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Glycerol as an alternative green medium for carbonyl compound reductions

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Abstract: Glycerol was employed as an alternative green reaction medium in various carbonyl reduction methodologies. The high polarity of glycerol allowed for the simple reduction of different carbonyl compounds with sodium borohydride and the enantioselective reduction of ethyl acetoacetate with both Ru-BINAP and baker's yeast. As a solvent, glycerol also allowed electro-reduction and microwave assisted reactions.

Keywords: Asymmetric hydrogenation; glycerol; green chemistry; metal hydride; reduction.

1. Introduction

Glycerol is the main by-product of oil and fat conversion in oleochemical production.[1,2] The increased production and use of fatty acid derivatives over the past decade in the food, cosmetics, and drugs industries and in the synthesis of biofuel, i.e., biodiesel, has led to a growth in the supply of glycerol and a subsequent dramatic decrease in its price.

Glycerol is a non-toxic, biodegradable, and recyclable liquid that is highly inert and stable, and compatible with many other non-toxic and non-irritating chemicals. These qualities make it ideal for use as a humectant, plasticizer, emollient, thickener, dispersing medium, lubricant, sweetener, bodying agent, antifreeze, and processing aid. Glycerol has been approved for food and drug use by many government agencies and is used as an ingredient or processing aid in cosmetics, toiletries, personal care, drugs, and food products. In addition, glycerol derivatives such as glycerol esters are also extensively used in many industries.

Glycerol is also a raw material in several chemical syntheses, including dendrimer and hyperbranched polyether and polyester production,[3] catalytic hydrogenolysis to propylene glycols, especially 1,3-propanediol, a high value chemical in the synthesis of polyesters,[4,5] and catalytic

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oxidation to form important compounds such as dihydroxyacetone and glyceraldehydes.[6] The use of glycerol as an energy source for microorganism fermenting systems, yielding ethanol and hydrogen, was also reported. However, whether employed as a reactant or as an additive, glycerol is usually used as a highly refined and purified product. And as the amounts of glycerol generated by the biodiesel industry continue to grow, it is vital that economical ways of utilizing it be explored to further defray the cost of biodiesel production.

We recently reported that glycerol's promising physical and chemical properties make it an ideal reaction medium for various catalytic and non-catalytic organic syntheses.[7,8] Specifically, it has a high boiling point and negligible vapor pressure, it is compatible with most organic and inorganic compounds, and it does not require special handling or storage. Similar to other polar organic solvents such as DMSO and DMF, glycerol facilitates the dissolution of inorganic salts, acids, and bases, and of enzymes and transition metal complexes. Furthermore, it also dissolves organic compounds that are poorly miscible in water and it is considered non-hazardous. Hydrophobic solvents such as ethers and hydrocarbons, which are immiscible in glycerol, enable the products to be removed by simple extraction. Additionally, the high boiling point of glycerol makes distillation of the products also a feasible separation technique. Finally, glycerol was successfully employed as a versatile and alternative green solvent in a variety of organic reactions and synthesis methodologies, in all of which high product conversions and selectivities were achieved.[7,8] In addition to the favorable solubilities of the reactants and the catalysts and the easy separation of the product in reactions with glycerol, its use also enabled transition metal complex recycling, microwave assisted reactions, and emulsion modes.
We report here on our investigation of the scope and limitations of glycerol as a solvent in the reductions of carbonyl compounds to their corresponding alcohols using various methods (Fig. 1).

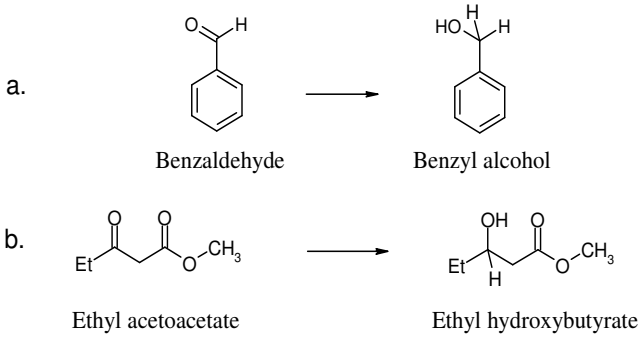


Figure 1. Representative reductions in glycerol: (a) benzaldehyde reduction to benzyl alcohol; (b) ethyl acetoacetate reduction to ethyl hydroxybutyrate

2. Results and Discussion

Carbonyl reduction is a fundamental organic transformation[9-11] done through a variety of synthetic procedures frequently used in the laboratory and in industry. Metal hydrides, and especially borohydrides, are cheap and simple reducing agents that can easily reduce many carbonyl compounds, producing characteristically high yields and selectivities. Although the addition of water is often essential to dissolve the metal hydride, the rapid and aggressive reaction of the hydride with water generates molecular hydrogen. The use of water by itself as the reaction medium, however, is limited because many organic compounds have low solubilities in water. Thus, an alcohol-water mixture, such as methanol or ethanol, is often used as the reduction medium. The product is usually separated by

first adding an acidic aqueous solution, which insures full decomposition of the hydride, and then extracting the product with hydrophobic organic solvents.

The reductions of both benzaldehyde (BA) and ethyl acetoacetate (EAA) in glycerol with sodium borohydride were performed under optimized condition, similar to those which are used when methanol or ethanol are the solvents of choice. The reductions were fast and selective yielding only benzyl alcohol and ethyl hydroxybutyrate respectively (Table 1, entry 1). The high boiling point and low volatility of glycerol prevented evaporation of the solvent during the reaction—a process that occurs in the cases of water, methanol, and ethanol—and as a result, the reaction required no cooling. Although glycerol could also be used as the proton donor (Table 1, entry 2), the addition of a non-concentrated acidic aqueous solution at the end of the reaction resulted in a higher product yield (Table 1, Entry 1). The products were easily removed by extraction with diethyl ether, which was then evaporated under reduced pressure. Other glycerol immiscible solvents such as dichloromethane and hexane can also be used.

Further studies of the effects of reaction time and sodium borohydride amount on product conversion showed that while reductions with borohydrides usually involved stoichiometrically excessive amounts, ethyl acetoacetate reduction in glycerol yielded full conversion even when the molar ratio of sodium borohydride to ethyl acetoacetate was 0.25, which is a stoichiometrically correct amount based on hydride (Table 2, entries 1-4). In addition, it was found that ethyl hydroxybutyrate was the only detected product under all tested conditions. Table 2 also shows that aromatic aldehyde (entries 5 and 6), aromatic ketone (entry 7), and cyclic ketone (entry 8) were all very active. The reductions of aliphatic ketones were, as expected, much slower (entries 9-12). In all the reduction only the corresponding alcohol was detected.

Table 1. Comparison of carbonyl compound reducing methodologies in glycerol[1]

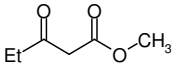
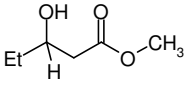
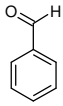
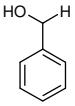
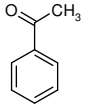
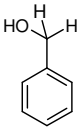
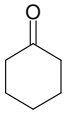
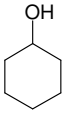
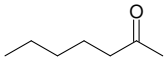
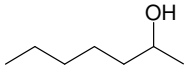
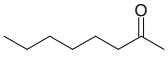
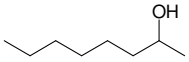
Entry	Catalyst (amount, g)	Reducing Agent (amount, g)	t (h)	Temp. (°C)	BA Conv. (%)	EAA Conv. (%)
1	-	$NaBH_4$ (0.3)	1.5	25	100[2]	100[2]
2	-	$NaBH_4$ (0.1)	1.5	25	23[3]	36[3]
3	-	$LiAlH_4$ (0.3)	10	40	65	30
4	Pd/C (0.05)	H_2 (60 atm)	5	60	52	60
5	$RuCl_2(TPPTS)_3$/ $RhCl_2(TPPTS)_3$ (0.05)	H_2 (60 atm)	5	60	0	0
6	(*S*)-Ru-BINAP (0.08)	H_2 (60 atm)	5	60	-	7 (99)[4]
7	Free baker's yeast (10)[5]	Glucose (5)	48	34	-	74 (99)[4]
7	Immobilized baker's yeast (10)[5]	Glucose (5)	48	34	-	100 (99)[4]

[1] Reaction conditions: 10 mL glycerol, 1 g substrate.
[2] After quenching with dilute acid.
[3] Without quenching .
[4] Enantiomeric excess for (*S*)-MHB.
[5] 50 mL Glycerol.

Another powerful reduction agent is lithium aluminium hydride. In addition to carbonyl compounds, it can also reduce carboxylic acids and their corresponding esters. The reduction with lithium aluminium hydride is usually performed in ether or THF, and since it reacts violently even with trace amounts of water, increasing the chances of an explosion, the solvent has to be completely dried. In contrast, the small scale reductions of both benzaldehyde and ethyl acetoacetate with lithium

aluminium hydride in glycerol (Table 1, entry 3) do not require pre-treatment to avoid explosion, and hydrogen was not rapidly formed. Yet, when ethyl acetoacetate was used as the substrate, selectivity to the hydroxy-ester was full, meaning that lithium aluminium hydride does not reduce esters in glycerol as it does in both ether and in THF. The reduction of other esters, amides, and carboxylic acids with lithium aluminium hydride in glycerol produced only negligible amounts of product. It is very important to note that although using lithium aluminium hydride in glycerol in small scale did not result in explosion it should be handled under high precaution as it is violently reacts with water, including atmospheric moisture. In addition a thermodynamic analysis of lithium aluminium hydride in glycerol should be carefully done if it is intended to be used in larger scale.

Table 2. Reductions of carbonyl compounds with sodium borohydride in glycerol[1]

Entry	Substrate	Product	Molar ratio ($NaBH_4$/substrate)	t (h)	Conversion (%)
1			1.25	0.5	100
2			1	0.5	100
3			0.5	0.5	100
4			0.25	0.5	97
5			1	0.5	75
6			1	1	100
7			1	0.5	100
8			1	0.5	80
9			1	0.5	4
10			1	1.5	12
11			1	0.5	7
12			1	1.5	18

[1] Reaction conditions: 10 mL glycerol, 25 °C,1 g substrate

Catalytic hydrogenation, with molecular hydrogen as the reducing agent and homogeneous or heterogeneous metal catalysts, is another common route for reducing carbonyl compounds.[12] Although synthesis along this pathway is substantially cleaner, it usually requires high hydrogen pressures, and as such, special equipment and procedures must be used. Employing molecular hydrogen and Pd/C as the catalyst under typical conditions adopted from literature[10,11] produced benzyl alcohol and ethyl hydroxybutyrate in moderate yields (Table 1, entry 4), but the reaction rate was lower than that in methanol or toluene, most likely because the hydrogen was less soluble in the viscous glycerol mixture. Other supported metal catalysts, such as Pt/C, Ru/C, and Pd/Al_2O_3, showed similar conversions. Again, the product was easily separated by extraction and the catalyst was successfully recycled.

Using simple ruthenium or rhodium complexes [$RuCl_2(TPPTS)_3$ and $RhCl_2(TPPTS)_3$] in glycerol did not yield any product (Table 1, entry 5), and it was hypothesized that the glycerol may have dissociated to the ruthenium complex, thereby deactivating the complex. In contrast, employing

Noyori's Ru-(*S*)-BINAP complex in the asymmetric reduction of ethyl acetoacetate under typical conditions[13] resulted in small amounts of pure (*S*)-ethyl hydroxybutyrate enantiomer (Table 1, entry 6). It was previously reported that Ru-(*S*)-BINAP worked in alcoholic solvents and that the solvent was also used as the proton donor in the catalytic cycle.[13] However, although Ru-(*S*)-BINAP dissolved easily in glycerol, required no previous modification as in water, and was fully retained in the glycerol phase after extraction of the product with diethyl ether, its low catalytic activity in glycerol make this route less practical for asymmetric hydrogenation.

Asymmetric reduction is an important transformation in the synthesis of enantiopure compounds, a process that, in turn, plays an important role in the synthesis of fine and special chemicals. [15] The enantioselective reduction of ethyl acetoacetate as a representative β-ketoester is also obtainable through biocatalysis under mild temperature.[8] Although either whole cell or purified enzymes can be used with different hydrogen sources, the whole cell method is easier, cheaper, and does not require the addition of a co-factor and its recycling.[15] Though water is the first solvent of choice for biocatalysis, the low solubility of organic compounds in water, difficult product separation, and potential side reactions caused by other enzymes in the cell have led to alternative solvents being sought. A green alternative, glycerol, which can dissolve glucose and ethyl acetoacetate and suspend baker's yeast, produced a high product yield and >99% enantioselectivity when either free or immobilized cells were employed (Table 1, entries 7 and 8, respectively).

Another green method for reducing organic molecules is electro-reduction. Electrochemistry in a non-aqueous polar organic solvent is widely applicable in organic synthesis.[16] Glycerol, like ethanol, was hypothesized to function well in electrochemistry, but it can dissolve a variety of salts at relatively high loading. The electro-reduction of benzaldehyde in glycerol resulted in 62% conversion of the aldehyde (Figure 2). As expected, several other, undesired products were also detected.

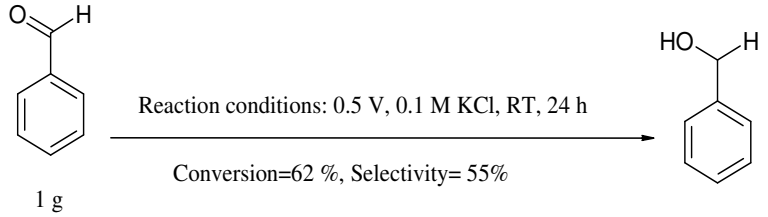


Figure 2. Electro-reduction of benzaldehyde in glycerol

Finally, benzaldehyde can also be fully reduced to toluene with hydrazine in basic conditions via the Wolff-Kishner reaction. Although usually conducted at elevated temperatures (about 200 °C) for hours, it can also be performed under microwave irradiation at lower temperatures and in much shorter times. As noted above a solvent is also utilized to transport heat. In microwave assisted heating, solvent selection is even more crucial. Microwave heating has many applications in organic synthesis as it is clean and it substantially reduces reaction times. Microwave promoted organic synthesis is based on the ability of a solvent to absorb microwave energy and convert it into heat, an ability that increases with increasing dielectric constants. Therefore, glycerol's high dielectric constant and high boiling point make it an attractive solvent. The microwave assisted reduction of benzaldehyde to toluene was performed in two steps using a conventional microwave oven. First, benzaldehyde and hydrazine were dissolved in glycerol and heated in the microwave oven for 5 min from room temperature to about 110 °C. Then the reaction mixture was cooled to room temperature in an ice bath, and KOH was added. Finally, the mixture was again heated for 5 min in the microwave oven. The reaction conversion was complete after 10 min in the microwave. Again, the product was easily separated by extraction with diethyl ether and evaporation of the solvent under reduced pressure.

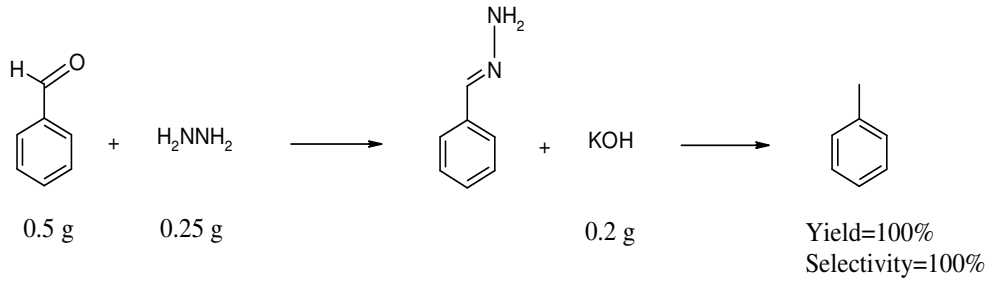


Figure 3. Wolff-Kishner reduction of benzaldehyde to toluene in glycerol

3. Conclusions

Glycerol was successfully employed as an environmentally friendly solvent in the reductions of benzaldehyde and ethyl acetoacetate with various reduction agents. It seems that the high polarity of glycerol enabled simple reduction with sodium borohydride followed by easy separation of the product. Enantioselective reductions of ethyl acetoacetate in glycerol were also performed with both baker's yeast and Ru-BINAP. Glycerol was also applicable in electro-reduction and microwave assisted reactions.

4. Experimental

All chemicals were purchased from Sigma-Aldrich except glycerol, which was purchased from Frutarom Ltd. (99.5% and 96% purity).

4.1 Metal hydride reductions

CAUTIONS: *It is very important to note that although using lithium aluminium hydride in glycerol in small scale did not result in explosion it should be handled under high* **precaution** *as it is violently reacts with water, including atmospheric moisture. In addition a thermodynamic analysis of lithium aluminium hydride in glycerol should be carefully done if it is intended to be used in larger scale.*

In a typical reduction with sodium borohydride ($NaBH_4$), 1 g of substrate and 10 mL of glycerol were added to a 25-mL vessel and mixed for 5 min. The corresponding (typically stoichiometric) amount of sodium borohydride was then added to the reaction mixture, which was then mixed. At the end of the reaction, 2 mL of 0.5 N H_2SO_4 aqueous solution were added to ensure borohydride decomposition, and the product was separated by extraction with 3*10 mL of diethyl ether.

When lithium aluminium hydride ($LiAlH_4$) was used instead of sodium borohydride, the metal hydride was first suspended in 10 mL of glycerol for 30 min. Then the substrate was added and the reaction was mixed at 60 °C under reflux for 10 h. Product separation was similar to the procedure used with sodium borohydride.

4.2 Catalytic hydrogenations

For the catalytic hydrogenations of benzaldehyde and ethyl acetoacetate, the metal complexes ($Ru(TPPTS)_3Cl_2$ and $Rh(TPPTS)_3Cl_2$, TPPTS=tris-(3-sulfophenyl)-phosphine trisodium salt, and Ru-(S)-BINAP) were dissolved in 10 mL glycerol in a 20-mL homemade stainless steel reactor, only after which was the substrate added. In reactions with a heterogeneous catalyst (Pd/C, Ru/C, etc.), substrates and catalyst were added together and mixed. Then the reactor was pressurized with molecular hydrogen to 60 bar and heated to 60 °C in an oil both. After the pressure was released and the reaction mixture was cooled, the product was separated by extraction with 3*10 mL of diethyl ether.

4.3 Asymmetric reduction with baker's yeast

Ethyl acetoacetate was asymmetrically reduced with both free and immobilized baker's yeast in glycerol. First, 10 g of free yeast (SIGMA, type II) or 50 g of immobilized yeast (prepared from 10 g of free cells[9]) was added to 50 mL of glycerol in a 250-mL bottle and then shaken for 30 min. Then, 5 g of sucrose was added and the bottle was shaken for another 10 min before 1 g of ethyl acetoacetate was added. Finally, the bottle was shaken at 300 rpm for 48 h at 37 °C. At the end of the reaction, the product was extracted with diethyl ether (3*50 mL).

4.4 Electro-reduction

The electro-reduction of benzaldehyde was performed in a closed, 25-mL glass vessel at room temperature. First, 1g of benzaldehyde was added to a 10 mL solution of 0.1 M KCl in glycerol. Then, a potential of 0.5V was applied for 24 h between platinum and zinc foils (4 cm^2 area), which functioned as electrodes. The product was extracted with 3*10 mL of diethyl ether at the end of the reaction.

4.5 Wolff-Kishner reduction

The microwave assisted Wolff-Kishner reaction was conducted in a domestic microwave (Crystal WP900, 900W) in a glass vessel that was closed with a watch glass and kept at atmospheric pressure. In the first step, 0.5 g benzaldehyde and 0.25 g hydrazine were dissolved in 10 mL glycerol in a 50-mL vessel. The mixture was heated in the microwave oven for 5 min from room temperature to about 90 °C. Then, the reaction mixture was cooled to room temperature in an ice bath. In the second step, 0.2 g of KOH was added and the mixture was heated again for 5 min in the microwave oven. The product was extracted with 3*10 mL of diethyl ether at the end of the reaction.

All products and substrates were analyzed by GC using an HP-1 column to determine the conversion of the reaction, while enantiomeric excess was detected by GC analysis using an Astec Chiraldex G-TA chiral column.

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