

A safer alternative to THF for Grignard reactions and other organometallic chemistry

There is increasing interest in alternative solvents to replace tetrahydrofuran (THF) for Grignard reactions. Di---n---Butyl Ether (DnBE) is a cost effective alternative to THF and 2---methyltetrahydrofuran in many organometallic reactions.

DnBE is a versatile ether solvent with a density of 0.769g/cm³ and a flash point of 25°C.

It is less dense than and immiscible with water, and will therefore be an upper layer in reactions where there is a water quench/separation. With a flash point of 25°C, somewhat higher than other common solvents used for upper layer separations – e.g. toluene (6°C), ethyl acetate (---4°C), isopropyl acetate (2°C), di---isopropyl ether (---28°C), it is safer to handle with reduced risk of ignition.

Its boiling point of 142°C makes it ideal for reactions that require high temperatures, and it boils close to the operational limit of most plant capabilities (based on 6 barg steam). It will allow higher reaction temperatures to be reached than those solvents listed previously above which may be typically used for upper layer phase separations, (toluene being the highest boiling at 110°C).

Table 1 :--- Comparative physical data for DnBE vs. traditional solvents used in organometallic and similar types of reactions

Names	DnBE	THF	Diethyl Ether	MTBE	2 Methyl THF
Structure					
Molecular Formula	C ₈ H ₁₈ O	C ₄ H ₈ O	C ₄ H ₁₀ O	C ₅ H ₁₂ O	C ₅ H ₁₀ O
Molecular Weight	130.23	72.11	74.12	88.15	86.13
CAS	142---96---1	109---99---9	60---29---7	1634---04---4	96---47---9
Boiling Point	142.4°C	66°C	34.6°C	55.2°C	80.3°C
Freezing Point	---97.9°C	---108°C	---116°C	---109°C	---136°C
Density (g/cm ³)	0.769	0.888	0.713	0.704	0.854
Solubility in Water (20°C)	0.03%	Miscible	6.9%	2.6%	14%
Flash Point	25°C	---17°C	---45°C	---10°C	---12°C

Table 1 illustrates that the major differences are in boiling point, flash point and water solubility which gives DnBE its definite advantages in manufacturing operations, allowing safer handling, easier and shorter processing time, less environmental impact and fewer losses. Its ease of recycling gives a strong commercial advantage.

Its high hydrophobicity/low water solubility allows easy separation and recovery from water, reducing emissions and waste water.

It is stable to oxidation, reduction and bases.

It can be cleaved by strong acids such as HBr and HI.

It is well used in the chemical world and has over 23,000 references in SciFinder® and is a key solvent used in over 300 patents. It has a wide range of uses, discussed below.

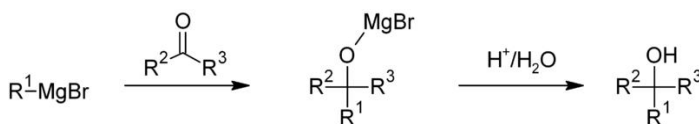
Use in manufacture of CD---Rs

The polarity (dipole of 1.18) and moderate vapour pressure of DnBE make it ideally suited for the manufacture of CD---Rs where, because of its excellent solvency for phthalocyanine multispeed dyes, it is used as a standard in CD---R manufacture.

DnBE has been tested and approved by Ciba Specialty Chemicals for use with Ciba Irgaphor® Ultragreen MX CD---R dye.

Use in Grignard reactions

The Grignard reaction is an organometallic chemical reaction in which an alkyl--- or aryl---magnesium halide (Grignard reagent) adds to a carbonyl group. This reaction is an important tool for the formation of carbon---carbon bonds in organic synthesis and is used copiously on an industrial scale.



The choice of solvent is critical in the process and it must be dry and free of oxygen. Other key considerations are the solubility of the Grignard reagent, the temperature required for initiation, and reactions of the solvent with the Grignard reagent. Organo---magnesium compounds are generally strongly solvated and changes in solvent property can cause a change in the rate of reaction and hence allow secondary reactions to take place.

There are many examples where DnBE has been used in Grignard reactions, whether to make intermediates for APIs for pharmaceuticals (e.g. 7---amino---3---chlorocephalosporanic acid, cefaclor, guanidine carbonate, L---carnitine, procabazine), or AIs for agrochemicals, (e.g. cyhexatin).



It has been used in these applications because of its ease of drying, low levels of peroxide (critical in Grignard reactions) and its good polarity. These properties make it a good solvent for many substrates. Additionally, its density makes it an ideal solvent for extractions, giving upper layer separations cleanly and efficiently.

Its flash point of 25°C means it is safer to handle than the usual solvents for Grignard reactions (eg THF which has a flash point of -17°C).

The other main benefit of DnBE is its water immiscibility – an advantage that is not seen with THF.

DnBE has also been used as solvent in the Grignard reaction of tin tetrachloride with a Grignard reagent, to make the tetraalkyl tins¹. It has also been used to make silanes², hexamethyldisiloxanes³, dicyclopentyl dimethoxy silanes⁴ and nipecotate esters⁵. Even the simplest of Grignard reactions has been performed in DnBE solvent efficiently and safely in processes designed to operate commercially⁶. Indeed n-butylmagnesium chloride is now offered as 1.3M solutions in DnBE at lab scale, and many companies now generate Grignard reagents in DnBE.

Use in Organolithium reactions

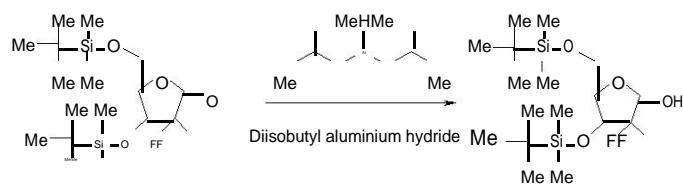
For similar reasons, organolithium chemistry can be run in DnBE. For instance it is well known that aryllithium compounds can be prepared in this solvent^{7,8,9}.

Again, materials are available, such as 2.0M solution of phenyl lithium in DnBE.

Use in Metal-Hydride reduction reactions

Metal hydride reductions are common in many syntheses, whether it is pharma (a number of generics require metal hydride reduction and there is a wide use of SDMA), agrochemical, flavours and fragrances, silicon chemistry etc. Metal hydride reducing agents are usually sold as solutions, examples are SDMA sold as 70% solution in toluene, LAH is commonly sold as 10 and 20% solutions in diethyl ether or THF (also sold neat), and DiBAL which is commonly sold in toluene or hexane.

An example is shown, for the conversion of a lactone to a lactol, as in the case of the drug gemcitabine, using DiBAL, but now as the drug is generic, manufacturers use SDMA.



Monoalkyl phosphines have been prepared by reduction of the phosphonyl dihalides using LAH in DnBE. Acid chlorides have also been reduced by LAH¹¹. Reductions of halosilanes have also been accomplished in DnBE¹², and there are examples of other silanes and group IV organometallic compounds being reduced by LAH and SDMA in DnBE, for use in vapour deposition in electronic devices¹³. Less sophisticated chemistry is also completed in DnBE, as can be seen by the preparation of 5-chloro-2-nitroaniline¹⁴. Even mono-aryl arsines have been manufactured by a combined Grignard, metal hydride reduction¹⁵.

Use in Alkylation reactions

Whether reactions are deprotonation using strong inorganic bases such as NaH or organic bases such as imidazole, DnBE is still a useful solvent, not only because of its elevated boiling point. Once the reaction is completed, the base can be easily washed out, along with any salts using bottom water separation, and because of the density, separations tend to be quick and clean. Examples of different types of alkylation can be seen throughout the literature, for instance, the reaction of 1-(cinnamoyl)benzotriazole with phenyl hydrazine in the presence of NaH at 120°C in DnBE to give 2,5-diphenyl-3-pyrazolidinone in good purity and 80% yield¹⁶. Another example is shown by the reaction of 1,3,5-trimethylbenzoic acid and chlorodiphenylphosphine using 1-methylimidazole as base at 80°C, which afforded 87% yield of the expected product¹⁷.

The solvent also works well in heterogeneous reactions such as demonstrated by the alkylation of salicylic acid by a supported catalyst¹⁸.

Use in other general reactions

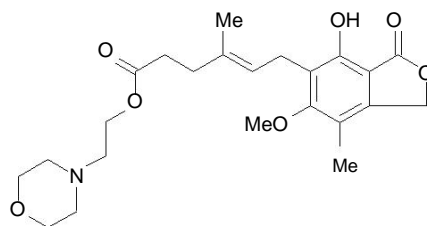
Many other general reactions use DnBE as the solvent, in a variety of applications, notably in the preparation of alkyl tin mercaptides used as polyurethane catalysts¹⁹.

Even in traditional heterogeneous catalytic hydrogenation the DnBE is a useful medium, and in the reduction of perfluoroalkyl nitriles, it was used as a solvent with temperatures of 100°C²⁰.

In the case of cycloadditions, an example which needs a high temperature (150°C), is that of ethyl acrylate with 1,3,5-trimethylheptatriene²¹.

Use in Esterification reactions

An example of the use of DnBE in esterification can be seen in the synthesis of the immunosuppressant mycophenolic acid 2-(morpholino)ethyl ester (mycophenolate mofetil).



In the development of a modified method (see reference), workers determined that DnBE was beneficial in that the reaction rate was increased and the colour issues were removed.

They also noted that in contrast to the usual solvents such as toluene, once azeotropic distillation was completed, isolation was easier because of the limited solubility of the API in the cooled solvent.

In contrast to earlier methods which used an excess of 2-(morpholino)ethanol, often 2-3 molar excess, with reaction time of 1-2 days, they complete the reaction in a few hours with one mole equivalent and obtained 80% yield of 99% purity²².



Uses in Azeotrope

Because of the good solvent properties, low water solubility and the high boiling temperature, as has been outlined, DnBE is a useful solvent for azeotrope. This is highlighted again in the preparation of N,N'---ethylenebis(octadecanamide), a lubricant for plastics, a foam suppression agent, and an additive for waxes and resins. The reaction is fairly simple in nature, that of stearic acid and ethylenediamine – however, normal reaction in toluene leads to by---products and oxidation, presumably because of the time taken to azeotrope out the water. In the case of DnBE, the reaction was complete at reflux after 1 hour and the product was isolated in 98% yield and was of high purity²³.

Uses in Surface coatings

DnBE is used in the water repellent coatings field, useful for windows, wheels, bumpers etc. The silanes and initiator are both dissolved in DnBE and applied on the substrate and then dried. This gives a stable coating with retention of contact angle²⁴.

What does the future hold?

Bio---DnBE is the latest 'green' solvent offering from Chemoxy International Ltd

Chemoxy is pleased to announce the launch of **Bio---DnBE**, manufactured from sustainable raw materials to supplement its existing DnBE manufacture. **Bio---DnBE** uses renewable carbon in manufacture to enhance your *green* profile, and to help meet your eco---impact targets.

Why use DnBE?

1. An excellent choice for room temperature Lithiations. THF gets cleaved with BuLi at room temperature at an appreciable rate and MTBE is very poor at solvating Lithium.
2. The higher boiling point of DnBE means that 'sluggish' reactions can be performed at a quicker rate.
3. The higher boiling point reduces loss of solvent from the reflux condenser and makes it easier to isolate the quenched reaction product and hence to recycle DnBE with good cost savings.
4. Common side reactions can often be diminished due to the increased reaction rate when operating at temperature.
5. Soon to be available in Bio! Using renewable carbon sources in manufacture.

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