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Straightforward selective synthesis of linear 1-*O*-alkyl glycerol and di-glycerol monoethers

Yan Shi [a,b], Wissam Dayoub [a], Alain Favre-Réguillon [a,c], Guo-Rong Chen [b], Marc Lemaire [a,*]

[a] *Laboratoire de Catalyse et Synthèse Organique, Institut de Chimie et Biochimie Moléculaires et Supramoléculaires (ICBMS), CNRS UMR5246, Université Lyon 1, Bâtiment Curien-CPE, 3° étage, 43 Bd du 11 Novembre 1918, 69622 Villeurbanne Cedex, France*
[b] *Laboratory for Advanced Materials and Institute of Fine Chemicals, East China University of Science and Technology, Shanghai 200237, PR China*
[c] *Laboratoire de Transformations Chimiques et Pharmaceutiques, UMR7084,CNAM, 2 Rue Conté, 75003 Paris, France*

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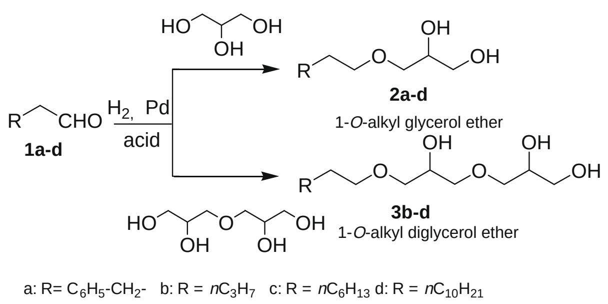
ABSTRACT

1-*O*-Alkyl glycerol and di-glycerol monoethers are, respectively, obtained in high yields and selectivity by catalytic reductive etherification of mono- and di-glycerol with linear aldehydes in the presence of 0.5 mol % of Pd/C under 10 bars of hydrogen using a Brønsted acid as co-catalyst.

Glycerol is one of the main co-products of the vegetable oil industry. Recently, a new trend influenced the glycerol production since renewable oils have been used for energy applications. ‘Bio-diesel’, that is, fatty acid methyl esters, has been widely implanted in the EU and US and as a consequence, the output of glycerol has risen. There are already a great number of applications of glycerol as an additive, as a raw material and for energy production.[1,2] However, as fossil raw material stocks irrevocably diminish and environmental awareness increases, there are opportunities to produce valuable chemicals, using renewable resources such as glycerol.[3] The conversion of glycerol into useful chemicals is a topic of great industrial interest.[3,4]

Glycerol monoether (GME) is one of the most valuable derivatives of glycerol. A lot of applications were patented in personal care, cosmetic, laundry, and cleaning formulations,[5] as well as in the pharmaceutical field.[6] GME could also be used as building blocks for the synthesis of bioactive molecules.[7] Traditionally, ethers are prepared via the Williamson ether synthesis despite the need for a strong base and for the formation of a stoichiometric amount of salts.[8] Since glycerol has three hydroxyl groups with similar pK_as, the control of the regioselectivity is the main key of the process to minimize waste and by-products production. Moreover, even though the direct synthesis of branched saturated glycerol ethers is easily realizable in acidic catalysis, the direct synthesis of linear ones is not.[9]

We report herein that the catalytic reductive alkylation is suitable for the synthesis of linear 1-*O*-alkyl mono- and di-glycerol ethers in one step (Scheme 1). More than 10 years ago, our group discovered an alternative method to Williamson etherification from linear alcohols and carbonyl compounds using Pd/C as a catalyst under hydrogen pressure.[10] However, to the best of our knowledge, this method has never been applied to polyfunctional alcohols in mild conditions. The few examples that can be found report two-step procedures, high pressures and temperatures.[11]



Scheme 1. Direct etherification from mono- and di-glycerol with different aldehydes.

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* Corresponding author. Tel.: +33 472 314 07; fax: +33 472 314 08.
E-mail address: marc.lemaire@univ-lyon1.fr (M. Lemaire).

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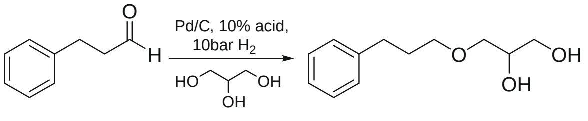
Table 1
Acid Screening for reductive alkylation of aldehyde **1a**



1a 2a

Entry	Acid	**2a** GC yield	Selectivity[c]
1[a]	HCOOH	Traces	nd
2[a]	TFA	9	>25/1
3[a]	PTSA·H_2O	25	>25/1
4[b]	PTSA·H_2O	37	>25/1
5[b]	CSA[d]	57	>25/1

[a] 110 °C, 0.5 mol % Pd, 10% acid, 10 bar H_2, 24 h.

[b] 140 °C, 0.5 mol % Pd, 10% acid, 10 bar H_2, 24 h.

[c] Selectivity between 1-*O*-alkyl glycerol monoether and 2-*O*-alkyl glycerol monoether.

[d] (*R*)-10-Camphorsulfonic acid.

Using the reductive conditions reported in earlier publications[8] with 3-phenylpropanal **1a** as a substrate and glycerol as a solvent, no traces of the expected 1-*O*-alkyl glycerol monoether **2a** were observed by GC/MS, after 24 h of reaction at 100 °C under 40 bars of hydrogen. The only detected products were the four possible corresponding acetals. The formation of these intermediates has already been reported in the literature.[9,12] In order to reduce the C–O bonds of acetals, we increased the amount of Pd to 5 mol % and added different Brønsted acids as co-catalysts. First, with formic acid, traces of ether **2a** were observed (Table 1, entry 1). Then, with trifluoroacetic acid, 9% of ether **2a** was detected (Table 1, entry 2). Considering this encouraging result, we continued our Brønsted acids screening while optimizing the reaction conditions; the amount of Pd, the nature and the amount of acid, the temperature, and hydrogen pressure. Thus, the yield of **2a** could be improved to 25% by using *p*-toluenesulfonic acid monohydrate (PTSA·H_2O) as a co-catalyst, 0.5 mol % of Pd and a ratio aldehyde/glycerol of 1/10, at 110 °C for 24 h. The conversion could be improved to 37% by increasing the temperature to 140 °C and diluting the medium to a ratio aldehyde/glycerol of 1/40. Nevertheless, the conversion of the acetals to the corresponding monoethers was still generally low, that is, 37%. (Table 1, entry 4). Finally, the best yield was obtained when camphorsulfonic acid (CSA) was used and the glycerol monoether **2a** was obtained in 57% GC yield (Table 1, entry 5).

Taking into account these encouraging results, we employed the optimized reductive alkylation conditions for the synthesis of linear, saturated 1-*O*-alkyl glycerol monoethers. After 24 h of reaction, ethers **2b–d** were separated from glycerol by extraction with toluene, and pure GMEs **2b–d** were isolated by column chromatography.[13] Thus, GMEs **2b–d** were obtained in high yields and selectivities (Table 2, entries 1–3).

Figure 1 discloses a GC spectrum of the obtained crude material (entry 1). It can be observed that the selectivity of the process is

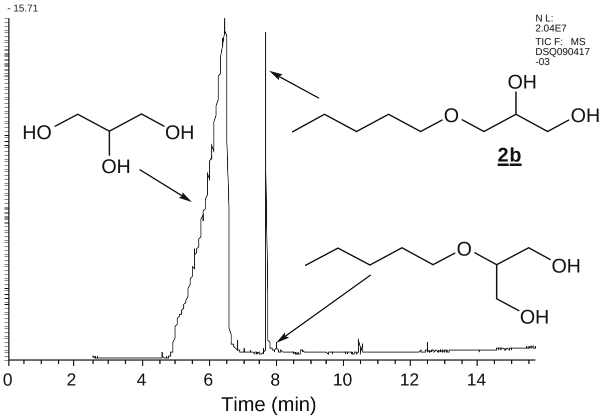
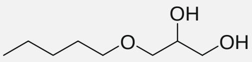
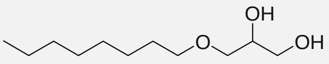
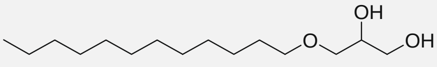
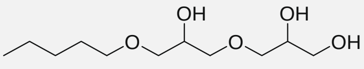
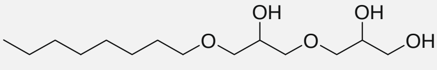
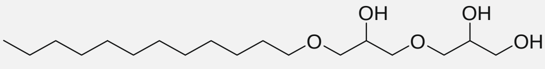


Figure 1. GC/MS analysis of crude of the reductive etherification of glycerol with valeraldehyde **1b** (entry 1).

Table 2
Etherification of mono- and di-glycerol with different aldehydes

Entry	Aldehyde	Alcohol/solvent	Product	Acid	GC yield	Selectivity[b]
1[a]	Valeraldehyde	Glycerol	 2b	CSA[c]	94	>25/1
2[a]	Octanal	Glycerol	 2c	CSA	79	>12/1
3[a]	Dodecanal	Glycerol	 2d	CSA	75	>10/1
4[a]	Valeraldehyde	Di-glycerol	 3b	CSA	83	>9/1
5[a]	Octanal	Di-glycerol	 3c	CSA	72	>9/1
6[a]	Dodecanal	Di-glycerol	 3d	CSA	71	>9/1

[a] 140 °C, 0.5 mol % Pd, 10% acid, 10 bar H_2.

[b] Selectivity between 1-*O*-alkyl glycerol monoether and 2-*O*-alkyl glycerol monoether.

[c] (*R*)-10-Camphorsulfonic acid.

very high since, in these conditions, the major product in the crude is the expected GME **2b** and a very small amount of 2-*O*-alkyl glycerol ether is detected. In this case, the ratio of 1-*O*-alkyl glycerol/of 2-*O*-alkyl glycerol is about 25/1.

In order to test the versatility of our approach, we finally applied these optimized conditions for the reductive alkylation of di-glycerol. Thus, we obtained the desired 1-*O*-alkyl di-glycerol monoethers **3b–d** in high yields and selectivity (Table 2, entries 4–6).

In conclusion, we report herein a benign, eco-friendly process for the synthesis of 1-alkyl mono- and di-glycerol monoethers with high yields and selectivity without the production of unwanted inorganic salts. Key features of the new process are the use of glycerol or di-glycerol as solvent and reactant, a small amount of Pd/C as a catalyst, and Brønsted acid as a co-catalyst. The linear 1-*O*-alkyl glycerol and di-glycerol ethers are recovered by a simple extraction with toluene. This highly selective process opens up a new alternative to the Williamson etherification for the synthesis of linear glycerol monoethers with different hydrophilic–lipophilic balances, which are of great interest in many research fields.

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13. *Typical procedure for reductive etherification of glycerol with aldehyde using H_2 as a reducing agent*: aldehyde (6 mmol) and glycerol (240 mmol) were mixed in a 100 mL steel autoclave. Pd/C (0.5 mol % Pd) and CSA (10 wt %) were added to this solution. The autoclave was first flushed with argon, then with hydrogen three times. The solution was then stirred (1500 rpm) at 140 °C under 10 bars of hydrogen for 24 h. After the reaction was complete, the solution was filtered off and extracted three times with toluene and the products were purified by silica column chromatography (eluent: cyclohexane/ethyl acetate = 4:1–1:1).