Aliquot-336 Catalysed Epimerisation of 2-Phenyl-2-(Piperidin-2-Yl) Acetamide Towards Synthesis of Dexmethylphenidate Hydrochloride

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Abstract

Dexmethylphenidate hydrochloride is chemically isolated d-threo isomer of (±)-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 immune deficiency syndrome (AIDS), AIDS related complex (ARC) and it also acts as dopamine reuptake inhibitor. Studies on racemic threo-methylphenidate have indicated that d-threo enantiomer is much more active than the corresponding l-threo enantiomer. The known process for erythro to threo epimerization is reported in organic media of toluene achieved by potassium tertiary butoxide (KOtBu) and potassium hydroxide in aqueous media. But use of KOtBu is avoided at industrial scale due to its hazardous nature and less solubility in most of the solvents and also require 16 hours for epimerisation while use of 50% aqueous KOH prolongs the reaction time upto 3 days as well as leads to incomplete epimerization, which is not feasible to implement the process at commercial scale. We herein developed an efficient process involving phase transfer agents which catalysed the epimerisation reaction effectively, the reaction completes within few hours with optimum conversion and best in isolated yield.

Introduction:

Dexmethylphenidate hydrochloride (**1**) is chemically isolated d-*threo* isomer of (±)-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 immune deficiency syndrome (AIDS), AIDS related complex (ARC) [1-3] and it also acts as dopamine reuptake inhibitor[4]. Studies on racemic *threo*-methylphenidate have indicated that d-threo enantiomer is much more active than the corresponding l-threo enantiomer[5].

Aliquot-336 is a quaternary ammonium salt (methyltricrotyl ammonium chloride), it is also known as Starks' catalyst.[6] Aliquot has many applications in organic synthesis such as environment friendly catalytic oxidation,[7] benzylation,[8] hydrogenation of arenes.[9] In continuation of our interest in the development of new organic synthetic methodology involving application of catalyst,[10] we report herein a rapid, simple and efficient method for epimerization of 2-phenyl-2-(piperidin-2-yl) acetamide, which is precursor for dexmethylphenidate hydrochloride.

Results and discussion:

The known process for erythro to threo epimerization is reported in organic media of toluene achieved by potassium tertiary butoxide (KOtBu)[11] and potassium hydroxide in aqueous media. But use of KOtBu is avoided at industrial scale due to its hazardous nature and less solubility in most of the solvents and also require 16 hours for epimerisation while use of 50% aqueous KOH prolongs the reaction time upto 3 days as well as leads to incomplete epimerization,[12] which is not feasible to implement the process at commercial scale.

Hence, there is a need to develop an efficient process for epimerisation and its scale up. To overcome this issue, we studied epimerisation reaction in aqueous as well as non aqueous media. Strong basic condition is absolute requirement for epimerisation so we primarily focused on aqueous 50 % KOH and searched for promoter that accelerate rate of reaction and yields optimum epimerisation. To achieve this, we investigated effect of phase transfer catalyst (PTC) [viz., tetra-n-butyl ammonium bromide (TBAB), tetraethyl ammonium bromide (TEAB), tetra-n-butyl ammonium iodide (TBAI), cetrimonium bromide (CTAB) and aliquot-336] on epimerisation of 2-phenyl-2-(piperidin-2-yl)acetamide, keeping the reaction parameter constant { 50% aqueous KOH (4 mmole equiv.), temperature (90 ± 5 ^{O}C), time (4hr), and amount of catalyst (5 wt. % of substrate)], and results are shown in Table 1.

Table 1 Effect of phase transfer catalyst on epimerisation

Entry	PTC	Epimerisation(%)[a]
1	No PTC	25
2	TBAB	45
3	TBAI	64
4	TEAB	52
5	CTAB	82
6	Aliquot-336	95

Under the reaction condition 50% aqueous KOH alone (without PTC) gave 32% conversion in 4 hour (Table 1; entry 1). Epimerisation of 2-phenyl-2-(piperidin-2-yl) acetamide using aqueous KOH condition was reported by Bar-Or etal.[12] Use of TBAB, TBAI and TEAB gave slight improvement in epimerisation [45%, 64%, and 52 % respectively: Table 1, entries 2, 3 and 4]. When reaction was carried out with CTAB conversion significantly increases to 82% [Table1; entry 5]. We presume that long carbon chain PTC has significant effect on epimerisation, to further confirm this , we utilised Aliquot-336 which is mixture of octyl and decyl carbon chain with octyl as predominating. To our expectation maximum epimerisation of 95% was obtained [Table1; entry 6]. Reaction condition for temperature, time and weight percent equivalent of catalyst is also optimised. Reaction is carried out at different temperature

and results are shown in Table 2. At room temperature only 12 % epimerisation was achieved and found to increase with temperature. Optimum conversion was observed at 90±5 ^{0}C in 4 hour.

Table 2 Effect of temperature on epimerisation

Entry	Temperature (± 5^{0}C)	Epimerisation(%)[a]
1	30	12
2	50	45
3	70	62
4	90	95
5	110	93

Table 3 Effect of time on epimerisation

Entry	Time (h)	Epimerisation(%)[a]
1	1	45
2	2	60
3	3	76
4	4	95
5	5	95
6	6	94

The reaction time was optimised by monitoring the reaction at time interval from 1 hour to 6 hour. Maximum conversion was achieved in 4 hour (Table 3), it is the optimum conversion achieved, and further maintaining has no effect on it. Amount of catalyst is also varied to observe the effect of relative rate of reactivity, it increases linearly till 5 weight percent of catalyst with respect to substrate [Table 4; entry 4] and rate of reaction tends to decrease with further increase of amount of catalyst as shown in Table 4. The non polar moiety of substrate in KOH solution is heterogeneous enough for slow reactivity. We presume that acceleration of reaction is due to homogeneity of the reaction mass as a result of addition of PTC. The obtained threo 2-phenyl-2-(piperidin-2-yl) acetamide was converted to dexmethylphenidate as per the literature process[13] and characterised.

An Experimental result shows that PTC plays significant role for epimerisation of 2-phenyl-2-(piperidin-2-yl) acetamide in aqueous conditions. Further we explored the concept and performed reactions in organic media. Evidently conversion of 92% was obtained with KOtBu in DMF solvent [Table 5; entry 4]. Reaction proceeds well with toluene and in biphasic condition of KOtBu and KOH respectively [Table 5; entry 1 and 5]. The obtained threo isomer is racemate as shown in scheme 1.

Table 4 Effect of amount of Aliquot-336 on epimerisation

Entry	Wt % of Aliquot	Epimerisation(%)[a]
1	1	46
2	2	52
3	3	66
4	4	88
5	5	95
6	7	92
7	10	90
8	15	84
9	20	76

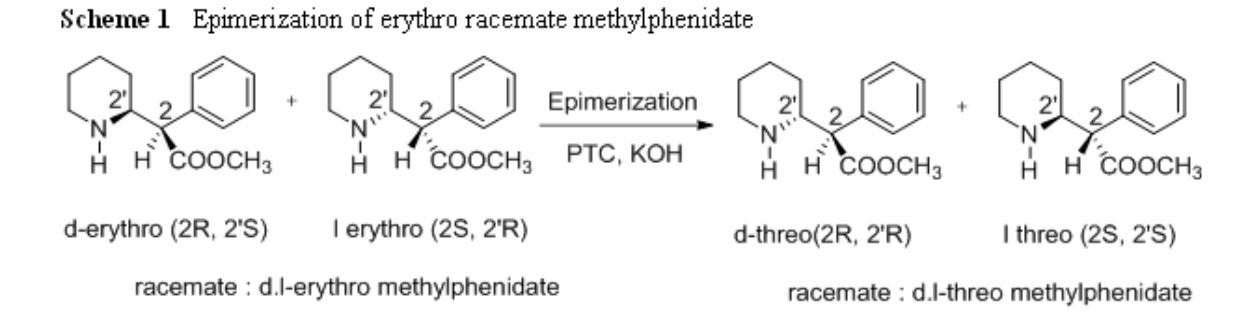
Threo-(2R,2'R)-(+) dexmethylphenidate hydrochloride:

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); $[\alpha]_D^{25}$ = + 88º (*c* = 1, MeOH); FTIR(KBr, cm^{-1}) 2937,1739; MS(m/z) 234(MH^+).

Table 5 Non aqueous epimerization using Aliquot-336

Entry	Base	Solvent	Time (h)	Epimerisation(%)[a]
1	KOtBu	Toluene	6	82
2	KOtBu	Tert- Butanol	12	48
3	KOtBu	THF	16	32
4	KOtBu	DMF	2	92
5	KOH[b]	Toluene : water	10	84
6	KOH	Methanol	12	78
7	KOH	Ethanol	14	70
8	KOH	2-Propanol	15	54
9	KOH	DMF	9	72

Scheme 1 Epimerization of erythro racemate methylphenidate



Conclusion:

In summary, we have successfully utilized Aliquot -336 in catalytic amount as a promoter and developed a efficient procedure for epimerisation

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