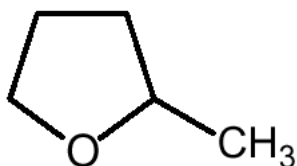




PENN
Specialty Chemicals, Inc.
Chemicals From Renewable Resources

METHYLTETRAHYDROFURAN



MeTHF

The Furan Chemistry Specialists

Grignard Solvent

Polar Reaction Solvent

Organometallic Chemistry Solvent

Dichloromethane Replacement Solvent

Chemical Reagent

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METHYLTETRAHYDROFURAN

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rev. 1.05

Introduction

2-Methyltetrahydrofuran (MeTHF) is a versatile aprotic solvent that is being used more often in industrial synthetic processes because of its favorable properties. Some of the useful properties of MeTHF are:

- Partial water miscibility (allows MeTHF to function as a solvent for both reaction and product isolation)
- Aprotic polar solvent (useful for many organometallic reactions)
- Boiling point of 89 °C (convenient for reaction and heat removal but easy to remove from product)
- Forms azeotrope with 10.6 % water (easy batch drying of product or recycle of dry MeTHF)
- Gives clean water phase separations (useful for two phase reactions and product recovery from organometallic reactions)
- Is derived from renewable resources (has low environmental impact)

Applications

Grignard Reactions. When used as a Grignard solvent,¹ MeTHF offers a number of important advantages over other commonly used solvents.

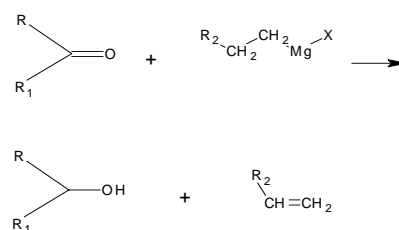
- Limited miscibility with water facilitates easy product recovery
- Can be easily dried with lower losses and lower recycle costs compared to THF
- Gives cleaner phase separations compared to processes that use solvent exchange of THF with toluene
- Especially useful for producing high concentrations of homogeneous solutions of bromo Grignard reagents
- Gives high yields of benzyl and allyl Grignard reagents
- Gives improved yields of addition product in systems where THF gives high yields of reduction product
- Permits higher reaction temperature and lower losses from reactor condensers

THF is the most common solvent used for commercial Grignard reactions. MeTHF has similar behavior to THF in most Grignard reactions but its higher boiling point and limited water solubility give it several distinct advantages over THF. The 80 °C boiling point of MeTHF compared to 66 °C boiling point for THF means that sluggish Grignard reactants can be formed quicker. The higher boiling point of MeTHF also reduces losses of solvent from the reflux condenser. Unlike THF, MeTHF has limited solubility in water and this property makes it easier to isolate the quenched reaction product and recycle dry MeTHF. Another advantage of MeTHF is that very clean phase separations are found from the quenched Grignard reaction product. Often when THF is solvent exchanged with toluene, emulsions or rag layers are formed that prevent clean phase separations.

MeTHF has a much higher solubility for magnesium bromide and iodide than THF. For example, the solubility of magnesium bromide is more than 40 g/100 g at 25 °C in MeTHF whereas the solubility is only about 5 g/100 g in THF. This makes MeTHF a preferred choice for preparing high concentrations of bromo Grignard reagents that do not need filtration to remove magnesium bromide. For companies that package and sell Grignard reagents, use of MeTHF insures that their aged inventory will be stable, precipitate free solutions.

MeTHF can be used to produce high yields of benzyl and allyl Grignard reagents at low magnesium ratios. THF can only be used to make benzyl and allyl Grignard reagents at reasonable yields by using high molar ratios of magnesium to benzyl or allyl halide. For instance, a yield of greater than 90% of benzylmagnesium bromide is made with MeTHF but mostly bibenzyl is made with THF at a magnesium:benzylbromide ratio of 1.2:1.

In many systems, MeTHF behaves more like ethyl ether than like THF. A common side reaction of Grignard reagents that contain beta hydrogens is reduction of the substrate instead of addition. This side reaction often causes reduced yields of the desired addition product when THF is the solvent. In these systems, replacement of THF with MeTHF as with ethyl ether will typically give improved yields of the addition product.



¹Gary S. Silverman and Phillip Rakita, Handbook of Grignard Reagents, Marcel Dekker, 1996.

Lithiation. MeTHF is a liquid down to $-136\text{ }^{\circ}\text{C}$ and so can be substituted for THF in low temperature lithiation reactions. In lithiation chemistry, in addition to providing a simpler isolation process, MeTHF is more stable to lithium reagents than THF^{2,3}. A comparison study of the stability of n-butyl lithium in THF and MeTHF showed a 70 minute half life in MeTHF and a 10 minute half life in THF at $35\text{ }^{\circ}\text{C}$ ⁴.

Other Organometallic Reactions. The similar solvent properties of MeTHF should make it a suitable replacement in most of the organometallic reactions where THF is used such as Heck, Stille and Suzuki coupling reactions. MeTHF was found to provide a stable solution and good yields in the Reformatsky reaction with ethylbromoacetate⁵. MeTHF was found to give better diastereoselection than THF with a model substrate in Copper-mediated biaryl couplings and was used to form a series of ring compounds via this coupling chemistry^{6,7}. Bayer Healthcare used MeTHF with toluene in a biphasic reaction of an acid chloride with an amine using NaHCO_3 in synthesis of Rivaroxaban⁸.

Biphasic Reactions. MeTHF has been found to be a very effective solvent for biphasic reactions, especially for reactions with aqueous NaOH. Ripin⁹ found that MeTHF was a good replacement for dichloromethane in biphasic alkylation, amidation and nucleophilic substitution reactions. MeTHF gives clean phase separations in these reactions and high reactivity. The high reactivity was attributed to the increased apparent polarity of MeTHF from the dissolved water. MeTHF has been used as a solvent for reductive amination¹⁰ and amine carbonation¹¹ because recovery of products was improved.

Recovery

The solubility behavior of MeTHF/water mixtures and the favorable MeTHF-water azeotrope make it possible to recover dry MeTHF with conventional distillation equipment.

The solubility of water in MeTHF does not increase very much as the temperature is increased from $0\text{ }^{\circ}\text{C}$ to $70\text{ }^{\circ}\text{C}$.

Solubility of Water in MeTHF

| Temperature $^{\circ}\text{C}$ | 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 |

Solubility of MeTHF in Water

| Temperature $^{\circ}\text{C}$ | Wt% Water |
|--------------------------------|-----------|
| 0.0..... | 21.0 |
| 9.5..... | 17.8 |
| 19.3..... | 14.4 |
| 29.5..... | 11.4 |
| 39.6..... | 9.2 |
| 50.1..... | 7.8 |
| 60.7..... | 6.6 |
| 70.6..... | 6.0 |

However, the solubility of MeTHF in water dramatically drops as the temperature is increased. Because of this drop in solubility of MeTHF in water as the temperature is increased, mixtures of water and MeTHF should always be separated at temperatures above $60\text{ }^{\circ}\text{C}$ to minimize the loss of MeTHF to the water phase.

² Hintze, M.; Wen, J., US 6861011.

³ Hage, M.; Ogle, C.; Rathman, T.; Hubbard, J., Main Group Metal Chemistry (1998), 21(12), 777-781.

⁴ R. Bates, J. Org. Chem. (1972), 37(4), 560.

⁵ Nuwa, S.; Handa, S.; Miki, S., US 20050043544.

⁶ Spring, D.; Krishnan, S.; Schreiber, S., J. Am. Chem. Soc. (2000), 122(23), 5656-5657.

⁷ Krishnan, S.; Schreiber, S., Organic Letters (2004), 6(22), 4021-4024.

⁸ Christian, T., WO2004060887.

⁹ Ripin, D.; Vetellno, M., Synlett (2003), 15, 2353.

¹⁰ Ragan, J.; am Ende, D.; Brenek, S.; Eisenbeis, S.; Singer, R.; Tickner, D.; Teixeira, J., Jr.; Vanderplas, B.; Weston, N., Organic Process Research Development (2003), 7(2), 155-160.

¹¹ Cai, W.; Colony, J.; Frost, H.; Hudspeth, J.; Ripin, D.; Stearns, J.; White, T., Organic Process Research Development (2005), 9(1), 51-56.

The MeTHF-water azeotrope contains 10.6 % water. Wet MeTHF can be dried at atmospheric pressure in a batch or continuous distillation process using this azeotrope. Also, products dissolved in MeTHF can be dried using this azeotrope.

Example of Batch MeTHF Recovery

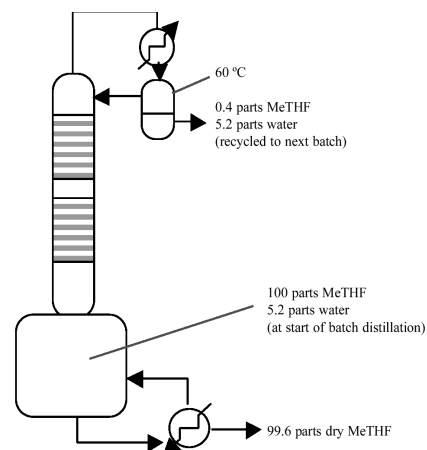
As an example of how dry MeTHF can be recovered, consider a process that has a stream that contains 100 parts MeTHF and 100 parts water. Separation of this mixture in a decanter that is held at 60 °C gives a MeTHF layer that has 4.4 parts water and a water layer that has 6.8 parts MeTHF. The MeTHF in the water phase and the MeTHF phase can both be recovered as dry MeTHF in batch distillations. The MeTHF in the

| | |
|-------------------------------|-------------------------------------|
| 100 parts MeTHF | 93.2 parts MeTHF 4.4 parts water |
| 100 parts water (at 60 °C) | 6.8 parts MeTHF 95.6 parts water |

water phase can be recovered by distilling the azeotrope (10.6% water) and adding the collected overheads to the MeTHF phase. A distillation set-up consisting of a reboiler, a fractionation tower and an overhead condenser with a liquid-liquid decanter can be used to recover dry MeTHF. The overhead condenser and decanter are operated at 60 °C to minimize the loss of MeTHF in the decanted water phase. The condensed MeTHF in the decanter is added back to the column as reflux. The water phase from the decanter is recycled to the next batch distillation to recover the MeTHF dissolved in it. With this process, essentially all of the MeTHF can be recovered as dry MeTHF.

The MeTHF azeotropic distillation is similar to drying with toluene except that the effective MeTHF azeotrope is 6% water since the refluxed MeTHF contains about 4.6% water.

The adjacent figure shows a schematic of the distillation equipment needed to recover dry MeTHF. The overhead decanter should be sized so that at the end of the batch distillation when no more water phase can be removed from the overhead decanter, the liquid and vapor hold-up in the column can be distilled without reflux. The MeTHF in the decanter can be used in the next batch distillation. After a batch distillation, the reboiler product typically has about 300 ppm water.



MeTHF Properties

Table 1 lists the common properties of MeTHF compared to THF.

Water Solubility. MeTHF is unique among industrial solvents in being a strong, polar ether solvent that is only partially miscible with water. As the temperature is increased from 20 to 60 °C, the solubility of water in MeTHF only increases from 4.1 to 4.6% and the solubility of MeTHF in water decreases from 14 to 6.6%. Because of this solubility behavior, water phase separations should be conducted at 50 to 60 °C to minimize loss of MeTHF to the water phase.

Stability. 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 with THF. MeTHF forms peroxides when exposed to oxygen at about the same rate as THF. Low levels of butylated hydroxytoluene (BHT) will prevent peroxide formation.

Solvent Strength. MeTHF is between THF and diethyl ether in solvent polarity and Lewis base strength. The dielectric constants are 7.6, 6.3, and 4.3 and the total Hansen Solubility Parameters are 9.4, 8.9 and 7.7 for THF, MeTHF and diethyl ether respectively. The Lewis base strength is reported to be in the order of THF>MeTHF>diethyl ether¹². Extraction studies¹³ show that MeTHF is a very efficient solvent for recovering water soluble and partially water soluble compounds when compared to less polar solvents like toluene.

Typical Analytical Values

MeTHF is a high purity product. GC analysis typically shows >99.0 % MeTHF with <0.03% water. It is stabilized with 150 to 400 ppm BHT.

¹² Ducom, J.; Brodzke, A., J. Organomet. Chem. (1973), 59, 83-96.

¹³ Available from Penn Specialty Chemicals, Inc. upon request.

Handling and Storage

Methyltetrahydrofuran requires only normal precautions recommended for volatile organic compounds. MeTHF should be used only in suitable equipment and with provision for adequate ventilation. Chemical goggles and face shield should be worn when handling MeTHF. It can be stored and handled in ordinary steel tanks and piping. Because MeTHF is an excellent solvent, welded piping is preferred to screwed fittings. Pump and valve packing must be tight and of a non-soluble type.

MeTHF is a flammable liquid and as such introduces a potential fire hazard where it is stored, handled or used. At ordinary temperatures vapor is given off, which when mixed with air, is explosive within certain limits (1.5 to 8.9 % by volume in air at 25 C). However, reasonable precautions, proper design and layout of equipment, care in handling the material and adequate ventilation will keep the fire hazard from becoming an issue.

Like other ethers such as diethyl ether or tetrahydrofuran, unstabilized MeTHF forms an organic peroxide when exposed to air. If the concentration of the peroxide is allowed to build up to greater than 0.1%, the peroxide may decompose with explosive violence if it is distilled to near dryness. MeTHF is stabilized with butylated hydroxytoluene (BHT) to reduce the buildup of peroxides. If conditions of use result in the destruction or removal of the stabilizer (BHT is nonvolatile), the MeTHF should be restabilized before storage or alternatively stored under an inert gas blanket. MeTHF forms peroxides at a slower rate than does THF.

Peroxide Testing

MeTHF forms an organic peroxide when exposed to air. When MeTHF is distilled the peroxide tends to accumulate in the residue and thus may concentrate to a level sufficient to cause violent decomposition. Before distillation, MeTHF should be tested for peroxide content and if more than trace quantities (0.1% peroxide) are present, the peroxide should be destroyed prior to distillation. When distilled, MeTHF should never be evaporated to dryness since this provides the maximum possibility for explosion. MeTHF should be checked regularly to make certain that the peroxide level is not excessive. The following test may be used to determine the peroxide content of MeTHF.

Place 100 ml of distilled water in each of two Erlenmeyer flasks. Add 35 ml of a 1:4 mixture of concentrated sulfuric acid and water, and then add 25 ml of 10% potassium iodide solution. Add a 25 ml sample of MeTHF to one flask, using the other as a blank. Stopper both flasks, shake and store in the dark for 15-20 minutes. Titrate each flask with 0.02 N sodium thiosulfate until the solution becomes colorless. Calculate the peroxide content of the MeTHF sample from:

$$\% \text{ peroxide} = (\text{ml of thiosulfate for sample} - \text{ml thiosulfate for blank}) \times \text{N of thiosulfate} \times 0.21$$

Waste

If spilled, MeTHF has a CERCLA reportable quantity of 100 pounds because of its low flash point. MeTHF could carry an EPA waste code of D001 for ignitability.

Material Compatibility

MeTHF is similar in behavior to THF and is compatible with a wide range of materials. Since it is a good solvent, many elastomers used as gaskets will be swollen or dissolved by MeTHF. Compatibility of MeTHF with a specific material should always be tested under appropriate conditions to avoid hazardous or unsafe situations. If needed, technical assistance can be obtained from Penn Specialty Chemicals, Inc.

Health and Safety

MeTHF is a flammable liquid with a mildly irritating odor. MeTHF vapors, when mixed with air, are hazardous when exposed to ignition sources. It should be handled only after consulting the material safety data sheet. The reported toxicity data for MeTHF are shown below (source: RTECS).

| Toxicity | Description | Value |
|------------|--------------|-------------|
| Skin | LD50 (rat) | 5720 mg/kg |
| Inhalation | LC50 (rat) | 6000 mg/kg |
| Irritation | Eye (rabbit) | 500 mg/24 h |

Availability

MeTHF is available in bulk tank trucks, in 55 gallon steel drums (375 lbs; 170 kg) and 5 gallon steel pails (35 lbs, 16 kg) net weights.

Shipping

The DOT HM 181 shipping name for MeTHF is methyltetrahydrofuran. It is a hazard class three (3) flammable liquid, Packing Group II material that requires a red flammable liquid label. The ID Number is UN 2536. Consult the MSDS for additional shipping information.

Table 1. Comparison of MeTHF and THF

| Property | MeTHF | THF |
|--|--|---------------------------------|
| CAS number..... | 96-47-9..... | 109-99-9 |
| EINECS number | 202-507-4..... | 203-726-8 |
| Molecular formula | C ₅ H ₁₀ O | C ₄ H ₈ O |
| Molecular weight | 86.13 | 72.11 |
| Boiling point (degrees C) | 80 | 66 |
| Freezing point (degrees C) | -136 | -108.5 |
| Vapor pressure (mm Hg) | | |
| -15 C | 18 | 25 |
| 0 C | 38 | 56 |
| 20 C | 102 | 143 |
| 50 C | 366 | 459 |
| Density at 20 C | 0.855 | 0.888 |
| Refractive index at 20 C | 1.4060 | 1.4073 |
| Viscosity at 25 C (cp) | 0.60 | 0.53 |
| Evaporation rate (n-butylacetate = 1) | 4.2 | 8.0 |
| Vapor density | | |
| at 20 C (g/liter) | 0.19 | 0.162 |
| at boiling point, 1 atm pressure (g/liter) | 3.04 | 2.59 |
| Latent heat of vaporization | | |
| at 20 C (cal/g) | 89.7 | 98.1 |
| at boiling point (cal/g) | 89.7 | 98.0 |
| Dielectric Constant (25 C) | 7.0 | 7.4 |
| 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 MeTHF | 4.4 | inf |
| Esters, alcohols, ketones, hydrocarbons, aromatics | | |
| chlorinated hydrocarbons | inf..... | inf |
| Flammability limits in air (vol %) | | |
| upper limit | 8.9 | 11.8 |
| lower limit | 1.5 | 1.8 |
| Flash point, TCC (deg C) | -11.1 | -14.5 |
| Autoignition temperature (deg C) | 270 | 215 |
| Water azeotrope | | |
| boiling point (deg C) | 71 | 63 |
| composition, wt% solvent | 89.4 | 93.3 |
| wt% water | 10.6 | 6.7 |

METHYLTETRAHYDROFURAN

Penn Specialty Chemicals, Inc. is a privately owned company with manufacturing operations in Memphis, Tennessee. A line of fine chemicals derived from furfural are produced at the site.

Fine Chemicals

| | | |
|---|--------------------------|----------------------------|
| Furan | Methylfuroate | Dihydropyran |
| Acetylfuran | Ditetrahydrofurylpropane | Methyltetrahydrofuroate |
| Furfurylamine | Furoic Acid | Methylfuran |
| Tetrahydrofurfurylamine | Tetrahydrofuroic Acid | Methyltetrahydrofuran |
| High purity furfural | Furfuryl Alcohol | Tetrahydrofurfuryl Alcohol |
| Ethyltetrahydrofurfurylether | 2-bromofuran | 3-bromofuran |
| Fact1 [®] Ethoxylated Furfuryl Alcohol | | |

Penn Specialty Chemicals, Inc. also has extensive pilot and production capability for custom manufacturing.

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