

Solvent Applications of 2-Methyltetrahydrofuran in Organometallic and Biphasic Reactions

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Abstract:

2-Methyltetrahydrofuran (MeTHF) is a commercially available solvent that is produced from renewable resources. The properties of MeTHF place it between tetrahydrofuran (THF) and diethyl ether in solvent polarity and Lewis base strength. In many cases, MeTHF can replace THF in organometallic reactions. The formation and reaction of Grignard reagents in MeTHF and THF are similar. MeTHF can be used as a solvent for low-temperature lithiation, for lithium aluminum hydride reductions, for the Reformatsky reaction, and for metal-catalyzed coupling reactions. MeTHF is also a good substitute for dichloromethane in biphasic reactions.

Comparative Solvent Behavior

2-Methyltetrahydrofuran (MeTHF) is an aprotic ether solvent that, while being a strong Lewis base like THF, is only partially miscible with water. MeTHF¹ is increasingly being used in organometallic and biphasic chemical processes because this interesting combination of properties provides opportunities for process simplification.

THF is the primary ether solvent used in organometallic reactions because it strongly coordinates with many metals and has a moderate bp 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 MeTHF, the product can be conveniently isolated without adding another solvent. MeTHF provides very clean organic–water phase separations with little tendency to form emulsions or rag layers. Also unlike THF, MeTHF can be used to azeotropically dry the product for a subsequent reaction, crystallization, or isolation step.

Besides MeTHF, diethyl ether (Et₂O) is the only other commercially available monodentate alkyl ether that is not water miscible and can be used in place of THF in organometallic reactions that require a strong Lewis base. However, the low bp (35.4 °C) of Et₂O makes it difficult to use in industrial processes. The available data put MeTHF between THF and Et₂O in solvent polarity and Lewis base strength. Table 1 shows that the dielectric constant, dipole moment, solubility of water in the solvent (g/100 g at 20 °C),

Table 1. Solvent polarity and Lewis base strength properties

property	MeTHF	THF	Et ₂ O
dielectric const	6.97	7.5	4.42
dipole moment, Debye	1.38	1.69	1.11
water solubility, g/100 g	4	mis	1.2
Hildebrand, MPa ^{1/2}	16.9	18.7	15.5
solvation energy, kcal/mol	0.6	0	2.3
donor number	18	20.5	19.2

and Hildebrand solubility parameter (MPa^{1/2}) of MeTHF place it between THF and Et₂O in solvent polarity. The donor number (DN) in Table 1 for MeTHF² suggests that it is a weaker Lewis base than Et₂O; however, an NMR study³ and two studies using heats of interaction^{4,5} with alkyllithium compounds put THF > MeTHF > Et₂O as the order of Lewis base strength. The differences in relative free energies of solvation⁴ (kcal/mol) of lithium hexamethyldisilazide in THF, MeTHF, and Et₂O listed in Table 1 indicate that MeTHF is closer to THF than to Et₂O in Lewis base strength.

Synthesis and Properties

An attractive feature of MeTHF is that it is derived from renewable resources. Figure 1 shows the two-step hydrogenation process for conversion of 2-furaldehyde to 2-methylfuran and then to MeTHF. 2-Furaldehyde is produced from agricultural waste like corncocks or bagasse.⁶

Table 2 lists the common properties of MeTHF. Commercial MeTHF has low impurities with less than 300 ppm water. MeTHF has a moderate 80.2 °C bp and a −136 °C melting point (mp). Because of the low mp and low viscosity (1.85 cp at −70 °C)⁷ MeTHF is a good solvent for low-temperature reactions. MeTHF forms an organic glass (does not crystallize) and is frequently used as a solvent for spectroscopic studies at −196 °C.⁸

Table 3 gives the data on azeotropes with MeTHF for some common solvents.

Recovery of MeTHF

The 10.6% water azeotrope of MeTHF can be used to recover dry MeTHF in a simple batch distillation. To make

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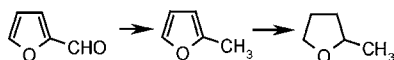


Figure 1. MeTHF production process.

Table 2. Properties of MeTHF

molecular weight	86.1
bp (°C)	80.2
mp (°C)	−136
vapor pressure at 20 °C (mm)	102
density at 20 °C (g/mL)	0.854
viscosity at 25 °C (cp)	0.46
viscosity at −70 °C (cp)	1.85
refractive index at 20 °C	1.408
flash point (°C)	−11
heat of vaporization (cal/g) at bp	87.1
solubility in water at 20 °C (g/100 g)	14
solubility water in MeTHF 20 °C g/100 g	4
azeotrope bp °C	71
azeotrope % water	10.6

Table 3. MeTHF Azeotropes

compound	azeo bp, °C	% compound in azeo
methanol (64.7 °C bp)	62.8	57
ethanol (78.5 °C bp)	74.4	34
n-propanol (97.2 °C bp)	79.5	1
2-propanol (82.3 °C bp)	77	18
toluene (110.6 °C bp)		no azeo

Table 4. % Degradation of THF and MeTHF in 5 N HCl at 60 °C

time (h)	% MeTHF degraded	% THF degraded
4	0.54	1.52
7.5	0.83	2.24

this distillation efficient, an overhead liquid–liquid-phase separator is operated at 60 °C to remove water and reflux MeTHF into the distillation column. The phase separator is operated at about 60 °C because the solubility of MeTHF in water drops from 14.5% at 20 °C to 6.6% at 60 °C but the solubility of water in MeTHF only increases from 4.0% at 20 °C to 4.6% at 60 °C.

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 acids⁹ but the cleavage rate is less than that with THF. In a 4% solution of MeTHF or THF in a 5 N HCl solution at 60 °C, THF degrades about 3 times faster than MeTHF (Table 4).

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 5). 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.

Table 5. % 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

Table 6. Formation of peroxides in THF and MeTHF nonstirred 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

Table 7. Formation of peroxides in THF and MeTHF stirred in air

time (h)	in MeTHF ppm H ₂ O ₂	in THF ppm H ₂ O ₂
0	0.5	0.4
10	10	18
50	150	100
70	275	200

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 (rt exposed to air). With no stabilizer, MeTHF forms peroxides at about the same rate as THF when stored exposed to air (Table 6). MeTHF forms peroxides at a faster rate than THF if air is intensively mixed with the solvents. For example, MeTHF forms about 150 ppm peroxide (as hydrogen peroxide) when stirred at rt for 50 h and THF forms about 100 ppm (Table 7). The diffusion rate of oxygen into the solvents clearly affects the rate of peroxide formation in MeTHF and THF.

Organometallic Reactions in MeTHF

Grignard Solvent. Grignard reactions are frequently used in pharmaceutical and fine chemical processes, and THF is the most common solvent used for Grignard reactions.¹⁰ In our studies, we found that MeTHF was similar to THF in the formation and reaction of alkyl and aryl Grignard reagents. Table 8 lists yields of addition products from Grignard reagents prepared in MeTHF with several halide compounds reacted with several electrophiles. Similar yields were found with THF as the solvent except for the reactions with benzyl Grignard reagents. Benzyl Grignard reagents prepared in THF gave mostly the coupled benzyl dimer. MeTHF has been reported to give good yields of benzyl and allyl Grignard reagents.¹¹

Bromo Grignard reagents tend to be more soluble, and chloro Grignard reagents tend to be less soluble in MeTHF

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Table 8. Grignard reactions in MeTHF and THF

halide reagent	electrophile	% yield ^a addition product in MeTHF	% yield addition product in THF
bromobenzene	butanal	75	73
chlorobenzene	butanal	71	76
1-chlorobutane	MEK	73	72
benzylbromide	MEK	76	20
2-chlorobenzyl chloride	MEK	58	12
2-bromofuran	triethylborate	75	78

^a Nonisolated yields

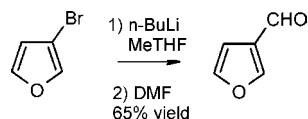


Figure 2. Lithium exchange in MeTHF.

than in THF. This solubility difference is reflected in the high solubility of anhydrous magnesium bromide in MeTHF (>40 g/100 g) compared to 7 g/100 g MgBr₂ soluble in THF. The high solubility of MgBr₂ in MeTHF means that highly concentrated homogeneous solutions of bromo Grignard reagents can be prepared. For example, 4.5 M ethylmagnesium bromide and 4.0 M phenylmagnesium bromide homogeneous solutions can be made in MeTHF at 25 °C (both are viscous solutions). Following this trend, about 10 g/100 g of MgI₂ dissolves in MeTHF at rt but <0.1 g/100 g is soluble in THF.

Reformatsky Reaction. MeTHF has also been used as a solvent for the Reformatsky reaction.¹² The high solubility of ZnBr₂ in MeTHF (measured in our labs at >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.

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. Figure 2 shows an illustrative example of lithium exchange of *n*-butyllithium with 3-bromofuran at -70 °C in MeTHF, followed by reaction with DMF to give 3-furaldehyde.

MeTHF is reported to be more stable than THF to some lithium reagents.^{13,14} A comparison study of the stability of *n*-butyllithium in MeTHF and THF showed a 70 min half-life in MeTHF and a 10 min half-life in THF at 35 °C.¹⁵

Hydride Reductions. LiAlH₄ has good solubility in MeTHF (at least 1.8 M), and our results 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

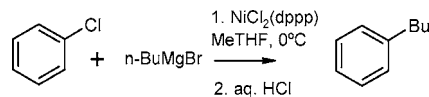


Figure 3. Nickel cross-coupling.

to work like THF as a solvent in the Ni-catalyzed coupling of alkynylzinc bromides with nitriles.¹⁶ MeTHF was found to give better diastereoselection than THF in a series of copper-mediated biaryl couplings.¹⁷ An illustrative example of nickel-mediated cross-coupling with MeTHF is shown in Figure 3.

Biphasic Reactions in MeTHF

MeTHF is finding applications as a replacement for highly regulated chlorinated solvents like dichloromethane in biphasic reactions. MeTHF can often be used as a direct replacement for dichloromethane and was shown to give high reactivity when used in several biphasic reactions.¹⁸ The advantages of MeTHF compared to dichloromethane are that it has a moderate bp, is more resistant to reactions with nucleophiles like amines, and provides clean organic–water phase separations. MeTHF has been used as a solvent in two-phase displacement reactions with allylbromide¹⁹ and to remove BOC from an amine group with an aqueous base mixture.²⁰ MeTHF was used as the solvent in a reductive amination process that first involved freeing-up an aldehyde from its sulfite adduct using aqueous NaOH then azeotropically drying the aldehyde with MeTHF before carrying out the reductive amination in MeTHF.²¹

Our work has shown that MeTHF is a very effective solvent for extracting polar compounds from water mixtures. For example, two extractions with equal portions of MeTHF removed about 94% of 2-propanol from water, but under the same conditions only 68% of 2-propanol was removed with toluene. This behavior was also seen in the efficient extraction of a water-soluble carbamate in a process where MeTHF was used to react an amine with dimethyl carbonate.²²

Conclusions

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. MeTHF can also be used as an efficient replacement for dichloromethane in biphasic

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reactions and as a solvent for efficiently recovering water-soluble compounds.

Experimental Section

General. Commercial grade MeTHF and 3-bromofuran from Penn Specialty Chemicals, Inc. were 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 300 ppm for the organometallic reactions. Product yields were determined by GC using standards of known purity.

Grignard Reagents Prepared in MeTHF. Mg turnings (2.7 g, 0.11 mol) were put in an oven dried flask equipped with a nitrogen bubbler, a stirrer, condenser and addition funnel. The flask was heated to 130 °C to dry the Mg and cooled to rt, and 20 g of MeTHF were added. 1,2-Dibromoethane (0.1 g, 0.54 mmol) was added, and the mix stirred for 15 min to activate the Mg surface. The bromo/chloro compound (0.094 mol) was dissolved in 15 g of MeTHF (with a small amount of dodecane as an internal standard) and added at a rate so that the exotherm could be controlled. Typically alkyl or aryl bromo compounds will form Grignard reagents quickly at 5–40 °C in MeTHF. The benzyl Grignard reagents were made at 5–10 °C. To react 1-chlorobutane and 2-chlorobutane as they were added, the reaction temperature was kept at about 70 °C. Refluxing in MeTHF for about 12 h was required to form the Grignard reagent of chlorobenzene. The yield of the Grignard reagent was checked by quenching a small amount in water and measuring the amount of reduced product by GC. The Grignard reagent was transferred away from the remaining Mg to another nitrogen blanketed flask before reacting with an electrophile. The electrophiles were added dropwise at a rate to keep the temperature below 10 °C. The reactions were quenched with 2 N HCl, and the product yields were determined by GC analysis of the MeTHF phase.

3-Furaldehyde. MeTHF (15 g), 3-bromofuran (2.35 g, 16 mmol), and dodecane (0.045 g, as internal standard) were cooled to –75 °C in a flask equipped with a nitrogen bubbler, stirrer, and dropping funnel. *n*-BuLi (10 mL 1.6 M in hexane) was added dropwise at a rate necessary to prevent the

temperature from increasing above –68 °C. 20 min after adding the *n*-BuLi, dimethylformamide (1.2 g, 16.4 mmol) in MeTHF (5 g) was added dropwise at a rate necessary to prevent the temperature from increasing above –68 °C. The mixture was allowed to increase to rt and then was quenched with 17 mL of 2 N HCl while the temperature was maintained at 5–10 °C. GC analysis of the MeTHF phase showed a 65% yield of 3-furaldehyde (1.0 g, 10.4 mmol).

***n*-Butylbenzene.** MeTHF (44 g), chlorobenzene (6.64 g, 0.059 mol), dodecane (0.12 g, as internal standard), and dichloro[1,3-bis(diphenylphosphino)propane]nickel(II) (NiCl₂-(dppp)) (0.073 g, 0.15 mmol) were added to a flask equipped with a nitrogen bubbler, addition funnel, mechanical agitator, and condenser. The mixture was stirred in an ice bath, and *n*-butylmagnesium bromide (20 g, 0.062 mol) was added dropwise in 20 min. The mixture was allowed to warm to room temperature and then was kept at 40–45 °C for 3 h. Hydrolysis with 2 N HCl and analysis by GC of the MeTHF phase showed an 83% yield of butylbenzene (6.57 g, 0.049 mol).

LiAlH₄ Reductions. MeTHF (12 g) was cooled to 1 °C in a flask equipped with a nitrogen bubbler, stirrer, and dropping funnel. LiAlH₄ (0.4 g, 10.5 mmol) was added, and after the mixture again reached 1 °C, a solution of the aldehyde, ester, or acid in MeTHF (15 g) with dodecane as an internal standard was added dropwise at a rate necessary to keep the temperature below 10 °C. The mix was stirred for 30 min at 5–10 °C and then was kept at 50 °C for 1 h. After the mixture cooled to 10 °C, ethylacetate was added to react the excess LiAlH₄ and then the mix was quenched with 2 N HCl. The Fieser procedure²³ (add in order, *n* grams of water, *n* grams of 15% NaOH, 3*n* grams of water, where *n* is grams of LiAlH₄) for removing the salts in an easily filterable form was also found to work with MeTHF. Using the above conditions, 4-methylbenzaldehyde (4.5 g, 33.3 mmol) gave (4-methylphenyl)methanol (3.9 g, 32 mmol); butylacetate (2.2 g, 18.9 mmol) gave butanol (1.25 g, 16.8 mmol); methylbenzoate (2.57 g, 18.9 mmol) gave benzylalcohol (1.86 g, 17 mmol); and benzoic acid (1.5 g, 12.3 mmol) gave benzylalcohol (1.12 g, 10.3 mmol).

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