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Cyclic glyceryl sulfate: a simple and versatile bio-based synthon for the facile and convergent synthesis of novel surface-active agents

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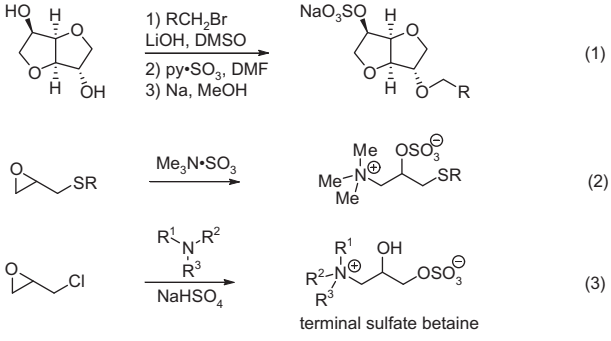
ABSTRACT

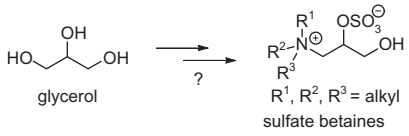
In the frame of biomass valorization, a novel and simple cyclic glyceryl sulfate was efficiently prepared in two steps from glycerol. It was shown to react efficiently with primary, secondary as well as tertiary amines to afford either the corresponding anionic or zwitterionic surface-active agents.

In the last few years, the synthesis of bio-based surfactants has become an active field of research with emphasis on the selection of novel hydrophilic building blocks from biomass. In particular, glycerol has attracted great interest since it is ubiquitous in nature. It is found in vegetal as well as animal fats and oils in its triesterified form.[1] At industrial level, glycerol is mainly obtained as a byproduct in the synthesis of biodiesel from the transesterification of triglycerides to their corresponding fatty acid methyl esters. This process unavoidably generates a large quantity of glycerol (ca. 100 kg per ton of biodiesel), which in turn makes this innocuous chemical widely available. Nowadays, it even suffers from a worldwide oversupply despite its traditional use in the pharmaceutical, food, and consumer care sectors.[1] Therefore it is highly desirable to seek new uses and applications to valorize this renewable feedstock further.

In this context, much attention has been paid recently to the synthesis of valuable chemicals from glycerol, such as acrolein via dehydration reactions,[2] glyceric acid via oxidations[3] or glycerol carbonate among many others.[4] Of particular interest is the replacement of the ethoxylated functionalities in traditional surface-active agents (surfactants) by glyceryl moieties,[5] since their



Scheme 1. Previous work on sulfation of polyols and synthesis of sulfate betaines.



Scheme 2. Looking for a facile synthesis of novel surfactants.

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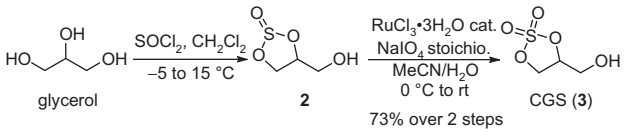


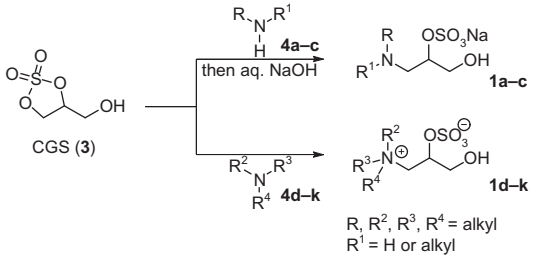
Scheme 3. Straightforward synthesis of **3** from glycerol.

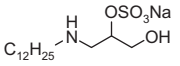
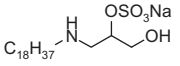
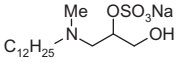
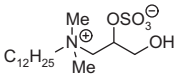
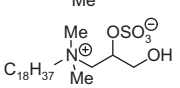
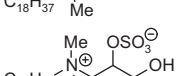
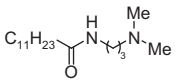
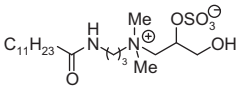
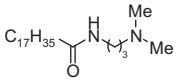
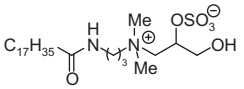
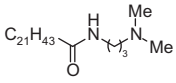
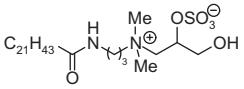
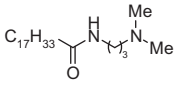
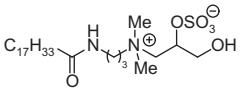
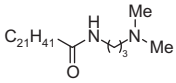
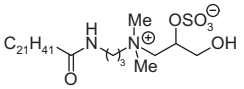
synthesis usually relies on petroleum-based epoxide derivatives. Poly- as well as monoglyceryl surfactants are indeed popular and rather common, especially in the food and cosmetic industries owing to their unique physical properties.[5]

The traditional preparation of these surfactants encompasses a first glycerol activation step via the formation of higher reactive intermediates (e.g., glycidol, epichlorohydrin, glyceryl carbonate),[6] followed by sulfation to afford the corresponding glyceryl sulfate surfactants. The sulfation of a free hydroxyl group is typically carried out with sulfuric acid, chlorosulfonic acid, sulfuryl chloride (SO_2Cl_2), amidosulfonic acid or complexes of sulfur trioxide ($Et_3N{\cdot}SO_3$, $py{\cdot}SO_3$ or $DMF{\cdot}SO_3$ are common), involving unavoidably the generation of salts. Unfortunately, the latter methods are discouraged for polyols (e.g., glycerol derivatives) due to their modest selectivities.[7] Different strategies have been reported to tackle this problem, but relying most often on a multi-step sequence (see for instance, Eq. 1 in Scheme 1).[8] Moreover, these synthetic approaches involve the generation of carcinogenic dioxane,[9] or make use of oxirane-based materials (Scheme 1, Eqs. 2 and 3), being derived either from a non-renewable source (e.g., ethylene) or glycerol itself.[10,11]

Betaines are well-known zwitterionic surfactants widely used in formulations. They are traditionally manufactured by the reaction of tertiary amines with hydrophilic intermediates, such as 2-chloroacetic acid, involving the concomitant and inevitable

Table 1
Test of CGS (**3**) as an entry point to novel surfactants[a]



Entry	Amine (**4a–l**)		Product (**1a–k**)		Yield[c] (%)
1	$C_{12}H_{25}NH_2$	**4a**		**1a**	33
2	$C_{18}H_{37}NH_2$	**4b**		**1b**	39
3	$C_{12}H_{25}NHMe$	**4c**		**1c**	63
4	$C_{12}H_{25}NMe_2$	**4d**		**1d**	65
5	$C_{18}H_{37}NMe_2$	**4e**		**1e**	94
6	$C_{22}H_{45}NMe_2$	**4f**		**1f**	71
7		**4g**		**1g**	78
8		**4h**		**1h**	22
9[b]		**4i**		**1i**	31
10		**4j**		**1j**	51
11[b]		**4k**		**1k**	48

[a] Reactions were performed in THF at room temperature using equimolar amounts of CGS and amine on a 0.1 mol scale.
[b] Amines **4i**, **k** were used in slight excess (1.5 equiv).
[c] Isolated yields.

production of large amounts of salts.[12] To our knowledge, betaines featuring a free (unprotected) hydroxyl group in the embedded glyceryl unit have been reported so far only with terminal sulfate groups (Scheme 1, Eq. 3).[13] In this Letter, we sought a novel, facile, green, and convergent synthesis of sulfate betaines **1** employing glycerol as a bio-based raw material (Scheme 2).

To this aim, we present here a facile and scalable synthesis of a novel activated form of glycerol. This unprecedented compound was termed CGS (**3**) for *Cyclic Glyceryl Sulfate* (Scheme 3).[14] This original synthon was shown to undergo facile nucleophilic attack of primary, secondary, and tertiary amines leading to a wide range of novel betaines and anionic surfactants substituted by a sulfate group at the glyceryl C-2 position.[15]

The one-step direct sulfation of glycerol with DMF·SO_3, H_2SO_4, and SO_2Cl_2 was initially attempted but yielded several byproducts. Sulfuryl chloride is indeed known to give chlorination side reactions thereby lowering significantly the yields of the desired sulfates.[16]

Eventually, CGS (**3**) could be easily prepared from glycerol employing a two-step procedure via cyclic glyceryl sulfite **2** using a protocol adapted from the literature.[17] Treatment of 1 mol of glycerol with one equivalent of thionyl chloride ($SOCl_2$) in dichloromethane at −5 °C afforded the desired crude sulfite **2** as a 1:1 mixture of diastereoisomers with sufficient purity to be engaged directly in the next step.[18] Gratifyingly, the catalytic RuO_4 oxidation method originally developed by Sharpless and Gao in the late 80s[19] affected the desired transformation without compromising the unprotected primary alcohol. The structure of sulfate **3** was secured by ^{1}H NMR and ^{13}C NMR.[20]

This unprecedented activated form of glycerol is relatively stable at neutral pH and room temperature (ca. three days). Above 50 °C, self-polymerization becomes a serious issue, especially under extreme acidic or basic conditions. In addition, in order to improve its shelf life, storage of well-sealed fresh samples in a refrigerator is recommended.

Considering the very good reactivity of cyclic sulfates toward nucleophiles[15] and our continuous interest in developing and bringing to the market new efficient surfactants,[21] **3** was reacted with various bio-based fatty amines (**4a**–**k**) (Table 1).

Slow addition of **3** to a THF solution of primary (**4a**–**b**) or secondary amines (**4c**) afforded the desired anionic surfactants **1a**–**c** in good yields through regioselective ring opening at the primary position of the cyclic sulfate moiety (Table 1, entries 1–3).[22] A typical work-up involved the addition of sodium hydroxide (10% aqueous solution), which led to the product precipitate. The resulting white solid was obtained after filtration, washing, and drying in vacuo. On the other hand, the reaction of tertiary amines **4d**–**k** (Table 1, entries 4–11) with **3** led smoothly to the corresponding sulfate betaines **1d**–**k** in generally good yields. Reactions involving fatty (C_{22}) amines including amide functionalities (**4i** and **4k**) exhibited lower reaction rates, but the conversion to the desired surfactants could be increased further by adding an extra half-equivalent to the reaction mixture.[23] All compounds **1a**–**k** were new and were thus fully characterized by LCMS (ELSD), ^{1}H NMR, and ^{13}C NMR.[24]

In summary, we have developed a new bio-sourced hydrophilic cyclic sulfate (CGS, **3**) as an alternative to oil-based cyclic ethylene sulfates for surfactant synthesis. This novel synthon was efficiently synthesized from glycerol by a simple procedure in good overall yield. Its reaction with a wide range of different amines (**4a**–**k**) gave a straightforward access to a series of new surfactants (**1a**–**k**) under very mild conditions with easy isolation and no salt formation. These unprecedented surfactants showed very promising properties in different applications, notably presenting encouraging perspectives for the replacement of classical betaines.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.068.

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18. Analytical data of sulfite **2** matched the reported ones. See: Ref.16a
19. Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538–7539.
20. *Synthesis of CGS (**3**):* A three-necked round-bottom flask (1 L) flushed with nitrogen was charged with glycerol (92 g, 1 mol) and cooled down to −5 °C. A solution of thionyl chloride (119 g, 1 mol) in CH_2Cl_2 (100 mL) was added dropwise while keeping the temperature below −2 °C. A large amount of HCl gas evolved and the reaction mixture changed from a viscous colorless oil to a suspension and finally to a colorless solution. The mixture was stirred for 24 h between 10 and 15 °C. The volatiles were then removed in vacuo to yield **2** as a light yellow liquid (137 g, 96%). It was engaged in the next step without further purification. A three-necked round-bottom flask (1 L) flushed with nitrogen was charged with **2** (27.6 g, 0.2 mol), acetonitrile (200 mL), $RuCl_3{\cdot}3H_2O$ (0.43 g, 2 mmol), and $NaIO_4$ (59.9 g, 0.28 mol) and was cooled down to 0 °C. Cold water (300 mL) was added and the reaction mixture was warmed to 30 °C and stirred for additional 5 min. Ethyl acetate (300 mL) and a saturated aq. $NaHCO_3$ solution (200 mL) were added successively to the green suspension. The aqueous phase was then extracted with ethyl acetate (2 × 300 mL). The combined organic layers were washed with water (160 mL), dried over Na_2SO_4, and filtered. The solvent of the filtrate was then removed in vacuo to yield **3** as yellow liquid (22.4 g, 73%). It was dissolved in dry THF (5 mL) and stored in a refrigerator. ^{1}H NMR (400 MHz, CD_3OD): δ_H = 5.08–5.04 (m, 1H), 4.82–4.78 (dd, *J* = 8.8, 6.8 Hz, 1H), 4.65–4.61 (dd, *J* = 8.8, 7.2 Hz, 1H), 3.89–3.85 (dd, *J* = 13.2, 3.2 Hz, 1H), 3.79–3.75 (dd, *J* = 13.2, 4.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, CD_3OD): δ_C = 83.2, 69.6, 59.7 ppm.
21. http://www.rhodia.com/en/markets_and_products/product_ranges/surfactants.tcm.
22. NMR data are in full agreement with the sulfate group positioned at the glyceryl C-2.
23. Amines **4g**–**k** were derived from the corresponding naturally occurring cis-unsaturated fatty acids.

24. *Analytical data for* ***1e***: ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 5.09 (dd, J = 6.4, 4.8 Hz, 1H), 4.53–4.50 (m, 1H), 3.75–3.71 (m, 1H), 3.49–3.31 (m, 5H), 3.12 (d, J = 5.2 Hz, 6H), 1.77–1.59 (m, 2H), 1.24 (br s, 30H), 0.85 (t, J = 6.8 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 71.6, 64.4, 64.2, 62.0, 51.7, 51.6, 31.8, 29.5–29.4 (9C), 29.3, 29.2, 29.0, 26.2, 22.6, 22.2, 14.4 ppm; IR (neat): ν_{max} = 3316, 2916, 1467, 1273, 1210, 719 cm^{-1}; MS (ESI$^+$): m/z = 452 [M+H]$^+$. HRMS (ESI$^+$): calcd for $C_{23}H_{49}N_1Na_1O_5S_1$ [M+Na]$^+$: 474.3224, found: 474.3245.