A call to (green) arms: Synthesis of Acetals and cyclic Acetals with and without Solvents - A comparison

Dr Sangeeta Gautam,

Associate Professor
Dept. Of Science, Faculty of Education and Methodology
Jayoti Vidyapeeth Women's University, Jaipur

Abstract: **The scope of green chemical synthesis and failure of conventional methods in synthesis of organic compounds has been examined. Green solvents (like-DMSO, DMF, Water) and green methods were chosen as model to determine suitable conditions of the reaction. In microwave synthesis a solvent-free reaction or in presence of universal solvent (water), the product 2-methyl-2, propyl dioxolane was obtained with high yields 87% and 88% respectively. The protonic acid (HCl) was the preferred choice as a catalyst and support to keep the reaction medium under mild and neutral conditions.**

Index Terms**: Green chemical synthesis, Alternative solvents, Non-corrosive, High yields, Stable to reaction conditions**

INTRODUCTION:

An organic compound is defined as any compound whose molecules contain **carbon** and **hydrogen** (hydrocarbons) and compound that is derived of it. Due to carbons ability to catenate, millions of organic compounds are known. It is difficult to study these millions of organic compounds together. Therefore, these organic compounds are divided and further sub-divided into different classes for an ease. It includes one of the classes of heterocyclic compounds.

Various compounds such as alkaloids[1], antibiotic, essential amino acids[2], vitamins, harmons, haemoglobin and large number of dyes[3] and synthetic drugs[4] contain hetero cyclic ring systems.

Substituted cyclic acetals are important intermediates in organic synthesis and are widely used as solvents, plasticizers, surfactants, etc.[5]. 1,3-Dioxacyclo-alkyl moiety is often present in complex molecules having biological activity[6]. Protection of carbonyl function as acetal is known to be the widely used synthetic route for the manipulation of various multifunctional organic molecules [7]. Acetals can also be used for C-C bond formations [8], synthesis of ethers [9], esters [10], and cyclization of diynes [11] (Fig.1). Additionally acetals have enormous industrial importance due to their potential utility as flavoring agents in distilled beverages, diesel additives and plastic materials [12].

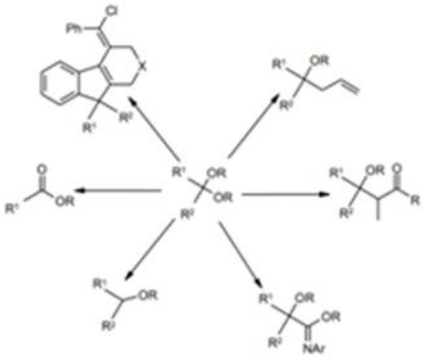


Fig.1- Uses of Acetals

1.1 Acetals and Cyclic Acetals

An acetal is an organic molecule where two separate oxygen atoms are single bonded to a central carbon atom [13].e.g.

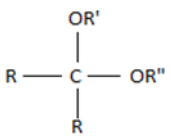


Fig. 2 - Structure of Acetal

A cyclic acetal is an acetal in the molecule of which the acetal carbon and one or both oxygen atoms thereon are members of a ring [14].Example,

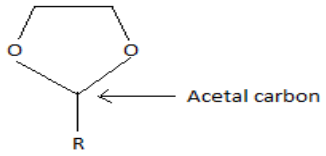


Fig. 3 - Structure of Cyclic Acetal

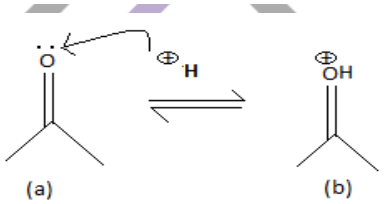
Formation of Acetals

Acetals are formed by aldehydes and ketones which reacts with alcohols or diols in presence of acid catalysts. Acid catalysts are acids that speed up the rate of a reaction. As catalyts are never eaten alive in a chemical reaction, they simply play the role as a super boost, ensuring the reaction reaches completion in record time.

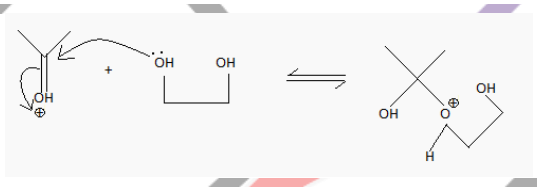
1.2. Mechanism of formation:

There are seven steps involved in acetal formation.

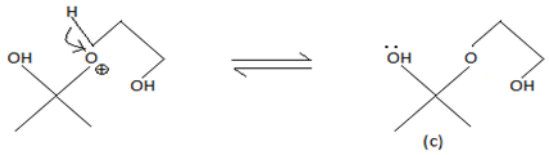
Step 1:- Protonate the carbonyl group on the ketone molecule (a) using the proton from an acid catalyst. Protonation refers to the transfer of a proton (H) to a molecule or atom in order to form a bond.



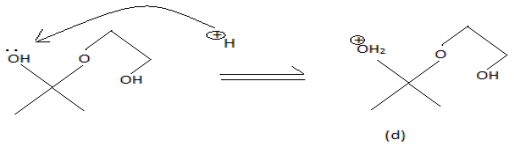
Step 2:- Take andiol and use it to perform a nucleophilic attack on the product formed in step one (b). A nucleophile is a species that graciously donates its electron pair in order to form a chemical bond.



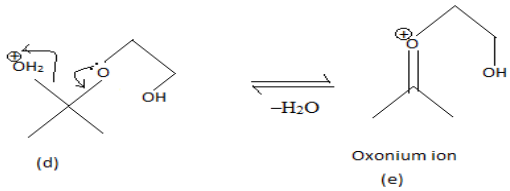
Step 3:- Deprotonate, or remove the proton (H), the product formed in step three, is an hemiacetal (c). A hemiacetal is a molecule formed when an diol is added to an ketone.



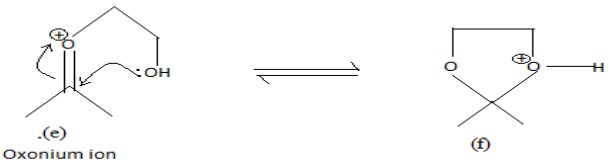
Step 4:- Take hemiacetal and protonate the alcohol group using the hydronium ion.



Step 5:- In this step, due to unstable charge water molecule bump off the product. To make stabilize the product (d) moves the electron pair from other oxygen molecule.

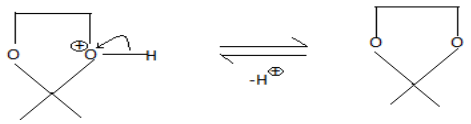


Step 6:- The lone pair of other oxygen atom of diol move on to the carbocation formed when double bond moves on former oxygen atom to complete its valency. This results in cyclisation of the product (e).



.(e) Oxonium ion (f)

Step 7:- In the final step,deprotonation of the final product (f) takes place. The so-called product is dioxolane.



Dioxolane

1.3. Qualities of a good protecting group in organic synthesis

A good protecting group should be such that –

(a) Simple to put on, in high yield.

(b) Stable to reaction conditions.

(c) Easy to remove, in high yield.

Protecting groups are more commonly used in small-scale laboratory work and initial development than in industrial production processes because their use adds additional steps and material costs to the process [15-17].

1.4. Application of dioxolane and its derivatives and protection of carbonyl group

-The reaction type i.e. protection of carbonyl compound is used in the total synthesis of many of the natural products such as - Total Synthesis of **Cholestrol**, **Geraniol**, etc.

-Dioxolane is an essential raw material for the production of the anti-viral compound acyclovir (an antiviral drug used chiefly in the treatment of herpes and AIDS) [18].

-1, 3-dioxolane is a powerful aprotic solvent for used in formulations, in production processes or even as a reactant itself. It is also an essential ingredient in important industrial polymers and certain niche pharmaceutical intermediates. Dioxolane can serve as a MV regulator in the polymerization of vinyl chloride. It can also serve to stabilize crosslinked PVC [19].

-Dioxolane is also used as an alternative for other more toxic organic solvents. For example, it is the best substitute for chlorinated organic solvents such as methylene chloride, 1,2-dichloroethane and 1,1,1-trichloroethane. Also it is the most powerful solvent for softening and dissolving polymers made from polar monomers, for e.g.- polycarbonates, acrylates, cellulosics urethanes, phenolics etc [20].

- A mixture of ethylene glycol and 1, 3-dioxolane (DOXL) forms an electrolyte and this electrolyte is used in lithium sulfur battery [21].

-2,2-dimethyl-1,3-dioxolane derivatives could serve as a promising compound for the development of novel anti-rhinoviral medicines. It works against HRV (human rhino-virus) protease [22].

-Glycerol acetals and Glycerol ketals can be synthesized through the acid-catalyzed reactions of glycerol with aldehydes and ketones respectively. And these are used as fuel (diesel) additives in biodiesel industry [23].

Classical methods for the synthesis of acetals involve the treatment of aldehydes or ketones with an alcohol by either protic or Lewis acid catalyst[7]. Unfortunately, these procedures have some disadvantages such as use of corrosive and costly reagents or additives, halogenated solvents, large waste and high catalyst loading[24-39].

In this work a novel and efficient metal-free protocol for the synthesis of acetals and cyclic acetals using green chemical procedures and green solvents has been discussed to obtain valuable information on reaction conversion, selectivity and reaction yield.

According to the green chemistry point of view reactions are important because these types of reactions would allow the minimization of waste compared to stepwise reactions the amount of solvents, reagents, adsorbents and energy would be dramatically decreased. Thus, these reactions would allow an ecologically and economically favorable production[40].

1.5. Materials and Methods-

[A]Chemicals

1. Ethylene glycol (Diol)
2. Methyl propyl Ketone
3. Hydrochloric acid
4. Solvents like- DMSO, DMF, Toluene, Distilled Water,
5. Solvent for TLC chamber- petroleum ether and benzene.
6. Iodine crystals

[B]Apparatus

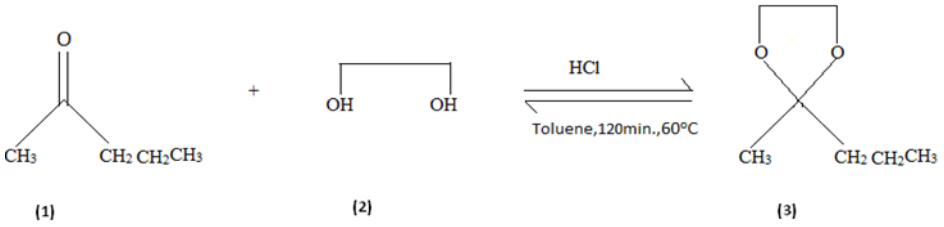
Water condenser, guard tube, glass wool, plastic pipes, stand to hold condenser, clamp, heating mantle, R. B. flask, dean-stark apparatus, cork, petroleum gel, TLC sheets, desicator, etc.

Methods-

[1] By **conventional heating** method-

General procedure for 2-methyl-2, propyl dioxolane

To a flame-dried 100ml flask add methyl propyl ketone **(1)** and ethylene glycol **(2)** in equimolar ratio. Add hydrochloric acid as a catalyst and then toluene as a solvent. Fix the reaction vessel using dean stark apparatus and condenser (**Fig.4**). As temperature rises, the reaction was monitored by TLC (**Fig.5**). After the completion of the reaction, the mixture was filtered and concentrated on sand bath to obtain pure product **(3)** 2-methyl-2, propyl dioxolane. The reaction was completed in 120min. with 70% yield **(scheme 1).**



Scheme- 1

Fig.4:- Reaction setup

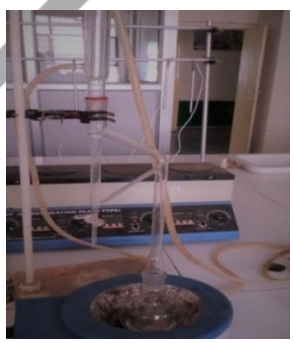


Fig.5:- Desicator showing TLC

Procedure using green solvents: [1] DMSO as a green solvent.To a flame-dried 100ml flask add reactant **(1)** and **(2)** in equimolar ratio. Add hydrochloric acid as a catalyst and then DMSO as a solvent. Set the reaction vessel using dean stark apparatus and condenser. As temperature rises, the reaction was monitored by TLC. After the completion of the reaction, the mixture was filtered and concentrated on sand bath to obtain pure product **(3)** 2-methyl-2, propyl dioxolane. The reaction was completed in 150min.with 60% yield.

[2] DMF as a green solvent:

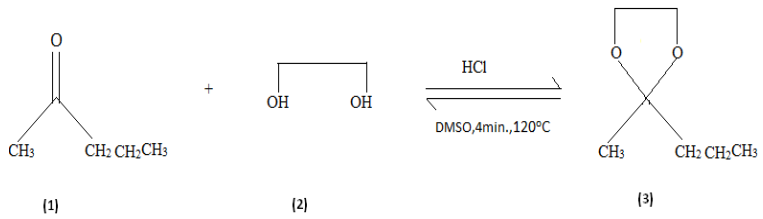
To a flame-dried 100ml flask add reactant **(1)** and **(2)** in equimolar ratio. Add hydrochloric acid as a catalyst and then DMF as a solvent. Fix the reaction vessel using dean stark apparatus and condenser. As temperature rises, the reaction was monitored by TLC. After the completion of the reaction, the mixture was filtered and concentrated on sand bath to obtain pure product **(3)** 2-methyl-2, propyl dioxolane. The reaction was completed in 133min. with 62% yield.

[3] Water as a universal green solvent:

To a flame-dried 100ml flask add reactant **(1)** and **(2)** in equimolar ratio. Add hydrochloric acid as a catalyst and then water as a solvent. Fix the reaction vessel using dean stark apparatus and condenser. As temperature rises, the reaction was monitored by TLC. After the completion of the reaction, the mixture was filtered and concentrated on sand bath to obtain pure product **(3)** 2-methyl-2, propyl dioxolane. The reaction was completed in 60min. with 80% yield.

[B] By **microwave heating** method-[1] Using DMSO

An equimolar ratio of reactant **(1)** and **(2)** in a neat, clean and flame dried reaction vessel. The mixture was irradiated with microwave at specified power level for several minutes and the progress of reaction was monitored by TLC. After completion of reaction, the product was concentrated on sand bath to obtain pure product **(3)** 2-methyl-2, propyl dioxolane. The reaction takes only 4min. with 78% yield (**scheme- 2**).



Scheme- 2

Microwave heating

[2] Using DMF as a solvent-

An equimolar ratio of reactant **(1)** and **(2)** in a neat, clean and flame dried reaction vessel. The mixture was irradiated with microwave at specified power level for several minutes and the progress of reaction was monitored by TLC. After completion of reaction, the product was concentrated on sand bath to obtain pure product **(3)** 2-methyl-2, propyl dioxolane. The reaction takes 5min. with 81% yield.

[3] Using Water as a solvent-

An equimolar ratio of reactant **(1)** and **(2)** in a neat, clean and flame dried reaction vessel. The mixture was irradiated with microwave at specified power level for several minutes and the progress of reaction was monitored by TLC. After completion of reaction, the product was concentrated on sand bath to obtain pure product **(3)** 2-methyl-2, propyl dioxolane. The reaction takes only 4min. and gives 87% yield.

[4] Solvent-free reaction-

An equimolar ratio of reactant **(1)** and **(2)** in a neat, clean and flame dried reaction vessel. The mixture was irradiated with microwave at specified power level for several minutes and the progress of reaction was monitored by TLC. After completion of reaction, the product was concentrated on sand bath to obtain pure product **(3)** 2-methyl-2, propyl dioxolane. The reaction takes 3min. and gives 88% yield.

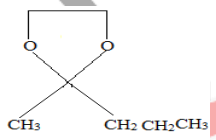
Table-1:- Preparation of 2-methyl-2, propyl dioxolane from ketone

Sr. no.	Reactant 1	Reactant 2	Solvents	Heating method	Time (min.)	Temp.(º C)	Yield (%)
1.	Methyl propyl ketone	Diol	Toluene	Conventional	120	60ºC	70%
2.	Methyl propyl ketone	Diol	DMSO	Conventional	150	60ºC	60%
3.	Methyl propyl ketone	Diol	DMF	Conventional	133	70ºC	62%
4.	Methyl propyl ketone	Diol	Water	Conventional	60	80ºC	85%
5.	Methyl propyl ketone	Diol	DMSO	Microwave	4	120ºC	78%
6.	Methyl propyl ketone	Diol	DMF	Microwave	5	110ºC	81%
7.	Methyl propyl ketone	Diol	Neat	Microwave	3	80ºC	87%
8.	Methyl propyl ketone	Diol	Water	Microwave	4	100ºC	88%

1.6. Result and discussion

[A] Result:

We obtain the product 2-methyl-2, propyl dioxolane **(3)**

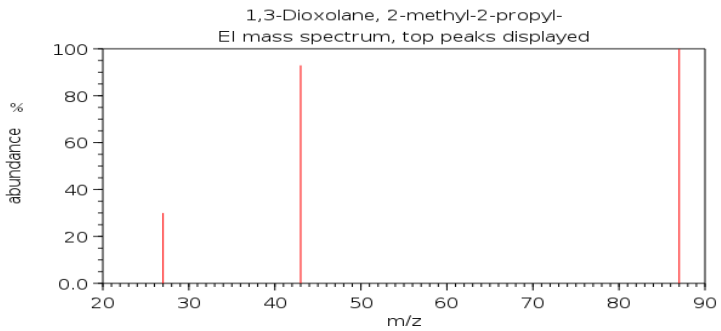


(3)

Colourless oil, B.P.136ºC.

Table-2: - EI mass spectrum

Total peaks	34
m/z top peak	87
m/z second highest peak	43
m/z third highest peak	27



B] Discussion:

Generally, dioxolanes are synthesized in presence of a p-toluene sulfonic acid which is extremely strong acidic. In many sulfonation reactions SO_2 are given off which may lead to bronchitis and conjunctivitis.

It is clear from the above mechanism that green solvent requires classically 1.5 – 2 hours and can be readily achieved under microwave irradiation in high yields in 3 – 5 minutes(**Table 1:** entry 5,6,7,8 can be chosen as representative examples). This might have been because of reactants are overheated by the conventional way of heating, and this may result in the decomposition of the reactants, reagent and/or products. But this is not the case with microwave heating as these radiations pass through the walls of reaction vessels. Microwave just heat up the sample and not the apparatus (reaction vessel) and therefore, energy consumption is much reduced.

Water appears to be a better option compared to other green solvents because of its abundant, non-toxic, non-corrosive and non-flammable nature. Recently, it has drawn much more attention, because water is cheap, safe and environmentally begins solvent.

Interestingly, the experimental procedure for methyl propyl dioxolane is remarkably simple and in absence of harmful solvents (such as TsOH) or inert atmosphere.

1.7.Conclusion

Green chemistry is definitely not another part of science; it is another philosophical approach that, through the introduction and expansion of its rules, could lead to a substantial development in chemistry laboratories.

Green chemistry has found alternative ways to cut energy consumption by changing processes. It also provides alternative solvents (**Table-3**) which reduces ecological problems because of its less toxicity, less hazard, safer than other organic solvents for industrial applications. In the coming decades, green chemical synthesis will be more attractive and practical. Researchers and pharmaceutical companies need to be encouraged to consider the principles of green chemistry while designing and choosing reagents.

Table-3: - Red solvents and their alternative green solvents

Sr. no.	Red Solvents	Alternative solvents	Other green solvents
1.	Benzene	Cyclohexane	Water, Glycerol, PEG
2.	CCl_4, $CHCl_3$	Dichloromethane(DMC)	
3.	Toluene, acetone and Xylene	Ethyl acetate, ethyl lactate	

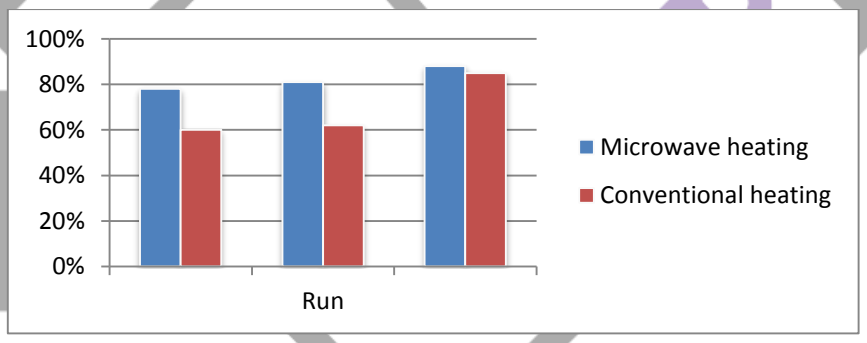


Fig.7:- - Chart indicating effect of microwave heating and conventional heating method of 2-methyl-2, propyl dioxolane. Conventional heating method takes a lot of time while microwave heating is not.

Acknowledgement-We thank JVWU, jaipur for providing me research environment and facilities that greatly improved the manuscript.

References

[1] Louis D .Quin and John A. Tyrell, "Fundamentals of Hetero Cyclic Chemistry",9th Ed., Wiley , New York , 2010.
[2] Paula Yurkanis Bruice ,"Organic Chemistry " 6th Ed., United.State , pp- 34, 2011.
[3] M. Issan Ahmed and Asniza Mustapha , Molecules , 15,P. pp-7498-7508, 2010.
[4] Pradnya R. Gadpayle , Sanjay P. Wate , Ashok P Mehere , KishorP. Bhusari and Nitin B. Charbe, Medicinal Chemistry & Drug Discovery , 3(1) ,P. pp-11-19 ,2012.
[5] A.A. Bogomazova, N.N. Mikhailova, and S.S. Zlotskii, Sovremennaya khimiya tsiklicheskikh atsetalei Poluchenie, reaktsii i svoistva (Modern Chemistry of Cyclic Acetals. Preparation, Reactions, Properties),Saarbrücken: LAPLAMBERT Academic Publishing GmbH&Co, 2011.
[6] Shavshukova, S.Yu., S.V. Shvetsov and S.S. Zlotskii, Sovremennye promyshlennye gerbitsidy. Poluchenie iprimenenie (Modern Industrial Herbicides. Preparation and Application), Ufa: OOO "Monografiya," 2011.
[7] Greene T. W. and Wuts P. G. M., Protecting Groups in Organic Synthesis, John Wiley and Sons, New York, 3rd edn, **1999**.

[8] (a) H. Fujioka, A. Goto, K. Otake, O. Kubo, Y. Sawamaz and T. Maegawa, Chem. Commun., 47, pp-9894, 2011. (b) J. W. Barlow, A. P. McHugh, O. Woods and J. Walsh, J., Eur. J. Med. Chem., 46, pp-1545, 2011. (c) T. M. Kubczyk, S. M. Williams, J. R Kean, T. E. Davies, S. H. Taylor and A. Graham, E., Green Chem., 13, pp-2320, 2011. (d) M. Tobisu, A. Kitajima, S. Yoshioka, I. Hyodo, M. Oshita and N. Chatani, J. Am. Chem. Soc., 129, pp-11431, 2007. (e) U. Schneider, H. T. Dao and S. Kobayashi ,Org. Lett., 12, pp-2488, 2010.
[9] (a) T. Ohta, T. Michibata, K.Yamada, R. Omori and I. Furukawa, Chem. Comm., 1192, 2003. (b) Y.J. Zhang, W. Dayoub, G.R. Chen and M. Lemaire, Green Chem., 13, pp-2737, 2011. (c) K. Motokura, H. Yoneda, A. Miyaji and T. Baba, Green Chem., 12, pp-1373, 2010. (d) A. Iwata, H. Tang and A. Kunai, J. Org. Chem., 67, pp-5170, 2002.
[10] (a) M. Curini, F. Epifano, M. C. Marcotullio and O. Rosati, Synlett, 777, 1999. (b) W. Panchan, S. Chiampanichayakul, D. L. Snyder, S. Yodbuntung, M. Pohmakotr, V. Reutrakul, T. Jaipetch, and C. Kuhakarn, Tetrahedron, 66, pp-2732, 2010. (c) T. Maegawa, K. Otake, A. Goto and H. Fujioka, Org. Biomol. Chem., 9, pp-5648, 2011.
[11] T. Xu, Q. Yang. Ye W., Q. Jiang and Z. Xu, J. Chen, Z. Yu, Chem. Eur. J., 17, pp-10547, 2011.
[12] (a) P. H. R. Silva., V. L. C. Goncolves and C. J. A. Mota, Bioresour. Technol., 101, 6225, 2010. (b) H. Maarse , Volatile Compounds in Foods and Beverages, Marcel Dekker Inc, New York, 1991.
[13] https://www.thoughtco.com .
[14] www.ochempal.org.
[15] https://profiles.uonbi.ac.ke (sch.504.protecting groups in organic synthesis.pdf).
[16] https://en.m.wikipedia.org. –Protecting groups.
[17] https://profiles.uonbi.ac.ke
[18] www.intermediates.basf.com- 1,3-Dioxolane-BASF intermediates.]
[19] www.intermediates.basf.com- 1,3-Dioxolane-BASF intermediates.
[20] Paul T. Anastas and David G. Hammond (2016), "Ch-4 Case Studies Green Chemistry in Practice".
[21] Duck-Rye Chang, Suck-Hyun Lee, Sun-Wook Kim and Hee-Tak Kim, "Binary electrolyte based on ethylene glycol and 1,3-Dioxolane for lithium sulfur battery," Journal of power Sources, vol. 112., Issue 2, 2002.
[22] Qiyan Zhang,et al., "Design, Synthesis & Evaluation of 2,2-dimethyl-1,3-dioxolane derivatives as human rhinovirus 3C protease inhibitors." Bioorganic & Medicinal Chemistry Letters., vol. 27., Issue 17, 2017.
[23] Ancuta Roxana Trifoi and Paul Serban Agachi., "Glycerol acetals and ketals as possible diesel additives: A review of their synthesis protocols," Renewable and Sustainable Energy Reviews., vol. 62, 2016.
[24] M. S. Newman and M. Renoll , J.Am.Chem.Soc, 67, pp-1621-1621, 1945.
[25] Andrzej Piasecki, "Alkoxyalkyl-substituted glycerol acetals: New hydrophobic intermediates forsurfactant synthesis", Journal of the American Oil Chemists' Society 1992.
[26] M. David, G. Collard Adolphus and Jones Robert M. Kriegel, "Synthesis and Spectroscopic Analysis of a Cyclic Acetal: A Dehydration Performed in Aqueous Solution", J. Chem. Educ., pp-178-170, 2001.
[27] Bimal K. Banik and Marin Chapa, Jocabed Marquez and Magda Cardona, "A remarkable iodine-catalyzed protection of carbonyl compounds", Tetrahedron Letters, vol 46, 2005.
[28] S.J. Yang, X.X. Du, L. He and J.T. Sun, "synthesis of acetals and ketals catalysed by tunstosilicic acid supported on active compound", 2005.
[29] Gyula Lukacs, Marta Porcs-Makkay, Anna Komaro and Gyula Simig , "Microwave assisted synthesis of benzophenone and acetophenone ethylene ketals", ARKIVOC (iii), pp-17-24, 2008. www.arkat-usa.org.
[30] V. B Vol'eva., I. S. Belostotskaya and others , "New approach to the synthesis of 1,3-dioxolanes", Russian Journal of Organic Chemistry., vol. 48, 2012.
[31] Cox and Sussanah Dawn, "Synthesis and Resolution of a Substituted Dioxolane from Glycerol", Undergraduate Honors Thesis Collection. 213, 2014.
[32] Marcio Jose da Silva, Martheus Oliveira Guimaraes and Armmanda Aparecida Julio., "A highly regioselective and Solvent Free Sn(II)-catalysed Glycerol Ketals Synthesis at room temperature", Vol.145, issue 3, Catalysis Letters, 2015.
[33] A. Denis, Bulanov and Irina A. Novokshonova, "highly efficient microwave assisted synthesis of polyfunctional 1,3-dioxolanes from γ-hydroxypropynals" .Tetrahedron Lett., 57.
[34] Qiyan Zhang, et.al., "Design, Synthesis and Evaluation of 2,2-dimmethyl-1,3-dioxolane derivatives as human rhinovirus 3C protease inhibitors". Bioorganic and Medicinal Chemistry Letters, 27, 2017.
[35] Yi Hong, Niu Linbin, Wang Shengchun, Liu Tianyi, Atul K. Singh and Aiwen Lei, "Visible-Light-Induced Acetalization of Aldehydes with Alcohols" *Org.* Lett., 19, pp-122-125, 2017.
[36] Q.Zhou, T.Jia, X. X. Li, L. Zhou, C.J. Li and Y.S. Feng, "Photoorganocatalytic Synthesis of Acetals from Aldehydes," Synth.commun., 48, pp-1068, 2018.
[37] Taoufik Rohand, Jerome savary, Istvan E.Marko, "Synthesis of dioxolanes and oxazolidines by silica gel catalysis" 2018.
[38] ref- Amin Talebian-Kikalaieh, Aishah Saidina, Neda Najaafi,Sara Tarighi, "A review on the catalytic acetalisation of bio-renevable glycerol to fuel additives" 2013.
[39] D. T. Belmont and L. A. Paquette, JOC, 50, pp-4102, 1985.
[40] Synthesis of cyclic acetals and esters, Chapter 5, p153-210, https://shodhganga.inflibnet.ac.in/bitstream/10603/22036/9/09_chapter_5.pdf