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Alcohol reduction of enamines

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ABSTRACT

Primary or secondary alcohols will reduce enamines to their corresponding saturated amines when heated in a microwave apparatus at a temperature of 160 °C for a period of one hour.

Enamines are typically reduced to saturated amines either by hydride transfer to a previously formed iminium salt or by catalytic hydrogenation.[1] The source of hydride ions can be from metal hydrides,[2] formic acid,[3] phosphorous acid,[4] the Hantzsch ester,[5] or secondary amines.[6]

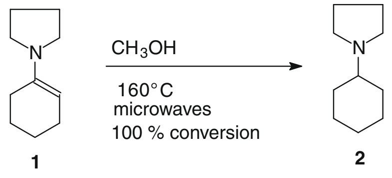
However, all the hydride reductions require the use of fairly strong acids to form the iminium ion. This can be a problem for acid-sensitive molecules. The catalytic hydrogenation involves expensive catalysts which are not 'green'.

The method of enamine reduction reported here does not involve strong acid catalysis and does not use expensive metal catalysts. Rather it uses inexpensive, green alcohols as a neutral medium and reagent. For example, 1-(1-cyclohexen-1-yl)pyrrolidine (**1**) is reduced with 100% conversion to 1-cyclohexylpyrrolidine (**2**) by heating the enamine with methanol at 160 °C in a microwave reactor[7] for one hour (Scheme 1).

A wide variety of enamines and primary alcohols are reduced by this method as shown in Table 1. Most secondary alcohols are less effective than primary alcohols and tertiary alcohols are completely ineffective in reducing enamines as shown in Table 2. There seems to be a correlation between the basicity of the enamine[8] and the ease of reduction by alcohols with the most basic enamine being the most readily reduced.

The mechanism for the reaction is shown in Scheme 2. The second step in this reaction mechanism involving a hydride transfer is the rate-determining step. The proof for this reaction mechanism is given by treating 1-(1-cyclohexen-1-yl)pyrrolidine (**1**) with ethanol-*d* and ethanol-d_6 in separate experiments using the microwave reactor at 160 °C (Scheme 3). When ethanol-*d* was used, labeled amines **3** and **4** are formed in 1:3 ratio with an overall 79% conversion. This shows that protonation is the first step of the reaction The large amount of **4** formed as compared to **3** shows that extensive equilibration between the enamine and the iminium ion takes place before the rate-determining hydride reaction occurs in the second step. When ethanol-d_6 was used, labeled amine **5** was formed showing that the hydride transfer is the second, rate-determining step of the reaction. Further proof of this mechanism is that there is an isotope effect in the second, rate-determining step of the reaction. This isotope effect is shown by the fact that the two reactions, one using normal ethanol and the other using ethanol-d_6 but identical enamines, under identical microwave, temperature conditions produce different amounts of reduction products over an identical period of time. The normal ethanol reaction produced six times as much reduction product as the deuterated ethanol reaction.

This alcohol reduction reaction is also stereospecific as shown by the reduction of 2-*N*-hexamethylenimine[2.2.1]hept-2-ene (**7**) with ethanol at 160 °C in a microwave apparatus to produce the *endo* isomer of 2-*N*-hexamethyleniminobicyclo[2.2.1]heptane (**8**) (Scheme 4). The product must be formed by *exo* addition of



Scheme 1.

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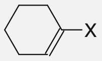
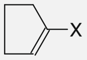
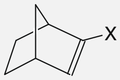
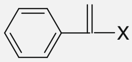
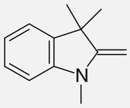
Table 1
Microwave reductions of enamines using primary alcohols

Enamine	X[a]	Alcohol	Temperature (C)	Time (h)	Reduction[b] (%)
	1	Methanol	160	1	100
	1	Benzyl Alcohol	160	1	100
	1	Ethanol	160	1	79
	2	Ethanol[c]	160	1	68
	4	Ethanol[c]	160	1	13
	4	Ethanol	160	3	26
	3	Ethanol	210	1	15
	1	Ethanol[c]	160	1	100
	2	Ethanol	160	1	42
	2	Ethanol	160	1	4
	–	Ethanol	160	1	9

[a] 1 = pyrrolidine, 2 = hexamethylenimine, 3 = morpholine, 4 = piperidine.

[b] Determined by GC/MS using Agilent 7890A GC with a Phenomenex Zebron ZB-5 30-meter column and Agilent 5975 MSD. The appearance of the enamine 'parent ketone' in the spectrum was assumed to come from hydrolysis of the enamine during the reaction by traces of water in the alcohol and was considered to be non-reduced enamine when calculating the percent reduction.

[c] Used Aldrich anhydrous ethanol with <0.005% water.

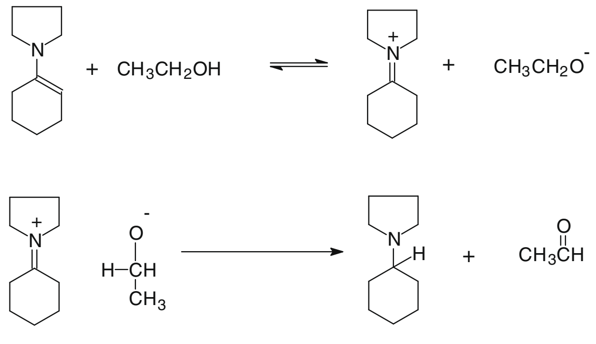
Table 2
Secondary/tertiary alcohol reductions of 1-(1-cyclohexen-1-yl)pyrrolidine (**1**)

Alcohol	Reduction[a,b] (%)	Time (h)
t-Butanol	0	1
1-Octanol	35	5
2-Pentanol	2	1
2-Pentanol	8	6
2-Pentanol	36	0.5
(−)-Menthol[c]	100	1

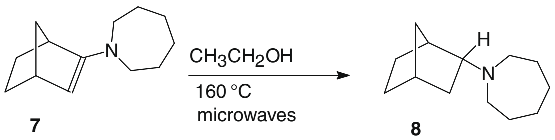
[a] Microwave, 160 °C.

[b] See footnote b of Table 1.

[c] Microwave, 220 °C, cyclohexane solvent.



Scheme 2.



Scheme 4.

Table 3
Thermo reduction of 1-(1-cyclohexen-1-yl)pyrrolidine (**1**) using ethanol

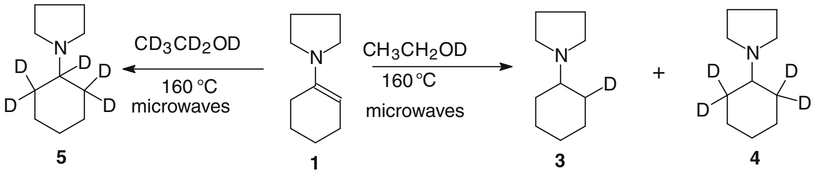
Temperature (C)	Time (h)	Reduction[a] (%)
25	20	0
25	96	<1
78	2	7
78	18	43
78	42	62

[a] See footnote b of Table 1.

hydride. The identity of this product was shown by comparison with an authentic sample.[9]

Heating an enamine in a microwave reactor at 160 °C for one hour with toluene solvent and no alcohol present produced no reduction products. Allowing an enamine to stand in ethanol at room temperature for four days produced essentially no reduction product. When this ethanolic enamine solution was refluxed (78 °C), it resulted in a 62% reduction of the enamine after 42 h (see Table 3).

All of the enamine reactants and amine products have been previously reported in the literature.



Scheme 3.

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