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MICROWAVE VERSUS CONVENTIONAL HEATING IN ORGANIC SYNTHESIS. A COMPARATIVE STUDY OF THE CONDENSATION OF POLYOLS WITH KETONES USING THE HYDROPHILIC SIO2-SO3H CATALYST UNDER SOLVENT-FREE CONDITIONS

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This paper is dedicated to the memory of our dear co-worker Stanlei I. Klein, who passed away while this paper was being peer-reviewed.

Abstract: SiO_2-SO_3H, with a surface area of 115 m^2/g, a pore volume of 0.38 cm^3g^{-1} and 1.32 mmol H^+/g, was used as a catalyst (10% w/w) for the synthesis of various ketals by the condensation of polyols and ketones in solvent-free reactions using both conventional heating (CH) and microwave irradiation (MW). The ketals were mostly obtained in higher yields with microwave irradiation. Fewer residual ketones and fewer side products were recovered; reaction times of 2-12 hours under conventional heating were reduced to 3-7 minutes using microwave irradiation.

Keywords: Sulfonated silica acid catalyst; ketals; glycerol; hydrophilic catalyst; condensation reactions, protecting groups.

INTRODUCTION

Ketals are useful intermediates in organic synthesis; they protect carbonyl groups of ketones and aldehydes or the two hydroxyl groups of diols when organic transformations are performed [1-3]. Furthermore, ketals are compounds with exciting and well-known industrial and commercial applications in many fields, especially as surfactants and emulsifiers [4,5]. Some applications include their use in adhesives [6] coatings [7], plasticizers [8], ointments [9] perfumes [10], and as an intermediate for the preparation of synthetic polysulfide rubber [11]. Large polymers and cross-linked polymers are made up of ketals because they have superior properties, such as high tensile strength and high glass transition temperatures [12,13]. An interesting use of certain ketals is in the realm of special-purpose fuels or fuel additives [14,15]. The use of ketals as fuel additives is one of the promising applications of the glycerol byproduct that is obtained in biodiesel synthesis [15].

Microwave technology has become very useful in organic synthesis. It has been greatly beneficial for chemists to achieve fast, clean, and high-yielding synthetic transformations. The heating is instantaneous and precise, and no contact is required between the energy source and the reaction vessel [16-19]. The principles of microwave dielectric heating have been described in several publications in the scientific literature [17].

We recently reported the use of SiO_2-SO_3H for the ketalization of ketones to 1,3-dioxolanes using the polyols ethylene glycol (EG), neopentyl glycol (NPG), trimethylolpropane (TMP) and glycerol (Gly), and the aldol condensation of the ketones cyclohexanone, acetophenone, 4-methylacetophenone, and benzophenone using microwave irradiation [20]. There have been reports of heterogeneous catalysts for acetalization reactions, and an excellent review by Trifoi on the specific field of the heterogeneous acetalization and ketalization of glycerol is available [21]. Our report on the use of microwave irradiation is still new in the area, and the use of the sulfonated catalyst SiO_2-SO_3H for the preparation of glycerol ketals is still unique. Therefore, we now wish to report a full comparison of those ketalization reactions in identical reactions using conventional heating and employing the same heterogeneous catalyst SiO_2-SO_3H (Scheme 1).

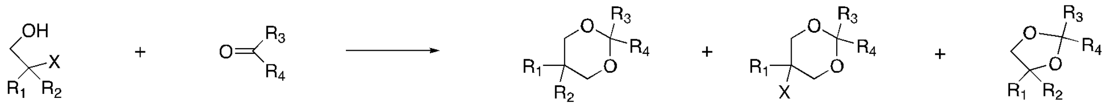
EXPERIMENTAL

RAW MATERIALS AND CHEMICALS

All the reagents (analytical grade) were supplied by Vetec, São Paulo, Brazil. All the commercial reagents were used directly; crude glycerol was obtained from the transesterification of waste cooking oil with methanol [22]. The sulfonated silica SiO_2-SO_3H was prepared as previously reported [15].

INSTRUMENTATION

NMR data were obtained on *Bruker Avance* 400, *Avance* 500, and AC-300 spectrometers. Ketal yields were determined with a *Shimadzu* GC-2010 gas chromatograph equipped with a flame ionization detector (FID). Ketal contents were determined with a *Perkin Elmer Claurus* 680 system equipped with an Elite-5 (5% diphenyl) dimethylpolysiloxane capillary column (50 m, 0.32 mm i.d., 1.00 mm film thickness). The injected volume was 1 mL, with a split ratio of 70:1. Helium was used as the carrier gas with a constant flow rate of 1 $mLmin^{-1}$. The injector temperature was 250 °C. The mass spectrometer was a *Claurus* SQ 8C (*Perkin Elmer*) with the El mass range set at 40-450 AMU. The progress of the reactions was accompanied by TLC. For TLC, 5 µL of the reaction mixture was loaded onto a pre-



1 $R_1 = R_2 = Me$; $X = CH_2OH$	5 Cyclohexanone	5+1	5+2	traces 5+3	5+3	5+4
2 $R_1 = Et$; $R_2 = X = CH_2OH$	6 $R_3 = Me$; $R_4 = Ph$	6+1	6+2	traces 6+3	6+3	6+4
3 $R_1 = H$; $R_2 = CH_2OH$; $X = OH$	7 $R_3 = Me$; $R_4 = p\text{-}MePh$	7+1	7+2	traces 7+3	7+3	7+4
4 $R_1 = R_2 = H$; $X = OH$	8 $R_3 = R_4 = Ph$	8+1	8+2			8+4

Scheme 1: Me= methyl; Et = ethyl, Ph = phenyl.

coated silica gel 60 TLC plate (*Merck*). The mobile phase was hexane/ethyl acetate (4:1), and the plate was developed with iodine, UV light, or by using an ethanolic vanillin developing agent. Silica gel (*Merck* 230-400 mesh) was used for purification of products by flash column chromatography using 8:2 hexane:ethyl acetate as the eluent.

TYPICAL PROCEDURES

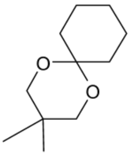
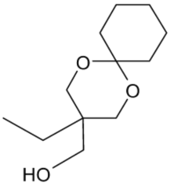
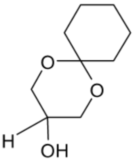
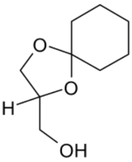
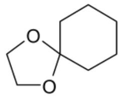
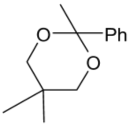
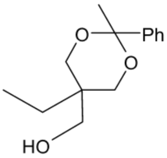
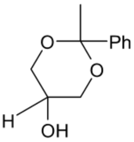
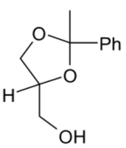
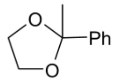
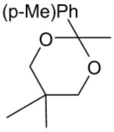
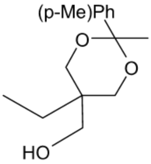
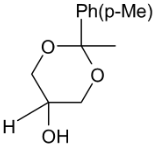
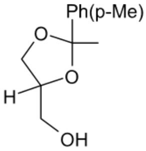
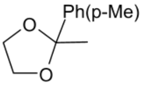
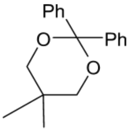
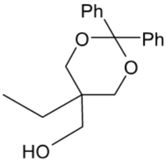
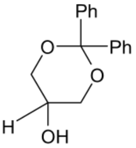
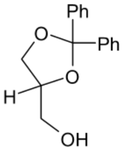
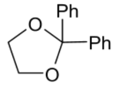
2.3.1. All the reactions were irradiated in an unmodified domestic microwave (MW) oven (900 GHz)/360 W using an open 125-mL two-necked round bottom flask, and they were accompanied by TLC or GC-MS. Typically, the amount of catalyst [10% (w/w) relative to the amount of ketone] was weighed directly into the flask, and the desired quantities of the ketone and alcohol were added in a 1:5 molar ratio. The mixture was quickly mixed by shaking and immediately irradiated. The silica catalyst does not allow the final temperature of the slurries to exceed 73 ºC. To each of the cooled vessels from the reactions, 30.0 mL of diethyl ether was added, and the mixture was filtered. The organic extracts were washed with 10.0 mL of saturated $NaHCO_3$, dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The residues were purified on chromatographic columns using 8:2 hexane:ethyl acetate as eluent to furnish the pure products as colorless oils. For the synthesis of ketals, the amounts of ketone (1.0 mmol) and alcohol (5.0 mmol) were maintained throughout. The amount of catalyst used in each run was adjusted to maintain a constant 10% mass-to-mass ratio to the ketone, and the reactions were irradiated for 2 to 7 min. The ketals were identified by GC-MS and ^1H and ^{13}C NMR spectroscopy.

2.3.2. The conventional heating reactions were performed in a standard reflux apparatus: water-cooled condenser with a $CaCl_2$ drying tube and access for sample removal for TLC. The quantities of ketones, polyols, and catalyst employed were the same as those used in section 2.3.1. The two-neck round bottom flask was heated in an oil bath at 120 ºC with magnetic stirring. To each of the cooled vessels from the reactions, 30 mL of diethyl ether was added, and the mixture was filtered. The organic extracts were washed with 10 mL of saturated $NaHCO_3$, dried over anhydrous $MgSO_{4,}$ and concentrated under reduced pressure. The residues were purified by flash chromatography using 8:2 hexane:ethyl acetate as the eluent to furnish the pure products as colorless oils.

RESULTS AND DISCUSSION

We used the SiO_2-SO_3H catalyst in ketalization and aldol condensation reactions in a previous work [20], where reactions were completed within minutes using microwave-assisted heating. One example involved the preparation of the cyclohexanone-glycerol ketal (**5-3**) in 70.5% yield in only five minutes (Table 1). Such compounds, with high carbon and oxygen contents, are of interest as additives for the biodiesel and related oil industries [23]. In particular, **5-3** is an example of a possible use for the surplus glycerol that exists in the world market as the side product of the biodiesel industry [24-26]. However, even though reactions accomplished with MW irradiation result in reasonable product yields in exceedingly short times, it is difficult to envisage reasonable laboratory set ups for its commercial application. Therefore, the understanding of the mechanisms of the reactions that lead to compounds such as **5-3** under the more standard conditions of conventional heating is important.

A better yield was observed with the conventional heating method after 2 h of reaction in two examples (ketals **5-1** and **5-4**, Table 1). Among those glycerol ketals shown

	Polyols*				
	NPG (**1**)	TMP (**2**)	Gly (**3**)	Gly (**3**)	EG (**4**)
Cyclo hexanone (**5**)					
	5-1	**5-2**	**5-3**	**5-3**	**5-4**
CH	72%; 2 h	47%; 4 h	Traces	90%; 2 h	92%; 1 h
MW	99%; 4 min	65.6%; 7 min	-	70.5%; 5 min	99.9%; 2 min
Aceto phenone (**6**)					
	6-1	**6-2**	**6-3**	**6-3**	**6-4**
CH	15%; 8 h	17%; 8 h	Traces	4%; 8 h	25%; 2 h
MW	93.6%; 4 min	66.3%; 3 min	-	58.9%; 2 min	50.5%; 2 min
4-Methyl acetophenone (**7**)					
	7-1	7-2	7-3	**7-3**	**7-4**
CH	19%; 6 h	21%; 8 h	Traces	8%; 8 h	29%; 4 h
MW	75.1%; 5 min	63.6%; 3 min	-	55.6%; 5 min	49.7%; 2 min
Benzo phenone (**8**)					
	8-1	**8-2**	**8-3**	**8-3**	**8-4**
CH	12%; 6 h	10%; 8 h	-	-	19%; 4 h
MW	49.3%; 5 min	53.5%; 3 min	-	-	28.9%; 2 min

*The numbers following the products correspond to the combination of the ketone number with the polyol number. NPG, neopentyl glycol; TMP, trimethylolpropane; Gly, glycerol; EG, ethylene glycol.

Table 1. Percentage yields and reaction times for the ketalization of polyols with selected ketones using conventional heating. Related MW data was extracted from ref. 20.

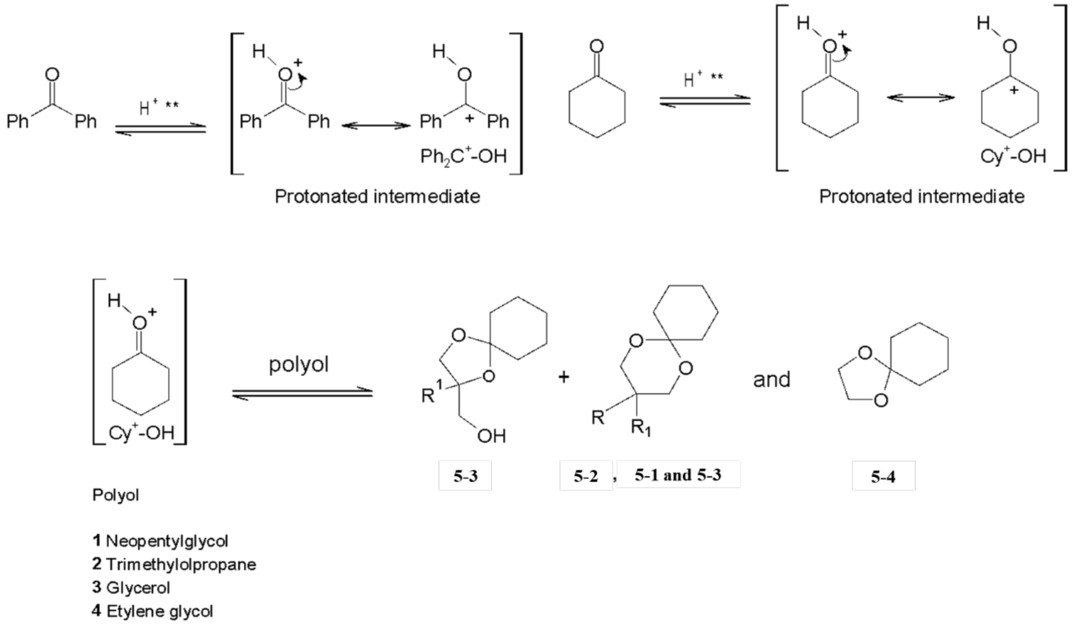
in Table 1, the cyclohexanone derivative had already been obtained in 90% yield by high power microwave irradiation (600 W, 140 °C, 15 minutes) [27].

Aromatic ketones did not give good yields, and large amounts of starting materials could be recovered (Figure 1). This observation is due to the greater stabilization of the carbonyl group as a result of conjugation with the aromatic ring. This stabilization is lost in the ketal. In addition, there is a certain steric hindrance to attack on the carbonyl group caused by the two phenyl groups bound to the carbonyl for the nucleophilic attack of the oxygen of glycerol on the positively charged carbonyl carbon. In summary, the formation of ketals from aromatic ketones is generally more difficult than that from aliphatic ketones because the conjugated carbonyl is more stable than the aliphatic ketone.

The diffusion of glycerol through SiO_2-SO_3H in solvent-free reactions might be difficult because of the fact that glycerol is very polar and would be highly attracted to the hydrophilic catalyst. Thus, it adheres to the surface of SiO_2-SO_3H. However, the retention of glycerol by the catalyst is markedly lower when the reaction system is under the effects of microwave irradiation. The yields were always higher in reactions with microwave irradiation compared to the yields obtained in processes carried out under conventional heating, with the exception of the reaction of glycerol with cyclohexanone during 5 min.

Not only was the use of direct MW heating able to reduce chemical reaction times from hours to minutes and increase the yields (in most of the reactions), but it also resulted in a decrease in side reactions and improved reproducibility. During our attempts to perform ketalization reactions using conventional heating, it became clear that side reactions occurred using the SiO_2-SO_3H catalyst, namely, formation of ethers and aldol condensations. These side products were observed after 4 h of conventional heating, and no further increase in the conversion of the reactants into ketals was observed after 4 h (Figure 2).

The great difference observed in the amount of side products, as with benzophenone NPG ketal (**8-1**) (Figure 1),



Scheme 2.

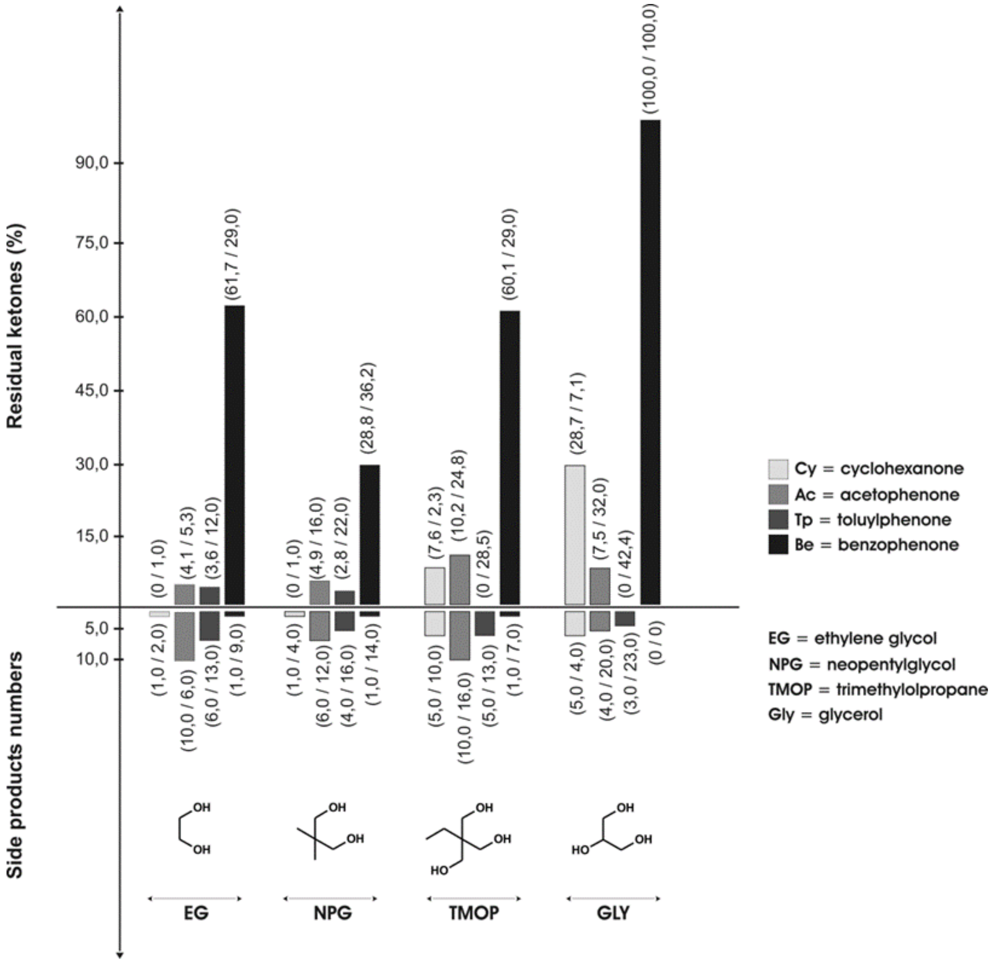


Figure 1. Recovered residual ketones (%)/side product ratios using microwave irradiation (MW) and conventional heating (CH) to form ketals with SiO_2-SO_3H catalyst and no solvent. The values in parenthesis refer to the percentages of recovered ketones with the (MW) and (CH) methods, respectively.

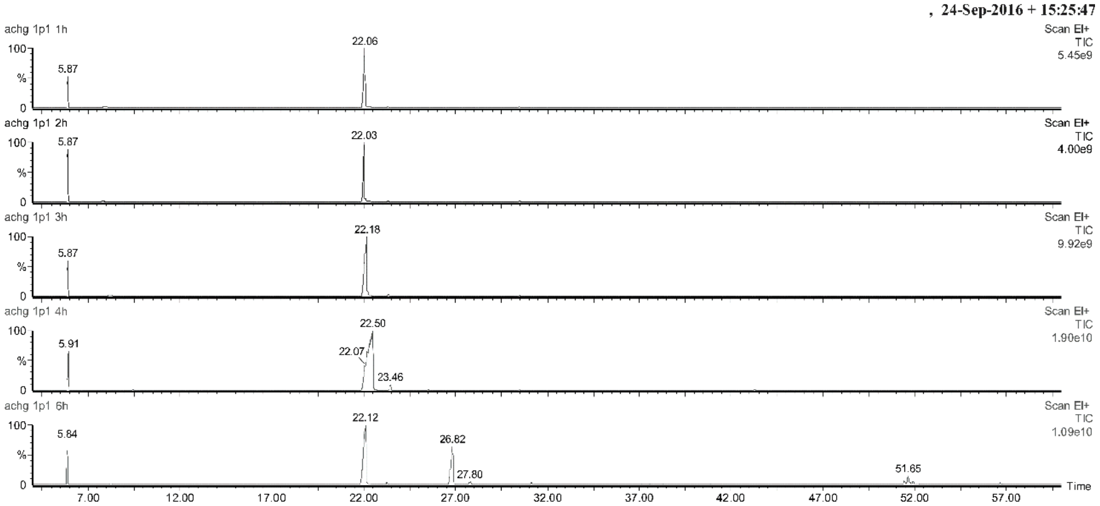


Figure. 2. Overlapped chromatograms (GC/MS) for synthesis of acetal **5-3** showing the formation of side products after 4 h of reaction; the optimum results were achieved after 2 h of reaction. Cyclohexanone, RT 5. 67 min; 1,4-dioxaspiro[4.5]dec-2-ylmethanol, RT = 22 min; [1,1'-bi(cyclohexylidene)]-2-one, RT = 26.82 min; [1,1':3',1"-tercyclohexane]-1(1'),1"(3')-dien-2'-one, RT = 51.65 min.

could be influenced by the thermal history of the reaction, a consequence of the rapid increase in the temperatures obtained by microwave heating. Chromatograms were developed to accompany the progress of the reactions. The progress of the reaction of glycerol with cyclohexanone to form **5-3** is shown in figure 2. Yields of 90% were obtained with heating for two hours. The same yields were obtained with heating for three hours. After this time, byproducts began to appear in the chromatograms. These byproducts are formed by decomposition or rearrangement of the initial ketal and by condensation reactions of the ketone.

The formation of six-membered ketals (1,3-dioxane) seems to be favored over the formation of 1,3-dioxolanes, in particular in the case of the less reactive acetophenone (Table 1). No formation of the six-membered isomers of the ketals involving glycerol was observed with MW-assisted condensations, although no reaction occurred with benzophenone under the solvent-free conditions. The selectivity for isomers of the five- and six-membered ring ketals is demonstrated in Fig. 2. One can see that the distribution is significantly affected by the structure of the ketones in the reaction with conventional heating, yielding about 99% of the five-membered ring acetal (***Z*** + ***E***) and 1% of the six-membered ring acetal (***Z*** + ***E***) in the reaction of glycerol with cyclohexanone.

CONCLUSION

The use of microwave - assisted heterogeneous catalysis reduced reaction times for the ketal formation from hours to minutes, with an increase in the yields, a decrease in the occurrence of side reactions and improved reproducibility when compared with the results obtained with conventional heating.

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REFERENCES

1. J Heeres, R Hendrickx, J Van Cutsem, Antimycotic azoles. 6. Synthesis and antifungal properties of terconazole, a novel triazole ketal. Journal of medicinal chemistry 26(4) (1983) 611-613.

2. W Lenselink, Cyclic acetals and ketals and their use in perfume compositions. U.S. Patent 4,211,674, 8 jul. 1980.

3. C Mertesdorf, N Muenzel, HE Holzwarth, PA Falcigno, H-T Schacht, O Rohde, R Schulz, SG Slater, D Frey, O Nalamasu, AG Timko, TX Neenan, Structural Design of Ketal and Acetal Blocking Groups in 2-Component Chemically Amplified Positive DUV-Resists. Advances in Resist Technology and Processing XII. International Society for Optics and Photonics, 2438 (1995) 84-99.

4. MO Sonnati, S Amigoni, EPT de Givenchy, T Darmanin, O Choulet, F Guittard, Glycerol carbonate as a versatile building block for tomorrow: synthesis, reactivity, properties and applications. Green Chemistry, 15(2) 2013 283-306.

5. P Tsakotellis, HL Johnson, WA Skinner, D Skidmore, HI Maibach. Topical mosquito repellents III: carboxamide acetals and ketals and related carbonyl addition derivatives. Journal of Pharmaceutical Sciences, 60(1) 1971 84-89.

6. R Haag, AG Leach, SV Ley, M Nettekoven,J Schnaubelt, New polyethylene glycol polymers as ketal protecting groups–a polymer supported approach to symmetrically substituted spiroketals. Synthetic Communications, 31(19) 2001 2965-2977.

7. a) LR Rieth, CM Leibig, M Grove, JD Pratt, M Jackson, Latex coating compositions including carboxy ester ketal coalescents, methods of manufacture, and uses thereof. Patent Nº US 9,074,065 B2 (2015). b) SF Wanat, JE Oberlander, RR Plass, D McKenzie, Photoresist compositions comprising acetals and ketals as solvents foreign patent documents. Patent Nº US 6,911,293 B2 (2005).

8. S Kandula, L Stolp, M Grass, B Woldt, D Kodali, Synthesis and Functional Evaluation of Soy Fatty Acid Methyl Ester Ketals as Bioplasticizers. J. Am. Oil Chem. Soc. 91 (2014) 1967-1974. b) DJ Yontz, F Stollmaier, KJ Bechtold, Plasticizer blends of ketal compounds. Patent Nº US 9,550,884 B2 (2017).

9. PHR Silva, VLC Gonçalves, CJA Mota, Glycerol acetals as anti-freezing additives for biodiesel. Bioresource technology, 101(15) (2010) 6225-6229.

10. MD Coon, Reaction products of formals, acetals and ketals with succinic acid or anhydride as lubricating oil and fuel additives. U.S. Patent Nº 3,910,845, 7 (1975).

11. DE Vietti, Polysulfides. Comprehensive Polymer Science and Supplements, 5 (1989) 533-542. doi:10.1016/b978-0-08-096701-1.00172-5

12. B Delfort, I Durand, A Jaecker, T Lacome, X Montagne, F Paille, Diesel fuel compounds containing glycerol acetals. U.S. Patent Nº 6,890,364 (2005).

13. MJ Climent, A Corma, S Iborra, Conversion of biomass platform molecules into fuel additives and liquid hydrocarbon fuels. Green Chemistry, 16(2) (2014) 516-547.

14. N Rahmat, A Norhasyimi, AZ Abdullah, AR Mohamed, Recent progress on innovative and potential technologies for glycerol transformation into fuel additives: a critical review. Renewable and Sustainable Energy Reviews, 14(3) (2010) 987-1000.

15. SL Barbosa, M Ottone, MC Santos, GC Junior, CD Lima, GC Clososki, NP Lopes, SI Klein, Benzyl benzoate and dibenzyl ether from benzoic acid and benzyl alcohol under microwave irradiation using a SiO_2-SO_3H catalyst. Catalysis Communications, 68 (2015) 97-100.

16. P Lidström, J Tierney, B Wathey, J Westman, Microwave assisted organic synthesis - a review. Tetrahedron, 57(45) (2001) 9225-9283.

17. CO Kappe, D Dallinger, Controlled microwave heating in modern organic synthesis: highlights from the 2004 - 2008 literature. Molecular diversity, 13(2) (2009) 71 - 193.

18. R Cerón-Camacho, JA Aburto, LE Montiel, R Martínez-Palou, Microwave-assisted organic synthesis versus conventional heating. A comparative study for Fisher glycosidation of monosaccharides. Comptes Rendus Chimie, 16(5) (2013) 427-432.

19. PGM Wuts, TW Greene, Greene's protective groups in organic synthesis. John Wiley & Sons, 2006.

20. SL Barbosa, M Ottone, MT de Almeida, GLC Lage, MAR Almeida, DL Nelson, WTP dos Santos, GC Clososki, NP Lopes, SI Klein, LD Zanatta, Ketalization of Ketones to 1,3-Dioxolanes and Concurring Self-Aldolization Catalyzed by an Amorphous, Hydrophilic SiO_2-SO_3H Catalyst under Microwave Irradiation. J. Braz. Chem. Soc. 29(8) (2018) 1663-1671.

21. A.R. Trifoi, P.Ş. Agachi, T. Pap. Glycerol acetals and ketals as possible diesel additives. A review of their synthesis protocols. Renew. Sustain. Energy Rev., 62 (2016) 804-814

22. SL Barbosa, ACP Rocha, DL Nelson, MS de Freitas, AAPF Mestre, SI Klein, GC Clososki, FJ Caires, DL Flumignan, LK dos Santos, AP Wentz, VMD Pasa, RDF Rios, Catalytic Transformation of Triglycerides to Biodiesel with SiO_2-SO_3H and Quaternary Ammonium Salts in Toluene or DMSO. Molecules, 27 (2022) 953-964.

23. A Talebian-Kiakalaieh, NAS Amin, N Najaafi, S Tarighi, A Review on the Catalytic Acetalization of Bio-renewableGlycerol to Fuel Additives. Frontiers in Chemistry 6 (2018) 573-597.

24. J Plácido, S Capareda, Conversion of residues and by-products from the biodiesel industry into value-added products. Bioresour. Bioprocess. 3(23) (2016) 1-12.

25. AB Leoneti, VA Leoneti, S Valle, WB de Oliveira. Glycerol as a by-product of biodiesel production in Brazil: Alternatives for the use of unrefined glycerol. Renewable Energy 45 (2012) 138-145.

26. A Rodrigues, JC Bordado, R G dos Santos, Upgrading the Glycerol from Biodiesel Production as a Source of Energy Carriers and Chemicals - A Technological Review for Three Chemical Pathways. Energies 10 (2017) 1817 (1-36).

27. KSW Sing, DH Everett, RAW Haul, L Moscou, RA Pierotti, J Rouquerol, T Siemieniewska, Physical and biophysical chemistry division commission on colloid and surface chemistry including catalysis. Pure Appl. Chem. 1985 57(4) 603-619.