



## AN EFFICIENT SINGLE-POT RACEMIZATION OF S (-) RASAGILINE: A BYPRODUCT OF ANTI-PARKINSON'S DRUG

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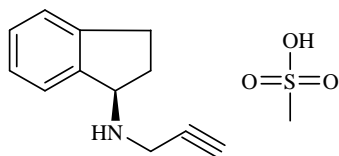
### ABSTRACT

A simple, cost-effective and robust process for the racemization of undesired S-(-)-N-propargyl-1-aminoindan, produced during the resolution step is developed. There is no racemization procedure reported till now. We have developed a single step racemization process with appropriate, low cost and commercially well available raw materials and allow the effective racemization during scale-up. The racemization has been achieved with high yield (85%) and purity (99.6 area %) by HPLC.

**Keywords:** Rasagiline mesylate, S (-) Rasagiline, racemization, high boiling solvent.

### INTRODUCTION

Rasagiline mesylate (1) is an active pharmaceutical substance with an empirical formula of C<sub>12</sub>H<sub>13</sub>N. CH<sub>4</sub>O<sub>3</sub>S and a molecular weight of 267.34. Rasagiline mesylate is the international common accepted name for R-(+)-N-propargyl-1-aminoindan mesylate, which is represented in figure 1.



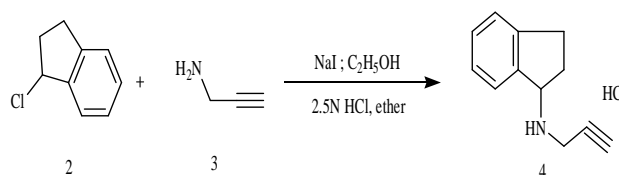
**Figure 1:** Chemical structure of Rasagiline mesylate (1)

Human cells contain two forms of monoamine oxidase (MAO) type A and type B. Both are found in the brain, but MAO type B is far more prevalent and is responsible for the breakdown of dopamine after its release into the synapse. Parkinson's disease is characterized by the death of cells that use dopamine to transmit their signals, which result in a decrease in synaptic signal strength and concomitant symptomology. By inhibiting the breakdown of dopamine in the synapse, Rasagiline mesylate (1) permits the signaling neurons to re-absorb more of it for re-use later, somewhat compensating for the diminished quantities. Rasagiline mesylate is an irreversible inhibitor of monoamine oxidase<sup>1</sup> used as a monotherapy in early Parkinson's disease or as an adjunct therapy in more advanced cases<sup>2</sup>. It is selective for MAO type B over type A by a factor of fourteen<sup>3</sup>.

Laboratory studies shown that Rasagiline has invitro and in vivo neuroprotective effects. But its neuroprotective effect in Parkinson's disease patients is unknown at present. These studies shown that MAO type B metabolizes an opioid-related chemical called MPTP (not an opioid itself), into a neurotoxin called MPP<sup>+</sup> that in turn creates free radicals. There is an uncertainty because

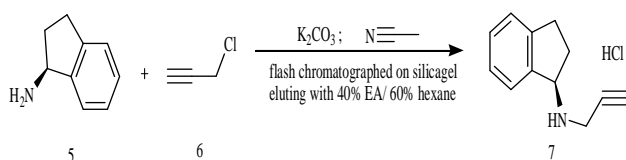
the mechanism of cell death in human Parkinson's disease may or may not involve the actions of free radicals, but there is suggestive evidence that the drug slows disease progression. The ADAGIO study found that early treatment with rasagiline at a dose of 1 mg per day provided benefits that were consistent.

Several approaches<sup>4-7</sup> were accessible in the literature for the synthesis of Rasagiline mesylate (1). Rasagiline was first reported<sup>8</sup> as a racemic mixture. Rasagiline was first synthesized<sup>9</sup> as a racemic hydrochloride salt (4) by Maurice Ward Gittos and co-workers in 1967 (scheme 1). Condensation of 1-chloroindane (2) and propargyl amine (3) in ethanol followed by hydrochloride salt formation in ethereal HCl precipitate racemic Rasagiline hydrochloride (4).



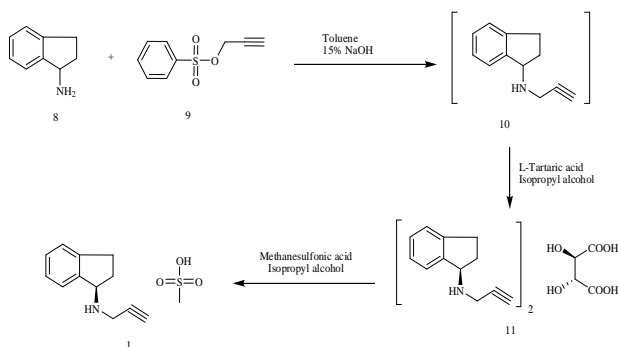
**Scheme 1:** Synthetic process of racemic Rasagiline hydrochloride (4)

R (+) enantiomer of Rasagiline hydrochloride (7) was reported by Moussa and co-workers<sup>10</sup> and did a single step process comprise reacting (R)-1-aminoindan (5) with propargyl chloride (6). The reaction was carried out in acetonitrile with potassium carbonate at a temperature of 60°C for 16 hours. The crude Rasagiline base obtained by this process is very impure and has to be purified by column chromatography. The overall yield of Rasagiline hydrochloride (7) is less than 40% and the process has other disadvantages such as a long reaction time and the need to isolate the product by column chromatography (scheme 2).



**Scheme 2:** Synthetic process of R(+) Rasagiline hydrochloride (7)

Commercial synthetic process of Rasagiline mesylate (1) was reported by Moussa and co-workers<sup>11</sup>. This process involves reaction of racemic 1-aminoindan (8) with propargyl benzenesulfonate (9) in the presence of 15% aqueous NaOH in toluene to form racemic Rasagiline (10), which is then resolved with L(+)-tartaric acid to form di[R-(+)-N-propargyl-1-aminoindan] tartrate (11) in isopropyl alcohol (Scheme 3). Compound 11 on base hydrolysis followed by mesylate salt formation with methanesulfonic acid resulted Rasagiline mesylate (1). However, the reported process is low yielding and high production cost.



**Scheme 3:** Synthetic process of Rasagiline mesylate (1)

After resolution step of compound 10, the filtrate contains undesired S (-)-enantiomer and unreacted L (+) tartaric acid. After resolution, yields of compound 11 are about 20-25%, which increases the manufacturing cost of Rasagiline mesylate (1).

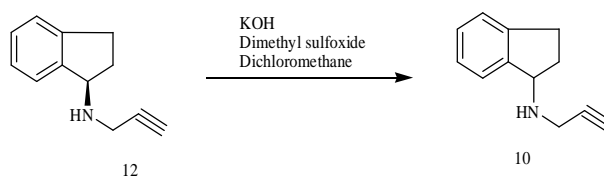
Till now, no process was reported in the literature for the racemization of unwanted S (-) enantiomer (12) to racemic Rasagiline (10). Therefore, we want to develop a simple, cost-effective and scale-up friendly single pot process for the racemization of 12.

## MATERIALS AND METHODS

Melting points were determined on Buchi 540 melting point apparatus and are uncorrected. FT-IR spectra were recorded as KBr pellet on Nicolet 380 FT-IR instrument (Model Thermo Electron Corporation-Spectrum One), <sup>1</sup>H (proton decoupled) spectra were recorded on Varian 400 MHz spectrometer using DMSO-*d*<sub>6</sub> as solvent, and tetramethylsilane (TMS) as internal standard. Mass spectra were recorded on Agilent triple quadrupole mass spectrometer equipped with turboion spray interface at 375°C. All the organic extracts were dried over sodium sulfate after work-up. All the solvents and reagents used were of commercial grade.

**Racemization of S (-) Rasagiline 12:** To a residue (10 g) containing S(-) Rasagiline added potassium hydroxide and dimethyl sulfoxide (50 mL) and stirred for about 15 minutes at ambient temperature. The mixture is heated to about 80°C and maintained for about 2 hours, followed by cooling to room temperature. Reaction mass was quenched with water (100 mL) and stirred for about 45 minutes at 25-30°C. To the solution, dichloromethane (20 mL) is added and stirred for about 15 minutes. Separated the organic layer and washed with water (2X5 mL). The organic layer is distilled off completely under vacuum at below 40°C, to afford 8.5 g of racemic Rasagiline 10 as a light brown colour residue.

Description: light brown color residue, Yield: 85%; M. F.: C<sub>12</sub>H<sub>13</sub>N; M. Wt.: 171.24; <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>): δ 1.75 (1H, m, ≡CH), 2.25-2.35 (2H, m, -CH<sub>2</sub>-), 2.7-2.8 (2H, m, -CH<sub>2</sub>-), 3.4 (2H, s, -CH<sub>2</sub>-), 4.25 (1H, t, -CH-), 7.2 (3H, m, ArH), 7.25 (1H, m, ArH); EI-MS: m/z = 172.32 (M+1); Anal. Calcd. for C<sub>12</sub>H<sub>13</sub>N: C, 84.17; H, 7.65; N, 8.18, Found: C, 84.16; H, 7.62; N, 8.22.



**Scheme 4:** Racemization process of S (-) Rasagiline (12)

**Table 1:** Base and solvent optimization

Entry No.	Base	Solvent	Temperature (°C)	Reaction time	Yield (%)	Chiral purity by HPLC (area %)
1	t-BuOK	t-BuOH	80			Material not isolated
2	NaOMe	MeOH	62			Material not isolated
3	NaOEt	EtOH	74			Material not isolated
4	KOH	DMSO	80	2	85.0	R-isomer: 50.01, S-isomer: 49.99
5	KOH	DMF	80	2.5	80.6	R-isomer: 50.09, S-isomer: 49.9
6	KOH	Toluene	100	4	82.3	R-isomer: 49.98, S-isomer: 50.02
7	NaOH	DMSO	80	2.5	78.3	R-isomer: 50.10, S-isomer: 49.90
8	NaOH	DMF	80	3.5	79.5	R-isomer: 50.03, S-isomer: 49.97
9	NaOH	Toluene	100	4.5	83.4	R-isomer: 49.92, S-isomer: 50.08



**RESULTS AND DISCUSSION**

The object of our work was to convert S (-) enantiomer 12 of Rasagiline into racemic mixture 10 by simple reaction with a base in high boiling solvent (scheme 4).

After resolution step, the isopropyl alcohol filtrate contained approximately 20-25% of the R(+) enantiomer and 75-80% of S(-) enantiomer 12 of Rasagiline 10. The mother liquor was distilled off completely under reduced pressure and obtained residue was extracted into ethyl acetate at basic conditions. Distillation of ethyl acetate under vacuum followed by heating the residue at elevated temperature in high boiling solvent with a base affords racemic Rasagiline (10) (scheme 4). Obtained compound 10 was confirmed by the <sup>1</sup>H NMR and mass spectral data.

A number of solvents and bases were screened during racemization reaction to optimize the reaction for better yield and quality of the compound 10 (table 1).

Material was not achieved with t-BuOK/t-BuOH, NaOMe/MeOH and NaOEt/EtOH and reaction mass was adapted dark brown color during reaction maintenance. Complete racemization was not witnessed with KOH or NaOH in toluene solvent. Entry numbers 4, 5, 7 and 8 are the best reaction conditions for the racemization of compound 12.

**CONCLUSION**

We reported an optimized, robust and single-pot process for the racemization of undesired S-enantiomer 12 which involves the usage of commercially well available and low cost raw materials. The optimized process was more economical and allows the effective racemization with high yield and purity.

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