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Transfer Hydrogenation of Ketones with 2-Propanol and Raney[®] Nickel

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Abstract: Raney nickel in refluxing 2-propanol containing a trace of HCl is an effective catalytic system for the reduction of ketones to secondary alcohols.

Keywords: ketone reduction, Raney nickel, transfer hydrogenation

We recently reported the efficient reduction of aldehydes to primary alcohols by transfer hydrogenation using Raney nickel and 2-propanol containing a trace of hydrochloric acid.^[11] The addition of acid was found to accelerate the transfer reduction by as much as three times. We have now extended this catalytic system to the reduction of ketones to secondary alcohols, and we report our results herein. In addition to being an effective method for reducing ketones, this catalytic combination of Raney nickel and 2-propanol does not produce metal sludge often encountered in metal hydride reductions^[2] and avoids the need for hydrogen containment as well as the use of pressure vessels needed in traditional catalytic hydrogenation reactions.^[3]

Raney-nickel-catalyzed transfer hydrogenation in refluxing 2-propanol has been employed by us and others for the reduction of a variety of compounds including nitriles,^[4] iodolactones,^[5] aromatic alcohols,^[6] phenols,^[7] olefins,^[7] aromatic nitro compounds,^[8] and certain aromatic

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Figure 1. Reduction of ketones by catalytic transfer hydrogenation.

hydrocarbons.^[9,7] Ketone reduction by this catalytic system has also been reported.^[7,10] However, alcohol yields tended to be low,^[10] particularly when acyclic ketones are used as substrates.^[7]

The experimental procedure for the reduction of ketones by catalytic transfer hydrogenation (CTH) employing Raney nickel and 2-propanol is simple and straightforward and affords secondary alcohols in good yields (Fig. 1). In a typical run, the ketone (2 g) is refluxed (condenser open to the atmosphere) in a magnetically stirred suspension of Raney nickel (5 g) in 2-propanol (20 mL) containing one drop of concentrated aqueous HCl. The progress of the reaction is conveniently monitored by GC-MS. A summary of our results is presented in Table 1. Reaction products were confirmed by comparison of NMR and mass spectra with authentic samples. No self-condensation products were detected by GC or NMR in any of our reactions.

Table 1. Reduction of ketones by catalytic transfer hydrogenation using Raney nickel[®] and 2-propanol as the hydrogen source

Entry	Ketone	Product(s)	Yield ^a (%)	Time ^b (min)
1	2-Octanone	2-Octanol	96	33
2	5-Methyl-2-hexanone	5-Methyl-2-hexanol	61	80
3	3-Pentanone	3-Pentanol	60	17
4	Cyclohexanone	Cyclohexanol	82	20
5	3-Heptanone	3-Heptanol	73	20
6	Cyclooctanone	Cyclooctanol	45^{c}	40
7	3-Octanone	3-Octanol	79	91
8	4-Methylcyclohexanone	<i>cis</i> -4-Methylcyclohexanol (29%) <i>trans</i> -4-Methylcyclohexanol (71%)	91	16
9	2-Methylcyclohexanone	<i>cis</i> -2-Methylcyclohexanol (33%) <i>trans</i> -2-Methylcyclohexanol (67%)	62	61
10	2-tert-Butylcyclohexanone	2-tert-Butylcyclohexanol	75 ^d	1983

^{*a*}Isolated yields. Product identities compared to authentic spectra or literature reference spectra and confirmed by ¹H NMR spectroscopy and GC-MS.

^bTime to completion determined by GC.

^cOnly 45% conversion by GC after 40 min of reflux.

^dOnly 75% conversion by GC after 1983 min of reflux.

Transfer Hydrogenation of Ketones

The substrate-to-catalyst ratio (w/w) used to reduce ketones in this study was approximately 2:5. The Raney nickel catalyst could be used repeatedly (at least six times) after a simple regeneration step consisting of refluxing the catalyst in 2-propanol containing KOH (20 mg/1 g of catalyst used) for 15 min, followed by rinsing the catalyst with cold 2-propanol (three times).

As seen in Table 1, cyclic and acyclic ketones are readily reduced to secondary alcohols by this reductive method. Except for cyclooctanone (entry 6) and 2-*tert*-butylcyclohexanone (entry 10), the conversions to secondary alcohols by CTH were essentially quantitative as determined by GC (isolated yields are reported in Table 1). As mentioned earlier, in a previous study employing Raney nickel and 2-propanol, the conversions of acyclic ketones to secondary alcohols were low.^[7] We attribute our increased conversions to employing a larger catalyst load and to the inclusion of a trace amount of HCl.

The sluggish reduction of cyclooctanone (entry 6) was somewhat surprising in light of the fact that cyclohexanone (entry 4) is rapidly reduced. A careful examination of the minimized structures (MM2) of cyclooctanone and cyclohexanone reveals the α -equatorial hydrogens in cyclooctanone may hinder the π -system of the ketone carbonyl from easily interacting with the catalysis surface. This unfavorable steric interaction of the α -equatorial hydrogens is absent in cyclohexanone. The sluggish reduction of 2-*tert*butylcyclohexanone (entry 10) indicates steric bulk around the ketone carbonyl hinders the reaction.

Reduction of 4-methylcyclohexanone (entry 8) and 2-methylcyclohexanone (entry 9) results in a mixture of diastereoisomers with the *trans* isomer (equatorial OH) predominating in each case. Interestingly, the *cis* isomer (axial OH) has been reported^[11] to be the major isomer formed in the Raney-nickel-catalyzed hydrogenation of 2-methylcyclohexanone using hydrogen gas and under neutral or basic (NaOH) conditions. (No data reported for acidic conditions using Raney nickel.) Our results may suggest that the mechanism by which substrates are reduced by catalytic transfer hydrogenation and conventional catalytic hydrogenation are not the same and that the hydrogen donor may play an unique role in the CTH process.^[12] Further work is needed to fully clarify this issue.

The reduction of ketones by CTH does occur without addition the of HCl; however, the conversions are slower. To illustrate, quantitative conversion of 2-octanone to 2-octanol (entry 1) occurs in just 33 min when trace HCl is included in the reduction, whereas only 90% conversion of ketone to alcohol is realized after 378 min when the HCl is excluded. As mentioned earlier, we observed a similar acceleration by HCl in the reduction of aldehydes^[1] by CTH. Acceleration of traditional catalytic hydrogenations by acid and using hydrogen gas has also been described,^[13] and although the mechanism of the acceleration is not fully understood, it may result from an increased interaction between the an activated carbonyl (protonated) and the catalysis surface.^[14]

In conclusion, we have demonstrated that secondary alcohols are conveniently prepared by CTH using Raney nickel and 2-propanol as a hydrogen donor. Trace HCl accelerates the reductions, and the catalyst can be used repeatedly after a simple regeneration with KOH in 2-propanol.

EXPERIMENTAL

Raney[®] 2800 nickel was obtained from W. R. Grace Company, Chattanooga Davison. The catalyst was washed prior to use with distilled water (three times) and 2-propanol (four times). All ¹H and ¹³C NMR spectra were obtained on a Jeol ECX 400-MHz spectrometer using tetramethylsilane as internal reference (CDCl₃). Mass spectra were recorded on a ThermoElectron PolarisQ GC-MS. The NMR and mass spectra of the alcohols prepared in this work were identical to authentic or known spectra.

As an illustrative example of the hydrogenation procedure, 2-octanone (2.00 g, 15.6 mmol) was added to a mixture of Raney nickel (5 g), 2-propanol (20 mL), and one drop of concentrated aqueous HCl, which had been refluxed for 5 min. While being magnetically stirred, this reaction mixture was refluxed for an additional 33 min with the condenser open to the atmosphere. After cooling to room temperature, the organic layer was decanted from the Raney nickel, and the catalyst was washed with 2-propanol (3×15 mL). (Raney nickel, is paramagnetic and sticks to the magnetic stir bar, which facilitates the decantation.) The combined organic layers were filtered through Celite[®], and the 2-propanol was removed by rotatory evaporation followed by a high vacuum to give 1.95 g (96%) of a colorless liquid whose ¹H and ¹³C NMR spectra and the mass spectrum were identical to authentic 2-octanol.

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Transfer Hydrogenation of Ketones

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