

APPLICATION OF GREEN CHEMISTRY PRICIPLES IN ORGANO-GRIGNARD REACTIONS

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ABSTACT

2-Methyltetrahydrofuran (MTHF) is a commercially available solvent that is produced from renewable resources. The properties of MTHF place it between tetrahydrofuran (THF) and diethyl ether (DEE) in terms of solvent polarity and Lewis base strength. The formation and reaction of Grignard reagents in MTHF and THF are similar. MTHF is partially miscible in water, whilst THF is infinite miscible in water resulting in simple solvent recovery and drying. This paper is intended to show that MTHF is a green and cost-effective alternative to THF, based on actual application of the solvent in pharmaceutical industry for production of anti-hypertension drug. By comparing performance of MTHF with THF, it is concluded that in MTHF, the reaction yield improved significantly, stability of solvent to acid and base increased and the work-up is simplified. This paper demonstrates through the practical commercial example the economic and environmental advantages offered by MTHF with improved productivity.

Keywords: Green Solvent, Green Chemistry, 2-Methyltetrahydrofuran, THF, Organo-Grignard Reaction

I. INTRODUCTION

2-Methyltetrahydrofuran (MTHF) is an aprotic ether solvent, while being a strong Lewis base like THF. It is only partially miscible with water and is increasingly being used in organo-metallic and biphasic chemical processes because this interesting combination of properties leading to process simplification [1, 2]. THF is the primary ether solvent used in organo-metallic reactions because it strongly coordinates with many metals and has a moderate boiling point of 65.7 °C. However since THF is completely water miscible, it often causes problems in the water-quenching step that is used to remove the metal. Typically another solvent like toluene must be added to partition the desired product into the organic phase or to provide a clean phase separation of the organic and water phase. With MTHF, the product can be conveniently isolated without adding another solvent. MTHF provides very clean organic-water phase separations with little tendency to form emulsions or rag layers. Besides MTHF, diethyl ether (Et₂O) is the only other commercially available mono-dentate alkyl ether that is not water miscible and can be used in place of THF in organo-metallic reactions that require a strong Lewis base. However, the low boiling point (35.4 °C) of Et₂O makes it difficult to use in industrial processes. Available data rates MTHF between THF and Et₂O in solvent polarity and Lewis base strength. Organo-metallic reagents in MTHF have recently become available on industrial scale due to increasing demand for these products around the world [3]. Various organo-metallic reagents in MTHF as well as the solvent itself are today a global emerging market in the fine chemical industry [4]. This paper demonstrates through examples from organo-grignard applications the advantages offered by MTHF.

II. FEATURES OF GREEN SOLVENT 2-MTHF

Available information suggests that MTHF can replace THF and DEE in organo-metallic reactions; the reaction yields are superior, the stability of the solvent to extreme pH is improved and the work-up is simplified. For example, it has been shown that the use of MTHF consistently *improves the yield* of benzyl and allyl organo-grignards generation (Table 1). Subsequent addition step results in comparable or better yield than in THF. The use of MTHF also allows for a much *higher concentration* of organo-grignard bromides as shown in Table 2.

Table 1 Yields of Organo-Grignard with THF and MTHF

Reagent	Solvent	Organo-magnesium Yield	Yield Difference MTHF/THF
Benzyl Chloride	THF	85 %	14 %
	MTHF	99 %	
Benzyl Bromide	THF	83 %	15 %
	MTHF	98 %	
O-Methylbenzyl Chloride	THF	78 %	15 %
	MTHF	97 %	
O-Chlorobenzyl Chloride	THF	20 %	66 %
	MTHF	86 %	
Allyl Chloride	THF	73 %	16 %
	MTHF	89 %	

Table 2 Grignard Bromides Are Highly Soluble At Low Temperatures In MTHF

RMgBr	Solution in MTHF			Solution in THF		
	w/w %	Mol/L	Cryst. Temp.	w/w %	Mol/L	Cryst. Temp.
MethylMgBr	35	3.2	< -10 °C	15	1.2	< 15 °C
EthylMgBr	40	3.4	< -10 °C	8	0.6	< 5 °C
PhenylMgBr	45	2.9	< -10 °C	17	0.9	< 20 °C

Table 3 Comparison Of Magnesium Turnings Requirement

Reagent	Solvent	Mg moles used per moles subtract	Yield	Yield Difference MTHF/THF
Benzyl Chloride	THF	2	85 %	14 %
	MTHF	1.05	99 %	
Benzyl Bromide	THF	2	83 %	15 %
	MTHF	1.2	98 %	

As a rule of thumb organo-grignard bromides are three times more soluble in MTHF than THF. Moreover, the organo-grignard solutions in MTHF have the crystallization temperature under -10°C, much lower than the crystallization temperature in THF. This in turn simplifies greatly transportation and storage conditions and creates the opportunity to carry out the reaction at higher concentration. The organo-grignards generation in MTHF is close to stoichiometric consumption in magnesium turnings as shown in Table 3. By contrast THF requires excess Mg turnings in an effort to minimize the competitive dimerization to dibenzyl[5].

From the perspective of physical properties the product isolation is easier in MTHF because MTHF is not water-miscible (whilst THF is). The recovery and drying of the solvent is simpler since MTHF forms a water-rich azeotrope at atmospheric pressure. The extraction yields are improved (MTHF reduces the number of extraction steps) [6,7].

2.1 Opportunity To Increase Productivity

Based on the examples given above the use of MTHF organo-grignards provide the opportunity to increase productivity by reducing cycle time and increasing throughput. Reduction in cycle time will result both from reduced set up times (loading/unloading, heating/cooling times) and also from faster production (e.g. quick phase separation) For example, the possibility to work at three time higher concentration with organo-grignard bromides, reduces loading/unloading as well as heating and cooling times to one third due to reduced solvent volume. THF, a water soluble solvent, is often mixed with hydrophobic solvents such as toluene to achieve phase separation [8]. These mixtures form oftentimes persistent emulsions and rag layers which are time consuming to get separated on an industrial scale. MTHF was shown to be a more efficient extraction solvent and throughput could increase through reduction of the number of the extraction steps needed to recover the product [9]. Another source of reducing the total cycle time is the higher boiling point of MTHF; it boils more than 10°C higher than THF, therefore the reaction time should be reduced by 50 percent (from the Arrhenius equation).

2.2 Environmental Advantages

From environment point of view, MTHF is obtained from naturally occurring pentoses in agricultural wastes like corncobs or bagasse (sugar cane). The carbon dioxide generated through incineration of spent MTHF will simply return the carbon dioxide absorbed by the crop from the atmosphere. MTHF could also qualify for carbon emission credits. By contrast THF and DEE are commercially produced from oil therefore carbon emission credits are not an option. MTHF will also ensure a reduced carbon footprint by reducing waste. The higher boiling point of MTHF (80°C) compared to THF (64°C) will decrease the amount of solvent released in the air, reducing reported VOC emissions. THF is water miscible therefore effluents are by definition rich in solvent.

2.3 Quality Control And Work Place Safety

MTHF is more stable under acidic and basic conditions than THF. From a quality control perspective this translates into a stable impurity profile of the product which automatically translates in reduced cost of quality. In the case of organo-grignard reagents, excess magnesium is not needed in MTHF compared to THF. The excess, pyrophoric magnesium powder does not need to be filtered and disposed of after the reaction, a distinct advantage from a safety perspective. Both MTHF and THF organo-grignard solutions have comparable thermal stability. The start of exothermic thermal decomposition is observed around 180°-200°C for both solutions, demonstrating that MTHF solutions are safe even at much higher concentration than THF saturated solutions. Stability to peroxide formation is also comparable for THF and MTHF with a slightly increased propensity to form peroxides for the latter solvent. From a storage and transportation safety perspective, peroxide formation rate increases with the stirring. The difference between the two solvents is negligible if the solvent is not stirred while a 50 percent increase in peroxide formation is observed under intense stirring³. Normal safety precautions similar to THF handling are recommended.

III. EXPERIMENTAL WORK

Grignard reactions are frequently used in pharmaceutical and fine chemical processes, and THF is the most common solvent used for Grignard reactions. MTHF could be used in similar reactions using THF in the formation and reaction of alkyl and aryl Grignard reagents. Laboratory Reagent grade MTHF from Spectrochem

Pvt. Ltd. Mumbai was used in the experiments. Other chemicals were obtained from Lab supply houses. Chemicals were used as obtained except the water level was checked to make sure it was below 500 ppm for the organo-metallic reactions. Product yields were determined by GC using standards of known purity.

Under nitrogen atmosphere, 145 ml MTHF was charged in an oven dried flask equipped with a nitrogen bubbler, a stirrer, condenser and addition funnel. Mg-turnings (19.3 g, 0.7942 moles) were added at 25-30 °C. The reaction mass was stirred and heated up-to 38 to 42 °C. Reaction assembly was insulated to prevent heat loss from the system. 3.5 gm Ethylene Di-Bromide (EDB) was added in reaction mass to activate Mg- tuning surface as well as to initiate the reaction. After that temperature was increased up to 50 °C. 1st lot (13 gm) of Phenyl Ethyl Chloride (PEC) was charged with dropping funnel and temperature was observed increase up-to 60 to 62 °C. 2nd lot (87 gm) of PEC dilution with 70 ml MTHF solvent was charged. With addition of PEC, exothermic reaction took place and reaction temperature was raised maximum up-to 102 °C. Reaction mass temperature was maintained at 97 to 102 °C for 60 min. and then reaction mass was cool to RT (30 – 35 °C). The yield of the Grignard reagent was checked by GC. The Grignard reagent was transferred to another nitrogen blanketed flask before reacting with an electrophile. 500 ml toluene and 105 ml Diethyl oxalate (DEO) were charged as an electrophile in three-neck flask and mixture was stirred under nitrogen. Reaction mass was chilled to –14 to –19 °C and stirred for 30 min. With maintaining the temperature under nitrogen, Grignard reagent solution was added drop by drop then temperature was raised to –5 to 0 °C. For hydrolysis of product with dilute acid, solution of 75 ml concentrated HCl and 232 ml water was charged at –5 to 13 °C and stirred for 15 min. Temperature was raised up-to 25 to 30 °C. From reaction mass, organic (toluene) and aqueous layers were separated and aqueous layer was discarded. Water wash (200 ml water) was given to toluene layer. Reaction mass was stirred and layers were separated. To neutralize the reaction mass, sodium bicarbonate washes were given (8 g sodium bicarbonate + 400 ml water) (three washing (100 ml + 100 ml + 200 ml)). Two water washes (200 ml + 200 ml) were given to toluene layer. pH of final aqueous layer was checked (pH = 6 to 7). Under high vacuum, Toluene layer was distilled out at 60 to 90 °C to get pure product in form of oily mass remaining in RBF. The product yields and % assay were determined by GC analysis.

Same reactions were performed using THF and MTHF solvent. In THF solvent, % Assay of Grignard reagent was observed 29.07 % by GC and same in MTHF was observed 37.21%. It is concluded that better quality of Grignard reagent can be prepared using MTHF solvent. In MTHF, % Assay of main product was noted 86.1 % with yield 1.18 compare to THF 86 % and 1.00 respectively. Approximately 18% improvement in yield is possible by using alternate MTHF solvent.

VI. CONCLUSION

2-Methyltetrahydrofuran can be used as a solvent for most organo-metallic reactions that require a strong Lewis base like THF. When MTHF is used to replace THF in organo-metallic reaction processes, it can conveniently be used to recover the reaction product because it is only partially water miscible. The MTHF/water azeotrope can be used to dry the reaction product for subsequent process steps and to recycle dry MTHF. MTHF can also be used as an efficient replacement for dichloromethane in biphasic reactions and as a solvent for efficiently recovering water soluble compounds. Switching processes from THF-based to MTHF-based technologies provides a great opportunity to move innovative companies to greener technologies while simultaneously obtaining a sustainable competitive cost advantage.

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