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COMPARATIVE PERFORMANCE EVALUATION & SYSTEMATIC SCREENING OF 2-METHF AS GREEN SOLVENT FOR COST EFFECTIVE, IMPROVED INDUSTRIAL PRODUCTION OF TRAMADOL HYDROCHLORIDE

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ABSTRACT

Tramadol is a drug with analgesic properties. 2-Methyltetrahydrofuran (2-MeTHF) is employed as single solvent system for synthesis of Tramadol base, which involves Mannich base preparation followed by Grignard reaction. The solvent effect on the Grignard reaction as well as subsequent stages either for isolation or extraction has been systematically evaluated based on reaction efficiency, ease of subsequent work-up, safety and greenness. 2-Methyltetrahydrofuran (2-MeTHF), which can be derived from renewable resources, had superior impact on overall process. It is therefore a recommended alternative solvent to Et₂O and THF for the preparation of Grignard reagents in Tramadol synthesis.

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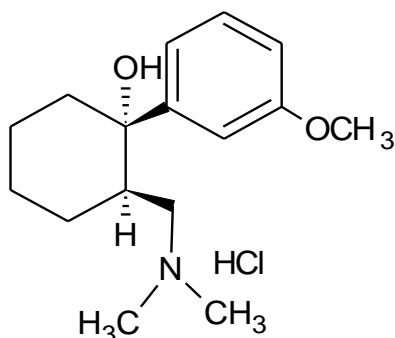
INTRODUCTION

Tramadol hydrochloride **1** [(±)cis-2-[(dimethylamino)methyl]1-(3-methoxyphenyl) cyclohexanol hydrochloride] is a mild, non-addictive, centrally acting binary analgesic agent. (Flick *et al.*, 1972; Flick *et al.*, 1974) It was approved for use in the United States in 1995 and is currently marketed as Ultram by Ortho-McNeil Pharmaceuticals, Inc; While the marketed form is the racemic hydrochloride salt of the *cis*-isomer. (Frankus *et al.*, 1978; Flick *et al.* 1978) Tramadol hydrochloride **1** (Figure 1) and some analogous have been synthesized previously. (Gruenenthal *et al.*, 1965; Gruenenthal *et al.*, 1967) The approach consisted in the coupling between aminoketones with aryl derivatives by means of a Grignard's reaction. Despite significant utility, Grignard reactions present challenges particularly on

scaling-up. From a safety point of view, the initiation step is often hard to control, and is strongly exothermic as is the subsequent Grignard reaction. For Grignard reactions solvents typically employed such as Et₂O and THF have low boiling points, and are capable of forming peroxides, which are both hazardous as well as detrimental to the reaction. Because of the broad use in the pharmaceutical and fine chemicals industry, benzyl, aryl and heteroaromatic halides were identified as the representative substrates to systematically evaluate the solvent effect for the Grignard reactions. The reaction solvent is the key component in the formation of the Grignard reagent and reaction. From a process standpoint, the solvent typically represents the largest fraction of the process mass and as such its judicious selection for work-up, safety, cost and reaction profile is critical. THF and in particular Et₂O are not optimal solvents for scale-up work due to their

potential for peroxide formation, as well as physical hazards such as their low boiling points and flashpoints. An ideal alternative solvent would present an improved reaction profile, and allow for an operationally simpler work-up. From an environmental point of view, the optimal solvent would also be one with a better safety profile, and ideally available from renewable sources. (Frenzel *et al.*, 2009; Comanita, B., 2008)

2-MeTHF can be derived from a renewable source, is more stable to acids and bases than THF and it is less prone to peroxide formation, and is immiscible with water thus enabling an easier phase-split for work-up. 2-MeTHF is more easily dried than typical other ethereal solvents due to formation of an azeotrope with water.



Cis-Tramadol HCl (RR, SS) 1

Figure 1.

Merck recently reported the results of oral toxicity studies for 2-MeTHF and it results negative for genotoxicity and mutagenicity (Scott *et al.*, 2011) which should assist in favourable long-term ICH classifications. Although widely promoted as greener solvents, only a handful of Grignard reagents are available in 2-MeTHF. 2-MeTHF has a number of properties that make it a preferred Grignard solvent. Limited miscibility with water facilitates easy product recovery which can be easily dried with lower losses and lower recycle costs compared to THF. It gives cleaner phase separations compared to processes that use solvent exchange of THF with toluene and hexane. THF is the most common solvent used for commercial Grignard reactions. 2-MeTHF has similar behavior to THF in most of the Grignard reactions, but its higher boiling point and limited water solubility give it several distinct advantages over THF. The 80°C boiling point of 2-MeTHF compared to 66°C boiling point for THF means that sluggish Grignard reactants can be formed quicker. The higher boiling point of 2-MeTHF also reduces losses of solvent from the reflux condenser. Unlike THF, 2-MeTHF has limited solubility in water and this property (Table 1) makes it easier to isolate the quenched reaction product and recycle dry 2-MeTHF. Another advantage of 2-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. 2-MeTHF has a much higher solubility for magnesium bromide and iodide than THF. For example, the solubility of magnesium bromide is more than 40g/100g at 25°C in 2-MeTHF, whereas the solubility is only about 5g/100g in THF. (Aycock *et al.*, 2007) This makes 2-MeTHF a preferred choice for preparing high concentrations of bromo Grignard reagents that do not need filtration to remove magnesium bromide. Recovery of dry THF from aqueous

mixtures requires special equipment and high energy costs. Also, another solvent must usually be added before or after the Grignard reaction product is quenched with acid water, since THF is completely miscible in water. With 2-MeTHF, the Grignard reaction product can be isolated in 2-MeTHF after water quenching. 2-MeTHF can be used to dry the reaction product in a simple batch operation by refluxing the 2-MeTHF phase of the condensed 2-MeTHF-water azeotrope. 2-MeTHF can also be dried for recycle by the same simple batch azeotropic drying procedure. The energy requirements for recovering dry 2-MeTHF are about 70% lower than for recovering dry THF by distillation. (Aycock *et al.*, 2007) In this paper we report the results of comparative performance evaluation of 2MeTHF as single solvent system over THF, Toluene and n-hexane for cost effective, improved industrial production of Tramadol base, which otherwise requires n-hexane or toluene for extraction during Mannich base manufacturing followed by THF for Grignard reaction wherein recovery of THF from aqueous solution requires special equipments and high energy costs as the reaction mass being quenched in aqueous ammonium chloride solution whereas the other two solvents toluene and n-hexane requires separate recovery arrangements respectively. Compared to traditional technology, this synthesis method has the advantages such as green solvent 2-MeTHF used for extraction of Mannich base instead of traditional n-hexane or toluene followed by same extracted 2-MeTHF layer used as such for subsequent Grignard stage, the reaction operation is easy with higher yields, energy efficient as it avoids solvent distillations and exchange of solvent, products are easy to separate and purify, the solvent consumption is less and easy to recycled and reused, the environmental pollution is minimised, and the synthesis method is suitable for industrial production.

MATERIALS AND METHODS

All reagents and solvents employed were of commercial grade and were used as such without further purification. All moisture and air-sensitive reactions were carried out under an atmosphere of dry nitrogen. TLC was performed on Kieselgel 60 F254 silica-coated aluminium plates (Merck) and visualized by UV light ($\lambda = 254$ nm). The melting points were determined in an open capillary tube using a Büchi B-540 melting point instrument and were uncorrected. The IR spectra were obtained on a Nicolet 380 FT-IR instrument (neat for liquids and as KBr pellets for solids). NMR spectra were recorded with a Varian 300 MHz Mercury Plus Spectrometer at 300 MHz.

RESULTS & DISCUSSION

To further examine the solvent effect for aryl Grignard reactions in Tramadol wherein the second step (Figure 2) of the synthesis featuring a Grignard reaction of (3-methoxy)phenylmagnesiumbromide, **3** with racemic 2-((dimethylamino)methyl) cyclohexanone, **4** to afford Tramadol base (**2a**, **2b**) as a mixture of diastereomers in an 80 : 20 ratio in favour of the desired cis isomer. The desired compound is then obtained by recrystallization as its nitrate or hydrochloride salt. Not only will this study enable a further comparison of the ability of the solvents screened to promote the Grignard reaction, but it will also allow us to examine whether the solvent has any influence on the diastereomeric ratio obtained from the reaction. Small-scale reactions for solvent screening were carried out to determine whether the

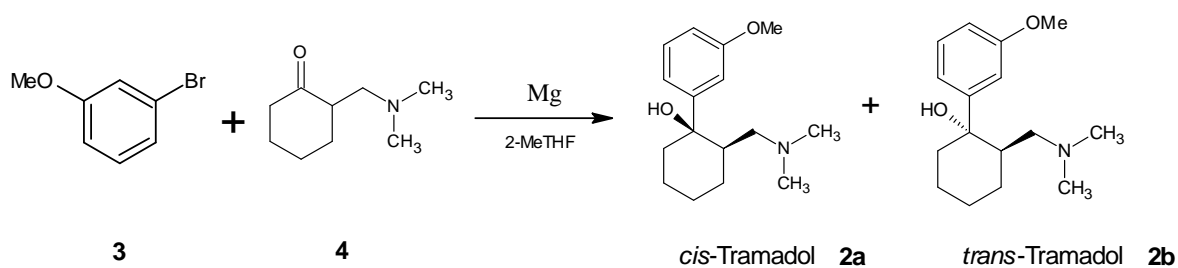


Figure 2.

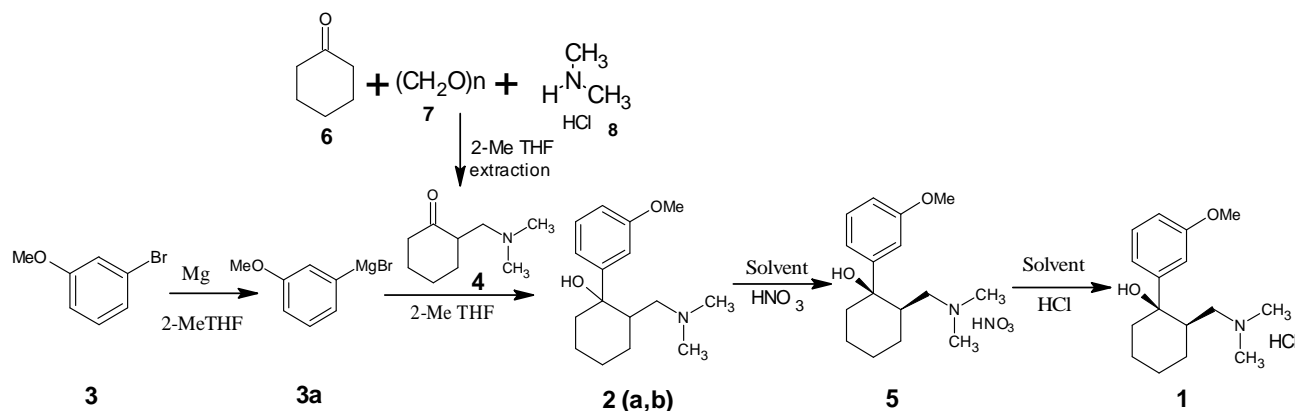


Figure 3.

Table 1. Property comparison data for THF & 2-MeTHF

Property	2-MeTHF	THF
Boiling Point (°C)	80	66
Freezing Point (°C)	-136	-108.5
Density at 20°C	0.855	0.888
Viscosity at 25°C (cps)	0.60	0.53
Evaporation Rate	4.2	8.0
Dielectric Constant	6.3	7.6
Donicity (kcal/mol)	18	20
Solubility of MgBr ₂ at 25°C	40	5
Water Azeotrope	Boiling Point (°C)=71 Composition,wt% Solvent.=89.4wt % Water=10.6.	Boiling Point (°C)=63 Composition,wt% Solvent.=93.3 wt% Water=6.7
Flash point, TC (°C)	-11.1	-14.8
Solubility at 20°C (wt %)	In water 14	miscible

Table 2. Solvent impact, comparative data

Entry	Solvent	Temp (°C)	Activator	Yield (%)	cis : trans
1	Et ₂ O	25–35	I ₂	70	80 : 20
2	THF	65 – 80	Ethylene dibromide	67	80 : 20
3	2-MeTHF	65 – 80	Ethylene dibromide	76	83 : 17

desired product was observed prior to optimization of the most promising conditions for scale-up, product isolation, and determination of the diastereomeric ratio. The results obtained were similar to our earlier findings with Et₂O, THF and 2-MeTHF standing out for further evaluation. For the gram-scale reactions, mild heating was applied to push the reactions to completion. The yield with 2-MeTHF was higher than the other two solvents possibly reflecting a more facile work-up and isolation. Examining the diastereomeric ratio for the reactions in 2-MeTHF (83:17) and THF (80: 20) indicated enhancement in the formation of the desired cis product in 2-MeTHF. (Table 2) Benefit of 2-Me THF as unique solvent for the synthesis of Grignard reaction is further extended to its subsequent stages wherein other solvents were used as reported in most of the literature or most widely utilised commercial manufacturing processes. In the very first step of

Mannich base preparation after reaction mannich base hydrochloride salt neutralised with caustic and further extracted using n-hexane which was further distilled under atmospheric conditions to get-rid off moisture prior to use for Grignard reaction by solvent exchange with THF. In this particular stage one can directly extract mannich base with the help of 2-MeTHF and can be directly used it for Grignard reaction by avoiding solvent exchange. (Figure 3) This also eliminates the extraction of Tramadol base in toluene after Grignard reaction and ultimately avoids use of an additional solvent recovery system for toluene.

Experimental Section

General procedure for the Mannich base using 2-MeTHF (4): Charge of Purified water (635 L), Para formaldehyde 7

(127.5Kg), Dimethylamine hydrochloride 8 (360 Kg), Cyclohexanone 6 (375 Kg) and hydrochloric acid (16.1 Kg) into the Reactor. Heat the Reaction mass to 80 – 85°C. Maintain for 8 hrs at 80 – 85°C. Cool the reaction mass to 25–35°C. Charge 2-Me THF (250L) into the Reactor and stir for 30 min. Settle the mass for 30 min. Separate the lower aqueous layer and 2-Me THF layer. Prepare caustic soda solution by dissolving Caustic soda (265Kg) flakes in Purified water (660 L). Adjust the pH to 12.0 -13.0 by adding caustic soda solution in aqueous layer. Charge 2-Me THF (250 L) into the Reactor. Settle the mass for 30 min. Separate the lower aqueous layer and upper organic layer. Further aqueous layer extracted With 2-Me THF (3X310L). Mix all 2-Me THF layer. Distill off 2-Me THF layer completely at temperature 60 -65°C under vacuum. Pale yellow colored oil 4 (600 Kg, 96.10%), purity 92%

General procedure for the Grignard reaction using 2-MeTHF (2a, 2b)

Charge 2-MeTHF (50 L), Magnesium turnings (81 kg) and Ethylene dibromide (2Kg). Heat the reaction mass to reflux (65.0-75.0°C). In the mean time charge meta bromo anisole (600kg) & 2-MeTHF (350 L) in receiver under Nitrogen purging. Add about 2-MeTHF and Meta bromo anisole (20L) mixture into the Reactor containing 2-MeTHF, Ethylene dibromide and magnesium and observe the initiation of the Reaction (initiation is indicated by vigorous bubbling of the mass). Start addition of 2-MeTHF and Meta bromo anisole mixture slowly into the Reactor at the temperature of between 65 – 80°C. Maintain the reaction mass at the temperature of below 80°C for 60 min. cool the contents in the Reactor to 0 – 10°C. In the mean time charge Mannich base (500 Kg) and 2-Me-THF(125 L) into the receiver. Charge 2-Me THF and Mannich base mixture into the Reactor at temperature below 25°C. After completion of addition maintain the reaction mass at below 25°C for 60 min. Raise the reaction mass temperature to 25-35°C and maintain at 25-35°C for 12 hrs. Charge of Purified water (2060 L) into another Reactor. Charge ammonium chloride (488 Kg) into the Reactor. Stir the mass for 20 -30 min. Start quenching the reaction mass into the Reactor having Ammonium chloride solution at temperature below 45°C. After completion of quenching charge 2-Me THF (50 L) into the Reactor containing Ammonium chloride solution. Stir the mass for 5 – 10 min at 40 – 45°C. Settle the mass for 50 – 60 min. Separate the aqueous layer and organic layer. Charge the aqueous layer was extract 2-Me THF.(2 X400 L). Combined all organic layer and concentrated under vacuum below 60°C. Cool the Reactor contents to the temperature 25 - 35°C. Pale yellow colored oil Racemic tramadol base mixture **2a**, **2b** (730 Kg, 86%) (cis : trans 83 : 17)

General procedure for the preparation of Tramadol Nitrate Salt (5)

Charge Methanol (1000L) and Tramadol base (1000kg) into the reactor. Stir the reaction mass for 30 min. cool the mass to 10 – 12°C. Charge of Nitric acid (300 kg) at 10 -15°C to the reaction mass till pH is 1.0 – 2.0. Cool the reaction mass to 0 – 5°C and maintain the temperature at 0 -5°C for 2 hrs. Centrifuge the product. Wash with Methanol (120L) and spin dry for 60 min. Off white crystalline powder (790.0 Kg 75.00 %), (cis : trans 99 : 01)

General procedure for the preparation of Tramadol Hydrochloride (1)

Charge Purified water (1000 L) 510 Kg of Tramadol Nitrate (510 Kg) , and Toluene(1250 L) into the reactor. Mean while prepare a solution of Sodium hydroxide by dissolving Caustic soda flakes (65 – 70 Kg) in Purified water (165L). Start stirrer and slowly add Sodium hydroxide solution into the reactor and adjust the pH to 12 -13. Stop stirrer, allow the mass to settle for 10 – 15 min. Separate the aqueous layer and organic layer. Aqueous layer Extracted Toluene (1X500L). Mix all Toluene layer distill off Toluene completely by maintaining the temperature below 75°C under vacuum. Cool the reaction mass of reactor to below 30 – 40°C. Charge Isopropyl alcohol (660 L) into the reactor. Adjust the pH of reaction mass to 1.0 – 2.0 by adding Isopropyl alcohol in HCl at 25-30°C from the receiver. Cool the reactor contents to 0 – 5°C. Maintain the reactor contents to 0-5°C for 2 hrs. Centrifuge the material. Wash with chilled Isopropyl alcohol(100 L) and spin dry for 60 min. Dry the material in vacuum tray drier at 60-65°C. White crystalline powder (421.0 Kg, 91.73%.) (Cis: Trans 99.97: 0.03)

Conclusion

In this study, we performed the systematic study focusing on the solvent effect on Grignard reaction in Tramadol synthesis. In the reactions that we have studied, 2-MeTHF has consistently either out-performed or performed in an equivalent manner to typical reaction solvents such as Et₂O and THF. Given this, 2-MeTHF should be the solvent of choice for such reactions from both safety and environmental standpoints. Utilization of such systems could have a dramatic effect in terms of facilitating the workup, and isolation of the desired products on commercial scale. Application of 2-MeTHF as a single solvent system for the commercial manufacturing of Tramadol base was demonstrated by successfully replacing other two solvents n-hexane and toluene along with THF for Synthesis of Mannich base and Tramadol base in API Tramadol hydrochloride.

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