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RESEARCH LETTER

Glycerol derivatives as green reaction mediums

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Representative glycerol derivatives were employed as green solvents for selected organic transformations. In all reactions it was found that both reaction performance and product extraction yields were affected by solvent type and polarity. The solubility of the substrates in the solvent was the key step in product yield determination, while the product solubility in the reaction solvent determined the effectiveness of its extraction.

Keywords: glycerol; glycerol derivatives; green solvent; nucleophilic substitution; Suzuki cross-coupling; asymmetric reduction

Introduction

Organic chemistry is traditionally carried out in solution to bring reactants and catalysts together to deliver mass, heat, and momentum. As solvents are responsible for a large part of the waste and pollution generated by chemical processes, a key factor to enabling a sustainable chemical process is solvent selection (1, 2).

The choice of a reaction solvent depends on its chemical, physical, and biological properties. Besides the solubilities of reactants (gases, liquids, and solids) and catalysts, solvent characteristics also affect reaction performance and as such, dictate the most effective separation method for product recovery (1, 2). Safety and the environment are also primary concerns in the selection of a solvent. Using a biodegradable solvent from a renewable resource such as plants is preferable. In addition, the chosen solvent should have minimal volatility and it should be chemically and physically stable, recyclable, and reusable.

The majority of chemical processes have traditionally employed petrochemical solvents, but these have severe implications for the environment. Hence, the search for environmentally friendly reaction media is of primary concern. In the past two decades, a variety of environmentally benign solvent alternatives have been proposed including water, ionic liquids (3), fluorous solvents (4), and supercritical fluids (5). However, their implementation in

industrial processes is still limited to few examples due to operational restrictions and high cost.

Several years ago, we reported for the first time on the use of glycerol as a reaction medium in both catalytic and non-catalytic organic syntheses (6). Since then, glycerol has been successfully employed as a green solvent in a wide variety of organic reactions and synthesis methodologies (7–10), showing its versatility as a solvent for organic synthesis, as was recently reviewed in two papers (11, 12). Glycerol's physical and chemical properties – it is non-volatile, non-hazardous, recyclable and biodegradable, compatible with most organic and inorganic compounds, and it does not require special handling or storage – hint at its promise as a sustainable solvent for organic reactions. In many reactions, the presence of glycerol as a solvent improved product yields and selectivities and enabled catalyst recycling, emulsion-like systems, and non-conventional heating such as in the microwave-assisted reaction (13–15).

Despite glycerol's promise as a sustainable solvent for liquid phase catalytic and non-catalytic organic syntheses, several obstacles to its utilization, including its high viscosity and the low solubility of highly hydrophobic compounds and gases in glycerol, are preventing its adoption at the industrial scale.

In an effort to design a viable protocol that will facilitate the acceptance of glycerol-based compounds as sustainable solvents, representative glycerol derivatives were used as green solvents. Three representative

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reactions were investigated: nucleophilic substitution of benzyl halides (Figure 1(a)), Suzuki cross-coupling of iodobenzene and phenylboronic acid (Figure 1(b)), and baker's yeast catalyzed asymmetric reduction of carbonyl compounds (Figure 1(c)). The effects of solvent type on reaction performance and on product extraction yield were examined.

Results and discussion

The drawbacks outlined above for using glycerol as a solvent can be overcome by the synthesis of a glycerol-based family of solvents whose properties can be tailored, tuned, and adjusted according to the requirement of each reaction and separation. Glycerol derivatives have divergent properties to the parent glycerol because of their different structural and functional groups. These characteristics affect both the viscosity of the solvent and the solubility of the chemical compounds within the solvent and, hence, they can increase the solubility of glycerol immiscible compounds and thereby improve reaction performance. In addition, in certain cases altering the functional/structural groups of the glycerol molecule can also facilitate simpler and more efficient product isolation and catalyst separation.

Glycerol has three hydroxyl groups and it represents a versatile opportunity to produce various glycerol derivatives that can be used as solvents (Figure 2). The elimination of each hydroxyl group of glycerol by hydrogenolysis can be used to yield 1,3-propanediol and 1,2-propanediol, which are less polar and less viscous solvents (16). Furthermore, each hydroxyl group of glycerol or of the two synthesized propanediols, alone or together, can be transferred into various ether groups (17). For example, 1,3-

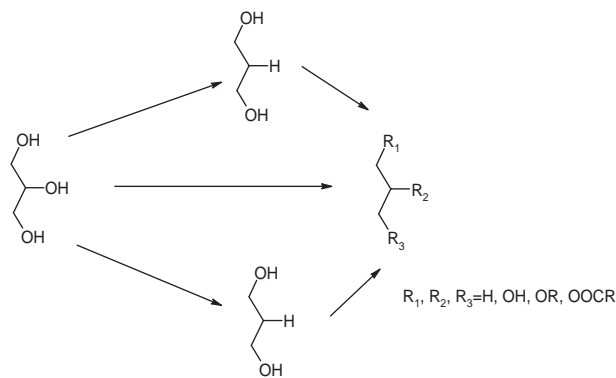


Figure 2. Glycerol-based solvents.

dialkoxy-2-propanols and 1,2,3-trialkoxypyrpanes were synthesized by either a symmetrical or an unsymmetrical epoxide ring opening reaction comprising commercially available glycidyl ethers with alcohols. In addition, glycerol mono-, di-, or tri-esters can be synthesized from glycerol by catalytic esterification or transesterification (18). However, the environmental impact and economical viability of the synthesis process of these glycerol-based solvents should also be considered before their utilization.

As previously mentioned, the key property of a reaction solvent is its solvation capability. A solvent should facilitate the combination of reactants and catalysts. Moreover, many organic reactions also require that salts and organic compounds or hydrophilic and hydrophobic molecules be dissolved simultaneously. In addition, the solubility of the reaction product in the reaction medium and the nature of the solvent also dictate separation technique. The nature of a solvent, in terms of its microscopic and macroscopic properties, is difficult to represent by a single parameter. As reaction performance and the procedure for product isolation depend mainly on the relative solubilities of reactants, catalysts, and products in the reaction solvent, the polarity of the solvent can be used as a valuable representative measurement for solvent comparison. Solvent polarity can be calculated by various empirical and theoretical methods representing physical and chemical properties of the solvent, intermolecular forces, and solute-solvent interactions (19).

Catalyst-free nucleophilic substitution of benzyl halides with different salts (20) was employed as the first example of organic transformation in glycerol-based solvents (Figure 1(a)). This reaction requires the dissolution of a non-polar organic compound and a polar ionic salt together and, thus, the polarity of the reaction medium is expected to be an influence. The investigation began by testing the yields of benzyl acetate in the nucleophilic substitution of benzyl

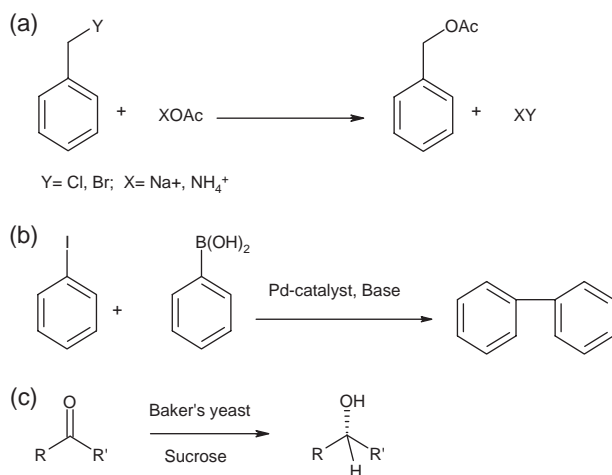


Figure 1. Representative reactions.

chloride and bromide with sodium and ammonium acetate in glycerol, 1, 2 propanediol, glycerol diacetate (diacetin), and glycerol triacetate (triacetin) (Table 1). As expected, increasing the polarity of the solvent as illustrated by decrease in LogP (the logarithm of the partition coefficient of each solvent between octanol and water) increased the product yield. This result is likely attributable to the fact that in order to facilitate the substitution, the salt has to split into ions, a phenomenon that increases in a more polar solvent. Likewise, the negligible reaction in triacetin, which is hydrophobic, can be explained. As illustrated in Table 1, benzyl bromide exhibits higher activity than benzyl chloride in all the tested solvents, as it is the more active of the two in substitution reactions. In addition, replacing sodium acetate with ammonium acetate produced higher yields in glycerol and lower yields in the other solvents, an outcome that may have resulted from the lower ionization power of ammonium acetate due to the higher ionic radius of the ammonium ion. It is important to mention that extraction of the reaction mixture at the end of the reaction to determine the product yield resulted also in extraction of residual substrate and traces of solvent.

Finally, the effect of solvent polarity on product extraction yield was also studied by extracting a mixture of neat benzyl acetate in each solvent (even in solvents that yielded low or negligible product yields) with the same amount of petroleum ether following by the evaporation of the extraction solvent under reduced pressure (Table 1). It can be seen that the solvent polarity also affected the extraction yield of benzyl acetate, which increased with the polarity of the solvent. This result is probably because the product, benzyl acetate, is non-polar and as such it prefers the hydrophobic petroleum ether phase over the more polar reaction solvent.

Cross-coupling reaction that utilizes palladium catalysts is a versatile tool for C–C bond formation and, recently, its inventors were awarded the Noble

Prize in chemistry (15, 21, 22). In these reactions, usually an organic polar solvent in a single homogeneous phase is used to dissolve together polar and apolar organic substrates with a strong inorganic base, which activates the reaction and a palladium complex. Here, the Suzuki cross-coupling of iodobenzene and phenylboronic acid (Figure 1(b)) was performed in representative glycerol-based solvents (Table 2). While the more polar glycerol easily dissolved phenylboronic acid and the inorganic base, more hydrophobic glycerol derivatives were expected to increase the solubilities of apolar organic compounds such as iodobenzene. As can be seen from the results in Table 2, the polarity of the glycerol derivative affected the yield of the reaction product, biphenyl, when both homogenous and heterogeneous palladium catalysts were used. It was found that the reaction in 1,2-propandiol resulted in the highest product yield, indicating that the average polarity of this solvent optimally dissolved all reaction components. The extraction yield of biphenyl was also tested by addition of neat biphenyl to each solvent and extraction with petroleum ether and was found to be affected by the polarity of the reaction solvent and the highest extraction yield was determined for glycerol, probably as the product is not polar at all.

The last tested reaction in glycerol derivatives was the asymmetric reduction of prochiral carbonyl compounds using baker's yeast as catalyst and glucose as hydrogen source (Figure 1(c)) (23–26). The asymmetric reduction of β -ketoesters to their corresponding chiral β -hydroxy esters was extensively studied with free and immobilized baker's yeast (FBY and IBY, correspondingly). Though water is the first solvent of choice for biocatalysis, the low solubilities of many organic molecules in water, the existence of undesired side reactions such as hydrolysis, and a difficult product separation procedure limit its application. Different organic solvents were tested for this purpose (23), but organic solvents not only have negative environmental impacts, they also affect yeast

Table 1. Nucleophilic substitution in representative glycerol-based solvents.^a

Solvent	LogP	Product yield (%)			Product extraction yield (%) ^b
		Benzyl chloride + sodium acetate	Benzyl bromide + sodium acetate	Benzyl chloride + ammonium acetate	
Glycerol	−4.15	63	87	100	94
1,2-Propanediol	−0.92	38	71	18.6	85
Diacetin	−0.64	33	60	2	45
Triacetin	0.25	0	0	0	23

^aReaction conditions: 0.7 mmol benzyl halide, 0.77 mmol salt, 5 mL solvent, 80°C, 1 h.

^bExtraction conditions: R.T., 0.5 g phenyl acetate, 5 mL petroleum ether.

Table 2. Suzuki cross-coupling of iodobenzene and phenylboronic acid in representative glycerol-based solvents.^a

Solvent	LogP	Product yield (%) 5% Pd/C	Product yield (%) Pd(OAc) ₂	Product extraction yield (%) ^b
Glycerol	−4.15	95	90	100
1,2-Propanediol	−0.92	100	100	81
Diacetin	−0.64	83	79	87
Triacetin	0.25	73	70	95

^aReaction conditions: 0.7 mmol iodobenzene, 0.84 mmol phenylboronic acid, 10 μmol palladium, 0.77 mmol sodium carbonate, 5 mL solvent, 80°C, 2.5 h.

^bExtraction conditions: R.T., 0.5 g biphenyl, 5 mL petroleum ether.

cell viability (26). We recently found that glycerol makes an ideal green reaction medium for asymmetric reduction, yielding activity and enantioselectivity comparable to those of water (24, 25). Therefore, we tested the performances of six representative glycerol derivatives and compared them with glycerol and water in terms of yeast cell viability and catalytic performance in the reduction of ethyl acetoacetate (EAA, Table 3, entries 2–8).

Cell viability was determined by plate counts of several samples that were taken from the fermentation mixture at different times. As illustrated in Figure 3, cell growth was significantly affected by exposure to the various organic solvents, and a correspondingly dramatic decrease in viability (about 100%) was observed after several minutes in the more polar glycerol derivatives, glycerol, 1,2- and 1,3-propanediol, and diacetin, while the more hydrophobic glycerol derivatives somewhat preserved cell viability: up to 48 h in triacetin and up to 4 h in glycerol tributyrate and glycerol diglycidyl ether. The negligible viability in the more polar solvents after short times can be explained by the high osmotic pressure that was imposed on the cell by the solvents,

which caused water to diffuse out of the cells, a process that may dry the cells thereby affecting their viability.

As illustrated in Table 3 (entries 1–8), solvent polarity also affected the reaction conversion; however, enantioselectivity was above 97% in all solvents. The reaction in water yielded the most product, while the reactions in glycerol, glycerol diglycidyl ether, triacetin, and glycerol tributyrate yielded almost similar amounts of product. In contrast, the reactions in both propanediols and in glycerol-diacetate produced surprisingly negligible yields.

Finally, replacing EAA with 2-heptanone, which is poorly miscible in both water and glycerol but fully miscible in triacetin, shows the effect of the relative polarities of the solvent and the substrate on catalytic performance (Table 3, entries 9–11). The yield of (*S*)-2-heptanol in triacetin was 50% higher than in water and over 150% higher than in glycerol.

Experimental

All chemicals were purchased from Aldrich.

Table 3. Comparison of the asymmetric reduction of EAA in water and glycerol derivatives.^a

Entry	LogP	Solvent	Conversion (%)	Ee (%)
1	—	Water	74	>99
2	−4.15	Glycerol	45	>99
3	−0.92	1,2-Propanediol	0	0
4	−1.00	1,3-Propanediol	0	0
5	n.a.	Glycerol diglycidyl ether	54	97
6	−0.64	Diacetin	0	0
7	0.25	Triacetin	52	97
8	3.31	Glycerol tributyrate	50	98
9 ^b	—	Water	20	>99
10 ^b	−4.15	Glycerol	8.8	97
11 ^b	0.25	Triacetin	30	97

^aReaction conditions: 35 mL solvent, 16 g IBY, 5 mmol ethyl acetoacetate, 3.5 g glucose, 37°C, 48 h.

^b5 mmol 2-heptanone, 72 h.

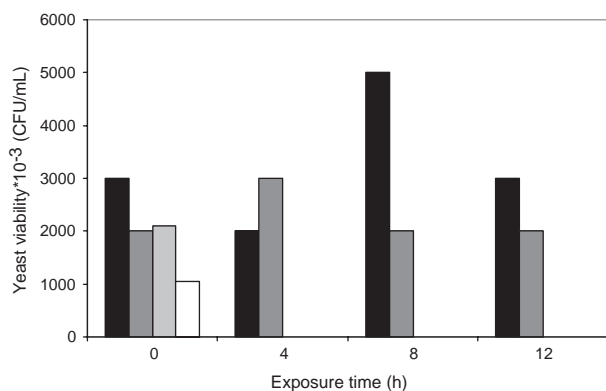


Figure 3. Comparison of free baker's yeast viability in glycerol-based solvents and water: water-black, triacetin-dark gray, glycerol tributyrat-light gray, glycerol diglycidyl ether-white.

Nucleophilic substitution

In a typical nucleophilic substitution procedure, 0.70 mmol of benzyl halide and the corresponding amount of salt (0.77 mmol) were added together to 5 mL of solvent. After mixing, the reaction mixture was heated in an oil bath to the required temperature (80°C). The reactions ran for 1 h and the mixtures were then allowed to cool. The product was separated after cooling by extraction with 2 mL of petroleum ether. The organic phase was concentrated under reduced pressure, and to determine product yield, the resulting crude was analyzed by gas chromatography (GC) using an HP-1 column.

Extraction experiments were performed by mixing 5 mL of each solvent, which contained 0.5 g of benzyl acetate with 5 mL of petroleum ether as extraction solvent. The extracting solvent was then evaporated under reduced pressure and the resulting product extraction yield was calculated.

Suzuki cross-coupling

A Suzuki cross-coupling procedure typically involved adding 10 μ mol of palladium acetate or the corresponding amount of 5% Pd/C to a vial containing 5 mL solvent including 0.5 mmol of iodobenzene, 0.6 mmol of phenylboronic acid, and 0.6 mmol of sodium carbonate. The mixture was placed in a preheated oil bath at 80°C and magnetically stirred for 2.5 h. At the end of the reaction, the mixture was cooled and extracted with 2 mL of petroleum ether. The organic phase was concentrated under reduced pressure and the resulting crude was analyzed to determine conversion by GC using an HP-1 column.

Extraction experiments were performed by mixing 5 mL of each solvent, which contained 0.5 g of biphenyl with 5 mL of petroleum ether as extraction

solvent. The extracting solvent was then evaporated under reduced pressure and the resulting product extraction yield was calculated.

Asymmetric reduction

The typical procedure for asymmetric reduction entailed adding 16 g of immobilized baker's yeast (IBY) [prepared from 3.33 g of free baker's yeast (FBY, SIGMA-type II) as described by Buque et al. (27)] to 35 mL of solvent in a 100-mL Erlenmeyer and shaking for 30 min (300 rpm, 34°C). Then 3.5 g of glucose was added and the Erlenmeyer was shaken for an additional 10 min before 5 mmol of ethyl acetoacetate (EAA) or 2-heptanone was added and the reaction mixture was shaken at 300 rpm and 37°C for 48 h and 72 h, respectively. At the end of the reaction the product was extracted with petroleum ether in three steps (3×10 mL). The conversion and the enantiomeric excess of the products were determined by GC analysis with Astec, Chiraldex G-TA[®] (30 m \times 0.25 mm, 0.25 μ m thickness).

Viability measurement

FBY viability was determined by plate counting after their exposure to glycerol, to glycerol derivatives, and to water as reference for different times. The cells were plated onto agar plates after dilution in water and incubated for 96 h at 30°C.

Conclusions

Glycerol derivatives were employed as green reaction mediums for representative organic transformations. Reaction performance was affected by the type and the polarity of the solvent in all reactions, but substrate solubility in the solvent was the key parameter. On the other hand, the solubility of the product in the reaction solvent determined the effectiveness of its extraction.

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