

2-MethylTetraHydroFuran (2-MTHF) A Green Alternative Solvent to Tetrahydrofuran

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Abstract--The solvent 2-methyl tetrahydrofuran (2-MeTHF) can provide a cost-effective, green alternative to tetrahydrofuran (THF) chemistry. 2-MeTHF's advantages include its origin from 2-furaldehyde known as 'furfural' which is produced from renewable naturally occurring pentose in agricultural waste like corn-cobs or bagasse (sugar cane) in two-steps hydrogenation process via 2-methylfuran. It is a price stable resource having beneficial physical and chemical properties that can provide increased yields at reduced costs.

The major benefits are easy product isolation (2-MeTHF is not water-miscible, whilst THF is); simple solvent recovery and drying saves around 70% energy compared to 'pressure swing distillation' used for THF recovery (2-MeTHF forms a water-rich azeotrope at atmospheric pressure); Clean phase separation with no emulsions and rag layers; and the higher boiling point of 2-MeTHF (80°C) compared to THF (64°C) will decrease the amount of solvent released into the air, reducing VOC emission.

This review paper is intended to show that 2-MeTHF is a green, cost-effective alternative to THF, based on 12 principles of green chemistry.

Index Terms: 2-MeTHF, THF, green chemistry, Biphasic Reactions, Organometallic Reactions

I. INTRODUCTION

The solvent 2-MeTHF is obtained from furfural through hydrogenation. In turn, furfural is obtained from renewable resources, such as corn cobs and sugar cane, through the intra-molecular cyclisation of the naturally-occurring pentoses. In contrast, THF is obtained from 1,4-butanediol, an oil derived substance. The recent political and legislative drive for reduction of CO₂ emissions should make solvents derived from renewable resources highly desirable due to their reduced CO₂ emissions impact.

2-MeTHF is currently the only solvent similar to THF that is derived from renewable resources and industrially available [1]. The market share for 2-MeTHF is growing rapidly. This is in sharp contrast to the long term trend for oil-derived THF, where prices have increased over the past decade by approximately 50%. The comparison of 2-MeTHF and THF are summarized in Table -1.

II. INNOVATION OPPORTUNITIES

The methyl substituted version of THF is partially miscible with water as shown in table-2. It is comparable or

even better than THF in terms of its chemical properties. However, 2-MeTHF resembles toluene in terms of physical properties and this creates huge innovation opportunities for cutting costs both in existing and new processes. The work-up for the THF-based reaction is complicated by THF's miscibility with water. 2-MeTHF is not water miscible.

TABLE-1

Comparison of Properties of MeTHF and THF

Property	MeTHF	THF
Boiling point (°C).....	80.....	66
Freezing point (°C)	-136.....	-108.5
Density at 20 °C	0.855	0.888
Viscosity at 25 °C (cps)	0.60	0.53
Evaporation rate (<i>n</i> -butylacetate=1).....	4.2.....	8.0
Dielectric constant.....	6.3.....	7.6
Donicity (kcal/mol).....	18.....	20
Solubility of MgBr ₂ at 25 °C.....	40.....	5
Solubility parameter	8.52	9.15
Hansen Solubility Parameter		
Non-polar	8.3	8.6
Polar.....	1.9	2.4
Hydrogen bond	3.0.....	2.7
Total	8.9	9.4
Solubility at 20 °C (wt %)		
In water	14	inf
Water in solvent	4.4	inf
Esters, alcohols, ketones, hydrocarbons, aromatics, chlorinated hydrocarbons.....	inf.....	inf
Flash point, TC (°C).....	-11.1	-14.5
Autoignition temperature (°C)	270.....	321
Water azeotrope		
boiling point (°C).....	71	63
composition, wt% solvent	89.4.....	93.3
wt% water	10.6	6.7

Advantages	Source of savings
Renewable resource	CO ₂ emissions credits Solvent from renewable resources Decreasing price trend Supply risk decoupled from oil
Physical properties	Increased throughput Easy aqueous phase separation Less solvent utilization More efficient extraction solvent reuse & recycling
Chemical properties	Less impurities Better solvent stability to acids and base Higher reaction yields Less solvent higher saturation concentrations Improved safety lower volatility Higher flash point

TABLE- 2 Solubility of Water in MeTHF

Temperature °C	Wt% Water
0.0.....	4.0
9.5.....	4.1
19.3.....	4.1
29.5.....	4.2
39.6.....	4.3
50.1.....	4.4
60.7.....	4.6
70.6.....	5.0

and provides easy and clean phase separation during work-up.

The methyl-substituted THF reduces the solvent and energy variable costs. Thus 2-MeTHF has better extractive properties than the classic THF/ toluene mixture [2]. This means the number of extraction steps can be reduced while the recovery of the product is simultaneously increased.

2-MeTHF is much easier to recycle and dry than THF. This has important advantages for dedicated production capacities consuming hundreds of metric tons of solvent per year. 2-MeTHF needs only a simple distillation at atmospheric pressure. The recycling and drying process is much more cost efficient for 2-MeTHF because the energy cost of distillation is reduced by an estimated 70%[3].

III. STABILITY OF MeTHF

MeTHF is very stable to bases and is stable to acids at concentrations that are typically found in most synthetic processes. Like most ethers, MeTHF can be cleaved at high concentrations of HCl or with many strong Lewis acids but

the cleavage rate is less than that with THF. With a 50:50 weight mixture of 2 N HCl at 60 °C (conditions typical of many isolation steps), THF degrades about 9 times faster than MeTHF (Table-3). This increased stability probably is because with MeTHF most of the HCl is present in the water phase compared to the homogeneous THF-HCl mixture [4].

TABLE-3 Degradation of THF and MeTHF in 2 N HCl at 60 °C

time (h)	% MeTHF degraded	% THF degraded
24	0.02	0.18
45	0.03	0.28

MeTHF will form peroxides when exposed to oxygen if no stabilizer is present. A small amount of butylated hydroxyl toluene (50 ppm) prevents peroxide formation for at least 1 year under normal storage conditions. With no stabilizer, MeTHF forms peroxides at about the same rate as THF when stored exposed to air as shown in Table-4 and figure-1.

TABLE-4 Formation of peroxides in THF and MeTHF non-stirred in air

time (h)	in MeTHF ppm H ₂ O ₂	in THF ppm H ₂ O ₂
0	0.5	0.4
120	2	1.8
200	17	23
300	42	51

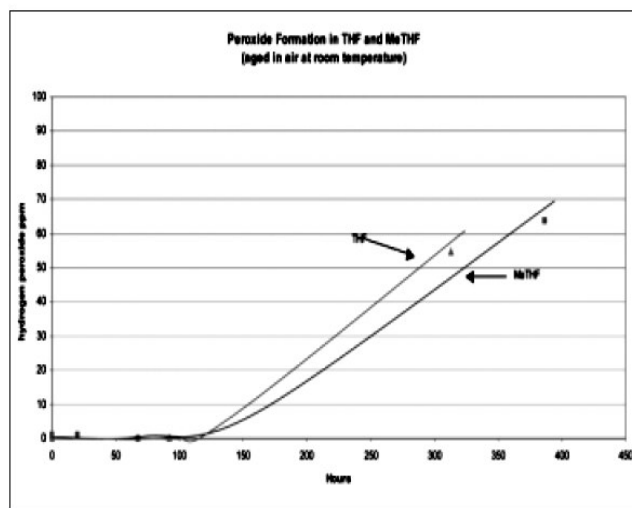


Fig.1 Peroxide formation in THF & MeTHF

IV. SOLVENT RECOVERY

THF reactions use co-solvent, such as toluene, to achieve phase separation. Otherwise, the water-miscible THF, together with reactants, will often form a persistent emulsion, making product isolation impossible.

It was expected that 2-MeTHF would be a better extraction solvent than toluene, based on its higher polarity. The limited solubility of water in 2-MeTHF should enhance the extraction capability, particularly for polar compounds.

Product isolation is not necessary after aqueous work-up; the next reaction step is carried out simply by adding the chemical reagent to 2-MeTHF solution. Thus, by carrying out two consecutive reactions in the same solvent, the overall volume is reduced by 50% for two steps or 66% for the three steps. As an added bonus, the 2-MeTHF-rich water azeotrope will help to dry the solution for the next step it requires anhydrous conditions as shown in figure-2.

Obviously, the higher boiling point of 2-MeTHF (80 °C) compared to THF (64 °C) will decrease the amount of solvent relaxed into the air, reducing VOC emission as well. As opposed to the THF/Co-solvent mixtures, 2-MeTHF is recovered from the reaction as a relatively pure solvent by simple distillation. No special equipment or up-front investment is required. This makes recycling the solvent or recovery for other uses much more attractive than incineration.

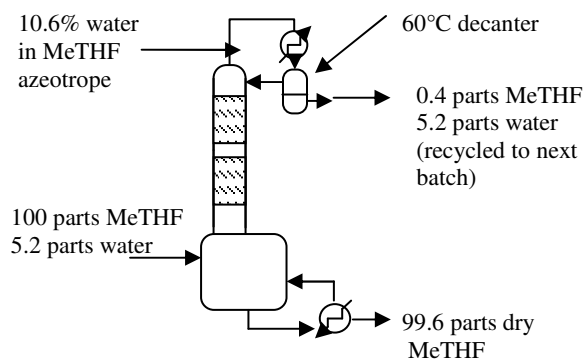


Fig. 2 Drying of MeTHF for solvent recycling or reuse in one pot reactions

V. APPLICATIONS OF MeTHF

ORGANOMETALLIC REACTIONS

Grignard Solvent: Grignard reactions are frequently used in pharmaceutical and fine chemical processes, and THF is the most common solvent used for Grignard reactions. Literature shows that MeTHF was similar to THF in the formation and reaction of alkyl and aryl Grignard reagents [5, 6].

Reformatsky Reaction: MeTHF has also been used as a solvent for the Reformatsky reaction. The high solubility of

ZnBr₂ in MeTHF (>40 g/100 g at 25 °C) means MeTHF should be a good solvent for formation of zinc reagents by reaction of ZnBr₂ with Grignard or lithium reagents [7].

Lithiation Reactions: MeTHF is a good solvent for low temperature lithiation reactions because of its low mp, low viscosity at low temperatures, and similar Lewis base strength as THF[8].

Hydride Reductions: LiAlH₄ has good solubility in MeTHF (at least 1.8 M), and literature showed similar product yields as found in THF for a survey of aldehydes, esters, and acids reduced with LiAlH₄.

Coupling Reactions: THF is often used as the solvent for many metal-catalyzed coupling reactions, and MeTHF should also work well in these reactions. MeTHF was found to work like THF as a solvent in the Ni-catalyzed coupling of alkynylzinc bromides with nitriles. MeTHF was found to give better diastereo selection than THF in a series of copper-mediated biaryl couplings[9].

Biphasic Reactions

MeTHF is finding applications as a replacement for highly regulated chlorinated solvents like dichloromethane in biphasic reactions. The advantages of MeTHF compared to dichloromethane are that it has a moderate boiling point, is more resistant to reactions with nucleophiles like amines, and provides clean organic-water phase separations. Literature shows that MeTHF is a very effective solvent for extracting polar compounds from water mixtures [10, 11].

Case Study

Production of cefixime Trihydrate is a three step process. Conventionally 2nd step condensation reaction is carried out in the presence of solvents THF and water. At temperature 3-5 °C raw material 7AVCA (7-Amino 3- Vinyl Cephalosporic Acid) and Active Ester condense to form product Cefixime Ester. P_H of the reaction mass is mentioned 7.8 to 8.0 using strong base Trimethylamine (TEA). Reaction of TEA and 7-AVCA form salt which is soluble in water and Active Ester is soluble in THF. Both solvents are having infinite solubility in each other. Being a homogeneous reaction mass reaction complete in 4-6 hrs with more than 90 % conversion. Same reaction in the presence of 2-MTHF and water giving approximately 90 % conversion in 19 hrs. 2-MeTHF and water form Biphasic reaction mass.

VI. CONCLUSION

The introduction of 2-MeTHF can provide an excellent opportunity for cost cutting solutions through innovation. Migration of technologies from THF to 2-MeTHF will automatically render greener technologies as the 3R – reduce, recycle and reuse. 2-Methyltetrahydrofuran can be used as a solvent for most organometallic reactions that require a strong Lewis base like THF. When MeTHF is

used to replace THF in organometallic reaction processes, it can conveniently be used to recover the reaction product because it is only partially water miscible. The MeTHF/water azeotrope can be used to dry the reaction product for subsequent process steps and to recycle dry MeTHF.

VII. REFERENCES

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