Synthesis & Application of New & Alternative Green Solvent Cyclopentyl Methyl Ether

Parin D. Shah, Jalpesh A. Parekh

Abstract - This paper summarizes the usage & principles of green chemistry & green solvents with its examples like Cyclopentyl Methyl Ether (CPME), Methyl TetraHydroFuran (MeTHF). It also discusses about synthesis of CPME by methylation process by using different methylating agent with different four routes like Methylation of cyclopentene by methanol, Methylation of cyclopentanol by dimethyl sulphate, Methylation of cyclopentanol by trimethyl phosphate, Methylation of cyclopentanol by methyl iodide. The general properties of CPME with compare to other solvent like MeTHF, TetraHydroFuran, Dimethyl ether, Methyl tetra butyl ether (MTBE) are also mentioned. The bench and plant scale applications of CPME are also mentioned.

Keywords - Cyclopentyl Methyl Ether, Green Chemistry, Green Solvent, Methylation

I. INTRODUCTION

1) Green chemistry

Green chemistry is utilization of a set of a principles that reduces or eliminates the use & generation of hazardous substances in the design, manufacture and application of chemicals products. The aim of green chemistry is to reduce chemical related impact on human health and virtually eliminate contamination of the environment through dedicated, sustainable prevention programs. Green chemistry searches for alternative, environmentally friendly reaction media and at the same time strives to increase reaction rates and lower reaction temperatures. The green chemistry concept applies innovative scientific solutions to solve environmental issues posed in the laboratory. It is based on 12 principles. These principles can be grouped into reducing risk and minimizing the environmental footprint [1]. Following are the 12 principles of green chemistry:


II) Green solvents:

Green solvents is defined as such chemical is designed that it will biodegrade more readily to nontoxic product, the risks posed by the chemical to human health and the environment are reduced. The criteria for what determines a green solvent will depend upon the use and ultimate fate of the solvent during the chemical process. The discussion of green solvents will include chemistry, ecology, and philosophy. The choice of solvents will include new criteria in addition to the traditional considerations of synthesis yield, perfect product recovery (separations), or commercial usefulness [2].

The considerations of a safe solvent might be summarized as follows [2]:

1. It must have reduced human and environmental absorption.
2. Its environmental toxicity should be understood.
3. Its environmental fate is understood.

II. SAILENT FEATURES OF CYCLOPENTYL METHYL ETHER(CPME)

1) Introduction

Cyclopentyl methyl ether has many properties that make it a greener, easy to use, and a more cost effective process solvent for many types of synthesis. CPME has proved to be quite useful as a process solvent for organic synthesis. Despite many useful solvents available for routine organic reactions, it is not recommended to use certain organic solvents (halogenated solvents, low-boiling ethers, or hazardous solvents) for contemporary plant synthesis (or process development). Typical ethereal solvents such as diethyl ether (Et₂O), Tetrahydrofuran (THF), dimethyl ether (DME), and dioxane have been widely used in synthesis. However, they have the drawbacks of low boiling point, easy peroxide (PO) formation, and solubility in water, thus resulting in inefficient recovery. cyclopentyl methyl ether (CPME) has proven to be quite useful as a process solvent for organic synthesis because it is free from those drawbacks that are associated with the classical ethereal solvents. CPME can be used not only as a reaction solvent but also as an extraction solvent and a crystallization solvent because of its higher hydrophobicity, lower peroxide formation and higher boiling point. This means that additional extraction and crystallization solvents could be unnecessary for CPME processes. The unique properties of CPME also give high recovery rate of more than 90%. The unique properties of CPME, such as high hydrophobicity, high boiling point and low peroxide formation, contribute to greener chemistry through a reduction in the total amount of solvents used, waste water and waste solvent created and carbon dioxide emissions produced. CPME also contributes to process innovation, where it can save process time and facilities by shortening work-up time and simplifying the total process, which means fixed costs are reduced. In addition, CPME can
reduce variable costs due to its high recovery rate and no need of extraction and crystallization solvents. Its good stability under acidic and basic conditions contributes to process innovation as well [4,6]. Cyclopentyl methyl ether has better quality & feature compare to MeTHF & THF as mention below [3]:


II) General Properties of CPME

a) Hydrophobicity

The recovery of the solvent is facile by usual extractive procedures, it becomes much more useful from the viewpoint of a green sustainable solvent. Water removal is done by molecular sieves 4A. After overnight conditions, moisture in CPME is reduced to less than 100 ppm in 3 h. This indicates the advantage of CPME for anhydrous reactions [4].

b) Formation of Peroxide

For safety concerns ethereal solvents closely relate to its explosive nature arising from PO generation. Accordingly, the formation of PO from CPME was carefully investigated and compared with those from other ethereal solvents. The PO formation in CPME was very sluggish as was that of Methyl tetrabutylether (MTBE), which hardly generates PO under certain conditions. As the ether radical is more stable, more PO is accumulated during the storage. The ether radical of CPME is unstable compared to that of Isopropylether (IPE). It is thus concluded that the peroxide formation from CPME is very slow compared to that of other ethers. For further safety reasons, however, CPME is commercially supplied with about 50 ppm Butylhydroxytoluene (BHT) as a peroxide inhibitor, while the commercially available THF contains 250 ppm BHT [4].

c) Stability Under Acidic and Basic Conditions

i) Under Homogeneous Acidic Conditions

In a typical homogeneous condition, 0.1 M camphorsulfonic acid (CSA) in CPME was heated at reflux for 8 h, revealing 0.2% of decomposition products that were easily identified as cyclopentanone and methanol without any polymerization product. Therefore, CPME can be applied for dehydration reactions under acidic conditions, provided the two above by products do not interfere with the reaction. At room temperature it is more stable compared to 40°C & 60°C [4].

Under Heterogeneous Acidic Conditions In typical heterogeneous conditions, CPME was heated with 18% HCl at 100°C for 8 h. Acidic decomposition was not a major problem (a very sluggish reaction) because of an oil-water separation (two-phase) mixture [4,7].

ii) Under Basic Conditions

Ether solvents are very good partners for strongly basic organometallic reagents such as organolithium, organomagnesium, and organozinc reagents; As often noted, n-BuLi (n-Butileolithium) cannot be compatible with THF at higher temperature because of the undesired deprotonation followed by ring opening. CPME exhibits superior stability at ambient temperature when compared to THF and is stable like ethyl ether [4,7]. Physical properties of CPME as mentioned in Table I.

III) Synthesis of CPME:

a) Methylation

In the chemical sciences, methylation denotes the addition of a methyl group to a substrate or the substitution of an atom or group by a methyl group. Methylation is a form of alkylation with, to be specific, a methyl group, rather than a larger carbon chain, replacing a hydrogen atom. The term methylation in organic chemistry refers to the alkylation process used to describe the delivery of a CH3 group. This is commonly performed using electrophilic methyl sources - iodomethane, dimethyl sulfide, dimethyl carbonate, or less commonly with the more powerful (and more dangerous) methylaing reagents of methyl triflate or methyl fluorosulfonate (magic methyl), which all react via SN2 nucleophilic substitution. Dimethyl sulfide (DMS) is a strong methylaing agent, it can be used to introduce a methyl group at the following reaction centers having unshared electron pairs: Oxygen, Nitrogen, Carbon, Sulfur, Phosphorus, Some metals. However, for commercial applications in which the reaction site is highly reactive. Methyl iodide is a reagent used for O-methylation, like dimethyl sulfide, but is less hazardous and more expensive. Dimethyl carbonate, which is less reactive, has far lower toxicity compared to both dimethyl sulfide and methyl iodide can be used to instead of dimethyl sulfide for N-methylation. High pressure can be used to accelerate methylation by dimethyl carbonate. In general, the toxicity of methylaing agents is correlated with their efficiency as methyl transfer reagents. So, Methanol is used for synthesis or methylaing of cyclopentene to produce cyclopentyl methyl ether[9,10,11].

There are mainly four routes to produce CPME:

1. CPME can be manufactured by the methylation of cyclopentanol by dimethyl sulphate. When deal with dimethyl sulphate, handling should be done properly. Because it is very carcinogenic & mutagenic[4].

\[
\text{C}_3\text{H}_6\text{O} + \text{Me}_2\text{SO}_4 \rightarrow \text{C}_5\text{H}_{12}\text{O}
\]

Cyclopentanol Di methyl Sulphate  Cyclopentyl Methyl Ether

2. The addition of MeOH to readily available cyclopentene. A tightly closable reaction vessel made of stainless steel was charged with cyclopentene, methanol, acidic ion-
exchange resin. After tightly closing the reaction vessel, the mixture was stirred for 6-8 hours at 120 °C under pressure of 2.5 MPa. It is very effective process compare to above process. Yield could be high. The former process is a nucleophilic substitution which produces byproducts as wastes, whereas the latter (addition reaction) produces no apparent waste [4-5].

\[
\begin{align*}
\text{C}_6\text{H}_{12} & \xrightarrow{\text{CH}_3\text{OH}} \text{C}_6\text{H}_{12}\text{O} \\
\text{Cyclopentane} & \xrightarrow{\text{Methanol}} \text{Cyclopentyl Methyl Ether}
\end{align*}
\]

3. Other method for manufacture CPME is that, it is two stage process. In first stage Cyclopentanol react with Sodium Hydroxide (NaOH) at 110 °C & 1 atmosphere pressure, 1 hour to get Sodium cyclopentoxide. Then in second stage, sodium cyclopentoxide reacts with methyl iodide as methylating agent at 110-120 °C & 1 atmosphere, 5 hours to get CPME & Sodium Iodide (NaI). In this process, reaction condition is better than other process. It is easy process compared above process. In this process handling should be proper. Because Methyl iodide as methylating agent is carcinogenic material[5].

\[
\begin{align*}
\text{R-OH} & \xrightarrow{\text{NaOH}} \text{R-ONa} + \text{H}_2\text{O} \\
\text{Cyclopentanol} & \xrightarrow{\text{Sodium Hydroxide}} \text{Sodium Water} \text{ cyclo- Pentoxide}
\end{align*}
\]

\[
\begin{align*}
\text{R-ONa} & \xrightarrow{\text{CH}_3\text{I}} \text{R-OCH}_3 + \text{H}_2\text{O} \\
\text{Sodium} & \xrightarrow{\text{Methyl CPME Water}} \text{Cyclo- Iodide}
\end{align*}
\]

4. Primary & Secondary alcohols react autocatalytically with Trimethyl phosphate(TMP) plus some amount of polyphosphoric acid(PPA) at 185 °C to give CPME. One liter three necked flask without stirrer was equipped with total reflux condenser with centrally located thermometer for monitoring reaction temperature. Mixture of TMP and PPA heat at 185 °C for 15 min for equilibrate. Cyclopentanol added intermittently at period of 1 to 3 h. Reaction time varies from 2 h to 30 h. compare the samples by Gas Chromatography. From which CPME are obtained in yields of 50-75%. Crude product was taken off at temperatures near or below its boiling point, as like olefin and water. In this process, yield could be low compared to above process & other disadvantage is waste is generated more compare to above process[12].

**IV) Applications**

CPME has attracted many synthetic chemists in challenges from the bench study to plant-scale application. CPME can thus replaces THF, DME, or other ethereal solvents as a reaction medium under basic conditions. CPME can participate as a crucial extractive tool. Sometimes, it can assist the isolation and crystallization of the products.

### a) Reactions with Alkylating Agents

As for methylating agents, Methyl triflate (Me-OTf), powerful methylating agent, is used for alcohol methylation. The decomposition of CPME is also sluggish at room temperature. Thus, methylation with Me-OTf in CPME will be an additional option for alcohol methylation[4].

### b) Friedel-Crafts Type Reactions

Friedel-Crafts (FC) reaction also requires Lewis-acid catalyzed and halogenated solvents. CPME can attain very anhydrous conditions, it is useful to keep anhydrous reaction media for metal triflates or prevent from decaying. It is further apparent that CPME cannot be compatible with a strong Lewis-acid catalyst (AlCl₃), some Ti Lewis acids are recommendable with CPME [4].

### c) Grignard types reaction

CPME can maintain anhydrous conditions without any particular precautions, it is a preferred solvent for Grignard-type reactions. Magnesium turnings placed on a flask. Covered with CPME and a small piece of iodine added. A solution of alkyl bromide was added while heating. After completion of the addition, the mixture was heated for a while. Formation of the Grignard reagent had completed. A small amount of magnesium still remained in the flask. The Grignard reagent thus prepared was cooled to 0°C before the addition of carbonyl compound. The solution became cloudy since the Grignard reagent precipitated out. A solution of carbonyl compound was added to the Grignard reagent. The solution was warmed to room temperature. The reaction was complete [4-8].

### d) Reactions with Transition Metal Catalysts

Ethereal solvents are good partners for transformations with transition metal catalysts (Pd, Ni, Rh, Ir). In particular, high reaction temperature is preferable for such catalytic reactions, and anhydrous conditions are useful for multicomponent couplings. CPME can also take part in the Pd-catalyzed asymmetric allylic alkylation in the same manner as for other ethers (THF) and toluene. It is obvious that the two-phase PTC system (PTC/CPME/H₂O) mentioned earlier is easily applicable to typical Pd-based transformations such as Heck, Suzuki, and related reactions. CPME supplanted for conventional ethereal solvents such as THF and dioxane. A high boiling point of CPME is capable of making such coupling reactions reach completion within short time. CPME was successfully employed as the solvent. High boiling points and easy workup made the overall reaction sequence very effective and convenient [4].
e) Enolate Chemistry

An interesting solvent effect of CPME emerged during enolate formation. While many ethereal solvents are involved in conventional enolate formation with a strong base, CPME has demonstrated its unique participation as described in the following examples. Kawabata’s group reported an asymmetric methylation (chirality transfer reaction; which might be manifested through the formation of a rigid enolate from O-methyl mandelic acid in the medium of CPME. Aggregated enolate formation is controlled by the interference of CPME with base or enolate itself [4].

f) Claisen Condensation

Aldol and Claisen condensations are typical transformations under basic media, thus compatible with CPME. A classical example of Claisen-Schmidt condensation with a pyridine derivative is feasible in CPME with the proper base catalysis with demonstrating a facile entry into the 2-acylpyridine skeleton from 2-picoline esters. Among many methods available for the acylpyridine derivatives, these are the most simple combinations of organometallic reagents. These base catalyzed reactions clearly indicate the usefulness of CPME for general condensation reactions. It also should be noted here that the desired product can be isolated by the simple extraction from CPME, leaving the polar starting materials (starting picoline and acids) in aqueous solution. Thus, CPME makes the workup process very easy in operation [4].

g) Transformations

Classical transformations utilized in the pharmaceutical company have been renewed by the use of CPME as a solvent, which demonstrated the utility of CPME in the manipulation of the heterocyclic intermediates. The mixed ether solvents were employed in the transformations [4].

| TABLE I | PHYSICAL PROPERTIES OF SOLVENT[4]: |
|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| Density(20°C)[g/cm³] | CPME                 | MeTHF                | THF                   | Diethyl ether        | Dioxane              | MTBE                 |
| 0.86                  | 0.85                 | 0.89                 | 0.71                  | 1.03                 | 0.74                 |
| Vapor specific gravity (air=1) | 3.45              | 2.97                 | 2.49                  | 2.56                 | 3.3                  | 3.03                 |
| Boiling Point[°C]     | 106                  | 80                   | 65                    | 34.6                 | 101                  | 55                   |
| Melting Point[°C]     | <140                 | -136                 | -108.5                | -116.3               | 11.8                 | -108.7               |
| Viscosity(20°C)[cP]   | 0.55                 | 0.6                  | 0.55                  | 0.2448               | 1.31                 |
| Surface tension(20°C)(mN/m) | 25.17             | Unknown              | 26.4                  | 17.3                 | 33.74                | 19.8                 |
| Heat of vaporization/boiling point[Kcal/kg] | 69.2              | 89.7                 | 98.1                  | 86.08                | 98.6                 | 81.7                 |
| Specific heat(20°C)[Kcal/kg] | 0.4346            | Unknown              | 0.469                 | 0.5385               | 0.41                 | 0.51                 |
| Refractive index(20°C) | 1.4189            | 1.406                | 1.407                 | 1.353                | 1.422                | 1.369                |
| Solubility parameter(cal/cm³)½ | 8.4              | 8.52                 | 9.5                   | 7.4                  | Unknown              | Unknown              |
| Dielectric constant(25°C) | 4.76              | 7                    | 7.58                  | 4.197                | 2.227                | Unknown              |
| Dipole moment[D]      | 1.27                 | Unknown              | 1.7                   | 1.12                 | 0.45                 | Unknown              |
| Azeotropic temperature with water[°C] | 83              | 71                   | 64                    | 34.2                 | 87.8                 | -                    |
| Solubility in water (23°C)[g/100g] | 1.1              | 14                   | ∞                     | 6.5                  | ∞                    | 4.8                  |
| Solubility of water in the solvent(23°C)[g/100g] | 0.3              | 4.4                  | ∞                     | 1.2                  | ∞                    | 1.5                  |
| Flash point[°C]       | -1                   | -11                  | -14.5                 | -0.45                | 12                   | -28                  |
| Ignition point[°C]    | 180                  | 270                  | 205                   | 180-190              | 180                  | 460                  |
| Log Pow               | 1.59                 | Unknown              | 0.47                  | 0.89                 | -0.42                | 1.06                 |
| Explosion range[vol%] | lower limit         | 1.1                  | 1.5                   | 1.84                 | 1.85                 | 2                    |
|                        | Upper limit          | 9.9                  | 8.9                   | 11.8                 | 48                   | 22                   | 15.1                 |
h) **Reactions with 4 N HCl in CPME**

Commercially available 4 N HCl in CPME is useful in the conventional transformations, particularly in the isolation of the precipitated products [4].

i) **Pinner Reaction**

The Pinner reaction is an organic reaction of a nitrile with an alcohol under acid catalysis for instance hydrochloric acid. The product formed is the hydrochloric acid salt of an imino ester or an alkyl imidate, which sometimes is called a Pinner salt. Cold 4N-HCl in CPME was added to a solution of nitrile and anhydrous methanol in CPME with stirring under a nitrogen atmosphere at 0°C for an hour before it was placed in a refrigerator (0–5°C) for 48 h (during this time, white crystalline material precipitated). The precipitate was immediately collected by filtration at room temperature, washed with CPME, and dried under vacuum to afford the crystalline imidate hydrochloride as a white solid (86–91%), which was identical with the authentic material[13].

### III. CONCLUSION

From literature survey, it can be concluded that it is better to use green solvent (CPME) with its benefits like less toxic, less hazardous, more safer rather than other organic solvents (THF, DME, MTBE) for industrial applications. CPME is very effective in laboratory and pilot scale with particular emphasis on the easy handling as low peroxide formation and higher boiling point which is highly effective for green sustainable processes with compare to other solvents like THF & MeTHF. CPME can be synthesized effectively by two routes such as, methylation of cyclopentene by methanol and methylation of cyclopentanol by methyl iodide because it offer favourable operating condition & better atom economy. CPME has more industrial applications compare to THF, MeTHF, MTBE.

### IV. REFERENCES