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A new process for the synthesis of enantiomerically pure R-(+)-N-propargyl-1-aminoindan mesylate(Rasagiline mesylate)

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ABSTRACT

A new processdeveloped for the synthesis of enantiomerically pure R-(+)-N-propargyl-1-aminoindan mesylate(Rasagiline mesylate) by using K_2HPO_4/Triethylbenzylammonium chloride (TEBAC) as a reagent. This approach controls the formation of other isomerS-(-)-N-propargyl-1-aminoindane. This new process may be useful for the preparation of enantiomerically pure Rasagiline mesylatein commercial scale with good yields.

Keywords: *R*-(+)-*N*-propargyl-1-aminoindan, mesylate(Rasagiline mesylate),R-(+)-*N*, *N*-bispropargyl-1-aminoindan,N,N-di-(1-indanyl)-propargyl minemesylateK_2HPO_4/ triethylbenzyl ammoniumchloride (TEBAC), *S*-(-)-*N*-propargyl-1-aminoindane.

INTRODUCTION

Human cells contains 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, *R*-(+)-*N*-propargyl-1-aminoindan mesylate (Rasagiline mesylate; Figure: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 of monoamine oxidase[1] used as a monotherapy in early Parkinson's disease or as an adjunct therapy in more advanced cases[2]. It is selective for MAO type B over type A by a factor of fourteen [3].

Laboratory studies shown that rasagiline has invitro and invivo 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+ 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.

RESULTS AND DISCUSSION

Several syntheses are reported in the literature [4-10] for the preparation of *R*-(+)-*N*-propargyl-1-aminoindan mesylate and its racemic compound, for eg.scheme-**A**[4]and scheme-B[5]**.** In scheme-**A**, formation of R-(+)-*N*, *N*-bispropargylaminoindan mesylate (*N*, *N*-bis impurity)is major and removal of this impurity by purificationis highly difficult once it is formed. Hence it is necessary and very important to control the formation during the reaction. In addition to this, usage of propargyl chloride is also toxic in nature. In scheme-B,1-chloro indane couple with propagyl amine forms (±)-N-propargyl-1-aminoindan mesylate via N,N-di-(1-indanyl)-propargyl-amine hydrochloride which is also an impurity in the final product.

Several experments carried out by tuning some parameters like solvent, temperature, reaction time and mode of addition to control the impurity formation in both scheme-**A** and scheme-B but none of these parameters played a significant role. To avoid the formation of these impurities completely in the reaction, we designed scheme-**C**.

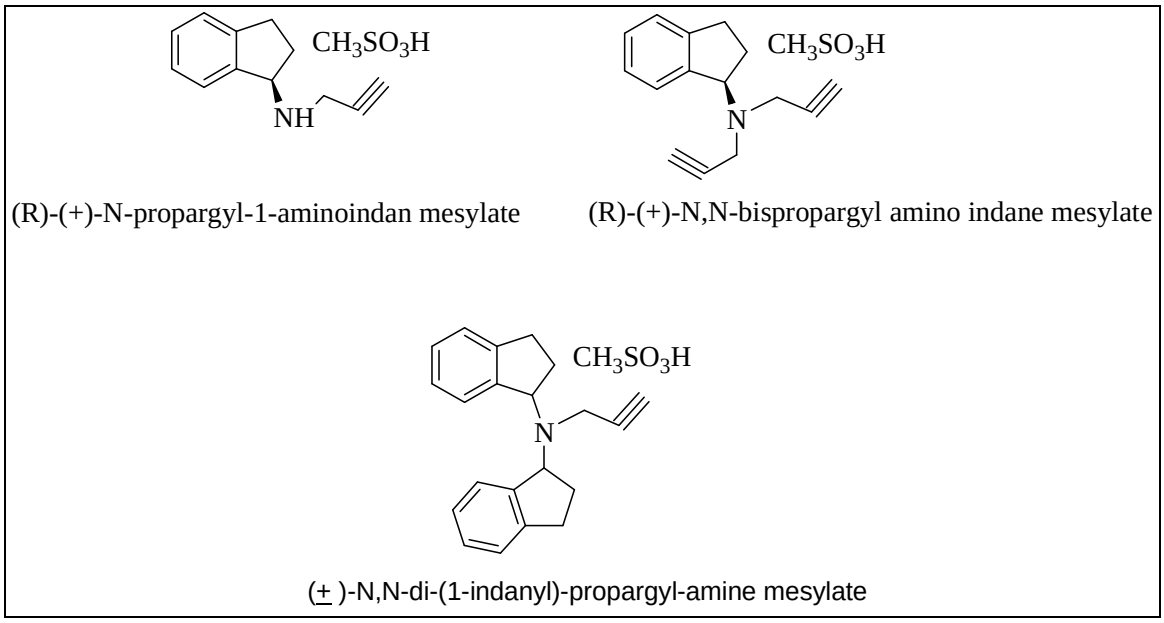
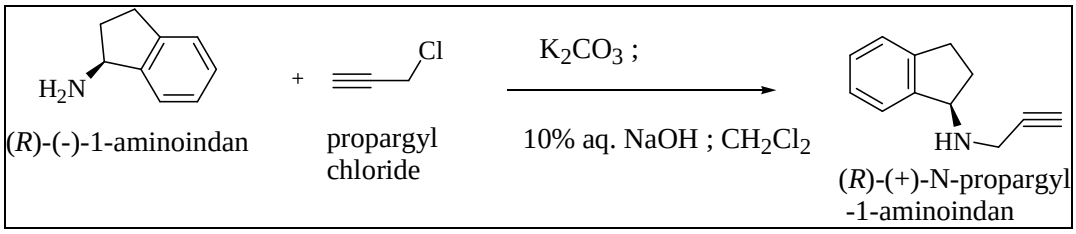
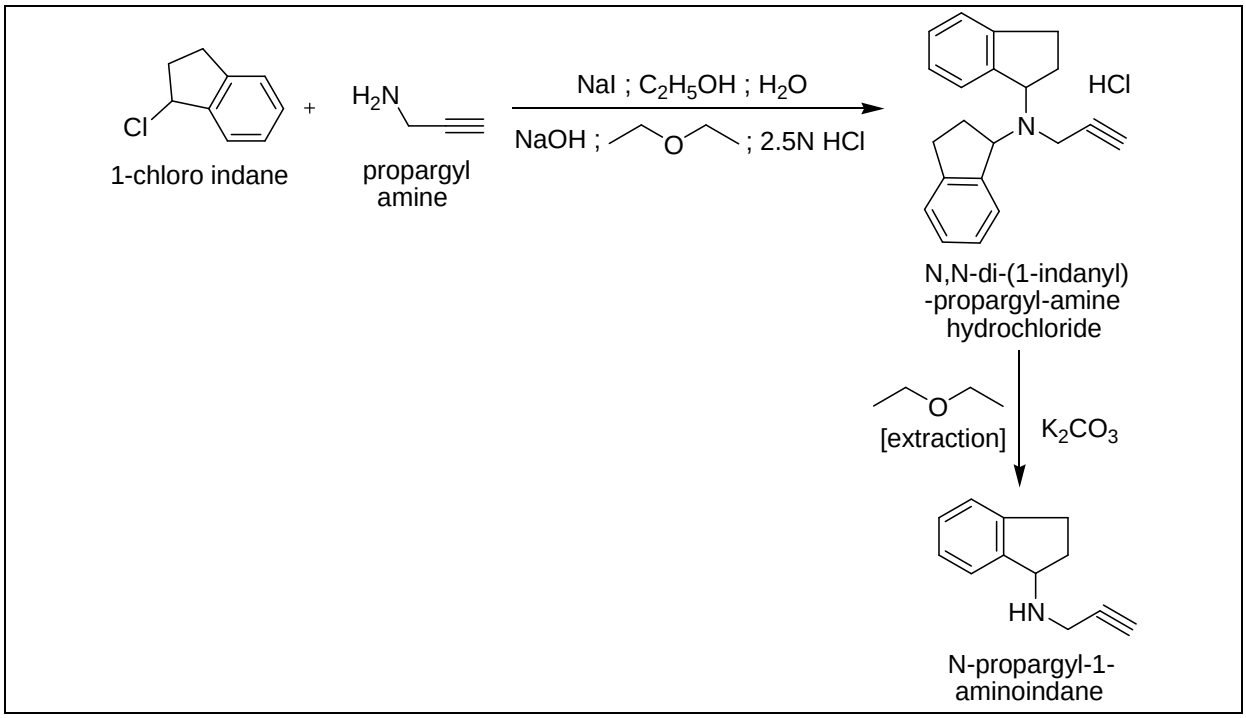


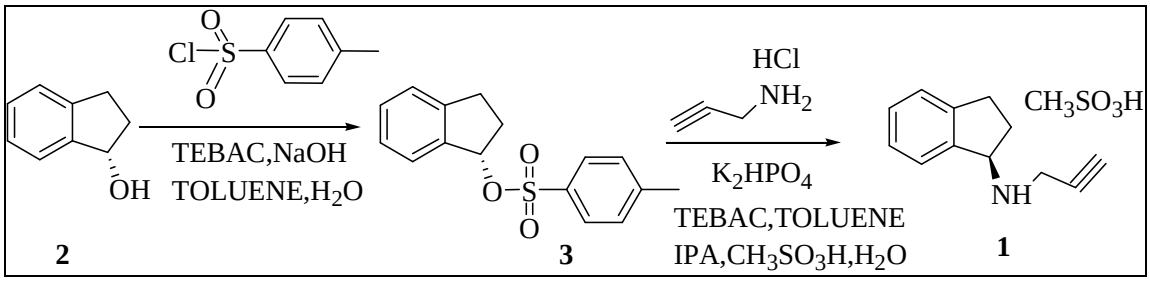
Figure 1



Scheme A



Scheme B



Scheme C

Reaction of S-(-)-1-indanol (**2)** with 4-methylbenzene-1-sulfonyl chloride in presence of triethylbenzylammonium chloride (TEBAC) and a base resultsS-(-)-2, 3-dihydro-1H-inden-1-yl-4-methylbenzenesulfonate (**3)**, in 92% yield. This product on treatment with prop-2-yn-1-amine hydrochloride in presence of K_2HPO_4/TEBAC forms pure *R*-(+)-N-propargyl-1-aminoindaneas a

residue. Initially we checked the direct reaction of compound **3 (**189.0g, 0.655 mol**)** with prop-2-yn-1-amine hydrochloride (40.0g, 0.436 mol**)** in presence of 2.0 eq of sodium hydroxide furnishes racemic *N*-propargyl-1-aminoindane **1**(entry 1 in Table-1). Addition of either 0.05 eq of TEBAC with 2.0 eq of sodium bicarbonate or 2.0 eq of K_2HPO_4 to prop-2-yn-1-amine hydrochloride (40.0g, 0.436 mol**)** yielded *R*-isomerin 90.83% and 94.57% respectively (entries 2&3 in Table-1). In the above two experiments *S*- isomer is minimized from 9.17% to 5.43% when K_2HPO_4 used rather than TEBAC as a reagent. When the reaction carried out by using a minimum quantity of TEBAC (0.0125 eq) and 2.0 eq of K_2HPO_4 99.08% of *R*-isomer obtained having *S*-isomer 0.92% (entry 4 in table-1). It is clearly evident that the presence of K_2HPO_4/TEBAC reagent system retains the selectivity. Finally 99.82% pure*R*-(+)-*N*-propargyl-1-aminoindane is obtained with 0.05 eq of TEBAC and 2.0 eq of K_2HPO_4(entry 5 Table-1). To our surprise, in the presence of K_2HPO_4/Triethylbenzylammonium chloride reagent system bisimpurity not observed at all. This on treatmentwith methanesulfonic acid, affordsmesylate salt of*R*-(+)-*N*-propargyl-1-aminoindan, [R-(+)-2,3-dihydro-*N*-(prop-2-ynyl)-1H-inden-1-amine mesylate] (**1)**, in 79% yield.

The base quantities used in table 1 are based on 40.0g input of prop-2-yn-1-amine hydrochloride.

Table-1: Purities of Product 1 (Scheme-C)

S.No.	NaOH (g)	$NaHCO_3$ (g)	TEBAC (g)	K_2HPO_4 (g)	Chiral purity of 1 by HPLC (%)		Chemical Purity of 1 by HPLC (%)
					S	R	
1.	17.5	--	--	--	51.94	48.06	99.22
2.	--	36.6	5.2	--	9.17	90.83	99.86
3.	--	--	--	152.2	5.43	94.57	99.97
4.	--	--	2.6	152.2	0.92	99.08	99.92
5.	--	--	5.2	152.2	0.18	99.82	99.82

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), ^{1}HNMR spectra were recorded on Varian 400 MHz spectrometer using $CDCl_3$ and D_2O 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 organic extracts were dried over sodium sulfate after work-up.

All dry reactions were carried out under nitrogen atmosphere with magnetic/mechanical stirring. Unless otherwise mentioned, all solvents and reagents used were of LR grade. TLC was performed on F 254 silica-gel plates, which were visualized using UV light.

Preparation of (R)-2, 3-dihydro-1H-inden-1-yl 4-methylbenzenesulfonate 3.

To a stirred solution of 400 mL water and sodium hydroxide (149.0g, 3.725 mol) a toluene (200 mL) solution of (*S*)-2,3-dihydro-1H-indan-1-ol (**2)** (100g, 0.745 mol) is added over 20 min at 0-5 °C. To this solution is added triethylbenzylammoniumchloride (5.0g, 0.025 mol), followed by

toluene (300 mL) solutionof 4-methylbenzene-1-sulfonyl chloride (170.5g, 0.894 mol) by drop wise over 90 min at 10-15 °C. The reaction mass maintained for 10 min, and raise the reaction temperature to 25-30 °C and the suspension is stirred for 2 hrs. After completion of the reaction checked by TLC, separate the organic layer from aqueous layer. The organic layer washed with water followed by saturated sodium chloride solution. Toluene is distilled completely under vacuum to yield a pale brown residue of **3** in 92% yield (197.7 g); ^{1}HNMR (**400**MHz, $CDCl_3$): δ 2.21 (s, 3H, tosyl methyl), 2.5-2.95 (t, 4H, indane), 7.00-7.65 (m, 4H, aromatic ring), 8.0-8.5 (d, 4H, tosyl aromatic), MS: *m/z* (M^++1) 289.36.

Preparation of (R)-2,3-dihydro-N-(prop-2-ynyl)-1H-inden-1-amine 1.

To a stirred solution of prop-2-yn-1-amine hydrochloride (40.0g, 0.436 mol) in water (200 mL) was added 200 mL toluene and adjust the mass pH to 8 with ammonia solution.The toluene layer is separated and washed with 200 mL water. Added (*R*)-2,3-dihydro-1H-inden-1-yl 4-methylbenzenesulfonate, (**3)** (189.0g, 0.655 mol), di-potassium hydrogen phosphate (152.2g, 0.873 mol) and triethylbenzylammonium chloride (5.2g, 0.023 mol) to above separated toluene layer and the obtained suspension is stirred at reflux temperaturefor 20 hrs. After completion of the reaction monitored by TLC, the mass is cooled to ambient temperature (25-30 °C) and added 300 mL water. The organic layer separated andwashed with 100 mL water and distilled completely under vacuum. The obtained residue is dissolved in 500 mL isopropyl alcoholand treated with methanesulfonic acid (41.9g, 0.415 mol) under reflux for 60 min. The obtained precipitate is cooled to ambient temperature (25-30 °C), filtered and washed with 100 mL isopropyl alcohol to furnish the product **1**as a white solidin79.1%yield (92.4g); m.p. 157-159 °C (Lit.[7]); ^{1}HNMR (**400**MHz, $CDCl_3$): 2.23 (s, 1H, methanesulphonic acid) 2.5-2.95 (complex, 4H, indane), 2.66 (s, 3H, -CH_3 methanesulphonic acid), δ 3.80 (s, 1H, -CH, acetylinic), 3.83 (s, 2H, -CH_2, propargyl), 4.5 (br, s, D_2o exchangeable, -N**H)** 7.00-7.45 (m, 4H, aromatic ring)**;** MS: *m/z* (M^++1) 172.2.

CONCLUSION

As a conclusion, we developed an efficient and simple method for the preparation of pure enantioselective*R*-(+)-*N*-propargyl-1-aminoindan mesylate(Rasagiline mesylate)**1** by controlling its isomer, S-(-)-N-propargyl-1-aminoindan.

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