formation of octen-2-al in THF and DMF with allyl diethylphosphate.

Scheme 4



The introduction of a double bond in the 6,7 position of cholesterol implies that the present dehydrogenation reaction system may also be reactive with carbon atoms other than those α to a carbonyl group. This assumption was tested and verified with citral as a substrate according to reactions shown in Scheme 4. A rather complex mixture (not separated) was obtained, in which the triene (isomers), identified by GC-MS, was formed in 32% (GC area).

No mechanism study for the dehydrogenation reaction described herein has yet been conducted. However, in any mechanism, a π-allyl palladium diethyl phosphate[9] complex intermediate must be invoked. Indeed, a ^{1}H NMR experiment with an equimolar quantities of Pd(PPh$_3$)$_4$ and allyl diethyl phosphate in benzene-d_6 indicated the fast disappearance of the resonance lines of the latter, and the appearance of new higher field signals. The unique and unexpected feature of the present reaction is that no allylation products of the carbonyl compounds could be detected. Thus, if an α carbon atom nucleophile is involved, it avoids reacting with the allyl moiety, but attacks exclusively the Pd atom of the π-allyl Pd complex.

In conclusion, the novel catalytic reaction described herein results in the direct regioselective dehydrogenation of aldehydes and cyclic ketones, in a straightforward manner with moderate to good yields. No prior derivatization[5,6] of the substrates is necessary. The circumvention of the use of oxygen[4] is of particular importance for the dehydrogenation of aldehydes which are susceptible to oxygen, as well as for other oxygen-sensitive functional groups which may be present in a carbonyl substrate. No extensive parametrization has been carried out yet. An effort will be made to apply this reaction to acylic ketones as well.

Experimental Section

General. Data regarding the quantities of the reactants and solvents, reaction temperature and duration, as well as percent conversions and yields are given in Table 1 and its accompanied footnotes.

Allyl diethyl phosphate (ADP) was prepared from the commercially available diethyl chlorophosphate and allyl alcohol.[10]

The following experiments are numbered according to the numbers in Table 1.

General Procedure. A general procedure is exemplified using experiment 1. To a 50 mL round-bottom flask equipped with a condenser and magnetic stirrer under argon were added sodium carbonate (0.64 g; 6 mmol), diethyl allyl phosphate (0.97 g; 5 mmol), THF (4 mL), cyclopentanone (0.42 g; 5 mmol), and Pd(OAc)$_2$ (0.045 g; 0.2 mmol). The flask was heated with stirring under argon in an oil bath at 86 °C for 21 h. After cooling, the reaction mixture was quantitatively analyzed by GC using *n*-decane as internal standard to give unreacted cyclopentanone (0.052 g; 86% conv) and 2-cyclopenten-1-one (0.188 g; 63% yield).

2-Cyclopenten-1-one was identified by repeating the above experiment throughout and then adding methylene chloride (20 mL) to the final reaction mixture, washing the organic solution with water (2 × 20 mL), drying over MgSO$_4$, and evaporating the solvents to give a residue. GC/MS: *m*/*z*, M$^+$ (82). IR ν (CCl$_4$): 1716 cm^{-1}. ^{1}H NMR (δ): 7.75 (dd, J = 6 Hz, 2.8 Hz, 1H); 6.22 (dt, J = 4 Hz, 2 Hz, 1H); 2.72 (m, 2H); 2.36 (m, 2H), conforming to a published spectrum.[11]

The same procedure and quantities of reactants were used with aldehydes, but sodium carbonate was replaced with sodium bicarbonate.

Experiment 9. To a 50 mL round-bottom flask equipped with a condenser and magnetic stirrer under argon were added sodium carbonate (0.742 g; 7 mmol), diethyl allyl phosphate (1.13 g; 5.85 mmol), Pd(OAc)$_2$ (0.015 g; 0.07 mmol), THF (4 mL); and cholesterol (0.644 g; 1.67 mmol). The flask was heated with stirring under argon in an oil bath at 86 °C for 40 h. After cooling, methylene chloride (20 mL) was added, and the organic solution was washed with water (2 × 20 mL), dried over MgSO$_4$, and then evaporated to dryness. TLC of the residue indicated total absence of the starting material and consisted of single spot. The residue was chromatographed on silica using methylene chloride:petroleum ether as eluent and increasing their ratio from 1:1 to pure methylene chloride. The emerging yellow solid, cholesta-1,4,6-trien-3-one, (0.47 g; 75% yield) gave a single spot on TLC. Mp 80−82 °C (lit.[12] 82−83 °C). MS: *m*/*z* 380 (M$^+$), 365, 267, 247, 173, 159, 133, 119, 107. IR ν (CCl$_4$): 1659 cm^{-1}. ^{1}H NMR (δ): 7.08(d, J = 10 Hz, 1H); 6.14(m, 4H); 1.19(s, 3H); 0.78(s, 3H), conforming to a published spectrum.[13]

Experiment 15. Workup of the reaction mixture according to the general procedure described in expt 1 gave a liquid mixture. GC/MS: *m*/*z*, M$^+$ (150) and additional peaks. No separaton was attempted; conversion (86%) and yield (32%) were estimated from GC peak areas.

Supporting Information Available: ^{1}H NMR, GC, GC/MS, and IR data are presented to support characterization of products from experiments 4, 5, 10, 11, and 12, Table 1 (1 page). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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