

Glycerol-derived solvents: Synthesis and Properties of symmetric glyceryl diethers

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ABSTRACT

Herein we report a systematic study of the synthesis of symmetric glyceryl diethers from epichlorohydrin and different alcohols. Several inexpensive alkaline hydroxides were tested and total conversions of epichlorohydrin achieved. Although high yields of the desired products were possible, the final selectivity of the reaction depends strongly on the alcohol used. Eleven symmetric glyceryl diethers were prepared employing this synthetic methodology and, in order to determine their usefulness as solvents, their physicochemical properties (density, dielectric permittivity, refractive index, viscosity, surface tension and boiling point) were measured and compared with those for similar conventional solvents. The results obtained prove the utility of these compounds as a green alternative to solvents obtained from non-renewable sources.

INTRODUCTION

In the recent years, Green Chemistry has become an important consideration when designing new synthetic chemical processes. Most industrial chemical processes and product formulations rely on the use of conventional organic solvents. However, it is known that such solvents come from non-renewable petrochemical sources, and sometimes present serious drawbacks, such as ecotoxicity, flammability and volatility. When Paul Anastas and John Warner, the “fathers” of Green Chemistry, enunciated their “12 Green Principles”, they stated the need to avoid the use of solvents, which is quite difficult in the majority of chemical processes, or to use benign solvents as far as possible.¹ These alternative solvents should present some favorable properties such as biodegradability, availability from renewable sources and low toxicity, volatility, flammability and cost.

Oils appear to be a readily available renewable raw biomaterial²⁻⁴ that can provide fatty esters or acids and glycerol. Glycerol is normally produced as a by-product in the oleochemical industry and its valorization is an important issue⁵ from a circular economy point of view. As such, the use of glycerol and its derivatives as possible renewable solvents has attracted great attention.⁶⁻
¹⁰ Carbonates, ketals, esters and ethers derived from glycerol have already been used in many different applications as fuel additives, humectants, plasticizers, surfactants, etc.,¹¹ and of these, glyceryl ethers present very interesting properties as alternative solvents due to their chemical stability, moderate reactivity, low acute ecotoxicity¹²⁻¹⁴ and tunable physicochemical properties, which can be modified simply by changing the number, size, substitution and nature of their substituents.¹⁵⁻¹⁹

Various attempts to design effective synthetic methodologies for glycerol-derived ethers have been reported to date. Thus, in 2015 Lemaire et al. reviewed all the different approaches for the production of glyceryl ethers.²⁰ The *a priori* easiest synthetic strategy, starting from glycerol, usually suffers from the drawback of providing low product selectivities,^{21,22} with mixtures of mono-, di- and triethers being obtained in variable proportions. Some attempts have been made to solve this problem by using Lewis acid catalysts in the reaction of glycerol with short alkyl alcohols. In this work, glyceryl monoethers are obtained as the major products in a maximum yield of 60%.²³ Despite being the most attractive option, the low selectivity reduces the practical interest of this approach for producing diethers. However, glycerol is easily transformed into platform molecules with high yields even on an industrial scale, and these molecules are attractive intermediates in the synthesis of glycerol derivatives with higher selectivity. Some of these molecules, which are produced in high amounts by the chemical industry, are glycidol (2,3-epoxy-1-propanol), 3-chloropropane-1,2-diol and epichlorohydrin (1-chloro-2,3-epoxypropane).

In general, glycidol or 3-chloropropane-1,2-diol are used for the synthesis of glyceryl monoethers (GMEs). To date, the most effective methodology for the synthesis of glyceryl monoethers with high yields involves reaction of the appropriate platform molecule with the corresponding alkoxide formed from the desired alcohol and metallic sodium.¹⁵ However, use of this reagent goes against some of the key principles of Green Chemistry as regards the safety of the process, its toxicity and the generation of unnecessary residues. Over the past two years, three interesting papers have been published concerning the synthesis of GMEs from glycidol.²⁴⁻²⁶ These studies described the production of GMEs in high yields and with high selectivity.

When the synthesis of glyceryl symmetric diethers (GDEs) is envisaged, the use of epichlorohydrin as building block is preferred as this platform molecule is now readily available thanks to the new Solvay synthesis.²⁷ Of the few studies dealing with the synthesis of GDEs, the most relevant results involve the use of NaH at high temperature (100 °C) or several reaction steps.²⁰

Herein we present a readily effective methodology for the synthesis of symmetric glyceryl diethers [R.O.R] starting from epichlorohydrin and different alcohols, thereby avoiding the use of other hazardous reagents, such as sodium, or an excess of epichlorohydrin or any additional co-solvent.

As mentioned above, the main aim of this research was to provide an environmentally suitable alternative to conventional solvents, therefore the main physicochemical properties of symmetric glyceryl ethers are also reported and compared with those for traditional solvents, thus making selection of the alternative glycerol-derived solvent easier.

EXPERIMENTAL SECTION

All products were characterized by ^1H , ^{13}C , and ^{19}F NMR spectroscopy, and by HRMS. Gas chromatography analyses were carried out using an HP 7890 Series II gas chromatograph equipped with a FID detector and a Zebron ZB-5HT Inferno column (30 m \times 0.25 mm \times 0.25 μm). NMR spectra (DMSO- d_6 , δ ppm, J Hz) were obtained using a Bruker AV-400 instrument with TMS as standard. MS spectra were obtained using a Bruker MicroTof-Q spectrometer with electrospray ionization.

Epichlorohydrin, diglyme, anisole, octanol, and LiOH were purchased from Sigma–Aldrich. Methanol, ethanol, isopropanol, KOH and NaOH were purchased from Scharlab. 1-Butanol, trifluoroethanol (TFE), 1-hexanol, 2-ethylhexan-1-ol, and phenol were purchased from Alfa Aesar, and 1-propanol and 1-pentanol from Acros. Alcohols were dried by refluxing over calcium hydride and distilled prior to use. The purity of hydroxides was determined by titration using potassium hydrogen phthalate as titrating agent.

Synthesis of symmetric glyceryl diethers 4

The corresponding alcohol (65 mmol), base (6.1 mmol), and diglyme or anisole as internal standard (15% w/w with respect to epichlorohydrin) were placed into a round-bottomed flask, then the reaction mixture was stirred at the desired temperature (65, 45, or 25 $^\circ\text{C}$) under argon until total dissolution of the base. Epichlorohydrin (4.35 mmol) was then added dropwise. All reactions were monitored by GC until total consumption of epichlorohydrin, at which point the reaction was quenched with HCl 0.3 M and the salts filtered off. Finally, unreacted starting alcohol was distilled and recovered and the resulting glyceryl diether was purified by vacuum distillation. Conversions and yields during the reaction were determined by GC and checked by ^1H NMR at the end of the reaction. Synthetic reactions were scaled up to 2 mol of epichlorohydrin (ECH) in order to obtain ca. 100 g of product.

Synthesis of alkyl glycidyl ethers 3

The methodology was the same as for the synthesis of **4**, but the optimized reaction parameters were 65 °C, 30:1 alcohol to epichlorohydrin molar ratio, and an equimolecular amount of base/epichlorohydrin. Once the maximum glycidyl ether yield had been achieved, the reaction was quenched with HCl 0.3 M and the salts filtered off. Finally, the unreacted starting alcohol was distilled under vacuum and recovered, and the product was purified by column chromatography prior to characterization.

Measurement of experimental properties

Density and sound propagation speed. Both properties were determined simultaneously using an Anton Paar DSA 5000 M, with an internal Peltier thermostat at ± 0.001 K. After appropriate calibration, the sample was introduced into a U-shaped glass tube and the density obtained from its frequency of vibration with an uncertainty of $\pm 5 \times 10^{-3}$ kg m⁻³. Correction due to the kinematic viscosity of the liquid was performed automatically. The sound propagation speed of the sample was calculated with an uncertainty of ± 0.1 m s⁻¹ by passing sound waves through the cell.

Polarity. The dielectric permittivity was measured using a WTW (DM01) dipolemeter (Kahlsico) at 2 MHz. Two thermostatted cylindrical condensers were used to cover the full range of experimental data (cell DFL2 for the range of 1–7 and cell MFL2/MS for 6–14). Both cells were previously calibrated with high purity reference liquids. The relative uncertainty in the dielectric values is estimated to be better than 0.05%. Finally, with the dielectric constant and other experimental data, an average dipole moment $\langle \mu^2 \rangle^{1/2}$ was calculated for every liquid (in Debye) using the Onsager equation (1).²⁸

$$\langle \mu^2 \rangle = \frac{9kT}{4\pi N_A} \cdot \frac{M}{\rho} \frac{(\epsilon - n_D^2)(2\epsilon + n_D^2)}{\epsilon \cdot (n_D^2 + 2)^2} \quad (1)$$

Where k is Boltzmann's constant, T the temperature in K, N_A Avogadro's number, M the molar mass, ϵ the dielectric permittivity, n_D the refractive index and ρ the density.

Refractive index. An Abbe ZUZI 315 refractometer with controlled temperature and a sodium lamp was used to measure refractive indices with an uncertainty of ± 0.0001 .

Viscosity. Three Ubbelohde viscometers with suspended ball level and intermediate flow time were used so as to cover the entire range of experimental values (instruments 50103/0c, 50110/I and 50111/Ia, with constants, k , of 0.002835, 0.01029 and 0.04957 mm² s⁻² respectively. The viscometers were placed in a thermostatted bath. Flow time was measured at least three times with differences not greater than ± 0.3 s. Viscosities were calculated with an uncertainty of 0.6% using equation 2:

$$\nu = k(t - \Delta_{HC}) \quad (2)$$

where ν is the kinematic viscosity, k the viscometer constant, t the average flow time (in seconds) and Δ_{HC} the kinetic energy correction.

Surface tension. A Lauda TVT-2 drop volume tensiometer was used to obtain the surface tension of solvents at a fixed temperature with a relative uncertainty not worse than 0.5%. A Lauda E-200 thermostat allowed the sample temperature to be maintained within ± 0.01 K.

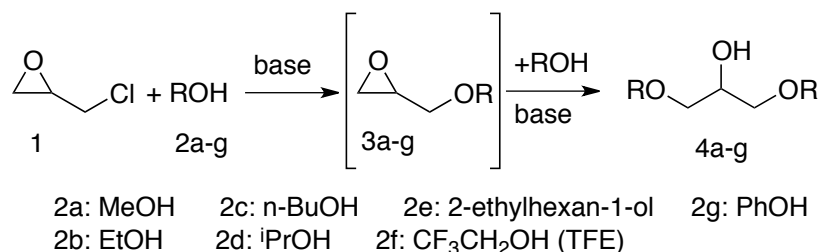
In all cases, the temperature was recorded using a $\Lambda\Sigma\Lambda$ digital thermometer with a Pt sensor, with a resolution of 0.001° and uncertainty of ± 0.01 K.

Boiling points. Boiling points were determined using the onset temperature of Differential Scanning Calorimetric (DSC) analysis in a TA Instruments DSC-Q20, calibrated with indium, using micropore aluminium pans at atmospheric pressure.

RESULTS AND DISCUSSION

For the synthesis of GDEs (**4**) we proposed the use of epichlorohydrin as starting material and alkaline hydroxides as base for alkoxide formation.

The synthetic process involves two sequential steps taking place in one-pot, with no isolation of the reaction intermediate **3** (Scheme 1).



Scheme 1. Synthesis of symmetric glyceryl diethers **4a-g** from epichlorohydrin (**1**) and alcohols **2a-g**

As the first step implies the nucleophilic substitution of chlorine in epichlorohydrin (**1**), stoichiometric amounts of base are needed, whereas only catalytic amounts are required for the subsequent epoxide ring opening.

Screening of the reaction conditions for the synthesis of GDEs

The reaction parameters were first optimized using the benchmark reaction between epichlorohydrin (**1**) and methanol (**2a**), using KOH as base. The influence of the quantity of base, temperature, reagent concentrations and epichlorohydrin addition rate were studied.

The base/epichlorohydrin molar ratio was studied first using KOH:**1** molar ratios of between 0 and 2:1. All reactions were carried out at 65 °C and with a **2a/1** ratio of 15:1.

Figure 1 shows the epichlorohydrin conversions and products yields for both glycidyl ether intermediate **3a** and final product **4a**.

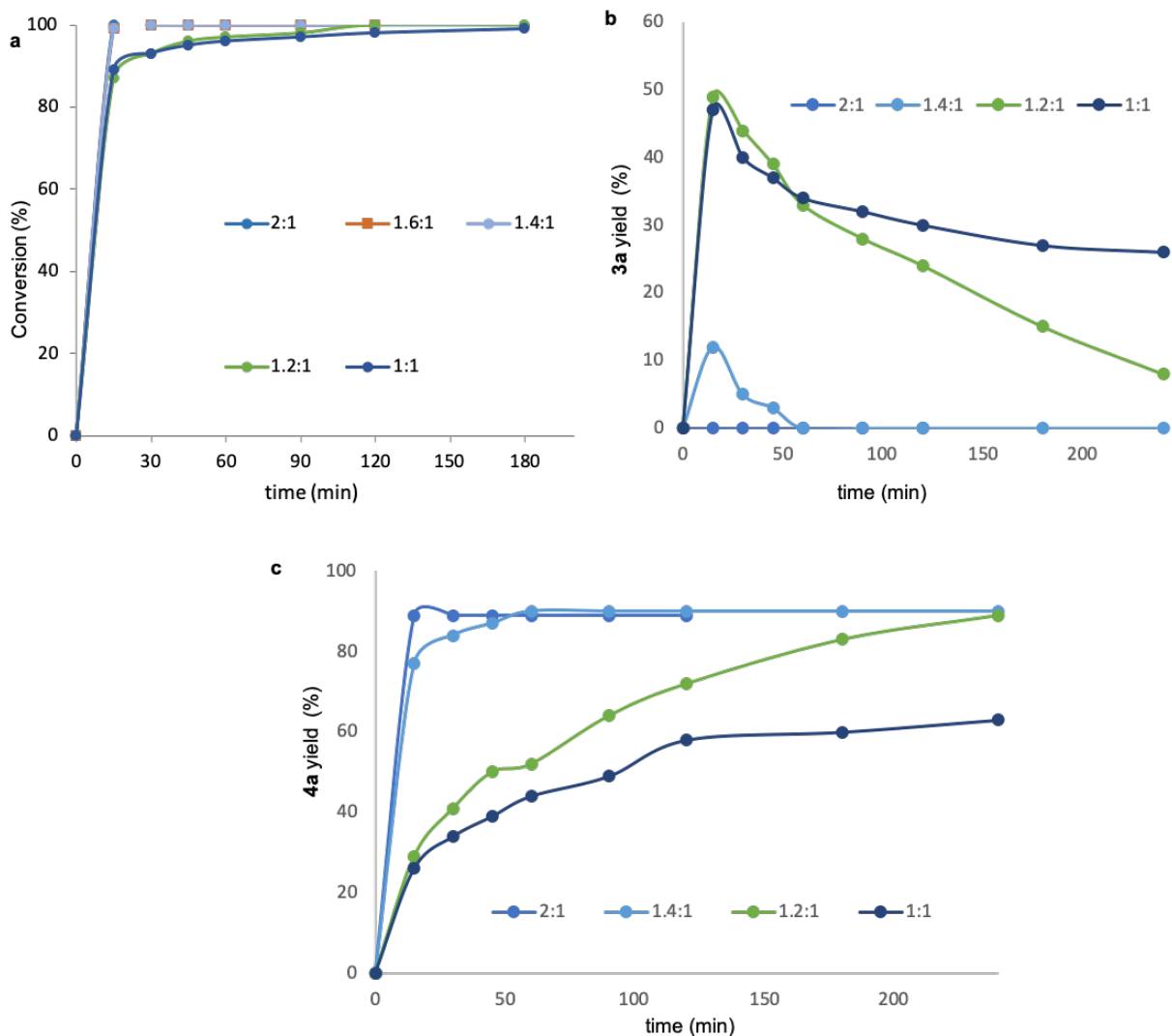


Figure 1. Optimization of the amount of base for the reaction between epichlorohydrin (**1**) and methanol (**2a**) to give **4a**

If no base is added, epichlorohydrin barely reacts (14% conversion in 48 hours), whereas when KOH is added, total conversions of **1** were achieved in between 15 and 120 min when using a molar ratio greater than 1:1 (Figure 1a). However, the rate of conversion of glycidyl ether **3a** into **4a** is very dependent on the quantity of base (Figure 1b). Thus, when using a KOH:**1** ratio of 2:1, no formation of the reaction intermediate **3a** is detected and the desired

product is obtained in only 15 min. We are aware that the amount of base should be reduced in order to minimise salt formation and to improve the green metrics of the process, therefore several studies were carried out to progressively reduce this ratio. As can be seen in Figure 1c, longer reaction times are needed when using a KOH/**1** ratio of less than 1.4:1 in order to totally convert **3a**. However, ratios higher than 1.4 did not markedly improve reaction times. As such, we decided to continue the study using 1.4 mol of KOH per mol of epichlorohydrin. Above this, a high selectivity of **4a** (90%) was achieved.

The influence of reaction temperature on the synthesis of **4a** was studied next (Table 1), using temperatures of 65, 45 and 25 °C.

Table 1. Effect of temperature on epichlorohydrin (**1**) conversion and yield of **3a** and **4a**

Time (min)	Conversion (%)			Yield (%)			
				3a		4a	
	65 °C	45 °C	25 °C	65 °C	45 °C	65 °C	45 °C
15	99	92	56	12	44	77	47
30	100	97	72	5	30	84	63
45	100	100	78	3	21	87	76
60	100	100	82	0	15	90	82
90	100	100	86	0	7	--	91
120	100	100	89	0	4	--	94

Reaction conditions: 1.4:1 molar ratio of KOH to **1**, 15:1 molar ratio of MeOH (**2a**) to epichlorohydrin (**1**). Conversions and yields were determined by GC.

When the reaction was carried out at 25 °C, a reaction time of more than 2 hours was required for total epichlorohydrin conversion. In contrast, when carrying out the reaction

at 45 °C total conversion of **1** was achieved in 45 min, whereas a time of 120 min was required to obtain the maximum yield of **4a**.

A temperature of 65 °C was chosen as the most convenient as total conversions and good yields were achieved in shorter times. This decision was also based on the fact that these conditions were subsequently to be used for less reactive alcohols.

A reduction in the amount of alcohol was also envisaged. Thus, as the alcohol is used as both reagent and solvent, results above gathered were carried out with a 15:1 molar ratio of MeOH to epichlorohydrin (ECH).

We now present the results using an excess of 7.5:1. An epichlorohydrin conversion of 100% was observed in 15 min. Moreover, as expected, conversion of glycidyl ether intermediate **3a** was also faster at higher concentration, although the final yield of the desired product **4a** was slightly lower than when using a 15:1 proportion (84% vs 90%). Competitive reactions, mainly dimerization and oligomerization processes, the products of which were detected by GC, are responsible for this yield decrease.

Finally, we considered the effect of speed of epichlorohydrin (**1**) addition on the yield of **4a**. As has been reported previously for the synthesis of GMEs, a marked influence of glycidol addition rate on the selectivity of the products was observed.²⁴ In our case, a slow addition of epichlorohydrin produced no significant effects on either reaction rate or product selectivity, thus confirming that this reagent does not participate in side reactions, probably due to its fast conversion.

To summarize, the standard reaction conditions finally chosen were 65 °C, a MOH:**1** molar ratio of 1.4:1 and an alcohol **2** to epichlorohydrin (**1**) molar ratio of 15:1.

Scope of the synthesis with different bases and alcohols

In addition to KOH, two other metal hydroxides, namely LiOH and NaOH, as well as seven alcohols, were tested for the synthesis of glyceryl diethers **4** (Figure 2). In order to prepare symmetric diethers with different substitution patterns, we selected alcohols with linear alkyl chains (**2a-c**), branched chains (**2d-e**), fluorinated chains (**2f**), and an aromatic substituent (**2g**). These alcohols were selected in order to provide diethers with a range of different properties, mainly boiling point, polarity and viscosity. Various applications have been described for these diethers. Thus, **4a** has been used as a fuel additive,²⁹ **4c** has been used as a reaction medium in enzymatic synthesis,³⁰ and **4f** has been successfully used as a solvent in epoxidation reactions and biocatalysis.^{31,32}

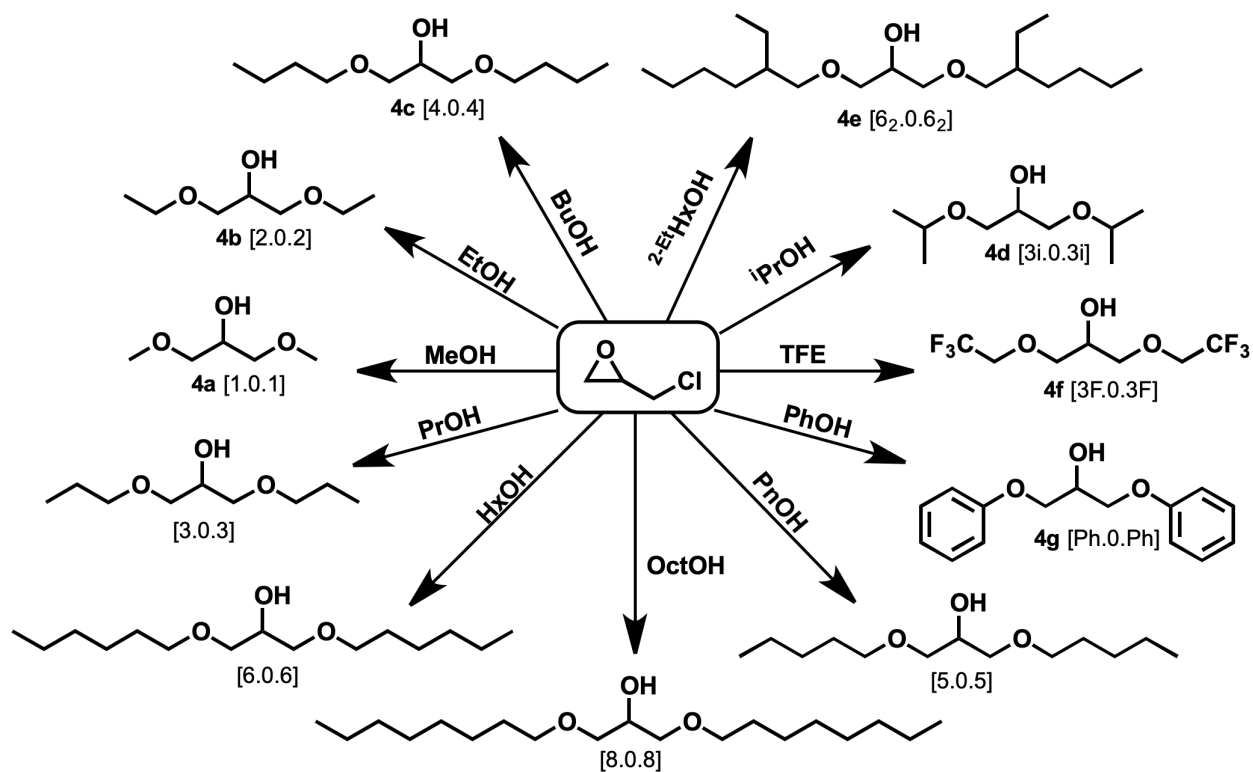


Figure 2. Structure and notation of the glyceryl diethers **4** synthesized in this work.

Table 2. Optimized conversions and yields for the reaction of epichlorohydrin (**1**) with different alcohols **2** and metal hydroxides.

Entry	Alcohol	Reaction time (h)	LiOH		NaOH		KOH	
			1 Conv. (%)	4 Yield (%)	1 Conv. (%)	4 Yield (%)	1 Conv. (%)	4 Yield (%)
1	MeOH 2a	1	75	15	100	88	100	90
2	EtOH 2b	2	78	18	100	91	100	91
3	<i>n</i> BuOH 2c	2	53	8	100	74	100	78
4	<i>i</i> PrOH 2d	24	23	1	100	40	100	29
5	2-EtHxOH 2e	24	49	9	100	44	100	87
6	TFE 2f	24	100	88	100	72	100	67
7	Phenol 2g	48	100	23	100	28	100	88

Reaction conditions: 1.4:1 base:1 molar ratio, 15:1 molar ratio of alcohol **2** to epichlorohydrin (**1**), 65 °C. Conversions and yields were determined by GC.

A marked influence of the nature of the base was observed (table 2). Thus, NaOH or KOH provided high conversions of epichlorohydrin (**1**) in quite short times for linear, branched and aromatic alcohols (**2a-e**, **2g**), whereas the use of LiOH also led to complete conversion with the more acidic alcohols, phenol (**2g**) and TFE (**2f**), and also gave higher product yields with TFE.

As expected, the reactivity of alcohols **2** decreases with both chain length and branching. In the case of methanol (**2a**) (Table 2, entry 1), a 90% yield of **4a** was obtained in 1 h using KOH or NaOH. When lengthening the alkyl chain of the alcohol, for example when using EtOH **2b** and *n*BuOH **2c** (Table 2, entries 2, 3), the maximum yield of the desired product **4** is maintained with respect to methanol but a reaction time of 2 h is required. When using branched alcohols, and hence less nucleophilic, such as isopropanol **2d** or 2-ethylhexan-1-ol **2e** (Table 2, entries 4, 5), reaction times of 24 h are required. As expected, more acidic,

but less nucleophilic, alcohols **2f** y **2g** are also less reactive nevertheless high yields can also be reached but in longer time reaction.

Finally, the selectivity towards GDEs **4** was also studied. A reduction in the yields of diethers **4** can be attributed to competing dimerization and oligomerization processes, which generate different species. When formed, these oligomers can be detected by gas chromatography and identified by mass spectrometry/NMR spectroscopy (See supporting information).

Very high product selectivities are achieved for more reactive alcohols such as MeOH and EtOH, whereas the values decrease slightly when using n-BuOH **2c**, TFE **2f**, PhOH **2g** or 2-ethylhexan-1-ol **2e**. In the case of isopropanol **2d**, the presence of a less reactive secondary alcohol leads to only a 40% selectivity for **4d**.

All these data show that NaOH and KOH are the best bases for the reaction of epichlorohydrin with alkyl alcohols. No significant differences are observed using both bases neither in yields nor in selectivities. It is worth mentioning the good results obtained with LiOH in the case of TFE. As mentioned, TFE is a more acidic alcohol, thus LiOH is basic enough to form the alkoxide and in this case the size of the cation plays an important role, thus the presence of lithium, a smaller cation, favors the reaction of trifluoroethoxyde with epichlorohydrin leading to an increase in product yield.

In order to prove the viability of this synthetic methodology, a scale up to 1 mol (120–316 g) was performed for each alcohol using the optimal conditions. Final yields were maintained in all cases. The isolated yields of glyceryl diethers **4a–f** after vacuum distillation at $3 \cdot 10^{-2}$ mbar depend strongly on the boiling point of the product (Table 3).

For diethers with a boiling point of 200°C or above, higher vacuum is needed in order to avoid high distillation temperatures (see product boiling points in table 7) and thus a loss of the product by side dimerization reactions. A proof of concept was carried out with product **4c**. A synthesis at 20g scale has been carried out and purification of the product

was done using a kugelrohr distillation at 10^{-3} mbar and 90°C . Thus, an improved yield of isolated product up to 60% was achieved.

Table 3. GC yields versus isolated yields for symmetric glyceryl diethers **4a–g**

Product	4a	4b	4c	4d	4e	4f	4g
	[1.0.1]	[2.0.2]	[4.0.4]	[3i.0.3i]	[6 ₂ .0.6 ₂]	[3F.0.3F]	[Ph.0.Ph] ^b
GC yield (%)	90	91	80	40	87	67	88
Isolated yield (%) ^a	85	72	47(60) a	30	61	47	32

Reaction conditions: 1.4:1 base:**1** molar ratio (KOH for **4a–c** and **4e–g**, and NaOH for **4d**), 15:1 molar ratio of alcohol **2** to epichlorohydrin (**1**), 65°C . Products were purified by vacuum distillation and a purity of 100% was determined for all products by HRMS a) distillation at 90°C and 10^{-3} mbar. b) column chromatography was used for purification

Screening of the reaction conditions for the synthesis of glycidyl ethers

When carrying out the synthesis of glyceryl diethers **4** with the different bases, the formation of glycidyl ethers **3** was observed in the early stages of the reaction (Figure 1). This fact prompted us to fine-tune the reaction conditions in order to optimize the production of these glycidyl ether intermediates (**3**), which are very interesting and useful platform molecules derived from glycerol that can subsequently react with different nucleophiles for conversion, for example, into non-symmetric glycerol-derived diethers.³³ In this regard, screening of the reaction conditions was carried out for the synthesis of **3a**, optimizing the reaction temperature and concentration of alcohol **2a** in order to provide the maximum amount of the glycidyl ether (Scheme 1). Equimolecular amounts of base were used in all cases.

The yields of glycidyl ether **3a** for each reaction temperature were 53% in 10 min at 65 °C, 54% in 30 min at 45 °C and 54% in 2 h at 25 °C. Varying amounts of epichlorohydrin (**1**) and diether **4a** were observed in all cases. As only differences in reaction time were observed, a temperature of 65 °C was chosen for subsequent reactions. The influence of reagent concentration appears to be decisive in order to avoid further transformation of **3a** into **4a**. As such, four different molar ratios of methanol (**2a**) and epichlorohydrin (**1**), namely 40:1, 30:1, 15:1 and 7.5:1, were tested. As expected, the highest yields of **3a** were obtained using higher dilutions (Table 4, entries 1 and 2). In a compromise between yield, selectivity and reaction time, a ratio of 30:1 seems to provide the best results.

Table 4. Yields of glycidyl methyl ether **3a** at different reagent concentrations

Entry	2a:1 ratio	Time (h)	Yield 3a (%)
1	40:1	4	59
2	30:1	1.5	61
3	15:1	0.2	53
4	7.5:1	0.2	46

Reaction conditions: 1:1 molar ratio of KOH to **1**, 65 °C.

The optimized reaction conditions were applied to the synthesis of different glycidyl ethers starting from **1** and previously selected alcohols **2a-g**. Again, the results obtained with LiOH and NaOH are presented together with those obtained for KOH. In all cases, KOH provided higher yields of **3** than NaOH, which in turn gave higher yields than LiOH (Table 5).

Table 5. Epichlorohydrin (ECH) conversion, alkyl glycidyl ether **3** yield and selectivities (%) for the reaction of ECH (**1**) and different alcohols **2** catalyzed by alkaline hydroxides^a

Entry	Alcohol	LiOH			NaOH			KOH		
		Time (h)	Conv. (%)	Yield (%)	Time (h)	Conv. (%)	Yield (%)	Time (h)	Conv. (%)	Yield (%)
1	MeOH	0.75	80	54 (67)	1	85	56 (66)	1.5	90	61 (68)
2	EtOH	1	83	61 (73)	1.5	92	63 (68)	0.5	87	70 (80)
3	<i>n</i> BuOH	3	78	51 (65)	0.25	83	59 (71)	2	90	65 (72)
4	<i>i</i> PrOH	96	70	37 (52)	1	87	58 (67)	1.5	86	53 (62)
5	2-EtHxOH	72	50	35 (70)	24	96	50 (52)	48	86	67 (77)
6	TFE	6	68 ^b	39 (57)	6	65	44 (67)	4	58	54 (93)
7	PhOH	6	84 ^b	46 (54)	24	100 ^b	55 (55)	6	93 ^b	63 (67)

^a Reaction conditions: 1:1 molar ratio of base to epichlorohydrin (**1**), 65 °C reaction temperature, 30:1 molar ratio of alcohol **2** to **1**, at the glycidyl ether maximum yield.

^b Formation of the corresponding 1-alkoxy-3-chloropropan-2-ol is observed.

^c Values in brackets correspond to product selectivity.

Moderate yields were obtained in all cases. It should be noted that the glycidyl ether is always obtained together with epichlorohydrin (**1**) and glyceryl diethers **4** in different ratios depending both on the reactivity of the starting alcohol and the base. In order to obtain the pure glycidyl ethers, purification, mainly distillation, must be performed.

Sustainability considerations regarding the synthetic methodology

We have presented a methodology for the synthesis of symmetric glycidyl diethers involving the reaction of epichlorohydrin with several alcohols in the presence of KOH as base. From a sustainability point of view, the use of epichlorohydrin, which is considered to be a hazardous chemical, can be considered a serious drawback, although some green metrics show that the

synthetic methodology discussed above may be competitive when compared to “similar” ones using glycerol as starting product.

We have taken the reaction of epichlorohydrin and methanol to form **4a** as reference as this is the most commonly described process in the literature. This reaction is carried out at 65 °C and leads to total conversion of epichlorohydrin in 15 min, with an isolated yield of 85% for 1,3-dimethoxy-2-propanol. The calculated atom economy (A.E.) is 0.67, including the stoichiometric amount of KOH needed for the $\text{S}_{\text{N}}2$ substitution reaction. The E Factor (EF) and stoichiometric factor (SF), taking into account the recovery of the excess methanol by distillation, are 1.37 and 1, respectively. Other mass-based green metrics, such as RME (reaction mass efficiency), which is defined as mass of product/total mass of reactants, and MP (mass productivity), defined as mass of product/total mass including solvents, were also calculated.³⁴ The values obtained for our process are 0.57 and 0.148, respectively. Some of these parameters are represented in Figure 3 for a clearer comparison. The optimal process is the one in which all values are equal to 1.

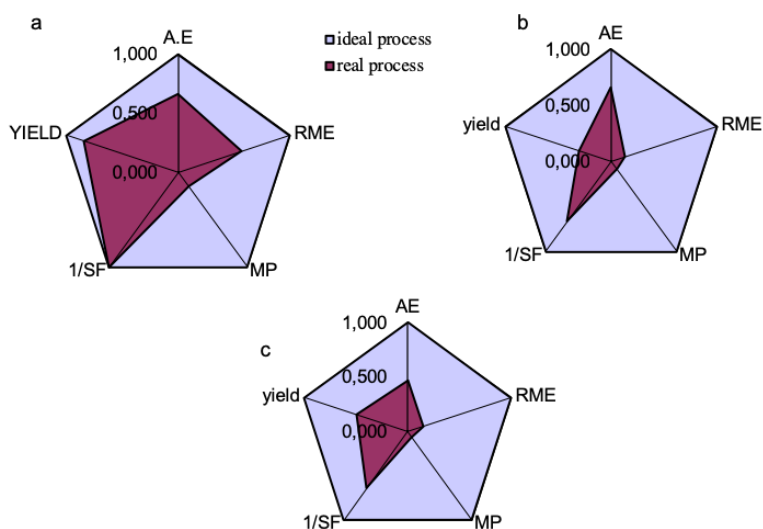


Figure 3. Green metrics for the synthesis of **4a**. a) From epichlorohydrin (in this work); b) from glycerol and TMAOH³⁵; c) from glycerol and dimethyl sulfate³⁶

In light of these parameters, the weak points of our synthetic methodology are the AE and MP values. The moderate AE value is due to the use of stoichiometric amounts of base, which gives KCl as the only byproduct of the reaction. In the case of MP, the low value is due to work-up of the reaction in which, again, KCl is obtained as residue, as well as use of the alcohol, which acts as both reagent and solvent in the process, in a large excess. Although this is a drawback from a green metrics point of view, it is also an advantage as no additional solvent is used, thus facilitating purification of the product and enabling recovery of the solvent for subsequent reactions.

Various studies concerning the synthesis of ethers using glycerol as reagent have been published. In order to compare the sustainability of these processes with the results presented in this work, we have calculated the same green metrics for these reactions. In the work presented by Waggoner and Hatcher,³⁵ glycerol is treated with tetramethylammonium hydroxide at 330 °C to give mixtures of mono-, di- and trimethyl glyceryl ethers. A 30% yield of 1,3-dimethoxy-2-propanol was reported. When using dimethyl sulfate as alkylating agent,³⁶ NaOH was used as base and chloroform as extraction solvent. In this case, a 50% yield of 1,3-dimethoxy-2-propanol was obtained. As can be seen from Figure 3, all the green metrics parameters are much more unfavorable for these processes compared to the methodology described herein. Finally, some consideration about reagents toxicity can be done. In the case of the methodology herein presented, the use of epichlorohydrin can be considered as a drawback due to its toxicity, but the use of ECH in stoichiometric amounts and its total conversion minimizes the risk. In the case of the synthesis using methylating agents such as tetramethylammonium hydroxide and dimethyl sulfate both are

also considered as toxic and are used in excess in respect to glycerol, that can be considered an additional drawback to the methodology.

With regard to the remaining publications, most of which are patents, several key values are lacking from the description, thus making calculation of the green metrics impossible. Acid catalysts such as β -zeolite³⁷, sulfuric acid³⁸ or Amberlyst 70²⁹ have been used in the reaction of glycerol and methanol. However, reaction temperatures exceeded 130 °C in all cases. The production of mixtures of mono-, di- and triethers is always reported, with glyceryl triethers being the major products; the yield of 1,3-glyceryl diethers is not recorded (Table 6). In these cases, although the use of glycerol is more favorable from a green chemistry point of view, the use of much higher temperatures and the production of product mixtures with a very low selectivity for 1,3-glyceryl diethers can be considered serious drawbacks.

In summary, we can conclude that, despite the use of epichlorohydrin, the methodology described herein is a much more straightforward method for the synthesis of glyceryl-1,3-diethers in high yield and selectivity, and with favorable green metrics.

Table 6. Comparison of synthetic methodologies for the synthesis of 1,3-dimethoxy-2-propanol (**4a**).^a

Reference	Starting material	Reagent/catalyst	solvent	Reaction conditions	Work-up	Yield of 4a
This work	ECH	MeOH/KOH	MeOH	65 °C 1 h	HCl	85%
Waggoner et al. ³⁵	glycerol	TMAOH ^a	MeOH	350 °C 2min.		30%
Chang et al. ³⁶	glycerol	Me ₂ SO ₄	H ₂ O	70 °C 6h	CHCl ₃	50%

Mota et al. ³⁷	glycerol	MeOH/ β zeolite (20%w/w)	MeOH	150 °C 5h	--	Mixtures of ethers
Dos Santos et al. ³⁸	glycerol	H ₂ SO ₄ or HX	MeOH	150 °C 1.5h	AC ^b	Mixtures of ethers
Chang et al. ²⁹	glycerol	1) MeOH/A70 2) Me ₂ SO ₄ /NaOH	1)MeOH 2) H ₂ O	1) 150 °C 24h 2) 70 °C 1 day		Mixtures of ethers

^aTMAOH: Tetramethylammonium hydroxide. ^bAC: Activated Carbon

Physicochemical properties of symmetric glyceryl diethers

The physicochemical properties of this family of ethers are closely related to their ability to form hydrogen bonds, therefore the shielding and dilution of the OH group when the alkyl chains of the ether groups are modified should allow these properties to be tuned.

The most interesting physicochemical properties as regards use of the synthesized symmetric glyceryl diethers **4** [R.O.R] as solvents were measured in the milder temperature range of 25–70 °C, and the experimental data were fitted to linear equations (see Supporting Information).

Some of the properties reported herein, such as density and refractivity, have been reported previously for some of the ethers, but always at a fixed temperature of 20 or 25 °C.^{15,39} It should be noted that, except for the boiling point, the physicochemical properties of **4e** [6₂.0.6₂], [8.0.8], [5.0.5] and **4g** [Ph.0.Ph] are reported here for the first time. In the case of viscosity, only the values for **4c** [4.0.4] and **4f** [3F.0.3F] at 20 °C have been reported previously by our group.¹⁵

Density (ρ). Density is an essential property of solvents for many chemical, industrial and engineering applications. The density values of these solvents at 25 °C range between 0.88 and 1.01 g·cm⁻³ (with the expected exception of fluorinated **4f** [3F.0.3F], 1.39 g·cm⁻³) and are therefore

comparable to those of other conventional organic solvents (0.75–1.00 g·cm⁻³; (Figure 4). These density values are similar to those for glyceryl monoethers [R.0.0] (0.96–1.36 g·cm⁻³) and glyceryl triethers [R.R.R] (0.85–0.95 g·cm⁻³), and are lower than that pure glycerol (1.26 g·cm⁻³), glyceline (1.19 g·cm⁻³), glycerol monoethers DES (1.05–1.30 g·cm⁻³) and the majority of ILs (ionic liquids) (1.21–1.45 g·cm⁻³).^{15,17} As is usually the case for organic liquids, density decreases with increasing temperature as a result of thermal expansion. However, this decrease is almost negligible in this case as it is counteracted by opposing effects (see Supporting Information), namely hydrogen bond breakage, which leads to a contraction in the liquid, and an increase in the free volume, which leads to an expansion in the liquid. Branching leads to a decrease in density (cf. **4d** [3i.0.3i] vs. [3.0.3], and **4e** [6₂.0.6₂] vs. [8.0.8]). Finally, the fluorinated diether **4f** [3F.0.3F] displays the highest density due to the high atomic mass of fluorine atoms (Figure 4).

Sound propagation speed (*u*). This property is inversely related to density, as can be seen from the basic thermodynamic relationship.

$$\kappa_S = \frac{1}{\rho u^2} \quad (3)$$

where κ_S is the isentropic compressibility coefficient.

As such, trends in u are parallel but opposite to those in density (see Supporting Information). For **4** [R.0.R], u values at 25 °C range from 1040 to 1388 m·s⁻¹ and are therefore similar to those for conventional solvents such as methanol (1103 m·s⁻¹), acetone (1170 m·s⁻¹), toluene (1306 m·s⁻¹) or water (1493 m·s⁻¹).¹⁷

Molar Volume (V_m). This property is related to the free volume of a molecule at a given temperature and, like density, presents interesting correlations with other properties such as

viscosity. Molar volumes were calculated using the semi-empirical equation 3, where M is the molar mass in $\text{g}\cdot\text{mol}^{-1}$ and ρ the solvent density ($\text{g}\cdot\text{cm}^{-3}$):

$$V_m = \frac{M (\text{g}\cdot\text{mol}^{-1})}{\rho (\text{g}\cdot\text{cm}^{-3})} \quad (4)$$

The molar volumes of these diethers at 25 °C vary widely between 120 and 360 $\text{cm}^3\cdot\text{mol}^{-1}$ and are intermediate between those for glyceryl mono- (95–180 $\text{cm}^3\cdot\text{mol}^{-1}$) and triethers (150–300 $\text{cm}^3\cdot\text{mol}^{-1}$).¹⁷ By definition, molar volume is inversely proportional to density, therefore trends with chain length, branching and temperature are the opposite (see Supporting Information).

Solvent Polarity. The polarity can be determined using both physical and chemical methods. We determined the dielectric permittivity and dipole moment as physical polarity parameters. The dielectric permittivity (ϵ) of these solvents shows values (3–14 at room temp.) lower than those for glyceryl monoethers (8–25) and other alcohols (18–40) due to the higher symmetry of the molecule.¹⁷ As the alkyl chain lengthens, the polarity of these liquids decreases. Although branching effect has only a minimal effect on polarity, fluorination markedly increases permittivity (from 11 to 14). The dipole moments (μ), as calculated from experimental ϵ , n_D and ρ values using Onsager's equation (1), show similar polarity trends as the permittivities, with values ranging between 2.0 and 3.1 D (4.0 D for **4f** [3F.0.3F]), which are slightly higher than those for conventional solvents (1.3–1.8 D) but lower than those for glycerol monoethers (3.0–4.4 D).¹⁷

Refractive index (n_D). The refractivity of a molecule is a well-known estimator of its polarizability, and it has also been used in organic chemistry as a purity indicator. [R.0.R] 4 diethers present very similar refractivity values in all cases (between 1.41 and 1.45 at room temp.), with the exception of **4f** [3F.0.3F] (1.35). These values are in the range of those for conventional solvents (1.32–1.50) and glycerol (1.47), and decrease slightly with temperature. Longer alkyl chains lead to higher refractivities due to the correlation between the polarizability and the strength

of chain interactions. In contrast, the high electronegativity of fluorine atoms markedly reduces the polarizability of **4f** [3F.0.3F]. Finally, both branched **4d** [3i.0.3i] and **4e** [6₂.0.6₂] solvents present lower n_D values than their linear counterparts.

Molar refractivity (R_m). This polarizability parameter was calculated using the Lorentz equation (4) from n_D and molar volume values (V_m). The molar refractivities of glyceryl diethers are in the range 30–100 cm³·mol⁻¹, and are thus higher than for most conventional solvents.

$$R_m = \frac{n_D^2 - 1}{n_D^2 + 2} \cdot V_m \quad (5)$$

Viscosity (η). Liquid viscosity is an important physical property used in the design of fluid-transport processes. As such, flow times were measured at 25 °C and kinematic viscosities were calculated after appropriate calibration of the viscometers. The viscosities of glyceryl **4** [R.0.R] diethers are much lower than those for glyceryl [R.0.0] monoethers,¹⁷ therefore their decrease with temperature is minimal (see Supporting Information). Dynamic viscosities were calculated from kinematic viscosities and densities according to equation 5.

$$\eta = \nu \cdot \rho \quad (6)$$

These solvents present very interesting fluency properties. Thus, their viscosities are in the range 3–17 cP at 25 °C, much lower than those for glycerol (1200 cP), glycerol-derived DES (130–550 cP) and glycerol-derived monoethers (35–110 cP). This is due to the lower number of interactions present in diethers as they are less able to form hydrogen bonds. It should also be noted that these solvents have similar viscosities to conventional ones (0.2–4 cP). This is important as it can lead to a reduction in energy and operating costs. In addition, longer ether chains lead to higher viscosities, with an exponential growth from 3.0 **4a** [1.0.1] to 3.3 **4b** [2.0.2], 5.6 **4c** [4.0.4], 9.5 **4e** [6.0.6] and 17.3 cP [8.0.8] being observed (Figure 4). Branched diethers exhibit a marked viscosity decrease of close to 20% compared with the linear compounds. Finally, the fluorinated solvent **4f**

[3F.0.3F] is three times more viscous than its non-fluorinated analog **4b** [2.0.2] due to hydrogen-bond formation.

Surface tension (γ). Surface tension can be considered to be a measure of the force acting on the boundary surface between a liquid phase and a gas (air) phase. As such, an understanding of surface tension is essential in order to be able to understand boiling and condensation processes, as well as the behavior shown by emulsions, foams, etc., which are common materials that can be formed when organic solvents pass into the environment. The range of surface tension values of the glyceryl 4 [R.0.R] diethers is 23.1–30.7 mN·m⁻¹ at room temperature (Figure 5). Interestingly, these values are not very different from those for glyceryl [R.0.0] monoethers (25–40 mN·m⁻¹) and even for conventional solvents such as common alcohols, such as methanol (23.8 mN·m⁻¹), acetone (24.9 mN·m⁻¹), aromatic solvents (29.1 mN·m⁻¹ for toluene) or halogenated solvents (29.5 mN·m⁻¹ for DCM).¹⁷ Although higher surface tensions are found for short alkyl chain ethers, the decrease with chain length is not linear. Short chain alkyl ethers show the highest surface tensions, subsequently decreasing from **4a** [1.0.1] to **4c** [4.0.4], which can be explained by the dilution effect of the OH group. A slight increase with length of the ether group chain is then observed on going from [5.0.5] to [8.0.8], with this increase probably being associated with an increase in the interactions between aliphatic chains. Branching and fluorination effects lead to a decrease in surface tension (about 10% with respect to the linear compounds; Figure 5a).

Boiling point. The boiling points for 4 [R.0.R] were determined in order to determine their volatility. Table 7 shows that longer alkyl chains result in a decrease in volatility. Branched ethers, in turn, exhibit fewer interactions, thus lowering their boiling points, with the opposite trend being found for [3F.0.3F]. All these solvents have a very low volatility, thus reducing working risks.

Table 7. Boiling points of the [R.0.R] solvents synthesized

4a [1.0.1]	4b [2.0.2]	[3.0.3]	4c [4.0.4]	[5.0.5]
170 °C	188 °C	219 °C	248 °C	285 °C
[6.0.6]	4f [3F.0.3F]	4d [3i.0.3i]	[8.0.8]	4e [6 ₂ .0.6 ₂]
316 °C	197 °C	202 °C	344 °C	334 °C

In order to gain a better view of the most important physicochemical properties measured for glyceryl diethers, two-dimensional graphs of density, surface tension and boiling point vs. dynamic viscosity were plotted. Values for similar conventional solvents have been added for comparison.

The following abbreviations for conventional solvents are used in these plots for the sake of clarity:

MeOH	Methanol	EGMME	Ethylene glycol monomethyl ether
BuOH	1-Butanol	EGDME	Ethylene glycol dimethyl ether
HxOH	1-Hexanol	DEGMME	Diethylene glycol monomethyl ether
OctOH	1-Octanol	DEGDME	Diethylene glycol dimethyl ether
DecOH	1-Decanol	SK	Solketal
TFE	Trifluoroethanol	W	Water

Figures 4a, 5a and 6a show the trends in **4** [R.0.R] properties discussed previously. These 2D graphs are very useful when choosing a solvent for a specific application. For example, Figure 5b shows the wetting ability of the solvents, which is essential for extraction processes. In this case, compounds **4a** [1.0.1] and **4b** [2.0.2] seem to be good candidates for replacing DEGMME, which has an intermediate wetting ability. Figure 6b, in which boiling point is plotted against dynamic viscosity, may be useful for choosing additives for cooling liquids, which should have a low viscosity and high boiling point. In this case, glyceryl diethers from **4a** [1.0.1] to **4b** [4.0.4] can be considered to be good candidates for replacing DEGDME and DEGMME.

Finally, these plots show that these glyceryl diethers are in the region corresponding to hydrogen bonding and aprotic polar solvents, where linear alcohols and diols coexist with ethers such as glymes (EGDME, DEGMME, etc.).

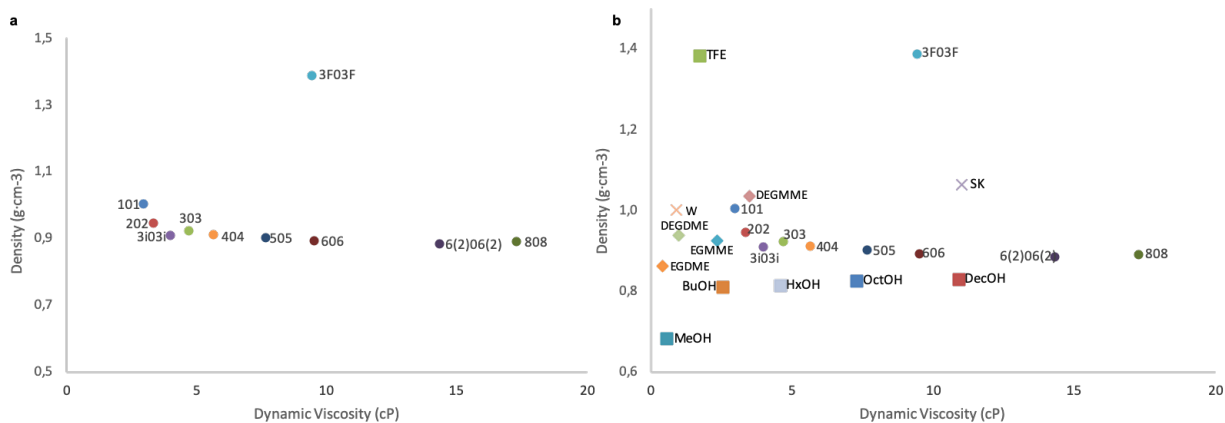


Figure 4. a) Plot of density vs. dynamic viscosity for glyceryl diethers **4** [R.O.R]; b) glyceryl diethers vs. some conventional solvents at 25 °C

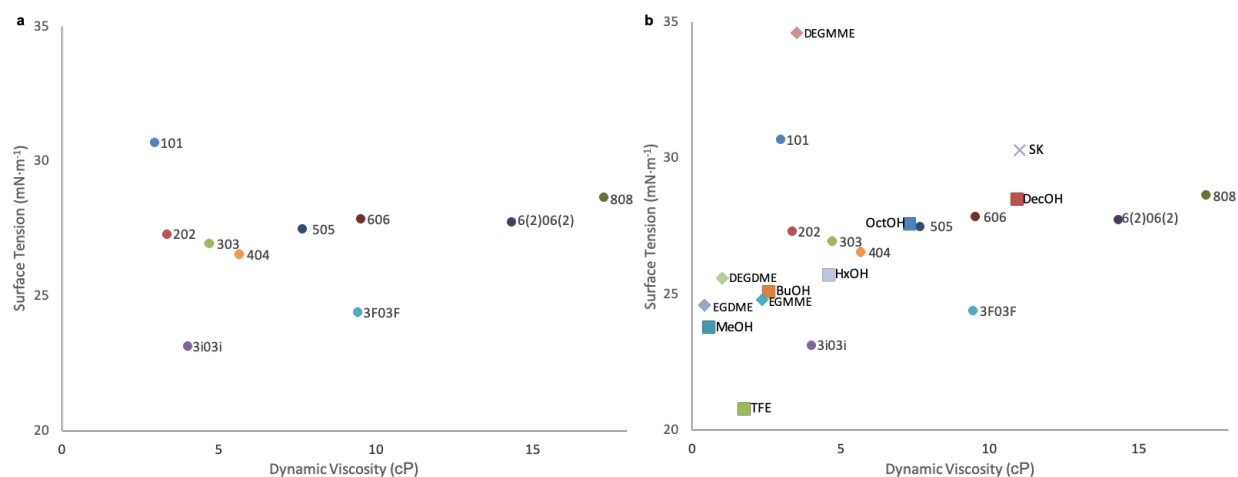


Figure 5. a) Plot of surface tension vs. dynamic viscosity for glyceryl diethers **4** [R.O.R]; b) glyceryl diethers vs. some conventional solvents at 25 °C

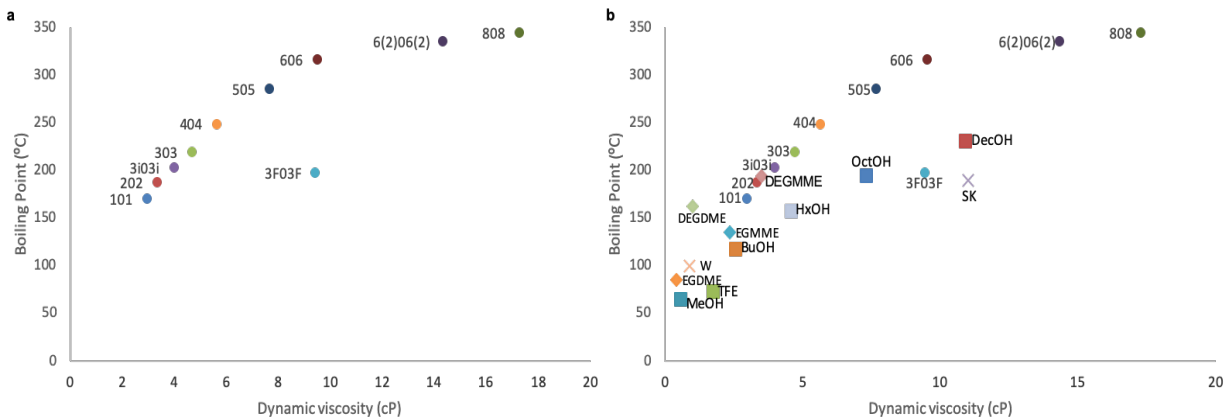


Figure 6. a) Plot of boiling point vs. dynamic viscosity for glyceryl diethers **4** [R.O.R]; b) glyceryl diethers vs. some conventional solvents at 25 °C

CONCLUSIONS

A systematic, alternative and efficient methodology for the synthesis of symmetric glycerol diethers, starting from epichlorohydrin, has been optimized using a range of alcohols with different structures and features. No excess epichlorohydrin is required and inexpensive alkaline hydroxides can be used to improve the sustainability of the process. This synthetic methodology avoids the use of co-solvents and uses milder reaction conditions and moderate reaction times. High yields of the desired product have been achieved, although the final selectivity of the reaction depends strongly on the alcohol used. In general, the best results are obtained with KOH, with the exception of NaOH for branched alcohols and LiOH for more acidic ones. In this case, only KCl is obtained as byproduct.

An attempt to adapt this synthetic methodology to the synthesis of glycidyl ethers has also been made, with moderate yields of these platform molecules being achieved.

The new symmetric glycerol diethers synthesized have been fully characterized, and several of their essential physicochemical properties, such as density, molar volume, polarity, refractive

index, viscosity, surface tension and volatility, have been measured, in most cases within the temperature range 25-70 °C. The values obtained highlight the versatility of these molecules and show that the properties of the solvent can be modified simply by varying the substitution pattern. A comparison of these properties with those for similar, non-renewable solvents highlights the possibility of using glyceryl diethers as a green alternative, with some of these solvents appearing to be highly suitable for two common uses, namely reaction and extraction media.

ASSOCIATED CONTENT

Supporting Information

The supporting information contains the products characterization and description, the diagram of physicochemical properties vs temperature and physicochemical adjust parameters.

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