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Synthesis and Characterization of Impurities in Rasagiline: A Novel MAO-B Inhibitor in Parkinson's Disease Therapy

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Rasagiline (**1**) is indicated as adjunctive therapy and monotherapy for treatment of Parkinson's disease approved by the FDA. During the process development of rasagiline, few processes related impurities were observed along with the final API. These impurities were identified as indanol (**2**), indanamine (**3**), allyl (**4**), keto (**7**), other isomer (**6**) and chloro allyl (**5,5a**) impurities. The present work describes the synthesis of all these impurities and characterized by ^{1}H NMR and Mass spectral analysis.

Keywords: 1-Indanone, *N*-(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-amine, Allyl bromide, Propargylamine hydrochloride.

INTRODUCTION

Among the various health problems, Parkinson's disease are very critical one and eternal decadent disorder of the central nervous system that probably influence the motor system [1]. Human cell having two forms of monoamine oxidase (MAO), which are MAO-A and MAO-B in the brain, but MAO-B is far most frequent and is responsible for the disruption of dopamine after its discharge into the synapse. Rasagiline [IUPAC: R-(+)-N-propargyl-1-aminoindan (Fig. 1), [m.f. $C_{12}H_{13}N$ and m.w. 171.23] avoids the disruption of dopamine by unreversible binding to MAO-B. So dopamine is respectively more available, somehow balancing for the decreased quantities made in the brains of humans with Parkinsons [2].

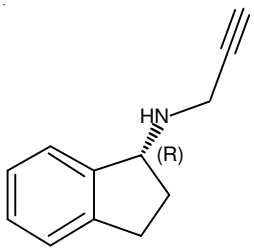


Fig. 1. Chemical structure of rasagiline

Drugs playing a prominent role in human life to fight various diseases. Unlike earlier days, most of the drugs currently are purely synthetically made. Unambiguously, the prepared drugs contain different impurities like chemicals or microbes. Most of the impurities are chemicals only. Impurities are additional compounds those are not the drug substance [also called as the active ingredient or the active pharmaceutical ingredient (API)], but rise while the synthesis, storage of the drug, extraction or purification. Knowing the source, prevail and quantification of impurities are critical to the preparation of good quality drug substances.

The consumption of medicines can lead to antagonistic effects, which in the maximum of cases, are relevant to the entry of various impurities and substances that take place in the remedy moreover the pharmacologically active ingredients into the body. Impurities can have a strong antagonistic effect due to unacceptable toxicological and pharmacological action, which can control over the certain effect of the medicine. Also impurities can prevent the effect of the pharmaceutical properties of the drug substance [3].

The potential impurities in a drug substance (API) can have a important impact on the safety and quality of the drug substance. The percentage of impurities in any drug substance are represented as per its toxicological or biological data. It is quite significant for "regulatory" aspect of drug substance approval also to provide limits of "relevant impurities". Therefore, it is mandatory to study the impurities of any drug substance and prevail it while manufacturing of a drug substance. As per the ICH guidelines, any impurity which is forming at equal/more than 0.10 % with respect to the drug substance should be synthesized, identified and characterized exhaustively [4].

There are several methods to synthesize rasagiline. In all methods, some common process related impurities like 1-indanol, 1-indanamine, allyl impurity, chloro allyl impurity, *S*-isomer and keto impurity. 1-Indanol is commercially available; remaining impurities synthesized and characterized by ^{1}H NMR and Mass spectral analysis.

EXPERIMENTAL

All reactions were carried out in oven-dried glassware (120 °C) under an atmosphere of nitrogen. Acetonitrile, chloroform and acetone were purchased from Merck Inc. *N*-Bromosuccinimide (NBS), azobisisobutyronitrile (AIBN), propargylamine hydrochloride and Lindlar catalyst were purchased from Aldrich Chemical Co.

Analytical thin layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254), which were purchased from Merck Inc. Purification by gravity column chromatography was carried out by use of silicycle ultrapure silica gel (particle size 40-63 μm, 230-400 mesh). Proton NMR spectra were obtained on a Varian Mercury-400 (400 MHz) spectrometer by use of chloroform-*d* ($CDCl_3$) and DMSO-d_6 as solvents.

Synthesis of 2,3-dihydro-1*H*-inden-1-amine or 1-indanamine (3): To a stirred solution of 1-indanone (**8**) (5 g, 0.0379 mol, 1.0 eq), ammonium formate (14.31 g, 0.227 mol, 6.0 eq) and Zn powder (6.9 g, 0.113 mol, 3.0 eq) in methanol (100 mL) was stirred under reflux. After completion of the reaction the mixture was filtered through celite and the solvent was removed by vacuum. The residue was treated with conc. HCl solution (4 mL) and water (30 mL) and then extracted with EtOAc (2 × 50 mL) to remove organic residues. The aqueous phase was alkalized with ammonia solution to and extracted with EtOAc (4 × 40 mL). The organic phase was washed with brine, dried over sodium sulphate and the solvent removed under vacuum resulted compound **3** 2.75 g as 56 % yield (80.18 % by HPLC). ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.72 (d, 1H, Ar-H), 7.24 (m, 3H, Ar-H), 5.82 (d, 1H, NH), 5.58 (d, 1H, NH), 4.90 (t, 1H, CH-NH_2), 3.79 (d, 1H, Ar-CH_2), 3.65 (d, 1H, Ar-CH_2), 3.17 (m, 1H, CH_2-CH), 2.89 (m,1H, CH_2-CH). Mass: *m/z* calcd. 133.09, found *m/z* 117.0 (M-NH_2)$^+$.

Synthesis of *N*-allyl-2,3-dihydro-1*H*-inden-1-amine or allyl impurity (4): A solution of *N*-(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-amine (**10**) (10 g, 0.0584 mol,1.0 eq), Lindlar catalyst (1.0 g, 10 % w/w) and catalytic amount of pyridine (0.456 g, 0.00584 mol, 0.1 eq) were taken in methanol (100 mL) and were hydrogenated by using hydrogen balloon pressure conditions for 6 h at ambient temperature. The reaction was monitored by using TLC, after completion of the reaction, the mixture was filtered through celite bed, MeOH was evaporated by high vacuum below 50 °C. The resultant crude was titrated by using EtOAc and *n*-hexane yielded 8.5 g (84.5 %) compound **4** as a brown colour oil. ^{1}H NMR (400 MHz, DMSO); δ 7.32 (dd, 1H, Ar-H), 7.21-7.14 (m, 3H, Ar-H), 5.93-5.86 (m, 1H, =CH), 5.23-5.03 (m, 2H, =CH_2), 4.10 (t, 1H, NH-CH), 3.60 (bs, 1H, NH) 3.29-3.22 (m, 2H, NH-CH_2), 2.89-2.69 (m, 2H, Ar-CH_2), 2.49-2.27 (m, 2H, CH-CH_2). Mass: *m/z* calcd. 173.12, found *m/z* 174.1 (M^{+1}). HPLC purity (%): 91.70.

Synthesis of 3-bromo-2,3-dihydro-1*H*-inden-1-one (9): 1-Indanone (**8**) (10 g, 0.0758 mol,1.0 eq) react with N-bromosuccinimide (NBS) (13.8 g, 0.0758 mol 1.0 eq) in a catalyst azobisisobutyronitrile (AIBN), was refluxed in $CHCl_3$ (100 mL) solvent for 3 h. After completion of reaction the reaction mixture was quenched with water, extracted with $CHCl_3$, washed with water, dried over sodium sulphate and concentrated under reduced pressure to obtain the 11 g compound **9**. ^{1}H NMR (400 MHz, $CDCl_3$); δ 7.70 (dd, 3H, Ar-H), 7.47 (m, 1H, Ar-H), 5.59 (q, 1H, CH-Br), 3.34 (dd, 2H, CH_2-CO), 3.03 (dd, 1H, CH_2-CO). Mass: *m/z* calcd. 211, found *m/z 212* (M^{+1})$^+$. HPLC purity (%): 98.58.

Synthesis of 3-(prop-2-yn-1-ylamino)-2,3-dihydro-1*H*-inden-1-one or keto impurity (7): A solution of compound **9** (5 g, 0.0235 mol, 1.0 eq) propargylamine hydrochloride (2.16 g, 0.0235 mol, 1.0 eq) and K_2CO_3 (6.50 g, 0.0472 mol, 2.0 eq) were taken in acetonitile (50 mL), then the reaction mixture was heated at 60 °C for 3 h. The reaction was monitored by using TLC, after completion of the reaction, acetonitile was evaporated by high vacuum below 50 °C added EtOAc and water. Organic layer was separated dried and concentrated. The resultant crude was purified by column chromatography by using EtOAc and *n*-hexane as a mobile phase resulted 3.1 g compound **7** as a brown thick mass. ^{1}H NMR (400 MHz, DMSO); δ 7.99 (d, 1H, Ar-H), 7.80 (dd, 1H, Ar-H), 7.78-7.68 (dd, 2H, Ar-H), 5.10 (d, 1H, NH-CH), 4.12 (d, 2H, NH-CH_2), 3.77 (s, 1H, CH),3.09 (m, 1H, CO-CH), 2.86 (dd,1H, CO-CH). Mass: *m/z* calcd185.07, found *m/z* 186.1 (M^{+1})$^+$. HPLC purity (%): 98.58.

Synthesis of (*S*)-*N*-(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-amine or *S*-isomer (6): A solution of *N*-(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-amine (**10**) (60 g, 0.531 mol, 1.0 eq), was taken in isopropyl alcohol (300 mL, 5 V) and methanol (420 mL, 7 V), D(-) tartaric acid was added and heated for 70 °C for 3h.The formed sold was filtered. The tartarate salt was basified by using aqueous $NaHCO_3$ solution and extracted with EtOAc. Organic layer was dried and concentrated under vacuum yielded 28 g (42 %) compound **6** as a brown thick mass. ^{1}H NMR (400 MHz, DMSO) δ 7.62 (d, 1H, Ar-H), 7.40-7.28 (m, 3H, Ar-H), 4.82-4.80 (m, 1H, NH-CH), 4.00 (s, 2H, NH-CH_2), 3.78 (1H, acetyl CH), 3.15-3.07 (m, 1H, Ar-CH), 2.92-2.84 (m, 1H, Ar-CH), 2.48-2.16 (m, 2H, CH-CH_2). Mass: *m/z* calcd. 171.10, found *m/z* 172.0 (M^{+1}). HPLC Purity (%): 99.20. Chiral HPLC (%): 99.70.

Synthesis of *N*-(2-chloroallyl)-2,3-dihydro-1*H*-inden-1-amine or chloro allyl impurity (5&5a): A solution of *N*-(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-amine (**10**) (10 g, 0.0584 mol, 1.0 eq), was taken in concentrated HCl (40 mL) and were heated for 6 h at 60 °C. The reaction was monitored by using TLC. After completion of the reaction, the reaction mixture was cooled to room temperature basified with aqueous NH_3 solution and extracted with EtOAc dried and concentrated. The resultant crude was purified by column chromatography by using EtOAc and n-hexane as a mobile phase resulted 4.2 g compound **5** and 2.8 g compound **5a**.

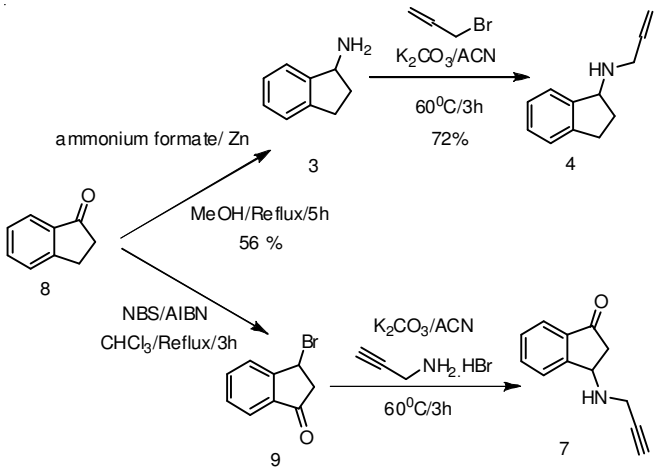
Spectral data of compound 5: ^{1}H NMR (400 MHz, DMSO); δ 7.66 (d, 1H, Ar-H), 7.40-7.29 (m, 3H, Ar-H), 5.89-5.70 (d, 2H, =CH_2), 4.85 (m, 1H, NH-CH), 4.00 (m, 2H, NH-

CH_2), 3.17-2.85 (m, 2H, Ar-CH_2), 2.49-2.15 (m, 2H, CH-CH_2). Mass: *m/z* calcd. 207.08, found *m/z* 208.1 (M^{+1}). HPLC Purity (%): 95.60.

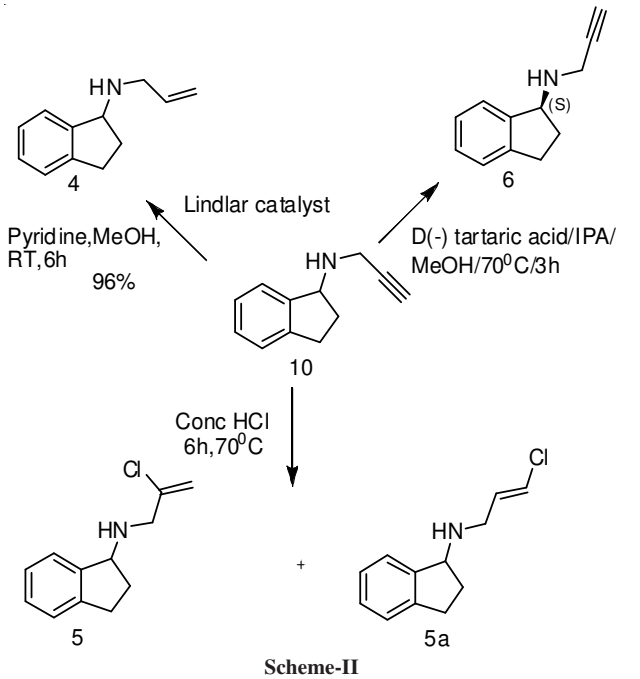
Spectral data of compound 5a: ^{1}H NMR (400 MHz, DMSO); δ 7.66 (d, 1H, Ar-H), 7.40-7.29 (m, 3H, Ar-H), 6.12 (d, 1H, =CH-Cl), 5.58 (d,1H.), 4.85 (m, 1H, NH-CH), 4.00 (m, 2H, NH-CH_2), 3.17-2.85 (m, 2H, Ar-CH_2), 2.49-2.15 (m, 2H, CH-CH_2). Mass: *m/z* calcd. 207.08, found *m/z* 208.1 (M^{+1}).

RESULTS AND DISCUSSION

Numbers of routes are reported in the literature for the synthesis of rasagiline and its recemic compound [5-11]. Our synthesis commenced with commercially available 1-indanone (**8**) and *N*-(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-amine (recemic compound) (**10**). 1-Indanone (**8**) was converted to 1-indanamine (**3**) [12] followed by coupling with allyl bromide [13] resulted allyl impurity (**4**). On the other hand 1-indanone (**8**) was brominated [14] followed by coupling with propargyl-amine hydrochloride resulted keto impurity (**7**) with good yield (**Scheme-I**).



Scheme-I



Scheme-II

N-(prop-2-yn-1-yl)-2,3-dihydro-1*H*-inden-1-amine (**10**) converted into allyl impurity (**4**) by using lindlar catalyst with good yield [15,16]. Markovnikov's and anti Markovnikov's addition of HCl on triple bond of compound **10** resulted compound **5** and compound **5a**. The recemic compound **10** was resoluted with D(-)tartaric acid resulted 99.7 % chiral pure S-isomer (**6**) (**Scheme-II**).

Conclusion

In **Scheme-I**, allyl impurity (**4**) preparation, we are not achieved yield and purity (72 % by HPLC) and isolation problem was observed, followed **Scheme-II** with good yield and purity (90 % by HPLC). Similarly keto impurity, S-isomer and chloro ally impurity were prepared good yields.

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