



Research Article

EFFICIENT METHOD FOR ENANTIOSELECTIVE SYNTHESIS OF DEXMETHYLPHENIDATE HYDROCHLORIDE (FOCALIN®)

Kartik S. Renalson^{1*}, Ashok B. Kalambe¹, Deepa Y. Panhekar²

1. Department of Chemistry, Institute of Science, R.T.M. Nagpur University, Nagpur, 440008, India.
2. Department of Chemistry, Dr. Ambedkar College, Nagpur, 440010, India

*Corresponding Author: Email kartik.renalson@gmail.com

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ABSTRACT

An improved economical and eco friendly process for the enantioselective resolution of methylphenidate free base to give (2R,2'R)-(+)-threo-methylphenidate via diastereomeric salt preparation with (+)-di-para-toluy-D-tartaric acid has been achieved. The racemic resolution performed under mild and neutral conditions having simple unit operation making process feasible for large scale production of dexmethylphenidate hydrochloride.

Keywords: Dexmethylphenidate, enantioselective, diastereomeric salt.

INTRODUCTION

Dexmethylphenidate hydrochloride (1) is chemically isolated d-threo isomer of (\pm)-threo-methylphenidate, marketed as Focalin® by Novartis pharmaceuticals Corporation (East Hanover, New Jersey). It is used for treatment of attention deficient hyperactivity disorder (ADHD), cognitive decline in acquired immunodeficiency syndrome (AIDS), AIDS related complex (ARC) 1-3 and it also acts as dopamine reuptake inhibitor⁴. Studies on racemic threo-methylphenidate have indicated that d-threo enantiomer is much more active than the corresponding l-threo enantiomer⁵. Furthermore l-isomer of methylphenidate has been postulated to impart side effects and also produces euphoric effect⁶. The l isomer is rapidly metabolized and degraded following oral administration and has little, if any, pharmacologic activity, whereas the d isomer is primarily responsible for the pharmacologic activity of methylphenidate hydrochloride (MP.HCl).

Ramaswamy et al resolved d,l-erythro-2-phenyl-(2-piperidin-2-yl)acetamide with D(-) tartaric acid to l-erythro-2-phenyl-(2-piperidin-2-yl)acetamide, epimerized to d-threo-2-phenyl-(2-piperidin-2-yl)acetamide which was further treated with methanolic sulphuric acid and hydrochloride gas to give 1 (scheme 1). This process involves loss of yield during epimerization and hydrolysis involve prolongs heating of 60 hours⁷. Use of expensive reagent (R)-(-)-1,1'-biphenyl-2,2'-diyl hydrogen phosphate 8-9 and enzymatic resolution has also been utilized¹⁰ which are not feasible in interest of large scale synthesis. Methods utilizing MP.HCl as a starting material for resolution have claimed the use of its free base as cumbersome process but those claims ignore the fact that MP.HCl was prepared from methylphenidate free base or ritalinic acid itself. Existing methods of resolution from MP.HCl employ base, aqueous alcoholic solvent and chiral agent.¹¹ Under these condition there is always possibility that aqueous phase will precipitate out (+) DPTTA instead of

diastereomeric salt. So it becomes necessary to develop a process which is simple, robust and failure free.

PRESENT ATTEMPT:

In our attempt we have avoided the unnecessary use of base by direct resolution of methylphenidate base and this improvisation resulted in increase of yield and enantiomeric purity drastically. It is also observed that polarity of solvent media is very crucial parameter for resolution, less polar media is not favorable for the reaction and hence in many processes water is utilized as an additive to increase polarity but this point is not significantly highlighted. Methanol was used as an additive with acetone and isopropyl acetate to achieve resolution of methylphenidate free base which also signifies the importance of solvent polarity. Also it is observed that yield obtained in basic media is less.

AIM & OBJECTIVE:

Our aim is to develop a process which is economically and process operation wise feasible for industrial scale production of dexmethylphenidate hydrochloride. The process where MP HCl has been used for resolution needed the use of stoichiometric ratio of base for the neutralization of hydrochloride. To overcome the use of base for neutralization process we thought of investigating the resolution with MP base to avoid the extra step of hydrochloride formation and its neutralization steps.

Our process involves esterification of ritalinic acid with methanol and thionyl chloride. Use of HCl gas for esterification in methanolic sulphuric acid is cumbersome, requires prolong maintaining of 60 hours which we have reduced to 15 hour with significant improvement in yield and quality. Also isolation of product becomes very easy as compared to isolation from solvent system of sulphuric acid as removal of sulphuric acid requires excess amount of water so the effluent generated will also be not suitable from industrial point of view as it leads to increase in E factor of the process.

The isolated methylphenidate free base which is oily in nature, consumes little amount of solvent to get freely soluble and thus has advantage over MP HCl. The isolated MP free base was then subjected to resolution. Earlier method utilizes (+) dibenzoyl D tartaric acid but the yield are at lower side and employ MP.HCl as substrate for resolution¹¹, whereas we are describing here to eliminate

hydrochloride preparation step, they mentioned resolution is incomplete with (+) DPTTA but is not true for our reaction conditions, in fact it is best agent to serve the purpose. (+) DPTTA was chosen since it is commercially available and cheaper than the above mentioned agents. The precipitated diastereomeric salt which was isolated by filtration gave enantiomeric purity greater than 99.5%. The process is robust enough to give consistent result for number of batches. Control of temperature plays significant role in getting resolution and in yield optimization. We first attempted the resolution at room temperature and observed that the initiation reaction is so fast that diastereomeric salt precipitation takes place before complete addition of (+) DPTTA, which resulted in incomplete resolution. To overcome this problem, the addition of (+) DPTTA to MP base in methanol was done at 40-45 OC with constant stirring to get clear solution. This helped us in achieving complete resolution. The reaction mixture was then cooled to 25-28 OC to precipitate out diastereomeric salt. Filtration of reaction mass gave product in 32 % yield. To improve the yield further, we attempted set of reactions in which reaction temperature was lowered below 15 OC and was monitored for every 5 OC down in reaction temperature which resulted in incomplete resolution. So the protocol was set to achieve complete resolution with optimized condition by manipulating time for reaction temperature in three steps. First to add (+) DPTTA at temperature of 40-45 OC, this operation avoids the prior precipitation of chiral reagent. Further maintaining reaction at ambient temperature and filtration at lower side of temperature (0-5 OC) gives the product in optimum yield and have desired quality. When diastereomeric salt was treated with aqueous NaOH, emulsion formation led to difficulty in layer formation which further resulted in loss of yield. To overcome this issue we quenched reaction mass in water adjusted pH 8.5 to 9 with aqueous ammonia and extracted product in dichloromethane. Initial screening of alcoholic solvent for resolution with (+) – di – para – toluyl – D - tartaric acid revealed methanol as the cheaper and suitable solvent over others. Results are summarized in table 1. The enantiomeric excess of dexmethylphenidate in diastereomeric salt was determined by chiral HPLC.

A different molar ratio of the chiral agent was studied. Resolution remains incomplete with 0.5 mol to 0.8 mol. 97 –

98% enantiopurity with 30% yield was obtained at molar ration 0.9 mol. The optimized the condition is 1 equivalent of chiral reagent since it gave 99.9 % chiral purity with yield 48.55 %. Reactions were also studied to observe the effect of water on resolution. In methanol water system (Table 1, entry 8), although the enantiopurity was achieved at 99.09 %, the yield remains at lower side. Somewhat similar results were observed for entry no 9. Experiments were conducted with isopropyl alcohol and ethanol but resolution could not be achieved (Table 1, entry no.1 to 6).

To make the process robust and cost effective our next objective was to recover and recycle the reagents used in the process. In the step of esterification, the recovered mixture of thionyl chloride and methanol mixture obtained by distillation was utilized further by quantifying the amount of thionyl chloride in it by gas chromatography.

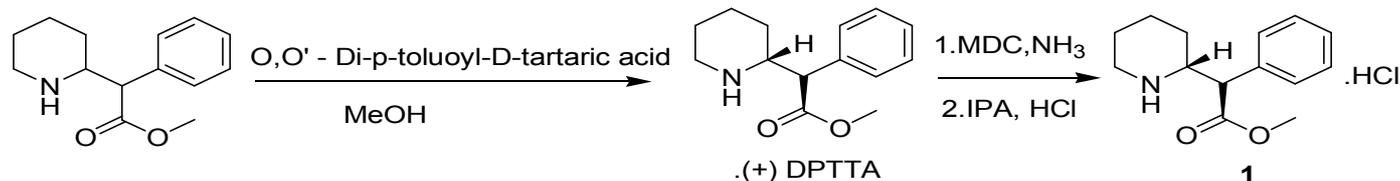
Recovery of (+) DPTTA was done from the filtrate of resolution step and was also recovered from diastereomeric salt. The solvent from filtrate was distilled out, the obtained residue contained 90% leavo MP isomer and (+) DPTTA. The residue was suspended in water and dichloromethane which was basified with aqueous ammonia, the aqueous phase containing (+) DPTTA was precipitated out by acidification. Similarly diastereomeric salt of dexmethylphenidate was cracked and (+) DPTTA was recovered from the filtrate solution of it. The recovered (+) DPTTA is of comparable quality to that of commercial sample and was used without any further purification.

Preparation of methylphenidate base: Clean and dry 500 mL 4 neck round bottom flask equipped with a overhead mechanical stirrer was charged with ritalinic acid (20g; 0.09132 mol) and methanol (160 mL, 8 vol.). This mixture was cooled to 0 to - 5 °C. To this solution, thionyl chloride (32.6 g, 0.274 mol) was added drop wise within 30 minutes maintaining the temperature conditions; further raised temperature to 27 to 30 °C Reaction was stirred at ambient conditions for 15 hours.

Methanol: thionyl mixture was distilled out. Water (200 mL) was added to reaction mass and pH adjusted 10.5 to 11 with 25% aq. NaOH solution and product was extracted in dichloromethane (200 mL), dichloromethane layer was washed with water (100 ml) and dried over anhydrous sodium sulphate. Solvent was distilled out to get oily mass of racemic methylphenidate base. Yield= 19 g, 95%.

Preparation of (2R,2'R)-(+)- dexmethylphenidate hydrochloride : Solution of methylphenidate base (15 g, 0.0642 m) and methanol was heated to 40 - 45 °C , (+) O,O' - Di-p-toluoyl-D-tartaric acid (DPTTA) (24.8 g, 0.0641 m) was added within 5 minutes and maintained for 30 minute. The reaction mass is clear solution. The heating was removed and allowed to attain room temperature spontaneously, diastereomeric salt starts precipitating out. Reaction mass was further stirred at 25 - 28 °C for 2 hours then cooled further to 0°C and maintained for 30 minutes. Diastereomeric salt of methylphenidate was filtered and washed with chilled methanol (45 mL) yield= 19.4g, 97%. To the suspended solution of (+) O,O' - Di-p-toluoyl-D-tartarate salt of (2R,2'R)-(-)- threo methylphenidate (17 g) (2), 68 mL dichloromethane (MDC) and 34 mL water was added, pH was maintained at 8.5-9.5 by adding aqueous ammonia (6.8 mL). MDC layer was washed with water, dried over anhydrous sodium sulphate and distilled out to get oil of dexmethylphenidate base. Yield= 6.1 g, 85%. To the precooled (0 to 5°C) solution of (2R,2'R)-(+)- dexmethylphenidate base (6 g) and 18 mL of isopropyl alcohol, concentrated HCl acid (3.6 mL) was added and mixture was stirred for 1 hour at 0 to 5°C. White crystalline solid of dexmethylphenidate hydrochloride was filtered and washed with chilled IPA (12mL). Enantiomeric purity (2R,2'R):(2S,2'S) = 99.9:0.1. Yield= 6.5g, 98%.

¹H NMR: (10.28, brs, 1H), (8.98, brs, 1H), (7.28-7.38, M, 5H), 4.31- 4.33 (S, 3H) , 3.84 (S, 3H), 3.65- 3.79 (M, 2H), 2.93- 2.95 (m, 1H), (1.33-2.13, m, 6H); [α]_D²⁵ = + 88° (c = 1, MeOH); FTIR (KBr, cm⁻¹) 2937, 1739; MS (m/z) 234 (MH⁺).



SCHEME 1: Synthetic scheme for dexmethylphenidate hydrochloride (1)

Table 1: Optimization of resolution of methylphenidate free base with (+)-di-para-toluyl- D-tartaric acid {(+) DPTTA}

Entry	Solvent ratio (V/V)	Temp. °C	Enantiopurity of Diastereomeric salt ^a (2S,2'S): (2R,2'R)	Yield * (%)
1	IPA:H ₂ O (4:4)	45→25→0	35.0:65.0	63.21
2	IPA: H ₂ O (4:2)	45→25→0	23.0:71.0	57.54
3	IPA: H ₂ O (3:2)	45→25→0	43.0:47.0	77.51
4	IPA: H ₂ O (3:3)	45→25→0	44.23:45.77	84.18
5	IPA: H ₂ O (4:0)	45→25→0	39.52:60.48	67.23
6	EtOH: H ₂ O (4:2)	45→25→0	23.22:76.78	53.91
7	EtOH: H ₂ O (4:0)	45→25→0	28.0:72.0	58.33
8	MeOH:H ₂ O (4:2)	45→25→0	0.91:99.09	39.23
9	MeOH:H ₂ O (3:2)	45→25→0	1.21:98.79	41.58
10	MeOH:H ₂ O (4:0)	45→25→0	0.10:99.90	48.55

*Theoretical yield= 50 %

^adetermined by chiral HPLC**CONCLUSION:**

In conclusion we have developed a very simple, economical and eco friendly process for synthesis of dexmethylphenidate hydrochloride that is applicable to commercial scale. The quality and yield obtained is best as compared to any known process in literature. Esterification and chiral reagent are recovered and recycled effectively making process feasible from commercial point of view.

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