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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: http://www.tandfonline.com/loi/lsyc20

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Version of record first published: 12 Mar 2010

To cite this article: Daniel R. Zuidema, Katherine J. Wert, Sarah L. Williams, Samuel T. Chill, Kimberly L. Holte, Nathanael K. Kokes & Robert C. Mebane (2010): Novel Method of Reducing Ketones Using Sodium Hydroxide in Isopropanol, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 40:8, 1187-1191

To link to this article: http://dx.doi.org/10.1080/00397910903061043

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Synthetic Communications[®], 40: 1187–1191, 2010 Copyright © Taylor & Francis Group, LLC ISSN: 0039-7911 print/1532-2432 online DOI: 10.1080/00397910903061043

NOVEL METHOD OF REDUCING KETONES USING SODIUM HYDROXIDE IN ISOPROPANOL

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Ketones are readily reduced to secondary alcohols with sodium hydroxide in refluxing isopropanol.

Keywords: Hydrogen transfer; ketone reduction; preparation of secondary alcohols; sodium hydroxide

The process of reducing a ketone to a secondary alcohol is a widely used and thoroughly studied synthetic technique.^[1–4] Conventional methods commonly used for the reduction of a ketone to a secondary alcohol include catalytic hydrogenation and metal hydride reduction. Another common method employed is the Meerwein– Ponndorf–Verley (MPV) reduction, which typically uses aluminum isopropoxide in isopropanol.^[5–7] Disadvantages to these methods include the flammability of hydrogen gas and metal hydride reagents and the expense of many of the catalysts. In the MPV reduction, removal of the aluminum salts can be tedious.

In this report, we describe an attractive alternative to the aforementioned methods that uses a solution of sodium hydroxide in isopropanol. The experimental procedure for this method of reduction is simple and straightforward and affords secondary alcohols in good yields. The overall reaction is described in Fig. 1, and a summary of our results is presented in Table 1. As seen in Table 1, isolated yields for the less volatile secondary alcohols were very good (entries 1, 3, 5, 9) but less so for the more volatile alcohols because of product loss while removing the isopropanol solvent by rotary evaporation. Surprisingly, no evidence of aldol condensation was observed for any of the ketones studied. In a typical run, the ketone was refluxed (container open to the atmosphere) in a magnetically stirred solution of sodium hydroxide in isopropanol. The progress of the reaction was conveniently monitored

Received February 11, 2009.

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Figure 1. Conversion of ketones to secondary alcohols by treatment with sodium hydroxide in refluxing isopropanol.

by gas chromatography–mass spectrometry (GC-MS). All of the secondary alcohols prepared in this study are known. Therefore, product identities were confirmed by comparison of NMR and mass spectral data with authentic samples or literature spectra.

To demonstrate that the presence of sodium hydroxide was indeed required, a control experiment was run in which acetophenone (12.5 mmol) was refluxed in isopropanol (50 mL) for 18.5 h (no sodium hydroxide added). No conversion to 1-phenylethanol was observed. By comparison, in the presence of sodium hydroxide (0.25 M), after 18.5 h of heating, well more than 50% conversion to 1-phenylethanol had been realized. This established that the presence of sodium hydroxide is necessary for the reduction to occur.

To verify that isopropanol was being converted to acetone in this redox reaction, an experiment was run in which benzophenone (1.2 mmol) was refluxed for 2 h in isopropanol (50 mL) that contained dissolved sodium hydroxide (1.2 mmol). A Dean–Stark trap was used to collect distillate over the course of the reaction. The distillate was tested for the presence of acetone by mixing several drops of a 3% solution of 2,4-dinitrophenylhydrazine with a few drops of distillate. The formation of a yellow precipitate suggested a positive test for the presence of acetone. Examination of the melting point of the precipitate revealed a melting point identical to that of acetone 2,4-dinitrophenylhydrazone (124.7–126.4 °C).^[8] One source has reported that this test easily detects 1 part of acetone in 500–1,000 parts of isopropanol.^[9]

Because we knew that the rate of a chemical reaction is often accelerated by microwave irradiation, due to superheating of the solvent,^[10,11] we decided to

Entry	Ketone	Secondary alcohol	Time (h)	Yield (%)
1	Benzophenone	Benzhydrol	27	90
2	Cyclohexanone	Cyclohexanol	22.5	71 ^{<i>a</i>}
3	4-t-Butylcyclohexanone	4-t-Butylcyclohexanol	22.5	95
4	2-t-Butylcyclohexanone	2-t-Butylcyclohexanol	20	0
5	2-Octanone	2-Octanol	22.5	97
6	3-Octanone	3-Octanol	26	71
7	Acetophenone	1-Phenylethanol	22.5	70^a
8	4'-Fluoroacetophenone	1-(4-Fluorophenyl)ethanol	26	65^{b}
9	4'-Methoxyacetophenone	1-(4-Methoxyphenyl)ethanol	26	85

 Table 1. Conversion of ketones to secondary alcohols by treatment with sodium hydroxide in refluxing isopropanol

^{*a*}Isolated yield was lowered because of the volatility of the alcohol.

^bNucleophilic aromatic substitution side products were observed in the product mixture.

explore the effect of microwave irradiation on the rate of this reduction reaction. In a typical procedure, a 10-mL, round-bottom flask was charged with 4.0 mL of a solution that was 0.25 M with respect to both the ketone and sodium hydroxide in isopropanol. Decane was present in a concentration of 0.175 M to serve as an internal standard for GC analysis. The flask was outfitted with a reflux condenser and irradiated in a modified 800-W Sharp household microwave oven. Isopropanol boils vigorously upon microwave irradiation. Thus, it was necessary to connect two reflux condensers in series to the top of the reaction flask. To accommodate this, a small hole was drilled in the top of the microwave oven. Simple tests revealed no leakage of microwave radiation through this hole. Also, to guard against burnout of the microwave oven, we placed a beaker of ice water on the microwave turntable and irradiated in 2-min increments. The progress of the reaction was followed by GC-MS. Because these reactions were run on a much smaller scale, isolated yields were not determined. Instead, percent conversions as measured by GC were determined. As seen in Table 2, the rate of secondary alcohol formation was significantly accelerated when the reaction was run in a household microwave oven. As was the case in the thermal reduction procedure, no evidence of aldol condensation was observed.

Again, we wished to demonstrate that sodium hydroxide was necessary for the microwave reduction to proceed. Thus, we set up a control experiment in which a 10-mL, round-bottom flask was charged with cyclohexanone (98 mg, 1.0 mmol) and 4.0 mL of isopropanol. Decane was present in a concentration of 0.175 M to serve as an internal standard for GC analysis. The flask was outfitted with a reflux condenser and irradiated in a modified 800-W Sharp household microwave oven. After 6 min of irradiation, no conversion to cyclohexanol was observed by GC. By comparison, in the presence of sodium hydroxide (0.25 M), after 6 min of irradiation, more than 50% conversion to cyclohexanol had been recognized.

In conclusion, ketones are readily reduced to secondary alcohols when refluxed in a solution of sodium hydroxide in isopropanol. This process is markedly accelerated when run in a conventional household microwave oven. This affords an attractive method of reducing ketones in that it offers cheap and readily available reagents, operational simplicity, easy workup, and high, clean product yields. The microwave procedure is easily adapted for laboratory use, and expensive commercial

Entry	Ketone	Secondary alcohol	Time (min)	Conversion (%)
1	Benzophenone	Benzhydrol	30	67
2	Cyclohexanone	Cyclohexanol	20	99
3	4- <i>t</i> -Butylcyclohexanone	4-t-Butylcyclohexanol	20	99
4	2- <i>t</i> -Butylcyclohexanone	2-t-Butylcyclohexanol	30	0
5	2-Octanone	2-Octanol	30	24
6	3-Octanone	3-Octanol	30	11
7	Acetophenone	1-Phenylethanol	30	79
8	4'-Fluoroacetophenone	1-(4-Fluorophenvl)ethanol	30	86
9	4'-Methoxyacetophenone	1-(4-Methoxyphenyl)ethanol	30	28

 Table 2. Conversion of ketones to secondary alcohols by treatment with sodium hydroxide in refluxing isopropanol under microwave conditions

microwave reactors are not necessary. Future work will elaborate on the scope of the reaction as to what other types of functional groups can be reduced by this method.

EXPERIMENTAL

¹H and ¹³C NMR spectra were recorded on a Jeol 400-MHz spectrometer using tetramethylsilane as an internal reference. Mass spectra were recorded on a ThermoElectron PolarisQ GC-MS. The NMR spectra and mass spectra of the alcohols prepared in this work were identical to authentic spectra.

As an illustrative example of the thermal reduction procedure, acetophenone (6.000 g, 49.94 mmol) was refluxed in a magnetically stirred solution of sodium hydroxide (1.989 g, 49.73 mmol) in isopropanol (200 mL) for 20.5 h with the condenser open to the atmosphere. After cooling to room temperature, the reaction mixture was partitioned between diethyl ether (200 mL) and water (100 mL). The layers were separated, and the organic layer was washed with water $(3 \times 100 \text{ mL})$ and brine $(1 \times 100 \text{ mL})$. The organic layer was dried with anhydrous magnesium sulfate and concentrated to yield an oil that was purified by vacuum distillation (4.294 g, 35.15 mmol, 70.38%) and whose spectral data (NMR, MS) were identical to those of authentic 1-phenylethanol. As an illustrative example of the microwave reduction procedure, cyclohexanone (98 mg, 1.0 mmol) and 4.0 mL of a solution of NaOH (0.25 M) in 2-propanol was charged to a 10-mL, round-bottom flask. Decane was present in a concentration of 0.175 M to serve as an internal standard for GC analysis. The flask was outfitted with a reflux condenser and irradiated in a modified 800-W Sharp household microwave oven. Complete conversion to cyclohexanol was observed by GC-MS after 20 min. The mass spectrum of the product was identical to the mass spectrum of authentic cyclohexanol.

ACKNOWLEDGMENTS

The authors gratefully acknowledge financial support from the Covenant College Kaleo Center, an NSF RSEC grant, Research Corporation, the University of Chattanooga Foundation, and the Grote Chemistry Fund.

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